South Russian Journal of Cancer. 2024. Vol. 5, No. 4. P. 14-19
https://doi.org/10.37748/2686-9039-2024-5-4-2
https://elibrary.ru/udwecg
ORIGINAL ARTICLE

Research on the expression of E-cadherin in lung cancer tumors with different histological structures

E. N. Kolesnikov, O. N. Stateshny, D. A. Kharagezov, E. A. Mirzoyan✉, T. G. Ayrapetova, A. G. Milakin, K. D. Iozefi

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

ABSTRACT

Purpose of the study. To conduct a comparative analysis of E-cadherin expression in inoperable patients with non-small cell lung cancer (NSCLC) cells and with different survival rates.

Materials and methods. The study included 96 patients with inoperable NSCLC: 84 (87.5 %) men and 12 (12.5 %) women, whose average age was 62.4 ± 0.68 years. Squamous cell carcinoma (SCC) was diagnosed in 78 (81.25 %) patients, and adenocarcinoma (AC) with a tumor differentiation grade of G2-G3 in 18 (18.75 %). The patients were treated and monitored at the National Medical Research Centre for Oncology. The expression of cadherins was determined in the tumor cells of the biopsy specimens. The obtained data have been processed using the Statistica 13.0 program (StatSoftInc., USA). The studied data have been checked for compliance with the normal distribution using the Shapiro-Wilk criterion.

Results. The following distribution of patients with NSCLC was noted: IIA – 2 (2.1 %), IIB – 14 (14.6 %), IIIA – 51 (53.1 %), IIIB – 29 (30.2 %), i. e. the frequency of stage III is higher than stage II (83.3 % (n = 80) versus 16.7 % (n = 16), p < 0.001). Fatal outcome occurred in the SCC group within 1 year in 28 patients, within 1 to 2 years – in 30, 20 patients survived for 3 years or more. For AC, these figures were 6, 5 and 7 respectively.

The analysis revealed that E-cadherin expression was noted in both squamous cell carcinoma and lung adenocarcinoma: Me 55 [LQ 37; UQ 65] and Me 50 [LQ 40; UQ 70], respectively.

Conclusions. 1. The analysis revealed that E-cadherin expression was observed in both squamous cell carcinoma and lung adenocarcinomas without statistically significant differences between the compared groups (p = 0.25).

2. Statistically significant differences in the levels of E-cadherin expression were noted in the biopsy samples of the 2 groups only with survival up to 1 year and up to 3 years or more (p < 0.05).

Keywords: non-small cell lung cancer, chemoradiation therapy, E-cadherin

For citation: Kolesnikov E. N., Stateshny O. N., Kharagezov D. A., Mirzoyan E. A., Ayrapetova T. G., Milakin A. G., Iozefi K. D. Reasearch on the expression of E-cadherin in lung cancer tumors with different histological structures. South Russian Journal of Cancer. 2024; 5(4): 14-19. https://doi.org/10.37748/2686-9039-2024-5-4-2, https://elibrary.ru/udwecg

For correspondence: Ellada A. Mirzoyan – Cand. Sci. (Med.), MD, researcher at the Thoracic Department, oncologist at the Department of Thoracic Oncology, National Medical Research Centre for Oncology, Rostov-on-Don, Russian Federation
Address: 63 14 line str., Rostov-on-Don 344037, Russian Federation
E-mail: ellada.mirzoyan@yandex.ru
ORCID: https://orcid.org/0000-0002-0328-9714
SPIN: 2506-8605, AuthorID: 1002948
ResearcherID: AAZ-2780-2021
Scopus Author ID: 57221118516

Compliance with ethical standards: the work was carries out in compliance with the ethical principles set forth by the World Medical Association Declaration of Helsinki, 1964, ed. 2013. The study was approved by the Committee on Biomedical Ethics at the National Medical Research Center for Oncology, the Russian Federation Ministry of Health (extract from the protocol of the meeting No. 16 dated 10/12/2021). Informed consents were obtained 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 14.10.2024; approved after reviewing 30.10.2024; accepted for publication 03.11.2024

Южно-Российский онкологический журнал. 2024. Т. 5, № 4. С. 14-19
https://doi.org/10.37748/2686-9039-2024-5-4-2
https://elibrary.ru/udwecg
3.1.6. Онкология, лучевая терапия
ОРИГИНАЛЬНАЯ СТАТЬЯ

Изучение экспрессии Е-кадгерина при немелкоклеточном раке легкого с различным гистологическим строением

Е. Н. Колесников, О. Н. Статешный, Д. А. Харагезов, Э. А. Мирзоян✉, Т. Г. Айрапетова, А. Г. Милакин, К. Д. Иозефи

ФГБУ «Национальный медицинский исследовательский центр онкологии» Министерства здравоохранения Российской Федерации, г. Ростов-на-Дону, Российская Федерация
✉ ellada.mirzoyan@yandex.ru

РЕЗЮМЕ

Цель исследования. Провести сравнительный анализ экспрессии Е-кадгерина в клетках немелкоклеточного рака легкого (НМРЛ) неоперабельных больных с разной выживаемостью.

Материалы и методы. В исследование было включено 96 больных НМРЛ: 84 (87,5 %) мужчин и 12 (12,5 %) женщин, средний возраст которых составил 62,4 ± 0,68 года. У 78 (81,25 %) пациентов диагностирован плоскоклеточный рак (ПКР), а у 18 (18,75 %) – аденокарцинома (АК) со степенью дифференцировки опухолей G2–G3. Пациенты получали лечение и находились под наблюдением в ФГБУ «Национальный медицинский исследовательский центр онкологии» Министерства здравоохранения Российской Федерации. В опухолевых клетках биоптатов определяли экспрессию кадгеринов. Полученные данные обрабатывали при помощи программы Statistica 13,0 (StatSoftInc., США). Изучаемые данные проверяли на соответствие нормальному распределению по критерию Шапиро-Уилка.

Результаты. Было отмечено следующее распределение больных НМРЛ: IIA – 2 (2,1 %), IIB – 14 (14,6 %), IIIA – 51 (53,1 %), IIIB – 29 (30,2 %), т. е. частота III стадии выше, чем II стадии (83,3 % (n = 80) против 16,7 % (n = 16), p < 0,001). Летальный исход наступил в группе ПКР в течение 1 года у 28 больных, в период от 1 до 2 лет – у 30, от 2 до 3 лет и более дожили 20 больных. Для АК эти показатели составили 6, 5 и 7 больных соответственно.

При проведении анализа выявлено, что экспрессия Е-кадгерина отмечена как в плоскоклеточном раке, так и в аденокарциномах легкого: Me 55 [LQ 37; UQ 65] и Me 50 [LQ 40; UQ 70] соответственно.

Заключение. В ходе проведенного анализа выявлено, что экспрессия Е-кадгерина отмечена как в плоскоклеточном раке, так и в аденокарциномах легкого без статистически значимых различий между сравниваемыми группами (p = 0,25). Статистически значимые различия по уровням экспрессии Е-кадгерина отмечены в образцах биоптатов 2 групп только с выживаемостью до 1 года и до 3 лет и более (p < 0,05).

Ключевые слова: немелкоклеточный рак легкого, химиолучевое лечение, Е-кадгерин

Для цитирования: Колесников Е. Н., Статешный О. Н., Харагезов Д. А., Мирзоян Э. А., Айрапетова Т. Г., Милакин А. Г., Иозефи К. Д. Изучение экспрессии Е-кадгерина при немелкоклеточном раке легкого с различным гистологическим строением. Южно-Российский онкологический журнал. 2024; 5(4): 14-19. https://doi.org/10.37748/2686-9039-2024-5-4-2, https://elibrary.ru/udwecg

Для корреспонденции: Мирзоян Эллада Арменовна – к.м.н., научный сотрудник торакального отделения, врач-онколог отделения торакальной онкологии, ФГБУ «Национальный медицинский исследовательский центр онкологии» Министерства здравоохранения Российской Федерации, г. Ростов-на-Дону, Российская Федерация
Адрес: 344037, Российская Федерация, г. Ростов-на-Дону, ул. 14-я линия, д. 63
E-mail: ellada.mirzoyan@yandex.ru
ORCID: https://orcid.org/0000-0002-0328-9714
SPIN: 2506-8605, AuthorID: 1002948
ResearcherID: AAZ-2780-2021
Scopus Author ID: 57221118516

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 ФГБУ «Национальный медицинский исследовательский центр онкологии» Министерства здравоохранения Российской Федерации (выписка из протокола заседания № 16 от 12.10.2021 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 14.10.2024; одобрена после рецензирования 30.10.2024; принята к публикации 03.11.2024

INTRODUCTION

Lung cancer takes the leading 1st place in the structure of general oncological morbidity in the male population [1–3]. Non-small cell lung cancer (NSCLC) accounts for more than 85 % of cases of malignant lung tumors. According to statistics, about 40 % of NSCLC cases are diagnosed in stage IV, and 25 % in stage III [4].

The main method of treating NSCLC is surgical [5]. Chemoradiotherapy is usually prescribed due to the inability to resect the tumor or inoperable patients, and its effectiveness is assessed by the overall and event-free survival of patients [6].

Recently, research based on the study of genetic characteristics, expression of various receptors has become widespread. These can potentially be the targets for targeted drugs and checkpoint inhibitors. These targets may have prognostic significance in the application of various treatment methods [7]. It is known that the process of metastasis begins with a violation of epithelial integrity, which leads to the fact that tumor cells begin to penetrate into the surrounding stroma, blood and lymph vessels, and infiltrate other organs.

E-cadherin is a transmembrane glycoprotein that is closely associated with the occurrence, invasion and metastasis of cancer [8]. It can promote adhesion between epithelial cells and maintain the integrity of the tissue structure, which is a deterrent to tumor metastasis. A decrease or loss of its expression weakens the adhesion between tumor cells, which leads to tumor metastasis [9]. Today, there are a number of studies devoted to the clinical and pathological features and prognosis of E-cadherin and non-small cell lung cancer, but the results are uneven. According to some authors, low expression of E-cadherin does not contribute to prognosis in patients with NSCLC [10], while others believe that the expression of E-cadherin is not associated with the prognosis of the clinical course [11, 12].

The purpose of the study was to conduct a comparative analysis of the expression of E-cadherin in the lung NSCLC cells of patients, depending on the histological type of tumor and clinical course.

MATERIALS AND METHODS

The study included 96 patients with inoperable NSCLC: 84 (87.5 %) men and 12 (12.5 %) women, with the average age of 62.4 ± 0.68 years. 78 (81.25 %) patients were diagnosed with squamous cell carcinoma (SCC), and 18 (18.75 %) – adenocarcinoma (AC) with a tissue differentiation grade of G2–G3. The following distribution of patients with NSCLC was noted: IIA – 2 (2.1 %), IIB – 14 (14.6 %), IIIA – 51 (53.1 %), IIIB – 29 (30.2 %), i. e. the frequency of stage III is higher than stage II (83.3 % (n = 80) vs. 16.7 % (n = 16), p < 0.001). Patients underwent simultaneous chemoradiotherapy at doses of 60 Gy in combination with drugs (paclitaxel + carboplatin, pemetrexed + carbolatin) in accordance with standards and clinical recommendations for the treatment of lung cancer [5].

The expression of cadherins was being determined in tumor cells of biopsy tissue samples.

To determine the expression of molecular markers by NSCLC tumor cells, the IHC method was used with primary monoclonal and polyclonal antibodies, the characteristics of which are shown in the Table 1.

The UltraVision Quanto Detection System HRP DAB was used to visualize the results. The results of the immunohistochemical reaction were evaluated using an AxioLab.A1 light microscope (Germany) with lens magnification of ×200, ×400. The data obtained were processed using the Statistica 13.0 program (StatSoftInc., USA). The studied data were checked for compliance with the normal distribution according to the Shapiro-Wilk criterion. Since the primary data did not obey the law of normal distribution, the comparison of groups was carried out using the nonparametric Mann-Whitney criterion (U-criterion): The median (Me), lower and upper quartiles (Q1–Q3) were calculated. The differences were considered statistically significant at p < 0.05.

STUDY RESULTS AND DISCUSSION

The fatal outcome occurred in the SCC group within 1 year in 28 patients, within 1 to 2 years in 30, and 20 patients lived to 3 or more years. For AC patients, these figures were 6, 5 and 7, respectively.

The analysis revealed that the expression of E-cadherin was noted in both squamous cell carcinoma and lung adenocarcinomas: Me 55 [LQ 37; UQ 65] and Me 50 [LQ 40; UQ 70], respectively. There were no statistically significant differences between the compared groups (p = 0.25) (Fig. 1).

Table 1 and Figure 2A, B reflect the features of E-cadherin expression in squamous cell carcinomas and adenocarcinomas in patients with different survival rates.

Analyzing the obtained data, it was found that statistically significant differences in the expression levels of E-cadherin were observed in biopsy samples of 2 groups only with a survival rate of up to 1 year and up to 3 years or more.

In the paperwork of Gkogkou P. et al. the expression levels of E-cadherin and syndecan-1 (SDC1) were determined in tissue samples of 64 patients with stage III disease at the time of treatment.

Thus, the negative expression of SDC1 correlated with squamous cell histology (p = 0.002). Positive expression of E-cadherin was significantly associated with an increase in overall survival rate (OS) over 2 years (p = 0.032). E-cadherin expression was an

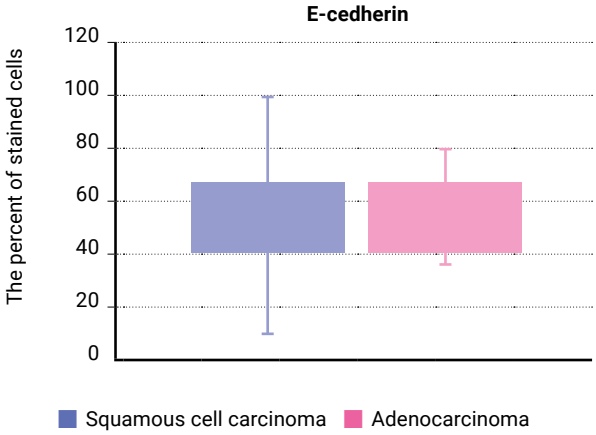

Fig. 1. Expression of E-cadherin in tumor samples taken from NSCLC patients

Table 1. Comparative characteristics of E-cadherin expression in squamous cell carcinomas and adenocarcinomas in patients with different survival rates

Expression levels %	Survival rate						*p*-value
	Up to 1 year (I)		1 to 2 years (II)		2 to 3 years (III)		
	Me	Q1–Q3	Me	Q1–Q3	Me	Q1–Q3	
Squamous cell carcinoma	43	40–62.5	55	30–65	65	45–67.5	(I–II) = 0.089 *(I–III) = 0.04 (II–III) = 0.134
Adenocarcinoma	48	32–61	61	48–67	85	52–91.5	(I–II) = 0.158 *(I–III) = 0.0126 (II–III) = 0.084

Note: * – statistically significant differences between the parameters of the subgroups (p < 0.05)

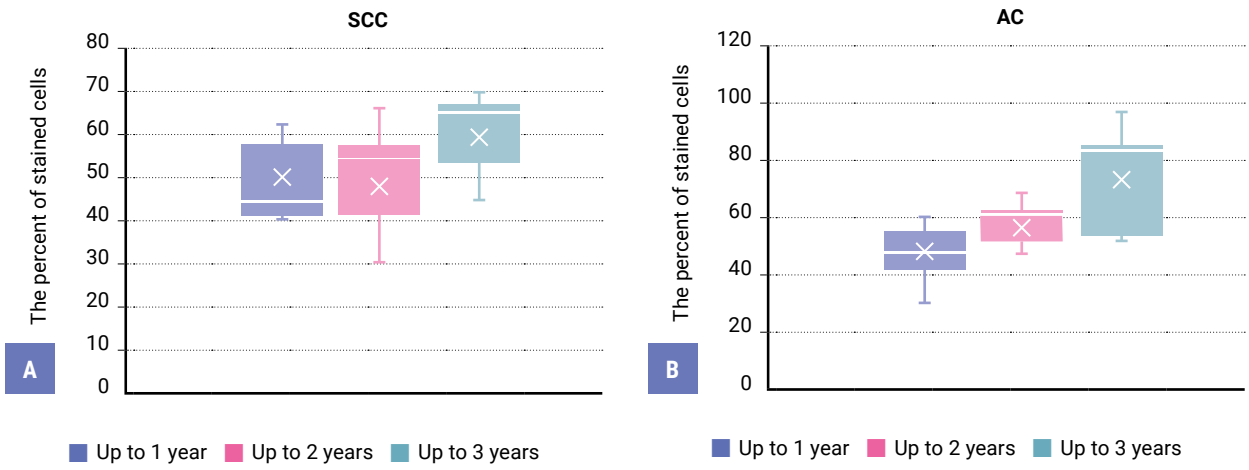

Fig. 2. Expression of E-cadherin in patients with NSCLC with varying survival rates. A – SCC; B – AC

independent predictor of overall survival (p = 0.007) and progression-free survival (p = 0.029). The results obtained by the authors show that positive expression of E-cadherin was associated with an increase in overall survival, as well as progression-free survival [13].

L.-Y. He and the authors studied the relationship between E-cadherin and Ki-67 and their clinical significance in NSCLC. The correlation analysis revealed an inverse relationship between the expression of E-cadherin and Ki-67 (r = 0.524, p = 0.000). Clinical and pathological characteristics (grade, TNM stage, lymph node metastases and pleural invasion) were significantly associated with the expression of E-cad and Ki-67 (p < 0.05). The authors concluded that E-cadherin and Ki-67 together play a key role in the development, invasion and metastasis of NSCLC, and their joint detection serves as a potential marker for clinical diagnosis in addition to use as a therapeutic target [14].

CONCLUSIONS

1. During the carried out analysis, it was revealed that increased expression of E-cadherin was noted in both squamous cell carcinomas and lung adenocarcinomas without statistically significant differences between the compared groups (p = 0.25).

2. Statistically significant differences in E-cadherin expression levels were noted in biopsy samples of the compared groups only with survival range up to 1 year and up to 3 years or more (p < 0.05). According to other criteria, there were no statistically significant differences.

SUMMARY

Therefore, E-cadherin may be a prognostic factor for overall survival and progression-free survival in patients with NSCLC, and its combination with Ki-67 may be used as a potential therapeutic target.

References

1. Kit OI, Turkin IN, Kharagezov DA, Lazutin YuN, Leiman IA, Chubaryan AV, et al. Sequential bronchoplastic upper lobectomy as a surgical component of multimodal treatment for synchronous bilateral multiple primary non-small cell lung cancer. Siberian Journal of Oncology. 2022;21(3):143–150. (In Russ.). https://doi.org/10.21294/1814-4861-2022-21-3-143-150
2. The state of cancer care for the Russian population in 2023. Edited by A. D. Kaprin, V. V. Starinsky, A. O. Shakhzadova Moscow: P. A. Herzen MNIOI – Branch of the National Medical Research Radiological Center, 2024, 262 p. (In Russ.).
3. Iozefi KD, Kharagezov DA, Lazutin YuN, Mirzoyan EA, Hayrapetova TG, Leyman IA, et al. Intraoperative pleurodesis as a way to prevent prolonged air leakage after anatomical lung resections for cancer. Modern Problems of Science and Education. (In Russ.). 2024;(1):27. https://doi.org/10.17513/spno.33286, EDN: NMZYZG
4. Price A. Emerging developments of chemoradiotherapy in stage III NSCLC. Nature Reviews Clinical Oncology. 2013;9(10): 591–598. https://doi.org/10.1038/nrclinonc.2012.135.
5. Malignant neoplasm of the bronchi and lung. Clinical Recommendations. 2021, 116 p. Available at: https://oncology-association.ru/wp-content/uploads/2021/02/rak-legkogo-2021.pdf?ysclid=m3gxqlmm8k225907433, Accessed: 24.10.2024.
6. Laktionov KK, Artamonova EV, Borisova TN, Breder VV, Bychkov YuM, Vladimirova LYu, et al. Malignant neoplasm of the bronchi and lung. Modern Oncology. 2021;23(3):369–402. (In Russ.). https://doi.org/10.26442/18151434.2021.3.20104, EDN: NPNNMP
7. Faurobert E, Bouin AP, Albiges-Rizo C. Microenvironment, tumor cell plasticity, and cancer. Curr Opin Oncol. 2015 Jan;27(1):64–70. https://doi.org/10.1097/CCO.0000000000000154
8. Edwards LA, Woolard K, Son MJ, Li A, Lee J, Ene C, et al. Effect of brain- and tumor-derived connective tissue growth factor on glioma invasion. J Natl Cancer Inst. 2011 Aug 3;103(15):1162–1178. https://doi.org/10.1093/jnci/djr224
9. Hornsveld M, Tenhagen M, van de Ven RA, Smits AMM, van Triest MH, van Amersfoort M, et al. Restraining FOXO3-dependent transcriptional BMF activation underpins tumour growth and metastasis of E-cadherin-negative breast cancer. Cell Death Differ. 2016 Sep 1;23(9):1483–1492. https://doi.org/10.1038/cdd.2016.33
10. Deeb G, Wang J, Ramnath N, Slocum HK, Wiseman S, Beck A, et al. Altered E-cadherin and epidermal growth factor receptor expressions are associated with patient survival in lung cancer: a study utilizing high-density tissue microarray and immunohistochemistry. Mod Pathol. 2004 Apr;17(4):430–439. https://doi.org/10.1038/modpathol.3800041

11. Yamashita T, Uramoto H, Onitsuka T, Ono K, Baba T, So T, et al. Association between lymphangiogenesis-/micrometastasis- and adhesion-related molecules in resected stage I NSCLC. Lung Cancer. 2010 Dec;70(3):320–328. https://doi.org/10.1016/j.lungcan.2010.02.013
12. Zhang H, Liu J, Yue D, Gao L, Wang D, Zhang H, et al. Clinical significance of E-cadherin, β-catenin, vimentin and S100A4 expression in completely resected squamous cell lung carcinoma. J Clin Pathol. 2013 Nov;66(11):937–945. https://doi.org/10.1136/jclinpath-2013-201467
13. Gkogkou P, Peponi E, Ntaskagiannis D, Murray S, Demou A, Sainis I, et al. E-Cadherin and Syndecan-1 Expression in Patients With Advanced Non-small Cell Lung Cancer Treated With Chemoradiotherapy. In Vivo. 2020;34(1):453–459. https://doi.org/10.21873/invivo.11795
14. He LY, Zhang H, Wang ZK, Zhang HZ. Diagnostic and prognostic significance of E-cadherin and Ki-67 expression in non-small cell lung cancer patients. Eur Rev Med Pharmacol Sci. 2016 Sep;20(18):3812–3817.

Information about authors:

Evgenii N. Kolesnikov – Dr. Sci. (Med.), MD, associate professor, head of the Department of Abdominal Oncology No. 1, National Medical Research Centre for Oncology, Rostov-on-Don, Russian Federation
ORCID: https://orcid.org/0000-0001-9749-709X, SPIN: 8434-6494, AuthorID: 347457, Scopus Author ID: 57190297598

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

Dmitriy A. Kharagezov – Cand. Sci. (Med.), MD, 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

Ellada A. Mirzoyan ✉ – Cand. Sci. (Med.), MD, researcher at the Thoracic Department, oncologist at the Department of Thoracic Oncology, National Medical Research Centre for Oncology, Rostov-on-Don, Russian Federation
ORCID: https://orcid.org/0000-0002-0328-9714, SPIN: 2506-8605, AuthorID: 1002948, ResearcherID: AAZ-2780-2021, Scopus Author ID: 57221118516

Tamara G. Ayrapetova – Cand. Sci. (Med.), PhD, MD, oncologist at the Department of Thoracic Oncology, National Medical Research Centre for Oncology, Rostov-on-Don, Russian Federation
ORCID: https://orcid.org/0000-0001-5287-5800, SPIN: 8121-4039, AuthorID: 794672

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

Kristian D. Iozefi – MD, thoracic surgeon at the Department of Thoracic Oncology, National Medical Research Centre for Oncology, Rostov-on-Don, Russian Federation
ORCID: https://orcid.org/0000-0002-5351-3251, SPIN: 1232-3097, AuthorID: 1122592, ResearcherID: AAZ-3632-2021

Contribution of the authors:

Kolesnikov E. N., Kharagezov D. A – scientific management;
Stateshny O. N., Mirzoyan E. A. – writing the draft, material processing;
Ayrapetova T. G., Milakin A. G, Iozefi K. D. – data collection and analysis, technical formatting, bibliography design.