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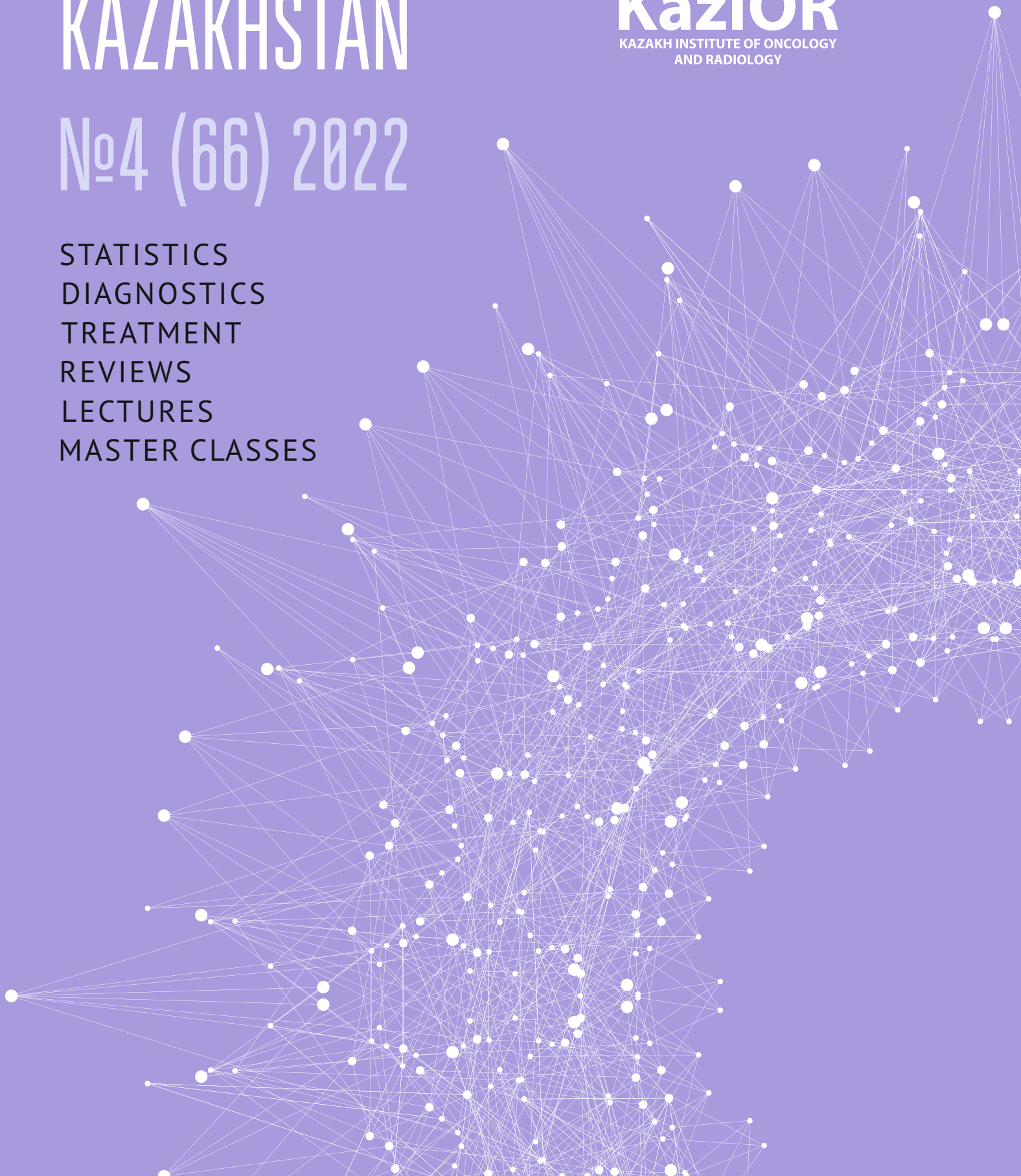

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Dear readers!

Welcome to the pre-new year 4th issue of the "Oncology and Radiology of Kazakhstan" journal!

Another year is coming to its end. We are reflecting on our professional activities, sharing scientific progress, and planning new projects and research. We will be glad to continue publishing the results and experiences of our colleagues in our journal.

We recommend to carefully read the manual for authors on our website before submitting a manuscript.

In this issue, we present research results of domestic and foreign oncologists and specialists in related spheres, for example, the articles on the role of PIVKAII tumor marker in hepatocellular carcinoma, a description of the stages of cytological examination using an immunocytochemical examination of effusion fluids, and information on the prevalence of COVID-19 among cancer patients in Kazakhstan.

The authors share the results of clinical cases of male breast cancer treatment, reconstructive plastic surgery involving the pectoralis major muscle for basal cell carcinoma of the facial skin, and the analysis of endotracheal tube cuff pressure control during anesthesia in cancer patients.

We also offer literature reviews on prostate cancer epidemiology in the East Kazakhstan region and the use of checkpoint inhibitors in treating locally advanced and metastatic gastric cancer.

Traditionally, the issue contains an article in English, "Endoscopic treatment of Barrett's esophagus in Kazakhstan."

Dear readers, we are looking forward to your new manuscripts and exciting results. Happy New Year! We wish you health, creative ideas and high achievements!

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

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EVALUATION OF TRENDS IN ONCOLOGICAL CARE FOR KIDNEY CANCER IN KAZAKHSTAN

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ABSTRACT

Relevance: *Worldwide, kidney cancer ranks sixth among the most frequently diagnosed cancers in men and 10th in women, accounting for 5% and 3% of all cancer diagnoses, respectively. In 2020, IARC reported 431,288 new cases and 179,368 deaths from kidney cancer worldwide. By 2040, they expect an increase of 40.4% in kidney cancer incidence (605,726 cases) and 59.4% in kidney cancer mortality (285,906 deaths).*

The study aimed to *analyze some kidney cancer indicators (incidence, mortality, early diagnosis, neglect, morphological verification) to evaluate the oncological care in Kazakhstan in 2010-2019.*

Methods: *A retrospective study using descriptive and analytical methods of biomedical statistics was used as the primary method.*

Results: *From 2010 to 2019, 10,966 new cases of kidney cancer and 3,866 deaths from this pathology were registered in Kazakhstan. kidney cancer incidence increased from 5.6±0.2‰ (2010) to 6.7±0.2‰ in 2019 (p=0.000). Over time, mortality rates from kidney cancer tended to decrease from 2.6±0.1‰ (2010) to 1.9±0.1‰ in 2019 (p=0.000). The study reveals a trend: the indicators of early diagnosis (the share of patients with stage I-II) improved from 50.7% (2010) to 69.1% in 2019, and, accordingly, the balance of neglected patients decreased significantly with stage III (from 31.2% to 14.6%) and with stage IV (from 18.1% to 16.0%). Morphological verification indicators for KC improved by 44.7%, from 58.5% and 84.6%, respectively, in 2010 and 2019.*

Conclusion: *The increase in kidney cancer incidence dictates further study of cause-and-effect relationships with risk factors for developing effective preventive measures and screening programs.*

Keywords: *Kidney cancer, incidence, mortality, early diagnosis, neglect, morphological verification, Kazakhstan.*

Introduction: Kidney cancer ranks sixth most frequent cancer in men and tenth in women worldwide, accounting for 5% and 3% of all oncological diagnoses, respectively [1]. In 2020, IARC reported 431,288 new cases and 179,368 deaths from kidney cancer worldwide. By 2040, they expect an increase of 40.4% in kidney cancer incidence (605,726 cases) and 59.4% in kidney cancer mortality (285,906 deaths) [3]. The underlying causes for this increase in incidence have yet to be studied.

Kidney cancer incidence rates are increasing in general [4]. In higher-income countries, this may be due, among other things, to an increased frequency of incidental detection of renal masses when doing abdominal imaging for non-specific musculoskeletal or gastrointestinal complaints. Even though most detected lesions are small tumors, the locally advanced disease is still diagnosed in many patients. At that, up to 17% of patients have distant metastases at diagnosis [5].

Kidney cancer incidence and mortality vary significantly between countries. Potential risk factors include behavioral [6, 7] and genetic factors [8, 9], concomitant diseases [10-12], and taking analgesics [13, 14]. Constant risk factors for kidney cancer are smoking [15, 16], obesity [15, 17], hypertension [18, 19], and chronic kidney disease [20, 21].

Early detection and screening are priorities in kidney cancer research [22]. Early diagnosis means better survival. Thus, 5-year survival with stage I and IV kidney cancer amount to 83% and 6%, respectively [23]. So, anti-cancer measures aimed at early detection and prevention of kidney cancer increase the quality of cancer care.

The study aimed to analyze some kidney cancer indicators (incidence, mortality, early diagnosis, neglect, morphological verification) to evaluate the oncological care in Kazakhstan in 2010-2019.

Materials and methods:

Case registration and patient enrollment. The research object was the data obtained from annual forms no. 7 and 35 of the Ministry of Healthcare of the Republic of Kazakhstan on kidney cancer (ICD 10 – C64) for 2010-2019 on incidence, mortality, early detection, neglect, and morphological verification.

Population denominators. Population denominators for calculating incidence rates were provided by the Bureau of National Statistics. We used data on the republic population for the respective regions; all data were obtained from the official website [24].

Statistical analysis. The primary method to analyze incidence was a retrospective study using descriptive and analytical methods of cancer epidemiology. Standardized incidence rates were calculated for eighteen different age groups (0-4, 5-9, ..., 80-84, and 85+) using the World population standard proposed by WHO with the recommendations of the National Cancer Institute (2013) [25].

Extensive, crude, and age-related incidence rates were determined by the generally accepted methodology used in sanitary statistics. The average annual values (M, P), average error (m), Student's criterion, 95% confidence interval (95% CI), and average annual growth/decline rates (T, %) were calculated. All calculation formulas used in the article are described in textbooks on statistics [26, 27]. Trends were determined using the least squares method, and the average annual growth rates were calculated using the geometric mean. We reviewed and processed the received materials using the Microsoft 365 software package (Excel, Word, PowerPoint). The Student's criterion was calculated when comparing average values using online statistical calculators [28].

Ethics approval. The review and approval by the ethics board were not required since this study included the analysis of publicly available administrative data and did not involve contacts with individuals. The data provided comply with the Law of the Republic of Kazakhstan No. 257-IV of March 19, 2010, "On State Statistics" [29]. The information in the summary report is confidential and can only be used for statistical purposes following the principles of the World Medical Association [30].

Results: From 2010 to 2019, 10,966 new cases of kidney cancer and 3,866 deaths from this pathology were registered in Kazakhstan. The average annual crude incidence of kidney cancer was 6.3±0.1‰ (95% CI=6.0-6.5) and increased from 5.6±0.2‰ (2010) to 6.7±0.2‰ in 2019 (p=0.000). Over time, mortality rates from kidney cancer tended to decrease from 2.6±0.1‰ (2010) to 1.9±0.1‰ in 2019, and the difference was statistically significant (p=0.000). Over time, the mortality from kidney cancer decreased statistically significantly (t=4.95, p=0.000) from 2.6±0.1‰ in 2010 to 1.9±0.1‰ in 2019, and the average annual crude mortality from kidney cancer was 2.2±0.1‰ (95% CI=2.0-2.4).

Trends in leveled crude incidence and mortality from kidney cancer in Kazakhstan are presented in Figure 1.

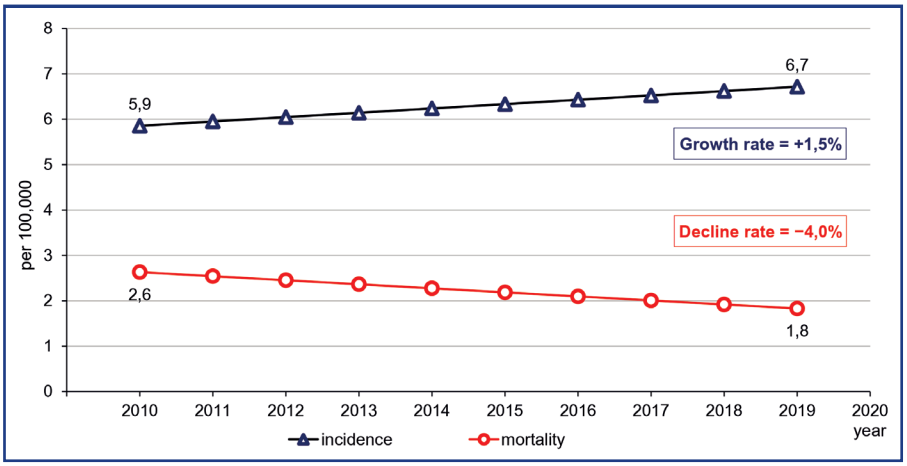

Figure 1 – Trends in leveled incidence and mortality from kidney cancer in Kazakhstan, 2010-2019

The average annual growth rate of leveled incidence rates was +1.5%, and the average annual decline rate of mortality was −4.0% (Figure 1).

Trends in leveled kidney cancer incidence by stages showed an increase in stage I-II cases and a decline in stage III cases. The number of cases registered at stage IV has grown insignificantly (Figure 2).

Over time, the share of patients with stage I-II kidney cancer improved from 50.7% in 2010 to 69.1% in 2019 (Figure 3), while an average annual leveled rate growth of +2.9%.

The share of patients with stage III decreased significantly, from 31.2% in 2010 to 14.6% in 2019 (Figure 3), with an average annual adjusted decline of -6.7%.

Over time, the share of stage IV kidney cancer cases decreased from 18.1% in 2010 to 16.0% in 2019 (Figure 3), with an average annual adjusted decline of -0.8%.

The share of morphologically verified kidney cancer cases increased from 58.5% in 2010 to 84.6% in 2019 (Growth rate = +1.2%) (Figure 4).

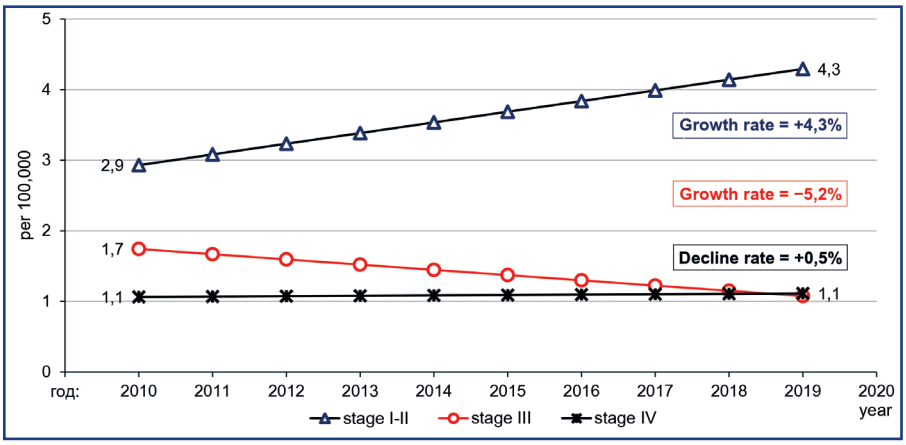

Figure 2 – Trends in leveled kidney cancer incidence rates by stage, Kazakhstan, 2010-2019

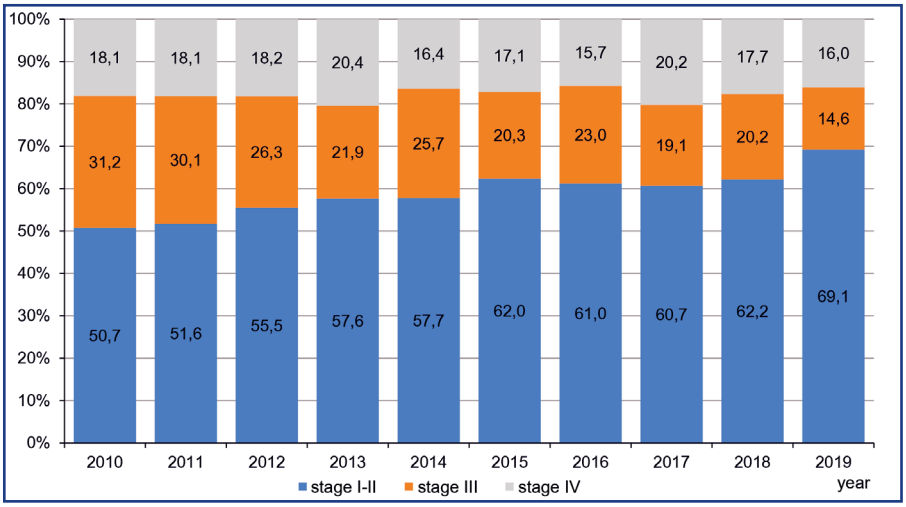

Figure 3 – Dynamics in kidney cancer early diagnosis (stage I–II) and neglect (stages III and IV) in Kazakhstan, 2010-2019

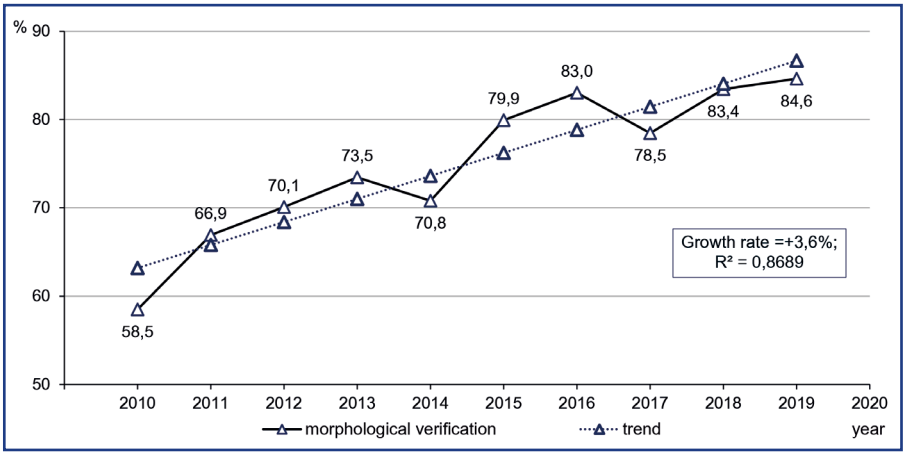

Figure 4 – Dynamics in morphological verification for kidney cancer, Kazakhstan, 2010-2019

Discussion: We observe a growth in incidence and a decline in mortality from kidney cancer in the Republic of Kazakhstan. Similar trends were observed in North America, Europe, and Asia [4, 31, 32].

The most important prognostic determinants of 5-year survival are the tumor stage, grade, local spread, metastases in regional lymph nodes, and metastatic signs at diagnosis. Kidney cancer is a slow-growing tumor that often remains clinically silent during most of its course. In 30% of cases, it is diagnosed by chance. The occurrence of symptoms is often associated with the disease progression. In 30% of cases, this cancer is metastatic; 25% of cases are locally advanced. Today, there is no clear evidence of the efficiency of early detection [33]. However, stratifying the population depending on the risk of developing kidney cancer could

help to develop an effective screening program aimed at the highest-risk group. The screening criteria, like screening start age and frequency, could be adjusted depending on the predicted risk for each person.

In the Republic of Kazakhstan, the absolute number of people first diagnosed with kidney cancer increased by 33.5% during the study period. Kidney cancer incidence per 100,000 population has increased by 17.7% over ten years. At the same time, there was a growing trend of kidney cancer stage I-II early detection and, respectively, a decrease in stage III incidence.

From 2010 to 2019, the absolute number of people who died from kidney cancer in Kazakhstan decreased by 16.7%. The mortality rate from kidney cancer per 100,000 population went down by 26.5% over ten years.

In the study period, the number of patients diagnosed with stage I-II kidney cancer increased by 81.8%, stage III cases decreased by 37.4%, and stage IV cases increased by 18.4%. Early detection showed a significant positive dynamic, and the indicators of neglect generally declined.

Conclusion: The increase in kidney cancer incidence dictates further study of cause-and-effect relationships with risk factors for developing effective preventive measures and screening programs. Reducing the burden of kidney cancer in Kazakhstan requires joint efforts. The use of interdisciplinary approaches based on new knowledge, including the results of epidemiological studies, can give a new impetus to prevention and early detection.

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АҢДАТПА

ҚАЗАҚСТАНДАҒЫ БҮЙРЕК ОБЫРЫ КЕЗІНДЕГІ ОНКОЛОГИЯЛЫҚ КӨМЕК КӨРСЕТКІШТЕРІНІҢ ӨЗГЕРІСТЕРІН БАҒАЛАУ

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Өзектілігі: *Бүкіл әлемде бүйрек қатерлі ісігі (БҚІ) ерлерде жиі диагноз қойылған қатерлі ісіктердің алтыншы, ал әйелдерде 10-шы орында, сәйкесінше барлық қатерлі ісік диагноздарының 5% және 3% құрайды. 2020 жылы Халықаралық қатерлі ісіктерді зерттеу агенттігінің мәліметтері бойынша әлемде БҚІ 431 288 жаңа жағдай және 179 368 өлім тіркелді, ал 2040 жылға қарай бүйрек қатерлі ісігінің жаңа жағдайлары 40,4%-ға (605 726 жағдай), ал осы патологиядан қайтыс болғандар саны 59,4%-ға (285 906 өлім) өседі деп болжануда.*

Зерттеудің мақсаты: *Қазақстандағы онкологиялық көмектің 2010-2019 жылдардағы қызметін бағалау үшін бүйрек обыры бойынша кейбір көрсеткіштерді (сырқаттанушылық, өлім-жітім, ерте диагностика, қараусыздық, морфологиялық верификация) талдау.*

Зерттеу әдістері: *Зерттеу материалы Қазақстан Республикасы Денсаулық сақтау министрлігінің 2010-2019 жылдардағы БҚІ (АХЖ 10 – С64) қатысты № 7 және 35 жылдық нысандары – сырқаттанушылық, өлім – жітім, ерте диагностика, қараусыздық, морфологиялық верификация деректері болды. Негізгі әдіс ретінде биомедициналық статистиканың сипаттамалық және аналитикалық әдістерін қолдана отырып, ретроспективті зерттеу қолданылды.*

Нәтижелер: *2010-2019 жылдары республикада БҚІ-нің 10 966 жаңа жағдайы және осы патологиядан 3 866 өлім тіркелді. БҚІ-нен сырқаттанушылық 5,9±0,2‰ (2010 ж.)-ден 6,7±0,2‰-ге дейін 2019 жылы өсті (p=0,000). Динамикада БҚІ-нен болатын өлім-жітім көрсеткіші 2,6±0,1‰ (2010 ж.)-дан 2019 жылы 1,8±0,1‰-ға дейін (p=0,000) төмендеу үрдісіне ие болды. Зерттеу кезінде мынадай үрдіс анықталады: ерте диагностика көрсеткіштері (I-II кезеңдегі науқастардың үлес салмағы) 50,7%-дан (2010 ж.) 2019 жылы 69,1%-ға дейін жақсарды және тиісінше асқынған III саты (31,2%-дан 14,6%-ға дейін) және IV сатыдағы (18,1%-дан 16,0%-ға дейін) науқастардың үлес салмағының көрсеткіштері айтарлықтай азайды. ТІҚІ кезінде морфологиялық верификация көрсеткіштері тиісінше 2010 жылдан 2019 жылға дейін 34,2%-ға, атап айтқанда 85,2%-дан 95,2%-ға дейін жақсарды.*

Қорытынды: *Бүйрек қатерлі ісігінің көбеюі тиімді алдын алу шаралары мен скринингтік бағдарламаларды әзірлеу үшін қауіп факторларымен себеп-салдарлық байланыстарды одан әрі зерттеуді талап етеді.*

Түйінді сөздер: *бүйрек қатерлі ісігі, сырқаттанушылық, өлім-жітім, ерте диагностика, қараусыздық, морфологиялық верификация.*

АННОТАЦИЯ

ОЦЕНКА ИЗМЕНЕНИЙ ПОКАЗАТЕЛЕЙ ОНКОЛОГИЧЕСКОЙ ПОМОЩИ ПРИ РАКЕ ПОЧКИ В КАЗАХСТАНЕ

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Актуальность: *В мире рак почки (РП) занимает шестое место среди наиболее часто диагностируемых видов рака у мужчин и 10-е место у женщин, составляя 5% и 3% всех онкологических диагнозов, соответственно. В 2020 году по данным Международно-*

го агентства по исследованию рака в мире зарегистрировано 431 288 новых случаев заболевания и 179 368 смертей от рака почки, а к 2040 году прогнозируется увеличение числа новых случаев рака почки на 40,4% (605 726 случаев), а число смертей от данной патологии – на 59,4% (285 906 смертей).

***Цель исследования** – анализ некоторых показателей по раку почки (заболеваемость, смертность, ранняя диагностика, запущенность, морфологическая верификация) для оценки онкологической помощи Казахстана за 2010-2019 гг.*

***Методы:** В качестве основного метода использовалось ретроспективное исследование с применением дескриптивных и аналитических методов медико-биологической статистики.*

***Результаты:** За 2010-2019 гг. в Республике Казахстан было зарегистрировано 10 966 новых случаев РП и 3 866 смертей от данной патологии. Заболеваемость РП в динамике имела тенденцию к росту с 5,9±0,2‰ (2010 г.) до 6,7±0,2‰ в 2019 году (p=0,000). В динамике показатели смертности от РП имели тенденцию к снижению с 2,6±0,1‰ (2010 г.) до 1,8±0,1‰ – в 2019 году (p=0,000). При исследовании изучаемого периода выявляется тенденция: показатели ранней диагностики (удельный вес больных с I-II стадией) улучшились с 50,7% (2010 г.) до 69,1% в 2019 году, и соответственно показатели удельного веса запущенных больных значительно уменьшились с III стадией (с 31,2% до 14,6%) и с IV стадией (с 18,1% до 16,0%). Показатели морфологической верификации при РП улучшились почти на 44,7%, с 58,5% до 84,6% соответственно в 2010 и 2019 годах.*

***Заключение:** Рост заболеваемости раком почки диктует дальнейшее изучение причино-следственных связей с факторами риска для разработки эффективных профилактических мероприятий и программ скрининга.*

***Ключевые слова:** рак почки, заболеваемость, смертность, ранняя диагностика, запущенность, морфологическая верификация.*

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COVID-19 PREVALENCE AMONG CANCER PATIENTS IN KAZAKHSTAN

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ABSTRACT

Relevance: *The new coronavirus infection, COVID-19, has been spreading rapidly around the world since 2019, affecting the healthcare systems of most countries. According to recent studies, malignant diseases increase the susceptibility to COVID-19 and are a risk factor for worse clinical outcomes in COVID-19 patients. COVID-19 also increases the risk of disease progression in patients with malignancies.*

The study aimed to *study the prevalence of COVID-19 among cancer patients in Kazakhstan.*

Methods: *The analysis included open-access articles published since 2019 and indexed in PubMed, Cochrane, Google Scholar, and e-Library by keywords "cancer," "malignant neoplasms," "COVID-19", "cancer patients," "mortality risk." The official statistics data, medical information systems of the Republic of Kazakhstan (Electronic Register of Cancer Patients, Electronic Register of Inpatient Patients), and official periodicals on cancer incidence and mortality for 2020-2021 and COVID-19 incidence and mortality for 2020-2022 in Kazakhstan were studied.*

Results: *In the Republic of Kazakhstan, in 2020-2021, the highest cancer incidence was registered in North Kazakhstan (1.79-1.87%), Pavlodar (1.57-1.63%), Karaganda (1.54-1.53%) and Kostanay (1.53%) regions. The lowest rates were recorded in the Turkestan (0.42-0.41%), Kyzylorda (0.57-0.59%), Mangistau (0.62%) regions, and the city of Shymkent (0.60%). The highest cancer mortality in Kazakhstan was registered in the Turkestan (11.1%), Kyzylorda (10.2%), and Zhambyl (10.02%) regions in 2020, and in the Atyrau (25.4%), Turkestan (10.68%), and West Kazakhstan (10.30%) regions in 2021.*

The mortality from COVID-19 among patients registered for cancer in 2020 was the highest in the city of Astana (1.06%), the Kyzylorda (0.46%), and Turkestan (0.33%) regions, and in 2021 – in the cities of Shymkent (1.05%) and Astana (1,00%), the Atyrau (0.93%) and West Kazakhstan (0.94%) regions.

Conclusion: *Thus, COVID-19 prevalence among cancer patients and their increased mortality during the pandemic, including the cases where the main cause of death was not an oncological process but the consequences of the viral infection, evidence the need to adjust the rules of statistical recording of cancer patients' morbidity and mortality, the algorithms, and protocols of diagnosis and treatment of cancer patients.*

Keywords: *cancer, malignant neoplasms (MN), COVID-19, cancer patients, mortality risk.*

Introduction: The new coronavirus infection, COVID-19, has been spreading rapidly around the world since 2019 [1-8]. Most patients with COVID-19 have mild or moderate respiratory symptoms [9-15]. However, 13.8% of patients have a severe form, as they get sick being in critical condition due to different symptoms of other diseases, which can lead to multiple organ failure and even death [16-23]. According to recent studies, patients with COVID-19 and comorbidities of the endocrine system, heart, kidneys, malignant neoplasms, and chronic respiratory or neurological diseases are more likely to have a relatively poor prognosis [24-34].

Cancer is a serious public health issue that threatens the health of the world's population [35]. According to recent studies, cancer increases susceptibility to COVID-19 and becomes a risk factor for worse clinical outcomes in COVID-19 patients [36-43]. Also, it should be noted that during the pandemic, 44% of worldwide ministries of health stressed an increase in the inferiority of screening for cancer diseases, which significantly affected the timeliness of early diagnosis [44]. However, cancer patients need a timely diagnosis, examination, and specialized anticancer treatment during and after the pandemic.

In this regard, recent years' studies aimed to analyze the data on the incidence and outcome in COVID-19 patients with malignant neoplasms (MNs). The Global Cancer Observatory reported 1.8 million new cancer cases and 606,000 new deaths from cancer worldwide in 2020 [45]. According to the information on COVID-19 morbidity in cancer patients from Wuhan, China, 12 out of 1524 (0.79%) patients admitted to the oncology department from December 2019 to February 2020 were infected with COVID-19. It is worth noting that among this group of patients, the infection rate was higher than the cumulative frequency of all diagnosed cases of COVID-19 registered in Wuhan over the same period (0.37%) [8]. According to other studies from Wuhan, among all those infected with COVID-19, approximately 1-2% had oncological diseases [9-11].

Other studies show a higher prevalence of cancer in people with COVID-19. Thus, in New York (USA), out of 5700 hospitalized patients with COVID-19, 6% had a concomitant oncological diagnosis [12].

In the region of Lombardy (Italy), 8% of patients admitted to the intensive care unit (ICU) for COVID-19 either had active cancer or were previously treated for can-

cer and were in remission [13]. Other sources report that 20.3% of deaths from COVID-19 in all of Italy are in patients with active tumors [14].

Unfortunately, data on the clinical characteristics of COVID-19-infected cancer patients are currently limited by sample sizes, such as a retrospective study of 28 COVID-19 cancer patients from three hospitals in Wuhan [17]. Among the cases, more than half (61%) were men, the median age of all patients was 65 years, and the most common oncological disease was lung cancer - in 7 (25%) patients. At the same time, 8 cases of infection are believed to have been associated with nosocomial transmission of the infection. Slightly more than half of the patients – 15 (54%) – had a severe course of the disease, and 6 (21%) were admitted to the intensive care unit. A significantly higher risk of developing severe complications of COVID-19 was noted among patients who received anticancer treatment within the last 14 days [17].

Another study included 105 cancer patients hospitalized with COVID-19 in 14 hospitals in Wuhan and 536 age-matched patients without a history of cancer (control group) [18]. Lung cancer was the most common site (n=22), followed by malignancies of the gastrointestinal tract (n=13), breast (n=11), thyroid (n=11), and blood (n=9). Compared with patients in the control group, patients with cancer had higher rates of mortality (odds ratio (OR) – 2.34, confidence interval (CI) 95%: 1.15-4.77), hospitalizations in the intensive care unit (OR – 2.84, 95% CI: 1.59-5.08), severe COVID-19 (OR – 2.79, 95% CI: 1.74-4.41); the likelihood of the need for artificial lung ventilation increased by twofold. It is noteworthy that oncological patients, more often than others, were infected with nosocomial infections (19% vs. 1.5%) and were smokers (34% vs. 9%). Patients with blood and lung cancers and metastatic cancers with various cancer locations had the highest incidence of severe COVID-19.

Another study of the severity of COVID-19 disease in cancer patients is presented in two New York hospitals' reports [19]. Of 5,688 patients with laboratory-confirmed COVID-19, 334 (6%) had cancer, including breast cancer (n=57), prostate cancer (n=56), lung cancer (n=23), urogenital cancer (n=18) and colorectal cancer (n=16) [19]. It was noted that cancer patients aged 66 to 80 years required lung intubation significantly more often than patients without cancer (relative risk (RR) – 1.76; 95% CI: 1.15-2.70); no significant differences were found in other age groups. At the same time, in cancer patients below 50, the mortality from COVID-19 was five times higher than at the same age without cancer (RR – 5.01; 95% CI 1.55-16.2). Interestingly, in elderly patients with cancer, such a significant difference was not observed compared with the corresponding control group.

Another New York hospital also noted higher mortality in patients with COVID-19 and cancer [20]. Within three weeks, 218 cancer and COVID-19 patients were identified; of them, 61 died, and the mortality amounted to 37% in blood cancer and 25% in solid tumors. The lung cancer in combination with COVID-19 mortality was 55% (6 out of 11 patients). In age- and sex-matched groups, among 1090 patients with COVID-19 but without cancer, from the same hospital and in the same period, cancer patients' mortality was twice as high as in patients without cancer (28% versus 14%).

Compared with the general population, the immunosuppressive states of cancer patients make them more vulnerable to severe complications that can affect the prognosis of the disease [38]. In addition to the immunosuppressive state, the average age of cancer patients is higher than the age of the general population, which may be another risk factor for severe COVID-19 [46-47]. Several studies have reported that cancer is a risk factor for patients with COVID-19 due to an immune response that can lead to adverse clinical outcomes [40]. However, it is known from the experience of virologists and immunologists that immunosuppression may not always cause serious complications and may even provide advantages in preventing "cytokine storms," which indicate an inadequate response of the patient's immune system to a viral infection.

W. Liang et al. [47] reported a cancer prevalence of 1.13% [95% confidence interval (CI): 0.61–1.65%] among 1590 cases of COVID-19 in China, which is 3. 8 times higher than the overall cancer incidence among the Chinese population (0.29%). In addition, VG Giannakoulis et al. [37] examined the results of a meta-analysis of systematic reviews involving 46499 patients with COVID-19 and MN and showed that all-cause mortality was higher in patients with cancer compared to patients without cancer [hazard ratio (RR): 1.66, 95% CI: 1.33-2.07, P<0.0001].

The cancer prevalence in China among COVID-19 patients was 1.13% and was 3.9 times higher than the overall cancer incidence (0.29%) among the Chinese population without COVID-19. At the same time, mortality among infected cancer patients in China was 28.6% compared with 2.3% among patients with COVID-19 without cancer [9, 46]. According to the American Association for Cancer Research in April 2021, mortality from COVID-19 among cancer patients is fixed at 11-35% depending on location, patient condition, age, etc. [48].

An increase in the number of patients with cancer and COVID-19 confirms several important clinical care considerations and highlights an urgent need for additional preventive measures and clinical management of such patients since cancer patients are immunocompromised and at increased risk of serious complications associated with COVID-19 (hospitalization in the intensive care unit, need for mechanical ventilation, or death) [9, 10].

A relatively small sample size limits all existing research on the interaction between COVID-19 and can-

cer in humans. Therefore, targeted studies of COVID-19 prevalence in patients with MN are required in each country to study cancer incidence in patients with COVID-19 and identify a correlation between cancer and COVID-19.

The study aimed to study the prevalence of COVID-19 among cancer patients in Kazakhstan.

Materials and methods: The analysis included open-access articles published since 2019 and indexed in PubMed, Cochrane, Google Scholar, and e-Library by keywords "cancer," "malignant neoplasms," "COVID-19", "cancer patients," "mortality risk." Fifty-two literary sources were identified and included in the analysis.

The official statistics data, medical information systems of the Republic of Kazakhstan (Electronic Register of Cancer Patients, Electronic Register of Inpatient Patients), and official periodicals on cancer incidence and mortality for 2020-2021 and COVID-19 incidence and mortality for 2020-2022 in Kazakhstan were studied.

Results: In Kazakhstan, the situation with COVID-19 infection is similar to other countries. Dynamic statistics (daily and monthly) reflect the trend in COVID-19 deaths and new infections. Figure 1 shows the dynamics of the spread of COVID-19 in Kazakhstan from January 2020 to December 2022, according to official statistics [49].

The main viral load was observed in the summer and autumn of 2020-2021 and in the winter of 2022 (January-February). These periods coincided with the partial lifting and weakening of organizational measures to prevent the spread of COVID-19 among the population.

A further (since March 2022) decrease in morbidity and mortality is due to the development and implementation of new effective protocols for the treatment of COVID-19, the introduction of mandatory vaccination of the population by the resolutions of the Chief State Sanitary Doctor "On the organization and implementation of sanitary, anti-epidemic and sanitary and preventive measures for COVID-19 in the Republic of Kazakhstan."

Official information on morbidity and mortality from oncopathology and COVID-19 in Kazakhstan by regions [50, 51], with recalculation for the population and analysis of mortality of cancer patients, depending on the indication of the cause of death of the patient in the Electronic Register of Cancer Patients (ERCP) and Electronic Register of Inpatient Patients (ERIP), is shown in Tables 1 and 2. Table 1 presents comparative data on mortality in Kazakhstan from the main disease (oncology or COVID-19), indicating the number of cancer patients infected with COVID-19 in 2020. The highest cancer incidence was registered in North Kazakhstan (1 .79%), Pavlodar (1.57%), and Karaganda (1.54%) regions. The lowest rates were recorded in the Turkestan (0.42%), Kyzylorda (0.59%), and Mangystau (0.62%) areas. The highest cancer mortality in Kazakhstan was registered in the Turkestan (11.1%), Kyzylorda (10.2%), and Zhambyl (10.02%) regions in 2020.

The mortality from COVID-19 among patients registered for cancer in 2020 was the highest in the city of Astana (1.06%), Kyzylorda (0.46%), and Turkestan (0.33%) regions, with lower incidence than in other areas.

Table 1 - Information on oncological patients with concomitant COVID-19 disease registered at the dispensary for January-December 2020

Region	Population, December, 2020	Registered in ERCP, abs. (%)	Deaths from cancer, 2020, abs. (%)	of them, according to ERIP		Deaths from COVID-19, abs. (%)
				U07.1*	U07.2**	
Akmola region	736735	9005 (1.22%)	707 (7.85%)	99	109	1 2 (0.13%)
Aktobe region	881561	7560 (0.85%)	513 (6.78%)	28	88	3 (0.03%)
Almaty region	2055274	15549 (0.75%)	1206 (7.75%)	102	204	11 (0.07%)
Atyrau region	645280	4161 (0.64%)	387 (9.3%)	36	44	4 (0.09%)
East Kazakhstan region	1369597	20549 (1.50%)	1642 (8.0%)	412	242	39 (0.18%)
Zhambyl Region	1130099	7663 (0.67%)	768 (10.02%)	63	99	2 (0.02%)
West-Kazakhstan region	656844	7531 (1.15%)	634 (8.4%)	112	38	6 (0.07%)
Karaganda region	1376882	21268 (1.54%)	1301 (6.1%)	321	164	4 (0.01%)
Kostanay region	868549	13088 (1.50%)	730 (5.57%)	145	165	1 0 (0.07%)
Kyzylorda Region	803531	4761 (0.59%)	487 (10.2%)	59	24	2 2 (0.46%)
Mangistau region	698796	4359 (0.62%)	322 (7.38%)	29	68	5 (0.11%)
Pavlodar region	752169	11850 (1.57%)	894 (7.54%)	133	198	5 (0.04%)
North-Kazakhstan region	548755	9863 (1.79%)	547 (5.54%)	281	195	6 (0.06%)
Turkestan region	2016037	8472 (0.42%)	942 (11.1%)	32	92	2 8 (0.33%)
Almaty	1916822	26560 (1.38%)	1643 (6.18%)	313	137	19 (0.07%)
Nur-Sultan (Astana)	1136156	11546 (1.01%)	808 (6.99%)	252	104	8 (1.06%)
Shymkent	1038152	6526 (0.62%)	649 (9.94%)	36	92	15 (0.22%)
Kazakhstan	18631779	190311 (1.02%)	14150 (7.43%)	2453	2063	199 (0.10%)

Notes: *U07.1 – COVID-19 confirmed by PCR test; **U07.2 – COVID-19 not confirmed by PCR test

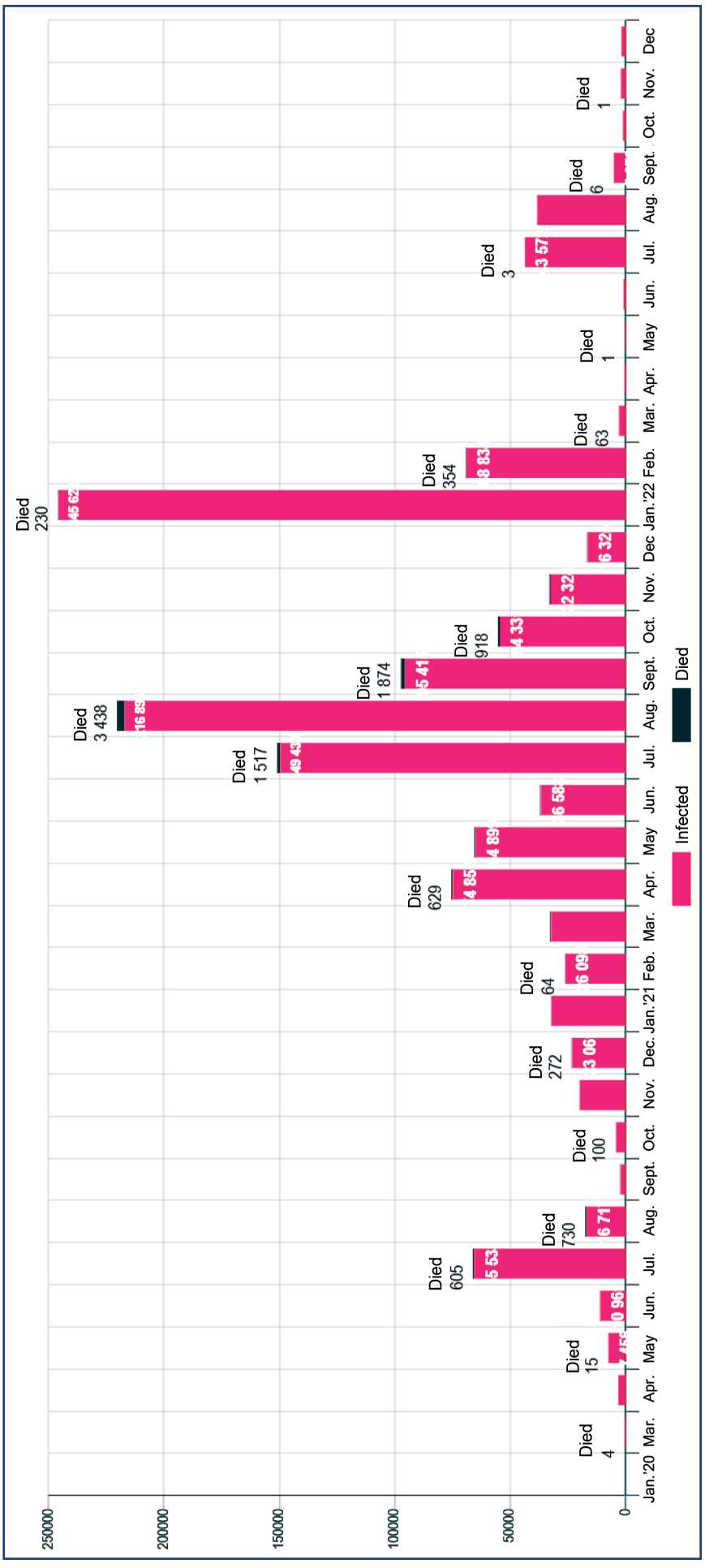

Figure 1 – New cases of infection and death from COVID-19 in Kazakhstan from January 2020 to December 2022 [49]

In 2021, high rates of cancer incidence were noted in North Kazakhstan (1.87%), Pavlodar (1.63%), Karaganda (1.53%), and Kostanay regions (1.53%). The lowest rates were noted in Turkestan (0.41%), Kyzylorda (0.57%) regions, and Shymkent (0.60%). The highest cancer mortality in Kazakhstan was registered in the Turkestan (11.1%), Kyzylorda (10.2%), and Zhambyl (10.02%) regions in 2020, and in the Atyrau (25.4%), Turkestan (10.68%), and West Kazakhstan (10.30%) regions in 2021.

The fact of increased mortality from COVID-19 oncological patients who were registered in the dispensary was recorded in Shymkent (1.05%), Astana, Atyrau (0.93%), and West Kazakhstan (0.94%) regions (Table 2).

Table 2 - Information on oncological patients with concomitant COVID-19 disease registered at the dispensary for January-December 2021

Region	Population, December 2021	Registered in ERCP, abs. (%)	Deaths from cancer, 2021, abs. (%)	Total patients with COVID-19, abs. (%)	of them, according to ERIP		Deaths from COVID-19, abs. (%)
					U07.1*	U07.2**	
Akmola region	734 413	9213 (1.25%)	662 (7.18%)	979 (10.6%)	765	214	49 (0.53%)
Aktobe region	905 355	8000 (0.88%)	521 (6.51%)	550 (6.8%)	373	177	17 (0.21%)
Atyrau region	667 300	4362 (0.65%)	1110 (25.4%)	392 (8.9%)	267	125	41 (0.93%)
Almaty region	2 105 195	15672 (0.74%)	372 (2.37%)	1450 (9.25%)	748	702	27 (0.17%)
East-Kazakhstan region	1 356 911	20760 (1.52%)	1607 (7.74%)	1132 (5.4%)	678	454	27 (0.13%)
West-Kazakhstan region	665 458	7605 (1.14%)	784 (10.3%)	729 (9.58%)	697	32	72 (0.94%)
Zhambyl Region	1 149 136	7777 (0.67%)	621 (7.98%)	1148 (14.7%)	318	830	33 (0.42%)
Karaganda region	1 372 199	21066 (1.53%)	1240 (5.88%)	2647 (12.5%)	2349	298	133(0.63%)
Kostanay region	858 347	13179 (1.53%)	738 (5.59%)	1025 (7.7%)	790	235	12 (0.09%)
Kyzylorda Region	826 958	4721 (0.57%)	426 (9.02%)	287 (6.0%)	189	98	40 (0.84%)
Mangistau region	738 861	4570 (0.61%)	368 (8.05%)	246 (5.3%)	142	104	39 (0.85%)
Pavlodar region	747 501	12199 (1.63%)	825 (6.76%)	1398 (11.4%)	1208	190	47 (0.38%)
North-Kazakhstan region	537 787	10073 (1.87)	547 (5.43%)	931 (9.2%)	713	218	28 (0.27%)
Turkestan region	2072804	8704 (0.41%)	930 (10.68%)	375 (4.3%)	122	253	12 (0.13%)
Nur-Sultan (Astana)	1 234 312	12581 (1.01%)	860 (6.83%)	1374 (10.9%)	1168	206	126 (1.0%)
Almaty	2020547	27421 (1.35%)	1560 (5.68%)	3284 (11.9%)	2842	442	124 (0.45%)
Shymkent	1 109 381	6732 (0.6%)	536 (7.96%)	555 (8.2%)	364	191	71 (1.05%)
Kazakhstan	19 102 465	194635 (1.01%)	13676 (7.02%)	18502 (9.5%)	13733	4769	898 (0.46%)

Notes: *U07.1 – COVID-19 confirmed by PCR test; **U07.2 – COVID-19 not confirmed by PCR test

The presented official statistics raise many questions. For example, why was the ratio of deaths to cases much lower at the peak of the pandemic (2020) than in 2021? Apparently, at the height of the pandemic (2020), all urgent measures and organizational measures were directed to fight COVID-19. Screening, diagnosis and treatment of other diseases, including cancer, were not carried out as usual. By 2021, most state public health institutions restored their operations. However, this temporary delay in diagnosis and treatment was fatal for some patients. In addition, a certain part of cancer mortality was "cannibalized" by COVID-19. This indicates the need to consider the mortality among oncological patients who died "from COVID-19" when analyzing oncological statistics.

Discussion: The results of our research are confirmed by the data obtained by T.A. Adylkhanov et al. about 883 patients with cancer and confirmed COVID-19 who were treated in different regions of Kazakhstan for 2.5 months (from March 13 to May 28, 2020). The authors identified features that are not typical for other patients with COVID-19, namely: "in addition to typical symptoms such as cough, fever, weakness, there was also a decrease in breathing, even with less physical activity, headache, general weakness, chills, sweating, decreased resistance to physical activity"; in some, the disease was accompanied by anemia and hypoproteinemia, which unequivocally negatively affected the immunocompetence and clinical course of the oncological disease. There is also evidence that in patients over 60 years of age, COVID-19 was more severe [51].

To help medical institutions during the pandemic, cancer societies around the world, in particular the European Society for Medical Oncology (ESMO), American Society of Clinical Oncology (ASCO), the National Comprehensive Cancer Network (NCCN), have developed recommendations to mitigate the negative impact of the COVID-19 pandemic on the diagnosis and treatment of cancer patients.

Patients with MN are at risk of developing severe COVID-19 and death from COVID-19. Therefore, vac-

cination against SARS-CoV-2 should be a preventive measure. The Kazakh Institute of Oncology and Radiology has developed recommendations for vaccination against COVID-19 in Kazakhstani cancer patients based on the recommendations of international organizations, such as NCCN, MSC, and ASCO, to minimize the risk of infection. The guidelines "Vaccination against coronavirus infection of the population in the Republic of Kazakhstan" were approved by the Decree of the Chief State Sanitary Doctor of June 11, 2021, No. 28 "On further measures to prevent coronavirus infection among the population of the Republic of Kazakhstan" [52].

Due to untimely diagnosis and treatment, cancer patients are less likely to get good results from the rehabilitation complex of antitumor measures. It is also important to remember that cancer patients are immunocompromised and at increased risk of serious complications associated with COVID-19 (ICU admission, need for mechanical ventilation, or death) compared with the general population [9, 46]. Current developments call for pragmatic approaches to treating cancer patients.

Conclusion: Thus, COVID-19 prevalence among cancer patients and their increased mortality during the pandemic, including the cases where the main cause of death was not an oncological process but the consequences of the viral infection, evidence the need to adjust the rules of statistical recording of cancer patients' morbidity and mortality, the algorithms, and protocols of diagnosis and treatment of cancer patients.

The consequences of COVID-19 disease, worsening the condition of cancer patients, challenge oncologists to develop effective organizational measures to prevent the spread of COVID-19 in patients with cancer. However, more specific conclusions require to obtain the results of studies involving a larger number of observations.

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АҢДАТПА

ҚАЗАҚСТАНДА ҚАТЕРЛІ ІСІКТЕРІ БАР НАУҚАСТАРДА COVID-19 КЕСЕЛІНІҢ ТАРАЛУЫ

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Өзектілігі: *COVID-19 жаңа коронавирустық инфекциясы 2019 жылдан бастап бүкіл әлемге тез таралып, көптеген елдердің денсаулық сақтау жүйелеріне әсер етті. Жақында жүргізілген зерттеулер қатерлі аурудың болуы COVID-19-ға сезімталдықты арттыратынын және COVID-19-бен ауырған емделушілерде клиникалық нәтижелердің нашарлауы қаупінің факторы екенін көрсетті. Сондай-ақ, қатерлі аурулары бар науқастарда COVID-19-дың болуы аурудың өршу қаупін арттырады.*

Зерттеудің мақсаты *– Қазақстанда қатерлі ісігі бар науқастарда COVID-19-дың таралуын зерттеу.*

Әдістер: *Әдебиетке шолу жасау үшін 2019 жылдан бастап ашық қолжетімділіктегі және ғылыми жарияланымдардың PubMed, Cochrane, Google Scholar, e-Library дерекқорларында индекстелген мақалаларға, «обыр», «қатерлі ісіктер (ҚІ)», «COVID-19», «онкологиялық науқастар», «өлім қаупі» кілт сөздері бойынша талдау жүргізілді. Қазақстан Республикасының ресми статистикасының, медициналық ақпараттық жүйелерінің (ОНЭТ, СНЭТ) және ресми мерзімді басылымдарының Қазақстандағы 2020-2021 ж.ж. қатерлі аурулардан және 2020-2022 ж.ж. COVID-19-дан сырқаттанушылық пен өлім-жітім бойынша деректері зерттелді.*

Нәтижелері: *2020-2021 2020-2021 жылдары Қазақстан Республикасында ҚІА-мен сырқаттанушылық көрсеткіштері Солтүстік Қазақстан (1,79-1,87%), Павлодар (1,57-1,63%), Қарағанды (1,54-1,53%) және Қостанай (1,53%) облыстарында ең жоғары болды. Ең төменгі көрсеткіштер Түркістан (0,42-0,41%), Қызылорда (0,59%), Маңғыстау (0,62%) облыстарында және Шымкент қаласында (0,60%) байқалды. 2020 жылы ҚР-да ҚІ-ден болатын өлім-жітім Түркістан (11,1%), Қызылорда (10,2%) және Жамбыл облыстарында (10,02%), ал 2021 жылы Атырау (25,4%), Түркістан (10,68%) және Батыс Қазақстан (10,30%) облыстарында ең жоғары болды.*

Онкологиялық ауру бойынша диспансерлік есепте тұрған COVID-19 науқастарынан болатын өлім - жітім 2020 жылы ең жоғары болды.

2020 жылы онкологиялық ауру бойынша диспансерлік есепте тұрған науқастардың COVID-19-дан болатын өлім-жітімі көрсеткіші Астана қаласында (1,06%), Қызылорда (0,46%) және Түркістан (0,33%) облыстарында және 2021 жылы Шымкент қаласында (1,05%), Астана қаласында (1,00%), Атырау (0,93%), Батыс Қазақстан (0,94%) облыстарында жоғары болды.

Қорытынды: *Осылайша, онкологиялық науқастар арасында COVID-19 таралуы және пандемия кезінде олардың өлімінің артуы, оның ішінде өлімнің негізгі себебі онкологиялық процесс емес, вирустық инфекцияның салдары болған жағдайларда, статистикалық есепке алу ережелеріне түзетулер енгізу.онкологиялық науқастардың аурушаңдық пен өлім-жітім, онкологиялық науқастарды диагностикалау және емдеу алгоритмдері мен хаттамалары.*

Түйінді сөздер: *COVID-19-бен ауырған емделушілер, КВИ, қатерлі ісіктер (ҚІ), онкологиялық науқастар, өлім-жітім қаупі.*

АННОТАЦИЯ

РАСПРОСТРАНЕННОСТЬ COVID-19 У БОЛЬНЫХ СО ЗЛОКАЧЕСТВЕННЫМИ НОВООБРАЗОВАНИЯМИ В КАЗАХСТАНЕ

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Актуальность: *Новая коронавирусная инфекция COVID-19 с 2019 г. стремительно распространилась по всему миру, оказав влияние на системы здравоохранения большинства стран. Недавние исследования показали, что наличие злокачественного заболевания повышает восприимчивость к COVID-19 и является фактором риска ухудшения клинических исходов у пациентов с COVID–19. Также, наличие COVID-19 у больных со злокачественными заболеваниями повышает риск прогрессирования заболевания.*

Цель исследования *– изучение распространенности COVID-19 у больных раком в Казахстане.*

Методы: *Проведен анализ статей, опубликованных с 2019 года, находящихся в открытом доступе и проиндексированных в базах данных PubMed, Cochrane, Google Scholar, e-Library, по ключевым словам «рак», «злокачественные новообразования (ЗНО)», «COVID-19», «онкологические больные», «риск смертности». Изучены данные официальной статистики, медицинских информационных систем Республики Казахстан (ЭРОБ, ЭРСБ) и официальных периодических изданий по заболеваемости и смертности от злокачественных заболеваний за 2020-2021 гг. и по заболеваемости и смертности от COVID-19 – за 2020-2022 гг. в Казахстане.*

Результаты: *Показатели Показатели заболеваемости ЗНО в Республике Казахстан в 2020-2021 гг. были наиболее высокими в Северо-Казахстанской (1,79-1,87%), Павлодарской (1,57-1,63%), Карагандинской (1,54-1,53%) и Костанайской областях (1,53%). Самые низкие показатели были отмечены в Туркестанской (0,42-0,41%), Кызылординской (0,57-0,59%), Мангистауской (0,62 %) областях и г.Шымкент (0,60%). Смертность от ЗНО в РК была наиболее высокой в 2020г. в Туркестанской (11,1%), Кызылординской (10,2%) и Жамбылской областях (10,02%), в 2021г. – в Атырауской (25,4%), Туркестанской (10,68%) и Западно-Казахстанской (10,30%) областях.*

Смертность от COVID-19 больных, состоявших на диспансерном учете по онкозаболеванию, в 2020 г. была наиболее высокой в г. Астана (1,06%), Кызылординской (0,46%) и Туркестанской (0,33%) областях, в 2021г. – в г. Шымкент (1,05%), г. Астана (1,00%), Атырауской (0,93%) и Западно-Казахстанской (0,94%) областях.

Заключение: *Таким образом, уровень распространенности COVID-19 среди онкологических больных и повышение их смертности в период пандемии, в том числе в случаях, где основной причиной смерти был не онкологический процесс, а последствия перенесенной вирусной инфекции, свидетельствуют, что требуется внести коррективы в правила статистического учета заболеваемости и смертности онкологических больных, алгоритмы и протоколы диагностики и лечения онкологических больных.*

Ключевые слова: *рак, злокачественные новообразования (ЗНО), COVID-19, онкологические больные, риск смертности.*

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Authors' input: *contribution to the study concept, study design, execution of the study, interpretation of the study, preparation of the manuscript – Menbaev S.K.*
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PROSTATE CANCER EPIDEMIOLOGY IN THE EAST KAZAKHSTAN REGION, 2010-2019

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ABSTRACT

Relevance: *From 2010 to 2019, prostate cancer incidence increased, and prostate cancer mortality decreased in Kazakhstan. The peak incidence was observed in patients aged 70 years and older. The East Kazakhstan region had a higher incidence and mor-tality from prostate cancer than the national average.*

The study aimed to *assess the indicators of prostate cancer epidemiology in the East Kazakhstan region from 2010 to 2019.*

Methods: *The study calculated prostate cancer incidence, mortality, one-year and five-year survival, and early detection from 2010 to 2019. The statistical significance was assessed by the one-factor linear regression method. Intensive epidemiological in-dicators were calculated per 100 000 male population.*

Results: *The prostate cancer incidence in East Kazakhstan increased from 2010 to 2019, while the mortality rate increased slightly. There was a statistically significant upward trend for incidence (p=0.009) and a statistically insignificant trend for mortali-ty (p=0.900).*

One-year survival with prostate cancer tended to decrease. However, the trend of one-year survival rates had no statistical significance (p=0.202).

Five-year survival with prostate cancer in East Kazakhstan during the study peri-od tended to decrease. However, the trend in the five-year survival rates of patients with prostate cancer in East Kazakhstan had no statistical significance (p=0.826).

Early detection of prostate cancer in the early stages remained sustainable in the range of 72.7-77.4. In 2019, this indicator decreased to 63.2%.

The share of prostate cancer cases detected at stage III tended to increase. The proportion of prostate cancer cases detected at stage IV tended to decrease during the study period.

Conclusion: *The prostate cancer epidemiological rates in East Kazakhstan were unstable in the study period. The incidence tended to increase; the mortality rate fluctu-ated within small limits and remained sustainable. The one-year survival rate tended to decrease. The five-year survival rate was slightly increasing. There was an increase in the detection of prostate cancer at stage III, while the detection at stage IV tended to decrease. Early detection of prostate cancer has decreased with an increase in detection at stage III. The proportion of prostate cancer cases detected at stage IV in the study pe-riod tended to decrease.*

Keywords: *Prostate cancer, incidence, mortality, survival, the East Kazakhstan region.*

Introduction: Oncological diseases lead among the causes of death globally and are the main obstacles to increasing life expectancy [1]. According to the World Health Organization, cancer has become the first or second leading cause of death in people below 70 years in 112 out of 183 countries and ranked third or fourth in 23 more countries in 2019 [2]. Worldwide, the burden of cancer incidence and mortality is growing due to population aging and growth and the changes in the prevalence and distribution of major cancer risk factors, including those related to socioeconomic development [3, 4].

Prostate cancer was the second most common cancer and the fifth leading cause of cancer death among men in 2020. Almost 1.4 million new cases and 375,000 deaths from prostate cancer were registered in the world. Prostate cancer was the most common cancer in men in 112 countries, followed by lung cancer (in 36 countries), colorectal cancer, and liver cancer (in 11 countries). Lung cancer was the leading cause of cancer mortality in men in 93 countries, followed by prostate cancer (48 countries) and liver cancer (23 countries). In 2020, prostate cancer ranked second in countries with a high human development index, with a prevalence of 37.5 per 100,000 population, and ranked first in countries with a low human development index, with a prevalence of 11.3 per 100,000 population [1].

In Kazakhstan, prostate cancer incidence rose sharply from 2010 to 2019 due to the implementation of screening for prostate cancer by detecting serum prostate-specific antigens. However, in 2015-2016, there was a decrease in prostate cancer mortality in Kazakhstan. In East Kazakhstan, prostate cancer incidence and

mortality were above the national average [5]. One of the reasons for that was a challenging environmental situation due to the chemical pollution from the extensive industrial production in Ust-Kamenogorsk – the administrative center of the East Kazakhstan region [6]. Radiation exposure from the long-term operation of the Semipalatinsk nuclear test site in East Kazakhstan also worsened the epidemiological situation for oncological diseases [7].

The study aimed to assess the indicators of prostate cancer epidemiology in the East Kazakhstan region from 2010 to 2019.

Materials and methods: Data for the analysis was obtained from official statistical sources: Form No. 35 Annual "Report on patients with malignant neoplasms" and statistical materials "Indicators of the Oncological service of the Republic of Kazakhstan" from 2010 to 2019. The study calculated epidemiological indicators for prostate cancer, including incidence, mortality, one-year and five-year survival, and early detection since stage I-II cases are the most favorable from the point of effective treatment and patient survival. The study included all registered incidence and mortality cases for the study period. Intensive epidemiological indicators were calculated per 100,000 males.

Statistical processing was made using the Statistical Package for the Social Sciences (SPSS) version 20.0 for Windows (Semey State Medical University). The average long-term epidemiological indicators for the specified period were calculated. One-factor linear regression was used to analyze and evaluate the statistical significance of the trends revealed [8]. The study results were presented in arithmetic averages for the average incidence levels for the studied period and non-standardized linear regression coefficients (B) with 95% confidence intervals (CI). For each regression coefficient, the achieved statistical significance was recorded.

Results: Figure 1 shows prostate cancer incidence and mortality dynamics in East Kazakhstan from 2010 to 2019. The figures are provided per 100,000 males.

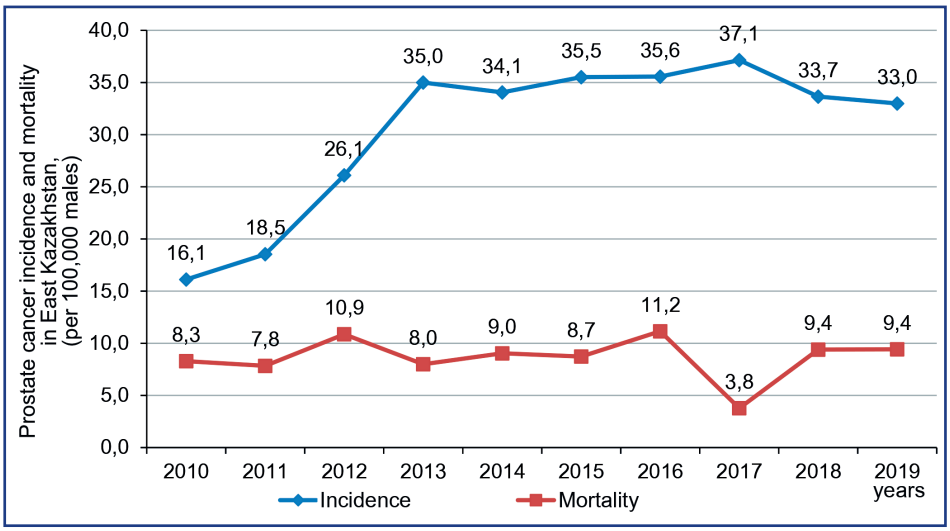

Figure 1 – Dynamics of prostate cancer incidence and mortality in East Kazakhstan, 2010-2019 (per 100,000 males)

According to Figure 1, prostate cancer incidence in East Kazakhstan increased significantly: from 16.1 in 2010 to 35.0 in 2013, obviously due to the implementation of prostate cancer screening by detecting serum prostate-specific antigens. Then the prostate cancer incidence rate decreased to 34.1 in 2014, slightly increased to 37.1 in 2017, and then decreased to 33.0 in 2019.

Prostate cancer mortality in East Kazakhstan fluctuated within small limits: from 8.3 in 2010 to 10.9 in 2012. Then there was a slight increase to 11.2 in 2016, a sharp decrease to 3.8 in 2017, and another increase to 9.4 in 2019.

Trend analysis showed a statistically significant upward incidence trend (B=0.31; 95% CI: -0.01, 0.52; p=0.009) and a statistically insignificant mortality trend (B=-0.07; 95% CI: -1.27, 1.14; p=0.900) during the study period.

The patients' one-year and five-year survival are key treatment effectiveness indicators, which depend on timely prostate cancer detection at early stages. Figure 2 shows the dynamics of one-year survival of prostate cancer patients in East Kazakhstan from 2010 to 2019.

The trends in one-year survival (Figure 2) demonstrated a wave-like fluctuation, decreasing to 36.8% in 2014. Then the one-year survival increased to 68.8% in 2016, dramatically decreased to 42.9% in 2017, and amounted to 33.3% in 2019. However, the regression analysis showed no statistical significance of changes in one-year survival (B=-0.114; 95% CI: -0.303, 0.075; p=0.202).

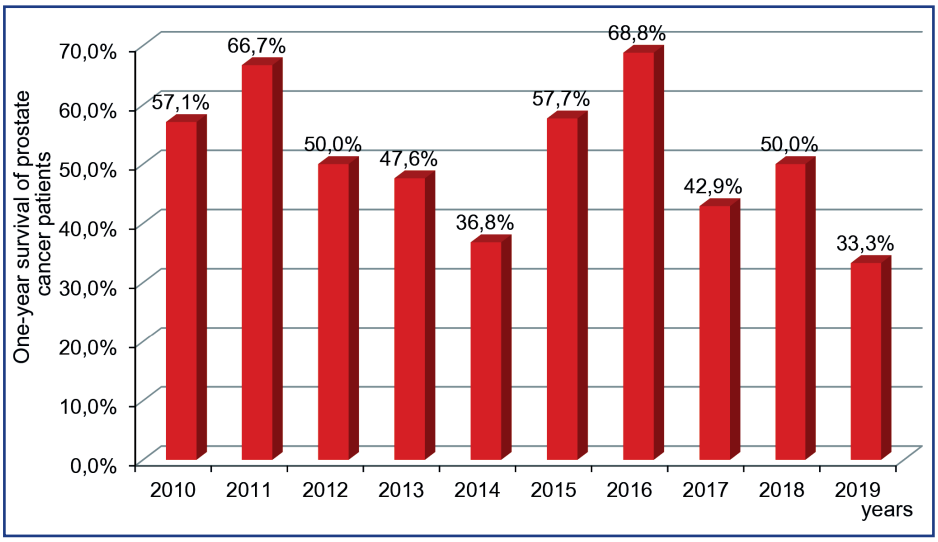

Figure 2 – Trends in one-year survival of prostate cancer patients, 2010-2019

The trends in the five-year survival of prostate cancer patients in East Kazakhstan from 2010 to 2019 are presented in Figure 3.

The dynamics of five-year survival of prostate cancer patients (Figure 3) showed that the five-year survival progressively decreased from 32.8% in 2010 to 17.5% in 2016 and began to increase in 2017, reaching 32.5% by 2019. However, the regression analysis showed no statistical significance of changes in five-year survival (B=-0.038; 95% CI: -0.428, 0.351; p=0.826).

Since the prostate cancer stage at detection is a critical prognostic factor for patient survival, early detection is crucial from both clinical and public health perspectives. Figure 4 shows the trends in prostate cancer detection by stages in East Kazakhstan from 2010 to 2019.

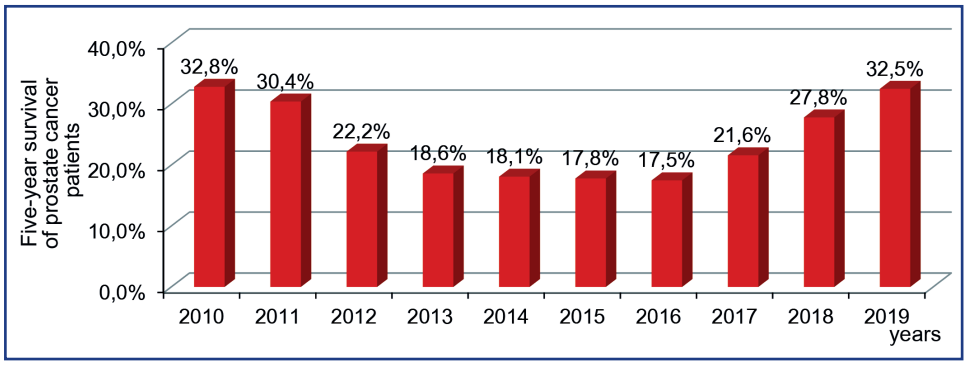

Figure 3 – Trends in five-year survival of prostate cancer patients, 2010-2019

As seen in Figure 4, in East Kazakhstan, during the study period, the share of prostate cancer detection at stages I-II increased from 55.7% in 2010 to 80.7% in 2013. The early prostate cancer detection rate varied from 72.7 to 77.4, with a decrease to 63.2% in 2019. The share of late prostate cancer detection (stages III and IV) tended to decrease. However, the share of prostate cancer cases detected at stage III, which equaled 21.7% in 2010, decreased to 10.5% in 2013 but reached 24.9% in 2019. The share of prostate cancer cases detected at stage IV decreased from 22.6% in 2010 to 12.0% in 2019. According to the regression analysis, the trend in early detection rate for prostate cancer was statistically insignificant (B=0.28; 95% CI: -0.01, 0.56; p=0.053).

One-year survival of prostate cancer patients in East Kazakhstan decreased from 66.7% in 2011 to almost twofold in 2014 but increased to 68.8% in 2016. Then, it decreased to 33.3% in 2019. However, the trend in one-year survival rates was not statistically significant (p=0.202).

The five-year survival of prostate cancer patients in East Kazakhstan during the study period decreased from 32.8% in 2010 to 17.5% in 2016. Then it increased and reached 32.5% in 2019. However, the trend in five-year survival of prostate cancer patients in East Kazakhstan was statistically insignificant (p=0.826).

In 2013-2015, in 11 regions of Kazakhstan, where the screening program was conducted, prostate cancer was detected at stages I-II in 1763 men (58.6%)

and stages III-IV – in 1244 (41.4%). In 5 regions with no screening, prostate cancer was detected at stages I-II in 372 men (43.5%), with 483 cases of prostate cancer detected at stages III-IV (56.5%) [9].

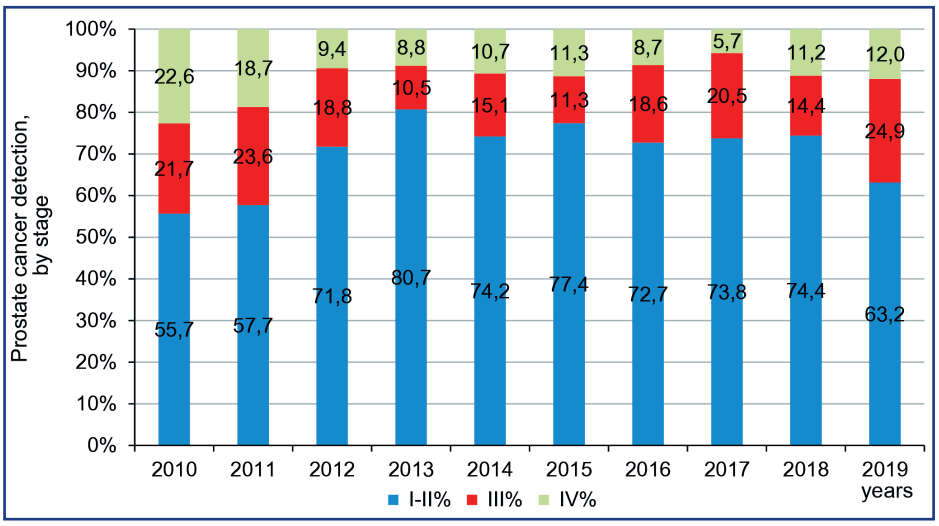

Figure 4 – Trends in prostate cancer detection by stage, 2010-2019

According to our study, early detection of prostate cancer in East Kazakhstan increased in 2013, remained stable between 72.7-77.4, and decreased to 63.2% in 2019. At that, the share of detection at late stages III and IV tended to decrease. Thus, the share of cases detected at stage III decreased till 2013 and then increased, reaching 24.9% in 2019. However, the share of cases detected at stage IV was decreasing.

Discussion: Prostate cancer incidence varies from 6.3 to 83.4 per 100,000 males in different regions of the world, with the highest rates in Northern and Western Europe, the Caribbean, Australia, New Zealand, North America, and South Africa, and the lowest rates in Asia and North Africa. Regional mortality rates correspond to the incidence. The highest mortality is registered in the Caribbean, Sub-Saharan Africa, and Micronesia/Polynesia. Prostate cancer is the leading cause of cancer death among men in 48 countries, including Sub-Saharan Africa, the Caribbean, Central and South America (Ecuador, Chile, and Venezuela), and Sweden [10].

In Kazakhstan, more than 1,200 new prostate cancer cases are registered yearly. This malignant pathology is more common in men of the Caucasian race than in Asians. Kazakhstan has a relatively high prostate cancer prevalence among elders. The number of patients with this pathology in Kazakhstan tends to increase [11].

Our study showed that the incidence rate in East Kazakhstan tended to increase from 2010 to 2019 and peaked in 2017, amounting to 37.1 per 100,000 males. The increase in prostate cancer incidence has been observed since 2013, when a screening program was introduced to detect serum prostate-specific antigens.

The prostate cancer mortality in East Kazakhstan was growing slightly. It peaked in 2016 at 11.2 per 100,000 males, then decreased to 9.4 per 100,000 male population. The upward trend was statistically significant for incidence (p=0.009) and statistically insignificant for mortality (p=0.900).

Survival rates are among the most important indicators to assess the quality of cancer control programs. Research shows an improving survival with prostate cancer [12]. However, studies on prostate cancer survival in Asia report contradictory results. In China, from 1992 to 2000, the five-year relative survival with prostate cancer amounted to 32.5% [13], while in South Korea, a study by K.W. Jung et al. registered a five-year survival of 67.2% in 1996-1999 and 93.3% in 2010-2014 [14-16]. In a study in Iran, the overall five-year survival rate was 36.1% [17]. In another study conducted among various ethnic groups in China for many years, the survival rate ranged from 26.6% to 78%, indicating a noticeable tendency to fluctuate and a significant difference between different ethnic groups [18]. A study by H. Xu et al. in China revealed a substantial difference in five-year survival with prostate cancer between patients with arterial hypertension (28.5%) and the control group (48.3%) [19].

Conclusion: The prostate cancer epidemiological rates in East Kazakhstan were unstable in the study period. The incidence showed a statistically significant upward trend, with no sharp fluctuations in mortality rates. The one-year survival showed a statistically insignificant decrease at a statistically negligible increase in the five-year survival. There was an increase in the detection of prostate cancer at stage III, while the detection at stage IV tended to decrease.

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АҢДАТПА

ШЫҒЫС ҚАЗАҚСТАН ОБЛЫСЫНДАҒЫ 2010-2019 ЖЫЛДАРДАҒЫ ҚУЫҚАСТЫ БЕЗІ ОБЫРЫНЫҢ ЭПИДЕМИОЛОГИЯСЫ

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Өзектілігі: *Қазақстанда 2007-2016 жылдар аралығында қуықасты безі обырымен (ҚБО) сырқаттанушылықтың өсуі және одан болатын өлім-жітімнің төмендеуі байқалды. ҚБО ісігі аурушаңдық 70 жастан жоғары. Шығыс Қазақстан облысы ҚБО аурушаңдығы мен өлім-жітімінің жоғары көрсеткіштерімен сипатталады.*

Зерттеудің мақсаты. *Шығыс Қазақстан облысында 2010-2019 жылдары ҚБО эпидемиологиялық көрсеткіштерін бағалау*

Әдістері: *№35 нысан жылдық "Қатерлі ісіктермен ауыратын науқастар туралы есеп". 2010-2019 жылдар аралығында аурушаңдық, өлім, бір жылдық, бес жылдық өмір сүру, ҚБО ерте сатысында анықтау есептелді. Статистикалық маңыздылығын бағалау үшін бір факторлы сызықтық регрессия әдісі қолданылды. Қарқынды эпидемиологиялық көрсеткіштер 100 000 ер адамға есептелген*

Нәтижелер: *ШҚО-да 2010-2019 жылдары аурушаңдық көрсеткіші өсу үрдісіне ие болды. ШҚО-да ҚБО болатын өлім-жітім көрсеткіші аздап өсу үрдісіне ие болды. Бұл ретте сырқаттанушылық үшін статистикалық маңызды өсу тренді байқалды (p=0,009), ал өлім көрсеткіштері үшін тренді статистикалық елеусіз болды (p=0,900). Науқастардың біржылдық өмірсіру көрсеткіш ҚБО болған кеміді. Алайда біржылдық өмір сүру көрсеткіштерінің тренді статистикалық мәнге ие болмады (p=0,202). ШҚО-да ҚБО бар пациенттердің бес жылдық өмір сүру динамикасы зерттелген кезеңде төмендеу үрдісіне ие болды. Алайда, ШҚО-да ҚБО бар пациенттердің*

бес жылдық өмір сүру көрсеткіштерінің тренді статистикалық мәнге ие болмады (p=0,826). ҚБО ерте сатысында тұрақты көрсеткіштерге ие болды және 72,7-77,4 аралығында өзгерді, ал 2019 жылы бұл көрсеткіш 63,2%-ға дейін төмендеді. Анықталған ҚБО үлесі III сатыда ұлғаю үрдісіне ие болды. IV сатыдағы ҚБО үлесі зерттелетін кезеңде төмендеу үрдісіне ие болды

Қорытынды: *Зерттеу кезеңінде ШҚО-да қуық асты безінің қатерлі ісігінің эпидемиологиялық көрсеткіштері тұрақсыз болды. ҚБО аурушаңдығы ұлғаю үрдісіне ие болды, өлім көрсеткіші аз шекте ауытқыды және тұрақты сипатқа ие болды. Біржылдық өмір сүру динамикасы ҚБО төмендеді. Бес жылдық өмір сүру серпіні статистикалық тұрғыдан шамалы өсу трендіне ие болды. III сатыда ҚБО анықтаудың жоғарылауы байқалды, IV сатысында ҚБО анықтау төмендеу тенденциясына ие болды. ҚБО ерте сатысында анықтау III кезеңде анықтаудың артуына байланысты төмендеді. IV сатыдағы ҚБО үлесі зерттелетін кезеңде төмендеу үрдісіне ие болды*

Түйінді сөздер: *Қуықасты безі обыры (ҚБО), аурушаңдық, өлім-жітім, өмір сүру деңгейі, Шығыс Қазақстан облысы.*

АННОТАЦИЯ

ЭПИДЕМИОЛОГИЯ РАКА ПРЕДСТАТЕЛЬНОЙ ЖЕЛЕЗЫ В ВОСТОЧНО-КАЗАХСТАНСКОЙ ОБЛАСТИ ЗА 2010-2019 годы

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Актуальность: *В Казахстане в 2010-2019 гг. наблюдался рост заболеваемости и снижение смертности от рака предстательной железы (РПЖ). Пик заболеваемости РПЖ приходится на возраст 70 лет и старше. Восточно-Казахстанская область характеризуется более высокими показателями заболеваемости и смертности от РПЖ, чем в среднем по стране.*

Цель исследования *– оценить эпидемиологические показатели РПЖ в Восточно-Казахстанской области за 2010-2019 гг.*

Методы: *Рассчитывались инцидентность, смертность, однолетняя, пятилетняя выживаемости, выявляемость РПЖ на ранних стадиях за период 2010-2019 гг. Для оценки статистической значимости использовался метод однофакторной линейной регрессии. Интенсивные эпидемиологические показатели рассчитывались на 100 000 мужского населения.*

Результаты: *Показатель заболеваемости в ВКО за 2010-2019 гг. имел тенденцию к значительному росту, а показатель смертности от РПЖ в ВКО – к небольшому росту. При этом наблюдался статистический значимый восходящий тренд для заболеваемости (p=0,009), а для показателей смертности тренд был статистически незначимым (p=0,900).*

Показатель однолетней выживаемости пациентов с РПЖ имел тенденцию к снижению, которая не была статистически значимой (p=0,202).

Динамика пятилетней выживаемости пациентов с РПЖ в ВКО за изучаемый период имела тенденцию к снижению, однако также без статистической значимости (p=0,826).

Выявляемость РПЖ на ранних стадиях была стабильной и варьировала в пределах 72,7-77,4, однако в 2019 г. этот показатель снизился до 63,2%.

Доля случаев РПЖ, выявленных на III стадии, имела тенденцию к увеличению. Доля случаев РПЖ, выявленных на IV стадии, за изучаемый период имела тенденцию к снижению.

Заключение: *Эпидемиологические показатели РПЖ в ВКО за изучаемый период имели нестабильный характер. Показатель заболеваемости имел статистически значимый тренд к увеличению, показатель смертности от РПЖ существенно не изменялся. Наблюдался статистически незначимый тренд снижения однолетней выживаемости. Также наблюдался статистически незначимый тренд увеличения пятилетней выживаемости. Отмечен рост выявляемости РПЖ на III стадии, выявляемость РПЖ на IV стадии имела тенденцию к снижению. Выявляемость РПЖ на ранних стадиях снизилась за счет увеличения выявляемости на III стадии. Доля РПЖ на IV стадии за изучаемый период имела тенденцию к снижению.*

Ключевые слова: *рак предстательной железы (РПЖ), заболеваемость, смертность, выживаемость, Восточно-Казахстанская область.*

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S-DETECT FUNCTION AS THE LATEST METHOD OF ULTRASOUND EXAMINATION OF MAMMARY GLAND FORMATIONS: COMPARATIVE CHARACTERISTICS

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ABSTRACT

Relevance: *Worldwide, mammary gland formations remain a public health dilemma. Breast cancer (BC) is one of the leading causes of cancer mortality. Breast cancer ranked 3rd with 8.7-8.1% in the structure of malignant disease mortality in Kazakhstan in 2018-2019.*

Female breast cancer is the most common cancer. Over 2.2 million cases of breast cancer were registered in 2020, according to the WHO. Worldwide, breast cancer ranks fifth among the causes of mortality (685,000 deaths per year).

On average, about 3,000 breast cancer cases are detected yearly in the Republic of Kazakhstan, and more than 1,380 women die from this disease. The high increment rate of breast cancer incidence and mortality, which is ahead of most other cancers, puts breast cancer at the top of the list.

Technological developments in medicine have positively influenced the diagnosis of mammary gland formations. The S-Detect function for the mammary gland formations had been introduced by Samsung Medison, which helps to determine the formation and characterize the affected area. The sonoelastography methods were used for reliable assessment in the early days.

The study aimed to *determine the role of the S-Detect function in the differential diagnosis of mammary gland formations.*

Methods: *A comparative analysis of images taken with the S-Detect function and by the sonoelastography process was carried out in 50 patients.*

Results: *S-Detect program showed correct diagnosis in 92% of cases (46 out of 50 people), confirmed by the results of morphological verification (histology, cytology). The sonoelastography method showed correct results in 80% of cases (40 out of 50 people).*

Conclusion: *The use of S-Detect technology in analyzing mammary gland formations showed good consistency with B-mode, color, and power Doppler mapping. S-Detect technology can effectively help novice radiologists in writing conclusions.*

Keywords: *S-Detect Breast, BI-RADS, breast ultrasound, breast cancer, elastography.*

Introduction: Breast cancer is one of the leading causes of cancer mortality. In 2018-2019, breast cancer ranked third in the Kazakhstani structure of cancer mortality, with a share of 8.7-8.1% [1].

Breast cancer is the most common female cancer. WHO reported over 2.2 million cases of breast cancer registered in 2020. Breast cancer ranks fifth among the causes of mortality in the world (685,000 deaths per year) [2, 3].

About 3,000 breast cancer cases are registered yearly in the Republic of Kazakhstan, and more than 1,380 women die from this disease each year. The annual breast cancer incidence in the Republic of Kazakhstan is growing by 26.6% or more. The high increment rate of breast cancer incidence and mortality, which is ahead of most other cancers, puts the problem of breast cancer at the top of the list [4-6].

Ultrasound examination plays a vital role in the determination of mammary gland formations. Ultrasound is used to analyze palpable formations that are not visualized mammographically and differentiate mammary gland formations in women below 30. Ultrasound is an inexpensive and effective method for distinguishing between cystic and solid mammary gland formations. Ultrasound makes it possible to describe the formation of the mammary gland without exposing the patient to ionizing radiation, which is especially important for pregnant and young patients since mammary glands are more sensitive to radiation in these patients. Mammography is associated with a slightly higher risk of acquiring a radiation-induced neoplasm than ultrasound. The introduction of additional modes of breast formation differentiation contributes to improving ultrasound diagnostics [7].

Recent innovations in breast ultrasound, including S-Detect artificial intelligence technology, have increased the sensitivity and specificity of diagnosing mammary gland formations.

The idea of creating a unified system for assessing the risks of malignancy of focal changes in the mammary gland came up at the end of the 20th century. The system was named BI-RADS by the initial letters of the

Breast Imaging Radiology Data System (Breast Imaging Reporting and Data System is an international system for describing and processing breast ultrasound data). The analysis of focal pathology was based on the criteria of shape, spatial orientation, contours, echogenicity, distal acoustic effects, and additional characteristics of Doppler mapping and elastography [8]. It is known that in ultrasound examination, malignant tumors of the mammary gland can look like a separate formation or just an area with an altered structure of surrounding tissues. The most significant difficulties arise in assessing the tumor focus contours and determining its boundaries with surrounding tissues [8].

On November 25, 2018, at the annual meeting of the Radiological Society of North America (RSNA) in Chicago, Samsung Medison, a leader in medical imaging technology, unveiled the latest development in ultrasound diagnostics: the AI-based S-Detect software. This software analyzes breast lesions and classifies them according to the BI-RADS system.

The U.S. BI-RADS system offers five gradations to assess focal changes in mammary glands. Category BI-RADS 1 – no changes, category BI-RADS 2 – no risk of malignancy, category BI-RADS 3 – the risk of malignancy up to 2%, category BI-RADS 4 – the risk ranges from 3 to 94%, category BI-RADS 5 – the malignancy probability is more than 95%. Two categories of risk of malignancy (4 and 5) require cytological confirmation and a mandatory biopsy [8-10].

Ultrasound sonoelastography is another method for differential diagnosis of mammary gland formations. Elastography, invented in the 1990s, allows tissue stiffness mapping but has just recently gained clinical relevance [11, 12].

Elastography is a non-invasive method that characterizes tissue changes by determining their elasticity (stiffness). Elasticity indicates the degree of a tissue or substance deformation by an external force and at the end of such impact when elasticity allows restoring the original shape and size of the tissue or substance. Different fabrics have different elasticity. Adipose tissue is more easily deformed, and fibrous tissue returns to its original state more slowly than adipose or muscle tissue [12].

The use of elastography with S-Detect technology helps characterize breast formations and distinguish between malignant and benign breast tumors. The stiffness of malignant tumors can be influenced by factors such as fibrotic degeneration, tumor infiltration of the interstitial tissue, or infiltration of the intraductal component [12].

Benign tumors have high elasticity, in contrast to malignant tumors, which have low elasticity. During elastography, ultrasonic beams emitted and perceived by a particular sensor "touch" the tissues of the organ under study like a doctor and evaluate their elasticity (stiffness) using a specific program [13, 14]. Due to its high accuracy, in most cases, S-Detect allows unambiguous and correct diagnosis. However, this technique is still relatively new, and its role in clinical practice has yet to be determined.

The study aimed to determine the role of the S-Detect function in the differential diagnosis of breast tumors.

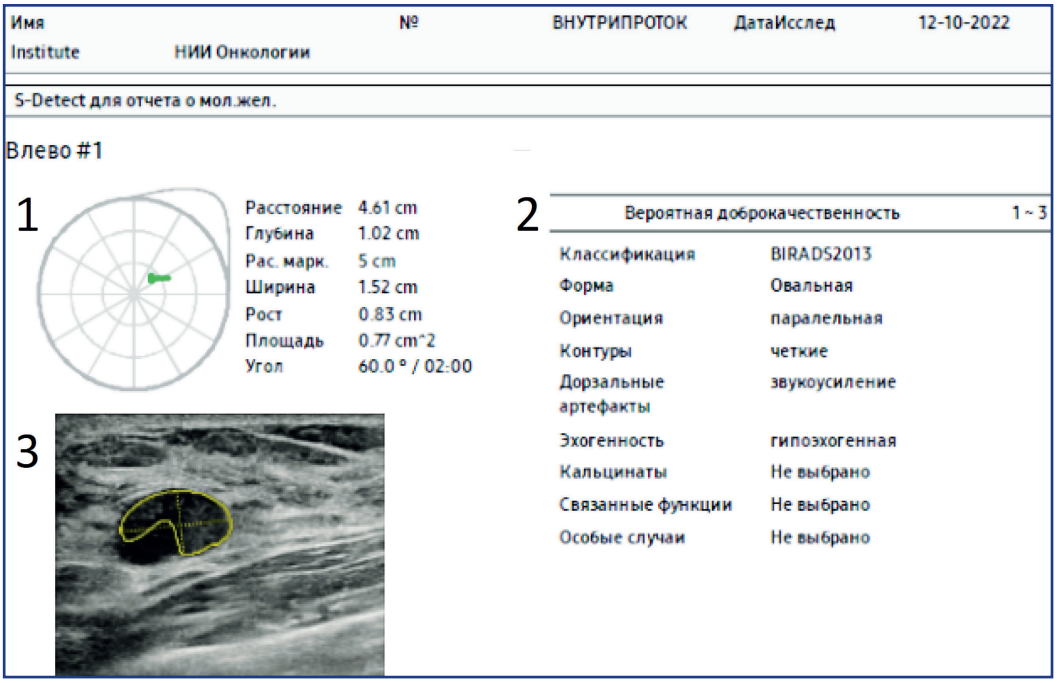


Figure 1 – Evaluation using S-Detect: 1 – position information area, 2 – BI-RADS classification area, 3 – *B*-mode

Materials and methods: This study was conducted at "Kazakh Institute of Oncology and Radiology" JSC (Almaty, Kazakhstan) on an ultrasound machine Samsung Medison RS85 (2022, South Korea). In addition to B-mode, color Doppler mapping (CDM), and power Doppler mapping (PDM), the S-Detect artificial intelligence software and sonoelastography were used to analyze the formations. In any discrepancies in the conclusions, the final diagnosis was established based on morphological verification.

The study included ultrasound data of breast neoplasms in 50 women. The S-Detect program evaluated the image in the transverse and sagittal planes. The procedure was to obtain an image in B-mode, press the Freeze Frame button, turn on the S-Detect program and select the affected area manually or automatically. Further, the program automatically classified the formation under the BI-RADS system [8, 15]. The BI-RADS system contains recommendations regarding the likely goodness or malignancy of the mass. Upon completion of the analysis, the result was printed as a report for the patient, including patient data, lesion location, version, classification, BI-RADS score, and the breast from the S-Detect screen (Figure 1).

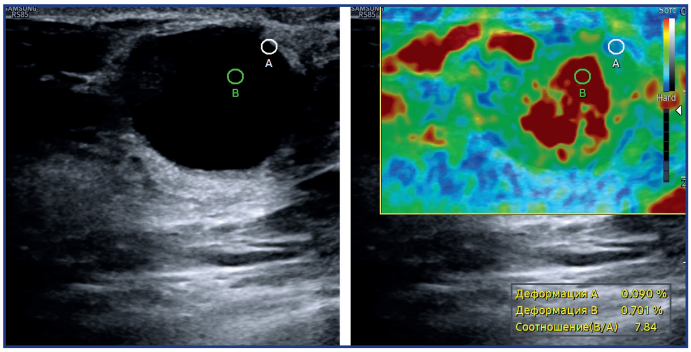
Accuracy, sensitivity, and specificity were calculated assuming all neoplasms classified in categories 4 and 5 were considered malignant, and those classified in categories 2 and 3 were regarded as benign.

In the B-mode, an elastographic image represented a color map obtained with moderate compression of the region under study.

The size of nodes on elastography and in B-mode differed due to tissue fibrosis in the affected area. B-mode and elastography's size differences might indicate a malignancy. The color scale represented relative hardness. On the resulting color map, tissues with greater rigidity were shown in blue, and tissues with less rigidity – in red (Figure 2).

The Tsukuba elasticity score (TES) [16] was used to qualitatively analyze breast formations detected by elastography.

According to the 5-point Tsukuba color scale, incompressible dense areas were displayed in blue (Figure 3). Elastograms of the first three types were benign (Figure 3, types 1-3), and the next 2 were malignant (Figure 3, types 4-5). The figure also showed an RGB (red, green, blue) sign related to benign cysts.



Legend: Деформация A - Deformation A, Деформация B - Deformation B, Соотношение B/A - B/A ratio

Figure 2 – Sonoelastography method

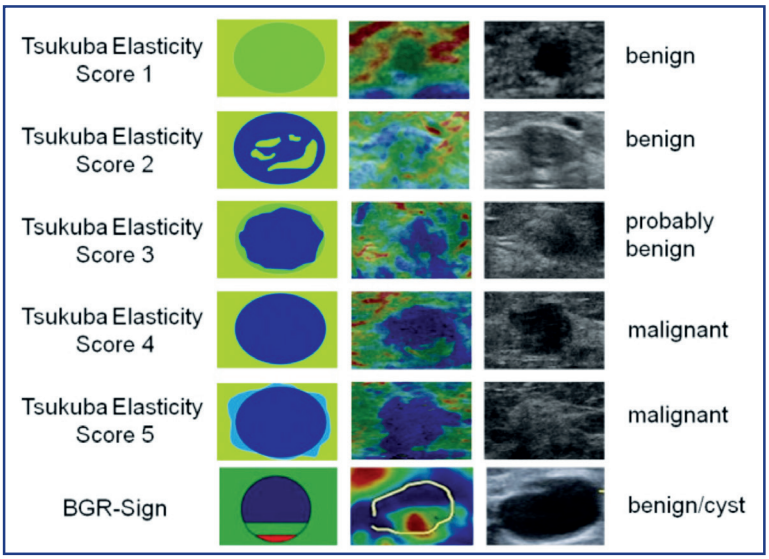
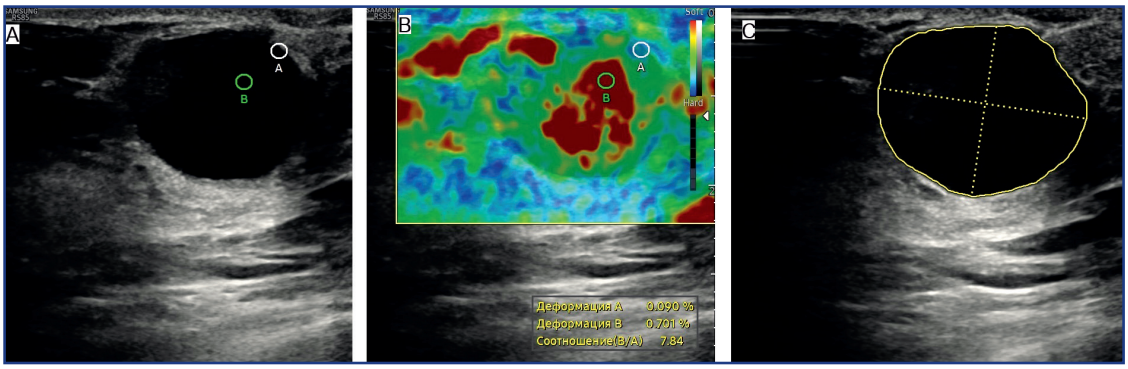


Figure 3 – Tsukuba scale (Wojcinski et al., 2013)

Quantitative analysis of mammary gland elastography utilizes the Strain Ratio of the formation and the Fat Lesion Ratio (FLR). The stiffness of the selected zone is calculated automatically, using the fat lesion deformation of the examined breast as a standard value [12, 17].

Results: The final diagnoses established using the S-Detect program and the sonoelastography method for neoplasms were as follows: fibroadenoma – 3, lipoma – 5, breast cancer – 3, recurrent breast cancer – 3, intraductal papilloma – 2, simple cyst – 5, inflamed cyst – 5, hormonal changes in the glandular tissue – 2, lobular hyperplasia – 3, lactostasis – 2, hematoma – 3, and hidradenoma – 2.

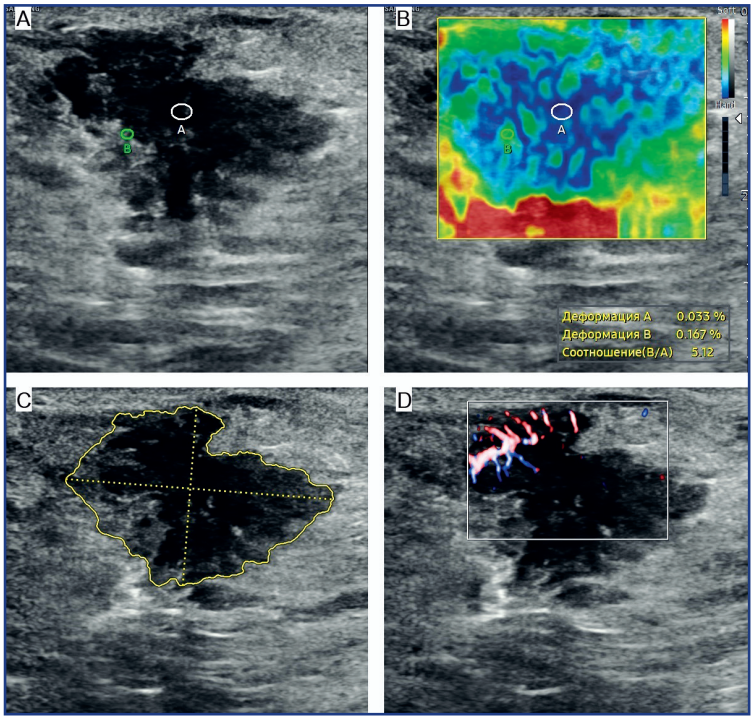
S-Detect allowed the correct diagnosis in 92% (46 out of 50 people) of cases, confirmed by the results of morphological verification (histology, cytology). The sonoelastography method showed correct results in 80% (40 out of 50 people) of cases.



Legend: Деформация A – Deformation A, Деформация B – Deformation B, Соотношение B/A - B/A ratio

Figure 4 - Breast cyst (cross-section): A – *B*-mode, B – elastography, C – S-Detect

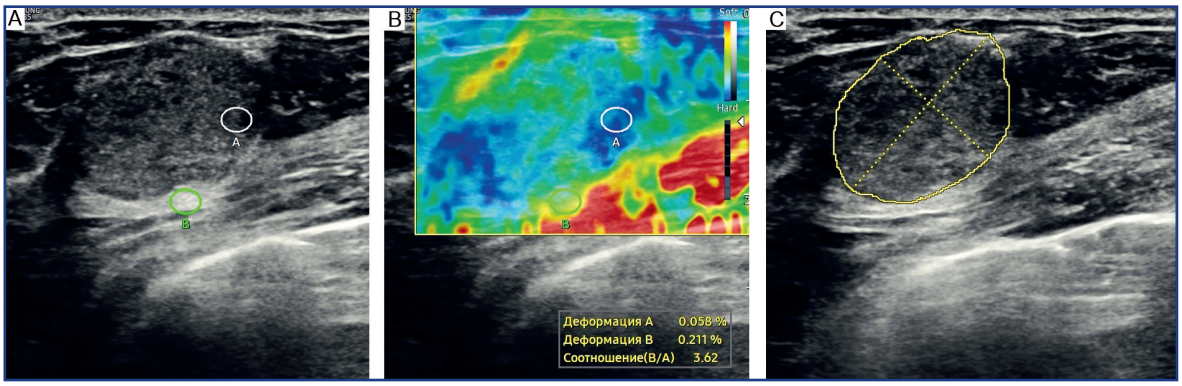
The B-mode (A) and S-Detect (B) images presented in Figure 4 showed the presence of anechoic formations of a round shape, and the contours were precise and even. According to S-Detect, the formation corresponded to BI-RADS 1.2 – a benign formation. The patient was diagnosed with a unilocular cyst. Elastography on the Tsukuba scale (B) showed type 2 and an RGB sign characteristic of benign formations, namely, breast cysts.



Legend: Деформация A – Deformation A, Деформация B – Deformation B, Соотношение B/A – B/A ratio

Figure 5 - Breast cancer (cross-section): A – *B*-mode, B – elastography, C – S-Detect, D – CDM

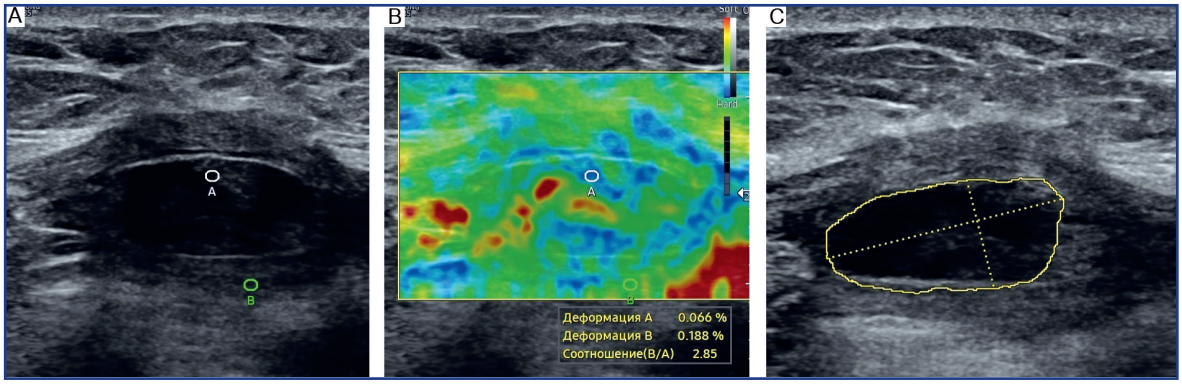
Figure 5 shows irregularly shaped hypoechoic formations with indistinct nerve contours containing calcifications visible in the B-mode (A) and the S-Detect (B) mode. The S-Detect image corresponded to BI-RADS 4.5 – a malignant formation. Elastography (B) showed an area of increased stiffness; according to the Tsukuba scale, it was type 4.5 – a malignant formation; CDM (D) showed a formation with own feeding vessels.



Legend: Деформация A – Deformation A, Деформация B – Deformation B, Соотношение B/A – B/A ratio

Figure 6 – Breast fibroadenoma (cross-section): A – *B*-mode, B – elastography, C – S-Detect

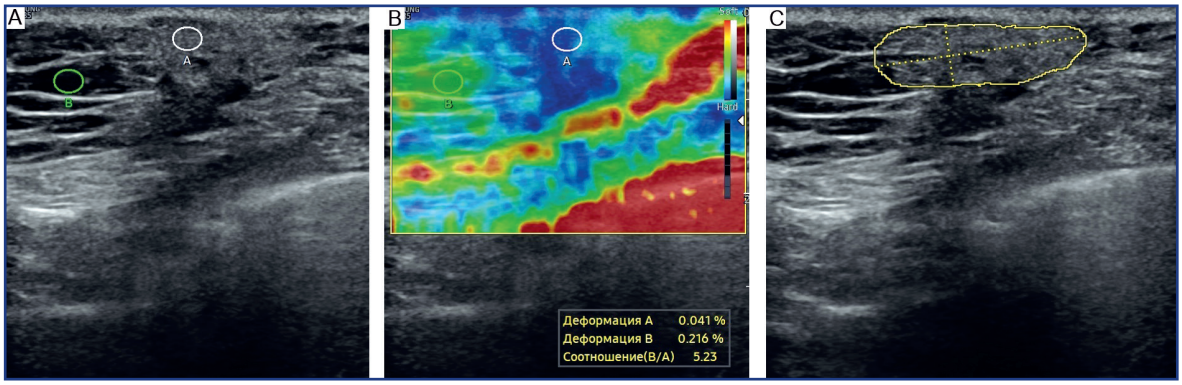
In Figure 6, B-mode (A) and S-Detect mode (B) showed a regular-shaped isoechoic formation with precise, even contours. According to S-Detect, the formation corresponded to BI-RADS 1, 2 – a benign formation. Elastography (B) showed an area of medium hardness; according to the Tsukuba scale, it was type 2 – a benign formation.



Legend: Деформация A – Deformation A, Деформация B – Deformation B, Соотношение B/A – B/A ratio

Figure 7 – Breast hematoma (cross-section): A – *B*-mode, B – elastography, C – S-Detect

Figure 7, B-mode (A) and S-Detect mode (B), shows a regular-shaped hypoechoic mass with precise, even contours. According to S-Detect, the formation corresponded to BI-RADS 1.2 – a benign formation. The Tsukuba scale (B) showed type 2 and an RGB sign, characteristic of benign formations.

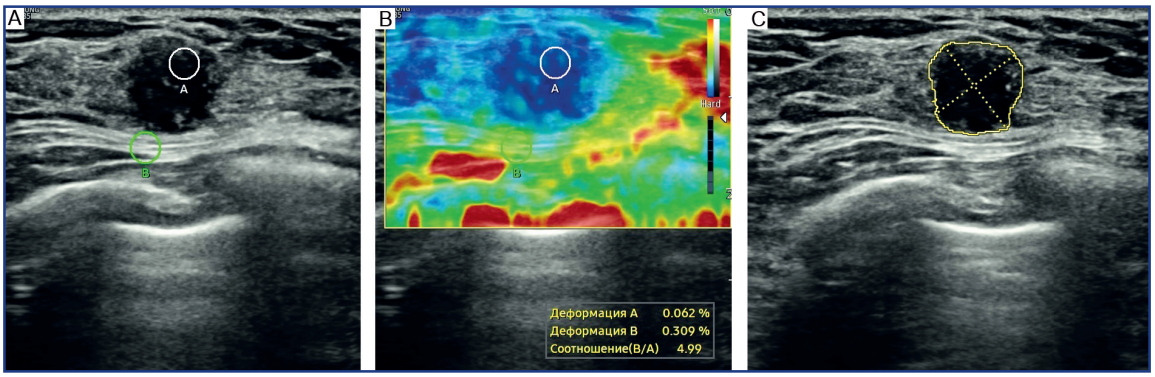


Legend: Деформация A – Deformation A, Деформация B – Deformation B, Соотношение B/A – B/A ratio

Figure 8 – Breast granuloma (cross-section): A – *B*-mode, B – elastography, C – S-Detect

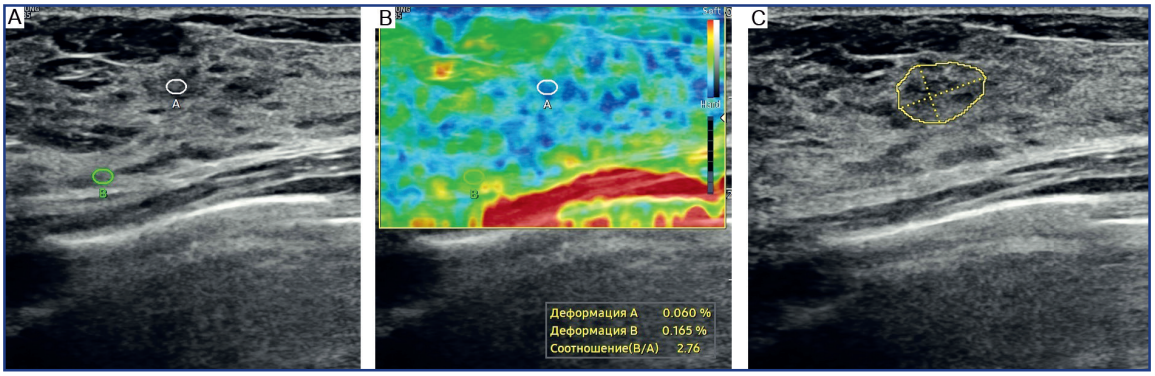
In Figure 8, B-mode (A) and S-Detect mode (B) show a regular-shaped isoechoic mass with precise, even contours. According to S-Detect, the formation corresponded to BI-RADS 1.2 – a benign formation. Elastography mode (B) showed an RGB sign; the Tsukuba score corresponded to type 4 – malignancy. The conducted biopsy confirmed a granuloma.

Figure 9, B-mode (A) and S-Detect mode (B), shows an irregularly shaped hypoechoic mass with precise, uneven contours. According to S-Detect, the formation corresponds to BI-RADS 4.5 – a malignant tumor. Elastography (B) showed a high-density (stiff) formation, type 4.5 on the Tsukuba scale – a malignant formation. The biopsy showed lactostasis (milk cells). In this case, morphological studies were the most informative.



Legend: Деформация A – Deformation A, Деформация B – Deformation B, Соотношение B/A – B/A ratio

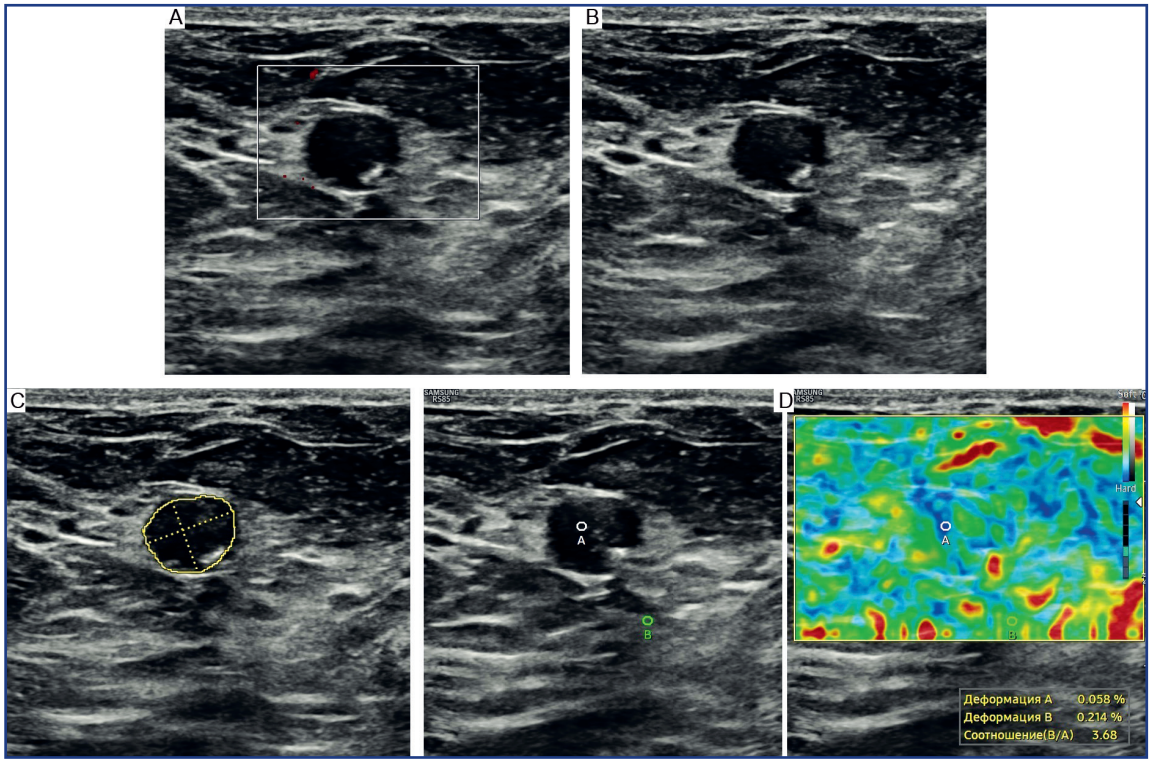
Figure 9 – Lactostasis in the mammary gland (cross-section): A – *B*-mode, B – elastography, C – S-Detect



Legend: Деформация A – Deformation A, Деформация B – Deformation B, Соотношение B/A – B/A ratio

Figure 10 – Breast fibroadenoma (cross-section): A – *B*-mode, B – elastography, C – S-Detect

As shown in Figure 10, B-mode (A) and S-Detect (B) illustrated a hypoechoic formation with precise, uneven contours. The S-Detect image corresponded to BI-RADS 1.2 – a benign formation. Elastography (B) showed a formation of medium density (stiffness); according to the Tsukuba scale, it was type 3 – a probably benign formation. The biopsy confirmed fibroadenoma.



Legend: Деформация A – Deformation A, Деформация B – Deformation B, Соотношение B/A – B/A ratio

Figure 11 – Cystadenoma of the breast (cross-section): A – CDI, B – *B*-mode, C – S-Detect, D – elastography

In Figure 11, B-mode (B) and S-Detect (C) show a well-shaped hypoechoic mass with precise, even contours. The S-Detect image corresponded to BI-RADS 1.2 – a benign formation. The elastography (D) results corresponded to an RGB sign characteristic of benign formations, type 2 on the Tsukuba scale – a benign formation. CDM (A) showed an avascular formation. Final diagnosis: breast cystadenoma.

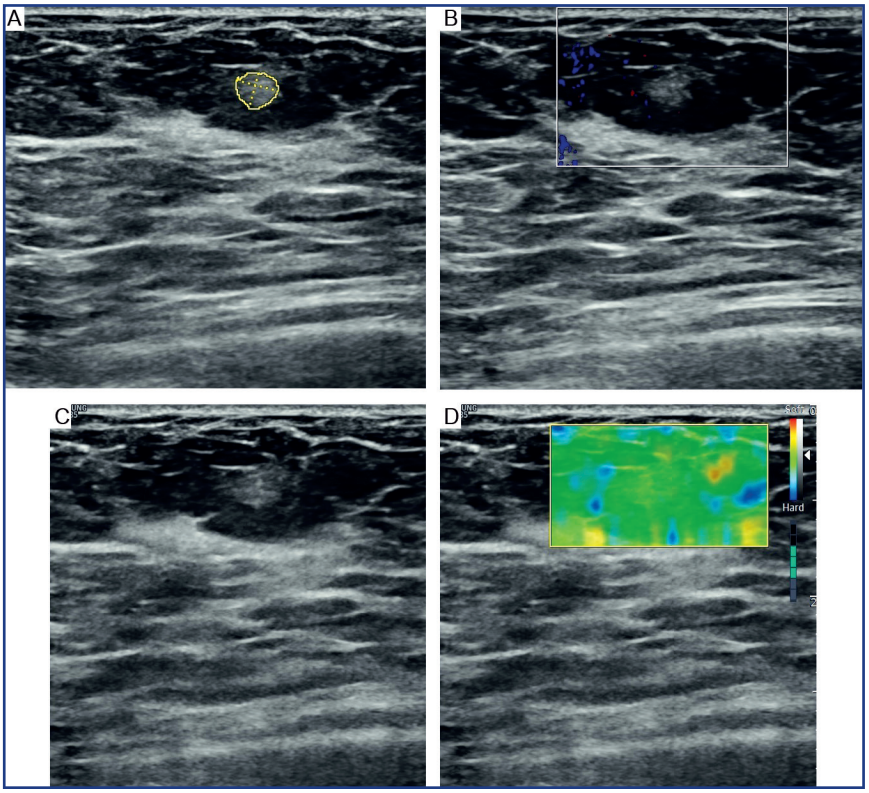


Figure 12 – Breast lipoma (cross-section): A – S-Detect, B – CDM, C – *B*-mode, D – elastography

Figure 12 shows S-Detect (A) and B-mode (B) images of a well-shaped hyperechoic mass with precise, even contours. The S-Detect image corresponded to BI-RADS 1.2 – a benign formation. Image (B) showed an avascular mass (CDM). Tsukuba scale type 2 – a benign formation. Elastography (D) showed low-density formation.

Discussion: In our study, S-Detect was more effective in diagnosing malignant and benign formations than Doppler or non-Doppler ultrasound examinations.

Comparative assessment of S-Detect and sonoelastography in the differential diagnosis of breast formations showed that S-Detect provided a correct, morphologically verified (histology, cytology) tumor diagnosis in 92% (46/50) of cases. Thus, S-Detect had a sensitivity of 92%, an accuracy of 90%, and a specificity of 91%. Sonoelastography showed a diagnostic accuracy of 80% (40/50), a sensitivity of 86.5%, a specificity of 89.8%, and an accuracy of 88.3%.

S-Detect characterizes neoplasms by differentiating them according to the BI-RADS system. Unfortunately, S-Detect is not always precise in classifying structural changes. Despite this, the S-Detect Breast system is an effective tool for processing and analyzing ultrasound images of breast neoplasms. S-Detect can be used as an additional diagnostic tool to improve breast ultrasound's specificity, accuracy, and sensitivity in clinical practice and guide decisions regarding US-detected breast masses. The S-Detect system has significantly improved the BI-RADS classification accuracy. Elastography is used for differential diagnosis of dubious formations. Images taken in B-mode, CDM, and PDM do not always allow for an unambiguous diagnosis. This requires utilizing all available additional ultrasound methods, including elastography. Such an approach ensures success and clearly improves the efficiency of primary US examination results. Assessing stiffness using elastography allows a more objective differentiation of both benign volumetric formations and malignant formations in the mammary gland. When the vertical axis of the tumor cannot be measured due to dorsal echo attenuation or acoustic shadowing, elastography defines the margin by tissue stiffness.

The S-Detect function enhances US diagnostic value by analyzing the image displayed regardless of the tumor depth and localization in the gland. Using the S-Detect function in breast ultrasound examinations can reduce the number of unnecessary interventions.

Conclusion:

Conventional B-mode 2D imaging will continue to serve as the main mode for breast ultrasound. However, several other modern ultrasound technologies can be used for differential diagnosis. 3D ultrasound allows holistic and reproducible tumor imaging, particularly in the frontal plane, which is impossible with conventional methods. Doppler ultrasound provides information about tumor vascularization. The S-Detect function expands the range of diagnostics by adding another level of perception that characterizes the lesion itself and its contact with surrounding tissues [10]. The S-Detect technology is especially valuable for radiologists since it provides a conclusion protocol with criteria for assessing the degree of malignancy.

Using the S-Detect function positively affects the results of primary breast ultrasound examinations.

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АҢДАТПА

СҮТ БЕЗІ ТҮЗІЛІМДЕРІН УЛЬТРАДЫБЫСТЫҚ ЗЕРТТЕУДІҢ ЕҢ СОҢҒЫ ӘДІСІ РЕТІНДЕ S-DETECT ФУНКЦИЯСЫ: САЛЫСТЫРМАЛЫ СИПАТТАМА

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Өзектілігі: *Сүт бездерінің қатерлі ісігі (СБҚІ) бүкіл әлемдік қоғамдық денсаулық мәселесі болып қалыптасқан. Барлық сүт бездерінің қатерлі ісігі өлім себебі болып табылады. Соңғы мәлімдеген бойынша сүт бездерінің қатерлі ісігі 3 орында болып 8,7-8,1% 2018-2019ж. көрсеткішке ие болған.СБҚІ әйелдер арасындағы жиі таратылатын ауру болып саналады. Дүниежүздік денсаулық сақтау ұйымының мәлімдемесі бойынша 2020 ж. СБҚІ-не 2,2 млн ісік аурулары тіркеліп бесінші орында тұр. Қазақстан Республикасында жыл сайын 3000 астам СБҚІ түртеп, оның ішінде,1380 аса әйелдер өлім себебі болып табылады. Диагностика СБҚІ компания Samsung Medison S-Detect тексерілу мүмкіндігін тереңдетіп қаптамасыу етті, сондай-ақ соноэластография әдісін жүргізді.*

Зерттеудің мақсаты: *СБҚІ S-Detect функциясымен дифференциалды диагностикалы тексеру*

Әдістері: *Орындалған талдауларды салыстыру барысында СБҚІ диагностикасын S-Detect функциясымен және соноэластографиямен асырдық.*

Нәтижелері: *S-Detect программасы 87-93% (50-ден 46дәлілде) диагноз қойылды, зерттеу морфологиялық (гистология, цитология) тұжырымына сәйкес келді, соноэластография әдесі 75-80% (50-ден 40 дәлелде) сәйкестік болып табылды.*

Қорытынды: *S-Detect технологиясын және соноэластография әдісі арқылы СБҚІ диагностикасы тамаша болып табылды. S-Detect жаңадан радиология салысындағы маммология мамандарына жақсы көмекші болып табылады.*

Түйінді сөздер: *S-Detect Breast , BI-RADS , сүт безінің ультрадыбыстық зерттеу, сүт безінің ісігі, соноэластография.*

ABSTRACT

ФУНКЦИЯ S-DETECT КАК НОВЕЙШИЙ МЕТОД УЛЬТРАЗВУКОВОГО ИССЛЕДОВАНИЯ ОБРАЗОВАНИЙ МОЛОЧНЫХ ЖЕЛЕЗ: СРАВНИТЕЛЬНАЯ ХАРАКТЕРИСТИКА

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Актуальность: *Образования молочной железы остаются дилеммой общественного здравоохранения во всем мире. Рак молочной железы (РМЖ) является одной из ведущих причин онкосмертности. Так, в Казахстане в 2018-2019 гг. РМЖ занимал 3 место в структуре смертности от злокачественных заболеваний с долей 8,7-8,1%.*

РМЖ – самое распространенное онкологическое заболевание среди женщин. По данным ВОЗ в 2020 г. было зарегистрировано свыше 2,2 млн. случаев РМЖ. В мире РМЖ занимает пятое место среди причин смертности (685 000 смертей в год).

В среднем в Республике Казахстан каждый год выявляют порядка 3000 случаев РМЖ, и более 1380 женщин умирают от данного заболевания. Высокий темп прироста заболеваемости и смертности, опережающий большинство других опухолей, выдвигает проблему РМЖ на ведущее место.

Стремительный прогресс технологических разработок в области медицины положительно повлиял на диагностику образований молочной железы. Компания Samsung Medison представила функцию S-Detect для молочной железы, которая позволяет выделить образование и дать характеристику зоне поражения. Ранее достоверные оценки проводились методами соноэластографии.

Цель исследования *– определить роль функции S-Detect в дифференциальной диагностике образований молочной железы.*

Методы: *Проведен сравнительный анализ снимков, снятых с функцией S-Detect и методом соноэластографии у 50 пациентов.*

Результаты: *Программа S-Detect позволила, верно, поставить диагноз в 92% (46 из 50 человек) случаев, что было подтверждено результатами морфологической верификации (гистология, цитология). Метод соноэластографии показал верные результаты в 80% (40 из 50 человек) случаев.*

Заключение: *Применение технология S-Detect при анализе характера образований в молочных железах показал хорошую согласованность с В-режимом, цветовым и энергетическим допплеровским картированием. Технология S-Detect может эффективно использоваться начинающими врачами-радиологами при написании заключений.*

Ключевые слова: *S-Detect Breast, BI-RADS, УЗИ молочной железы, рак молочной железы, эластография.*

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STAGES OF CYTOLOGICAL EXAMINATION (USING IMMUNOCYTOCHEMICAL EXAMINATION) OF EFFUSION FLUIDS

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ABSTRACT

Relevance: *Cytological criteria of tumors in exudate fluids are associated with specific subjective difficulties, one of which is the differential diagnosis of proliferating mesothelial and adenocarcinoma cells.*

The study aimed to *increase the informational value of cytological diagnostics in a multidisciplinary hospital.*

Methods: *From 2018 to 2021, 10,082 serous cavity effusions (pleural – 8,166 (81%), abdominal cavity – 1,512 (15%), pericardial – 404 (4%)) were included in the cytological examination. Microscopic examination of traditional preparations was carried out, and immunocytochemical (ICC) examination was carried out in difficult diagnostic situations.*

Results: *In this study, in women, the traditional cytological examination of effusion fluids revealed metastatic lesions of the serous cavities in 672 cases (58%), mainly due to breast cancer progression (26%). In men, pleurisy was primarily due to metastasis of adenocarcinoma of the lung – 266 cases (23%). ICC research increased the diagnostic accuracy of cytological examination by 62-93% and the specificity – by 95-99%.*

Conclusions: *An algorithm for conducting ICH studies, differing in the number of panels of monoclonal antibodies used to determine the histological form and organ - the source of the tumor, has been developed. In specific cases, conducting ICR studies with 2-3 monoclonal antibodies may be enough to confirm the histological form of cancer and, where necessary, perform additional ICR studies without significant loss of time for obtaining results.*

Keywords: *immunocytochemistry (ICC), monoclonal antibodies, malignant tumors, pleural fluid, ascitic fluid, conventional cytology, liquid-based cytology.*

Relevance: The significance of cytological examination in modern medicine is indisputable. In contrast to histological examination, it is performed not on tissue but on the cellular level. Clinical cytology differs from other clinical laboratory diagnostic methods because it aims to identify atypical cells with cytomorphological diagnoses in non-tumor and tumor processes. Detecting the signs of exudate malignancy at the cellular level is difficult, and one of the challenges is the differential diagnosis of mesothelial cells with signs of proliferation and cells suspicious of adenocarcinoma (ADC). The discernible reactivity of the sulfur cavity cover, the desquamation, and the regenerative ability of the mesothelium cause a great variety of cellular compositions.

Often, malignant cells in exudates of serous cavities cannot be detected even at the late stages of the disease due to their insufficient number in the studied material [1]. Recently, the widespread introduction of liquid cytology and immunocytochemical (ICC) examination methods have significantly reduced the factor of subjectivity [2].

This requires optimal management in morphological and clinical diagnostic laboratories (CDL), establishing cytological criteria for differential tumor diagnosis in examining exudative fluids, and developing an algorithm for ICC examinations. Signs of cell atypia in various lesions intersect with the signs of malignancy, creating difficulties in identifying the nature of the lesion and can cause false-positive or false-negative cytological diagnoses [3, 4].

A cytologist is to inform the clinician how important it is to observe and follow the instructions adopted at a CDL cytology department, which contain an algorithm for referring biological material and preparing cytological material, as well as performing a microscopic examination and interpreting the results.

The study aimed to increase the informational value of cytological diagnostics in a multidisciplinary hospital.

Materials and methods: The study was performed at the clinical diagnostic laboratory of the Center for Thoracic Surgery (CTS) of GBUZ "Scientif-

ic Research Institute – Regional Clinical Hospital No. 1 after S.V. Ochapovsky" (Krasnodar, Russia). In 2018-2021, 10,082 samples of serous cavity effusion fluids (8,166 (81%) pleural, 1,512 (15%) abdominal, and 404 (4%) pericardial) were subjected to cytological examination in outpatient and other hospital departments for suspected malignant neoplasm of thoracic organs (most often, for lung cancer).

Before serous cavity punctures to assess the extent of the tumor process, all patients underwent a comprehensive examination using radiation (ultrasound, X-ray, computed tomography, magnetic resonance imaging) and other diagnostic methods. The surgeons followed standard procedures when performing serous cavity punctures for diagnostic and/or therapeutic purposes.

An anticoagulant (5% sodium citrate solution of 5 ml per 100 ml or heparin of 1 ml (5,000 IU) per 500 ml fluid) was added to the exudative fluid. All the obtained exudate samples were referred to the CDL for examination. At the first preanalytical stage, a medical laboratory technician evaluated the physical and chemical properties and the presence of sediment before and after centrifugation in a standard centrifuge. The glass slides for ICC were prepared by one of the two methods: liquid (using poly-L-lysine-coated slides) on a Cytospin 4 cytocentrifuge or traditional. The obtained micro slides were fixed by the May-Grunwald method and stained by Romanowsky-Giemsa.

The analytical stage included a microscopic examination of traditional preparations. In complicated diagnostic cases, we performed an ICC examination using different manufacturers' mono- or polyclonal antibody panels. The most common antibody panels contained general cytokeratins (AE1/AE3), Ber-EP4 epithelial antigen, cancer-embryonic antigen (CEA), epithelial membrane antigen (EMA), mesothelial antigen HBME-1, Vimentin, Calretinin, Mesothelin, thyroid transcription factor-1 (TTF-1), Cytokeratins (CK) 7, 20, 5/6, Napsin, CA-125, and Wilms tumor marker (WT-1).

Results: The number of cytological examinations performed in the CDL decreased by 34% in 2020 compared to 2019, as shown in Table 1. This was due to epidemiological limitations caused by the new coronavirus infection, COVID-19. In 2021, the number of examinations increased by 12% compared to 2020.

Table 1 – The number of cytological examinations performed in the clinical diagnostic laboratory of GBUZ "Scientific Research Institute – Regional Clinical Hospital No. 1 after S.V. Ochapovsky" (2018-2021)

Cytological material	2018		2019		2020		2021	
	Abs.	%	Abs.	%	Abs.	%	Abs.	%
Total examinations	48,308	100	47,403	98	31,911	66	38,030	78

According to the retrospective analysis of morphological examination results obtained from 2019 to 2021, metastatic lesions of serous cavities (pleural and abdominal) in the exudative fluids in women were mostly diagnosed by traditional cytology – 672 cases (58%) of the total number of metastatic lesions of serous cavities. This was mainly due to breast cancer progression (26%). The immunocytochemical pattern versus IHC in breast cancer metastases is presented in Figure 1. In men, metastatic pleurisy was mainly caused by lung ADC metastasis – 266 cases (23%). The immunocytochemical pattern of lung cancer metastasis is shown in Figure 2.

By morphological structure, ADCs were more frequent (75, 54.3% of cases) than squamous cell cancer (35, 25.36%). Other histological forms were less frequent and included small cell lung cancer (16, 1.59%) and neuroendocrine tumors (12, 8.7%) (Table 2).

Table 2 – Verification of primary lung cancer diagnosed by cytology and ICC and confirmed by histopathology and IHC

Squamous cell carcinoma	Adenocarcinoma	Small cell cancer	Neuroendocrine tumor	Total
35 (25.36%)	75 (54.35%)	16 (11.59%)	12 (8.70%)	138 (100%)

Table 2 compares the results of the routine cytological examination and ICC examination with histological and IHC examination for cytological material obtained from lung tumors, lymph nodes of the mediastinum, and pleura to estimate the accuracy of cytological and ICC examinations for tumors of various histogenesis.

The most significant difficulties in the differential diagnosis of cells arose in inflammatory processes. In most cases, mesothelium acquires signs of atypia and polymorphism, which may cause an erroneous assumption of tumor presence.

In all cases when cytology supposed a malignant neoplasm, we conducted an ICC examination using Cytokeratin AE1/AE3 and/or CD 45 (LCA) and Vimentin. CK AE1/AE3 (+) and Vimentin (-) indicated a malignant neoplasm of epithelial nature. In those cases, we conducted an ICC exam-

ination with TTF1 antigens (a marker for lung ADC and thyroid cancer). TTF1(+) and thyroglobulin (Tg) (-) indicated lung ADC. Notably, lung tumor cells are always Tg-negative. TTF1 (+) and Tg (+) suggested thyroid cancer.

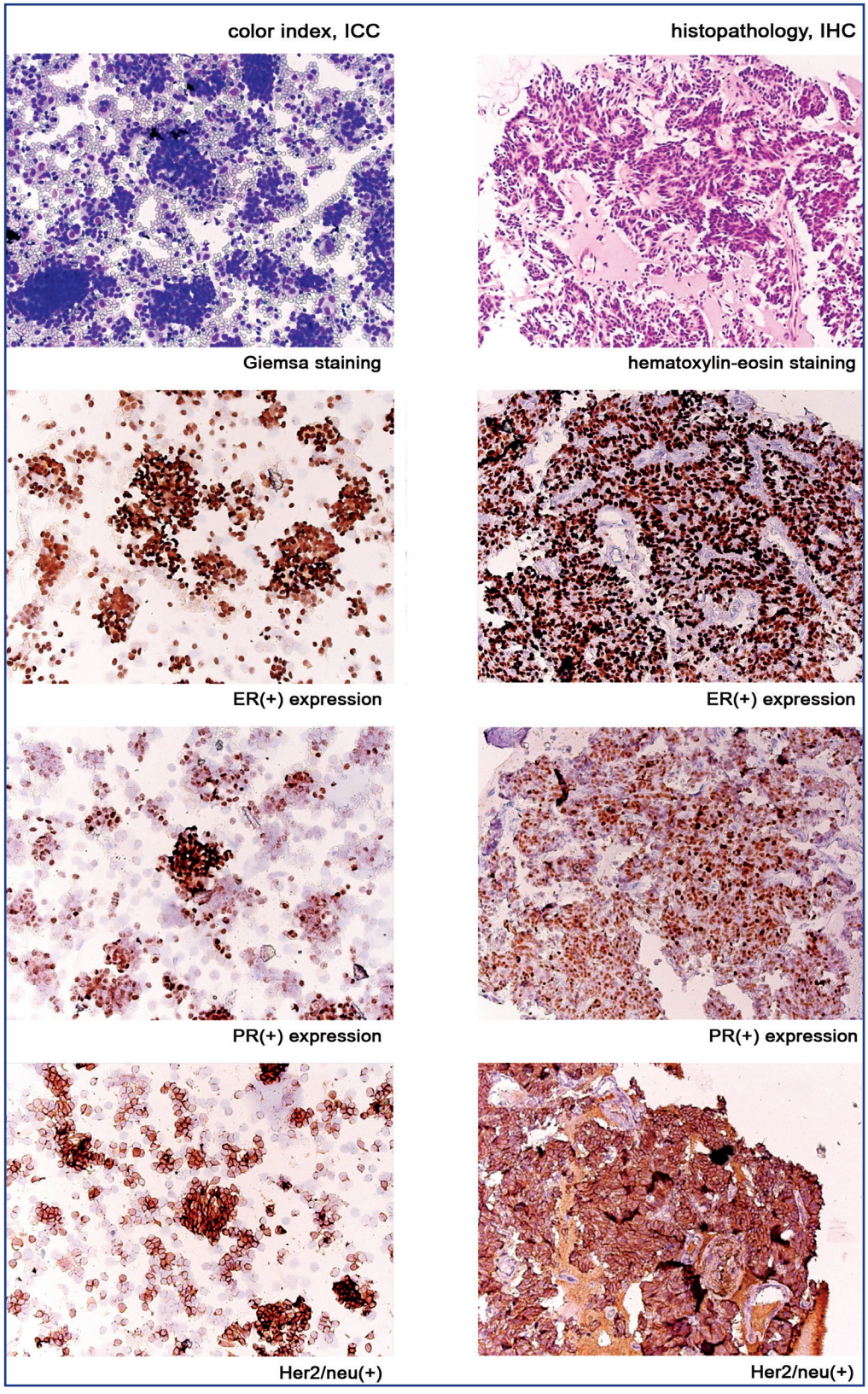

Figure 1 – ICC examination: Breast cancer metastases, ×10

The conducted morphological examination of 5,800 exudates collected over the past three years revealed that the exudative fluid in serous cavities was due to the presence of a malignant process in 20% of cases, had an inflammatory genesis in 30%, and a lymphoid origin – in 35% (Table 3).

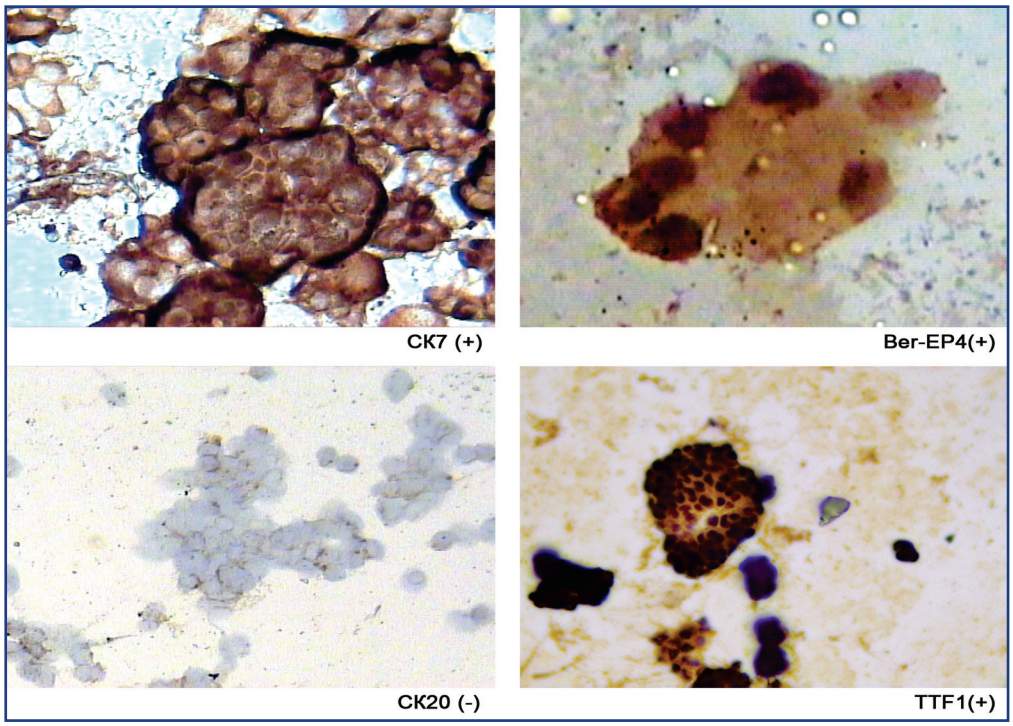

Figure 2 – ICC examination: Lung adenocarcinoma metastases

Table 3 – Morphological characteristic of exudative fluids (n = 5,800)

Nature of the exudate	Quality of examinations	%
Lymphoid exudate	2,030	35
Inflammatory exudate	1,740	30
Exudate with the presence of malignant neoplasm	1,160	20
Other	870	15
Total	5,800	100

Discussion: Thus, in complex cases, ICC increases the diagnostic accuracy of cytology from 62% to 93% and the specificity from 95% to 99%.

In pulmonary tuberculosis, pneumonia-caused pleurisy, and transudate syndrome in patients with cardiovascular insufficiency, a cytological examination is enough for properly classifying pleural exudate by cellular composition. The exudative fluid in patients with non-tumor pleurisy contains mesothelial-lymphocytic, granulocytic-macrophage, and macrophage-histiocytic cells.

Conclusion: Cytological examination of transudates and exudates of serous cavities is a routine daily procedure in cytological laboratories and a method for morphological diagnostics of pathological processes. Examining exudative fluids informs a physician about the exudate pathogenesis to correctly choose treatment tactics and predict the dynamics of disease development.

An established productive clinical-laboratory dialogue significantly increases the informational value of cytological diagnosis. We analyzed the results obtained from different approaches using different sets of mono- or polyclonal antibody panels to determine the tumor histological form and organ affiliation and developed an algorithm for exudative fluids' ICC examination. Namely, a cytologist reviews the material prepared by the traditional method and can make weighted step-by-step decisions on further diagnostic actions. In certain cases, ICC examination with 2-3 antibodies may be enough to determine the tumor's histological form and organ affiliation. If necessary, additional ICC examinations should be performed without significant loss of time in obtaining the results.

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АҢДАТПА

ИЦХ КӨМЕГІМЕН ПЛЕВРАДАН ЭФФУЗИЯЛЫ СҰЙЫҚТЫҚТАРДЫ ЦИТОЛОГИЯЛЫҚ ЗЕРТТЕУ КЕЗЕҢДЕРІ

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Өзектілігі: *Экссудатты сұйықтықтардағы ісіктердің цитологиялық критерийлері белгілі бір субъективті қиындықтармен байланысты, олардың бірі пролиферацияланатын мезотелий жасушалары мен аденокарцинома жасушаларының дифференциалды диагностикасы болып табылады.*

Зерттеудің мақсаты *– көпсалалы аурухана жағдайында цитологиялық диагностиканың ақпараттылығын арттыру.*

Әдістері: *2018-2021 жылдар аралығы Цитологиялық зерттеуге 10 082 серозды қуыстар эффузиясы (плевра – 8 166 (81%), құрсақ қуысы – 1512 (15%), перикардиальды – 404 (4%)) жатқызылды. Дәстүрлі препараттарды микроскопиялық зерттеу жүргізілді, қиын диагностикалық жағдайларда ІСС зерттеуі жүргізілді.*

Нәтиже: *Зерттеудің талдауы көрсеткендей, әйелдерде эффузия сұйықтығында дәстүрлі цитологиялық әдіспен 672 жағдайда (58%), негізінен сүт безі қатерлі ісігінің (26%) өршуіне байланысты серозды қуыстардағы метастатикалық зақымданулар, ал ерлерде, плеврит негізінен өкпенің аденокарциномасының метастазына байланысты болды – 266 жағдай (23%). ІСС зерттеулерін қолдану цитологиялық әдістің диагностикалық дәлдігін 62%-дан 93%-ға және ерекшелігін 95%-дан 99%-ға дейін арттырады.*

Қорытынды: *Гистологиялық пішінді және органды - ісік көзін анықтау үшін қолданылатын моноклональды антиденелердің панельдерінің санымен ерекшеленетін ІСС зерттеулерін жүргізу үшін алгоритм әзірленді. Арнайы жағдайларда 2-3 моноклоналды антиденелермен ІСС зерттеулері ісіктің гистологиялық түрін растау үшін жеткілікті болуы мүмкін және қажет болған жағдайда нәтижелерді алу үшін уақытты айтарлықтай жоғалтпай қосымша ІСС зерттеулерін жүргізеді.*

Түйінді сөздер: *иммуноцитохимия (ІСС), моноклоналды антиденелер, қатерлі ісіктер, плевра сұйықтығы, асциттік сұйықтық, дәстүрлі цитология, сұйықтық негізіндегі цитология.*

АННОТАЦИЯ

ЭТАПЫ ЦИТОЛОГИЧЕСКОГО ИССЛЕДОВАНИЯ (С ПРИМЕНЕНИЕМ ИЦХ) ВЫПОТНЫХ ЖИДКОСТЕЙ

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Актуальность: *Цитологические критерии опухолей в выпотных жидкостях связаны с определенными субъективными трудностями, одной из которых является дифференциальная диагностика клеток пролиферирующего мезотелия и клеток аденокарциномы.*

Цель исследования *– повышение информативности цитологической диагностики в условиях многопрофильной больницы.*

Методы: *За период 2018-2021 гг. цитологическому исследованию было подвергнуто 10 082 образца выпотных жидкостей серозных полостей (плевральной – 8 166 (81%), абдоминальной – 1 512 (15%), перикардиальной – 404 (4%)). Проводилось микроскопическое исследование традиционных препаратов, в сложных диагностических случаях выполнялось иммуноцитохимическое (ИЦХ) исследование.*

Результаты: *Традиционный цитологический метод анализа выпотных жидкостей показал наличие метастатических поражений серозных полостей у женщин в 672 случаях (58%), главным образом за счет прогрессирования рака молочной железы (26%). У мужчин в основном регистрировались плевриты за счёт метастазирования аденокарциномы легкого – 266 случаев (23%). Применение ИЦХ исследования повышало диагностическую точность цитологического метода с 62% до 93% и специфичность с 95% до 99%.*

Заключение: *Разработан алгоритм проведения ИЦХ исследований, отличающихся по количеству используемых панелей моноклональных антител, для определения гистологической формы и органа – источника опухоли. В конкретных случаях проведения ИЦХ исследований с 2-3 моноклональными антителами может быть вполне достаточно для подтверждения гистологической формы опухоли. При необходимости, можно выполнить дополнительные ИЦХ исследования без значительных потерь времени на получение результатов.*

Ключевые слова: *иммуноцитохимия (ИЦХ), моноклональные антитела, злокачественные новообразования, плевральная жидкость, асцитическая жидкость, традиционная цитология, жидкостная цитология.*

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ENDOTRACHEAL TUBE CUFF PRESSURE CONTROL DURING ANESTHESIA IN CANCER PATIENTS

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ABSTRACT

Relevance: *An endotracheal tube (ETT) cuff provides a seal and encloses the lower airway from aspiration. Normally, the pressure in the ETT cuff is in the range of 20 to 30 cm of water column. Both increased and insufficient inflation of the ETT cuff is associated with a number of complications.*

The study aimed to *compare the palpation and apparatus methods of pressure control in the endotracheal tube cuff during anesthesia in cancer patients.*

Methods: *A prospective observational study included 60 patients during general anesthesia in the department of anesthesiology and intensive care of KazIOR. Air was injected into the ETT cuff using a syringe, followed by palpating the ETT cuff balloon and pressure control using the IntelliCuff device (Hamilton Medical, Switzerland). The actual pressure was compared with normal values, then the air volume, actual and necessary to achieve normal pressure, was estimated.*

Results: *Assessment of the pressure level by the "classic" palpation method led to errors in the pressure level in the ETT cuff in more than 50% of cases; the normal level of pressure was only in 25 patients (42%), while the measured air volume in the cuff was on average 5.9±1.9 mL, although for the average air volume to achieve a pressure of 25 mm of water column was 3.9 mL, which led to an overestimated level of pressure in the ETT cuff.*

Conclusion: *Determining ETT cuff pressure by palpating the control balloon is a common practice that often results in incorrect pressure readings. At the same time, both high and low pressure in the ETT cuff is associated with complications. Using devices for measuring pressure in the ETT cuff allows you to control its level, while devices that allow prolonged monitoring of pressure in the ETT cuff have an advantage.*

Keywords: *endotracheal tube, cuff pressure control, microaspiration, tracheal intubation, lung ventilation.*

Introduction: Since the first use of endotracheal tubes (ETT) in 1900, this technique has been the "gold standard" in maintaining airway patency [1]. Ensuring the tightness of the respiratory tract after the ETT installation provides prevention of aspiration of gastric content into the respiratory tract by inflating the intubation tubes cuff. Modern ETTs often have low-pressure cuffs, which prevent trachea wall injury. The palpation of the pilot cylinder is the standard way for ETT cuff pressure control. For a long time, it was considered that trained clinicians could determine the correct pressure in the ETT cuff, but that viewpoint had no scientific basis. Numerous clinical studies have shown that the traditional approach often leads to excessive ETT cuff pressure [2, 3]. Concerning the norm, in adult patients, the pressure level in the intubation tube cuff composes 20-30 cm of water column (on average 25 cm of water column) [4]. Exceeding this pressure level leads to deterioration of perfusion of the trachea walls, as well as the development of pain syndrome, ischemia of the trachea mucous membrane, and consequently, elevation of the risk of the complications such as the tracheal mucosa necrosis, rupture or stenosis of the trachea walls, paralysis of the laryngeal nerve and formation of the tracheoesophageal fistula [5-7]. Incorrect pressure in the ETT cuff leads to micro-aspirations and is a risk factor for ventilator-associated pneumonia [8-10]. In this regard, it is recommended to use the devices for measuring pressure in the ETT cuff. However, today there are also modern device-pressure controllers that allow not only to determine its level but also to set the target pressure values and maintain them throughout lung ventilation [11-13].

The study aimed to compare the palpation and apparatus methods of pressure control in the endotracheal tube cuff during anesthesia in cancer patients.

Materials and methods: The study was conducted in October 2022 at "Kazakh Institute of Oncology and Radiology" JSC (Almaty, Kazakhstan). Every patient or relevant legal representative gave his informed consent. A prospective observational study included 60 patients over 18 years old with malignant neoplasms (MN) of various localization who received planned surgical treatment under general anesthesia and artificial lung ventilation conditions.

Exclusion criteria: emergency surgical interventions, upper respiratory MN, childhood age, pregnancy, the physical status of the patient class III and above according to the classification of the American Society of Anesthesiologists, predicted difficult airways (3-4 points according to the Mallampati score) [14].

The study cohort profile is shown in Table 1.

Table 1 – Summary of the study cohort (n=60)

Indicator	Value
Sex	Male – 32 (53.33%) Female – 28 (46.67%)
Age	42 [36÷47]
Body Mass Index	22 [20÷23]
Basic oncological pathology	MN of the uterus and its appendages, cervix MN – 18 (30%) MN of the abdominal cavity and retroperitoneal space – 5 (8.33%) MN of eyes – 3 (5%) MN of kidneys, bladder, and prostate gland – 17 (28.33%) MN of skin and face soft tissues – 8 (13.33%) MN of the thyroid gland – 3 (5%) MN of connective and soft tissues of the lower limb, including the hip joint area – 6 (10%)
Concomitant pathology	CHD – 3 (5%) Arterial hypertension – 13 (21.67%) Diabetes mellitus types 1 and 2 – 3 (5%) Other – 11 (18.33%)
Physical status according to ASA	I – 39 (65%) II– 21 (35%)

Anesthesia in all patients was induced intravenously (with propofol 1% and fentanyl 0.005% in recommended dosages) and maintained by inhalation (with sevoflurane in combination with fentanyl). Muscle relaxation was achieved by rocuronium bromide. All patients underwent orotracheal intubation by direct laryngoscopy. The ETT cuff was inflated using a syringe. The pressure in the cuff was assessed by palpating an outer control balloon. The tightness was assessed by the absence of audible leakage of the respiratory mixture and by leakage data displayed in the anesthesia-respiratory apparatus. One hour after trachea intubation, the actual pressure in the ETT cuff was measured using the IntelliCuff device, and the result was compared with the established normal values. After determining the cuff pressure, all air was removed by a syringe, and the removed air volume was registered. The cuff was considered empty when a syringe could remove no more air. Then, the ETT cuff was connected to the IntelliCuff device, and the target value was set to 25 cm of water column. After the target pressure was achieved, the air was removed from the cuff, and its volume was measured. The nature of the main and concomitant pathologies (Table 1) did not influence the ETT cuff pressure values.

Results: The following ETT tube pressures were measured: in 25 patients (42%), ETT cuff pressure was in the range of 20-30 cm of water column; in 29 (48%), it was within the range of 31-40 cm of water column; and in 6 patients (10%), it exceeded 41 cm of water column (Figure 1).

The measured air volume in the ETT cuffs after deflating was, on average, 5.9±1.9 mL, while the required volume should average 3.9 mL. Using the IntelliCuff device allowed for avoiding wrong pressure levels and maintaining an optimal level during lung ventilation, thus preventing complications [2, 15].

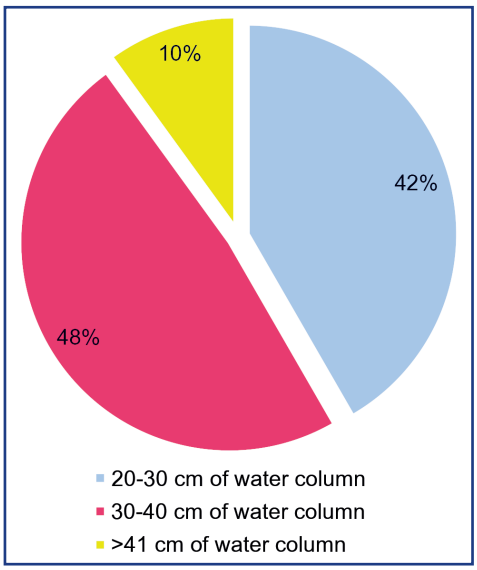

Figure 1 – Actual pressure in the ETT cuff

Discussion: Assessment of pressure in the ETT cuff by "classical" palpation can lead to incorrect – overestimated or underestimated – determination of pressure [16]. One of the studies showed that the use of the "classical" palpation method for measuring pressure in the ETT cuff led to 83% of errors, regardless of the service record of anesthesiologists [17]. However, high and low pressure in the ETT cuff is associated with worsening outcomes [15]. For example, insufficient pressure in the ETT cuff leads to microaspirations and the development of ventilator-associated pneumonia [8, 9]. In turn, a high level of pressure can lead to various complications: from pain and hoarseness to stenosis of the larynx and trachea and rupture of the trachea walls [5, 18].

The pressure control in the ETT cuff with a manometer leads to fewer complications after the tracheal intubation [7, 19]. However, modern clinical studies have shown an advantage and improvement in clinical outcomes within the frames of continuous monitoring of pressure in the ETT cuff compared with periodic measurements [20, 21].

The use of technological devices such as the IntelliCuff allows not only to control of the pressure in the ETT cuff but also to maintain it at a target level during the entire period of artificial lung ventilation, including changes in the body position and fluctuations of pressure in the respiratory tract [22].

As demonstrated in our study, using the classical palpation method to assess the pressure in the ETT cuff led to an overestimated pressure level in over half of the cases. At the same time, the pressure level in the ETT cuff was within the normative values – 20-30 cm of water column – only in 42% of patients, and in 10% of cases, an extremely high level of pressure was noted – above 41 cm of water column.

Our study had several limitations: first of all, the pressure in the ETT cuff was measured only once, one hour after tracheal intubation during the general anesthesia, and was not monitored for a longer period; secondly, the study was performed only during the general anesthesia and did not include patients on ample ventilation in the intensive care unit.

Conclusion: Determining ETT cuff pressure by palpating the control balloon is a common practice that often results in incorrect pressure readings. Both high and low pressure in the ETT cuff is associated with complications, especially in patients on prolonged ventilation. Using devices for measuring pressure in the ETT cuff allows you to control its level. However, modern technological devices, such as IntelliCuff, use a more progressive and clinically convenient approach: setting the pressure fixed by the doctor in the ETT cuff, its continuous measurement, and automatic maintenance at the proper level during the entire lung ventilation. Using these devices allows comprehensive monitoring of the pressure level in the ETT cuff and maintains it at an optimal level, reducing the risk of complications.

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АҢДАТПА

ОНКОЛОГИЯЛЫҚ НАУҚАСТАРДА АНЕСТЕЗИЯ КЕЗІНДЕ ЭНДОТРАХЕАЛЬДІ ТҮТІК МАНЖЕТІНІҢ ҚЫСЫМЫН БАҚЫЛАУ

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Өзектілігі: *Эндотрахеальды түтік (ЭТТ) екі негізгі функция орындайды: қымтаулықты қамтамасыз етеді және төменгі тыныс алу жолдарды ауыз жұтқыншақтан шыққан ластанған бөліністердің аспирациясынан қорғайды. Қалыпты жағдайда эндотрахеальды түтікше манжетасының ішіндегі қысым 20 до 30 см су бағанын құрайды. ЭТТ манжетасын шамадан тыс немесе жеткіліксіз үрлеу әр-түрлі асқынуларға әкелуі мүмкін.*

Зерттеудің мақсаты: *Онкологиялық науқастарда анестезия кезінде эндотрахеальды түтік манжетіндегі қысымды бақылаудың аппараттық әдістері мен пальпациялық әдісті салыстыру.*

Материалдар мен әдістер: *«ҚазҰҒЗИ» АҚ анестезиология, реанимация және интенсивті терапия бөлімшесінде жалпы анестезия кезіндегі проспективті бақылау 60 науқасты қамтыды. Шприцтің көмегімен ЕТТ манжетіне ауа енгізіліп, содан кейін ЕТТ манжетінің баллонын пальпациялау және IntelliCuff құрылғысы (Hamilton Medical, Швейцария) арқылы қысымды бақылау жүргізілді. Нақты қысым қалыпты мәндермен салыстырылып, содан кейін қалыпты қысымға жету үшін нақты және қажетті ауа көлемі бағаланды.*

Нәтижелері: *қысым деңгейін «классикалық» пальпациялау әдісімен бағалау 50% жоғары жағдайда қателіктерге әкелді, қалыпты қысым деңгейі тек 25 (42%) науқаста анықталды, манжетаның ішіндегі өлшенген ауа көлемі орташа 5,9±1,9мл құрады, бірақ 25 мм су бағанына сәйкес қысымға жету үшін үрленетін ауа көлемі 3,9 мл құрады, нәтижесінде ЭТТ манжетасының ішіндегі қысым деңгейі шамадан тыс болды.*

Қорытынды: Бақылау баллонын пальпациялау арқылы ЭТТ манжетінің қысымын анықтау әдеттегі тәжірибе болғанымен, жиі қысымның дұрыс емес көрсеткіштеріне әкеледі. Сонымен бірге ЭТТ манжетіндегі жоғары қысым да, төмен қысым да көптеген асқынулардың дамуына әкелуі мүмкін. ЭТТ манжетіндегі қысымды өлшеуге арналған құрылғыларды пайдалану қысым деңгейін бақылауға мүмкіндік береді, ал ЭТТ манжетіндегі қысымды ұзақ уақыт бақылауға мүмкіндік беретін құрылғылардың артықшылығы дәлелденді.

Түйінді сөздер: *эндотрахеальді түтік, манжетінің қысымын бақылау, микроаспирация, трахея интубациясы,өкпені жасанды желдету.*

АННОТАЦИЯ

КОНТРОЛЬ ДАВЛЕНИЯ В МАНЖЕТЕ ЭНДОТРАХЕАЛЬНОЙ ТРУБКИ ВО ВРЕМЯ АНЕСТЕЗИИ У ОНКОЛОГИЧЕСКИХ ПАЦИЕНТОВ

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Актуальность: *Манжета эндотрахеальной трубки (ЭТТ) обеспечивает герметичность и защищает нижние дыхательные пути от аспирации. В норме давление в манжете ЭТТ находится в диапазоне от 20 до 30 см водного столба. Как повышенный, так и недостаточный уровень раздутия манжеты ЭТТ ассоциирован с рядом осложнений.*

Цель исследования *– сравнение пальпаторного и аппаратного методов контроля давления в манжете эндотрахеальной трубки во время анестезии у онкологических пациентов.*

Методы: *В проспективное обсервационное исследование были включены 60 пациентов во время проведения общей анестезии в отделении анестезиологии, реанимации и интенсивной терапии АО «КазНИИОиР». Нагнетание воздуха в манжету ЭТТ проводили с помощью шприца, затем осуществляли пальпаторный контроль баллона манжеты ЭТТ и контроль давления при помощи устройства IntelliCuff (Hamilton Medical, Швейцария). Далее фактическое давление и объём воздуха сравнивали с нормальными показателями.*

Результаты: *Оценка уровня давления «классическим» пальпаторным методом приводила к ошибкам в уровне давления в манжете ЭТТ более чем в 50% случаев; нормальный уровень давления наблюдался только у 25 пациентов (42%). Для достижения давления в 25 мм вод. ст. средний объем воздуха составил 3,9 мл. Измеренный объем воздуха в манжете в среднем составил 5,9±1,9 мл, что приводило повышенном уровне давления в манжете ЭТТ.*

Заключение: *Определение давления в манжете ЭТТ путем пальпации контрольного баллона, хоть и является общепринятой практикой, зачастую приводит к неверному определению давления. При этом как высокое, так и низкое давление в манжете ЭТТ ассоциировано с развитием осложнений. Применение устройств для измерения давления в манжете ЭТТ позволяют контролировать его уровень, при этом преимущество имеют устройства, позволяющие проводить продленный мониторинг давления в манжете ЭТТ.*

Ключевые слова: *эндотрахеальная трубка (ЭТТ), контроль давления в манжете, микроаспирация, интубация трахеи, вентиляция легких.*

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ENDOSCOPIC TREATMENT OF BARRETT'S ESOPHAGUS IN KAZAKHSTAN

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ABSTRACT

Relevance: *Barrett's esophagus (BE) is a special disease characterized by metaplasia of the flat epithelium of the esophagus.*

The main danger of esophageal epithelial metaplasia is the high probability of develop-ing a malignant neoplasm at the site of the lesion – esophageal adenocarcinoma or can-cer of the cardioesophageal zone.

The study aimed to *evaluate the clinical effectiveness of new BE endoscopic treat-ment methods for their subsequent implementation in wide practice throughout the Re-public of Kazakhstan.*

Methods: *This article presents cases of clinical use of argon plasma coagulation of dysplasia lesions less than 2.0 cm in two patients with Barrett's esophagus and the use of loop resection of dysplasia lesions more than 2.0 cm in three patients with Barrett's esophagus.*

Results: *All the presented cases have shown the effectiveness of applied treatment. Control morphological examination showed no signs of BE in the epithelium.*

Conclusion: *The presented article describes the results of the introduction of endo-scopic BE treatment methods in our clinic and is available for wide implementation throughout Kazakhstan. A widespread introduction of endoscopic treatment of precan-cerous pathology will reduce the incidence of esophageal cancer in the Kazakhstani population.*

Keywords: *Barrett's esophagus (BE), metaplasia, endoscopy, esophageal neoplasms, gastroesophageal reflux.*

Introduction: Barrett's esophagus (BE) is a special condition characterized by metaplasia of the esophageal squamous epithelium. This pattern is observed during the long course of gastroesophageal reflux disease and is one of its most serious complications.

The incidence of BE is about 10% of all identified cases of gastroesophageal reflux (among treated patients); in the general population, the disease occurs in about one in 100 adults. According to statistics, in a year, cancer degeneration into esophageal adenocarcinoma occurs in 6-7 patients out of 1000 suffering from Barrett's esophageal disease [1]. Unfortunately, there is no data on BE incidence and detectability in Kazakhstan. This article describes the first successful experience of administering new endoscopic treatment in patients with Barrett's esophagus in Kazakhstan. For further scientific research, we propose monitoring such patients to identify the effectiveness of treatment, the radicality of treatment when using endoscopic methods of ablation of Barrett's esophagus, the presence of relapse, complications, and other indicators.

The main danger of esophageal epithelial metaplasia is the high probability of developing a malignant neoplasm at the site of the lesion – esophageal adenocarcinoma or cancer of the cardioesophageal zone.

The only reliable method of diagnosing Barrett's metaplasia is detecting a special type of goblet cells of the intestinal epithelium in biopsy material taken from the affected area of the esophageal mucosa. These cells indicate the transformation that has occurred with the epithelium of the esophagus, which is dangerous for further degeneration into cancer.

Endoscopy can help establish a preliminary diagnosis since Barrett's metaplasia has a characteristic visual picture: foci of metaplasia against the background of light pink normal esophageal epithelium look like "flames." This sign occurs due to atrophy of the mucous membrane and the transmission of small blood vessels passing longitudinally through its surface layer [2].

Endoscopic treatment methods are used with severe dysplasia or early esophageal cancer. The most common methods of BE endoscopic treatment are "aspiration and resection": using a distal cap and ligature, as well as argon plasma coagulation (APC). In the first case, the pathological site is aspirated into the cavity of a plastic cap, which is pre-installed at the distal end of the endoscope, and resection is performed using an electrosurgical loop previously opened inside the cap. Before resection, a saline solution is injected into the submucosal layer under the base of the pathological site to prevent perforation. In the second case, the pathological site is coagulated by an argon plasma coagulator. Both methods are equally effective and safe for the ablation of BE [3, 4].

The study aimed to evaluate the clinical effectiveness of new BE endoscopic treatment methods for their subsequent implementation in wide practice throughout the Republic of Kazakhstan.

Materials and methods: In 2020-2022, the BE endoscopic resection was performed in 3 patients and the endoscopic APC – in 2 patients with BE. All patients provided informed consent before the endoscopic intervention. APC was used with BE up to 2.0 cm in size. Endoscopic loop resection was used in BE with a segment size > 2 cm [5, 6].

Endoscopic mucosal resection of sections of the metaplastic esophageal mucosa with dysplasia sites was performed in an endoscopic operating room under intubation anesthesia using a 6-charge captivator (Boston

Scientific, USA) for a semicircular endoscopic mucosal resection (EMR). All resected areas were extracted and sent for morphology. Endoscopic treatment was accompanied by antisecretory therapy using proton pump inhibitors for effective and rapid healing of mucosal defects and creating conditions for the appearance of multilayer flat epithelium of the esophagus in these areas. The control examination was carried out after 1.5 months with a mandatory sampling of biopsy material from the esophagus; subsequent morphological examination confirmed that the new epithelium had no signs of mucosal metaplasia (Figure 1).

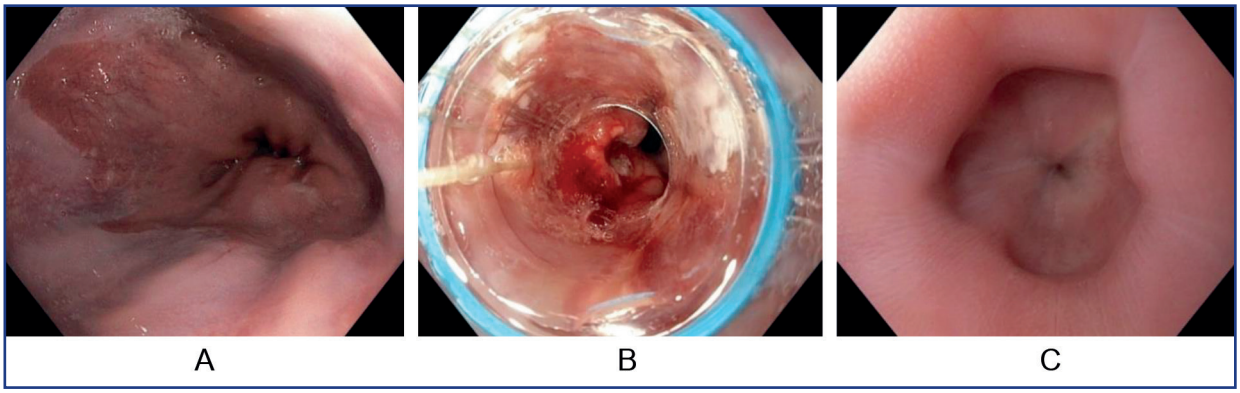

Figure 1 – Endoscopic Barrett's esophagus loop resection using EMR Captivator: A – before resection, B – during resection, C – one month after resection

APC was performed using an "Olympus ESG 300/APU300" (Japan) high-frequency generator and two "Olympus" probes of 2.3 and 3.2 mm in diameter. The argon feed rate was from 0.5 to 1 l/min; the power ranged from 20 to 50 W. The choice of the coagulation program in each case was carried out individually, taking into account the localization and nature of the pathological focus and the visible effect of coagulation. During the APC, the necessary precautions were observed: coagulation was carried out only under visual control, the probe was not allowed to come into contact with tissues, an aspirator was used to prevent overgrowth of the hollow organ, and the insufflation of the esophageal lumen was carried out with a CO_2 insufflator (Figure 2).

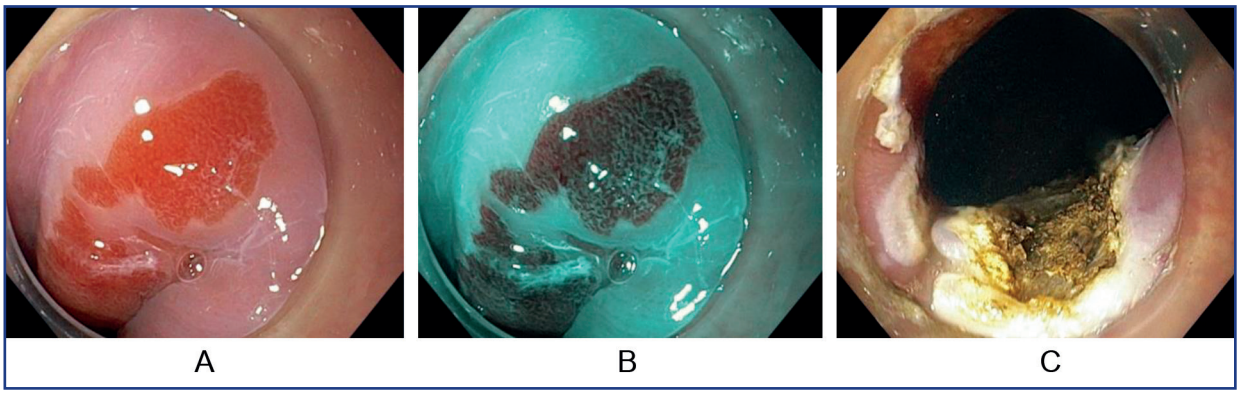

Figure 2 – Barrett's esophagus (BE) endoscopic argon plasma coagulation (APC): A – BE image, B – BE with narrow band imaging; C – BE after APC

APC method was used for BE with epithelial dysplasia, BE with segment size < 2 cm, and pathomorphologically confirmed diagnosis. APC in patients with BE was started from the edges of the metaplastic segment to clearly distinguish the pathological focus for ablation. After APC, the patient received omeprazole 20 mg 2 times a day for four weeks. All patients underwent a mandatory biopsy (from 2 to 4 fragments, depending on the segment size) a month after APC. The biopsy sample was taken from the BE segment previously subjected to APC.

Results: No complications after APC was registered. One patient developed a circular stricture after loop resection in the postoperative period, successfully resolved after four gullet bougienages. Deep sedation allows the operator to work in a calm environment without fear of uncontrolled movements on the part of the patient. This is especially important when working in the esophageal-gastric junction zone when a conscious patient's vomiting actions do not allow for rapid, targeted coagulation and increase the risk of iatrogenic damage. All patients underwent one-stage intervention; the second stage of ablation or loop resection was not required. The pathomorphological examination of the material taken at the control examination showed no metaplastic and/or dysplastic changes in the mucous membrane of the lower third of the esophagus. Thus, a single APC was radical in all patients with a BE size

of <1 cm and loop resection in all patients with a BE size of more than 2 cm.

Discussion: In Kazakhstan, endoscopic treatment of patients with dysplasia in Barrett's esophagus has just started at the National Research Oncology Center. It will take a long time to monitor a large group of patients for ten years after therapy to publish far-reaching results. Endoscopic treatment of dysplastic BE is known to be successful in 90% of patients [6]. What is less well understood is how long this benefit lasts and whether it contributes to a significant reduction in cancer progression. Further research requires a larger number of patients and the division of patients into groups with low and severe dysplasia. Long-term monitoring of patients for recurrence and progression of dysplastic changes is also required. And, of course, a national registry of patients with Barrett's esophagus is required for further epidemiological surveillance.

Conclusions: Thus, the tactics of managing patients with BE in the presence of dysplasia involve conducting a thorough endoscopic examination of the metaplasia area in a specialized expert center using modern endoscopic techniques to identify visible pathological areas. In the absence of visible pathological areas in the metaplasia segment, BE eradication using modern ablation methods is required. A detected pathological site should be removed by endoscopic resection followed by histological evaluation. A severe dysplasia or intra-mucosal cancer in a remote area requires eliminating the remaining segment of BE metaplasia using endoscopic ablation methods. This experience of BE endoscopic treatment at the National Research Oncology Center can be put into wide practice in all oncology clinics of the Republic of Kazakhstan.

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АҢДАТПА

ҚАЗАҚСТАНДА БАРРЕТТ ӨҢЕШІН ЭНДОСКОПИЯЛЫҚ ЕМДЕУ

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Өзектілігі: *Барреттің өңеші (БӨ) – бұл өңештің жалпақ эпителий метаплазиясымен сипатталатын ерекше ауру. Өңеш эпителийінің метаплазиясының негізгі қауіптілігі зақымдану орнында қатерлі ісіктің даму ықтималдығы жоғары – өңеш аденокарциномасы немесе кардиоэзофагеальды аймақтың қатерлі ісігі.*

Зерттеудің мақсаты *кейіннен Қазақстан Республикасы бойынша кең тәжірибеге енгізу үшін БӨ емдеудің жаңа эндоскопиялық әдістерінің клиникалық тиімділігін бағалау болды.*

Әдістері: *Бұл мақалада Баррет өңеші бар екі пациентте 2,0 см-ден аз дисплазия ошақтарының аргоноплазмалық коагуляциясын клиникалық қолдану және Баррет өңеші бар үш пациентте 2,0 см-ден астам дисплазия ошақтарының циклдік резекциясын қолдану жағдайлары келтіріл-ген.*

Нәтижелер: *барлық ұсынылған жағдайлар қолданылатын емнің тиімділігін көрсетті.Бақылау морфологиялық зерттеуі эпителийде БӨ белгілерін анықтаған жоқ.*

Қорытынды: *ұсынылған мақала біздің клиникада БӨ емдеудің эндоскопиялық әдістерін енгізу нәтижелерін сипаттайды және бүкіл Қазақстан бойынша кеңінен енгізу үшін қолжетімді. Қатерлі ісікке дейінгі патологияны эндоскопиялық емдеуді кеңінен енгізу Қазақстан халқы арасында өңеш обырымен сырқаттанушылықты азайтуға мүмкіндік береді.*

Түйінді сөздер: *барреттің өңеші, метаплазия, эндоскопия, өңештің ісіктері, газоэзофагеальды рефлюкс.*

АННОТАЦИЯ

ЭНДОСКОПИЧЕСКОЕ ЛЕЧЕНИЕ ПИЩЕВОДА БАРРЕТТА В КАЗАХСТАНЕ

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Актуальность: *Пищевод Барретта (ПБ) – это особое заболевание, характеризующееся метаплазией плоского эпителия пищевода. Основной опасностью метаплазии эпителия пищевода является высокая вероятность развития злокачественного новообразования на месте поражения – аденокарциномы пищевода или рака кардиоэзофагеальной зоны.*

Целью исследования *была оценка клинической эффективности новых эндоскопических методов лечения ПБ для их последующего внедрения в широкую практику по всей Республике Казахстан.*

Методы: *В данной статье представлены случаи клинического применения аргоноплазменной коагуляции очагов дисплазии менее 2,0 см у двух пациентов с пищеводом Барретта и применения петлевой резекции очагов дисплазии более 2,0 см у трех пациентов с пищеводом Барретта.*

Результаты: *Все представленные случаи показали эффективность применяемого лечения.Контрольное морфологическое исследование не выявило признаков ПБ в эпителии.*

Заключение: *Представленная статья описывает результаты внедрения эндоскопических методов лечения ПБ в нашей клинике и доступна для широкого внедрения по всему Казахстану. Широкое внедрение эндоскопического лечения предраковой патологии позволит снизить заболеваемость раком пищевода среди населения Казахстана.*

Ключевые слова: *пищевод Барретта, метаплазия, эндоскопия, новообразования пищевода, газоэзофагеальный рефлюкс.*

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RECONSTRUCTIVE PLASTIC SURGERY INVOLVING THE PECTORALIS MAJOR MUSCLE FOR BASAL CELL CARCINOMA OF THE FACIAL SKIN: A CLINICAL CASE

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ABSTRACT

Relevance: *Basal cell skin cancer is the most common malignant skin tumor originating from epithelial cells. Reconstruction of al-tered tissues and organs is an urgent and significant medical and social problem. In particular, head and neck injuries are complicated for functional, cosmetic, and aesthetic reconstruction.*

The study aimed to *share the experience of performing reconstructive plastic surgery using the pectoralis major muscle at the Head and Neck Tumor Center of Kazakh Institute of Oncology and Radiology, JSC (KazIOR, Almaty, Kazakhstan).*

Methods: *The article describes the experience, operation steps, and results of postoperative wound healing after reconstructive surgery for skin cancer progression. A split musculocutaneous flap with the inclusion of the pectoralis major on a vascular pedicle was used. The surgery was performed at the Center for Head and Neck Tumors of KazIOR.*

Results: *Follow-up control 6 and 12 months after surgery showed that the musculocutaneous flap was intact. There was no evidence of recurrence or metastasis.*

Conclusion: *Musculocutaneous flaps involving the pectoralis major can successfully reconstruct combined extensive head and neck injuries.*

Keywords: *basal cell carcinoma, pectoralis major, replacement flap, osteomyelitis, plastic, defect, fatty skin flap.*

Introduction: Skin cancer refers to malignant neoplasms, one of the indicators of the population's health, with a significant degree of dependence on habitat quality. High morbidity is often considered a medical indicator of the territory's environmental woes. According to the literature, skin cancer most often occurs in the 50-69 age range, but in recent years there has been a tendency to its rejuvenation [1].

Non-melanoma tumors include basal cell skin cancer (basalioma) – 75 to 97% of all epithelial skin cancers, squamous cell cancer - 5 to 15%, and rare skin appendage cancer (sebaceous and sweat glands, hair follicles) less than 1%.

In the Republic of Kazakhstan, the incidence of intense skin cancer is as follows: 75.0 in the total population, 63.4 in men, and 85.1 in women. The standardized morbidity rates are 41.1, 45.9, and 39.8, respectively.

The main treatment methods for patients with locally standard head and neck cancer are combined and complex processes that include different combinations of radiation therapy, chemotherapy, and surgery [2]. The complexity of treating patients with locally spread head and neck tumors is that extended-combined surgeries often lead to significant complex defects and functional and aesthetic disorders. Therefore, in many cases, locally-spread primary, recurrent, and regional metastatic tumors are defined as inoperable due to their prevalence and the impossibility of closing postoperative defects using local tissues. This forces the surgeon to seek complete restoration of anatomical and functional abnormalities that can occur after radical surgical intervention [3]. One of the first steps in planning the reconstruction is to assess the defect nature, the condition of the anatomical structures requiring repair, and the functional deficit resulting from the surgical intervention. Finally, malignant skin neoplasms remain one of modern medicine's most important and priority problems [4].

The study aimed to share the experience of performing reconstructive plastic surgery using the pectoralis major muscle at the Head and Neck Tumor Center of "Kazakh Institute of Oncology and Radiology" JSC (KazIOR, Almaty, Kazakhstan).

Materials and methods: This manuscript describes the experience, operation steps, and results of postoperative wound healing after reconstructive surgery for skin cancer progression. A split musculocutaneous flap with the inclusion of the pectoralis major on a vascular pedicle was used. The surgery was performed at the Center for Head and Neck Tumors of KazIOR.

Patient information: Patient S., born in 1958, was referred to the Head and Neck Tumor department of KazIOR in March 2021 with "T2N0M0 st2 skin cancer on the chin, condition after chemotherapy, disease progression."

Clinical data:

Anamnesis morbi: The patient was registered at the local oncologist in April 2019, when he developed a formation on his chin, with the primary diagnosis of a "T2N0M0 st2 skin cancer on the chin." Histological report of April 2019: "Skin basalioma, solid type." The patient was referred to KazIOR.

This clinical case was discussed at the meeting of the interdisciplinary group. Considering the data from CT studies and the prevalence of the tumor process, it was decided to perform the following surgical treatment: removal of the skin tumor on his chin, and muscles of the mouth floor with resection

of the lower jaw fragment, with a skin and fat flap with a large pectoral muscle (LPM) on the left. In addition, the patient was hospitalized in the head and neck tumors center of KazIOR.

Diagnostics: General condition on admission: The patient's condition is closer to satisfactory. Consciousness is clear. The physique is average. Visible skin and mucous membranes were pale pink. The subcutaneous fatty tissue and muscular system were evenly developed, and the osteoarticular apparatus was without deformity. The thorax was regular. Lung breathing was vesicular, with no audible rales, and the heart boundaries were normal. Cardiac tones were muffled and rhythmic. BP – 120/80 mm Hg, HR – 76 bpm. The abdomen was soft and painless on palpation. The liver and spleen were not enlarged. The Pasternatsky's symptom was negative on both sides. Stool and diuresis were regular.

Locally: External examination determined a tumor formation in the lower jaw central area up to 8.0 cm in diameter. The skin above the tumor was ulcerated, with purulent discharge. Single lymph nodes up to 1.5 cm were detected in the submandibular area on both sides. Oroscopy showed no evidence of oncopathology.

Figure 1 shows the preoperative view of the patient.

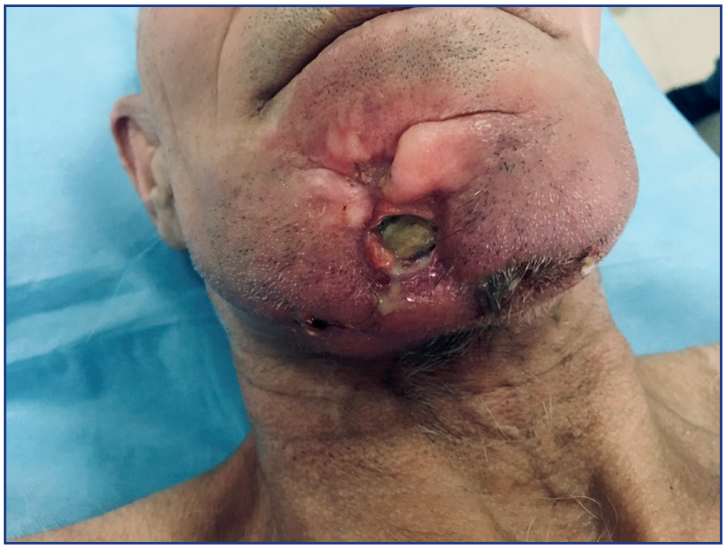

Figure 1 – Preoperative view of Patient S., born in 1958. Diagnosis: T2N0M0 st2 skin cancer on the chin, condition after chemotherapy, the disease progression

Examinations at admission: A CT scan of the mandible was performed in the preoperative period to assess the process's extent and select an adequate scope of surgical treatment. A series of tomograms dated March 2021 revealed a defect of the external skin of the genian up to 19.2x17.5 mm, reaching the outer cortical layer of the mandible. There was thickening and infiltration of adjacent soft tissues with heterogeneous contrast accumulation. Areas of lytic destruction of bone tissue with free gas bubbles were detected in the mandible, and the integrity of the outer and inner lamina of the cortical layer was compromised. There was also a nidus of lytic destruction in the proper alveolar process up to 8.2 x 6.2 mm. Genian, upper, and middle jugular lymph nodes of the neck on both sides were up to 11x5.8 mm.

Conclusion: CT signs of a defect in the external skin of the mandibular area with thickening and infiltration of the adjacent soft tissues. Areas of lytic destruction of the bone tissue of the mandible with free gas bubbles and disruption of the integrity of the outer and inner lamina of the cortical layer (signs of osteomyelitis). A focal point of lytic destruction in the alveolar process of the mandible on the right. Lymphadenopathy of the neck's genian, upper and middle jugular lymph nodes on both sides (Figure 2).

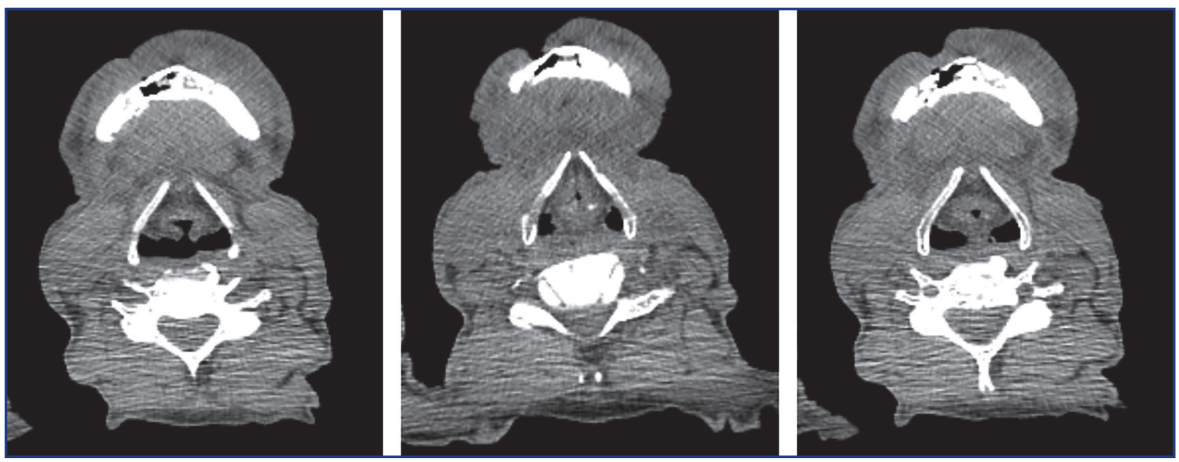

Figure 2 – Patient S., born in 1958: a contrast-enhanced CT scan of the mandible and soft tissues of the neck (March 2021)

Treatment: After histological verification, the patient received close-focus X-ray therapy with a total boost dose of 60 g from June to July 2019. The patient remained under clinical observation. In April 2020, he developed a relapse of an ulcerative dermal tumor in the chin. The cytology of scraping from the neoplasm in June 202 showed post-radiation dysplasia and single carcinoma cells. In July 2020, the Overall Multidisciplinary Team recommended polychemotherapy. Two conducted scheduled courses included cisplatin 130 mg and doxorubicin 90 mg. Against the treatment, the ulcerative formation with purulent discharge increased.

The surgery performed at KazIOR in March 2021 included the removal of the skin tumor on the chin, resection of muscles of the oral cavity and the alveolar process of the mandible from the 4th tooth on the right to the 4th tooth on the left, and reconstruction by adipose-dermal flap with the inclusion of the GPM on the left with a tracheostomy.

Stages of the surgery: The first stage of the process in aseptic conditions produced a boundary incision of the skin, subcutaneous tissue of the mandibular area deviating from the tumor by 1.0 cm, within healthy tissues, a branch of the mandible was allocated (Figure 3).

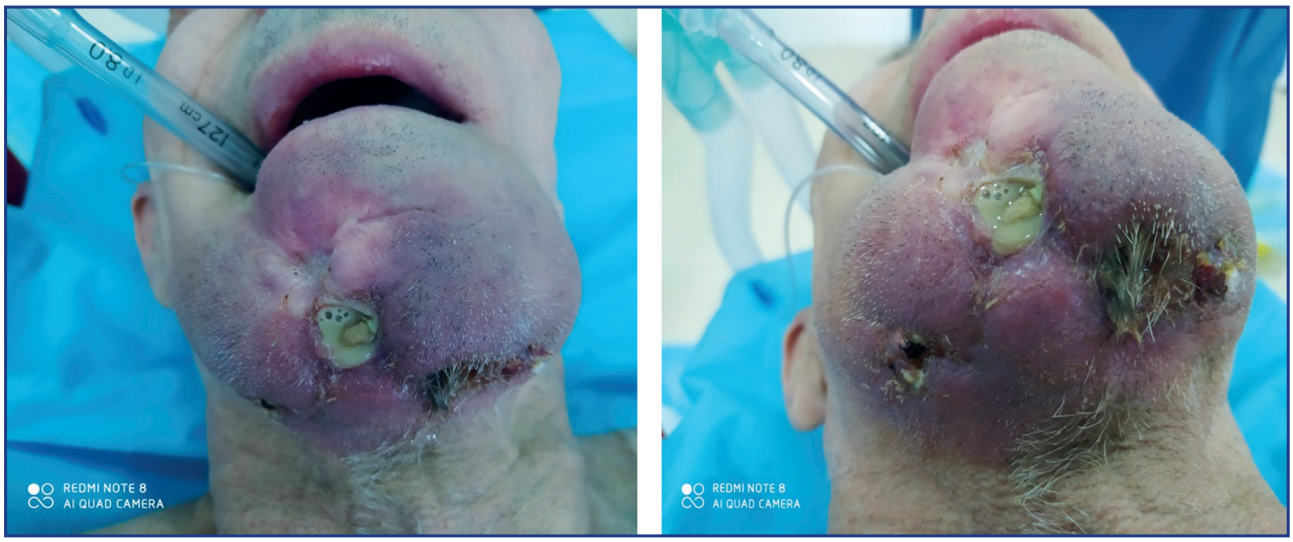

Figure 3 – The appearance of Patient S. during the first stage of surgery

The revision revealed lithic destruction of the alveolar process of the mandible. A mandible fragment from the 4th tooth on the right to the 4th tooth on the left was resected using a Jiggly saw (Figure 4). Hemostasis was performed.

In the second stage, a dermal-muscular flap with BPM inclusion on the left side was excised and moved to the defect site, hemostasis, layer-by-layer sutures, drains, and a nasogastric probe, and imposed aseptic bandage. Then a longitudinal incision of the skin and subcutaneous tissue was made under general anesthesia above the jugular notch. The rectus muscles of the neck were pulled aside with a sharp-blunt straight; the isthmus of the thyroid was exposed and led to the top; the front surface of the trachea was exposed, and a tracheostomy was formed between the 2 and 3 tracheoles (Figure 5).

Figure 6 shows a macro preparation of the skin tumor on the chin, with a jaw fragment, extracted from patient S.

The patient was treated with antibacterial and supportive therapy in the postoperative period. The patient was discharged in satisfactory condition on the 8th postoperative day.

Locally: On the 8th postoperative day: Facial asymmetry due to the postoperative defect of the frontal mandible was replaced by a skin-fat flap with GPM. The flap is intact. There were no signs of necrosis (Figure 7).

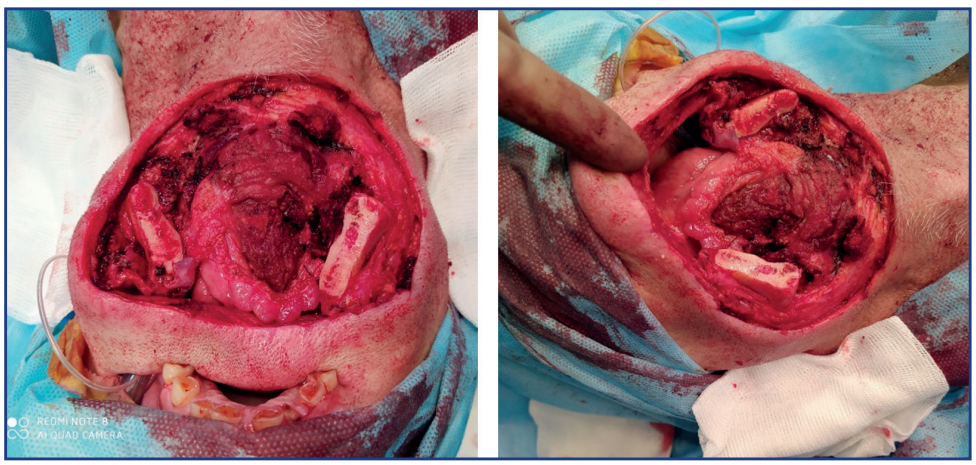

Figure 4 – The resected mandibular fragment

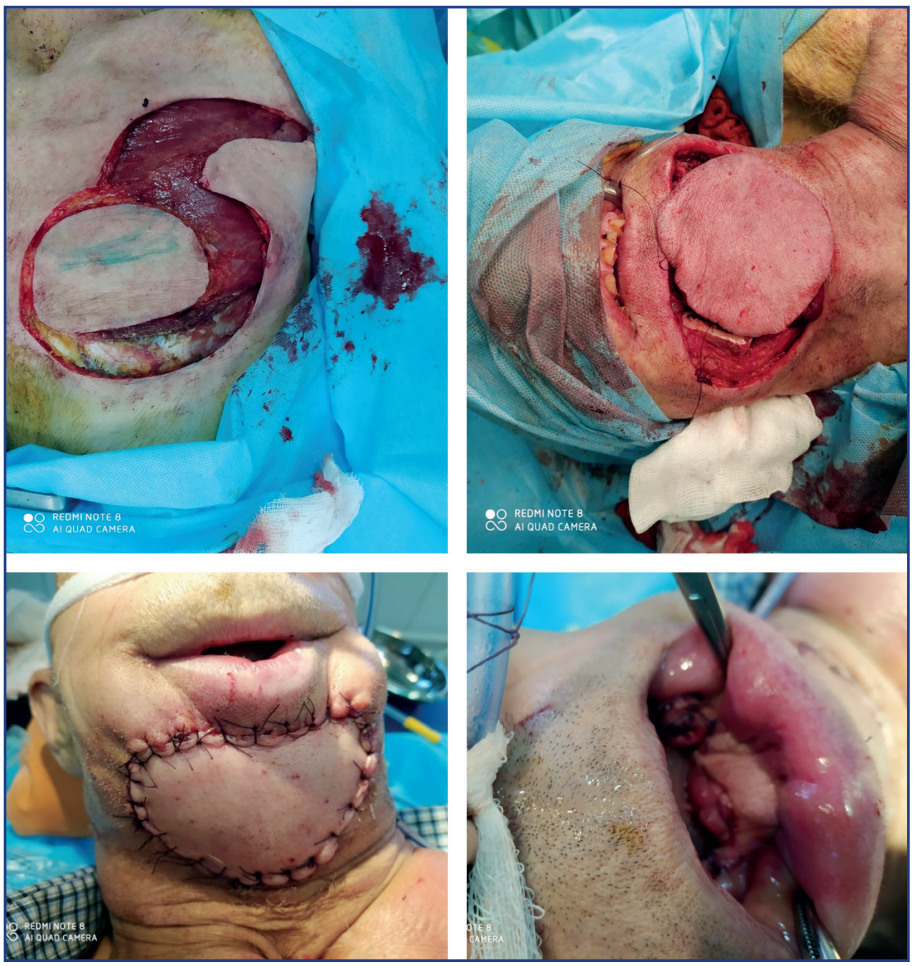

Figure 5 – Cutting and fixation of the flap

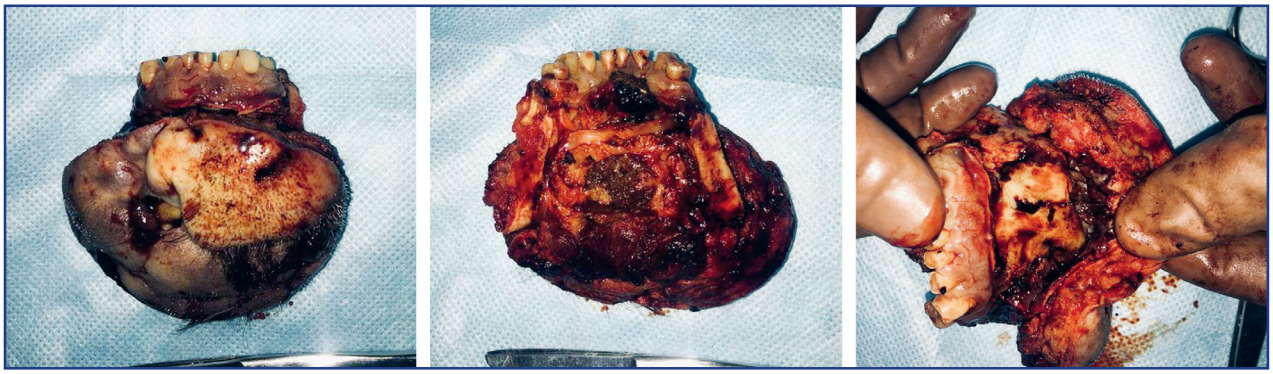

Figure 6 – Macro preparations: skin tumor on the chin, with a fragment of the jaw

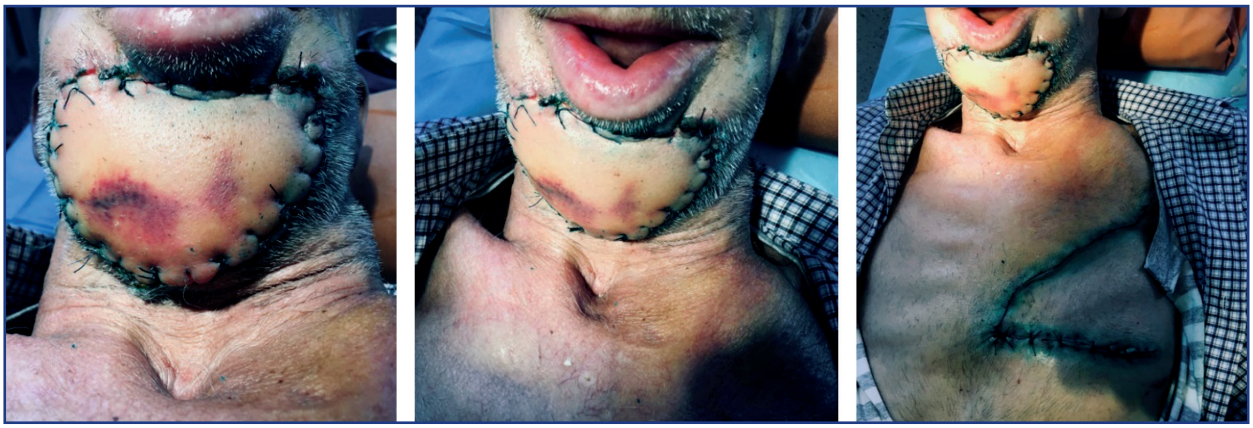

Figure 7 – The appearance of Patient S., Day 8 after surgery

Postoperative histology report dated March 2021: purulent-productive inflammation, purulent actinomycotic osteomyelitis. No tumor cells were detected-grade 4 pathomorphosis.

Results: The musculocutaneous flap was intact during follow-up visits 6 and 12 months after surgery. There was no evidence of recurrence or metastasis (Figures 8 and 9).

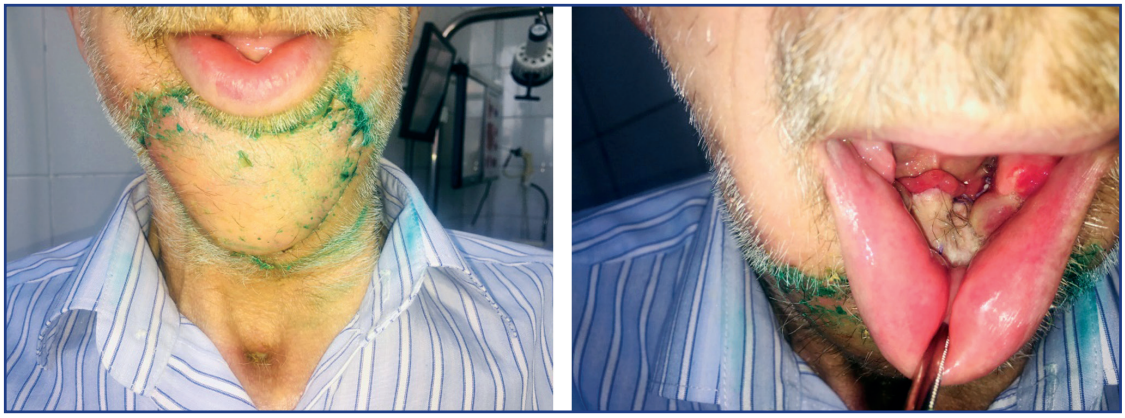

Figure 8 – The appearance of Patient S., 6 months after surgery

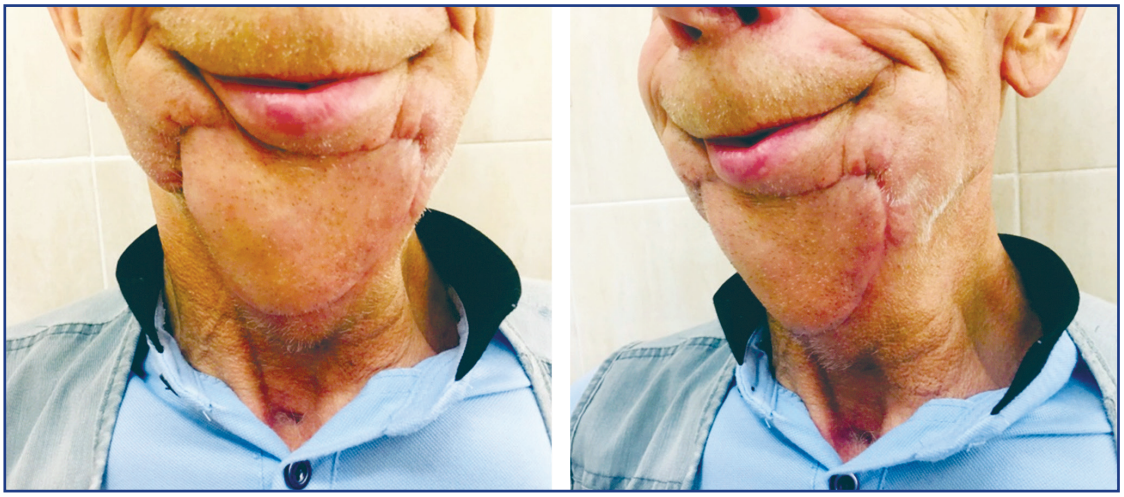

Figure 9 – The appearance of Patient S., 12 months after surgery

Follow-up CT scan dated September 2021: CT image of the condition after complex treatment for skin cancer on the chin. There was no evidence of recurrence of the underlying process and no MTS lesion (Figure 10).

As of today, the patient is under control and follow-up with an oncologist at the place of residence.

Time scale:

The described clinical case time scale is shown in Figure 11.

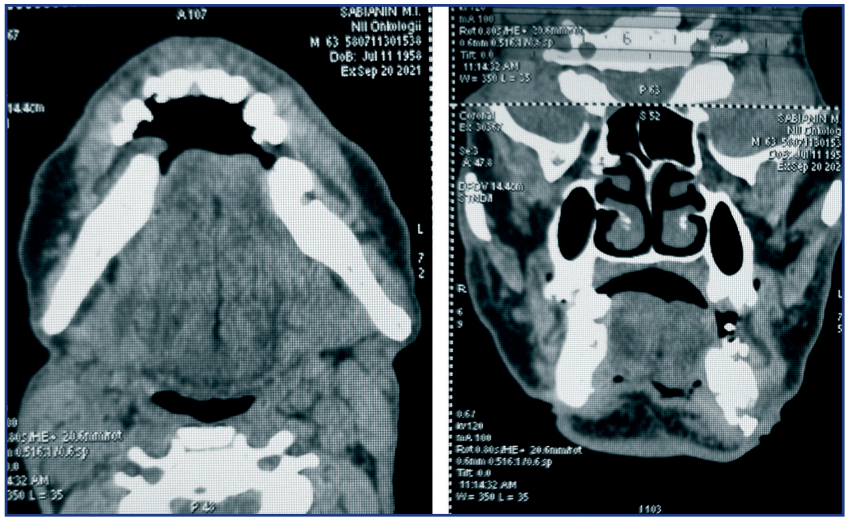

Figure 10 – CT picture of the condition after complex treatment for skin cancer on the chin

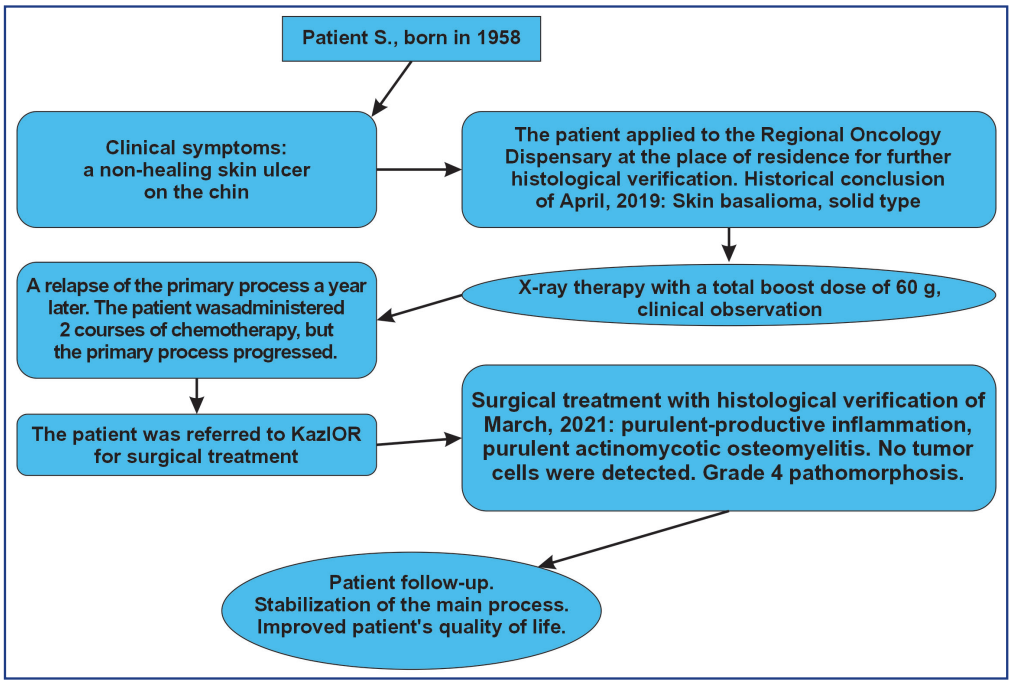

Figure 11 – Time scale of the clinical case of basal cell skin cancer on the chin with reconstructive and plastic surgery

Discussion: Patients with extensive injuries, defects, and deformities of the head and neck represent a particular clinical group; their treatment and rehabilitation pose a complex problem for surgeons. As a rule, ample head, face, and neck defects imply damage to the tissue complex. Its recovery requires plastic material of a large area and thickness, including skin, cellulose, muscles, and bone [5].

The presented case describes the surgery results and the experience of the Center's surgeons in treating the primary process and restoring the patient's function and quality of life after an extensive disabling surgical intervention.

Conclusion: According to our experience, authorized transplants based on the pectoralis major muscle can successfully reconstruct combined extensive head and neck injuries. Satisfactory results of these plastic reconstructive surgeries have been clinically confirmed (Figures 8, 10).

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АҢДАТПА

БЕТТІҢ БАЗАЛЬДЫ ЖАСУШАЛЫ ТЕРІ ІСІГІ КЕЗІНДЕ КЕУДЕ БҰЛШЫҚЕТІНІҢ НЕГІЗГІ БӨЛІГІН ҚАМТИТЫН РЕКОНСТРУКТИВТІК ПЛАСТИКАЛЫҚ ОПЕРАЦИЯ: КЛИНИКАЛЫҚ ЖАҒДАЙ

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Өзектілігі: *Базальды жасушалы тері қатерлі ісігі – эпителий жасушаларынан пайда болатын ісіктердің ішінде ең көп таралған түрі. Өзгертілген тіндер мен мүшелерді қайта қалпына келтіру адамзаттың медициналық және әлеуметтік өзекті және маңызды*

проблемаларының бірі болып табылады. Әсіресе, Бас және мойын зақымданулары функционалдық және әсемдік тұрғыда қалпына келтіру үшін өте қиын.

Зерттеудің мақсаты: *АҚ ҚазОжРҒЗИ Бас және мойын ісіктері орталығында үлкен кеуде бұлшықетін қолдана отырып, реконструктивті пластикалық операцияларды жүргізу тәжірибесімен бөлісіңіз*

Әдістері: *Мақалада «Қазақ онкология және радиология ҒЗИ» АҚ бас және мойын ісіктері орталығының (Алматы, Қазақстан) тері қатерлі ісігінің прогрессирленуі кезіндегі үлкен кеуде бұлшықетін (ҮКБ) қосумен тамырлы аяқшадағы лоскут арқылы реконструктивті-пластикалық операциядан кейінгі тәжірибесі, ота кезеңдері және отадан кейінгі жараны емдеу тәжірибесі және нәтижелері көрсетілген.*

Нәтижелер: *Операциядан кейін 6 және 12 айдан кейін динамикада бақылау нәтижесінде тері-бұлшықетті лоскут қалпында, ісіктің қайталануы және метастазына объективті деректер жоқ.*

Қорытынды: *ҮКБ негізіндегі тері-бұлшықетті лоскуттар бас және мойын комбинирленген, үлкен ауқымды тіндердің жетіспеушілігі кезінде сәтті пайдалануға болады.*

Түйінді сөздер: *Базальды жасушалық ісік, үлкен кеуде бұлшықеті (ҮКБ), алмастырушы қақпақ, остеомиелит, пластика, тін жетіспеушілігі, тері-майлы қақпақ.*

АННОТАЦИЯ

РЕКОНСТРУКТИВНО-ПЛАСТИЧЕСКАЯ ОПЕРАЦИЯ С ВКЛЮЧЕНИЕМ БОЛЬШОЙ ГРУДНОЙ МЫШЦЫ ПО ПО-ВОДУ БАЗАЛЬНОКЛЕТОЧНОГО РАКА КОЖИ ЛИЦА: КЛИНИЧЕСКИЙ СЛУЧАЙ

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Актуальность: *Базальноклеточный рак кожи – наиболее часто встречающаяся злокачественная опухоль кожи, проис-ходящая из эпителиальных клеток. Реконструкция измененных тканей и органов является одной из актуальных и значимых медико-социальных проблем. В частности, наиболее сложными для функциональной, косметической и эстетической рекон-струкции являются повреждения головы и шеи.*

Цель исследования *– поделиться опытом проведения реконструктивно-пластических операций с использованием боль-шой грудной мышцы в Центре опухолей головы и шеи АО «Казахский научно-исследовательский институт онкологии и ра-диологии» (Алматы, Республика Казахстан).*

Методы: *В статье освещается опыт, этапы операции и результаты заживления послеоперационной раны после ре-конструктивной операции по поводу прогрессирования рака кожи с использованием расщепленного кожно-мышечного лос-кута с включением большой грудной мышцы (БГМ) на сосудистой ножке.*

Результаты: *По данным контрольного наблюдения через 6 и 12 месяцев после операции кожно-мышечный лоскут со-стоятелен, объективных данных за рецидив и метастазирование нет.*

Заключение: *Кожно-мышечные лоскуты с включением БГМ могут быть успешно применены для реконструкции комби-нированных обширных повреждений головы и шеи.*

Ключевые слова: *Базальноклеточный рак, большая грудная мышца (БГМ), замещающий лоскут, остеомиелит, пластика, дефект, кожно-жировой лоскут.*

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MALE BREAST CANCER TREATMENT: A CLINICAL CASE*

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ABSTRACT

Relevance: *Male breast cancer (BC) has always been behind female BC in detection, treatment, and surveillance. Lower BC frequency in men limits the usefulness of screening. However, BC incidence in men is growing.*

The study aimed to *demonstrate the results of surgical treatment and typical changes in clinical and morphological manifestations of male breast cancer under chemotherapy and surgery.*

Methods: *The article describes a clinical case of a male patient diagnosed with "Cancer of the right breast St III (T4NxM0), edematous-infiltrative form with an intraductal component, upper outer localization. Immunohistochemically luminal subtype B without Her2neu expression"; the condition – after six neoadjuvant chemotherapy courses.*

Results: *Ultrasonography of the mammary glands conducted after six preoperative courses of chemotherapy showed a hypoechoic formation, centralized, with fuzzy, uneven contours, 52.5×48.2×46.1 mm in size, V=60.98 cm^3. Compared to March 2022 (the presence of a formation in the right breast craniolateral quadrant, with precise uneven contours, 9.0 cm in size, with infiltrating growth), the tumor formation decreased to US BI-RADS R6, L2. The multidisciplinary council prescribed surgery to the extent of radical mastectomy by Madden on the right and simple mastectomy on the left. The surgery was performed in August 2022. According to a postoperative histological conclusion, the therapeutic pathomorphism was index RCB-2.233, class RCB-II.*

Conclusion: *This article shares the results of systemic and surgical treatment of a man with breast cancer. Considering the clinical picture and anamnesis, literature data, and the clinical protocol, the multidisciplinary group recommended radiation therapy with adjuvant endocrine therapy with tamoxifen for an initial period of five years.*

Keywords: *clinical case, male breast cancer (BC), luminal subtype B without Her2neu expression, mastectomy, therapeutic pathomorphism, radiation therapy, endocrine therapy.*

Introduction: Male breast cancer (BC) has always been behind female BC in detection, treatment, and surveillance. However, male BC incidence is growing [1]. Currently, male breast cancer is an independent nosological unit with its own biological, molecular, and clinical features that require an interdisciplinary approach [2]. A male hormonal milieu is a unique and powerful determinant for assessing risk, prognosis, and treatment outcomes [3]. Multimodal breast cancer treatment includes surgery, radiation, and drug therapy [4].

The study aimed to demonstrate the results of surgical treatment and typical changes in clinical and morphological manifestations of male breast cancer under chemotherapy and surgery.

Materials and methods: The article describes a clinical case of a male patient diagnosed with "Cancer in the right breast St III (T4NxM0), edematous-infiltrative form with an intraductal component, upper outer localization. Immunohistochemically luminal subtype B without Her2neu expression"; the condition – after six neoadjuvant chemotherapy courses. [5].

The clinical case description

Patient information: The patient, A., a male born in 1958, condition – after six neoadjuvant chemotherapy courses administered at "Kazakh Institute of Oncolo-gy and Radiology" JSC (completion of chemotherapeutic treatment – July 2022) [5], second clinical group. From April to July 2022, after the performance of adequate diagnostics and establishing a clinical diagnosis, the patient underwent six preoperative chemotherapy courses according to the "AS" scheme Doxorubicin 60 mg/m^2 (DD 120 mg) + Cyclophosphamide 600 mg/m^2 (DD 1200 mg).

Relevant instrumental examinations were routinely scheduled to assess the treatment outcomes.

Clinical data:

Locally: During the follow-up examination in May 2022, the right areola was compacted, the pre-areolar skin was thickened, and the nipple was fixed. A pronounced glandular component remained in both mammary glands. In the right mammary gland, at the upper quadrants' border, a formless subareolar formation had slightly decreased in size, 5.0 cm locally (initial dimensions according to the mammography of May 2022 were 6.8×6.1 cm). In the right axillary region, an intramammary lymph node of about 1.3 cm was palpated (the previous lymph node size was about 2.0 cm). Gynecomastia remained on the left side (Figure 1).

** Extension of the clinical case results published in Oncology and Radiology of Kazakhstan, No. 2(64), 2022*

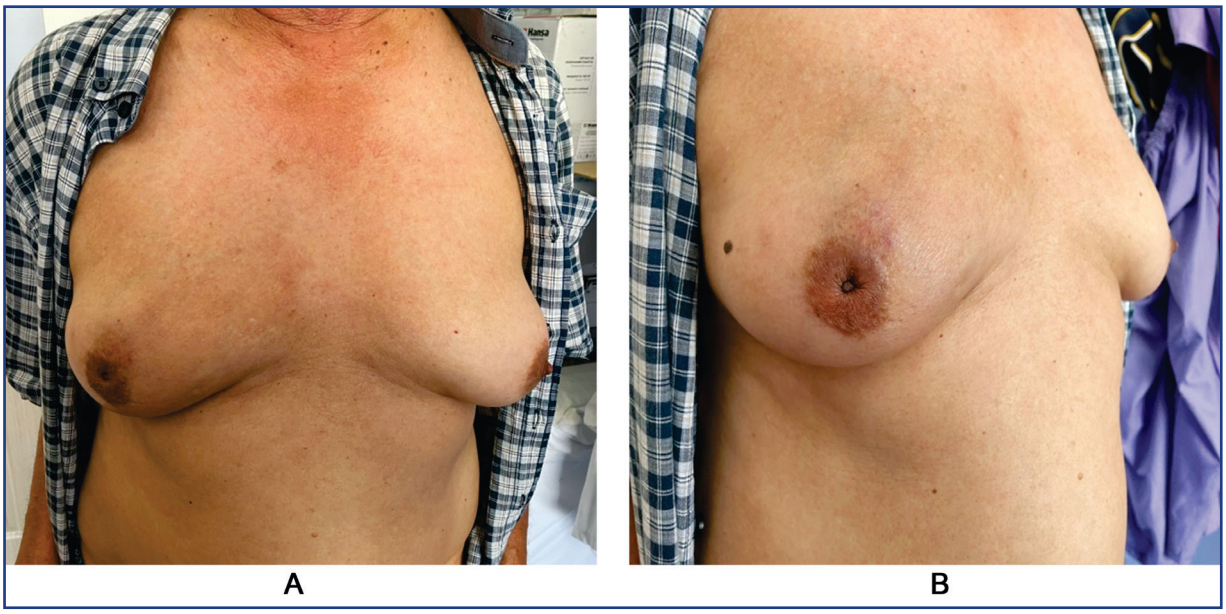

Figure 1 - Cancer of the right breast in a man, St III (T4pN0M0), edematous-infiltrative form with an intraductal component, upper outer localization. Immunohistochemical luminal subtype B without Her2neu expression. Condition – after six courses of neoadjuvant chemotherapy: A – front view, B – side view

Diagnostics: After six courses of chemotherapeutic treatment, the patient underwent preoperative diagnostics using appropriate instrumental examination methods.

Contrast-enhanced brain MRI, August 2022: A lacunar cyst was detected in the area of the basal nuclei on the left side.

Ultrasonography of the mammary glands, August 2022: The condition after six courses of chemotherapy. A hypoechoic formation, centralized, with fuzzy, uneven contours, 52.5×48.2×46.1 mm in size, V=60.98 cm^3. Compared to March 2022 (the presence of a formation in the right breast craniolateral quadrant, with precise uneven contours, 9.0 cm in size, with infiltrating growth), the tumor formation decreased. Gynecomastia of the mammary glands on both sides. US BI-RADS R6, L2.

Ultrasonography of the axillary lymph nodes on both sides, August 2022: a heterogeneous hypoechoic node with clear uneven contours was visualized at the border with the axillary region on the right, 13.2×10.9×12.1 mm in size, V=0.91 cm^3. The formation slightly decreased compared with the presented ultrasound examination of the axillary lymph nodes of March 2022 (previous size – 2.0 cm^3).

Follow-up bilateral mammography of both mammary glands in 2 projections, August 2022: Compared to May 2022, the asymmetric pronounced glandular component of the density type C remained in both mammary glands. The formless formation of high intensity with fuzzy contours in the right mammary gland, in the sub-areolar region, at the upper quadrants' border decreased to 5.0 cm in diameter (previous size – 6.8×6.1 cm). More evident signs of stromal edema were observed. In retro mammograms, the intensive formation of 1.3 cm in diameter (intramammary lymph node) remained. BI-RADS VI. Gynecomastia on the left side was noted.

Neck ultrasonography, August 2022: No focal changes were revealed in the neck on both side.

Contrast-enhanced abdominal cavity and chest CT scan, August 2022: Small calcifications in the liver and both lungs and microliths in kidneys were detected.

Contrast-enhanced pelvic MRI, August 2022: The picture of prostatic hyperplasia (Pi-Rads1).

Treatment: Breast cancer treatment requires a multimodal approach. After six neoadjuvant chemotherapy courses and an assessment of the treatment effectiveness based on the instrumental examinations, further treatment was discussed jointly with the heads of the 24/7 Chemotherapy Day Hospital and the Center of Breast Tumors and resident doctors of the Kazakh Institute of Oncology and Radiology (Almaty, Kazakhstan). Based on the protocol for diagnostics and treatment of malignant neoplasms in the Republic of Kazakhstan, the data from current literature sources, international standards, and considering the effectiveness of previously conducted chemotherapy courses, the consensus decision has been made to perform the surgery to the extent of radical mastectomy by Madden on the right and simple mastectomy on the left. In August 2022, within the approach to surgical treatment in aseptic conditions after intubation and treatment of the operating field in the patient's position on the back, the skin bordering the mammary gland (left/right) was incised.

The skin flaps were separated according to the general rules: upside - to the edge of the clavicular, medially - to the edge of the sternum, downside - to the edge of the costal arch, laterally - to the edge of the broadest muscle of the back. The right mammary gland, along with the fiber of the subclavian, subscapular, and axillary regions, has been removed by Madden. The left mammary gland was also removed as a prophylactic (Figure 2).

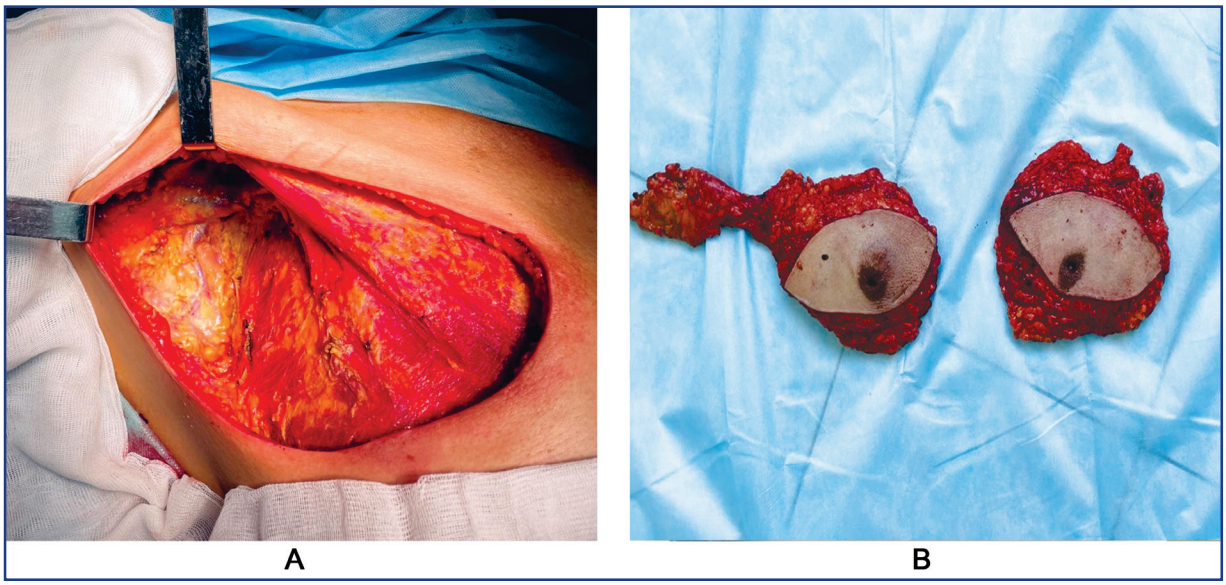

Figure 2 – Patient A., 64 years old. Surgery in the volume of radical mastectomy by Madden on the right side and prophylactic removal of the left mammary gland: A - the surgical field view, mastectomy by Madden on the right side, B – the back-table examination

The postoperative histological conclusion, August 2022: 1) The residual tumor was an infiltrating ductal carcinoma of the right mammary gland G II, 5.0×4.2 cm in size, with tumor embolisms in vessels, invasion into the skin dermis. The intraductal component composes 15% of the tumor, nGII solid crib Rosic type. Tumor cellularity – 40%. The tumor metastases were not found in eight examined lymph nodes of the axillary tissue on the right side.

The therapeutic pathomorphosis: index RCB-2.233, class RCB-II. The skin-pigmented seborrheic keratosis of the right mammary gland. 2) The apparent stroma fibrosis and hyalinosis were identified in the left mammary gland tissue.

In September 2022, the multidisciplinary group recommended radiation therapy with adjuvant endocrine therapy with tamoxifen for the next five years.

The timeline of the clinical case is presented in Figure 3.

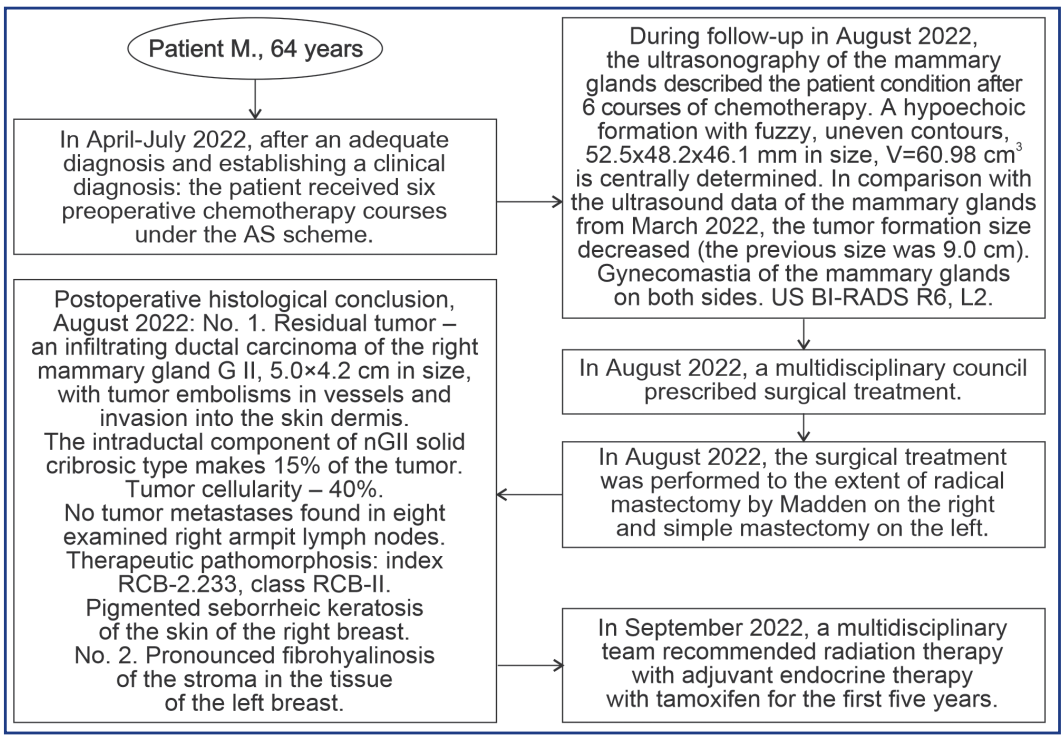

Figure 3 – Timeline of the described clinical case of right breast cancer treatment in a man

Results: Figure 4 shows the patient after the combined treatment involving six preoperative chemotherapy courses by the "AS" scheme (Doxorubicin 60 mg/m^2 (120 mg per day) + Cyclophosphamide 600 mg/m^2 (1200 mg

per day)) and surgical treatment in the extent of radical mastectomy by Madden on the right and prophylactic mastectomy on the left. The patient presented no complaints throughout the treatment. The patient developed a moderate emetic syndrome during chemotherapy. The patient has started radiation therapy with consecutive adjuvant endocrine therapy with tamoxifen for the first five years. The long-term radiation and endocrine treatment results will be assessed after three months.

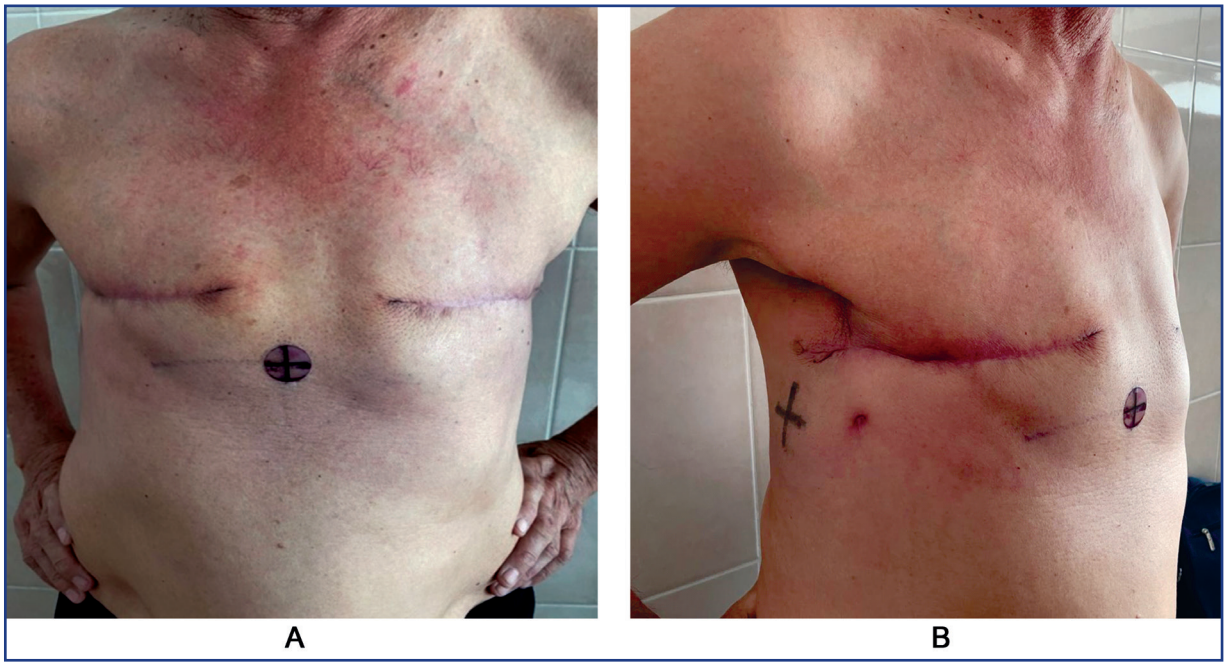

Figure 4 – Condition of the patient after combined treatment: A – front view, B – side view

Discussion: Breast cancer in men is very uncommon [6]. Due to the rare incidence of that disease in men, the literature sources, modern research, and development of new approaches for diagnostics and treatment, and the BC clinical protocols are primarily focused on female cancer. However, when making decisions about treatment in men, biological factors such as hormonal background should be considered [7].

The recent data shows that men are diagnosed with breast cancer at an average age of 67, while the average age of women with BC is 62 years. As with many cancers, the risk of developing breast cancer increases with age. Primarily, the clinical manifestation of breast cancer is a palpable formation, discharge, or bleeding from the nipples and skin retraction with penetration [8]. The following recommendations were made given the rarity of breast cancer screening in men and based on current literature data: in suspected breast cancer as a differential diagnosis, in men with Klinefelter syndrome below 25 shall pass breast ultrasonography, men after 25 shall pass mammography or digital breast tomosynthesis [9]. Other genetic disorders have been associated with an increased risk of breast cancer in men with Cowden syndrome (PTEN tumor suppressor gene), Li-Fraumeni syndrome (TP53), and Lynch syndrome (PALB2 and nonconformance repair synthesis genes) [10, 11]. Men, like women, have a higher risk of developing breast cancer if there is a history of breast cancer in relatives of the first or second degree of kinship. Studies have shown that the presence of malignant breast disease in brothers, sisters, or parents of either sex elevates the risk of breast cancer in both men and women. It was studied that the relative risk (RR) of breast cancer was the same in offspring when the father or mother was affected by the disease (RR=1.73 and 1.74, respectively), but the risk was slightly higher in women when a brother suffers rather than a sister (RR=2.48 and 1.39, respectively) [12]. In addition to a family history of breast cancer, having a BRCA mutation in men also increases the risk of breast cancer. Although the BRCA mutation is rare in men, carriers of the BRCA2 mutation have a 6% increased risk of developing the disease, and BRCA1 by 4% [11]. As in women, the standard instrumental examinations, thick-needle or fine-needle tumor aspiration biopsy (TAB), also apply to men.

About 90% of all breast tumors in men belong to invasive ductal carcinomas. Since there are no terminal lobules in the male breast unless exposed to high doses of endogenous and/or exogenous estrogens, the lobular histotype accounts for only 1.5% of invasive cancers, whereas in women, more than 10% of all breast carcinomas are lobular. Therefore, despite some of the differences with female cancer described above, men with breast cancer require systemic treatment (neoadjuvant, adjuvant, or metastatic), and the choice between chemotherapy or hormone therapy should be based on tumor biology [13, 14]. In the presented clinical case, at the 1st stage, the patient received six neoadjuvant chemotherapy courses. The local-regional approaches should include surgical and radiation treatment. In the 2nd stage, the operation to the extent of radical mastectomy by Madden

on the right and prophylactic removal of the left mammary gland have been performed [15, 16].

Conclusion: Breast cancer in men is rare, accounting for approximately 1% of all breast cancer cases and less than 1% of all neoplasia in men. The presented rare clinical case of breast cancer in a man is divided into two parts. The first article is devoted to the primary instrumental and laboratory diagnostics, clinical diagnosis, and performance of preoperative chemotherapy courses. The second part of the case demonstrates the results of the systemic treatment, surgery, and the degree of therapeutic pathomorphosis. Considering the clinical picture and anamnesis, literature data, and the clinical protocol, the multidisciplinary group recommended radiation therapy with adjuvant endocrine therapy with tamoxifen for an initial period of five years. The article shows the effectiveness of neoadjuvant chemotherapeutic and local surgical treatment. Due to the rarity of this disease, there is an urgent need for extensive studies, screening programs, and raising awareness of the male population for early detection and successful treatment of patients with that diagnosis.

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АҢДАТПА

ЕР АДАМДАР АРАСЫНДАҒЫ НАУҚАСТАРДА СҮТ БЕЗІ ОБЫРЫН ЕМДЕУ: КЛИНИКАЛЫҚ ЖАҒДАЙ*

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Өзектілігі: *Сүт безі қатерлі ісігін анықтау, емдеу және бақылау барысында ерлер арасындағы сүт безі қатерлі ісігі әйелдерге қарағанда артта қалуда. Жалпы алғанда, сүт безі қатерлі ісігі ерлер арасында сирек кездеседі, бұл скринингтің пайдалылығын шектейді, бірақ ерлерде сүт безі қатерлі ісігінің жиілігі артып келеді.*

Зерттеудің мақсаты *– химиотерапия мен хирургиялық емнің әсерінен, ер адамда сүт безі обырының клиникалық және морфологиялық көріністерінің хирургиялық емдеу нәтижелерін, типтік өзгерістерін көрсету болып табылады.*

Әдістер: *Мақалада «Оң жақ сүт безінің St III обыры (T4pN0M0), интрадуктальды компоненті, ісіну-инфильтративті түрі, жоғарғы-сыртқы локализациясы, Her2neu экспрессиясы жоқ иммуногистохимиялық люминальды В қосалқы түрі» диагнозы бар ер науқастың клиникалық жағдайы сипатталған. Негізгі жағдайы – химиотерапияның 6 неоадъювантты курсынан кейін.*

Нәтижелері: *операцияға дейінгі алты химиотерапия курсынан кейін, сүт бездерінің УДЗ өлшемдері 52,5×48,2×46,1 мм, V=60,98 см³, айқын емес жүйке контурлары бар орталықтан анықталған гипоэхогендік түзіліс бар екенін көрсетті. 2022 жылдың наурыз айындағы деректермен салыстырғанда (оң жақ сүт безінің жоғарғы сыртқы квадрантында орналасқан, контуры айқын біркелкі*

емес 9,0 см инфильтрациялық өсумен), ісік көлемінің US BI-RADS R6, L2. дейін төмендеуі байқалады. Мультидисциплинарлық кеңестің шешімімен хирургиялық ем жүргізу туралы шешім қабылданды. 2022 жылдың тамыз айында оң жақта радикалды Madden мастэктомиясы және сол жақта қарапайым мастэктомия жасалды. Операциядан кейінгі гистологиялық қорытындының нәтижесі бойынша емдік патоморфоз: индекс РКБ-2,233, РКБ-II класы.

Қорытынды: *Бұл мақалада сүт безі қатерлі ісігі бар ер адамда жүйелі және хирургиялық емдеудің нәтижелері көрсетілген. Клиникалық және анамнестикалық деректерді, әдеби деректерді, клиникалық хаттаманы ескере отырып, мультидисциплинарлық топтың шешімімен пациентке бастапқы бес жыл бойы тамоксифенмен адъювантты эндокриндік терапиямен біріктірілген сәулелік терапия ұсынылды.*

Түйінді сөздер: *Клиникалық жағдай, ерлердің сүт безі қатерлі ісігі (БК), Her2neu экспрессиясы жоқ люминальды «В» субтипі, мастэктомия, терапевтік патоморфоз, сәулелік терапия, эндокриндік терапия.*

** «Қазақстанның онкологиясы мен радиологиясы» журналында жарияланған зерттеу нәтижелерінің жалғасы, №2 (64) 2022 ж.*

АННОТАЦИЯ

ЛЕЧЕНИЕ РАКА МОЛОЧНОЙ ЖЕЛЕЗЫ У ПАЦИЕНТА МУЖСКОГО ПОЛА: КЛИНИЧЕСКИЙ СЛУЧАЙ**

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Актуальность: *В выявлении, лечении и последующем наблюдении рак молочной железы (РМЖ) у мужчин исторически отставал от РМЖ у женщин. В целом РМЖ менее распространен среди мужчин, что ограничивает полезность скрининга, однако заболеваемость РМЖ у мужчин растет.*

Цель исследования *– представить результаты хирургического лечения и типовые изменения клинических и морфологи-ческих проявлений РМЖ у мужчины под воздействием химиотерапевтического и хирургического лечения.*

Методы: *В статье описан клинический случай пациента мужского пола с диагнозом «Рак правой молочной железы St III (T4pN0M0), отечно-инфильтративная форма с внутрипротоковым компонентом, верхне-наружная локализация. Имму-ногистохимический люминальный подтип В без экспрессии Her2neu». Состояние – после 6 неоадъювантных курсов химио-терапии.*

Результаты: *после шести предоперационных курсов химиотерапии УЗИ молочных желез показало, что центрально определяется гипоэхогенное образование, с нечеткими, неровными контурами, размерами 52,5×48,2×46,1 мм, V=60,98 см^3. В сравнении с данными от марта 2022 года (отмечается наличие образования правой молочной железы, лоцируемое в верх-ненаружном квадранте, с четкими неровными контурами размером 9,0 см с инфильтрирующим ростом) наблюдается уменьшение опухолевого образования до US BI-RADS R6, L2. Решением мультидисциплинарного консилиума было решено выполнить оперативное лечение. В августе 2022 года была произведена операция в объеме радикальной мастэктомии по Маддену справа и простой мастэктомии слева. Лечебный патоморфоз по результатам послеоперационного гистологиче-ского заключения: индекс RCB-2.233, class RCB-II.*

Заключение: *В данной статье продемонстрированы результаты проведенного системного и хирургического лечения у мужчины с РМЖ. Учитывая клинико-анамнестические данные, данные литературных источников, клинического протоко-ла, решением мультидисциплинарной группы пациенту была рекомендована лучевая терапия в сочетании с адъювантной эндокринной терапией препаратом тамоксифен в течение первоначального периода в пять лет.*

Ключевые слова: *Клинический случай, рак молочной железы (РМЖ) у мужчин, люминальный подтип «В» без экспрессии Her2neu, мастэктомия, лечебный патоморфоз, лучевая терапия, эндокринная терапия.*

** Продолжение описания клинического случая, опубликованного в журнале «Онкология и радиология Казахстана», №2 (64) 2022 г.*

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THE ROLE OF PIVKA-II TUMOR MARKER IN HEPATOCELLULAR CARCINOMA: A LITERATURE REVIEW

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ABSTRACT

Relevance: *Hepatocellular carcinoma (HCC) ranks sixth among the most common malignant neoplasms in the world and accounts for about 5.6% of all human malignant neoplasms. Despite encouraging progress in the diagnosis and treatment of HCC, the prognosis remains unsatisfactory, i.e., with a 5-year overall survival rate below 10.3%. However, the survival rate can reach 50-74% if early detection and therapeutic intervention are carried out on time. However, unfortunately, about 50% of HCC cases are diagnosed at a late stage.*

The protein induced by the absence of vitamin K or antagonist-II (PIVKA-II), also known as Dez-γ-carboxyprothrombin (DCP), is another marker specific to HCC. In several studies, elevated PIVKA-II serum levels were associated with HCC. Many authors have proven the PIVKA-II applicability for HCC monitoring.

This study aimed to *compare the efficiency of alpha-fetoprotein and des-gamma-carboxyprothrombin serological markers in HCC.*

Methods: *The study included reviewing published articles on the causes of HCC and analyzing literature to compare cancer markers' efficacy, including PIVKA-II and alpha-fetoprotein (AFP), in detecting HCC.*

Results: *The published results evidence an important role of PIVKA-II in HCC early detection since PIVKA-II elevation in risk-group patients predicts HCC development in two years. Higher PIVKA-II levels can indicate a bigger tumor or a higher clinical stage. Besides, HCC patients with metastasis to the lymph nodes and distant metastasis had much higher PIVKA-II levels than non-metastatic patients. So, high PIVKA-II levels can, to a certain extent, reflect poor prognosis in HCC patients.*

Conclusion: *The reviewed publications report much higher PIVKA-II serum levels in patients with HCC than in patients with benign liver diseases or healthy people. Besides, PIVKA-II has a higher diagnostic capacity than AFP due to its higher levels, sensitivity, and specificity. Thus, we can expect high sensitivity and efficiency of the PIVKA-II tumor marker in early HCC diagnostics.*

Keywords: *Hepatocellular carcinoma, protein, liver, biomarker, serum.*

Introduction: Hepatocellular carcinoma (HCC) is the most common primary liver tumor with an aggressive course and adverse prognosis. In the case of late diagnosis and untimely treatment, the 5-year survival rate is below 15% [1]. HCC ranks 5th among the most common malignant tumors and 2nd in cancer mortality [2]. According to GLOBOCAN 2018, Kazakhstan ranks second and third in HCC incidence and mortality among Central Asian countries [3]. The highest HCC incidence and mortality are observed in the West Kazakhstan, Kyzylorda, and East Kazakhstan regions in Kazakhstan. In men, HCC incidence and mortality are twice higher as in women. HCC incidence is significantly higher in men aged 50 to 74 and women aged 55 to 79 with viral hepatitis C [4].

Due to the absence of clinical symptoms at early stages, 60% of patients are diagnosed late, often against the background of multiorgan metastasis [1, 4]. However, in early detection, the prognosis is relatively good, and the 5-year survival exceeds 70% [4-5].

There are several hypotheses for HCC carcinogenesis, but the viral theory is still dominant. Thus, the hepatitis B virus (HBV) initiates the disease development by incorporating the viral genome into the host cells of DNA, leading to translocation, point mutations, and deletions in the embedding of the virus genome. In this case, the hepatocyte DNA is reconstructed with an increase in tissue malignancy due to lower cell differentiation. The Hepatitis B surface antigen (HBsAg) suppresses the apoptosis gene p53, which is responsible for cell division suppression, leading to uncontrolled cell division. Commonly, hepatocytes express a transforming factor that induces apoptosis. In hepatitis, tumor cells lack the transforming factor α, which is suppressed by HBsAg, which leads to cell cycle disruption [6].

The prevalence of viral hepatitis B from screening in 2012 in Kazakhstan was 16.3 per 100,000 population [6]. Serological signs of past or current HBV infection are detected in about 1/3 of the global population, and 350-400 million people are chronic carriers of HBsAg [3].

The hepatitis C virus supports degenerative and necrotic hepatocyte activity. HCC is more common in patients with 1b genotype chronic viral hepatitis C, as NS5A 1b genotype HCV blocks interferon-dependent protein kinase, typically providing antiviral activity and tumor suppression. In addition, HCC can occur against congenital

liver diseases, such as hemochromatosis, α-1-antitrypsin deficiency, and tyrosinemia. Patients with these pathologies have mutations in hepatocytes genes responsible for DNA repair, cell division control, and cell apoptosis [7].

Viral hepatitis C is the leading cause of HCC in Japan, the United States, Latin America, and Europe. Every year, 2-8% of patients with chronic hepatitis C and diagnosed liver cirrhosis develop HCC. In Japan, current HCC mortality is more than threefold higher than in the mid-1970s [8, 9].

More than 6,000 cases of chronic viral hepatitis are registered annually in Kazakhstan. Of them, chronic viral hepatitis B accounts for 48%, and chronic viral hepatitis C makes up 52% of cases. The highest incidence of viral hepatitis established forms (about 87%) is registered at 30 to 60 years [7].

The third most common cause of HCC is liver alcoholic cirrhosis. In the U.S., HCC occurs in 15% of patients who consume alcohol regularly and in large doses. The main factor leading to HCC is the inflammatory process in the liver, accompanied by oxidative damage to hepatocytes [7].

Risk factors for developing HCC include:

– HBV+HCV co-infection, which increases the cumulative risk of developing HCC by 35%. HBV infection itself can lead to malignancy, even without liver cirrhosis. The five-year HCC cumulative risk in these patients ranges from 10% in the West to 15% in countries with high HCV prevalence [10];

– HCV infection, which is present in every third patient with HCC [7].

A literature review was conducted to determine the PIVKA-II efficiency as a tumor marker since early diagnosis increases the HCC treatment efficacy. The HCC prognosis depends on the tumor stage. If liver cancer is detected early, therapy after liver resection or transplantation can improve survival rates by up to 70%. However, only palliative treatment is available in advanced malignant processes, increasing patient survival by no more than one year [11].

The study aimed to compare the efficiency of alpha-fetoprotein and des-gamma-carboxyprothrombin serological markers in HCC.

Materials and methods: The study included reviewing published articles on the causes of HCC and analyzing literature to compare the efficacy of tumor markers, including PIVKA-II and alpha-fetoprotein (AFP), in detecting HCC. The sources published in English over the last five years were obtained from PubMed and Scopus databases; the review also involved domestic publications and cases interesting for evaluating the tumor markers' efficacy from a 2004 publication.

Results: Although the serum AFP is the most studied HCC marker and is considered the gold standard against which other markers are compared, about 30% of patients, especially in the disease's early stages, had an average AFP level [12]. Elevated AFP is sometimes observed in patients with liver cirrhosis or chronic hepatitis [13]. Ultrasound is an essential diagnostic tool, but its effectiveness depends on the operator's experience [12]. Accordingly, the significance of other biomarkers in diagnosing HCC, including PIVKA-II, needs to be investigated.

Currently, extrahepatic HCC lesions or multifocal tumor growth at the diagnosis is recorded in about 15% and 75% of cases, respectively. In addition, randomized controlled studies have shown that with an adequate screening at least twice a year, deaths decrease by 37% [12].

Screening methods include ultrasound, computed tomography, magnetic resonance imaging, and serological markers. In addition, we can increase the proportion of diagnosed HCC patients at an early stage and thereby increase treatment efficiency using PIVKA-II as a tumor marker.

AFP is a glycoprotein produced in the fetus's embryonic yolk sac, liver, and intestinal epithelium. This protein has a molecular mass of about 70,000 daltons and a half-life of 5-7 days. In the fetus, it performs the adult albumin functions: it transports certain substances necessary for the development of the fetus, binds estrogens, limiting their effect on the developing body, and protects against adverse impacts of the mother's immune system [13].

The reasons for AFP formation in adult patients with liver cancer have not yet been established. Embryo-specific cells are assumed to appear in a malignant tumor due to a violation of intercellular-matrix interactions. Thus, low differentiation of a new tumor cell generation resumes the process through AFP synthesis [14].

AFP has been used as a marker for diagnosing HCC since the 1970s. An increase in AFP levels of over 10 μg/L was observed in almost 75% of HCCs [15]. Serum AFP analysis is still considered the most critical marker for HCC diagnosis. This method can be used in conjunction with ultrasonography to increase diagnostic value. However, AFP values may be high in some non-malignant liver diseases (hepatitis, cirrhosis without HCC nodules) and low in some patients with HCC [16].

One of the new markers is des-gamma-carboxyprothrombin (DCT). Its level is increased in 67% of HCC patients and only 8% of patients with small tumors (<2 cm). This marker, also known as PIVKA-II (vitamin K deficiency or antagonist-II induced protein), is a pathological inactive prothrombin with insufficient carboxylation of 10 glutamic acid residues on the N-terminus, resulting from a post-translational defect of the prothrombin precursor in HCC cells. Desacarboxylated prothrombin is functionally defective due to the inability to bind calcium and phospholipids. In the case of malignant transformation in hepatocytes, the vitamin K-dependent carboxylation pathway of γ-glutamic acid is disrupted, leading to des-gamma-carboxyprothrombin (DCT) formation. Typically, PIVKA-II is absent in human serum. PIVKA-II effectively increases the detection rate of hepatocellular carcinoma so that it can be used as an adjunct to AFP. PIVKA-II is also used in the prognosis of hepatocellular carcinoma. If HCC is present, the level of this protein is much higher

than in patients with chronic hepatitis or liver cirrhosis. It has previously been argued that the sensitivity of the DCT depends on the tumor size. For example, in the case of a neoplasm larger than 5 cm, it is comparable to the sensitivity of AFP [17]. For the first time in 1984, Liebman et al. described a high level of PIVKA II in patients with initially diagnosed HCC and its recurrence. Some researchers believed that PIVKA-II was superior to AFP and could replace it in diagnosing HCC [16], but most studies did not come to that conclusion. They suggested that the combined detection of PIVKA-II and AFP could improve HCC diagnostics compared to using each biomarker separately [18].

Recently, much attention has been paid to the diagnostic role of PIVKA-II. Typically, vitamin K is necessary for synthesizing blood coagulation factors II, VII, IX, and X in the liver. The absence of vitamin K or the presence of antagonists suppresses the activity of vitamin K-dependent carboxylase, leading to impaired carboxylation of the N-terminal glutamic acid residues of blood coagulation factors. This abnormal coagulation factor cannot function as a blood clotting and is known as vitamin K deficiency prothrombin or antagonist-II (PIVKA-II) [19].

In 2009, the Japanese physicians M. Kobayashi, K. Ikeda, Y. Kawamura, et al. showed that serum levels of PIVKA-II in HCC patients were significantly higher than in patients with benign liver diseases or healthy people. Moreover, the diagnostic ability of PIVKA-II was higher than that of AFP. PIVKA-II showed higher values and greater sensitivity and specificity than AFP, as indicated by diagnostic efficacy indicators [17]. A specific increase in PIVKA-II in HCC showed PIVKA-II as a potential HCC marker. Some researchers suggested that the increased PIVKA-II levels could be caused by abnormal enzymes associated with vitamin K metabolism and generated during malignant hepatocyte transformation [18].

The studies of tumor markers showed the possibility of using PrEP for early HCC diagnosis since an increase in PrEP was observed in 67% of HCC patients. As we know, early diagnosis of HCC increases the survival rate by up to 70%.

PIVKA-II could play an important additional role for AFP, so combining PIVKA-II and AFP is more desirable. Some researchers evaluated the diagnostic value of PIVKA-II in the AFP-deficient group. In the study, PIVKA-II showed a moderate diagnostic ability for AFP-negative HCC patients, which once again proved the additional role of PIVKA-II for AFP in HCC diagnostics [18-20].

According to the articles presented in the review, PIVKA-II is more effective in HCC than other tumor markers. The collected data also suggest that PrEP with AFP might be the most efficient tumor marker.

According to the reviewed publications, a high PIVKA-II level in patients at risk indicates the development of HCC after two years. A higher PIVKA-II concentration may indicate a larger tumor volume and a higher clinical stage. Besides, HCC patients with metastasis to the lymph nodes and distant metastasis had much higher PIVKA-II levels than non-metastatic patients [21]. So, high PIVKA-II levels can reflect poor prognosis in HCC patients [22, 23].

Discussion: Thus, the diagnostic value of PIVKA-II is debatable. A correlation between PIVKA-II and AFP and whether PIVKA-II can completely replace or supplement the role of AFP in diagnosing HCC [20]. In addition, the relationship between PIVKA-II and clinical pathological characteristics, as well as the role of PIVKA-II in assessing HCC therapeutic effects, are yet to be studied. These results may contribute to a better understanding of PIVKA-II significance in HCC.

The relationship between PIVKA-II and HCC progression and prognosis has been studied. Thus, in 2017, Chinese researchers analyzed clinical and pathological characteristics, including sex, age, tumor size, number and stage, metastases, general classification, differentiation, and complications in HCC patients, and found that serum levels of PIVKA-II positively correlated with tumor stage and size. This suggests that PIVKA-II may play a role in predicting disease severity. A total of 1,016 HCC patients were detected using PIVKA-II in this study. Using the PIVKA-II tumor marker helped identify patients with primary tumors (88.7% of all examined patients); 61.3% of them had HCC metastases. PIVKA-II levels were significantly higher in patients with an advanced stage (4,650.0 mIU/mL, 667.0-33,438.0 mIU/mL) than with an early stage (104.5 mIU/mL, 61.0-348.8 Mme/mL, $P<0.001$). PIVKA-II levels were significantly higher in the relapse group than in the recovery group ($P<0.001$). A total of 1,054 PIVKA-II-positive patients without HCC were selected. Most of them had liver cirrhosis (46.3%), followed by hepatitis (20.6%) and benign nodules (15.3%).

Several studies of PIVKA-II have mentioned its role in assessing the treatment effect. Analysis of changes in serum levels of PIVKA-II in HCC patients treated surgically showed a significant difference in serum levels of PIVKA-II in HCC patients before and after surgery. This suggests the possibility of using PIVKA-II as an indicator for assessing the therapeutic effects of liver cancer surgery. In addition, changes in PIVKA-II levels after surgery were more significant than changes in AFP levels, which may be due to a shorter serum half-life of PIVKA-II (40-72 h) than that of AFP (5-7 days) [24, 25]. This evidence suggests that PIVKA-II may better reflect the treatment effects of liver cancer surgery.

Thus, PIVKA-II can be considered a promising biomarker for diagnosing HCC. However, most studies have shown no correlation between PIVKA-II and AFP in HCC, and some have shown little correlation.

Conclusion: The presented literature review on laboratory diagnostics of HCC and the use of PIVKA-II as a screening biomarker showed the relevance and timeliness of PIVKA-II determination in HCC and its significance in this disease diagnosis and prognosis. For the first time, this method was introduced into clinical diagnostics at the «National Scientific Center of Surgery named after A.N. Syzganov» JSC

at the end of 2021. Currently, the material is being collected for a complete analysis of the use of PIVKA-II in HCC. We hope to obtain and publish statistically reliable and scientifically based HCC diagnosis and prognosis results.

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АҢДАТПА

ГЕПАТОЦЕЛЛЮЛЯРЛЫҚ КАРЦИНОМАДАҒЫ PIVKAII ОНКОМАРКЕРІНІҢ РӨЛІ: ӘДЕБИЕТКЕ ШОЛУ

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Өзектілігі: *гепатоцеллюлярлық карцинома (ГЦК) әлемдегі ең көп таралған қатерлі ісіктердің арасында алтыншы орын алады және адамның барлық қатерлі ісіктерінің 5,6%-ын құрайды. ЦКБ диагностикасы мен емдеудегі үміт күттіретін прогреске қарамастан, болжам қанағаттанарлықсыз болып қалуда, яғни 5 жылдық жалпы өмір сүру деңгейі 10,3%-дан төмен. Алайда, егер ерте анықтау және емдік араласу уақтылы жүргізілсе, өмір сүру деңгейі 50-74% жетуі мүмкін. Бірақ, өкінішке орай, ЦКБ жағдайларының шамамен 50%-ы кеш сатысында диагноз қойылады.*

Зерттеу мақсаты: *ГЦК жанындағы альфа-фетопротеин және дес-гамма-карбоксипротромбин серологиялық маркерлерінің тиімділігін салыстыру.*

Әдістері: *скрининг, ультрадыбыстық зерттеу, гепатоцеллюлярлық карциноманы ерте диагностикалау үшін онкомаркерлерді қолдану.*

Нәтижелері: *онкомаркерлерге жүргізілген зерттеулер кезінде дес-гамма-карбоксипротромбин (ДКП) пайдалану кезінде деңгейінің жоғарылауы ГЦК-мен ауыратын науқастардың 67%-ында байқалатын ерте диагностика жүргізуге болатындығы атап өтілді. Гепатоцеллюлярлық карциноманы ерте диагностикалау кезінде біз білетіндей, пациенттердің өмір сүру деңгейі 70%-га дейін артады. DCP PIVKA-II ретінде де белгілі (К дәрумені немесе антагонист-II болмауынан туындаған ақуыз).*

Қорытынды: *К дәрумені немесе антагонист-II (PIVKA-II) болмауынан туындаған ақуыз, сонымен қатар дез-γ-карбоксипротромбин (DCP)-бұл ГЦК-ге тән тағы бір маркер. Сарысудағы PIVKA-II деңгейінің жоғарылауы ГЦК-мен байланысты болатын зерттеулер бар. Көптеген зерттеулер PIVKA-II ГЦК-ны бақылау үшін қолданылатынын және ұсыныста ұсынылғанын көрсетті жапондық бауыр қоғамы, PIVKA-II биомаркерінің анықтамасы өте жақсы нәтижелерге қол жеткізуге мүмкіндік береді.*

Түйінді сөздер: *гепатоцеллюлярлық карцинома, ақуыз, бауыр, биомаркер, сарысу.*

АННОТАЦИЯ

РОЛЬ ОНКОМАРКЕРА PIVKA-II ПРИ ГЕПАТОЦЕЛЛЮЛЯРНОЙ КАРЦИНОМЕ: ОБЗОР ЛИТЕРАТУРЫ

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Актуальность: *Гепатоцеллюлярная карцинома (ГЦК) занимает шестое место по распространенности среди злокачественных новообразований в мире и составляет около 5,6% всех злокачественных новообразований человека. Несмотря на обнадеживающий прогресс в диагностике и лечении ГЦК, прогноз остается неудовлетворительным, поскольку 5-летняя общая выживаемость не превышает 10,3%. Однако при раннем выявлении и своевременном лечебном вмешательстве выживаемость может достигать 50-74%. К сожалению, около 50% случаев ГЦК диагностируется на поздней стадии.*

Белок, индуцируемый отсутствием витамина К или антагонистом-II (PIVKA-II), также известный как дез-γ-карбоксипротромбин (ДКП), является маркером, специфичным для ГЦК. Есть исследования, где повышенный уровень PIVKA-II в сыворотке был связан с ГЦК. Многие авторы показали, что PIVKA-II применим для наблюдения за ГЦК.

Цель исследования *– сравнение эффективности серологических маркеров альфа-фетопротеина и дес-гамма-карбоксипротромбина при ГЦК.*

Методы: *Был проведен обзор опубликованных статей о причине возникновения ГЦК и анализ литературных данных для сравнения эффективности онкомаркеров, в частности сероlогического маркера PIVKA-II и альфа-фетопротеина (АФП), в определении ГЦК.*

Результаты: *Опубликованные данные показывают важную роль онкомаркера PIVKA-II для ранней диагностики ГЦК, поскольку повышение уровня PIVKA-II у пациентов из группы риска является индикатором развития ГЦК через два года. Более высокая концентрация PIVKA-II может указывать на больший объем опухоли и более высокую клиническую стадию. Кроме того, уровни PIVKA-II у пациентов с ГЦК с метастазами в лимфатические узлы и отдаленными метастазами были значительно выше, чем у пациентов без метастазов, поэтому высокая концентрация PIVKA-II может в некоторой степени отражать плохой прогноз у пациентов с ГЦК.*

Заключение: *Согласно включённым в анализ публикациям, уровни PIVKA-II в сыворотке у пациентов с ГЦК были значительно выше, чем уровни, наблюдаемые у пациентов с доброкачественными заболеваниями печени и у здоровых людей. Более того, диагностическая способность PIVKA-II выше, чем у АФП: PIVKA-II показал более высокие значения и большую чувствительность и специфичность, чем у АФП. Таким образом, можно предположить высокую чувствительность и эффективность онкомаркера PIVKA-II при ранней диагностике ГЦК.*

Ключевые слова: *гепатоцеллюлярная карцинома (ГЦК), белок, печень, биомаркер, сыворотка.*

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THE USE OF IMMUNE CHECKPOINT INHIBITORS IN TREATING LOCALLY ADVANCED AND METASTATIC GASTRIC CANCER: A LITERATURE REVIEW

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ABSTRACT

Relevance: *Gastric cancer is one of the most common malignant neoplasms and ranks fifth in cancer incidence worldwide. The only curative approach to localized gastric cancer is radical surgery with or without prior chemotherapy. But chemotherapy is the main treatment method for metastatic or locally advanced gastric cancer. Later stages of gastric cancer are highly resistant to chemotherapy; therefore, there is a need for modern treatment approaches. Particular attention is paid to therapy for metastatic/locally advanced gastric cancer.*

The study aimed to *describe the possibilities of using immune checkpoint inhibitors (ICIs) to treat metastatic or locally advanced gastric cancer.*

Methods: *The data from modern literary sources of recent years were studied using specialized sci-entific search engines: Scopus, PubMed, Google Scholar, and Web of Science for the possibility of promising application of various immunotherapeutic approaches in treating metastatic or locally advanced gastric cancer.*

Results: *The article describes modern methods of treatment of metastatic or locally advanced SC using ICIs, including PD-1, PD-L1, and CTLA-4, demonstrates the mechanisms of immunological surveillance, characteristics of PD-1, PD-L1, CTLA-4, and their significance in suppressing the T-cell response. The effectiveness of using ICIs, particularly PD-1, PD-L1, and CTLA-4, has been es-tablished in the first and subsequent lines of therapy.*

Conclusion: *ICIs are a recent finding in antitumor therapy. Frequent resistance of gastric cancer to chemotherapy urges the use of ICIs to treat advanced gastric cancer.*

Keywords: *Immunotherapy of metastatic or locally advanced gastric cancer, immune checkpoint in-hibitors (ICIs), PD-1, PD-L1, CTLA-4, immune response mechanisms.*

Introduction: Gastric cancer (GC) is one of the most common malignant neoplasms and ranks fifth in the structure of cancer incidence in the world [1]. The only curative approach to localized gastric cancer is radical surgery with or without prior chemotherapy. However, with metastatic or In locally advanced gastric cancer, chemotherapy is the primary treatment [2]. According to modern sources and clinical guidelines, the use of combined chemotherapy regimens increases the objective response rate (ORR) and overall survival (OS) compared with monotherapy. At the same time, the use of combined chemotherapy regimens does not give significant practical results due to their high toxicity. In the later stages of gastric cancer, there is high resistance to chemotherapy, so there is a need to search for modern treatment approaches. This article studies the use of immune checkpoint inhibitors (ICIs) in therapy, in particular, PD-1 (Programmed cell death-1), PD-L1 (Programmed death-ligand 1), CTLA-4 (Cytotoxic T – lymphocyte-associated protein 4). Monoclonal antibodies that block PD-1, PD-L1, and CTLA-4 are currently the most studied [3]. ICIs can be used as monotherapy or as part of combination therapy. This drug therapy has become a breakthrough in treating solid tumors, including gastric and colorectal cancer [4]. This review explores the prospects and emerging pathways for using immunotherapy to treat gastric cancer, especially in its metastatic/locally advanced forms.

The study aimed to describe the possibilities of using immune checkpoint inhibitors (ICI) to treat metastatic or locally advanced SC.

Materials and methods: The data from peer-reviewed sources published over the past ten years and indexed in the scientific search engines Scopus, PubMed, Scholar, Web of Science, and Google were studied. A total of 89 sources, including research articles and NCCN Clinical Guidelines in Oncology (NCCN Guidelines®), were analyzed for study keywords. Of these, 18 sources were included in the analysis, which considered the mechanisms

of avoidance of protective immune responses by the tumor cell and the use of immunotherapy in treating metastatic or locally advanced gastric cancer.

Results:

Immunosurveillance

Every day in the human body, cells are formed with signs of tumor cells, which are destroyed by the human immune system due to the body's immunological control over tumor cells [5]. Without exception, all tumor cells are potentially immunogenic and trigger the mechanisms of the immune system to recognize and destroy cancer cells [6]. One of these well-known subpopulations is T-killers, which can destroy defective body cells. They are also called cytotoxic lymphocytes (CD8+T lymphocytes).

Immunoscape

However, the immune system does not always have sufficient influence because the tumor has properties that prevent the immune system from recognizing and destroying cancer cells. The mechanism for avoiding immunological surveillance may be the production of several co-inhibitory receptors by the cancer cell [4, 7]. For example, PD-1 and CTLA-4 receptors bind to tumor cell ligands (PD-L1 ligand) and inhibit T cell activation. Figure 1 shows the presence of the PD-1 protein on the surface of T-lymphocytes.

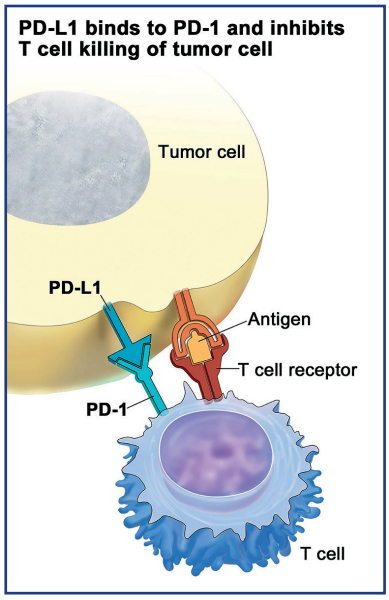

Figure 1 – Expression of a transmembrane protein, PD-L1 ligand, on tumor cells [8]

Antitumor effect of ICI immunity in the treatment of solid tumors, including gastric cancer

Monoclonal antibodies that block ligands or receptors of immune checkpoint inhibitors were developed to overcome this phenomenon. ICIs inhibit negative T-cell co-stimulation, resulting in a T-cell response. Thus, the antitumor effect is achieved due to the activation of one's immune system and not through the effect on tumor cells (Figure 2).

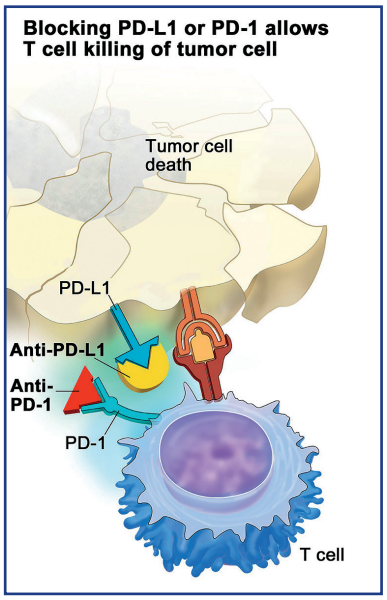

Figure 2 – ICIs' mechanisms of action [9]

Currently, ICIs provide reliable clinical results in treating metastatic or locally advanced gastric cancer [10].

Immunotherapy in anti-PD-1/PD-L monotherapy

In the ATTRACTION-2 phase III trial, anti-PD-1 ICIS (nivolumab) was used as monotherapy in patients with locally advanced or metastatic gastric cancer after two or more lines of chemotherapy. Improved OS compared to placebo (median OS 5.26 vs. 4.14 months). The median time to progression (TTP) was 1.61 months vs. 1.45 months. The ORR was 11.2% vs. 0%; p<0.0001. These results led to the approval of nivolumab in Asian countries. The analysis showed that the expression status of PD-L1 on tumor cells did not affect the OS of patients with locally advanced or metastatic gastric cancer in the phase III ATTRACTION-2 study. Of the undesirable effects, there was a decrease in appetite, diarrhea, and general fatigue [11].

In the KEYNOTE-059 phase II study, three cohorts of patients with advanced gastric cancer/CEC were identified who received three or more lines of chemotherapy. We want to focus on the first largest cohort of patients (n=259) who received anti-PD-1 ICI therapy in mono mode (pembrolizumab) as the third and subsequent lines of therapy. The ORR was 15.5% for patients with PD-L1-positive tumors (CPS≥1) and 6.4% for patients with CPS<1. The median OS was 5.6 months [12].

In the JAVELIN 300 phase III study, an anti-PD-L1 antibody (avelumab) showed no improvement in OS compared with third-line chemotherapy in patients with locally advanced or metastatic gastric cancer [13].

The KEYNOTE-061 phase III randomized trial studied the efficacy of an ICI drug (pembrolizumab) compared with chemotherapy in patients with metastatic PD-L1 CPS≥1 with locally advanced or metastatic gastric cancer after 1st line chemotherapy. The median OS was 9.1 months when using ICI vs. 8.3 months during chemotherapy [14].

In the ATTRACTION-02 Asian phase III study, the role of nivolumab in the treatment of advanced gastric cancer after two lines of therapy was evaluated in 493 patients, regardless of PD-L1 status. In patients treated with nivolumab compared with placebo, the ORR was 11.4%, with an improvement in OS (median OS, 5.3 vs. 4.1 months). After one year, 26.2% of patients treated with nivolumab were alive compared to 10.9% in the placebo group [11]. Based on these results, nivolumab was approved as a monotherapy in Japan in 2017. In Europe, the approval was rejected since the population included only patients from Asian countries.

In the KEYNOTE-012 study (the first trial of an anti-PD-1 antibody for the treatment of gastric cancer), pembrolizumab was used in the second and subsequent lines to treat metastatic gastric cancer, with an objective response rate of 22%, a median OS of 11.4 months was obtained. [15].

Anti-PD-1/PD-L1 antibodies plus chemotherapy

In the KEYNOTE-062 study, chemotherapy in combination with anti-PD-L1 (pembrolizumab) showed no benefit in terms of OS and TTP in both populations (CPS≥1 and CPS≥10). However, the ORR was higher in the pembrolizumab plus chemotherapy group (49% vs. 37% for CPS≥1).

ESMO 2020, ASCO 2021, and ASCO – GI 2022 presented significant results from CHECKMATE-649, a global phase III trial of first-line combination immunotherapy of PD-1 co-inhibitors (nivolumab) and CTLA-4 (ipilimumab) without chemotherapy and CTLA-4 (ipilimumab) in combination with chemotherapy vs. chemotherapy alone. The large population of 1581 patients with locally advanced gastric cancer (histological type adenocarcinoma) included 24% Asians and 76% non-Asians. 60% of patients treated with chemotherapy (n=955) had a PD-L1 CPS ≥ 5. Combination treatment with CTLA-4 (ipilimumab) plus chemotherapy for PD-L1 CPS≥5 provided a significant improvement in median OS (14, 4 months vs. 11.1 months in patients receiving chemotherapy alone). The median TTP was 7.7 months vs. 6.0 months. Survival rates at 12 months with PD-L1 CPS≥5 were significantly higher in the nivolumab plus chemotherapy combination group compared to chemotherapy alone (57% vs. 46%). All CPS≥5 subgroups improved ORR in response to nivolumab plus chemotherapy. The combination of nivolumab plus ipilimumab without chemotherapy showed no clear benefit in terms of OS compared with chemotherapy alone.

Based on these results, the Food and Drug Administration (FDA) and Taiwan food and drug Administration (TFDA) have approved nivolumab in combination with chemotherapy in patients with advanced/metastatic gastric cancer regardless of PD-L1 CPS status in the US and Taiwan, respectively. In Europe, the European Medicines Agency (EMA) has approved nivolumab in combination with chemotherapy in patients with PD-L1 CPS≥5. These results allow patients with advanced or metastatic gastric cancer to access promising, effective ICI immune response therapy in a first-line setting.

The ORIENT-16 Asian phase III trial studied a placebo-controlled PD-1 inhibitor (sintilimab) in combination with chemotherapy (XELOX) in 650 patients with advanced gastric adenocarcinoma (61% with PD-L1 CPS≥5). As presented at ESMO 2021, early results show a survival benefit of combination therapy in all randomized patients compared to chemotherapy plus placebo (median OS 15.2 vs. 12.3 months), with longer TTP and higher ORR [16]. This effect was even more evident in the group of patients with PD-L1 CPS≥5 tumors (median OS 18.4 vs. 12.9 months) [16].

The JAVELIN Gastric 300 trial compared avelumab with chemotherapy as a third-line treatment in patients with advanced gastric cancer. In 371 randomized patients, the primary endpoint (improvement in OS: median OS 4.6 vs. 5.0 months) and the secondary endpoints of OS and ORR were not met. However, avelumab was safer than chemotherapy [15].

Anti-PD-1 antibody plus anti-CTLA4 antibody

The CheckMate-032 study compared the ORR of nivolumab 1 mg/kg plus ipilimumab 3 mg/kg (ORR – 24%) with nivolumab 3 mg/kg plus 3 mg/kg . kg of ipilimumab (ORR – 12%) [17].

The CheckMate-649 phase III study included a cohort treated with nivolumab (1 mg/kg) and ipilimumab (3 mg/kg) vs. chemotherapy. The combination of nivolumab plus ipilimumab did not improve OS compared with chemotherapy in patients with PD-L1 CPS≥5 (median 11.2 months vs. 11.6 months). Regardless of PD-L1 expression, a combination of nivolumab plus ipilimumab produced a median OS of 2.8 months compared with 6.3 months after chemotherapy. ORR was lower in the nivolumab plus ipilimumab group (27%) compared with chemotherapy (47%) for CPS≥5 in all randomized populations.

The ATTRACTION-6 phase III trial is currently underway. Study of the combination of nivolumab (1 mg/kg) with ipilimumab and chemotherapy vs. chemotherapy. The study is being conducted in Asian countries.

The negative side of immunotherapy is immune-mediated adverse events, including nephrotoxicity, cardiotoxicity, gastric toxicity, and damage to lung tissues, skin, and endocrine glands [18].

Discussion: Gastric cancer treatment is a complex task that requires a multidisciplinary approach for optimal treatment. In particular, special attention is paid to the treatment of metastatic/ locally advanced gastric cancer. Immunotherapy is a new anticancer treatment that uses antitumor antibodies (our article presents the most studied ICIs, such as PD-L1 and CTLA-4). Immunotherapy is a rapidly growing area of research in treating gastric cancer. The approval of ICIs in patients with progressive gastric cancer expands the existing treatment options and represents a viable option for personalized therapy. Many studies continue to assess the possibility of using ICIs to treat locally advanced or metastatic gastric cancer. Ongoing phase II and III trials give

patients access to immunotherapy in every line of therapy. Combination therapy with nivolumab and chemotherapy provided a clinically significant improvement in OS as first-line therapy in all patients with advanced gastric adenocarcinoma (CPS≥5). It was approved for use in Europe, the USA, Taiwan, and other countries. As a third-line drug, Nivolumab prolonged OS compared to a placebo and was approved in Japan. In addition, pembrolizumab significantly prolonged the duration of a positive response to immunotherapy, leading to its approval for patients with PD-L1 CPS≥1 tumor in the United States. Today, the efficacy of different biomarkers (such as MSI and TMB) is studied in the personalized treatment of locally advanced or metastatic gastric cancer.

Conclusion: ICIs are the main valuable recent success in anticancer therapy. Their use has led to significant results in treating tumor diseases and improved patient prognosis. ICIs are the preferred option for gastric cancer, which is often resistant to chemotherapy. ICIs are included in various gastric cancer treatment regimens currently studied in many clinical trials. Other promising biomarkers, such as MSI and tumor mutation load, have been isolated in addition to PD-L1 expression. Searching for different biomarkers of ICI efficacy is required to achieve better treatment outcomes.

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АҢДАТПА

ЖЕРГІЛІКТІ ТАРАЛҒАН ЖӘНЕ МЕТАСТАЗДЫҚ АСҚАЗАН ОБЫРЫН ЕМДЕУДЕ БАҚЫЛАУ НҮКТЕСІ ИНГИБИТОРЛАРЫН ҚОЛДАНУ: ӘДЕБИЕТТЕРГЕ ШОЛУ

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Өзектілігі: *Асқазанның қатерлі ісігі (ҚІ) ең көп таралған қатерлі ісіктердің бірі болып табылады және әлемде қатерлі ісік ауруларының арасында бесінші орында. Асқазанның оқшауланған қатерлі ісігін емдеудің жалғыз әдісі – алдын ала химиотерапиямен немесе радикалды хирургия. Бірақ, метастаздық немесе жергілікті дамыған асқазан обырында химиотерапия негізгі ем болып табылады. Асқазан қатерлі ісігінің соңғы сатыларында химиотерапияға төзімділігі жоғары, сондықтан заманауи емдеу тәсілдерін іздеу қажет. Асқазанның метастаздық/жергілікті асқынған обырын емдеуге ерекше көңіл бөлінеді.*

Зерттеудің мақсаты *метастаздық немесе жергілікті асқынған асқазан обырын емдеу үшін иммундық бақылау нүктелерінің ингибиторларын (БНИ) пайдалану мүмкіндіктерін сипаттау болып табылады.*

Әдіс-тәсілдері: *арнайы ғылыми іздеу жүйелері арқылы, соңғы жылдардағы заманауи әдебиет дереккөздері бойынша зерттелді: Scopus, PubMed, Google Scholar, Web of science, метастаздық немесе жергілікті асқынған асқазан обырын емдеуде иммунотерапияның әртүрлі тәсілдерін ұтымды қолдану мүмкіндігі үшін.*

Нәтижелер: *Мақалада метастаздық немесе жергілікті асқынған асқазан обырын АКТ көмегімен емдеудің заманауи әдістері сипатталған, соның ішінде PD-1, PD-L1, CTLA-4, иммунологиялық қадағалау механизмдері, PD-1, PD-L1, CTLA- 4 сипаттамалары көрсетілген және олардың Т-жасушасының супрессиясына жауабының маңыздылығы. БНИ-ды қолданудың тиімділігі, атап айтқанда, PD-1, PD-L1, CTLA-4, терапияның бірінші және кейінгі бағыттарында да белгіленді.*

Қорытынды: *БНИ ісікке қарсы терапиядағы соңғы жылдары ашылған жаңалық. Асқазан қатерлі ісігінің химиотерапияға жиі төзімділігі нәтижесінде, БНИ-ды асқазанның кеш сатысындағы қатерлі ісігін емдеуде қолданған жөн.*

Түйінді сөздер: *Метастатикалық немесе жергілікті асқынған асқазан қатерлі ісігінің иммунотерапиясы, бақылау нүктесі ингибиторлары (СРТ), PD-1, PD-L1, CTLA-4, иммундық жауап механизмдері.*

АННОТАЦИЯ

ПРИМЕНЕНИЕ ИНГИБИТОРОВ КОНТРОЛЬНЫХ ТОЧЕК В ЛЕЧЕНИИ МЕСТНОРАСПРОСТРАНЕННОГО И МЕТАСТАТИЧЕСКОГО РАКА ЖЕЛУДКА: ОБЗОР ЛИТЕРАТУРЫ

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Актуальность: *Рак желудка (РЖ) является одним из самых распространенных злокачественных новообразований и занимает пятое место в структуре онкозаболеваемости в мире. Единственным лечебным подходом к локализованному РЖ является радикальная операция с предшествующей химиотерапией или без нее. Но при метастатическом или местнораспространенном РЖ химиотерапия является основным методом лечения. На поздних стадиях РЖ наблюдается высокая резистентность к химиотерапии, в связи с чем существует необходимость поиска современных подходов лечения. Особое внимание уделяется терапии при метастатическом/местнораспространенном РЖ.*

Цель исследования *– описать возможности применения ингибиторов контрольных точек иммунитета (ИКТ) для лечения метастатического или местнораспространенного РЖ.*

Методы: *Были изучены данные современных литературных источников последних лет с использованием специализированных научных поисковых систем: Scopus, PubMed, Google Scholar, Web of science, для возможности перспективного применения различных подходов иммунотерапии в лечении метастатического или местнораспространенного РЖ.*

Результаты: *В статье описаны современные методы лечения метастатического или местнораспространенного РЖ с использованием ИКТ, включая PD-1, PD-L1, CTLA-4, продемонстрированы механизмы иммунологического надзора, характеристики PD-1, PD-L1, CTLA-4 и их значение в супрессии Т-клеточного ответа. Установлена эффективность применения ИКТ, в частности PD-1, PD-L1, CTLA-4, как в первой, так и последующих линиях терапии.*

Заключение: *ИКТ являются находкой последних лет в противоопухолевой терапии. В результате частой резистентности РЖ к химиотерапии, целесообразно использовать ИКТ в терапии РЖ поздних стадий.*

Ключевые слова: *Иммунотерапия метастатического или местнораспространенного РЖ, ингибиторы контрольных точек (ИКТ), PD-1, PD-L1, CTLA-4, механизмы иммунного ответа.*

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