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# Южно-Российский онкологический журнал

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# South Russian Journal of Cancer

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РЕЦЕНЗИРУЕМЫЙ НАУЧНО-ПРАКТИЧЕСКИЙ

# Южно-Российский онкологический журнал

Журнал входит в рекомендованный ВАК РФ перечень рецензируемых научных журналов и изданий для опубликования основных научных результатов диссертаций на соискание учёной степени кандидата и доктора наук.

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# CONTENTS

# СОДЕРЖАНИЕ

South Russian Journal of Cancer. 2025. Vol. 6, No. 2. P. 6-13
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ORIGINAL ARTICLE



# The assessment of the cytotoxic activity of 2-(1,1-dimethyl-1H-benzo[e]indolin-2-yl)-5,6,7-trichloro-1,3-tropolone against the human glioblastoma U87 MG cell line

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## ABSTRACT

**Purpose of the study.** To study the cytotoxic effect of 2-(1,1-dimethyl-1H-benzo[e]indolin-2-yl)-5,6,7-trichloro-1,3-tropolone (JO-122 (2)) on the U87 MG cell line.

**Materials and methods.** The investigation of the cytotoxic effect of synthesized tropolone JO-122 (2) was performed using the standard MTT colorimetric assay on the human glioblastoma cell line U87 MG. Test substance samples were prepared by sequential twofold dilutions of the original stock solution with concentrations of 24 μM. Temozolomide was used as a reference drug, and its tested doses fell in the range of 250 to 0.4883 μM. Incubation time after the addition of the substances were 24, 48, and 72 hours. The statistical processing of the obtained data was carried out using Microsoft Excel 2013 and Statistica 10 software.

**Results.** The cytotoxic effect of 2-(1,1-dimethyl-1H-benzo[e]indolin-2-yl)-5,6,7-trichloro-1,3-tropolone on the U87 MG cell line was investigated in the study. The assessment of cytotoxicity showed that at all investigated doses of tropolone, there was a statistically significant inhibition of cell growth in the U87 MG cell line. After 24, 48, and 72 hours, the necessary minimum concentration of JO-122 (2) for suppressing tumor cell growth was 3 μM, 0.0469 μM, and 0.1875 μM, respectively.

The comparison drug showed less pronounced suppression of tumor cell growth compared to tropolone. For an incubation time of 24 hours, no significant decrease in cell viability was observed in any of the tested concentrations. The minimum concentration of Temozolomide required to inhibit U87 MG cell culture growth was obtained after 72 hours and was 3.9063 μM.

**Conclusion.** The conducted research demonstrated that both substances exhibited concentration-dependent toxicity towards the human glioblastoma cell line. However, tropolone JO-122 (2) showed a more pronounced ability to suppress the growth of the U87 MG cell line.

**Keywords:** glioblastoma, tropolone, U87 glioblastoma cell line, MTT assay, cytotoxicity assay

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**ОРИГИНАЛЬНАЯ СТАТЬЯ**

# Оценка цитотоксического действия 2-(1,1-диметил-1h-бензо[e]индолин-2-ил)-5,6,7-трихлор-1,3-трополона в отношении клеточной линии U87 MG глиобластомы человека

**Д. В. Ходакова[1]✉, Н. С. Кузнецова[1], С. Ю. Филиппова[1], А. С. Гончарова[1], А. В. Галина[1], С. В. Гурова[1], Е. А. Гусаков[2], Ю. А. Саяпин[3], Э. Е. Росторгуев[1]**

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## РЕЗЮМЕ

**Цель исследования.** Изучить цитотоксический эффект 2-(1,1-диметил-1h-бензо[e]индолин-2-ил)-5,6,7-трихлор-1,3-трополона (JO-122 (2)) на клеточной линии глиобластомы человека U87 MG.

**Материалы и методы.** Исследование цитотоксического эффекта трополона JO-122 (2) было выполнено колориметрическим анализом с применением 3-[4,5-диметилтиазол-2- ил]-2,5-дифенилтетразолия бромида (МТТ-тест) на клеточной линии глиобластомы человека U87 MG. Образцы тестируемого вещества были подготовлены путем последовательных двукратных разведений исходного стокового раствора с концентраций 24 мкМ. В качестве препарата сравнения был использован Темозоломид, его исследуемые дозы находились в диапазоне 250–0,4883 мкМ. Время инкубации после добавления веществ: 24, 48 и 72 ч. Статистическая обработка полученных была проведена в программах Microsoft Excel 2013 и Statistica 10.

**Результаты.** В работе был исследован цитотоксический эффект трополона JO-122 (2) на клеточную линию U87 MG. Оценка цитотоксичности показала, что при исследуемых дозах трополона наблюдалось статистически значимое ингибирование роста клеток линии U87. Через 24, 48 и 72 часа необходимая минимальная концентрация JO-122 (2) для подавления роста опухолевых клеток составила 3 мкМ, 0,0469 мкМ и 0,1875 мкМ соответственно.

Препарат сравнения показал менее выраженное подавление роста опухолевой линии в сравнении с трополоном. Для времени инкубации 24 часа не наблюдалось достоверного снижения жизнеспособности клеток ни в одной из исследуемых концентраций. Минимальная концентрация Темозоломида, необходимая для ингибирования роста клеток культуры U87 MG, была получена через 72 часа и составила 3,9063 мкМ.

**Заключение.** В результате проведенного исследования было показано, что оба вещества продемонстрировали зависящую от концентрации токсичность в отношении клеточной линии глиобластомы человека. Однако трополон JO-122 (2) показал более выраженную способность подавлять рост культуры U87 MG.

**Ключевые слова:** глиобластома, трополон, опухолевая культура клеток U87, МТТ-тест, оценка цитотоксичности

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## INTRODUCTION

Malignant primary brain tumors originate from the tissues that make up the central nervous system and its membranes and are dangerous types of neoplasms. This is due to both, the deterioration of cognitive functions and the quality of life of patients in general, and to an extremely unfavorable prognosis [1]. The causes of primary brain malignancies may be genetic abnormalities, changes in metabolism or hormonal background, environmental influences, ionizing radiation, viral infections or injuries, however, to date, the pathogenesis of brain tumors has not been fully elucidated [2].

Among malignant primary brain tumors, glioblastoma (GBM) is the most common, characterized by rapid progression over several months, as well as, like most gliomas, diffuse growth with invasion into surrounding normal brain tissues [1]. GBM treatment includes neurosurgery, fractional radiation and chemotherapy. One of the standard antitumor drugs widely used in GBM treatment is temozolomide (TMZ), which has a cytostatic effect, as well as targeted drugs such as bevacizumab (vascular endothelial growth factor inhibitor), dabrafenib and vemurafenib (BRAF kinase inhibitors with activating mutations in the V600E codon) [3], however, the effectiveness of treatment is very low. The median overall survival of patients with GBM does not exceed 15 months [4]. Therefore, at the present, the urgent task is to develop new drugs for the treatment of GBM.

In recent years, tropolone alkaloids (tropolones), which can have antioxidant, antibacterial, anti-inflammatory, and antitumor effects, have been of great interest in this aspect. Among the proposed mechanisms of antitumor activity of tropolones and their derivatives are activation of caspases-3 and -9, inhibition of tubulin polymerization, inhibition of matrix metalloproteinases and histone deacetylases, induction of apoptosis, and other actions [5]. The most studied tropolones are β-thujaplicin (hinokitiol), colchicine, and colhamine. The studies of foreign scientists have shown their cytotoxic effect on some tumor lines [6–8].

It was previously found that 2-(1,1-dimethyl-1h-benzo[e]indoline-2-yl)-5,6,7-trichloro-1,3-tropolone (JO-122(2)) has cytotoxic activity against skin cancer cell culture A431 and lung cancer H1299 [9]. In this regard, it was suggested that this tropolone may have a cytotoxic effect on other tumor cell lines.

**Purpose of the study:** to study the cytotoxic effect of 2-(1,1-dimethyl-1h-benzo[e]indoline-2-yl)-5,6,7-trichloro-1,3-tropolone (JO-122(2)) on the human glioblastoma cell line U87 MG.

## MATERIALS AND METHODS

2-(1,1-dimethyl-1h-benzo[e]indoline-2-yl)-5,6,7-trichloro-1,3-tropolone with the non-commercial name JO-122 (2) was synthesized at the Research Institute of Physical and Organic Chemistry, Southern Federal University. The substance under study belongs to the compounds of the 2-hetaryl-1,3-tropolones family. It is a yellow powder formed because of several stages of the expansion reaction of the o-quinone cycle [9].

The cytotoxic effect of tropolone JO-122 (2) was studied on a culture of human glioblastoma U87 MG cells, which is widely used in biological research related to the study of brain cancer. Tumor cells were cultured in DMEM medium (Gibco, USA) with the addition of 10 % fetal bovine serum (BioloT, Russia), 2 mM L-glutamine (PanEco, Russia) and an antibiotic (100 u/ml penicillin, 100 mg/ml streptomycin, BioloT, Russia) at a temperature of 37 °C and an atmosphere of 5 % $CO_2$. The U87 MG culture was replanted 2–3 times a week to achieve 80 % monolayer confluence.

The viability of tumor cells was analyzed with use of the MTT colorimetric test. For this purpose, the U87 MG cell culture was seeded into 96-well plates at a concentration of $5 \times 10^3$ cells per well. A day later, after attaching tumor cells to the tablet, a solution of tropolone JO-122 (2) was added to the wells in concentrations of 24, 12, 6, 3, 1.5, 0.75, 0.375, 0.1875, 0.0938, 0.0469 μm with further incubation under standard conditions in three time intervals – 24, 48 and 72 hours. Then, the medium with the test substance was replaced with a medium without serum and 20 μl of a working solution of 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (Maclin Inc., China) was added. After 2 hours of incubation, the medium was removed, 100 μl of DMSO was added to each well (BioloT, Russia),

pipetted, and then incubated in a thermostat for 5 minutes. The optical density was then measured using a Stat Fax 2100 microplate reader (Awareness Technology, USA) at a wavelength of 540 nm. DMSO at a concentration of 1 % was used as a control. Temozolomide was used as a comparison drug in concentrations of 250, 125, 62.5, 31.25, 15.625, 7.8125, 3.9063, 1.9531, 0.9766, 0.4883 μm. In total, there were 8 repetitions for each experience option. The experiment was performed three times.

The effect of tropolone on the distribution of the cell population by phases of the cell cycle was evaluated using an ADAMII LS analyzer (Nano Entek, Korea). Previously, JO-122 (2) was introduced into the U87 MG cell culture at concentrations of 2, 1, and 0.5 μm and incubated for 24 hours. At the end of incubation, the cells were washed with a solution of phosphate-salt buffer. Propidium iodide was added in equal volume to an aliquot containing 106 washed pipetted cells, and the sample was placed on an ADAMII slide. The analysis was performed by ADAMII LS software. For control of each concentration, the experiment was repeated three times.

**Statistical analysis**

Statistical data processing was performed using Microsoft Excel 2013 and Statistica 10 software. The IC50 concentration of tropolone, which caused 50 % death of tumor cells, was determined for a time interval of 72 hours by constructing dose-effect curves. A comparative analysis of the values was performed using the Student's t-test at a confidence level ($p < 0.05$). When making multiple comparisons, the Bonferroni correction was used.

## STUDY RESULTS AND DISCUSSION

Despite the progress in the treatment of cancer, glioblastoma is one of the most aggressive and resistant to existing types of tumor therapy. Therefore, the search and testing of new substances with antitumor potential is an urgent task.

To assess the cytotoxic effect of tropolone JO-122 (2) on glioblastoma, a DNA analysis was performed on the human glioblastoma cell line U87 (Fig. 1).

The minimum concentration of JO-122 (2) at which there was a statistically significant inhibition of tumor cell growth compared with the control at incubation times of 24, 48 and 72 hours was 3 μm, 0.0469 μm and 0.1875 μm, respectively. With an increase in the concentration of the test substance, the proportion of living cells in the culture decreased naturally, which indicates the dose-dependent nature of the action of the test compound.

Temozolomide is known to be used for the treatment of glioblastoma after surgical resection [2, 3]. Therefore, this drug was chosen as a reference drug during the MTT test (Fig. 2).

Inhibition of cell growth in U87 culture at an incubation time of 48 hours after the addition of Temozolomide occurred at a concentration of 62.5 microns, and at 72 hours – 3.9063 μm and increased as the dose of the drug increased. 24 hours after exposure to the reference drug, there was no significant decrease in cell viability in any of the studied concentrations.

During this work the IC50 of substances was also compared at an incubation time of 72 hours (Fig. 3).

At an exposure time of 72 hours, both substances demonstrated dose-dependent toxicity to U87 MG cells. The IC50 value for JO-122(2) was 1.9559 microns, and for Temozolomide it was 191.824 microns, which is significantly higher than that of tropolone. This indicates a more pronounced ability of JO-122 (2) to inhibit the growth of U87 MG culture cells.

Cell cycle assessment using a cell analyzer showed that incubation for 24 hours with JO-122 (2) at concentrations of 2 μm, 1 μm and 0.5 μm for U87 MG culture showed a decrease in the percentage of cells in the G1 phase and an increase in cells in the G2/M phases of the cell cycle, suggesting induction of apoptosis (Table 1).

The obtained data is comparable with the results of other scientists. For example, in the work of Ma QG et al. [10], the antiproliferative activity of 9 new tropolones and 14 known tropolone derivatives was investigated. Of all the candidates, 5 demonstrated moderate antiproliferative activity *in vitro* against the following human tumor cell lines: HGC-27, MDA-MB-231, A-549, HCT-116, and A2780, with IC50 values ranging from 0.5 ± 0.2 to

15.5 ± 2.7 μm. Balsa LM et al. [11] demonstrated a stronger cytotoxic effect of tropolone copper (II) than when exposed to cisplatin against human breast cancer cells cultured in 2D and 3D. The IC50 for MCF7 culture was 5.2 ± 1.8 μm, for MDA-MB-231–4.0 ± 0.2 μm. In a study by Haney SL et al. [12], the antitumor effect of α-substituted tropolone was evaluated on five human osteosarcoma cell lines (143B, CAL-72, HOS, MG-63, and SaOS-2). To varying degrees, 72-hour incubation with the test substance induced concentration-dependent cytotoxicity in all 5 cell lines, with the HOS cell line being the most sensitive (IC50 = 0.67 μm) and SaOS-2 being the least sensitive (IC50 = 5.93 μm). The authors believe that tropolone leads to activation of the unfolded protein response pathway (UPR), which in turn leads to induction of caspase-dependent cell death.

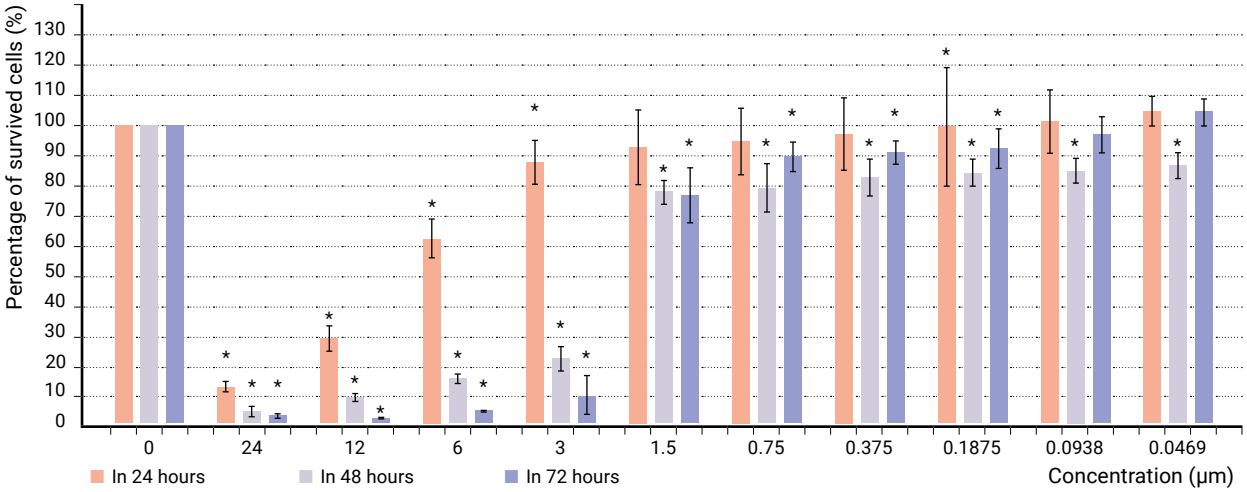


Fig. 1. The effect of tropolone JO-122 (2) on the survival of U87 tumor cells. The data is expressed as an average ± standard deviation.
Note: * – the differences are statistically significant at $p < 0.05$ compared to the control

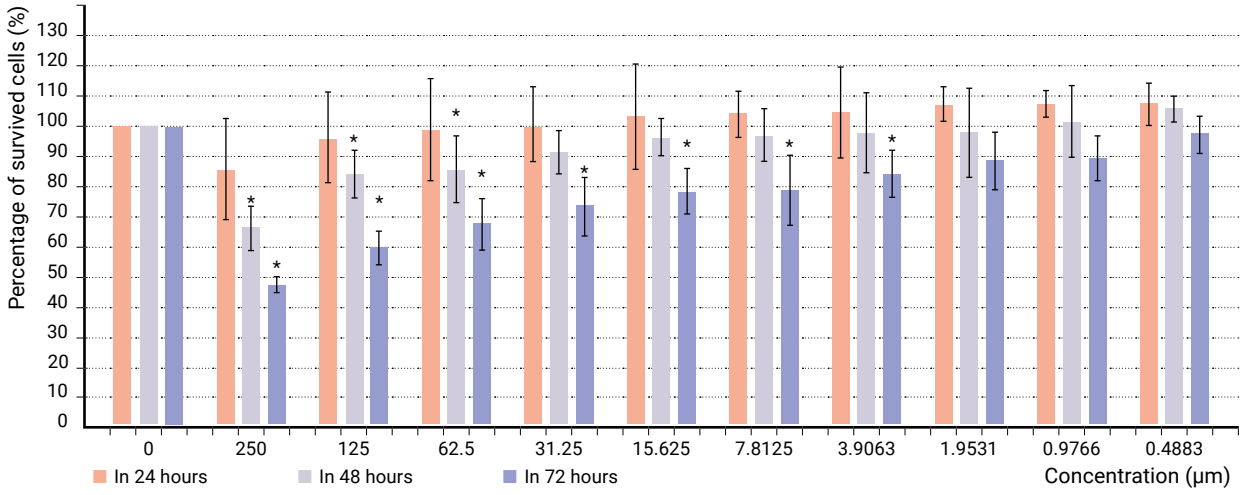


Fig. 2. The effect of Temozolomide on the survival of U87 MG tumor cells. The data is expressed as an average ± standard deviation.
Note: * – the differences are statistically significant at $p < 0.05$ compared to the control

## CONCLUSION

According to the outcomes of the study, the cytotoxic activity of 2-(1,1-dimethyl-1h-benzo[e] indoline-2-yl)-5,6,7-trichloro-1,3-tropolone against U87 MG tumor cell culture has been studied, and an inhibitory IC50 concentration of the suggested compound has been obtained, which turned out to be lower than that for Temozolomide. The obtained data are of considerable scientific interest

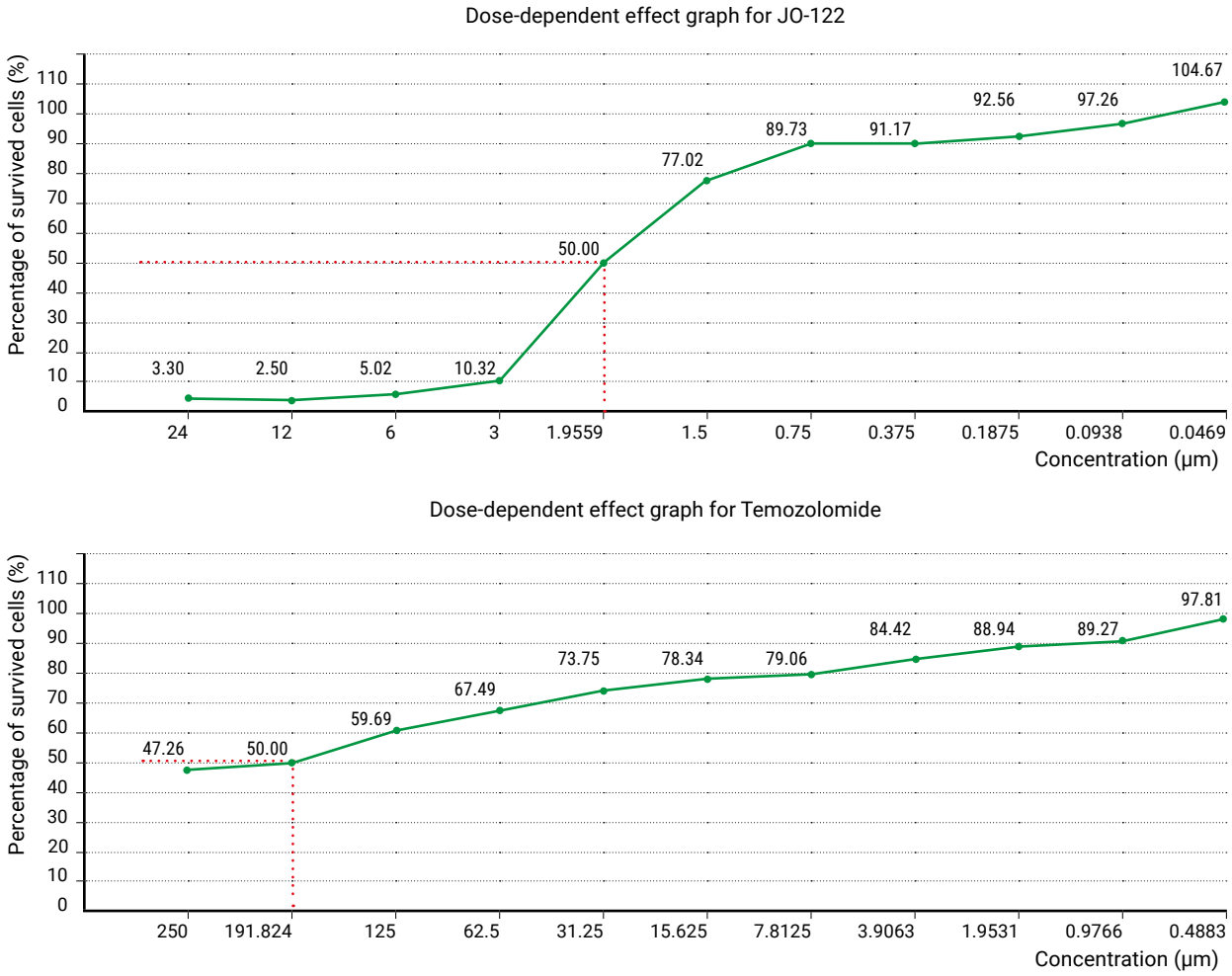


Fig. 3. comparison of IC50 tropolone JO-122 (2) with temozolomide

**Table 1. Distribution of the U87MG cell population by cell cycle phases in the control group and 24 hours after the addition of the tested tropolone. The data is expressed as mean ± standard deviation**

| Group | Cell cycle phases | | |
|---|---|---|---|
| | G1 | S | G2/M |
| Control | 71.77 ± 0.91 | 6.79 ± 0.54 | 17.63 ± 0.83 |
| JO-122 (2) – 2 μm | 28.08 ± 1.02* | 10.63 ± 1.70 | 58.56 ± 0.83* |
| JO-122 (2) – 1 μm | 29.71 ± 0.67* | 11.81 ± 0.77 | 56.61 ± 0.54* |
| JO-122 (2) – 0.5 μm | 34.45 ± 1.55* | 9.06 ± 0.65 | 52.65 ± 1.56* |

Note: * – the differences are statistically significant at $p < 0.05$ compared to the control

and indicate the prospects for further research on 2-(1,1-dimethyl-1h-benzo[e]indoline-2-yl)-5,6,7-trichloro-1,3-tropolone. One possible direction is to study the effect of JO-122(2) on other cell lines, including evaluation of the proliferative activity of tumor cells and the cell cycle, as well as CDX and PDX models, which will allow us to more fully assess the effect of tropolone on glioblastoma.

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Kuznetsova N. S. – performed writing the text of the article, search for literature data;
Filippova S. Yu. – executed conduction of the study;
Goncharova A. S. – performed editing of the article, final approval of the manuscript for publication;
Galina A. V. – took part in the preparation of the illustrations and the bibliography design;
Gurova S. V. – took part in the preparation of the article;
Gusakov E. A. – took part in the editing of the article;
Sayapin Yu. A. – took part in the study design and concept development;
Rostorguev E. E. – took part in the study design and concept development.

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ORIGINAL ARTICLE



# Apoptosis-Inducing Factor (AIF) content in tumor cell mitochondria from colorectal cancer patients

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## ABSTRACT

**Purpose of the study.** To investigate the level of protein AIF in the mitochondria of tumor cells and visually unchanged tissues of the colon in male and female patients with colorectal cancer.

**Materials and methods.** The study included results, obtained from 132 patients with stage T2-3N0M0 colon cancer, comprising 52 women and 80 men. Mitochondria were isolated from human colon and tumor tissue cells using differential centrifugation in a high-speed refrigerated centrifuge. The concentration of protein AIF (pg/mg protein) in mitochondria was determined using ELISA «Human AIF Elisa Kit» (Cloud-CloneCorp., China).

**Results.** It was established that in males, the AIF level in the mitochondria of rectal, sigmoid colon and ascending colon tumor cells was 2.4 times, 1.9 times ($p < 0.05$) and 3.1 times higher, respectively, than in the mitochondria of the corresponding tissues not affected by the tumor. In the mitochondria of the intestinal tissue not affected by the tumor, significant differences in the AIF content were observed, with levels varying depending on the anatomical location. In the sigmoid colon, the level of this factor was found to be 1.9 ($p < 0.05$) and 2.6 times higher than in the rectum and ascending colon, respectively. Concurrently, no notable discrepancies in the AIF concentration within the mitochondria of conditionally unimpaired tissues were observed in the female subjects. The AIF content was found to be higher in the mitochondria of tumor cells in women than in conditionally intact tissues. Specifically, it was observed to be 2.1 times higher in rectal tumors, 4.4 times higher in sigmoid colon tumors and 1.7 times ($p < 0.05$) higher in ascending colon tumors. Significant discrepancies in the AIF content between men and women, as well as between the mitochondria of tumor sample cells, were identified. In the rectal and ascending colon tumor, the AIF level in women was found to be markedly elevated in comparison to men, exhibiting a ratio of 1.3 ($p < 0.05$) and 2.4, respectively.

**Conclusion.** In patients with colorectal cancer, the content of AIF in tumor mitochondria is observed to increase. This can be considered to represent stimulation mechanism of tumor proliferative activity due to its NADH/NADPH oxidase function, which promotes the survival of malignant cells.

**Keywords:** mitochondria, colorectal cancer, males, females, AIF, tumor tissue, intestinal tissue

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Compliance with ethical standards: the study was carried out in compliance with the ethical principles set forth in the World Medical Association Declaration of Helsinki, 1964, ed. 2013. Signed informed consent was received from all patients for the removal and transfer of biological material for scientific research, government assignments for socially and socially useful purposes. Protocol No. 1 of the Ethics Committee of the National Medical Research Center for Oncology, the Russian Federation Ministry of Health, was approved on 01/30/2023

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Conflict of interest: Kit O. I. has been the member of the editorial board of the South Russian Journal of Cancer since 2019, however he has no relation to the decision made upon publishing this article. The article has passed the review procedure accepted in the journal. The authors did not declare any other conflict of interest

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**ОРИГИНАЛЬНАЯ СТАТЬЯ**

# Содержание апоптоз-индуцирующего фактора (AIF) в митохондриях клеток опухоли у больных колоректальным раком

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## РЕЗЮМЕ

**Цель исследования.** Исследовать уровень белка AIF в митохондриях клеток опухоли и визуально неизмененных тканей отделов толстой кишки у больных колоректальным раком.

**Пациенты и методы.** В исследование включены результаты, полученные у 132 больных раком толстой кишки со стадией T2-3N0M0, из которых 52 составили женщины и 80 мужчин. Митохондрии из клеток тканей кишки и опухоли человека выделяли с применением дифференциального центрифугирования на высокоскоростной рефрижераторной центрифуге. В митохондриях методом ИФА определяли концентрацию белка AIF (пг/мг) с использованием тест-системы «Human AIF Elisa Kit» (Cloud-CloneCorp., China).

**Результаты.** Выявлено, что у мужчин, в митохондриях клеток опухоли прямой кишки, сигмовидной кишки и восходящего отдела ободочной кишки уровень AIF был выше, чем в митохондриях соответствующих тканей, не пораженных опухолью, в 2,4 раза, в 1,9 раз ($p < 0,05$) и в 3,1 раза соответственно. В митохондриях непораженной опухолью ткани кишки отмечали значимые различия в содержании AIF в зависимости от анатомического расположения: в сигмовидной кишке уровень данного фактора оказался в 1,9 ($p < 0,05$) и в 2,6 раза выше, чем в прямой и восходящем отделе ободочной кишки. При этом у женщин значимых различия в уровне AIF в митохондриях условно непораженных тканей не выявлено. В митохондриях клеток опухоли у женщин содержание AIF было выше, чем в условно интактных тканях: в опухоли прямой кишки в 2,1 раза, в опухоли сигмовидной кишки в 4,4 раза, в опухоли восходящего отдела ободочной кишки в 1,7 раза ($p < 0,05$). Установлены значимые различия в содержании AIF у мужчин и женщин и в митохондриях клеток опухолевых образцов: в опухоли прямой кишки и восходящего отдела ободочной кишки, у женщин уровень AIF был значимо выше, чем у мужчин от в 1,3 раза ($p < 0,05$) и в 2,4 раза.

**Заключение.** У больных колоректальным раком в митохондриях опухолей возрастает содержание AIF, которое можно рассматривать как механизм стимулирования пролиферативной активности опухоли за счет своей NADH/NADPH оксидазной функции, способствующей выживанию злокачественных клеток.

**Ключевые слова:** митохондрии, колоректальный рак, мужчины, женщины, AIF, ткань опухоли, ткань кишки

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Соблюдение этических стандартов: в работе соблюдались этические принципы, предъявляемые Хельсинкской декларацией Всемирной медицинской ассоциации (World Medical Association Declaration of Helsinki, 1964, ред. 2013). Получено от всех пациентов подписанное информированное согласие на взятие и передачу биологического материала для проведения научных исследований, государственных заданий в общественно и социально-полезных целях. Протокол № 1 этического комитета ФГБУ «Национальный медицинский исследовательский центр онкологии» Министерства здравоохранения Российской Федерации утвержден 30.01.2023 г.

Финансирование: финансирование данной работы не проводилось

Конфликт интересов: Кит О. И. является членом редакционной коллегии журнала «Южно-Российский онкологический журнал» с 2019 г., но не имеет никакого отношения к решению опубликовать эту статью. Статья прошла принятую в журнале процедуру рецензирования. Об иных конфликтах интересов авторы не заявляли

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## BACKGROUND

Colorectal cancer (CRC) is a malignant tumor derived from the glandular epithelial cells of the colon; it is the third most frequently diagnosed cancer that ranks second in terms of mortality in the world [1–4]. CRC is a genetically heterogeneous disease that includes various molecular pathways of tumor formation and metastasis [5].

Mitochondria are vital for energy production, cell signaling, and metabolic homeostasis. Meanwhile, mitochondria influence processes such as cellular differentiation and proliferation. In malignant cells, mitochondrial functions undergo transformation, which promotes rapid proliferation, survival, and resistance to neoplasm death [6]. During the development of CRC, mitochondrial dysfunction and mutations in the tumor suppressor gene TP53 were revealed, which leads to impaired regulation of the cell cycle, mitochondrial respiration, cellular metabolism, and an imbalance between survival and cell death [7, 8]. Malignant cells have metabolic flexibility, using and regulating the tricarboxylic acid cycle not only for survival and proliferation, but also and to evade immune "surveillance" and suppress the cytotoxic function of immune cells [6].

The cellular protein AIF was initially identified as a 57 kDa soluble fragment that is released from mitochondria during apoptosis and translocated into the nucleus in a caspase-independent manner, causing caspase-independent chromatin condensation and DNA fragmentation [9].

It is currently recognized that AIF plays a vital role in mitochondrial bioenergetics under physiological conditions, as it supports normal oxidative phosphorylation of the cell, influencing multiple catabolic and anabolic pathways, as well as epigenetic processes that depend on mitochondrial metabolites [9]. It was found that the oxidoreductase activity of AIF gives malignant cells resistance to oxidative stress and supports their transformational status [10, 11]. Undoubtedly, the available data on the role of AIF in mitochondrial metabolism in the development of the malignant process, both in experiment and in the clinic, indicate the important role of this factor [12]. However, to date, there is not enough data on the functional features of AIF in human oncological diseases, in particular in the mitochondria of tissue cells in colorectal cancer.

**Purpose of the study** was to investigate the level of AIF protein in the mitochondria of tumor cells and visually unchanged colon tissues in patients with colorectal cancer.

## PATIENTS AND METHODS

The study included the results obtained from 132 patients with T2-3N0M0 colon cancer, 52 of them women and 80 men. The average age was 66 (58–73) years, 68 (51.5 %) people were over the age of 65, and 64 (48.5) people were under the age of 65. 46 (34.8 %) patients suffered from sigmoid colon cancer, including 19 women, 44 (33.7 %) patients with rectal cancer, including 18 women, and 42 (31.5 %) patients with ascending colon cancer, including 15 women. The tumor differentiation grade in all patients corresponded to G2. None of the patients received neoadjuvant treatment before surgery. 98.5 % of patients had a good indicator status (ECOG 0 or 1). All patients were operated on. The work followed the ethical principles set forth in the World Medical Association Declaration of Helsinki, 1964, ed. 2013. Signed informed consent was received from all patients to take and transfer biological material for scientific research, government assignments for socially and socially useful purposes. Protocol No. 1 of the Ethics Committee of the National Medical Research Center for Oncology was approved on 01/30/2023.

During the operation, after laparotomy, the colon affected by the tumor was mobilized with ligation and intersection of the feeding blood vessels, then lymphodissection was performed and the affected organ was resected (right-sided hemicolectomy, left-sided hemicolectomy, sigmoid colon resection, rectal resection) to remove the malignant tumor from the patient. A part of the tumor material and a fragment of intestinal tissue along the resection line were immediately placed in a cold sterile isolation medium containing 0.22 M mannitol, 0.3 M sucrose, 1 mM EDTA, 2 mM TRIS-HCL, 10 mM HEPES, pH 7.4. The further course of the operation was completed with a restorative stage with the application of an intestinal anastomosis, drainage of the abdominal cavity and suturing of the laparotomy wound.

Mitochondria from tumor and intestinal tissue cells were isolated using differential centrifuga-

tion on an Avanti J-E high-speed refrigerated centrifuge, BECMAN COULTER, USA using the method of Egorova MV, Afanasyev SA, 2011; Gureev AP, Kokina AV, 2015 [13, 14]. To destroy the intercellular connections, cell wall and plasma membranes, mechanical processing of tissues with crushing with scissors and homogenization in a glass homogenizer with a Teflon pestle (Potter-Elwegame homogenizer) was used. 10 ml of sterile isolation medium (0.22 M mannitol, 0.3 M sucrose, 1 mM EDTA, 2 mM TRIS-HCL, 10 mM HEPES, pH 7.4) was added to each gram of tissue. The tissues were homogenized and centrifuged for the first time for 10 min at a speed of 1000 g, a temperature of 0–2 °C. The second and third centrifugation was carried out at 20,000 g, 20 min, a temperature of 0–2 °C. Between centrifugation, the mitochondrial precipitate was resuspended in the isolation medium. Mitochondria were additionally purified from lysosomes, peroxisomes, melanosomes, etc., by centrifugation in a 23 % percolation gradient. The suspension of subcellular structures was layered on a Percall gradient, centrifuged for 15 min at 21000 g, after which separation into 3 phases was observed, the lower layer of mitochondria was left and resuspended with isolation medium. The next "washing" of mitochondria was carried out by centrifugation for 10 min at 15000 g, temperature 0–2 °C. The obtained mitochondrial samples were stored at –80 °C before analysis. Before the analysis, the samples were diluted to a protein concentration of 6 g/l [13]. ELISA was used to determine concentrations of: AIF (pg/mg protein) (Cloud-CloneCorp., China), protein by biuretic method (Olvex Diagnostics, Russia).

**Statistical analysis**

Statistical analysis of the results was performed using the Statistica 10.0 software package. The distribution of normality was evaluated using the Shapiro-Wilk criterion (for small samples). The comparison of quantitative data in groups (independent samples) was carried out using the Student and Mann-Whitney criteria. The value of $p < 0.05$ was retained as the limit of statistical significance. The table data is presented as M ± m, where M is the arithmetic mean and m is the standard error of the mean.

## STUDY RESULTS

Statistically significant differences in the level of AIF factor were revealed, both in tumor tissue and in intact tissue, depending on gender. Thus, in women, the concentration of AIF in the mitochondria of cells of the rectal and ascending colon tissue exceeded the values in similar samples in men by 1.6 times ($p < 0.05$) and 2.4 times, respectively (Table 1). Only in the mitochondria of cells of the sigmoid colon tissue in men, the content of AIF was higher than in women 1.8 times ($p < 0.05$).

A comparative analysis of the AIF content in the mitochondria of tumor cells showed a statistically significantly higher level of the studied factor, compared with the values in the mitochondria of the corresponding tissue. Thus, in men, in mitochondrial samples of tumors of the rectum, sigmoid colon and ascending colon, the AIF level was statistically significantly higher than in the mitochondria of the corresponding tissues not affected by the tumor by 2.4 times, 1.9 times ($p < 0.05$) and 3.1 times, respectively (Table 1). The highest AIF index in men was found in the mitochondria of the sigmoid colon tumor – it exceeded the corresponding level in the mitochondria of the rectal and colon tumors by an average of 1.6 times. At the same time, significant differences in AIF content were also noted in the mitochondria of non-tumor-affected tissue, depending on the anatomical location: in the sigmoid colon, the level of this factor was 1.9 ($p < 0.05$) and 2.6 times higher than in the rectum and ascending colon.

In women with CRC, there were no significant differences in the level of AIF in the mitochondria of conditionally unaffected tissues, while in the mitochondria of tumor cells the content of this factor was statistically significantly higher than in conditionally intact tissues: in tumors of the rectum by 2.1 times, in tumors of the sigmoid colon by 4.4 times, in tumors of the ascending colon by 1.7 times ($p < 0.05$).

Statistically significant differences in the AIF content in men and women and in the mitochondria of tumor samples were revealed: in tumors of the rectum and ascending colon, the AIF level in women was significantly higher than in men by 1.3 times ($p < 0.05$) and 2.4 times. No significant sex differences were found in the mitochondria of sigmoid colon tumor cells.

## DISCUSSION

There are scientific studies of several active substances that stimulate the death of malignant cells, both in cell lines and in tumors in patients by influencing apoptosis factors, including AIF [2, 3, 15]. These studies are relevant and promising, since limiting the uncontrolled growth of malignant cells and inducing apoptosis in them would be a promising direction in the fight against malignant tumors. However, there is a problem of reducing the expected percentage of positive effect of various targeted antitumor drugs, which can be explained by the multifunctionality of the selected targets. Thus, in addition to participating in the signaling pathway of cell apoptosis, AIF plays a key role in maintaining mitochondrial homeostasis, is an important factor in maintaining the functional integrity of the mitochondrial respiratory chain and participates in the regulation of the redox state of cells by regulating the activity of NADF-hydroxylase to influence the levels of reactive oxygen species (ROS) [9, 16].

Our study revealed a seemingly paradoxical (given its pro-apoptotic properties) increase in the level of AIF in all samples of the mitochondria of the CRC tumor, compared with the conditionally intact intestine in both men and women. There are several other works that also describe increased AIF levels in ovarian, prostate, and hemoblastosis cancers [17–19].

The revealed paradox of overexpression of AIF in mitochondrial tumor samples in colorectal cancer can be explained by the polyfunctionality of this factor, since AIF allows mitochondria to regulate cell survival due to the balance between pro-apoptotic and energetic pathways [16]. Malignant cells reprogram their metabolism to support the increased biosynthetic and energy requirements necessary for their growth and motility, and AIF is overexpressed to maintain cellular energy and metabolic homeostasis.

In order for AIF to perform its apoptotic function, it must be cleaved into a soluble apoptotic protein with a mass of 57 kDa in the mitochondria and translocated through the mitochondrial membrane to the nucleus. The release of apoptosis factors in mitochondria is caused by the loss of mitochondrial function, which is closely related to an increase in mitochondrial membrane permeability and depolarization of membrane potential [20]. At the same time, the release of AIF from mitochondria towards the nucleus, for the initiation of apoptosis, is regulated by many factors [21, 22]. In particular, studies on the example of breast cancer have shown that P21-activated kinase 5 (PAK5), which is an oncogenic pro-

**Table 1. AIF content in the mitochondria of male and female colon tissue cells (pg/mg protein)**

| Samples | Males | Females |
|---|---|---|
| Rectal tissue | | |
| Intact | 237.7 ± 14.1 | 381.4 ± 30.9<br>$p^2$ = 0.0000 |
| Tumor | 559.3 ± 36.9<br>$p^1$ = 0.0000 | 817.7 ± 49.9<br>$p^1$ = 0.0000<br>$p^2$ = 0.0001 |
| Sigmoid tissue | | |
| Intact | 451.5 ± 20.8 | 247.8 ± 16.6<br>$p^2$ = 0.0000 |
| Tumor | 859.3 ± 57.9<br>$p^1$ = 0.0000 | 1087.1 ± 69.9<br>$p^1$ = 0.0000 |
| Ascending colon tissue | | |
| Intact | 176.8 ± 8.9 | 426.4 ± 39.1<br>$p^2$ = 0.0000 |
| Tumor | 541.4 ± 30.2<br>$p^1$ = 0.0000 | 716.4 ± 85.3<br>$p^1$ = 0.0044<br>$p^2$ = 0.0247 |

Note: statistically significant differences in relation to: $p^1$ is the indicator in the corresponding tissue along the resection line; $p^2$ is the indicator in men

tein and is overexpressed in multiple cancers and promotes tumor progression [23, 24], can prevent the release of AIF from mitochondria by reducing the permeability of mitochondrial membranes and increasing membrane potential and inhibit apoptosis by phosphorylation of AIF. This fact indicates that in malignant cells, the balance of AIF functional activities shifts from pro-apoptotic to a predominance of energetic, as a result of which AIF is localized on the inner membrane of mitochondria and performs the function of oxidoreductase [25]. It has been shown that depletion of AIF in tumor cells leads to metabolic reprogramming, inhibition of cell proliferation and tumor growth, elimination of cancer stem cells, changes in inflammation in the tumor microenvironment, and induction of differentiation of malignant cells into normal cells [26].

## CONCLUSION

Thus, in patients with colorectal cancer, the content of AIF increases in the mitochondria of tumors, which can be considered as a mechanism for stimulating the proliferative activity of the tumor due to its NADH/NADPH oxidase function, which promotes the survival of malignant cells.

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ORIGINAL ARTICLE



# Viral infections in cancer patients at the stages of antitumor treatment

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## ABSTRACT

**Purpose of the study.** To analyze cases of viral infection in cancer patients at the stages of antitumor therapy.
**Patients and methods.** We conducted a retrospective analysis of the medical histories of 50 patients with acute respiratory failure (I–III st.), hospitalized in the Department of anesthesiology and intensive care in 2017–2020. Of these, 34 are children and 16 are adults. Sputum, tracheobronchial aspirate, and blood were examined for the presence of viral agents.
**Results.** Viral infection was confirmed in 35 (70 %) patients. During CT, it developed more often than in the early postoperative period (72.2 % vs 64.3 %, $p > 0.05$), but this situation is true only for the general group of patients. In children, viral infection was diagnosed only on CT (71.9 % of those receiving CT, $p = 0.098$, F = 0.13), and in adults it was equally common (75 % each), both during CT and after surgery. In lung cancer, viral infection was confirmed in 7 (100 %), pelvic fever in 7 (63.6 %), bones, connective and soft tissues in 6 (66.7 %), hemoblastoses in 3 (75 %), central nervous system tumors in 5 (71.4 %) patients. Herpesvirus infection (HVI) was confirmed in 15 (42.9 % of the infected), respiratory viral infection (RVI) in 13 (37.1 %), and their combination in 7 (20 %) patients. In general, we note a slight predominance of HVI over RVI (22/62.9 % vs. 20/57.1 %, $p > 0.05$). Mixed infection with a combination of two to four pathogens and mono-infection developed equally frequently: in 18 (51.4 %) and 17 (48.6 %) patients, respectively.
**Conclusions.** Infectious complications are an important component of modern antitumor treatment. Therefore, it is necessary to monitor the spectrum of viral infections in cancer patients with signs of respiratory dysfunction at the stages of antitumor therapy. Proper assessment of the situation will help to avoid the development of critical consequences, reduce the time of hospitalization, and improve the course and prognosis of cancer.

**Keywords:** viral infection, respiratory complications, antitumor therapy, respiratory failure

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Compliance with ethical standards: the ethical principles presented by the World Medical Association Declaration of Helsinki, 1964, ed. 2013 were observed in the study. Informed consent was received from all participants of the study. The study was conducted with the permission of the Ethics Committee of the National Medical Research Centre for Oncology (Protocol No. 19 dated 11/22/2021). Informed consent was obtained from all participants in the study.

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**ОРИГИНАЛЬНАЯ СТАТЬЯ**

# Вирусные инфекции у онкологических больных на этапах противоопухолевого лечения

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## РЕЗЮМЕ

**Цель исследования.** Провести анализ случаев проявления вирусной инфекции у онкологических пациентов на этапах противоопухолевой терапии.

**Пациенты и методы.** Был проведен ретроспективный анализ историй болезни 50 больных с признаками острой дыхательной недостаточности (I–III ст.), госпитализированных в отделение анестезиологии и реанимации в 2017–2020 гг. Из них 34 ребенка и 16 взрослых. Исследовали мокроту, трахеобронхиальный аспират, кровь на наличие вирусных агентов.

**Результаты.** Вирусная инфекция была подтверждена у 35 (70 %) больных. При проведении химиотерапии (ХТ) она развивалась чаще, чем в раннем послеоперационном периоде (72,2 % vs 64,3 %, $p > 0,05$), однако это положение справедливо лишь для общей группы больных. Среди детей вирусная инфекция была диагностирована только у пациентов, которым проводилась ХТ (71,9 % получавших ХТ, $p = 0,098$, $F = 0,13$), а у взрослых одинаково часто (по 75 %) как в результате проводимой ХТ, так и после хирургического вмешательства. При раке легкого вирусная инфекция была подтверждена у 7 (100 %) больных, злокачественных новообразованиях малого таза – у 7 (63,6 %), костей, соединительной и мягких тканей – у 6 (66,7 %), гемобластозами – у 3 (75 %), опухолях центральной нервной системы – у 5 (71,4 %) больных. Герпесвирусная инфекция (ГВИ) была подтверждена у 15 (42,9 % от числа инфицированных), респираторно-вирусная (РВИ) – у 13 (37,1 %), а их сочетание – у 7 (20 %) больных. В целом можно отметить некоторое преобладание ГВИ над РВИ (22/62,9 % против 20/57,1 %, $p > 0,05$). Микст-инфекция с сочетанием от двух до четырех возбудителей и моноинфекция развивались одинаково часто: у 18 (51,4 %) и 17 (48,6 %) больных соответственно.

**Заключение.** Осложнения инфекционного характера являются важной составляющей современного противоопухолевого лечения. В этой связи необходимо проводить мониторинг спектра вирусных инфекций у онкологических пациентов с признаками развития респираторной дисфункции на этапах проведения противоопухолевой терапии. Правильная оценка ситуации позволит избежать развития критических последствий, сократить сроки госпитализации, улучшить течение и прогноз онкологического заболевания.

**Ключевые слова:** вирусная инфекция, респираторные осложнения, противоопухолевая терапия, дыхательная недостаточность

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Конфликт интересов: все авторы заявляют об отсутствии явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи

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## BACKGROUND

To date, the success of the diagnosis and therapy of malignant neoplasms has significant results. At the same time, the use of standard treatment approaches does not always lead to the expected effect, which serves as a prerequisite for the development of personalized approaches to the treatment of cancer patients [1]. Meanwhile, it is necessary to take into account the role of complications that occur against the background of antitumor treatment, which not only worsen the quality of life of patients and provoke their refusal to carry out planned therapy, but also cause serious functional disorders of the body, up to life-threatening conditions requiring timely and urgent measures [2]. In this regard, special attention should be paid to the study of risk factors for the development of negative consequences during complex antitumor treatment. It is known that cancer patients are the most vulnerable group and are more susceptible to various complications, including those of an infectious nature [3]. This is due to the fact that the defect of the immune system is provoked by the development of the tumor itself and deeper functional changes in the patient's body due to the use of aggressive courses of chemoradiotherapy, corticosteroids and antimicrobial treatment, as well as due to extended and combined surgical interventions [4]. According to Egorov AYu (2019) infectious complications are the cause of death of cancer patients in 39–43 % of cases [5]. Meanwhile, mortality from respiratory complications reaches 27 % [6, 7].

Many viral agents are involved in the occurrence of respiratory complications in these patients, such as influenza virus, parainfluenza, respiratory syncytial virus, adenovirus, rhinovirus, coronavirus, metapneumovirus and human bocavirus [6–10]. Respiratory syncytial (RS), influenza virus and rhinovirus are diagnosed with the highest frequency (60 %) [6]. Parainfluenza viruses, metapneumoviruses, bocaviruses and adenoviruses are less common: the frequency of their detection in patients ranges from 2 % to 10 % [6, 7]. Other well-known pathogens, such as cytomegalovirus (CMV), Epstein-Barr virus (EBV), herpes simplex virus types 1 and 2 (HSV 1, 2), human herpes virus type 6 (HCV6), also often cause serious diseases in cancer patients, but are not truly respiratory. CMV after hematopoietic stem cell transplantation occurred in 29 % of patients, and in 26.5 % with RS, and if pneumonia with CMV monoinfection developed in 31 %, then with coinfection with RS it was 2 times more common in 68 % of patients [11].

In this context, it is necessary to take into account the fact that the main danger of respiratory viruses lies in their ability to provoke the development of pneumonia and secondary bacterial complications. According to Katsurada N (2016), in a study of patients over 65 years of age diagnosed with pneumonia, viral pathogens were detected in 23 % of cases, while rhinoviruses (9.9 %) were the most common cause of pneumonia, the RS virus was detected in 4.1 % of cases, and influenza viruses in 3.9 % of cases [12]. A meta-analytical review of patients with pneumonia of different age groups conducted in 2017 by Korean researchers showed that any of the representatives of respiratory viruses can be the trigger of generalized bacterial infection [13].

It should be emphasized that respiratory infections in patients with a complicated premorbid background, including cancer patients with secondary immunodeficiency, are poorly predictable and do not always have a favorable prognosis [5]. As a rule, the virus, penetrating the mucous membrane of the respiratory tract, has a cytopathic effect on epithelial cells, which leads to fullness of the microcirculatory bed, swelling of the mucous layer, increased vascular permeability and excessive production of interferon. These pathological changes are the starting point of stimulation of the transient microbiota, when epithelial cell membranes are destroyed, and phospholipids are released with activation of arachidonic acid metabolism processes. There is an increased production of bradykinin, leukotrienes, and the activity of cytokines and neutrophils increases. The secondary microbial lesion is aggravated by the adhesion of several pathogenic microorganisms to the mucous membrane of the respiratory tract, which occurs as a result of a decrease in the concentration of immunoglobulin A, lactoferrin, interferon and lysozyme in the mucocellular secretion. Together, there is a decrease in antiviral and antibacterial activity with uncontrolled inflammation, impaired ventilation, and the development of hypoxia [14]. As a result, damage to the respiratory epithelium and the microcirculatory bed leads to the rapid development of acute respiratory distress syndrome (ARDS), which actually causes the death of one in three patients [15].

It is obvious that viruses are the cause of the development of a chain of pathological transformations that can later lead to the development of severe systemic complications. At the same time, it is almost impossible to assess a full-scale lesion from a viral infection, since the data on mortality from bacterial pneumonia do not actually take into account the role of the viral etiological aspect as a provocateur of the development of secondary infection [14].

The number of studies devoted to the problem of bacterial infection in various groups of patients with a variety of pathological conditions, prevention and treatment measures is increasing annually [14]. At the same time, there are practically no publications on the problem of the development and course of viral infections in cancer patients at the stages of antitumor treatment.

**Purpose of the study:** to analyze the cases of viral infection in cancer patients at the stages of antitumor therapy.

## PATIENTS AND METHODS

The study was performed with the consent of patients or their representatives to the processing of personal information and the use of the obtained biological material for scientific purposes (Protocol No. 19 of 11/22/2021). A retrospective analysis of the medical histories of 50 patients with signs of acute respiratory failure (ARF) (Grades I–III) hospitalized in the Department of anesthesiology and intensive care at the National Medical Research Center for Oncology of the Russian Federation Ministry of Health in 2017–2020. Of these, 34 children were aged 7.0 ± 5.7 years and 16 adults aged 61 ± 15.3 years. The most represented were malignant neoplasms of the pelvis and retroperitoneal space – 11 (22 %), bones, connective and soft tissues – 9 (18 %), lungs – 7 (14 %), central nervous system (CNS) – 7 (14 %), gastrointestinal tract (GIT) – 6 (12 %), hemoblastoses – 4 (8 %). The remaining diseases are presented in isolated cases.

There were 14 (28 %) patients in the early postoperative period, 2 (4 %) received radiation therapy, and 34 (68 %) patients received chemotherapy (CT). The severity of the critical condition on the APACHE II (Acute Physiology and Chronic Health Evaluation) scale in children ranged from 10 to 28, in adults ranged from 18 to 26 points. To determine the degree of ARF, the parameters of saturation ($SpO_2$) and partial pressure of oxygen in arterial blood ($PaO_2$) were taken into account. $PaO_2$ of 60–79 mmHg and $SpO_2$ of 90–94 % corresponded to the first stage, $PaO_2$ of 40–59 mmHg and $SpO_2$ of 75–89 % corresponded to the second stage, $PaO_2$ of less than 40 mmHg corresponded to the third stage and $SpO_2$ is less than 75 %. The intensity of the initial clinical symptoms was analyzed: hyperthermia (fever to subfebrile or febrile levels), intoxication syndrome (general weakness, nausea, headache and muscle pain, seizures). Sputum, tracheobronchial aspirate, bronchoalveolar lavage, nasopharyngeal smears, and blood were examined to detect the infectious component. Biological samples were taken during the first hours of hospitalization of patients in the ICU. The isolation of viral RNA/DNA was performed using the RIBO-prep kit (FBIS CRIER). Qualitative determination of the RNA of influenza A/B virus (*Influenza virus* A/B) and influenza B, respiratory syncytial virus (RS, *hRSv*, *Orthopneumovirus hominis*), metapneumovirus (*hMPV*), parainfluenza viruses of types 1, 2, 3 and 4 (*hPiV*), coronaviruses of types OC43, E229, NL63, HKUI (*HCoV*), rhinoviruses (*hRv*), adenovirus DNA of groups B, C and E (*HAdV*), bocavirus (*HBoV*) and herpes simplex virus types 1, 2 (HSV 1, 2) were performed using reagent kits "AmpliSens® Influenza virus A/B-FL", "AmpliSens® ARVI-screen-FL", "AmpliSense® HSV I, II-FL". DNA quantification of CMV, EBV, HCV6 was performed using AmpliSens® EBV/ CMV/ HHV6A/B-screen-FL reagent kits. When CMV, EBV and HCV6 were detected in the blood, the number of more than 2 lg copies of the virus DNA/$10^5$ leukocytes was considered etiologically significant, in non-sterile loci-more than 2000 copies of the virus DNA/ml. The calculation was carried out in accordance with the manufacturer's instructions. Virus-specific antibodies (AT) of classes M and G to HSV 1, 2, CMV, EBV and HCV6 in blood serum were also determined in all patients by ELISA (Vector-Best AO).

### Statistical analysis

Statistical data processing was carried out using Microsoft Excel 2016 and Statistica 10 (StatSoft, Inc.) programs. Statistically significant differences were considered at $p < 0.05$.

## STUDY RESULTS

Viral infection (VI) was confirmed in 35 (70 %) patients. In patients undergoing CT, it developed more often than in the early postoperative period (72.2 % vs 64.3 %, the differences were not statistically significant, $p > 0.05$), however, this position is valid only for the general group of patients. Among children, VI was diagnosed only in patients who underwent CT (71.9 % of those who received CT, $p = 0.098$, F = 0.13), and in adults it was equally common (75 % each), both as a result of CT and after surgery. In lung cancer, VI was confirmed in 7 (100 %), pelvic cancer in 7 (63.6 %), bone, connective and soft tissue in 6 (66.7 %), hemoblastosis in 3 (75 %), CNS tumors in 5 (71.4 %) patients. VI was least often detected in patients with malignant neoplasms of the gastrointestinal tract – in 2 (33.3 %). Herpesvirus infection (HSV) was confirmed in 15 (42.9 % of the infected), respiratory viral infection (RVI) in 13 (37.1 %), and their combination in 7 (20 %) patients. In general, there is a slight predominance of HSV over RVI (22/62.9 % versus 20/57.1 %, the differences were not statistically significant, $p > 0.05$). Mixed infection with a combination of two to four pathogens and mono-infection developed equally frequently: in 18 (51.4 %) and 17 (48.6 %) patients, respectively. Cases of mixed infection were presented in the following combinations:

- HSV 1, 2 + EBV + *hRv* (1/18; 5.6 %);
- HSV 1, 2 + EBV (2/18; 11.1 %);
- EBC + HSV6 (2/18; 11.1 %);
- CMV + EBV + HSV6 (1/18; 5.6 %);
- HSV 1, 2 + influenza B (1/18; 5.6 %);
- *hRv* + *hCoV* (*HKU-1 / OC 42*) (1/18; 5.6 %);
- *hAdV* + *hRv* (1/18; 5.6 %);
- EBV + HSV6 + *hBv* + *hRv* (1/18; 5.6 %);
- HSV6 + *hRv* (3/18; 16.7 %);
- Influenza A + *hRSv* (1/18; 5.6 %);
- HSV 1, 2 + HCV6 (1/18; 5.6 %);
- *hRSv* + *hCoV* (*NL-63 / 229E*) (1/18; 5.6 %);
- HSV 1, 2 + CMV + EBV + HSV6 + *hRv* (1/18; 5.6 %);
- *hBv* + *hRv* (1/18; 5.6 %).

Respiratory viruses circulated in the population of cancer patients not only during the seasonal increase in the incidence of acute respiratory viral infections from October to March (61.9 %). A significant number of respiratory viruses (31.8 %) were detected in the period from April to September.

The patterns of the spread of VI differed in children and adults. Contrary to expectations, they were somewhat less common in children than in adults (23/67.6 % vs. 12/75 %, the differences were not statistically significant, $p > 0.05$). Respiratory viruses prevailed in children (16/69.6 % vs. 12/52.2 %, differences were not statistically significant, $p > 0.05$) and mixed infections (14/60.9 % vs. 9/39.1 %, differences

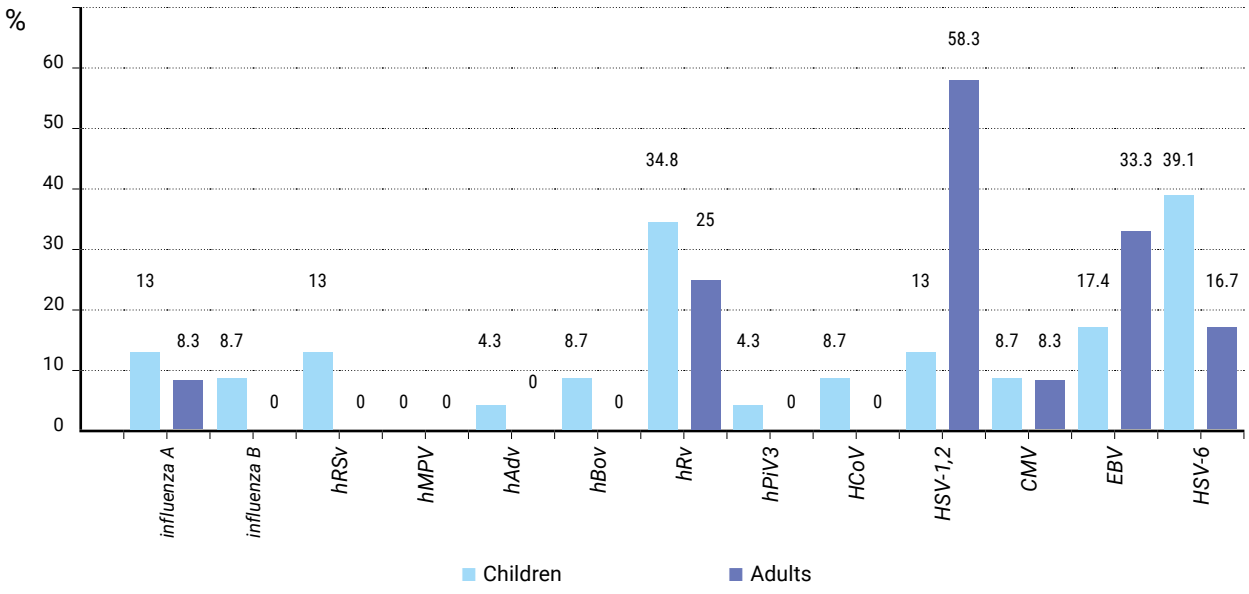


Fig. 1. Frequency of viral infection detection in cancer patients depending on age

were not statistically significant, $p > 0.05$). On the contrary, herpesviruses were more often detected in adults (10/83.3 % vs. 4/33.3 %, $p = 0.018$, F = 0.0257) and mono-infections (8/66.7 % vs. 4/33.3 %, differences were not statistically significant, $p > 0.05$). The spectrum of pathogens also differed: rhinoviruses (34.8 %) and HSV6 (39.1 %) prevailed in children, while the spectrum of respiratory viruses was quite wide (influenza A and B, RS, adenovirus, bocavirus, parainfluenza virus, seasonal coronaviruses). Rhinovirus also prevailed in adults (25 %), but apart from it, only the influenza A virus was detected from the respiratory group. A significant predominance was noted in the herpes simplex virus (58.3 %). EBV infection was the second most common infection in children (17.4 %) and adults (33.3 %) (Fig. 1).

A comparison of laboratory and clinical data revealed certain trends in the possible influence of VI on the intensity of the development of pathological symptoms. However, the results did not show statistical significance. Thus, in the general population, hyperthermia (45.7 % with VI versus 60 % without VI, the differences were not statistically significant, $p > 0.05$) and intoxication (65.7 % versus 73.3 %, the differences were not statistically significant, $p > 0.05$) were more common in patients without viral infection. On the contrary, there is a critical decrease in saturation at ARF stage III. (45.7 % vs. 33.3 %, the differences were not statistically significant, $p > 0.05$), respiratory failure of grades I–II (94.3 % vs. 33.3 %, $p = 0.058$, F = 0.087, and in children 100 % vs. 72.7 %, $p = 0.028$, F = 0.202) and pneumonia (diagnosis confirmed X-ray examination of the lungs) (20.0 % versus 13.3 %, the differences were not statistically significant, $p > 0.05$) were more common in patients with VI (Fig. 2). And if the first four parameters developed unidirectionally in children and adults, then pneumonia in adults was diagnosed only in the group with VI (33.3 % vs. 0 %, the differences were not statistically significant, $p > 0.05$), and in children, on the contrary, in the group with VI less often than without it (13.0 % vs. 18.2 %, the differences were not statistically significant, $p > 0.05$).

In addition to the DNA of the pathogen, 55.6 % of patients had serological markers of acute HVI. The determination of the serological status helped to determine that all adults developed HVI reactivation against the background of pre-existing class G immunoglobulins. Four cases of primary HVI caused by HSV6 were identified in children. In two patients, it developed as a primary mono-infection, and in two more, it was caused by the activation of another HVI.

As an example of the development of a critical respiratory complication in an oncological patient with a viral mixed infection, we present a clinical case. Patient K, 64 years old, admitted to the National Medical Research Center for Oncology with complaints of periodic rises in body temperature

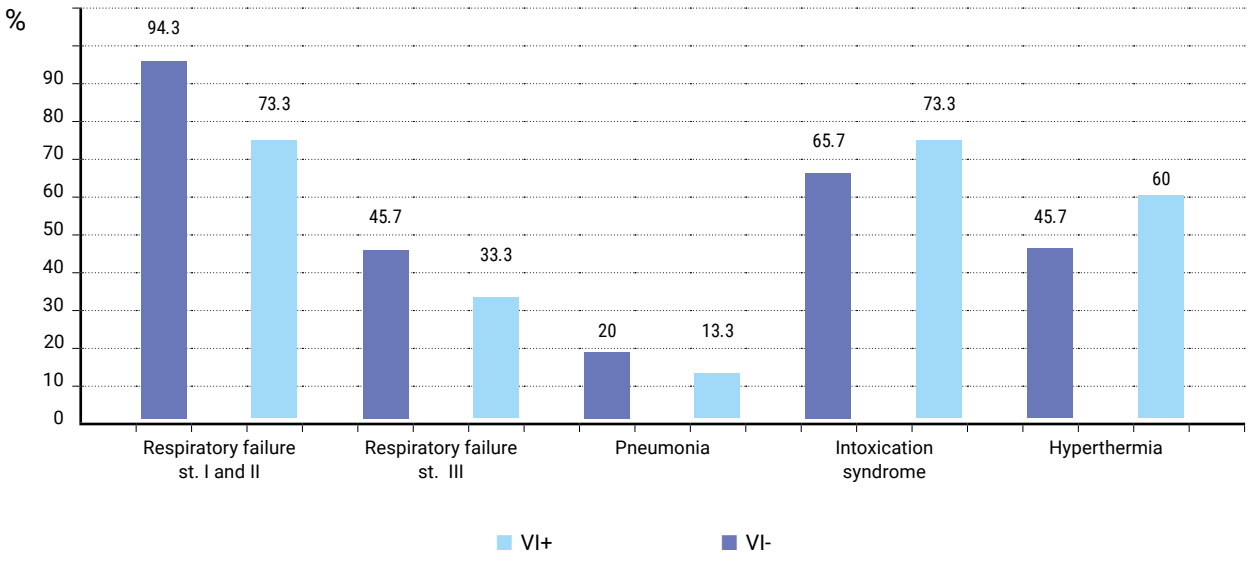


Fig. 2. Frequency of clinical symptoms of RVI/complications depending on the presence of identified pathogens in cancer patients

and cough. The diagnosis was established: (C34.1) Central cancer of the left lung with lesions of the lobar and left main bronchus pT4N2M0 stIIIb, cl.gr 2. Concomitant diagnosis: stage III COPD, severe; coronary heart disease, arrhythmic variant, rhythm disturbances of the type of normosystolic atrial fibrillation; CHF IIA, FC 2; Hypertension stage 3, risk 3. The patient underwent radical surgery – pneumonectomy on the left. The treatment was carried out without serious surgical and therapeutic complications. However, after the start of chemotherapeutic treatment on the fourth day, the patient's condition deteriorated sharply, and with clinical and laboratory signs of decompensated respiratory failure, the patient was hospitalized in the ICU. ARDS of a single lung was diagnosed against the background of progression of febrile neutropenia. The main clinical symptoms were respiratory failure, hypoxemia, and hemodynamic instability. X-ray examination revealed areas of consolidation with increased density of lung tissue. Arterial blood gas analyses revealed hypercapnic respiratory alkalosis, which demonstrated significant gas exchange disorders with an unfavorable prognosis. At the same time, laboratory examination revealed: the presence of leukocytosis up to $23 \times 10^9$/l, against the background of a significant increase in markers of systemic inflammation in the blood serum, the concentration of procalcitonin was 2.1 ng/ml (norm – up to 0.05), C-reactive protein was 87.6 mg/l (norm 0–5), the serum concentration of IL-6 was 36 pg/ml (the norm is up to 7), as well as an increase in calculated intoxication indices – the leukocyte intoxication index is 5.8 units (the norm is 1–1.6) and an increase in the neutrophil-lymphocyte ratio is 8.7 units. (norm 1–2.1), which was interpreted as the presence of endogenous intoxication of moderate severity, presumably due to the addition of bacterial agents. The patient has confirmed a respiratory viral mixed infection. Examination of the tracheobroncheal aspirate revealed rhinovirus RNA, DNA of HSV 1, 2, EBV in the amount of 119,350 copies/ml. The DNA of EBV and HCV6 was detected in the blood in the amount of 1.9 and 2.1 lg copies of DNA in terms of $10^5$ leukocytes, respectively. In addition, Klebsiella pneumoniae was detected during microbiological examination. Intensive treatment of the patient was carried out within the framework of standard therapy measures. Prolonged invasive ventilation was used for respiratory support. Unfortunately, despite the incredible efforts made to save the patient, it was not possible to avoid death.

## DISCUSSION

Infections are one of the most important complications in cancer patients and are often life-threatening. On the one hand, the progress of therapeutic strategies has led to an increase in the survival and recovery of cancer patients, on the other hand, the widespread use of chemotherapy and immunosuppressive therapy has further increased the risk of infection for these patients. At the same time, viral infections of the respiratory system often remain underestimated, despite the severity of the clinical picture and the associated impact on the duration of hospitalization and mortality rate. Even sadder, there is no unified approach to screening, diagnosis, and clinical management of such patients.

This study made it possible not only to establish a significant frequency of viral pathogens involved in the formation of respiratory disorders in cancer patients receiving antitumor therapy, but also to identify some differences in the spread of viral lesions of the respiratory system in children and adults. Thus, viral infections were more often detected in adults than in children; herpes viruses and mono-infections prevailed in adults, while respiratory viruses and mixed infections prevailed in children. The high detection rate of respiratory viruses in complications in children can be explained by the wide spread of their asymptomatic carriage in children (from 22.2 % to 40.9 %, on average 30.9 %), which was shown in our early study [16]. In a state of immunosuppression resulting from both the disease itself and the ongoing antitumor therapy, the initial lesion of the upper respiratory tract in the presence of the virus can progress to lower respiratory tract disease (LRT).

Just like other researchers [6, 17], we found that rhinoviruses are most common in adults and children in the group of respiratory viruses, and syncytial virus is also common in children. At the same time, this study differs from other studies in the wider range of viral agents studied, which means it provides a more complete picture of their prevalence. As a rule, either

respiratory or herpes viruses were included in the study, and only influenza, MS, and rhinoviruses from the respiratory group were studied.

During the study, HSV 1, 2 was identified in 58.3 % of adults as an etiologically significant agent. In the LRT lavage and blood, HSV 1, 2 DNA was detected 7.0 times more often than CMV, 1.8 times more often than EBV, and 3.5 times more often than HCV6. These results are fundamentally different from the data presented by Aisenberg GM and co-authors, who believe that pneumonia caused by HSV is rarely reported in patients with solid tumors, and the clinical significance of the virus in LRT samples remains unknown, since, according to the authors, it can be asymptomatic in 5 % of adults [18]. At the same time, the authors show that patients with proven HSV pneumonia were more likely to be on a ventilator (100 % versus 40 %), had a longer stay in the intensive care unit (26 days versus 12), and mortality among patients receiving antiviral therapy was lower than among those who did not (16 % versus 30 %).

In this context, when conducting antitumor therapy, it is necessary to take into account the possibility of reactivation of latent viral infections as a risk factor for the development of severe respiratory complications. Our practical efforts are aimed at providing full-fledged antitumor treatment to all patients without limiting the volume of operations and with a maximum reduction in the risk of complications. The given clinical example vividly demonstrates the situation when the pathological activity of infectious agents increases with a significant weakening of the immune barrier and a violation of the body's reserve forces against the background of a tumor disease, aggressive radical surgical and chemotherapeutic treatment. A mixture of viral agents against the background of immune-mediated processes can undoubtedly trigger critical respiratory dysfunction.

## CONCLUSION

Complications of an infectious nature are an important component of modern antitumor treatment. In this regard, it is necessary to monitor the spectrum of viral infections in cancer patients with signs of respiratory dysfunction at the stages of antitumor therapy. A correct assessment of the situation will help to avoid the development of critical consequences, shorten the time of hospitalization, and improve the course and prognosis of cancer.

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Popova N. N. – study design;
Solovova E. A. – analysis of results;
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Shulga A. V. – clinical support of the study.

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ORIGINAL ARTICLE



# Survival of patients with malignant neoplasms to be screened as part of the adult medical examination during the COVID-19 pandemic

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## ABSTRACT

**Purpose of the study.** To assess the variations of survival in malignant neoplasms subject to screening as part of the regular adult population check-up (index MN, iMN) during the COVID-19 pandemic according to the data of the Arkhangelsk Regional Cancer Registry (ARCR).

**Materials and methods.** Data on nine iMN in the Arkhangelsk region were extracted from the ARCR database. Using the actuarial method, 1-year cancer-specific (CSS) and overall (OS) survival were estimated during the COVID-19 pandemic in 2020–2021. This period was compared with the 2018–2019 period before the pandemic. Differences between the periods were assessed using the log-rank method. Cox regression analysis was used to identify possible causes of differences in survival between the periods.

**Results.** A total of 12,354 records of nine iMNs were selected to analyze the survival during the COVID-19 pandemic. For all malignant neoplasms, there was a decrease in the one-year OSR rates, which was statistically significant for lung cancer (from 42.4 % to 32.8 %, $p = 0.0001$) and cervical cancer (from 90.3 % to 80.8 %, $p = 0.02$), and OS (by 2.6 %–11.0 %, significant for seven of the nine iMNs). Compared with the pre-COVID period, during the pandemic, the proportion of deaths of patients with iMNs from respiratory diseases increased by 1.5 times and the proportion of deaths from external causes increased from 3 % to 9 %, chi-square (4) = 41.8, $p = 0.00001$. In the regression models of CSS and OS, after adjusting for stage, the hazard ratio decreased from 1.15 (95 % confidence interval (CI) 1.07–1.24) to 1.10 (95 % CI 1.03–1.19) and from 1.22 (95 % CI 1.14–1.31) to 1.18 (95 % CI 1.10–1.26). In multivariable regression, the risk of cancer-specific and all-cause death in patients with malignant neoplasms during the pandemic remained higher by 16 % and 24 %.

**Conclusion.** The 15–33 % higher risk of cancer-specific and all-cause death during the COVID-19 pandemic is explained by an increase in the proportion of advanced stages due to limited access to screening. Longer-term survival analysis is required.

**Keywords:** adult population regular check-up, cancer screening, COVID-19 pandemic, causes of death of patients with malignant neoplasms, survival

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Compliance with ethical standards: the work followed the ethical principles set forth in the World Medical Association Declaration of Helsinki, 1964, ed. 2013. The study was approved by the Committee on Biomedical Ethics at the Higher Medical Education of the Ministry of Health of the Russian Federation (extract from the minutes of meeting No. 7 dated 04/08/2021). Personal information about patients was excluded from the database before the analysis began. Informed consent from the study participants is not required for population analyses

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**ОРИГИНАЛЬНАЯ СТАТЬЯ**

# Выживаемость больных злокачественными новообразованиями, подлежащих скринингу в рамках диспансеризации взрослого населения, во время пандемии COVID-19

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## РЕЗЮМЕ

**Цель исследования.** Оценка динамики выживаемости при злокачественных новообразованиях, подлежащих скринингу в рамках диспансеризации взрослого населения (индексных злокачественных новообразований (иЗНО)), в период пандемии COVID-19 по данным Архангельского областного канцер-регистра (АОКР).

**Материалы и методы.** Из базы данных АОКР были извлечены сплошные данные о девяти иЗНО в Архангельской области. С помощью актуарного метода оценивали 1-летнюю опухолеспецифическую (ОСВ) и общую выживаемость (ОВ) в период пандемии COVID-19 в 2020–2021 гг. Этот период сравнивали с периодом 2018–2019 гг. до пандемии. Различия между периодами оценивали с помощью лог-рангового метода. Для выявления возможных причин различий в выживаемости между периодами применяли регрессионный анализ Cox.

**Результаты.** Всего для анализа динамики выживаемости в период пандемии COVID-19 было отобрано 12 354 записи о девяти иЗНО. При всех иЗНО произошло снижение показателей одногодичной ОСВ, статистически значимое при раке легкого (с 42,4 % до 32,8 %, $p$ = 0,0001) и шейки матки (с 90,3 % до 80,8 %, $p$ = 0,02), и ОВ (на 2,6–11,0 %, значимое у семи из девяти иЗНО). Сравнительно с доковидным периодом, в период пандемии возросла в 1,5 раза доля смертей больных иЗНО от заболеваний легких и с 3 % до 9 % доля смертей от внешних причин, хи-квадрат (4) = 41,8, $p$ = 0,00001. В регрессионных моделях ОСВ и ОВ после поправки на стадию отношение рисков уменьшилось с 1,15 (95 % доверительный интервал (ДИ) 1,07–1,24) до 1,10 (95 % ДИ 1,03–1,19) и с 1,22 (95 % ДИ 1,14–1,31) до 1,18 (95 % ДИ 1,10–1,26). В многофакторной регрессии риск смерти от рака и от всех причин у больных иЗНО в период пандемии оставался на 16 % и 24 % более высоким.

**Заключение.** Повышенный риск смерти от рака и всех причин в период пандемии COVID-19 на 15–33 % объясняется увеличением доли распространенных стадий вследствие ограниченного доступа к скринингу. Требуется анализ выживаемости в более отдаленном периоде.

**Ключевые слова:** диспансеризация взрослого населения, скрининг рака, пандемия COVID-19, причины смерти больных ЗНО, выживаемость

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Соблюдение этических стандартов: в работе соблюдались этические принципы, предъявляемые Хельсинкской декларацией Всемирной медицинской ассоциации (World Medical Association Declaration of Helsinki, 1964, ред. 2013). Исследование одобрено Комитетом по биомедицинской этике при ФГБОУ ВО СГМУ Минздрава России (выписка из протокола заседания № 7 от 08.04.2021 г.). Персональные сведения о больных были исключены из БД перед началом анализа. Информированное согласие от участников исследования для популяционных анализов не требуется

Финансирование: финансирование данной работы не проводилось

Конфликт интересов: все авторы заявляют об отсутствии явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи

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## BACKGROUND

The medical regular check-up of the adult population was introduced in Russia in 2013, its main goal is to reduce mortality from non-communicable diseases through their primary prevention and screening [1]. Colorectal cancer, breast cancer, lung cancer, cervical cancer, and prostate cancer are among the oncological diseases to be screened as part of a medical examination [2–5]. At the initial stages of medical examination, cancers of the uterus, ovaries, and kidneys were also among the screened diseases [1].

Earlier, population analysis showed that after the introduction of the check-up, the incidence of more early cancers increased in most index malignancies [6] and patient survival improved [7]. Mortality rates from iMNs had a pronounced downward trend [8].

The COVID-19 pandemic has caused significant changes in the organization of cancer care and check-up. In March 2020, the check-up was temporarily suspended [9]. Special conditions were created for those who wanted to undergo a medical examination at this time, including a separate entrance and the opportunity to avoid visiting the registry. In countries with a long history of population-based screening, the decrease in the number of studies used for screening ranged from 51 % to 77 %, according to the meta-analysis [10]. The suspension of screening led to a catastrophic decrease in the proportion of early stages in most cases, especially in cervical cancer [11, 12], as well as to a decrease in the incidence, or rather, detectability, in most cancers [13].

**Purpose of the study** was to evaluate the dynamics of survival in case of iMN during the COVID-19 pandemic according to the Arkhangelsk Regional Cancer Registry (ARCR).

## MATERIALS AND METHODS

The study received an approval No. 04/05-16 by the Ethics Committee of the Northern State Medical University dated 05/24/2016.

*The Arkhangelsk Regional Cancer Registry* (ARCR) has been continuously recording patients with MNs since 2000. The quality of the registry data (completeness, timeliness, reliability) has been confirmed by the results of international [14, 15] and domestic audits [16].

*Index values.* Taking into account the screening conditions within the check-up, cancers of the colon (International Classification of Diseases code 10 revision C18), rectosigmoid junction, rectum (C19, C20), trachea, bronchi and lung (C33, C34), breast (C50), cervix (C53), and uterine body were selected as the best (C54), ovaries (C56, C57), prostate (C61), kidneys (C64).

In August 2024, depersonalized data was extracted from the ARCR database to analyze the survival rate for each of the nine iMNs, for the period from 2018 to 2021. For the analysis, variables were used, including the identification number, full date of birth, gender, place of residence (city or village) of the patient, date of diagnosis, morphological code and topography of the tumor according to ICD-10, as well as the stage of the disease according to the classification of TNM UICC 8th edition, 2017.

*Methods of analysis.* The actuarial method was used to evaluate the 1-year cancer-specific (CSS) and overall survival (OS) during the COVID-19 pandemic in 2020–2021. This period was compared with the period 2018–2019 before the pandemic. The differences between the periods were assessed using the log-rank method. Cox regression analysis was used to identify possible causes of differences in survival between periods [17]. At the first stage of the analysis, the stage was introduced into the regression model of the one-year CSS and OS as an indicator of check-up cancellation during the pandemic, at the second stage all available variables were introduced. All calculated survival rates were presented with 95 % confidence intervals (95 % CI).

## STUDY RESULTS

In total, 12,354 records of nine iMN cases were selected to analyze the dynamics of survival during the COVID-19 pandemic. Of these, 892 cases were accounted for posthumously, and therefore they were excluded from the analysis. The final survival analysis included 11,462 observations. At the time of the start of the survival analysis, 3133 (27 %) had died. The data on the studied localizations are presented in Table 1.

In general, with all the iMNs, there was a decrease in the indicators of the one-year CSS (Fig. 2).

A statistically significant decrease in CSS rates occurred in lung cancer (from 42.4 % to 32.8 %, $p$ = 0.0001) and cervical cancer (from 90.3 % to 80.8 %, $p$ = 0.02). In cancer of the colon, rectum, uterus, ovaries, prostate, kidney, the decrease in CSS by 2.5 %–7.3 % did not reach statistical significance. In breast cancer, the CSS index did not change significantly during the pandemic. The dynamics of the one-year OS is shown in the Fig. 3.

OS indicators during the pandemic period decreased for all iMNs by from 2.6 % for breast cancer to 11.0 % for ovarian cancer, the differences are statistically significant for seven out of nine iMNs. The structure of mortality from causes unrelated to index cancer has changed. From other causes, 726 patients died in 2018–2019, and 445 patients died in 2020–2021. Compared with the pre-epidemic period, the proportion of deaths from lung diseases increased 1.5 times during the pandemic and the proportion of deaths from external causes increased from 3 % to 9 %, chi-squared (4) = 41.8, $p$ = 0.00001 (Fig. 4).

**Table 1. Patients with iMN in AR for survival analysis in the periods 2018–2019 and 2020–2021. ARCR Data**

| Topography ICD-3 | Total number of registered in 2018–2021 DB | Accounted after death, *n* (%) | Included in the survival rate analysis | iMN deaths during the analysis (out of included in the analysis), *n* (%) |
|---|---|---|---|---|
| C18 | 1821 | 153 (8 %) | 1668 | 566 (34 %) |
| C19-20 | 1173 | 75 (6 %) | 1098 | 340 (31 %) |
| C34 | 2314 | 321 (14 %) | 1993 | 1316 (66 %) |
| C50 | 2089 | 45 (2 %) | 2044 | 201 (10 %) |
| C53 | 696 | 11 (2 %) | 685 | 120 (18 %) |
| C54 | 802 | 27 (3 %) | 775 | 106 (14 %) |
| C56-57 | 558 | 34 (6 %) | 524 | 142 (27 %) |
| C61 | 1922 | 110 (6 %) | 1812 | 175 (10 %) |
| C64 | 979 | 116 (6 %) | 863 | 167 (19 %) |
| Overall | 12354 | 892 (7 %) | 11462 | 3133 (27 %) |

Note: hereafter, the codes and iMNs for the international classification of diseases 10 are: C18 – colon, C19-20 – rectosigmoid junction, rectum, C33-34 – trachea, bronchi and lung, C50 – mammary gland, C53 – cervix, C54 – uterine body, C56-57 – ovaries, C61 – prostate gland, C64 – kidneys

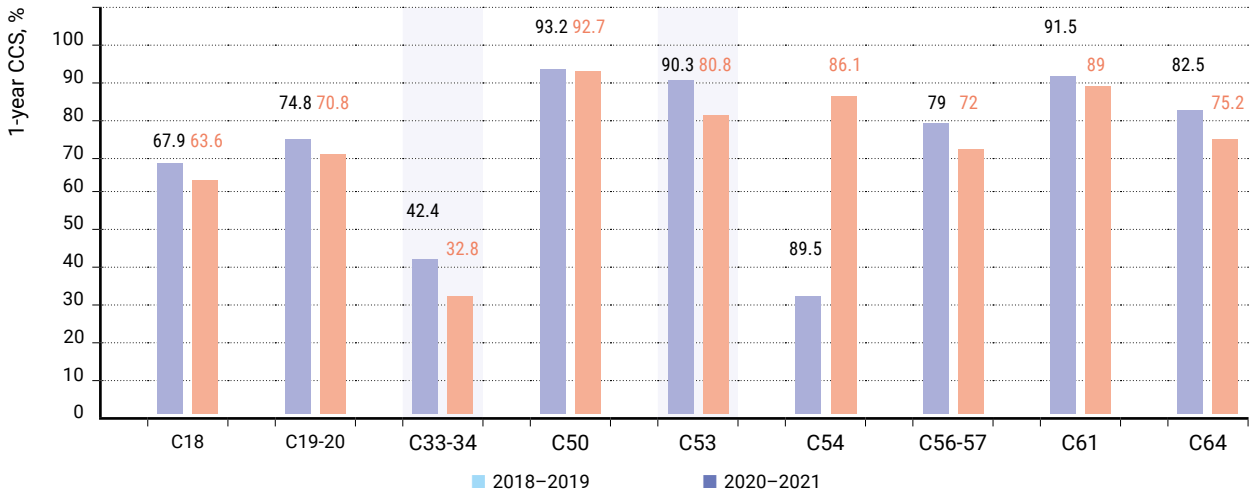


Fig. 1. Dynamics of one-year cancer-specific survival rates in the periods 2018–2019 and 2020–2021. ARCR data. The boxes show statistically significant differences

Among them, the most significant increase in the proportion of deaths from diseases of the respiratory system occurred in patients with cancer of the rectum (from 21 % to 38 %, $p$ = 0.08), lung (from 11 % to 38 %, $p < 0.0001$), breast (from 25 % to 32 %, $p$ = 0.009), uterus body (from 11 % to 35 %, $p$ = 0.03). In prostate and kidney cancers, the proportion of deaths from lung diseases did not increase.

The results of the regression analysis of OS and CSS are presented in the Tables 3 and 4.

During the COVID-19 pandemic, the risk of death from cancer during the first year after the establishment of the iMN increased by 15 %, $p$ = 0.0002, compared with the nearest previous period in 2018–2019. The correction for the stage (the effect of the cancellation of the medical examination) reduced the risk ratio to 1.10, $p < 0.0001$; in the multiple regression, after adjusting for all the factors available in the register, the HR returned to the initial value, the

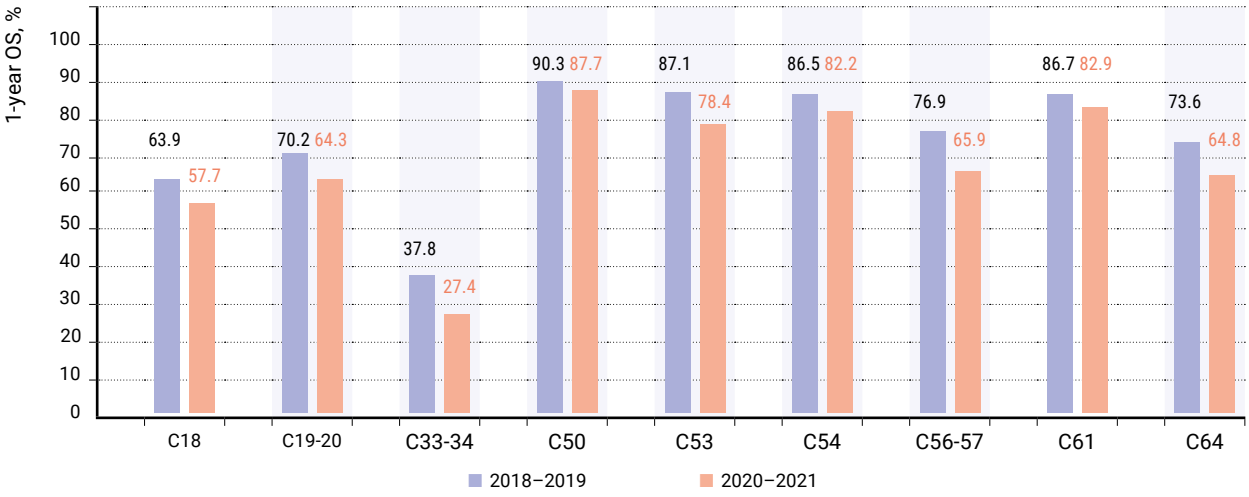


Fig. 2. Dynamics of one-year overall survival rates in the periods 2018–2019 and 2020–2021. ARCR data. The boxes show statistically significant differences

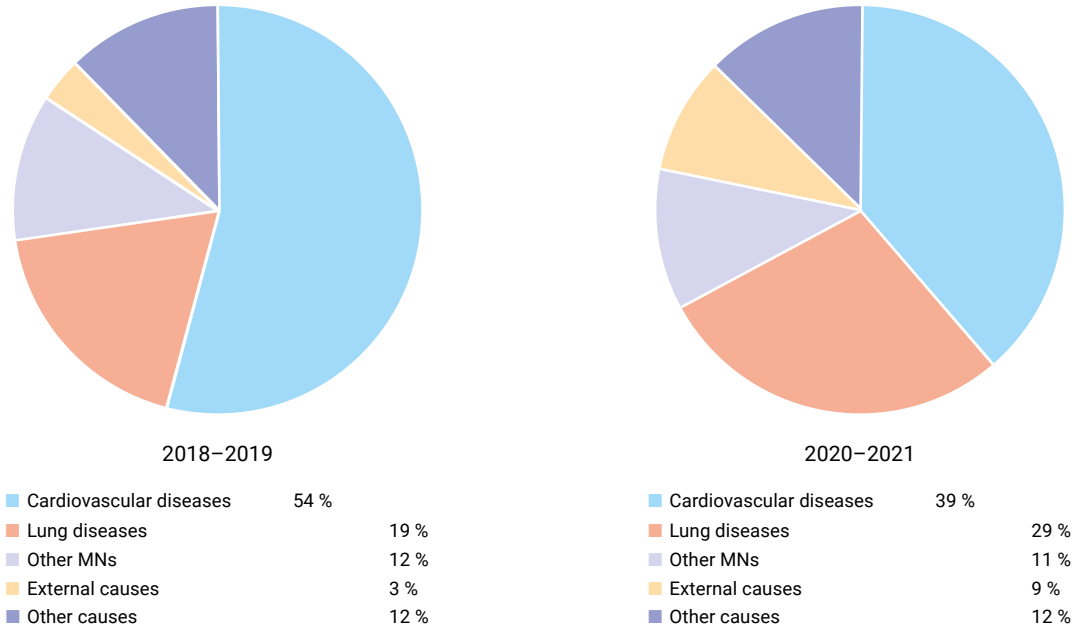


Fig. 3. The structure of mortality from other causes of iMN in the periods 2018–2019 and 2020–2021

differences between the periods, $p < 0.0001$. Among individual patients, a significant increase in the risk of cancer death during the pandemic occurred in lung cancer (HR = 1.24, $p = 0.0002$) and cervical cancer (HR = 1.60, $p = 0.02$). The correction for stage left significant differences for lung cancer; in multiple regression, the risk of death from iMN was significantly higher for colon and lung cancers.

The risk of death from any cause with iMN during the pandemic was 15–52 % higher than in the previous period, and for seven out of nine iMN it was statistically significant. The stage adjustment left a significant higher risk of death for colon, lung, and prostate cancers. The COVID-19 pandemic remained an independent factor of unfavorable prognosis in multiple regression in all cases, with the exception of breast, cervical, and uterine cancers.

**Table 2. Results of the Cox regression analysis of the 1-year CSS with iMN compared to the data obtained in the periods of 2018–2019 and 2020–2021. ARCR Data**

| Topography ICD-3 | 1-year CSS, death risk ratio for the period 2020–2021 compared with the reference period 2018–2019 (95 % CI) | | |
|---|---|---|---|
| | Model 1 one-factor analysis | Model 2 stage correction | Model 3 multifactorial |
| C18 | 1.05 (0.89–1.26) | 1.08 (0.91–1.30) | 1.26 (1.06–1.51) |
| C19-20 | 1.22 (0.96–1.54) | 1.06 (0.84–1.35) | 1.20 (0.95–1.52) |
| C33-34 | 1.24 (1.11–1.39) | 1.17 (1.05–1.32) | 1.12 (1.01–1.26) |
| C50 | 1.09 (0.79–1.52) | 1.01 (0.73–1.41) | 1.04 (0.75–1.45) |
| C53 | 1.60 (1.08–2.37) | 1.15 (0.78–1.71) | 1.19 (0.80–1.78) |
| C54 | 1.32 (0.88–1.98) | 1.35 (0.89–2.05) | 1.18 (0.78–1.81) |
| C56-57 | 1.26 (0.88–1.79) | 1.18 (0.83–1.70) | 1.28 (0.89–1.86) |
| C61 | 1.24 (1.10–1.76) | 1.30 (1.02–1.65) | 1.11 (0.79–1.53) |
| C64 | 1.23 (0.89–1.71) | 1.04 (0.75–1.45) | 1.37 (0.98–1.94) |
| All iMNs | 1.15 (1.07–1.24) | 1.10 (1.03–1.19) | 1.16 (1.08–1.26) |

**Table 4. The results of the regression analysis of the 1-year OS with iMN in comparison with the data obtained in the periods of 2018–2019 and 2020–2021. ARCR Data**

| Topography ICD-3 | 1-year OS, death risk ratio for the period 2020–2021 compared with the reference period 2018–2019 (95 % CI) | | |
|---|---|---|---|
| | Model 1 one-factor analysis | Model 2 stage correction | Model 3 multifactorial |
| C18 | 1.15 (0.98–1.34) | 1.19 (1.01–1.39) | 1.38 (1.17–1.62) |
| C19-20 | 1.29 (1.05–1.59) | 1.15 (0.94–1.42) | 1.32 (1.07–1.63) |
| C33-34 | 1.26 (1.14–1.40) | 1.20 (1.08–1.34) | 1.15 (1.03–1.28) |
| C50 | 1.33 (1.03–1.72) | 1.26 (0.98–1.63) | 1.25 (0.97–1.63) |
| C53 | 1.52 (1.07–2.16) | 1.11 (0.78–1.58) | 1.16 (0.81–1.66) |
| C54 | 1.44 (1.01–2.04) | 1.38 (0.97–1.98) | 1.21 (0.84–1.74) |
| C56-57 | 1.39 (1.00–1.93) | 1.32 (0.95–1.84) | 1.43 (1.02–2.01) |
| C61 | 1.40 (1.10–1.76) | 1.30 (1.02–1.65) | 1.32 (1.04–1.68) |
| C64 | 1.27 (0.96–1.69) | 1.12 (0.84–1.49) | 1.42 (1.06–1.91) |
| All iMNs | 1.22 (1.14–1.31) | 1.18 (1.10–1.26) | 1.24 (1.16–1.33) |

## DISCUSSION

In our study conducted according to the ARCR data, we found a significant decrease in the rates of one–year OS in lung and cervical cancer, and one-year OS in seven out of nine cases. At the same time, for most of them, these changes were associated with a decrease in the proportion of early stages, which is naturally associated with limitations in conducting check-up. During the pandemic, the proportion of deaths from respiratory diseases increased by 48 % and from suicide tripled.

A statistically significant decrease in CSS indicators in our analysis was recorded in cases of pulmonary and cervical fever. It was for these types of cancer that in a previously published study according to the cancer registry of the Arkhangelsk region, we found the most significant decrease in the proportion of early stages among all of them – by 20–35 %. Moreover, there was also an increase in the proportion of neglected cases by 25 % in lung cancer, and the proportion of cervical cancer patients diagnosed in stages III and IV increased by 80 % and 30 %, respectively, compared with the pre-pandemic period [12].

Our data is consistent with the data of other authors. Thus, Barclay NL, et al. A population-based cohort study of electronic medical records of several common cancers from the UK National Database was conducted. A total of 12,259,744 patients aged ≥ 18 years with a history of cancer ≥ 1 year, detected from January 2000 to December 2022, were included. Short-term survival in many cancers was reduced, albeit minimally, during the period, while the decrease in survival in colorectal cancer was equivalent to a return to the mortality rate observed in the first decade of the 2000s. Although data on long-term survival is needed to fully understand the impact of COVID-19 on cancer treatment, the authors conclude that these results illustrate the need for urgent and significant action by the UK National Health Service to address the existing backlog in cancer screening and diagnosis procedures to improve cancer treatment and reduce mortality [18].

Adjusting for all the factors available in the registry database in our study led to a further increase in the value of the death risk ratio when comparing OS and OS during the pandemic compared with the pre-pandemic period. This may indicate that a higher risk of death is influenced not only by the high prevalence of heart disease at the time of diagnosis, but also by other important factors, including delayed diagnosis, lower availability of treatment, especially for elderly patients and during a pandemic.

These factors have been studied in a number of studies. Thus, in a meta-analysis, Tope P, et al. Comparable estimates of mortality risk were found for the time intervals from surgery to adjuvant chemotherapy for breast cancer, colorectal cancer, and ovarian cancer. Risk assessments of a complete pathological response indicated an optimal time window of 7–8 weeks for completion of neoadjuvant chemotherapy before surgery for rectal cancer [19], which, accordingly, could not be performed in absolutely all patients during the pandemic.

The advantage of our analysis is its population-based nature: we analyzed the outcomes of all patients with index-related iMNs registered in the Arkhangelsk region, which allows us to extrapolate the results obtained to the population of the entire country. The limitation of the study is also related to the type of study itself. The registry data, as a rule, does not include detailed information about the genetics and morphology of tumors, the condition of patients and the details of treatment. Therefore, the results of the analysis should be interpreted carefully.

The relatively short period that has passed since the pandemic does not allow us to draw definitive conclusions about the impact of COVID-19 on the survival rates of cancer patients. Further analyses are required in a more distant period of time.

## CONCLUSION

Thus, the COVID-19 pandemic had a significant impact on the outcomes of treatment for iMNs. An increase in the initial prevalence and other pandemic-related factors led to a significant decrease in one-year OS by 10 % in lung and cervical cancers and one-year OS by 3–10 % in cancers of the rectum, lung, breast, cervix and uterus, ovaries and prostate. In most cases, the contribution of an unfavorable change in the stage distribution in the period 2020–2021 to the deterioration of the indicators of CSS and OS was significant. Further analysis of survival in a more distant period is required.

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CLINICAL CASE REPORT

# Tactics of preventive correction of critical respiratory failure in patients with resectable forms of lung cancer in combination with chronic obstructive pulmonary disease

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## ABSTRACT

The article describes clinical examples of the effectiveness of preventive puncture-dilatation tracheostomy (PDT) in preventing critical respiratory complications and improving the immediate results of radical surgical treatment of patients with severe manifestations of chronic obstructive pulmonary disease (COPD) and resectable forms of lung cancer (LC). According to the generalized literature data, the incidence of LC and COPD is 72.8 % among the male population and 52.5 % among women. The combination of LC and COPD causes a significant decrease in respiratory reserves in cancer patients, which leads to an increase in the frequency of complications and an increased risk of death during their treatment. For resectable forms, LC surgical treatment involves removal or resection of the lung, which reduces the total area of the respiratory surface of the lung tissue and oxygen supply to the lungs. These changes are accompanied by a critical violation of the ventilation-perfusion ratio, i. e. alveolar ventilation and cardiac output with an aggravation of hypoxia. This situation is most dangerous for patients with COPD, who after radical surgery have an aggravation of obstructive manifestations in the lungs with an already initially altered gas exchange. As a result, insufficient oxygen enrichment of the organs leads to a cascade of uncontrolled reactions with an intensification of lipid peroxidation and an imbalance in the antioxidant system with fatal consequences for the patient. These clinical examples demonstrate the obvious advantage of preventive PDT, which allows timely changes in the tactics of respiratory support in the early postoperative period and treatment in general (clinical case 1). Routine PDT allows avoiding emergency measures to replace the respiratory function with reintubation, and the use of adapted intelligent artificial lung ventilation modes eliminates additional sedation, muscle relaxation and analgesia in patients LC with severe forms of COPD. Clinical case 2 shows that emergency replacement of the patient's respiratory function has significant difficulties in terms of treatment and prognosis of the course of the disease, and increases the duration of his stay in the intensive care unit.

**Keywords:** lung cancer, chronic obstructive pulmonary disease, respiratory failure, preventive puncture tracheostomy, modes of assisted ventilation

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**КЛИНИЧЕСКИЙ СЛУЧАЙ**

# Тактика превентивной коррекции критической респираторной недостаточности у больных резектабельными формами рака легкого в сочетании с хронической обструктивной болезнью легких

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## РЕЗЮМЕ

Описаны клинические примеры эффективности применения превентивной пункционно-дилятационной трахеостомии (ПДТ) в предупреждении критических респираторных осложнений с улучшением непосредственных результатов радикального хирургического лечения больных с тяжелыми проявлениями хронической обструктивной болезни легких (ХОБЛ) и резектабельными формами рака легкого (РЛ). По данным литературы, частота встречаемости РЛ и ХОБЛ составляет среди мужского населения 72,8 % и 52,5 % среди женщин. Сочетание РЛ и ХОБЛ является причиной значительного снижения респираторных резервов у онкологического больного, что приводит к увеличению частоты осложнений и повышению риска летального исхода в ходе их лечения. При резектабельных формах РЛ хирургическое лечение предусматривает удаление или резекцию легкого, что снижает общую площадь дыхательной поверхности легочной ткани и оксигенацию. Данные изменения сопровождаются критическим нарушением вентиляционно-перфузионного отношения, т. е. альвеолярной вентиляции и сердечного выброса с усугублением гипоксии. Эта ситуация наиболее опасна для пациентов с ХОБЛ, у которых после радикальной операции имеет место усугубление обструктивных проявлений в легких с уже исходно измененным газообменом. В результате недостаточное обогащение органов кислородом приводит к каскаду неконтролируемых реакций с интенсификацией перекисного окисления липидов и дисбалансом в антиоксидантной системе с фатальными последствиями для больного. Данные клинические примеры демонстрируют очевидное преимущество превентивной ПДТ, которая позволяет своевременно менять тактику респираторного обеспечения в раннем послеоперационном периоде и лечения в целом (клинический случай 1). Плановое проведение ПДТ позволяет избежать экстренных мероприятий по замещению респираторной функции с реинтубацией, а применение адаптированных-интеллектуальных режимов искусственной вентиляции легких исключает дополнительную седацию, миорелаксацию и анальгезию у больных РЛ с тяжелыми формами ХОБЛ. Клинический случай 2 показывает, что экстренное замещение дыхательной функции больного имеет значительные сложности в плане лечения и прогноза течения заболевания, а также увеличивает продолжительность его нахождения в отделении интенсивной терапии.

**Ключевые слова:** рак легкого, хроническая обструктивная болезнь легких, респираторная недостаточность, превентивная пункционная трахеостомия, режимы вспомогательной вентиляции легких

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Соблюдение этических стандартов: в работе соблюдались этические принципы, предъявляемые Хельсинкской декларацией Всемирной медицинской ассоциации (World Medical Association Declaration of Helsinki, 1964, ред. 2013). Исследование одобрено Комитетом по этике ФГБУ «Национальный медицинский исследовательский центр онкологии» Министерства здравоохранения Российской Федерации (выписка из протокола заседания № 19 от 22.11.2021 г.). Информированное согласие получено от всех участников исследования

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Конфликт интересов: все авторы заявляют об отсутствии явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи

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## BACKGROUND

Multimodal antitumor therapy of lung cancer (LC) using an organ-preserving surgical approach in combination with various radiation and drug techniques undoubtedly creates prerequisites for improving patient survival rates at virtually all stages of the disease [1]. Nevertheless, LC is consistently leading in terms of morbidity and mortality among the population of Russia and the world. It is known that the effectiveness of antitumor therapy depends on the morphological characteristics, the stage of the disease, as well as on the presence of concomitant pathology and the degree of compensatory capabilities of the body [2]. In this context, the combination of LC and chronic obstructive pulmonary disease (COPD) is often the reason for the rejection of radical surgical treatment, which is associated with a high risk of death in these patients [3].

The Global strategy for the diagnosis, management and prevention of chronic obstructive pulmonary disease (2023) information source notes that COPD is diagnosed in 15–25 % of the adult population and ranks 4th among the leading causes of death in the world [4]. COPD is a progressive disease characterized by a prolonged inflammatory process, persistent bronchial obstruction with marked changes in respiratory function and significant extrapulmonary complications [5].

According to generalized literature data, the incidence of LC and COPD is 72.8 % among the male population and 52.5 % among women. Complex pathology consists of two comorbid diseases with similar pathogenetic mechanisms of formation of pathological processes in the bronchopulmonary system caused by induced inhalation exposure to damaging factors [3, 5]. The combination of LC and COPD is the reason for a significant decrease in respiratory reserves in cancer patients, which undoubtedly leads to an increase in the frequency of complications and an increased risk of death during their treatment [6]. The presence of severe forms of COPD of stages III and IV in these patients actually puts them in the category of incurable. According to the clinical recommendations for the treatment of LC, patients with limited parameters of forced lung capacity less than 50 % and forced exhalation volume in 1 second less than 50 % of the required value are considered functionally inoperable. In such cases, radical surgical treatment is recommended only in small amounts – atypical lung resection or segmentectomy, which undoubtedly does not exclude the recurrence of the tumor and does not guarantee a complete cure for these patients [7]. It was found that in the early postoperative period, COPD progression is observed in 34 % of cases. In addition, postoperative pneumonia leads to severe respiratory deficiency in 17–39 % of cases, pleurisy and pleural empyema in 5–13 % of cases, acute lung injury in 3 % of cases. A significant proportion of complications in 38 % of cases is represented by cardiac decompensation with clinical manifestation in the form of a respiratory component [6].

In cases of full-fledged surgical treatment, the primary cause of the severity of COPD should be taken into account and the development of postoperative complications and death in these patients should be prevented as much as possible. Of particular importance is the occurrence of respiratory failure (RF) in the first hours of the postoperative period, when the patient's body must compensate for respiratory deficiency in the short term [8].

It is known that RF in patients with LC with COPD in the postoperative period, against the background of these pathological changes, most often develops rapidly and requires urgent measures to adequately replace respiratory function. According to Burton BN, et al. (2018) the presence of COPD in men over the age of 65, with a history of smoking, the state of physical status according to the scale of the American Society of Anesthesiologists (ASA) 4 or more points, shortness of breath with little physical exertion, as well as the duration of surgery significantly affect the frequency of unplanned/emergency intubations in patients after thoracotomy operations. At the same time, there are research results stating that unscheduled intubation increases the patient's stay in the intensive care unit and hospital, may be the cause of repeated surgery, and is also significantly associated with a 30-day mortality rate [9].

At the same time, it should be borne in mind that artificial ventilation with emergency tracheal intubation is an extremely aggressive procedure for any patient. Research by Ramachandran SK, et al. (2011) showed that reintubation after noncardiac surgeries is directly related to a 9-fold increase in mortality in these patients [10]. The high probability of developing decompensated RF with possible adverse con-

sequences for patients with severe forms of COPD leads to the search for methods of commensurate replacement of respiratory function in the early postoperative period, preferably with immediate implementation and high efficiency.

The aim of the study was to demonstrate the effectiveness of preventive puncture-dilated tracheostomy (PDT) and adapted intelligent ventilation modes in preventing critical respiratory complications in patients with severe COPD (stages III and IV).

**Clinical case 1**

Patient V., 66 years old, was admitted to the clinical diagnostic department of the National Medical Research Center for Oncology, for examination and treatment purposes. The main complaints of the patient were the following: periodic rise in body temperature, prolonged cough, shortness of breath. Examination of the patient: 1. Fibrobronchoscopy showed a tumor of the upper lobe of the left lung. 2. The result of histological examination of the tumor biopsy identified a squamous cell carcinoma. 3. Positron emission tomography of the chest visualized a 6.2 × 6.6 cm tumor of the upper lobe of the left lung with disintegration and damage to the upper lobe bronchus. 4. Assessment of the function of external respiration – vital lung capacity 40.69 %, forced vital lung capacity 40.76 %, forced air volume during exhalation in 1 second 41.29 %, a significant decrease in all indicators. 5. Echocardiography showed ejection fraction 52 %; left ventricular myocardial hypertrophy, left ventricular systolic function is compensated, aortic wall thickening, left atrium dilation, mitral valve arrhythmogenic insufficiency. The main clinical diagnosis was established as central cancer of the upper lobe of the left lung cT2aN2Mo st IIIa, clinical group 2. Concomitant diagnosis: COPD stage III; coronary heart disease: arrhythmic variant, permanent normosystolic type of atrial fibrillation with episodes of asystole over 3500 ms (implanted pacemaker); Chronic heart failure II A, functional class 2; Hypertension stage 3, risk 3.

By the decision of the council of doctors of the National Medical Research Center for Oncology of the Russian Federation Ministry of Health, in accordance with clinical recommendations and treatment standards, surgical treatment in the amount of an upper lobectomy on the left was recommended for the patient V. Taking into account the initial respiratory deficiency associated with the subcompensated course of COPD, preventive PDT was agreed with the patient immediately after thoracoplastic surgery. The patient has received voluntary informed consent to the treatment and use of personal data for scientific purposes. Under conditions of multimodal combined anesthesia, the patient underwent an upper lobectomy on the left. Previously, catheterization of the epidural space at the Th3-Th4 level was performed under aseptic conditions for the dosed administration of 0.25 % ropivacaine solution with an elastomer pump at a rate of 7 ml/hour. After the upper lobe of the left lung was removed and adequate pneumostasis was performed, the patient was transferred to a double-lung ventilator in pressure control mode with constant forced ventilation. The set respiratory volume was 460 ml, respiratory rate (RR) 16 per minute, minute respiratory volume (MRD) 4.9 l/min, fraction of oxygen in the inhaled mixture (Fraction of Inspired Oxygen $FiO_2$) 45 %, SpO2 saturation 97 %. The gas composition of arterial blood corresponded to normal parameters: $pCO_2$ 4.2 mmHg, $pO_2$ 135 mmHg, pH 7.332, BE 5.4 mmol/l, $HCO_3$ 29.2 mmol/l, $SpO_2$ 92 %. These parameters were monitored in connection with the initial severe COPD disease, as well as due to a significant decrease in the area of the oxygenating surface, as a result of complete resection of the anatomical lobe of the left lung. After the lung surgery was completed, an additional surgical intervention, preventive PDT, was performed under ongoing anesthesia. To do this, a small incision was made in the anatomical area above or below the isthmus of the thyroid gland, followed by puncture with an adapted 14 G needle with a cannula. Then, a screw-shaped buge was inserted into the trachea through a thin conductor and a stoma was formed [11] (Fig. 1). The advantages of PDT should be indicated. This minimizes tracheal injury and infection of surrounding tissues. Dilated tracheostomy significantly reduces the development of lung infections, reduces the time of hospitalization of patients in the intensive care unit [12].

At the end of the operation, due to the high probability of developing a critical RF, the patient's respiratory care was continued in the mode of auxiliary-forced ventilation (Pressure support ventilation (PSV)). In this ventilation mode, the device initiates an auxiliary inhalation for each respiratory effort of the patient. Under the control of the dynamics of the

blood gas composition, 6 hours after the operation, the patient was switched to Synchronized Intermittent Mandatory Ventilation (SIMV) mode. In this mode, if the patient is not breathing independently enough, an extraordinary hardware inhalation is programmed. The absence of an orotracheal intubation tube provided more comfortable and functionally adequate ventilation without additional sedation of the patient. The patient was on a ventilator in full consciousness, there were no signs of discomfort. However, according to the indicators of the gas composition of the patient's blood, a certain deficiency of gas exchange was detected. When individually selecting the parameters of an auxiliary ventilator, the patient was most comfortable in the Synchronized Intermittent Mandatory Ventilation-Volume Guarantee (SIMV–VG) mode. This ventilation mode is susceptible to minimal respiratory efforts of the patient with the possibility of maximum correction of respiratory support. At the same time, the patient did not experience excessive muscle tension and functional discomfort. There were no signs of an increase in hypoxia and hypercapnia for two days. With the appearance of stable dynamics of independent inspiratory efforts without signs of muscle exhaustion, the patient was transferred to spontaneous ventilation mode with constant positive airway pressure at the end of exhalation. The advantage of this ventilation mode is the guaranteed provision of gas exchange, which is ensured by the initiation of respiratory support equipment in cases of changes in the patient's breathing mechanics. When conducting a spontaneous breathing test for patients with COPD (BH 24 per minute, $SpO_2$ >88 % and $PaO_2$ ≥ 65 mmHg absence of negative dynamics of hemodynamic parameters and muscle fatigue) patient V. was excommunicated from the ventilation system. Further, the oxygen-air mixture under tracheostomy conditions was supplied by a high-flow AIRVO-2 generator (flow 5 l/min, temperature 35 degrees, $FiO_2$ 45 %) against this background, blood oxygen saturation was 97 %. In the early postoperative period, the patient received standard drug therapy, which included liberal infusion, antibacterial and inhalation therapy (mucolytics and bronchodilators), prevention of thrombogenic complications. During the entire period of the patient's stay on respiratory replacement support, no life-threatening complications were recorded. Several episodes of rhythm disturbance were stopped in a short time, there were no thrombogenic complications. On the 8th day, the patient was transferred to the surgical department to continue the planned treatment.

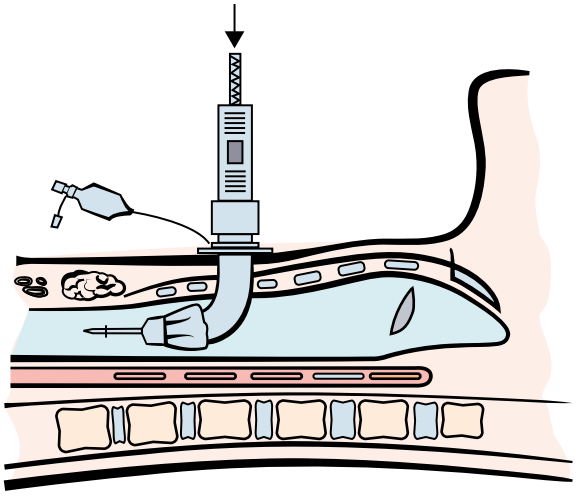

Fig. 1. The scheme of puncture-dilated tracheostomy [11]

**Clinical case 2**

Patient P, 68 years old, was admitted to the clinical diagnostic department of the National Medical Research Center for Oncology, with complaints of prolonged and unproductive cough and shortness of breath. After a comprehensive examination, central cancer of the left lung, cT3N2M0 st IIIb, clinical group 2 was detected. Concomitant diagnosis: COPD stage III; Angina pectoris, functional class 3. Hypertension stage 3, risk 3. According to the treatment standards, surgical treatment in the amount of upper lobectomy on the left is recommended. Some research data: 1. Histological analysis: squamous cell carcinoma. 2. Significant impairment of respiratory function. 3. Echocardiography: multifocal atherosclerotic lesion of the coronary arteries, stenosis of the mouth of the left coronary artery up to 50 %. After a comprehensive examination, the patient underwent surgery: thoracotomy, upper lobectomy on the left. The stages of the operation and anesthetic care met the standards of medical care for patients with LC. Taking into account the initial cardiac disorders and a clear deficit in respiratory function, the patient was on an extended ventilator for the first day after surgery. Ventilation was provided by means of standard intubation of

the tracheobronchial tree with a single-light intubation tube. On the second day after the operation, with full recovery of consciousness and muscle tone, as well as normal parameters of the arterial blood gas composition, the patient was extubated and transferred to non-invasive ventilation (NIV). There were no clinical and laboratory violations during the day. Nevertheless, by the end of the third day after surgery, an episode of sinus tachysystole was noted, which was accompanied by critical hypotension and severe respiratory deficiency. Despite active oxygen therapy, blood oxygen saturation decreased rapidly. Intensive therapy aimed at restoring normal heart rhythm and blood pressure parameters was performed. To prevent critical respiratory failure, tracheal intubation with an endotracheal tube was performed on an emergency basis. During the day, the patient's condition was extremely severe, with no signs of stabilization. By the decision of the council of doctors of the National Medical Research Center for Oncology, it was recommended to perform an additional intervention in the amount of tracheostomy. For the next 16 days, the patient was on a ventilator with various adapted regimens. With independent respiratory support without a pronounced clinical and laboratory deficiency, the patient was weaned from the ventilator and transferred to a NIV AIRVO-2 generator under tracheostomy conditions. On the 20th day, the patient was transferred to the surgical department in a stable condition. However, on the 22nd day, he had an episode of cardiac arrhythmia with signs of hemodynamic and respiratory deficiency. The patient was urgently hospitalized in the intensive care unit for correction of critical disorders. Objective data: consciousness stunning I, skin pale, cyanotic, hemodynamics with a tendency to hypotension, blood pressure 67/52 mmHg, heart rate 128 per minute, atrial fibrillation, $SpO_2$ 76 %. After emergency insufflation with a moistened oxygen-air mixture by a high-flow AIRVO-2 device with preset parameters: flow 38 l/min, temperature 32 degrees, $FiO_2$ 75 %, a rapid recovery of $SpO_2$ to 93 % was noted. The following day, the Airvo parameters were: $FiO_2$–40 %, flow-26 l/min, while $SpO_2$ was 98 %. The patient was in the intensive care unit for another 3 days, then, with complete stabilization of his functional state, he was transferred to a specialized department to continue treatment.

## DISCUSSION

The above clinical examples consider approaches to radical surgical treatment of LC in patients with extremely low functional respiratory reserves due to the sub- and decompensated course of COPD (stages III and IV).

In resectable forms of LC, standard surgical treatment involves removal or resection of the lung, which reduces the total respiratory surface area of the lung tissue and oxygenation. This situation is most dangerous for patients with COPD, who have bronchoconstriction and worsening of obstructive pulmonary manifestations in the postoperative period with an already initially altered gas exchange. These changes are accompanied by a critical violation of the ventilation-perfusion ratio, i. e. alveolar ventilation and cardiac output with worsening hypoxia [3]. In addition, any factors that cause increased stress on the respiratory muscles (impaired evacuation of bronchial secretions, increased hyperinflation of the lungs) reduce alveolar ventilation and lead to an increase in hypercapnia. Increased pulmonary hyperinflation leads to an increase in positive pressure at the end of exhalation, which also increases the load on the respiratory apparatus and increases respiratory effort. A closed chain of pathological reactions occurs with the lack of adequate gas exchange and the development of tissue hypoxia [8]. The insufficiency of the active drainage function of the bronchopulmonary system against the background of a prolonged inflammatory process in the bronchi, a change in the architecture of normal blood flow and the formation of atelectated areas in the lung tissue further complicates the situation. As a result, ineffective oxygen enrichment of organs leads to a cascade of uncontrolled reactions with fatal consequences for the patient [3]. In our opinion, it is possible to avoid a life-threatening respiratory complication in the early stages after surgery and, at the same time, reduce mortality with the rational use of artificial ventilation support in conditions of proactive PDT.

These clinical examples demonstrate the obvious advantage of preventive PDT, which allows timely changes in the tactics of respiratory care in the early postoperative period and treatment in general (clinical case 1). Routine PDT avoids emergency measures to replace respiratory func-

tion without repeated and aggressive translaryngeal tracheal intubation, and the use of adapted intelligent ventilation modes eliminates additional sedation, muscle relaxation, and analgesia in patients with severe COPD. Clinical case 2 shows that emergency replacement of the patient's respiratory function has significant difficulties in terms of treatment and prognosis of the disease, and also increases the duration of his stay in the intensive care unit.

According to open sources in the Russian Federation, we have not found a description of such a medical technique. In this regard, the authors proposed and patented a "Method for the prevention of decompensated respiratory failure after radical surgical treatment of lung cancer in patients with severe forms of chronic obstructive pulmonary disease" (Patent for invention No. 2829259 dated 10/30/2024).

## CONCLUSION

Clinical cases have demonstrated the effectiveness of preventive puncture-dilated tracheostomy and adapted intelligent ventilation modes in the occurrence of urgent respiratory conditions with respiratory decompensation in patients with resectable forms of LC in combination with COPD. The use of the method seems promising in the full-fledged antitumor treatment of patients with LC with extremely low functional reserves due to the sub- and decompensated course of COPD.

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**REVIEW**



# Modern methods of treatment of precancerous vulvar diseases, with a focus on photodynamic therapy: literature review

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## ABSTRACT

Precancerous diseases of the vulva, such as dysplasia and leukoplakia and lichen sclerosus, are a significant problem in gynecology, since their progression can lead to the development of invasive cancer, which endangers the health and life of women. Modern treatment methods, including surgery and topical medications, do not always provide adequate effectiveness, which underscores the importance of finding alternative approaches. Photodynamic therapy (PDT), which is an innovative method, shows promising results in the treatment of precancerous and early tumor diseases, including those affecting the mucous membranes of the vulva. This method, acting on pathological cells with the help of photosensitive drugs and light, minimizes damage to healthy tissues, which makes it promising in clinical practice. The novelty of this study lies in the systematic analysis of the use of PDT specifically for the treatment of precancerous diseases of the vulva, which is still poorly understood.

**Purpose of the study.** To study the effectiveness of various methods of treating precancerous diseases of the vulva, with a focus on photodynamic therapy (via literature review).

**Materials and methods.** A literature search for studies published over the past 5 years was conducted in the Pubmed, Google Scholar, ClinicalTrial.gov, The Cochrane Library, NICE, eLIBRARY and CyberLeninka databases in English and Russian. Global statistical data on tumors of the female genital organs were also studied, especially in the Russian Federation and the Republic of Kazakhstan. As a result of a search query, 5,369 articles were submitted to the above databases. In total, this review examines 50 scientific articles exploring various methods of treating precancerous diseases of the vulva.

**Results.** The results of the study showed that various treatments for precancerous vulvar diseases, including surgical and drug approaches, have limited effectiveness and may be accompanied by side effects such as scarring or recurrence. At the same time, photodynamic therapy has demonstrated high clinical efficacy, providing significant improvement in tissue condition with minimal damage to healthy cells. The method has shown good results in reducing pathological changes such as hyperkeratosis and dysplasia, with a low recurrence rate and rapid tissue repair. In addition, PDT has demonstrated good tolerability and safety, which confirms its promise as an effective and minimally invasive method of treating precancerous diseases of the vulva.

**Conclusion.** PDT can provide high efficiency in disease regression and human papillomavirus (HPV) clearance, as well as help reduce the recurrence of precancerous vulvar diseases.

**Keywords:** vulvar leukoplakia, vulvar kraurosis, vulvar lichen sclerosus, vulvar intraepithelial neoplasia, High-grade SIL of the vulva, vulval HSIL, etiology, pathogenesis, oncogenicity

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**ОБЗОР**

# Современные представления о возможности фотодинамической терапии в лечении предопухолевых заболеваний вульвы: обзор литературы

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## РЕЗЮМЕ

Предопухолевые заболевания вульвы, такие как дисплазия и лейкоплакия и крауоз, представляют собой значимую проблему в гинекологии, поскольку их прогрессирование может привести к развитию инвазивного рака, что ставит под угрозу здоровье и жизнь женщин. Современные методы лечения, включая хирургическое вмешательство и местные препараты, не всегда обеспечивают должную эффективность, что подчеркивает важность поиска альтернативных подходов. Фотодинамическая терапия (ФДТ), являющаяся инновационным методом, показывает многообещающие результаты в лечении предопухолевых и ранних опухолевых заболеваний, включая те, что затрагивают слизистые оболочки вульвы. Этот метод, воздействуя на патологические клетки с помощью светочувствительных препаратов и света, минимизирует повреждения здоровых тканей, что делает его перспективным в клинической практике. Новизна данного исследования заключается в систематическом анализе применения ФДТ именно для лечения предопухолевых заболеваний вульвы, что до сих пор малоизучено.

**Цель исследования.** Изучить эффективность различных способов лечения предопухолевых заболеваний вульвы с углублением на фотодинамическую терапию (по данным литературы).

**Материалы и методы.** Проведен поиск литературы в базах данных Pubmed, Google Scholar, ClinicalTrial.gov, The Cochrane Library, NICE, eLIBRARY и КиберЛенинка на английском и русском языках, опубликованной в течение последних 5 лет. Также изучены общемировые статистические данные опухолей женских половых органов, в особенности в Российской Федерации и Республике Казахстан. По результату поискового запроса вышеуказанных базах данных было представлено 5 369 статей. В общей сложности в настоящем обзоре рассмотрено 50 научных статей, изучающих различные способы лечения предопухолевых заболеваний вульвы.

**Результаты.** Результаты исследования показали, что традиционные методы лечения предопухолевых заболеваний вульвы имеют ограниченную эффективность и могут вызывать побочные эффекты. В то же время фотодинамическая терапия продемонстрировала высокую клиническую эффективность, улучшая состояние тканей с минимальными повреждениями здоровых клеток. Метод показал хорошие результаты в уменьшении гиперкератоза и дисплазии, с низким уровнем рецидивов и быстрой регенерацией, а также хорошей переносимостью и безопасностью.

**Заключение.** ФДТ может обеспечить высокую эффективность в регрессии заболевания и клиренсе вируса папилломы человека (ВПЧ), а также способствовать снижению рецидивов предопухолевых заболеваний вульвы.

**Ключевые слова:** лейкоплакия вульвы, крауроз вульвы, склерозирующий лишай вульвы, интраэпителиальная неоплазия вульвы, SIL вульвы высокой степени тяжести, HSIL вульвы, этиология, патогенез, онкогенность

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## INTRODUCTION

Cancer of the vestibule of the vulva (or vulvar cancer) is a malignant neoplasm that develops on a woman's external genitalia, including the vulva, clitoris and labia. This is a relatively rare disease that accounts for less than 5 % of all cases of cancer of the reproductive system in women, however, it has a significant impact on the health and quality of life of patients [1].

According to the WHO, in 2022, there were about 20 million new cases of cancer and 9.7 million deaths. The estimated number of people who were alive within 5 years of being diagnosed with cancer was 53.5 million. Approximately 1 in 5 people develop cancer during their lifetime, approximately 1 in 9 men and 1 in 12 women die from this disease [2].

Worldwide, cancer of the female genital organs (further referred to as FGM) – vulva, vagina, cervix, uterus, ovaries accounts for approximately 15 % of all fatal cancers in women. According to Chinese researchers, 1,472,801 new cases and 680,041 deaths related to female genital cancer were reported worldwide in 2022 [3].

According to WHO GLOBOCAN data (2022) [4], vulvar cancer ranks 4th in terms of prevalence worldwide, also similar in the Russian Federation and the Republic of Kazakhstan (RF and RK). Globally, 47,336 new cases (0.83 per 100,000 population) and 18,579 deaths (0.30 per 100,000) are recorded annually. In the Russian Federation, the incidence of GPO cancer is 1.1, and the mortality rate is 0.51 per 100,000 population. In the Republic of Kazakhstan, morbidity and mortality are similar to global data: 0.92 per 100,000 and 0.34 per 100,000, respectively. These data indicate that vulvar cancer is characterized by a low prevalence and mortality rate.

In addition, according to the researchers' forecasts, if the incidence remains stable, and population growth and population aging continue in accordance with recent trends, it is predicted that by 2040, the incidence of cancer worldwide will increase by 55 % compared to 2024 (approximately 28 million new cases) [5], and by By 2050, more than 35 million new cases of cancer will be registered, which is an increase of 77 % [2].

**Purpose of the study:** To study the effectiveness of various methods of treating precancerous diseases of the vulva, with a focus on photodynamic therapy.

## MATERIALS AND METHODS

A literature search was conducted in the databases Pubmed, Google Scholar, ClinicalTrial.gov, The Cochrane Library, NICE, eLIBRARY, CyberLeninka using the following keywords: vulvar leukoplakia, vulvar kraurosis, vulvar lichen sclerosus, intraepithelial neoplasia of the vulva, high-severity vulvar SIL, vulvar HSIL etiology, etiology, pathogenesis, pathogenetic development, oncogenicity. Exclusion criteria included articles that did not match keywords, poor quality, or insufficient information in the articles. As a result, 50 articles were analyzed that explore various aspects of the treatment and pathogenesis of precancerous vulvar diseases.

The following types of articles in English and Russian were included: systematic review, meta-analysis, review, guideline, randomized controlled trial, clinical trial. The search depth was 5 years (from 2019 to July 2024).

We also studied the global statistical data of FGO tumors, especially in the Russian Federation and the Republic of Kazakhstan.

Over the years, different terms have been used to refer to vulvar diseases, which has led to different interpretations between clinicians and pathologists. In this regard, in 1993, the International Society for the Study of Vulvar and Vaginal Diseases (ISSVD), together with the International Society for Gynecological Pathology (ISGP), developed and implemented a new classification of vulvar diseases based on pathomorphological changes in the tissues of FGO. This classification, accepted and widely used all over the world, includes three main groups [6–8]:

– Precancerous diseases (sclerotrophic lichen, squamous cell hyperplasia, other dermatoses);
– Intraepithelial neoplasia of the vulva (VIN), which is divided into VIN 1 (mild dysplasia), VIN 2 (moderate dysplasia), VIN 3 (severe dysplasia and cancer in situ) and non-squamous cell intraepithelial neoplasia (Paget's disease, melanoma in situ);
– Invasive cancer.

## STUDY RESULTS

The main goal of therapy is to eliminate itching in the genitals, which is a serious problem for the patient. Treatment of vulvar itching can be divided into four stages: identification of the underlying disease; restoration of the barrier function of the skin; reduction of any inflammatory complications; and elimination of the itching cycle by psychological methods. Asymptomatic cases of vulvar lichen sclerosis (VLS) also need treatment. Topical corticosteroids are the gold standard of treatment for this group of patients. Potent corticosteroid ointments or creams are used. According to the results of clinical studies, they alleviate the symptoms in almost all patients: in about 70 % of cases, the symptoms disappear completely, and in 20 % there is a complete restoration of the skin [9].

Treatment of vulvar leukoplakia is a significant challenge due to a variety of factors, including vulvovaginal dysbiosis on the background of immune disorders and the lack of a unified pathogenetic approach to therapy [10]. Microflora disorders and immune dysfunctions support the pathological processes of keratinization, creating a risk of recurrence and complicating the restoration of the epithelium. As a result, recurrence of hyperplastic dystrophy is observed in 45–67 % of cases [11].

According to the European Guidelines for the Treatment of Vulvar Diseases from 2021, the treatment of lichen sclerosing (LS) includes the use of ultra-strong or potent topical steroids (for example, clobetazole propionate, mometasone furoate) as the first line of therapy for genital LS, with mandatory adherence to the regimen of use. Proactive ointments (mometasone furoate 0.1 %, clobetazole propionate 0.05 %) are effective for maintaining remission. In case of secondary infection, antibacterial and antifungal agents are used. Alternative second-line methods include topical calcineurin inhibitors, systemic retinoids, phototherapy, therapy, surgery (only with concomitant changes), as well as stem cells and PRP plasma (low level of evidence). Surgical intervention may be required to treat adhesions and scarring, but is contraindicated in cases of active inflammation.

Treatment of intraepithelial neoplasia of the vulva (VIN) in HSIL includes the following methods: surgical treatment remains the main choice, however, it is associated with a high recurrence rate and a negative impact on quality of life and sexual function. Imiquimod cream (an immune response modifier with antiviral and antitumor properties) (GRADE 1B), laser $CO_2$ therapy, loop electrosurgical excision (LEEP) and surgical excision by cold plasma coblation are also used. In some cases, it is possible to follow up without treatment, expecting spontaneous regression. Surgical excision by cold plasma coblation is preferable for differentiated vulvar intraepithelial neoplasia (dVIN) [12].

According to the Bulletin of the American College of Obstetricians and Gynecologists, for the initial treatment of lichen sclerosis, it is recommended to use a local corticosteroid ointment of medium or high efficacy, such as 0.05 % ointment with clobetazole propionate or 0.1 % ointment with mometasone furoate. According to the recommendations of experts, in particular the British Association of Dermatologists, clobetazol propionate should be applied once a day at night for 4 weeks, then alternated at night for the next month, and then twice a week for 4 weeks. Follow-up is necessary after 3 months to assess the response to therapy and the correctness of the drug use. With good disease control, a follow-up examination should be carried out after 3–6 months, with poor control, more frequent visits are necessary. Patients should seek medical attention if persistent ulceration or neoplasm occurs; in such cases, a biopsy is important to rule out intraepithelial neoplasia or invasive squamous cell carcinoma. A randomized study of 27 patients with lichen sclerosis showed that twice weekly administration of 0.1 % mometasone furoate ointment for 56 weeks effectively prevents relapses without side effects [13]. A prospective cohort study involving 507 patients who had been followed for at least 2 years demonstrated that compliance with long-term corticosteroid therapy (defined as permanent or in most cases) significantly exceeds partial compliance in symptom control (93.3 % vs. 58.0 %; $p < 0.001$), prevention of adhesions and scarring (3.4 % vs. 40.0 %; $p < 0.001$) and reduction of vulvar cancer prevalence (0 % vs. 4.7 %; $p < 0.001$) [14].

A study by Gallio N, et al. (2024) revealed a high risk of developing both primary and recurrent squamous cell carcinoma of the vulva in patients with dVIN. It was recommended to optimize early detection of diseases, long-term follow-up, and adequate topical treatment with ultrapotent corticosteroids. The use of laser ethylmethylhydroxypyridine succinate can significantly improve the results of treatment of kraurosis, although contraindications and potential problems with resistance must be taken into account [15].

Also, a study conducted by Popa A, et al. (2024) shows that potent topical corticosteroids are currently widely recognized as the most effective treatment method for achieving remission in LS, but given the potential complications of long-term treatment, understanding the evolution of LS during puberty becomes especially important to determine the need for aggressive or more conservative therapeutic interventions. New treatments, including PRP (platelet-rich plasma), stem cell therapy, and energy-based laser therapy such as fractional carbon dioxide ($CO_2$) laser and yttrium aluminum garnet doped neodymium (Nd-YAG) laser, are being investigated to identify more effective treatments for LS than potent topical corticosteroids. Currently, the use of clobetazol 0.05 % ointment on a daily basis for 4–12 weeks is the gold standard for the treatment of LS [16].

In recent years, there has been increasing evidence regarding the effectiveness of using PRP in various fields of medicine [17]. The basis of the action of various varieties of PRP is the release of biologically active factors from alpha-granules of platelets. Leukocytes and fibrin contained in some of its varieties, as well as other components (for example, hyaluronic acid), also contribute to the action of PRP. Activated PRP has a higher biological activity than inactive PRP. PRP preparations are widely used in the field of traumatology, cosmetology and trichology, surgery and proctology, gynecology and urology [18, 19]. The method is based on the collection of 10–20 ml of the patient's own whole blood, which is placed in a specialized tube, where it is centrifuged to obtain platelet-rich plasma. Several milliliters of this enriched plasma obtained by centrifugation are injected into the required tissue. There are several types of tubes for PRP preparations: a tube designed to produce autologous platelet-rich plasma with prolonged platelet degranulation, which ensures maximum tissue regeneration effect; a tube designed to produce an autologous thrombin-fibrin gel, which serves as a volumetric matrix and activator of platelet growth factors degranulation formed in the previously mentioned tube; The cell matrix method, which uses test tubes to produce a patented combination of hyaluronic acid and platelet-enriched plasma [20]. Plasma administration in periodic courses demonstrates a steady positive effect even in those women in whom standard glucocorticoid therapy has proved ineffective [21].

The literature describes clinical cases of improvement in the histological picture and female sexual function index after plasma therapy [22–24]. In a study by Behnia-Willison F, et al. ($n$ = 28) patients with LS that did not respond to steroid therapy received PRP injections 3 times with an interval of 4–6 weeks and again a year later in all affected areas of the vulva. The patients showed clinical improvements, including a reduction in the size of the lesions, and 28.6 % of them had complete disappearance of the lesions after a course of PRP therapy. The author of the study concluded that PRP injections can be considered as an effective method of treating LS [25]. Although the use of PRP drugs is usually effective and safe, there are a number of contraindications for which caution should be exercised when prescribing this procedure. Contraindications to PRP include thrombocytopenia, septicemia, platelet dysfunction syndrome and exogenous diseases, hypofibrinogenemia, systemic connective tissue diseases, anemia, and the use of corticosteroids or nonsteroidal anti-inflammatory drugs (NSAIDs) prior to the procedure [18].

According to research, against the background of laser therapy, patients experienced a significant regression in complaints related to dystrophic diseases of the vulva, and there was also an increase in satisfaction with the quality of sexual life. Patients in the control group who used local glucocorticosteroids noted a resumption of itching symptoms in the vulvar region, which required continued maintenance therapy for up to 6 months and indicated a short-term effect of glucocorticosteroids [26, 27].

One potential solution that can meet these criteria is photodynamic therapy (PDT). PDT is a recommended treatment for precancerous diseases of the vulva [28–30]. The PDT mechanism is based on the use of photosensitizers in combination with visible light of a certain wavelength to produce oxygen and free radicals, which leads to apoptosis and necrosis of cells in the affected area to alleviate skin damage without affecting the surrounding normal tissues and cells [31–33].

Studies show that PDT can alleviate clinical symptoms and signs such as itching and loss of skin elasticity by improving microcirculation in skin lesions, regulating local cellular immune function, stimulating fibroblast activity and synthesis of types I and III collagen [34, 35].

Some researchers also note that the use of curcumin with PDT may become a promising therapy in the treatment of vulvar lesions, leading to the death of only cells exposed to radiation [36, 37]. Since curcumin is a natural bioactive compound with antitumor properties. The use of nanoparticles containing curcumin can provide better efficacy of this compound in therapy, because they achieve good biocompatibility and do not exhibit cytotoxicity [38, 39].

In addition, preclinical studies are available for the potential use of other types of molecules in PDT that can destroy precancerous and cancer cells, such as hypericin [40, 41], indocyanine green (ICG) [42], methylene blue dye [43], zinc phthalocyanine, and other chlorophyll derivatives other than E6 chloride [44], methyl violet [45], bacteriochlorins [46], fullerenes [47, 48], xanthene molecules (eosin and erythrosine) [49].

Against the background of PDT use, 95 % of patients experienced complete clinical remission, confirmed by cytological and morphological studies. This indicates the high efficiency of PDT as an organ-preserving treatment method, which has a minimal level of side effects [50, 51].

Maździarz A (2019) used 5 % aminolevulinic acid (5-ALA) with 2 % dimethyl sulfoxide, performing 10 procedures with a weekly interval, which led to partial remission and negative results on human papillomavirus (HPV) DNA in 50 % of patients. Li Z, et al. (2020) used 20 % 5-ALA with fewer procedures (4–9), which resulted in a significant reduction in symptoms in 92.31 % of patients, although relapses were observed in 20 %. Liu J, et al. (2021) also used 20 % 5-ALA, but with more treatments (6) such as improved clinical and dermatoscopic characteristics, although pain and erosion were common. Zhang F, et al. (2021) and Zielińska A, et al. (2021) used different concentrations of 5-ALA and treatment regimens. Zhang F, et al. a significant decrease in lesions was observed in 56.6 % of patients and an improvement in histological results. Zielińska A, et al. Clinical remission was recorded in 75.3 % of patients, but histopathological remission was low (2.7 %). All studies noted complications such as pain and burning, which varied in severity and duration. Study participants typically experienced short-term discomfort such as pain and burning for several days after the procedures, as well as paresthesia, erythema, and edema.

Zhou M, et al. (2023) note that photodynamic therapy with 5-aminolevulinic acid (ALA-PDT) has demonstrated the same clinical efficacy as surgical intervention in the treatment of vulvar SIL, but with milder side effects and preservation of the integrity of the vulvar structure. In a prospective study by Han Q, et al. (2022), cases of recurrence are observed, indicating the need for long-term follow-up and possible re-treatment to achieve better HPV clearance. Studies have also reported various complications, including itching and mild pain. These data indicate the high potential of 5-ALA therapy in the treatment of VIN but emphasize the importance of further monitoring and management of possible complications and relapses.

In a recent study, Avin M and Gomberg MA (2024) compared the effectiveness of treatment of patients suffering from involutive changes in the vulva using PDT and PDT combined with PRP plasma therapy. As a result, there was no statistically significant difference in the effectiveness of the effect on quality of life ($p = 0.07$), however, combining PDT with PRP showed a significant improvement in symptoms such as burning and dryness, while no side effects were observed ($p < 0.001$), which further positively affected physical activity, psycho-emotional state and sexual activity. the life of patients [50, 51].

Antimicrobial photodynamic therapy (aPDT) is also one of the fundamental tools in modern therapy of precancerous conditions and cancers

associated with HPV, in particular, due to the increasing versatility of photosensitizers and the numerous possibilities of combining aPDT with other antimicrobial treatments to combat localized infections [52]. Thus, aPDT and its numerous therapeutic combinations can become an advanced routine treatment method for combating microorganisms [53].

Ozone-bacteriophage therapy is noted as another method of treating involutive and dystrophic LPO processes, which, according to the authors, contributed to the restoration of the expression of estrogen and progesterone receptors in the glands and stroma of the endometrium [56].

In addition, scientists from Russia note that in the treatment of precancerous vulvar conditions, the factor of the psychoemotional state of women is very important, in the treatment of which supportive and cognitive behavioral therapy, as well as methods of distraction from negative inner feelings, are effective. Autogenic training combined with meditation can help improve the emotional background. Couples therapy, which includes discussing sexual issues and fears with a partner, can be helpful. In addition, it is important to conduct educational conversations that help increase treatment adherence, as the doctor's recommendations can slow down the progression of the disease and improve the condition of patients [54].

## CONCLUSION

The treatment of precancerous vulvar diseases covers a wide range of methods and tools, but the use of topical corticosteroids remains the gold standard of therapy. In recent years, PDT has established itself as a promising treatment method, demonstrating significant potential in combating precancerous vulvar conditions.

Existing studies show that PDT can be highly effective in disease regression and HPV clearance, as well as help reduce relapses. Despite the positive results, there is a need for further study and publication of modern randomized clinical trials and systematic reviews that could provide a more extensive and reliable assessment of the effectiveness of PDT in the treatment of precancerous vulvar conditions.

To improve understanding and optimize the treatment of precancerous vulvar conditions, it is recommended to conduct research aimed at studying combined treatment methods, which, according to some reports, can lead to improved treatment outcomes, reduced relapses and reduced risk of complications. Studies of combined approaches will allow us to determine the most effective strategies and optimal treatment regimens, considering the individual characteristics of patients.

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Shanazarov N. A., Alchimbaeva M. A., Kisikova S. D. – analysis of the obtained data;
Seitbekova K. S., Galiev I. Z. – writing the article;
Shanazarov N. A., Alchimbaeva M. A. – editing of the article;
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