South Russian Journal of Cancer 2023, Vol. 4, No. 2. P. 16-27
https://doi.org/10.37748/2686-9039-2023-4-2-2
https://elibrary.ru/xvfmlt
ORIGINAL ARTICLE

LEVELS OF BIOGENIC AMINES IN LUNG TISSUES OF PATIENTS WITH NON-SMALL CELL LUNG CANCER AFTER COVID-19 OF VARIOUS SEVERITY

O. I. Kit, E. M. Frantsiyants, D. A. Kharagezov, V. A. Bandovkina✉, N. D. Cheryarina, Yu. A. Pogorelova, Yu. N. Lazutin, A. G. Milakin, I. A. Leyman, O. N. Stateshny, N. D. Ushakova

National Medical Research Centre for Oncology, Rostov-on-Don, Russian Federation
✉ valerryana@yandex.ru

ABSTRACT

Purpose of the study. Was to analyze levels of biogenic amines (serotonin and its metabolite 5-HIAA, dopamine, norepinephrine and histamine) in lung tissues of patients with lung cancer with previous COVID-19 infection.
Patients and methods. The study was carried out on samples of intact lung tissues, tumor tissues and peritumoral lung tissues obtained during open biopsy while performing radical surgery from patients with morphologically verified non-small cell lung cancer (NSCLC), stage I–IIIA ($cT_{1-3}N_xM_0$). The main group included 30 NSCLC patients (15 men and 15 women) after severe or moderate to severe COVID-19 who required hospitalization. The control group included 15 men and 15 women with NSCLC after asymptomatic or mild SARS-CoV-2 infection. The mean age of patients was 59.11 ± 2.9 years. Levels of dopamine, norepinephrine, serotonin, 5-hydroxyindoleacetic acid (5-HIAA) and histamine were measured by ELISA (IBL, Germany).
Results. All studied lung tissue samples from men and women of the main group, compared to the control group, showed deficiency of catecholamines with their ratio unchanged, and changes in serotonin metabolism to ensure its stable level. Thus, levels of dopamine in samples of patients of the main group were lower on average by 1.3 times, norepinephrine by 1.3–3.3 times, serotonin by 1.6 times, and 5-HIAA by 1.8–4 times. At the same time, sex differences were observed in histamine levels. Regardless of the COVID-19 severity, levels of diamine in women were lower in the resection line tissue by an average of 2.4 times, and in the peritumoral tissue by 1.6 times, compared with men, but there were no sex differences in the tumor tissue.
Conclusion. Apparently, changes in the levels of dopamine, norepinephrine, and serotonin in lung tissues could be associated with the severity of SARS-CoV-2 infection. Since dopamine is involved in counteracting the carcinogenic action of the adrenergic system and in the regulation of various immunocompetent cells in the tumor microenvironment, such changes in the biogenic status in the lungs of patients of the main group could lead to a more severe tumor course.

Keywords: dopamine, serotonin, histamine, lung cancer, COVID-19

For citation: Kit O. I., Frantsiyants E. M., Kharagezov D. A., Bandovkina V. A., Cheryarina N. D., Pogorelova Yu. A., Lazutin Yu. N., Milakin A. G., Leyman I. A., Stateshny O. N., Ushakova N. D. Levels of biogenic amines in lung tissues of patients with non-small cell lung cancer after COVID-19 of various severity. South Russian Journal of Cancer. 2023; 4(2): 16-27. https://doi.org/10.37748/2686-9039-2023-4-2-2, https://elibrary.ru/xvfmlt

For correspondence: Valeriya A. Bandovkina – Dr. Sci. (Biol.), senior researcher of the laboratory for the study of pathogenesis of malignant tumors, National Medical Research Centre for Oncology, Rostov-on-Don, Russian Federation.
Address: 63 14 line str., Rostov-on-Don 344037, Russian Federation
E-mail: valerryana@yandex.ru
ORCID: http://orcid.org/0000-0002-2302-8271
SPIN: 8806-2641, AuthorID: 696989

Compliance with ethical standards: The ethical principles presented by the World Medical Association Declaration of Helsinki, (1964, ed. 2013) were observed in the study. The study was approved by the Ethics Council of the NMRC for Oncology of the Ministry of Health of the Russian Federation (extract from the protocol of the meeting No. 6 dated 01/17/2022). Informed consent was received from all participants of the study.

Funding: this work was not funded.

Conflict of interest: the authors declare that there are no obvious and potential conflicts of interest associated with the publication of this article.

The article was submitted 13.09.2022; approved after reviewing 19.04.2023; accepted for publication 05.06.2023.

Южно-Российский онкологический журнал 2023, Т. 4, № 2. С. 16-27
https://doi.org/10.37748/2686-9039-2023-4-2-2
https://elibrary.ru/xvfmlt
3.1.6. Онкология, лучевая терапия
ОРИГИНАЛЬНАЯ СТАТЬЯ

УРОВЕНЬ БИОГЕННЫХ АМИНОВ В ТКАНИ ЛЕГКОГО БОЛЬНЫХ НЕМЕЛКОКЛЕТОЧНЫМ РАКОМ ЛЕГКОГО ПЕРЕНЕСШИХ COVID-19 РАЗЛИЧНОЙ СТЕПЕНИ ТЯЖЕСТИ

О. И. Кит, Е. М. Франциянц, Д. А. Харагезов, В. А. Бандовкина✉, Н. Д. Черярина, Ю. А. Погорелова, Ю. Н. Лазутин, А. Г. Милакин, И. А. Лейман, О. Н. Статешный, Н. Д. Ушакова

НМИЦ онкологии, г. Ростов-на-Дону, Российская Федерация
✉ valerryana@yandex.ru

РЕЗЮМЕ

Цель исследования. Изучение содержания биогенных аминов – серотонина и его метаболита 5-ОИУК, дофамина, норадреналина и гистамина в тканях легкого у больных раком легкого перенесших COVID-19 различной степени тяжести.
Пациенты и методы. Для исследования послужили образцы легочной ткани вне зоны опухолевого роста, ткани опухоли и ее перифокальной зоны, полученные в результате открытой биопсии при выполнении радикальных операций у больных морфологически верифицированным немелкоклеточным раком легкого (НМРЛ) I–IIIA стадии ($cT_{1-3}N_XM_0$). В основную группу вошли 30 больных НМРЛ (15 мужчин и 15 женщин), перенесших COVID-19 в тяжелой и средней тяжести форме, потребовавшей госпитализации, контрольную группу аналогично составили 15 мужчин и 15 женщин с НМРЛ, у которых инфекция SARS-CoV-2 протекала бессимптомно или в легкой форме. Средний возраст пациентов составил 59,11 ± 2,9 года. Количественную оценку содержания дофамина, норадреналина, серотонина, 5-оксииндолуксусной кислоты (5-ОИУК) и гистамина выполняли методом ИФА (IBL; Германия).
Результаты. Во всех исследованных образцах тканей легкого мужчин и женщин основной группы, по сравнению с контрольной группой, имеет место недостаточность катехоламинов, без нарушения их соотношения и изменение метаболизма серотонина для обеспечения его устойчивого уровня. Так, уровень дофамина в образцах пациентов основной группы был ниже в среднем в 1,3 раза, норадреналина в 1,3–3,3 раза, серотонина в среднем в 1,6 раза, а 5ОИУК в 1,8–4 раза. В тоже время установлены половые различия в содержании гистамина, когда у женщин, вне зависимости от тяжести перенесенного COVID-19 уровень диамина был ниже в линии резекции в среднем в 2,4 раза, а в перифокальной зоне в 1,6 раза, по сравнению с мужчинами, но отсутствие половых различий в ткани опухоли.
Заключение. Очевидно, изменения уровня дофамина, норадреналина и серотонина в тканях легкого могут быть связаны с тяжестью перенесенной инфекции SARS-CoV-2. Учитывая то, что дофамин участвует в противодействии канцерогенному эффекту адренергической системы и в регуляции различных иммунокомпетентных клеток в микроокружении опухоли, подобные изменения биогенного статуса в легком у больных основной группы могут приводить к более тяжелому течению злокачественного процесса.

Ключевые слова: дофамин, серотонин, гистамин, рак легкого, COVID-19

Для цитирования: Кит О. И., Франциянц Е. М., Харагезов Д. А., Бандовкина В. А., Черярина Н. Д., Погорелова Ю. А., Лазутин Ю. Н., Милакин А. Г., Лейман И. А., Статешный О. Н., Ушакова Н. Д. Уровень биогенных аминов в ткани легкого больных немелкоклеточным раком легкого перенесших COVID-19 различной степени тяжести. Южно-Российский онкологический журнал. 2023; 4(2): 16-27. https://doi.org/10.37748/2686-9039-2023-4-2-2, https://elibrary.ru/xvfmlt

Для корреспонденции: Бандовкина Валерия Ахтямовна – д.б.н., старший научный сотрудник лаборатории изучения патогенеза злокачественных опухолей, ФГБУ «НМИЦ онкологии» Минздрава России, г. Ростов-на-Дону, Российская Федерация.
Адрес: 344037, Российская Федерация, г. Ростов-на-Дону, ул. 14-я линия, д. 63
E-mail: valerryana@yandex.ru
ORCID: http://orcid.org/0000-0002-2302-8271
SPIN: 8806-2641, AuthorID: 696989

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 советом по этике ФГБУ «НМИЦ онкологии» Минздрава России (выписка из протокола заседания № 6 от 17.01.2022 г.). Информированное согласие получено от всех участников исследования.

Финансирование: финансирование данной работы не проводилось.

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

Статья поступила в редакцию 13.09.2022; одобрена после рецензирования 19.04.2023; принята к публикации 05.06.2023.

BACKGROUND

Coronavirus disease (COVID-19) is caused by a new virus – severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1–3], which can be transmitted from one person to another. By January 3, 2022, more than 290 million people worldwide had been diagnosed with COVID-19, and more than 5.4 million of these patients had died [4]. Lung cancer (LC) ranks second among the most common malignant neoplasms in the world in terms of morbidity and mortality [5–7]. Patients with LC may be at a higher risk of infection with SARS-CoV2 and have a worse prognosis for the course of the disease [8]. As a rule, multiple immune disorders are observed in patients with LC [9], which may affect the effectiveness of COVID-19 treatment.

There is still insufficient information on the impact of COVID-19 infection on the survival of patients with-LC, as well as on complications associated with infection and prognostic factors. In a meta-analytical study conducted by Desai A. D. and co-authors (2022) [10], with data on 2,922 cancer patients at various stages hospitalized with COVID-19, it was found that male gender, middle age and recent active cancer therapy were factors associated with mortality. Other authors note that in addition to age and chronic concomitant diseases, the need for invasive or non-invasive mechanical ventilation and female gender are identified risk factors for respiratory long-term complications of COVID-19 [11].

Data on subacute and long-term consequences of COVID-19 are accumulating. The most severe manifestation of post-infectious lung damage is pulmonary fibrosis, which has a profound long-term effect on the respiratory health of patients. More than a third of patients who survived severe COVID-19 pneumonia developed pulmonary fibrosis [12]. In animal models, SARS-CoV-2 infection also induced the expression of profibrotic cytokines and the occurrence of pulmonary fibrosis [13]. Although the specific mechanism requires further study, lung fibrosis caused by SARS-CoV-2 has much in common with lung fibrosis caused by other viruses.

It is worth noting that pulmonary fibrosis after a viral infection may not be a direct result of infection, and other factors, such as trauma caused by ventilation, may also play a role. Many severe patients with viral infection undergo artificial lung ventilation (AVL) during treatment, and available studies have shown that patients with a longer period of ventilation had a higher probability of developing pulmonary fibrosis and a worse prognosis [14]. Diem K. et al. (2020) showed that alveolar cells under mechanical stress can produce signaling molecules to communicate with neighboring cells and promote a fibrous reaction [15].

The mechanisms underlying the pulmonary fibrosis caused by the virus need to be studied in depth. Research can help doctors assess the risks of a combination of COVID-19 and lung cancer, which can ultimately reduce or even prevent deaths. A key gap in knowledge and acute unmet medical need in the clinical management of lung cancer patients in the era of the COVID-19 pandemic is the characterization of the molecular mechanisms linking these two diseases. Of particular interest, from our point of view, is the study of biogenic amines in lung tissue of lung cancer patients who have undergone COVID-19.

It has been shown that histamine and the histamine receptor signaling pathway can play a crucial role in the penetration of the virus into endothelial cells. SARS-CoV-2 causes an inflammatory reaction in infected patients [11]. The authors believe that a local increase in histamine levels, for example, in the lungs, brain or heart, can change the penetration of the virus into cells directly in the body. Wu M. L. et al. (2022) showed that mast cell degranulation caused by spike protein initiates inflammation of the alveolar epithelium to destroy the barrier, and suggested using antihistamines not for their intended purpose, but as mast cell stabilizers to block degranulation and, consequently, suppress inflammation and prevent lung damage [16]. High levels of histamine and histamine receptors, including H1R~H4R, were found in various types of tumor cells and cells of the tumor microenvironment, which suggests their involvement in tumor progression [17].

Research by Fabre A. with co-authors (2008) [18] showed the involvement of serotonin in the pathophysiology of bleomycin-induced pulmonary fibrosis in mice and identified it as a potential therapeutic target for fibrotic lung diseases. Serotonin (5-hydroxytryptamine; 5-HT) is a vasoactive peptide synthesized from tryptophan by enterochromaffin cells of the intestine and endothelial cells. There is a very low level of circulating free serotonin in the blood, since most of the serotonin is concentrated in platelets. Under physiological conditions, the lungs

are exposed to low levels of circulating serotonin. In pathological conditions, the release of serotonin stored by platelets and endothelial cells can increase the concentration of serotonin both locally and in the bloodstream. It has been shown that 5-HT2A and 5-HT2B receptor subtypes play the most important role in the lungs, where serotonin is involved in the control of vaso- and bronchoreactivity [18]. Studies have shown the potential stimulating effect of serotonin on proliferation, invasion, dissemination of cancer cells and tumor angiogenesis. Although the underlying mechanism is complex, it is assumed that serotonin levels in the tumor and its interaction with specific receptor subtypes are associated with disease progression [19].

The role of norepinephrine in malignant growth is associated with cancer cell survival, proliferation, resistance to apoptosis, invasion, metastasis, angiogenesis and stromal compartments in the tumor microenvironment [20]. Norepinephrine can inhibit oxidative phosphorylation and induce angiogenic switching, stimulating the metabolism of endothelial cells in a direction that promotes cancer progression [21]. There are several mechanisms underlying the role of norepinephrine in the development of tumors. Activation of β2-adrenoreceptors promotes tumor growth and angiogenesis by increasing the expression of vascular endothelial growth factor (VEGF), metalloproteases MMP2 and MMP9, which additionally potentiate angiogenic and metastatic processes in adrenal cancer, lung cancer, and breast cancer. These effects are largely mediated by a β-adrenergic increase in cyclic adenosine monophosphate (cAMP) levels and subsequent activation of protein kinase A, which performs the corresponding functional regulation by phosphorylation of downstream targets, such as protein binding the cAMP response element, nuclear factor kappa B and activator protein 1 [22].

Dopamine is a biological precursor for the synthesis of norepinephrine. In addition to the common angiotensin-converting enzyme receptor 2, new coronaviruses may use other alternative pathways. The first putative receptor or coreceptor is dopamine. Dopamine is known to reduce SARS-CoV-2 replication *in vitro* by suppressing its D2 receptors and enhancing type I interferons [23]. Recent evidence suggests that SARS-CoV-2 interferes with immune responses through dopamine-related mechanisms [24]. However, dopamine can suppress the immune response during infection, thereby increasing the life cycle of SARS-CoV-2. Elevated dopamine levels reduce oxygen levels, especially when considering the "happy" hypoxemia associated with COVID-19 [23]. This happens because dopamine has a known ability to dull the ventilation response of the basal carotid arteries of a person to hypoxia. However, to date, no studies have examined the potential role of dopamine and dopaminergic receptors in COVID-19 infection.

As for the role of dopamine in cancer, the available information is quite contradictory. Some epidemiological and molecular biological studies have shown that dopamine has different effects on different types of cancer and even on cancer of the same localization [22]. These results mean that an imbalance in the dopaminergic system may be associated with the development of a malignant tumor.

Purpose of the study was to study the content of biogenic amines – serotonin and its metabolite 5-HIAA, dopamine, norepinephrine and histamine in lung tissues in patients with lung cancer who had suffered COVID-19 of varying severity.

PATIENTS AND METHODS

The material for the study was samples of lung tissue outside the tumor growth zone, tumor tissue and its perifocal zone obtained as a result of open biopsy during radical operations in patients with morphologically verified non-small cell lung cancer (NSCLC) of stage I–IIIA ($cT_{1-3}N_xM_0$). The study included 60 male and female patients in a 1:1 ratio who underwent a standard X-ray examination before surgery to exclude metastatic disease: computed tomography (CT) of the chest and abdominal cavity, as well as brain imaging (CT or MRI); part of the patients underwent 1-F-FDG PET-CT, but this study was optional. Osteoscintigraphy was performed according to clinical indications. The clinical stage of NSCLC was established using the TNM lung Cancer classification Union for International Cancer Control / American Joint Committee on Cancer classification system, version 8.

Patients who had suffered SARS-CoV-2 infection 3–6 months ago, aged 18 years and older with morphologically verified NSCLC, who were scheduled for radical surgical intervention in the volume of lobectomy, bilobectomy or pneumonectomy with mediastinal lymph dissection, were considered suitable.

The initial status of the patients should have been 0–2 points on the ECOG scale, the volume of forced exhalation in 1 second more than 1.5 liters or more than 70 % of the required and normal indicators of standard laboratory tests, including a general blood test, biochemical serum analysis, coagulogram, indicating the absence of functional disorders of organs and systems. The study did not include patients who had undergone neoadjuvant chemotherapy, with synchronous contralateral lung cancer, with malignant neoplasms of other localizations, except basal cell skin cancer, in the past or current history and with recent less than 6 months. severe cardiac, pulmonary or inflammatory diseases, except COVID-19, as well as patients with diabetes mellitus.

Upon hospitalization, all patients had a negative PCR test for SARS-CoV-2 from the nasopharynx. Based on anamnestic data collected using a special questionnaire, depending on the severity of the clinical course of COVID-19, the main and control groups were formed. The main group included 30 patients with NSCLC (15 men and 15 women) who had suffered COVID-19 in severe and moderate form that required hospitalization, the control group similarly consisted of 30 patients with lung cancer in whom SARS-CoV-2 infection was asymptomatic or mild. The average age of the patients was 59.11 ± 2.9 years, there were no significant differences between the compared groups in terms of anthropometric and clinical indicators.

The study participants gave written informed consent to medical intervention, surgery, processing of personal data and collection of biological material in accordance with the Helsinki Declaration. The study was approved by the Ethics Council of the NMRC for Oncology of the Ministry of Health of Russia, Rostov-on-Don (Protocol No. 6 of 01/17/2022).

Quantitative assessment of the content of dopamine, norepinephrine, serotonin, 5-hydroxyindolacetic acid (5-HIAA) and histamine was performed by the ELISA method using standard kits (IBL; Germany).

Statistical analysis was carried out using the Statistica 10 program. The normality of the distribution was assessed using Kolmogorov-Smirnov methods, differences between groups were determined using the Student's t-test or the Mann-Whitney U-test, depending on the normality of the distribution. The value of $p < 0.05$ was considered as an indicator of statistical significance.

RESEARCH RESULTS

It was found that in intact tissue (resection line) of men and women of the main group, the level of dopamine and norepinephrine was lower than in the corresponding samples of patients of the control group: in men on average 1.3 times, in women on average 1.4 times. Since dopamine is a precursor to norepinephrine, we found it interesting to study the ratio of dopamine and norepinephrine. The ratio of dopamine to norepinephrine (D/NA) had no significant differences, both between groups and depending on gender (Table 1). The histamine level in the patients of the main group had no significant differences from the values in the control group, however, in both groups the indicator was higher in men than in women: in the control group – 2.5 times, in the main group – 2.3 times. The serotonin content was 1.5 times higher in patients of the control group on average, regardless of gender. Significant differences were found in intact tissue and in the content of the serotonin-5-HIAA metabolite. The values of this indicator were 4.2 times and 2.8 times higher in men and women of the control group, respectively. At the same time, gender differences are noted: in men, the indicator was 1.9 times higher than in women in the control group, in the main group – 1.3 times. The ratio of serotonin/5-HIAA (5-HT/5-HIAA) reflects the process of synthesis/decay of this biogenic amine. It turned out that in patients of the main group, this indicator was higher than in the control group: in men – 2.7 times, in women – 1.9 times. At the same time, there were gender differences: in the control group, the indicator for women exceeded the values for men by 1.5 times. In the main group, 5-HT/5-HIAA was the same for women and men.

In the tumor tissue of men and women of the main group, the level of dopamine had no significant differences from the corresponding samples of patients of the control group, only in the main group the level of D in the tumor was 1.5 times higher in women, whereas in the control group no sex differences were detected.

At the same time, relative to the indicators in intact tissue, the level of dopamine in the tumor tissue of male and female patients of the control group was reduced by 1.3 times and 1.4 times, while the values in the tumor tissue of patients of the main group had no significant differences. The content of norepinephrine in the tumor tissue of patients in the control group,

Table 1. The content of biogenic amines and their ratios in the lung tissues of patients with NSCLC, depending on the severity of COVID-19

Groups	Sex	D ng/g t	NA ng/g t	5-HT ng/g t	5-HIAA ng/g t	Histamine ng/g t	D/NA	5HT / 5HIAA
Resection line tissue								
Control	M	72.8 ± 7.4	60.1 ± 6.5	2.0 ± 0.19	0.54 ± 0.06	1572.9 ± 159.4	1.2 ± 0.02	3.8 ± 0.14
	F	85.7 ± 7.9	74.1 ± 9.1	1.6 ± 0.17	0.28 ± 0.02 $p^2 = 0.0001$	634.9 ± 71.9 $p^2 = 0.0000$	1.22 ± 0.05	5.6 ± 0.2 $p^2 = 0.0000$
Main	M	55.6 ± 3.9 $p^1 = 0.0495$	44.7 ± 3.4 $p^1 = 0.0455$	1.3 ± 0.14 $p^1 = 0.0062$	0.13 ± 0.01 $p^1 = 0.0000$	1437.3 ± 135.8	1.26 ± 0.04	9.9 ± 0.45 $p^1 = 0.0000$
	F	66.2 ± 5.1 $p^1 = 0.0477$	51.2 ± 6.1 $p^1 = 0.0462$	1.1 ± 0.12 $p^1 = 0.0234$	0.1 ± 0.008 $p^1 = 0.0000$ $p^2 = 0.0374$	628.4 ± 71.4 $p^2 = 0.0000$	1.38 ± 0.07	10.8 ± 0.61 $p^1 = 0.0000$
Tumor tissue								
Control	M	54.2 ± 3.97 $p^3 = 0.0350$	113.6 ± 5.47 $p^3 = 0.0000$	3.3 ± 0.22	0.25 ± 0.02	2026.9 ± 129.4 $p^3 = 0.0353$	0.47 ± 0.02 $p^3 = 0.0000$	13.35 ± 0.21 $p^3 = 0.0000$
	F	60.1 ± 3.2 $p^3 = 0.0138$	118.8 ± 6.1 $p^3 = 0.0003$	3.8 ± 0.39	0.27 ± 0.04	1992.7 ± 210.6 $p^3 = 0.0000$ $p^4 = 0.0014$	0.51 ± 0.01 $p^3 = 0.0000$	14.5 ± 0.79 $p^3 = 0.0000$
Main	M	45.3 ± 4.9	37.5 ± 3.8 $p^1 = 0.0000$	2.1 ± 0.23 $p^1 = 0.0008$	0.2 ± 0.02	1901.7 ± 155.9 $p^3 = 0.0327$	1.2 ± 0.02 $p^1 = 0.0000$	10.6 ± 0.19
	F	67.8 ± 7.4 $p^2 = 0.0170$	35.6 ± 3.9 $p^1 = 0.0000$	2.8 ± 0.26 $p^1 = 0.0441$	0.2 ± 0.02	1571.1 ± 165.0 $p^3 = 0.0000$ $p^4 = 0.0060$	1.92 ± 0.04 $p^1 = 0.0000$ $p^2 = 0.0000$ $p^3 = 0.0000$	14.3 ± 0.77
Periodical zone tissue								
Control	M	71.8 ± 7.8	64.5 ± 7.2	1.7 ± 0.18	0.5 ± 0.07	1710.1 ± 190.7	1.1 ± 0.01	3.7 ± 0.24
	F	77.8 ± 8.4	67.1 ± 7.36	1.8 ± 0.19	0.3 ± 0.04 $p^2 = 0.0220$	1135.3 ± 121.2 $p^3 = 0.0013$	1.2 ± 0.03	6.2 ± 0.29 $p^2 = 0.0000$
Main	M	55.5 ± 5.6	51.5 ± 5.7	1.4 ± 0.16	0.18 ± 0.02 $p^1 = 0.0002$ $p^3 = 0.0392$	1473.9 ± 161.2	1.1 ± 0.06	7.8 ± 0.17
	F	63.3 ± 6.4	43.7 ± 4.5	1.5 ± 0.18	0.17 ± 0.02 $p^1 = 0.0036$ $p^3 = 0.0077$	942.9 ± 103.2 $p^3 = 0.0182$	1.4 ± 0.03	8.8 ± 0.29

Note: statistically significant in relation to: [1] – to the corresponding indicator in the control group; [2] – to the indicator in men in the corresponding group; [3] – to the corresponding indicator in the tissue of the resection line; [4] to the corresponding indicator in the tissue of the perifocal zone; g t – grams of tissue. D – dopamine, NA – norepinephrine, 5NT – serotonin, 5HIAA – 5-hydroxyindoleacetic acid.

regardless of gender, was 3.2 times higher than the level of biogenic amine in the tumor tissue of the main group on average. At the same time, relative to intact tissue, the indicators were increased in men and women of the control group by 1.9 times and 1.6 times, respectively, and in the main group had no significant differences. The ratio is D/NA the tumor tissue of patients of the control group was lower than in patients of the main group: in men by 2.4 times, in women by 3.9 times. Gender differences were noted only in the main group of patients: in women, the indicator was 1.6 times higher. With respect to intact tissue, the coefficient is D/NA in the tumor tissue of patients in the control group, regardless of gender, was reduced by an average of 2.4 times.

In the tumor tissue of the main group, relative to the corresponding intact tissue, the level of D/NA was increased in women by 1.5 times, and had no significant differences in men. The histamine content in the tumor tissue of patients of the control and main groups did not differ either between the groups or depending on gender, but was increased relative to the values in the corresponding intact tissue: in men and women of the control group by 1.3 times and 3.1 times, respectively, in men and women of the main group – by 1.3 times and 2.4 three times, respectively. The level of serotonin in the tumor tissue of patients in the control group was 1.4 times higher than in the main group, regardless of gender, on average, and the level of its metabolite 5-HIAA K had no significant differences. The 5-HT/5-HIAA coefficient in the tumor tissue did not differ between the groups and did not differ by gender, but in the control group there were differences with the indicators in the corresponding intact tissue: in men, the indicator was 3.6 times higher, in women – 2.5 times.

In the tissue of the perifocal zone, the content of dopamine, norepinephrine and their ratios in all the studied samples had no significant differences from the indicators in the corresponding intact tissue and tumor. There were also no significant differences in the content of serotonin in the samples of the perifocal zone and the corresponding intact tissue, but at the same time, the level of 5NT was lower than in the tumor itself by an average of 1.5–2 times. In the perifocal zone, the level of 5-HIAA did not differ from the indicators of the corresponding intact tissue in patients of the control group, whereas there were differences in the samples of patients of the main group. So in men, the level of the metabolite was 1.4 times higher, and in women – 1.7 times. In this regard, the ratio of 5-HT/5-HIAA in the tissue of the perifocal zone in patients of the control group had no significant differences from the values in the intact tissue, maintaining the same sex differences – 1.8 times higher in women. In the tissue of the perifocal zone of the tumor of patients of the main group, the ratio of 5-HT/5-HIAA also had no differences with the corresponding intact tissue and tumor tissue. The histamine level in the tissue of the perifocal zone of the tumor in men of both groups had no significant differences from the values in the corresponding intact tissue, and in women of both groups, the level of this diamine occupied an intermediate position between the indicators in the corresponding intact tissue and tumor tissue. Thus, in the tissue of the perifocal zone of the tumor of women of the control and main groups, the histamine level was 1.8 times and 1.5 times higher, respectively, than in the intact lung tissue, but 1.8 times and 1.6 times lower, respectively, than in the tumor.

Thus, it was found that in all the studied lung tissue samples of men and women of the main group, compared with the control group, there is an insufficiency of catecholamines without violating their ratio and a change in serotonin metabolism to ensure its level. Obviously, changes in the biogenic status of lung tissues may be associated with the severity of the SARS-CoV-2 infection.

DISCUSSION

Neurotransmitters, which include biogenic amines, are usually considered as substances secreted by nerves that mediate the stimulating or inhibitory functions of neurons by binding to the corresponding receptors. In recent decades, many new discoveries have appeared explaining the regulatory role of neurotransmitters in the physiological and pathological functions of tissues and organs. It is noteworthy that new data suggest that cancer cells use a signaling pathway initiated by neurotransmitters to activate uncontrolled proliferation and dissemination [22]. In addition, neurotransmitters can affect immune cells and endothelial cells in the tumor microenvironment, regulating tissue homeostasis, influencing various tumor phenotypes and contributing to tumor progression [22; 24; 25]. Neurotransmitters can affect cancer

cells and immune cells in an autocrine/paracrine way. Similar to the processes of neoangiogenesis and lymphangiogenesis, more and more evidence points to the possibility of the formation of new nerve endings in tumors, a phenomenon called neoneurogenesis [25]. Neurotransmitters of nerve fibers released in the tumor microenvironment activate tumor cells by binding specific neurotransmitter receptors. This process has further expanded our knowledge of the complex network of neurotransmitters associated with tumor progression. In addition, immune cells and endothelial cells infiltrated in the tumor microenvironment also express various neurotransmitter receptors and react with neurotransmitters, which is known to have a strong effect on the outcome of cancer in humans [26].

In this study, it was shown that in lung tissue unaffected by the malignant process (resection line), there were gender differences in the level of histamine, regardless of the severity of COVID-19: in men, its content was more than twice as high as in women [27]. This fact may be associated, on the one hand, with inflammatory changes in lung tissue in men, on the other, with an increased possibility of virus penetration into cells, and possibly with hormonal security of the tissue. In the tumor tissue, regardless of gender and infection, the histamine level was higher than in the corresponding conditionally intact tissue, which indicates the likelihood of its participation in tumor progression [17]. The histamine content in the tissue of the perifocal zone of the tumor occupied an intermediate position between the tumor tissue and the resection line, which indicates the involvement of this zone in the process of carcinogenesis.

Non-small cell lung cancer (NSCLC) is the most common form of lung cancer and is characterized by a chronic inflammatory process, which is associated with high infiltration of mast cells and a decrease in patient survival [28]. It is known that high levels of histamine and histamine receptors in a wide range of different types of cancer, including lung cancer, indicate their involvement in the complex biology of cancer [29]. In addition, histamine has been shown to stimulate various events related to carcinogenesis, such as cell invasion, migration, and angiogenesis, demonstrating its crucial role in cancer progression [17].

5-HT is known to regulate epithelial homeostasis of the breast, lungs, pancreas, liver and prostate. A violation of the regulation of 5-HT signaling is often observed in epithelial tumors [19]. We have shown that the absolute level of serotonin, as well as the ratio of 5-HT/5-HIAA in the tumor tissue in the control group were significantly higher than in the conditionally intact lung tissue and tissue of the perifocal zone of the tumor and had no fundamental differences depending on gender.

The available data clarified the biology of the tumor from the positions of 5-HT. It was found that 5-HT promotes cell proliferation in cancer through various 5-HT receptors [30]. Jiang S. H. and co-authors (2017) demonstrated that human pancreatic cancer tissues have elevated levels of 5-HT, and pancreatic cancer cells increase the expression of its receptor, HTR2B. This increase promotes tumor glycolysis under metabolic stress and promotes the growth of pancreatic cancer [22].

However, we drew attention to the fact that in patients of the main group, the level of serotonin and the ratio of 5-HT/5-HIAA in the tumor tissue and its perifocal zone had no fundamental differences from the indicators in the control group of patients, and the ratio of 5-HT/5-HIAA in intact tissue along the resection line was significantly different from the indicators in the control group and was similar to the indicators in the tumor tissue of patients in the main group. This could not be explained in any way from the standpoint of the participation of serotonin in tumor progression, since in the tissue of the corresponding perifocal zone, the indicators were significantly lower, as well as in patients of the control group. We considered that this was due to the severity of COVID-19, namely, the ability of serotonin to influence the formation of fibrosis in the lungs. Moreover, in the intact tissue of patients of the main group who had suffered severe and moderate infection, the relative level of serotonin was increased not due to its de novo synthesis, but due to a sharp drop in its decay.

The results obtained by Petrić M. with co-authors (2022) indicate that serotonin may play a profibrotic role in lung tissue, especially due to the fact that half of patients with low lung capacity had interstitial lung diseases [31]. In mouse models, data were obtained that serotonin is involved in the pathogenesis of pulmonary fibrosis through 5-HT/Akt signaling pathways and enhanced TGF-β1-induced collagen synthesis [32]. A Swedish group of authors identified the serotonin receptor as a therapeutic target for the

fibrosing phenotype of interstitial lung diseases [33]. At the same time, there is a study showing a violation of the regulation of tryptophan metabolism, characterized by a decrease in serotonin production in combination with the accumulation of quinoline in patients with COVID-19 during the acute phase of infection, especially in patients with the most unfavorable outcomes [34].

Perhaps in situations where available serotonin levels are reduced, inhibition of its local metabolism may have a beneficial effect, helping to maintain adequate levels of serotonin signaling.

There are several mechanisms underlying the role of adrenaline and norepinephrine in the development of tumors. Norepinephrine can stimulate the metabolism of endothelial cells in the direction of inhibition of oxidative phosphorylation and induction of angiogenic switching, which contributes to the progression of cancer [21].

In our study, it was shown that in the tumor tissue of patients in the control group, the level of norepinephrine was significantly higher than in the corresponding intact tissue and tissue of the perifocal zone of the tumor, which is consistent with the literature data. No gender differences were noted. The other was observed in lung tissues of patients of the main group. In the tissue of the resection line of these patients, the level of norepinephrine was significantly lower than in the intact tissue of men and women with lung cancer of the control group. The same pattern was found in the tumor tissue and in the tissue of its perifocal zone. At the same time, there were no differences in indicators between all samples, i.e. the level of norepinephrine was approximately the same, and significantly lower than in patients of the control group. Explanations for this fact were difficult to find. Then we turned to the content of dopamine in the lung tissues of patients with NSCLC, since it is known that dopamine is a precursor of norepinephrine.

It is known that hormones such as glucagon, adrenaline or norepinephrine trigger an intracellular signaling cascade that triggers the activation of protein kinase A. Dopamine weakens the activation of protein kinase A, which is initiated by lowering the cellular level of cAMP. Protein kinase A activates the NF-kB pathway by phosphorylation of p65 by serine 276, which promotes oncogenesis of NSCLC in mice and significantly correlates with progressive stages of TNM and poor prognosis in patients with NSCLC [22].

We found that the levels of dopamine, as well as norepinephrine in the intact tissue of men and women of the main group were significantly lower than in the corresponding samples of patients of the control group, possibly due to a violation of tyrosine metabolism. The metabolism of amino acids in the tumor microenvironment plays a key role in the development and progression of the tumor. Tumor cells often consume exclusively local nutrients, such as amino acids, for their survival and compete for them with other surrounding cells, such as antitumor immune cells [35]. In the tumor tissue of patients of both sexes of the control group, the level of dopamine was reduced due to increased norepinephrine formation. Not equivalent changes were found in tumor tissue in men and women of the main group. Thus, the levels of dopamine and norepinephrine in the tumor tissue of men were reduced almost as well as in intact tissue, and in women the content of norepinephrine was kept almost at the level of values in intact tissue and tissue of the perifocal zone, dopamine was significantly higher, as well as in the tissue of the perifocal zone.

It is known that dopamine is involved in countering the carcinogenic action of the adrenergic system. The antitumor effects of dopamine can manifest themselves in the regulation of various immunocompetent cells in the tumor microenvironment. Dopamine is able to inhibit the function of Gr-1 + CD115+ suppressor cells of myeloid origin through D1-like receptors and enhance antitumor immunity [22]. Recent intriguing evidence suggests that SARS-CoV-2 may interfere with immune responses through dopamine-related mechanisms. On the one hand, it has been suggested that dopamine receptors are used by the virus to improve both its penetration and the life cycle inside cells; on the other hand, it has been documented that SARS-CoV-2 suppresses L-DOPA decarboxylase, an enzyme that limits the rate of conversion of L-DOPA to dopamine, which, obviously affects the content of normadrenaline [36].

CONCLUSION

Obviously, changes in the levels of dopamine, norepinephrine and serotonin in lung tissues may be associated with the severity of SARS-CoV-2 infection

and should be reflected in the course of lung cancer. The influence of biogenic amines on tumor development and progression includes their direct role in tumor growth and metastasis not only through cancer cells and stromal cells, but also through endothelial cells and immune cells, contributing to angiogenesis, lymphangiogenesis and inflammatory response. The transferred COVID-19 contributes its modifying effect on the biogenic status in the lung in patients of the main group, which can lead to a more severe course of the malignant process and a change in the response to standard antitumor therapy.

References

1. Kaprin AD, Gameeva EV, Roshchin DO, Kostin AA, Alekseeva GS, Khoronenko VE, et al. Remodeling the cancer service in the context of the COVID-19 pandemic at the Federal research center of the 1st level. Research and Practical Medicine Journal. 2020;7(2):10–21. (In Russ.). https://doi.org/10.17709/2409-2231-2020-7-2-1, EDN: ENOWVJ
2. Kulchenko NG. Epidemiology of kidney disease in patients with COVID-19. Research and Practical Medicine Journal. 2020;7(3):74–82. (In Russ.). https://doi.org/10.17709/2409-2231-2020-7-3-7, EDN: YWIALJ
3. Drzhevetskaya KS, Korzhenkova GP. Breast cancer screening during the adverse COVID-19 epidemiological situation. Research and Practical Medicine Journal. 2021;8(3):34–44. (In Russ.). https://doi.org/10.17709/2410-1893-2021-8-3-3, EDN: COIEFA
4. Hopkins J. COVID-19 dashboard by the Center for Systems Science and Engineering (CSSE) at Johns Hopkins University (JHU) 2022. Available at: https://coronavirus.jhu.edu/map.html, Accessed: 03.04.2023.
5. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. CA Cancer J Clin. 2020 Jan;70(1):7–30. https://doi.org/10.3322/caac.21590
6. Kolbanov KI, Trakhtenberg AK, Pikin OV, Glushko VA, Ryabov AB. Surgical treatment of patients with resectable non small cell lung cancer. Research and Practical Medicine Journal. 2014;1(1):16–23. (In Russ.). https://doi.org/10.17709/2409-2231-2014-1-1-16-23, EDN: TOUQCD
7. Usachev VS, Smolenov EI, Ragulin YuA. Morphological and molecular genetic diagnosis of lung cancer: methods and problems. Research and Practical Medicine Journal. 2020;7(3):51–62. (In Russ.). https://doi.org/10.17709/2409-2231-2020-7-3-5, EDN: HDJHTV
8. Liang W, Guan W, Chen R, Wang W, Li J, Xu K, et al. Cancer patients in SARS-CoV-2 infection: a nationwide analysis in China. Lancet Oncol. 2020 Mar;21(3):335–337. https://doi.org/10.1016/S1470-2045(20)30096-6
9. Dasanu CA, Sethi N, Ahmed N. Immune alterations and emerging immunotherapeutic approaches in lung cancer. Expert Opin Biol Ther. 2012 Jul;12(7):923–937. https://doi.org/10.1517/14712598.2012.685715
10. Desai AD, Lavelle M, Boursiquot BC, Wan EY. Long-term complications of COVID-19. Am J Physiol Cell Physiol. 2022 Jan 1;322(1):C1–C11. https://doi.org/10.1152/ajpcell.00375.2021
11. Nalbandian A, Sehgal K, Gupta A, Madhavan MV, McGroder C, Stevens JS, et al. Post-acute COVID-19 syndrome. Nat Med. 2021 Apr;27(4):601–615. https://doi.org/10.1038/s41591-021-01283-z
12. Han X, Fan Y, Alwalid O, Li N, Jia X, Yuan M, et al. Six-month Follow-up Chest CT Findings after Severe COVID-19 Pneumonia. Radiology. 2021 Apr;299(1):E177–E186. https://doi.org/10.1148/radiol.2021203153
13. Munster VJ, Feldmann F, Williamson BN, van Doremalen N, Pérez-Pérez L, Schulz J, et al. Respiratory disease in rhesus macaques inoculated with SARS-CoV-2. Nature. 2020 Sep;585(7824):268–272. https://doi.org/10.1038/s41586-020-2324-7
14. Shan C, Yao YF, Yang XL, Zhou YW, Gao G, Peng Y, et al. Infection with novel coronavirus (SARS-CoV-2) causes pneumonia in Rhesus macaques. Cell Res. 2020 Aug;30(8):670–677. https://doi.org/10.1038/s41422-020-0364-z
15. Diem K, Fauler M, Fois G, Hellmann A, Winokurow N, Schumacher S, et al. Mechanical stretch activates piezo1 in caveolae of alveolar type I cells to trigger ATP release and paracrine stimulation of surfactant secretion from alveolar type II cells. FASEB J. 2020 Sep;34(9):12785–12804. https://doi.org/10.1096/fj.202000613RRR
16. Wu ML, Liu FL, Sun J, Li X, Qin JR, Yan QH, et al. Combinational benefit of antihistamines and remdesivir for reducing SARS-CoV-2 replication and alleviating inflammation-induced lung injury in mice. Zool Res. 2022 May 18;43(3):457–468. https://doi.org/10.24272/j.issn.2095-8137.2021.469
17. Nguyen PL, Cho J. Pathophysiological Roles of Histamine Receptors in Cancer Progression: Implications and Perspectives as Potential Molecular Targets. Biomolecules. 2021 Aug 18;11(8):1232. https://doi.org/10.3390/biom11081232

18. Fabre A, Marchal-Sommé J, Marchand-Adam S, Quesnel C, Borie R, Dehoux M, et al. Modulation of bleomycin-induced lung fibrosis by serotonin receptor antagonists in mice. Eur Respir J. 2008 Aug;32(2):426–436. https://doi.org/10.1183/09031936.00126907
19. Balakrishna P, George S, Hatoum H, Mukherjee S. Serotonin Pathway in Cancer. Int J Mol Sci. 2021 Jan 28;22(3):1268. https://doi.org/10.3390/ijms22031268
20. Renz BW, Takahashi R, Tanaka T, Macchini M, Hayakawa Y, Dantes Z, et al. β2 Adrenergic-Neurotrophin Feedforward Loop Promotes Pancreatic Cancer. Cancer Cell. 2018 Jan 8;33(1):75-90.e7. https://doi.org/10.1016/j.ccell.2017.11.007
21. Hondermarck H, Jobling P. The Sympathetic Nervous System Drives Tumor Angiogenesis. Trends Cancer. 2018 Feb;4(2):93–94. https://doi.org/10.1016/j.trecan.2017.11.008
22. Jiang SH, Hu LP, Wang X, Li J, Zhang ZG. Neurotransmitters: emerging targets in cancer. Oncogene. 2020 Jan;39(3):503–515. https://doi.org/10.1038/s41388-019-1006-0
23. Dhont S, Derom E, Van Braeckel E, Depuydt P, Lambrecht BN. The pathophysiology of "happy" hypoxemia in COVID-19. Respir Res. 2020 Jul 28;21(1):198. https://doi.org/10.1186/s12931-020-01462-5
24. Limanaqi F, Zecchini S, Dino B, Strizzi S, Cappelletti G, Utyro O, et al. Dopamine Reduces SARS-CoV-2 Replication In Vitro through Downregulation of D2 Receptors and Upregulation of Type-I Interferons. Cells. 2022 May 19;11(10):1691. https://doi.org/10.3390/cells11101691
25. Boilly B, Faulkner S, Jobling P, Hondermarck H. Nerve Dependence: From Regeneration to Cancer. Cancer Cell. 2017 Mar 13;31(3):342–354. https://doi.org/10.1016/j.ccell.2017.02.005
26. Sarkar C, Chakroborty D, Basu S. Neurotransmitters as regulators of tumor angiogenesis and immunity: the role of catecholamines. J Neuroimmune Pharmacol. 2013 Mar;8(1):7–14. https://doi.org/10.1007/s11481-012-9395-7
27. Kulchenko NG, Druzhinina NK, Myandina GI. Male infertility along with the era of coronavirus infection SARS-CoV-2. Research and Practical Medicine Journal. 2022;9(4):123–133. (In Russ.). https://doi.org/10.17709/2410-1893-2022-9-4-12
28. Stoyanov E, Uddin M, Mankuta D, Dubinett SM, Levi-Schaffer F. Mast cells and histamine enhance the proliferation of non-small cell lung cancer cells. Lung Cancer. 2012 Jan;75(1):38–44. https://doi.org/10.1016/j.lungcan.2011.05.029
29. Massari NA, Nicoud MB, Medina VA. Histamine receptors and cancer pharmacology: an update. Br J Pharmacol. 2020 Feb;177(3):516–538. https://doi.org/10.1111/bph.14535
30. Liu Y, Zhang H, Wang Z, Wu P, Gong W. 5-Hydroxytryptamine1a receptors on tumour cells induce immune evasion in lung adenocarcinoma patients with depression via autophagy/pSTAT3. Eur J Cancer. 2019 Jun;114:8–24. https://doi.org/10.1016/j.ejca.2019.03.017
31. Petrić M, Perković D, Božić I, Marasović Krstulović D, Martinović Kaliterna D. The Levels of Serum Serotonin Can Be Related to Skin and Pulmonary Manifestations of Systemic Sclerosis. Medicina (Kaunas). 2022 Jan 21;58(2):161. https://doi.org/10.3390/medicina58020161
32. Janssen W, Schymura Y, Novoyatleva T, Kojonazarov B, Boehm M, Wietelmann A, et al. 5-HT2B receptor antagonists inhibit fibrosis and protect from RV heart failure. Biomed Res Int. 2015;2015:438403. https://doi.org/10.1155/2015/438403
33. Löfdahl A, Tornling G, Wigén J, Larsson-Callerfelt AK, Wenglén C, Westergren-Thorsson G. Pathological Insight into 5-HT2B Receptor Activation in Fibrosing Interstitial Lung Diseases. Int J Mol Sci. 2020 Dec 28;22(1):225. https://doi.org/10.3390/ijms22010225
34. Oskotsky T T, Maric I, Tang A, Oskotsky B, Wong RJ, Aghaeepour N, et al. Mortality Risk Among Patients With COVID-19 Prescribed Selective Serotonin Reuptake Inhibitor Antidepressants. JAMA Netw Open. 2021 Nov 1;4(11):e2133090. https://doi.org/10.1001/jamanetworkopen.2021.33090
35. Azuma K, Xiang H, Tagami T, Kasajima R, Kato Y, Karakawa S, et al. Clinical significance of plasma-free amino acids and tryptophan metabolites in patients with non-small cell lung cancer receiving PD-1 inhibitor: a pilot cohort study for developing a prognostic multivariate model. J Immunother Cancer. 2022 May;10(5):e004420. https://doi.org/10.1136/jitc-2021-004420
36. Nataf S, Pays L. Molecular Insights into SARS-CoV2-Induced Alterations of the Gut/Brain Axis. Int J Mol Sci. 2021 Sep 28;22(19):10440. https://doi.org/10.3390/ijms221910440

Information about authors:

Oleg I. Kit – Academician at the Russian Academy of Sciences, Dr. Sci. (Med.), professor, general director, National Medical Research Centre for Oncology, Rostov-on-Don, Russian Federation. ORCID: https://orcid.org/0000-0003-3061-6108, SPIN: 1728-0329, AuthorID: 343182, Scopus Author ID: 55994103100, ResearcherID: U-2241-2017

Elena M. Frantsiyants – Dr. Sci. (Biol.), professor, deputy general director for science, National Medical Research Centre for Oncology, Rostov-on-Don, Russian Federation. ORCID: https://orcid.org/0000-0003-3618-6890, SPIN: 9427-9928, AuthorID: 462868, ResearcherID: Y-1491-2018, Scopus Author ID: 55890047700

Dmitriy A. Kharagezov – Cand. Sci. (Med.), oncologist, surgeon, head of the department of thoracic oncology, National Medical Research Centre for Oncology, Rostov-on-Don, Russian Federation. ORCID: https://orcid.org/0000-0003-0640-2994, SPIN: 5120-0561, AuthorID: 733789, ResearcherID: AAZ-3638-2021, Scopus Author ID: 56626499300

Valeriya A. Bandovkina ✉ – Dr. Sci. (Biol.), senior researcher of the laboratory for the study of pathogenesis of malignant tumors, National Medical Research Centre for Oncology, Rostov-on-Don, Russian Federation. ORCID: https://orcid.org/0000-0002-2302-8271, SPIN: 8806-2641, AuthorID: 696989

Natalya D. Cheryarina – MD, physician at the laboratory for the study of the pathogenesis of malignant tumors, National Medical Research Centre for Oncology, Rostov-on-Don, Russian Federation. ORCID: https://orcid.org/0000-0002-3711-8155, SPIN: 2189-3404, AuthorID: 558243

Yuliya A. Pogorelova – Cand. Sci. (Biol.), senior researcher at laboratory of malignant tumor pathogenesis study, National Medical Research Centre for Oncology, Rostov-on-Don, Russian Federation. ORCID: https://orcid.org/0000-0002-2674-9832, SPIN: 2168-8737, AuthorID: 558241

Yuriy N. Lazutin – Cand. Sci. (Med.), associate professor, leading researcher of the department of thoracic surgery, National Medical Research Centre for Oncology, Rostov-on-Don, Russian Federation. ORCID: https://orcid.org/0000-0002-6655-7632, SPIN: 5098-7887, AuthorID: 364457

Anton G. Milakin – MD, oncologist of the department of thoracic surgery, National Medical Research Centre for Oncology, Rostov-on-Don, Russian Federation. ORCID: https://orcid.org/0000-0002-2589-7606, SPIN: 7737-4737, AuthorID: 794734

Igor A. Leyman – Cand. Sci. (Med.), MD, oncologist of the department of thoracic surgery, National Medical Research Centre for Oncology, Rostov-on-Don, Russian Federation. ORCID: https://orcid.org/0000-0003-2572-1624, SPIN: 2551-0999, AuthorID: 735699

Oleg N. Stateshny – MD, oncologist at the department of thoracic surgery, National Medical Research Centre for Oncology, Rostov-on-Don, Russian Federation. ORCID: https://orcid.org/0000-0003-4513-7548, SPIN: 9917-1975, AuthorID: 1067071

Natalia D. Ushakova – Dr. Sci. (Med.), professor, doctor anesthesiologist-resuscitator of the department of anesthesiology and resuscitation, National Medical Research Centre for Oncology, Rostov-on-Don, Russian Federation. ORCID: https://orcid.org/0000-0002-0068-0881, SPIN: 9715-2250, AuthorID: 571594

Contribution of the authors:

Kit O. I. – scientific management of the research, final analysis of scientific work;

Franzyants E. M. – scientific guidance, research concept, material analysis, writing the source text, final conclusions;

Kharagezov D. A. – management of patients, surgical stages of treatment, critical analysis of the material;

Bandovkina V. A. – preparation and editing of the manuscript, verification of critical intellectual content;

Cheryarina N. D. – statistical analysis of the results obtained, editing of the manuscript;

Pogorelova Yu. A. – conducting IFA research, data analysis;

Lazutin Yu. N. – analysis of clinical data of patients;

Milakin A. G. – management of patients, review of publications, technical editing of the article;

Leyman I. A. – patient management, critical data analysis;

Stateshny O. N. – patient management, critical data analysis;

Ushakova N. D. – management of patients, editing of the manuscript.

All authors have made an equivalent contribution to the preparation of the publication.