ФГБУ "НМИЦ ОНКОЛОГИИ"
МИНЗДРАВА РОССИИ

ISSN 2686-9039 (Online)

South Russian Journal of Cancer

PEER-REVIEWED SCIENTIFIC AND PRACTICAL

Южно-Российский онкологический журнал

РЕЦЕНЗИРУЕМЫЙ НАУЧНО-ПРАКТИЧЕСКИЙ

vol. 5 № 4/2024
том

www.cancersp.com

ISSN 2686-9039 (Online)

PEER-REVIEWED SCIENTIFIC AND PRACTICAL JOURNAL

South Russian Journal of Cancer

The journal is included in the list of peer reviewed scientific journals and publications recommended by the Higher Attestation Commission of the Russian Federation for publishing the main scientific results of dissertations for the degree of candidate and Doctor of Sciences.

The "South Russian Journal of Cancer" is a quarterly scientific and practical peer–reviewed journal. A professional medical publication that reflects the results of current research on the subject of publications: diagnosis and treatment of oncological diseases, issues of carcinogenesis and molecular oncology, new medicines and technologies. It was founded in 2019.

The purpose of the journal:

- To promote the development of oncological medicine in the South of Russia and the implementation of its achievements in practice.
- High-quality published content that includes the latest and trustworthy scientific papers, research or work on oncology issues.

Tasks of the journal:

- Popularization of modern achievements of the oncological service in the South of Russia;
- Facilitating the exchange of experience and transfer of advanced knowledge between specialists;
- Informing readers about the results of major medical forums;
- Giving scientists the opportunity to publish the results of their research;
- Achieving an international level in scientific publications;
- Promotion of the magazine on the international and Russian markets;
- Drawing attention to relevant, promising and interesting areas of scientific research related to the journal's subject matter;
- Involvement of reputable national and international high-level authors;
- Expansion of the editorial board and reviewers by attracting well-known experts from Russia and other countries;
- Providing full-text access to scientific articles and increasing the accessibility and openness of the journal in Russia and abroad;
- Increasing the impact factor of the journal.

The journal accepts for publication:

the results of original research, literature reviews, and descriptions of clinical cases.

The journal "South Russian Journal of Cancer" is part of the core of the RSCI in the Russian Science Citation Index on the Web of Science platform and is presented in the following scientometric databases and reference publications: RSCI (Russian Science Citation Index), Scientific Electronic Library E-library, CyberLeninka, DOAJ, Scilit, Mendeley, Research4life, Google Scholar, Wikidata, Internet Archive.

Founder and Publisher:
Autonomous Non-profit Organization "Perspectives of Oncology"
(ANO "Perspectives of Oncology")

Editorial and publisher address:
63, G, room 1, 14 line, Rostov-on-Don 344037, Russia
E-mail: edition@cancersp.com, info@cancersp.com
Phone: +7 (903) 547-04-62, +7 (863) 295-53-62
www.cancersp.com
For correspondence: 111555, Moscow, PO box 3

The journal is registered at the Roskomnadzor on 28.10.2019,
EL No. FS 77-80665 – online.
Frequency: 4 issues per year.

Published 12.12.2024

ISSN 2686-9039 (Online)

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.

«Южно-Российский онкологический журнал» – ежеквартальный научно-практический рецензируемый журнал. Профессиональное медицинское издание, в котором отражаются результаты актуальных исследований по тематике публикаций: диагностика и лечение онкологических заболеваний, вопросы канцерогенеза и молекулярной онкологии, новые лекарственные средства и технологии. Основан в 2019 г.

Цель журнала:

- Способствовать развитию онкологической медицины Юга России и внедрению её достижений в практику.
- Качественный опубликованный контент, включающий последние и заслуживающие доверия научные труды, исследования или работы по проблемам онкологии.

Задачи журнала:

- Популяризация современных достижений онкологической службы на Юге России;
- Содействие обмену опытом и передаче передовых знаний между специалистами;
- Информирование читателей о результаты крупных медицинских форумов;
- Предоставление ученым возможности опубликовать результаты своих исследований;
- Достижение международного уровня в научных публикациях;
- Продвижение журнала на международном и российском рынках;
- Привлечение внимания к актуальным, перспективным и интересным направлениям научных исследований, связанных с тематикой журнала;
- Привлечение авторитетных национальных и международных авторов высокого уровня;
- Расширение состава редакционной коллегии и рецензентов путем привлечения известных экспертов из России и других стран;
- Обеспечение полнотекстового доступа к научным статьям и повышение доступности и открытости журнала в России и за рубежом;
- Повышение импакт-фактора журнала.

Журнал принимает к публикации: результаты оригинальных исследований, обзоры литературы, описание клинических случаев.

Издатель и учредитель:
Автономная некоммерческая организация «Перспективы онкологии» (АНО «Перспективы онкологии»)

Адрес редакции и издателя:
344037, Россия, Ростов-на-Дону, 14-я линия, д. 63, литер Г, комната 1
E-mail: edition@cancersp.com, info@cancersp.com
Телефон: +7 (903) 547-04-62, +7 (863) 295-53-62
Сайт: www.cancersp.com
Для корреспонденции: 111555, Москва, а/я 3

Журнал зарегистрирован в Роскомнадзоре 28.10.2019 г.,
ЭЛ № ФС 77-80665 – сетевое издание.
Периодичность: 4 номера в год.

Опубликовано 12.12.2024

CONTENTS

South Russian Journal of Cancer
2024. Vol. 5, No. 4

СОДЕРЖАНИЕ

South Russian Journal of Cancer. 2024. Vol. 5, No. 4. P. 6-13
https://doi.org/10.37748/2686-9039-2024-5-4-1
https://elibrary.ru/ohijav
ORIGINAL ARTICLE

Intravenous radionuclide therapy with radium chloride [223Ra] in patients with bone metastases from castration-resistant prostate cancer

O. I. Kit, N. A. Maksimova, M. A. Gusareva, A. N. Shevchenko, M. S. Zinkovich, M. G. Ilchenko✉, K. P. Boyko, A. V. Faenson, S. N. Dimitriadi, L. Ya. Rozenko

National Medical Research Centre for Oncology, Rostov-on-Don, Russian Federation
✉ maria_ilchenko80@mail.ru

ABSTRACT

Purpose of the study. Assessment of clinical safety and effectiveness of radium-223 in patients with bone metastases from castration-resistant prostate cancer.
Patients and methods. The study involved materials on 15 patients with bone metastases from castration-resistant prostate cancer aged 58–81 years, with the mean age of 67.2 ± 6.5 years, who were examined and received full treatment with 6 intravenous injections of radium-223 chloride [223Ra] at the National Medical Research Centre for Oncology. Most patients (73.3 %) showed ECOG 1 performance status. Pain syndrome before the treatment was registered in 12 (80 %) patients.
Results. Evaluation of the tolerability of radium chloride did not show hematological reactions such as anemia and thrombocytopenia. One patient had grade II intestinal toxicity after the 3rd injection managed with medication. Assessment of indirect signs of the treatment effectiveness demonstrated that 6 people showed an increase in PSA during treatment, while alkaline phosphatase levels were within normal range indicating no bone destruction. 8 of 12 patients with pain syndrome showed its relief during the therapy. The following results were obtained during a follow-up examination after 3 months in 15 patients who received the full treatment course: stabilization in 8 patients; improvement in 4 patients with decreased metabolic activity and lower numbers of metastatic foci; progression with the appearance of new metastatic foci in the bones in 3 patients.
Conclusion. Radium chloride showed good results in the treatment of patients with bone metastases from castration-resistant prostate cancer. Low toxicity and improvement in the quality of life by pain relief make this treatment technique promising.

Keywords: castration-resistant prostate cancer, bone metastases, radium chloride [223Ra], quality of life

For citation: Kit O. I., Maksimova N. A., Gusareva M. A., Shevchenko A. N., Zinkovich M. S., Ilchenko M. G., Boyko K. P., Faenson A. V., Dimitriadi S. N., Rozenko L. Ya. Intravenous radionuclide therapy with radium chloride [223Ra] in patients with bone metastases from castration-resistant prostate cancer. South Russian Journal of Cancer. 2024; 5(4): 6-13. https://doi.org/10.37748/2686-9039-2024-5-4-1, https://elibrary.ru/ohijav

For correspondence: Maria G. Ilchenko – Cand. Sci. (Med.), MD, Researcher at the Department of Tumor Diagnostics, National Medical Research Centre for Oncology, Rostov-on-Don, Russian Federation
Address: 63 14 line str., Rostov-on-Don 344037, Russian Federation
E-mail: maria_ilchenko80@mail.ru
ORCID: https://orcid.org/0000-0002-9126-0646
SPIN: 2856-7946, AuthorID: 734046
ResearcherID: AAT-9807-2020

Compliance with ethical standards: the ethical principles presented by the World Medical Association Declaration of Helsinki, 1964, ed. 2013, were observed in the work. The study was approved by the Committee on Biomedical Ethics at the National Medical Research Centre for Oncology (extract from the protocol of the meeting No. 7 dated 08/08/2022). Informed consent was received from all participants of the study.

Funding: this work was not funded

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

The article was submitted 01.12.2023; approved after reviewing 12.10.2024; accepted for publication 30.10.2024

Южно-Российский онкологический журнал. 2024. Т. 5, № 4. С. 6-13
https://doi.org/10.37748/2686-9039-2024-5-4-1
https://elibrary.ru/ohijav
3.1.6. Онкология, лучевая терапия
ОРИГИНАЛЬНАЯ СТАТЬЯ

Применение внутривенной радионуклидной терапии радия хлоридом [223Ra] у пациентов с костными метастазами кастрационно-резистентного рака предстательной железы

О. И. Кит, Н. А. Максимова, М. А. Гусарева, А. Н. Шевченко, М. С. Зинькович, М. Г. Ильченко✉, К. П. Бойко, А. В. Фаенсон, С. Н. Димитриади, Л. Я. Розенко

ФГБУ «Национальный медицинский исследовательский центр онкологии» Министерства здравоохранения Российской Федерации, г. Ростов-на-Дону, Российская Федерация
✉ maria_ilchenko80@mail.ru

РЕЗЮМЕ

Цель исследования. Оценка клинической безопасности и эффективности применения радия-223 у пациентов с костными метастазами кастрационно-резистентного рака предстательной железы (РПЖ).

Материалы и методы. В исследование включены сведения о 15 пациентах с костными метастазами кастрационно-резистентного РПЖ в возрасте от 58 до 81 года, средний возраст 67,2 ± 6,5 года, обследованных и получивших полный курс лечения из 6 внутривенных радиотерапий препаратом радия хлорида [223Ra] на базе ФГБУ «Национальный медицинский исследовательский центр онкологии» Министерства здравоохранения Российской Федерации. Функциональное состояние большей части пациентов (73,3 %) соответствовало 1 по шкале ECOG. Перед началом лечения болевой синдром отмечался у 12 (80 %) пациентов.

Результаты. При оценке переносимости радия хлорида было отмечено отсутствие гематологических реакций, таких как анемия и тромбоцитопения. У одного пациента была отмечена кишечная токсичность II степени, которая появилась после 3-го введения и была медикаментозно купирована. Оценка косвенных признаков эффективности проведенного лечения: у 6 человек за время лечения был отмечен рост простатического специфического антигена (ПСА), при этом показатели уровня щелочной фосфатазы находились в пределах нормы, что может говорить об отсутствии костной деструкции. У 8 из 12 человек с болевым синдромом наблюдалось его снижение уже на этапе терапии. У 15 пациентов, получивших полный курс лечения, при контрольном обследовании через 3 месяца были получены следующие результаты: у 8 человек – стабилизация процесса, у 4 человек – улучшение в виде снижения уровня метаболической активности и уменьшение количества метастатических очагов, у 3 пациентов отмечено прогрессирование заболевания с появлением новых метастатических очагов в костях скелета.

Заключение. Радия хлорид показал хорошие результаты в терапии пациентов с костными метастазами кастрационно-резистентного рака предстательной железы. Низкие уровни токсичности и возможность улучшить качество жизни за счет снижения выраженности болевого синдрома позволяют говорить о перспективности данной лечебной методики.

Ключевые слова: кастрационно-резистентный рак предстательной железы, метастазы в кости, радия хлорида [223Ra], качество жизни

Для цитирования: Кит О. И., Максимова Н. А., Гусарева М. А., Шевченко А. Н., Зинькович М. С., Ильченко М. Г., Бойко К. П., Фаенсон А. В., Димитриади С. Н., Розенко Л. Я. Применение внутривенной радионуклидной терапии радия хлоридом [223Ra] у пациентов с костными метастазами кастрационно-резистентного рака предстательной железы. Южно-Российский онкологический журнал. 2024; 5(4): 6-13. https://doi.org/10.37748/2686-9039-2024-5-4-1, https://elibrary.ru/ohijav

Для корреспонденции: Ильченко Мария Геннадьевна – к.м.н., научный сотрудник отдела диагностики опухолей, 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: maria_ilchenko80@mail.ru
ORCID: https://orcid.org/0000-0002-9126-0646
SPIN: 2856-7946, AuthorID: 734046
ResearcherID: AAT-9807-2020

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 № 7 от 08.08.2022). Информированное согласие получено от всех участников исследования.

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

Статья поступила в редакцию 01.12.2023; одобрена после рецензирования 12.10.2024; принята к публикации 30.10.2024

INTRODUCTION

Prostate cancer (prostate cancer) ranks second in the structure of cancer incidence in the male population and is one of the leading causes of cancer mortality in the world [1, 2]. Its share is 15.1 % in the structure of the incidence of malignant neoplasms in the male population in Russia [1]. Over 10 years, the increase in Russia amounted to 41.69 %, so in 2021, the incidence of prostate cancer almost doubled compared to 2011 and reached 59.24 per 100,000 population [1]. The mortality rate in Russia from prostate cancer remains high, in 2021 it is 19.03 per 100,000 population, an increase of 23.87 % over 10 years [1]. In Russia, up to 50 % of patients suffering from prostate cancer are already treated with advanced stages III–IV of the disease, metastatic cancer accounts for up to 18.1 % of patients [3, 4]. It is generally accepted for patients with prostate cancer to undergo hormonal treatment in the form of maximum androgenic blockade, including pharmacological castration. The development of resistance to the therapy leads to the progression of the disease with a fatal outcome. According to literature data, castration-resistant prostate cancer (CRPC) develops within 5 years of treatment in 10–20 % of patients. Currently, the issue of finding methods to overcome castration resistance remains relevant, since the appearance of bone metastases, the generalization of the process is accompanied by a significant deterioration in the quality of life of patients and an increase in overall mortality rates from prostate cancer [2, 5].

The property of radium chloride [223Ra] to competitively bind to bone hydroxyapatites makes it possible to use it as an osteotropic radiopharmaceutical therapy (RPT) in the presence of metastatic foci in skeletal bones associated with increased bone mineralization [6]. Radium chloride [223Ra] is an approved drug for the treatment of CRPC with direct effects on foci in metastatic bone lesions. Radium-223 is recognized as the drug of choice in patients with CRPC in the presence of bone metastases of the 1st and subsequent lines of therapy according to the recommendations of the European Association of Urologists (high degree of recommendation) [6, 7] and the National Cancer Control Network (1st level of evidence) in 2020. Since radium chloride therapy [223Ra] the presence of visceral metastases is a contraindication to its use, it should be used as early as possible before their appearance. When radium chloride [223Ra] is prescribed for the diagnosis of bone metastases, the results of osteoscintigraphy are of fundamental importance, which does not require the use of additional research methods such as CT or MRI [6, 8].

The purpose of the study was to evaluate the clinical safety and efficacy of radium-223 in patients with bone metastases of castration-resistant prostate cancer.

MATERIALS AND METHODS

The study included 15 patients who received therapy with the drug "Xofigo" radium chloride [223Ra] at the National Medical Research Centre for Oncology. The average age of the patients was 67.2 years (ranged from 58–81 years). The objective status of the majority of patients on the ECOG scale corresponded to 1 (73.3 %) [9]. Patients were assessed for pain intensity before treatment and before each course of radiotherapy using a visual analog pain scale (VAS) [6]. VAS is a straight-line segment 10 cm long. Its beginning corresponds to the absence of pain – "there is no pain", and the end point reflects excruciating unbearable pain – "unbearable pain". The line can be either horizontal or vertical. The patient was asked to make a mark on it corresponding to the intensity of the pain he was experiencing at the moment. The distance between the beginning of the segment ("there is no pain") and the mark made is measured in centimeters and rounded to the whole. Each centimeter on the line corresponds to 1 point. At a mark of up to 2 cm, the pain is classified as mild, from 2 to 4 cm – moderate, from 4 to 6 cm – severe, from 6 to 8 cm – the strongest and up to 10 cm – unbearable. At the time of initiation of therapy, pain syndrome of varying severity was noted in 12 patients (80 %). Radium-223 was received as 1st-line therapy by 4 patients (26.7 %), 2nd-line – 7 people (46.6 %), 3rd-line – 4 patients (26.7 %). All patients received a full course of radiotherapy – monthly intravenous injections of radiopharmaceutical radium chloride [223Ra] for 6 months in the required volume [9]. In total, 90 patients underwent intravenous radiotherapy with radium chloride [223Ra].

Radium chloride solution [223Ra] is a radium solution in ionic form with an activity of 1100 kBq/ml. The specific activity of radium-223 is 1.9 MBq/ng.

The half-life of radium is 223 11.4 days. At the stages of the decay of radium-223 to stable lead, alpha, beta and gamma particles are emitted with an alpha radiation energy value of 95.3 % (energy range 5.0–7.5 MeV), 3.6 % beta radiation (energy range 0.45–0.49 MeV) and 1.1 % gamma radiation (energy range 0.01–1.27 MeV) [10] Being a competitor of calcium, radium-223 selectively affects bone metastases in prostate cancer, forming a complex compound with the bone mineral hydroxyapatite. The therapeutic effect is because of alpha particles, which have a cytotoxic effect on tumor cells and microenvironments (osteoclasts, osteoblasts). The high energy of radium chloride alpha particles (80 keV/μm) and the low range of action – less than 100 μm (less than 10 cell diameters) make treatment safe with minimal damage to healthy tissues [10, 11].

Due to its good tolerability and minimal side effects, the treatment of bone metastases with radium isotope does not require special preparations. The main amount is excreted through the intestines and about 5 % of the drug is excreted by the kidneys. For these reasons, on the day of administration, we recommended using products that do not have an irritating effect on the intestinal mucosa and immediately before administration, we recommended drinking about 1 liter of water to reduce the load on the urinary system. And, a few days before the introduction of the isotope, it was recommended to stop taking drugs containing calcium or vitamin D because of the possibility of its interaction with calcium and phosphates [10, 12].

The method of therapy: a full course of radium chloride treatment [223Ra], consisting of 6 injections of the isotope with an interval of 28 days, is designed for six months. Before each course of treatment, we monitored blood counts [10, 13]. The drug was administered intravenously slowly, at the rate of 55 kBq/ kg, through a peripheral or central venous catheter.

We calculated the required dose of activity using the formula: the patient's body weight (kg) × 55 (kBq/kg) = activity (kBq), then the required volume of RPT was determined by the formula: activity (kBq)/ (1100 kBq/ml × radioactive decay coefficient) = volume of the drug (ml). The activity in the vial at the date of administration was calculated using the formula: 6600 kBq × decay factor = activity in the vial on the day of administration (kBq), then the activity in the unopened vial was measured and the required volume of the drug was collected into a syringe. The activity in the syringe was measured and the drug was administered intravenously slowly. After administration, the dose rate of photon radiation was determined at 1.0 meters from the patient's body with the injected RPT activity at the exit from the unit, which should not exceed 3 mSv/h (NRB-99). The measured doses of photon radiation in all patients were within the acceptable standard parameters, on average 0.83 mSv/h.

After intravenous radiotherapy of radium chloride [223Ra], the patient was provided with the necessary protocols and medical documents with recommendations on the peculiarities of behavior, considering radiation safety standards.

STUDY RESULTS

A full course of treatment (6 injections of radium-223) was performed in 15 patients. Radium-223 showed low levels of toxicity, so hematological reactions (anemia, thrombocytopenia) were not observed in any patient. The level of alkaline phosphatase was within the normal range before and during treatment. In 6 patients (40 %), an increase in PSA levels by more than 100 % was noted during treatment, which, according to the literature, is not a reliable indicator of progression and does not require a change in the line of therapy [10]. One patient (6.6 %) had grade 2 intestinal toxicity after the 3rd administration, which was medically stopped and did not recur. Of the 12 patients with pain syndrome, 8 (66.6 %) had a decrease after 3–4 intravenous radiotherapy sessions with radium chloride [223Ra]. So, before the start of radiotherapy, 2 patients (16.6 %) noted pain by 8 on the scale, 4 people (33.3 %) gave 7 points, 3 patients (25 %) gave 6 points, 2 (16.6 %) – 5 points and 1 (8.3 %) – 4 points. After completing 6 courses, all patients assessed a decrease in pain intensity by almost two times (Fig. 1).

In patients who received a full course of treatment, the following results were obtained during a control examination after 3 months: stabilization of the process in 8 people (53.3 %), improvement in 4 people (26.6 %) in the form of a decrease in metabolic activity and a decrease in the number of metastatic foci, and only 3 patients (20 %) revealed the progression of the disease in the form of the appearance of new foci.

A clinical example

Patient R., born in 1962, presented with castration-resistant prostate cancer sT2cN1M0, st.IV, after hormonal and radiation therapy, progression (bone metastases), bisphosphonate therapy and 6 courses of systemic radionuclide therapy (Ra 223), cl. gr. 2.

From the anamnesis: during a routine examination, an increase in PSA to 75 ng/ml was noted in June 2019. Prostate biopsy of G. A. No. 7243–7254 moderately differentiated adenocarcinoma, Gleason index 7 (4 + 3) was concluded on 06/20/2019. In magnetic resonance computed tomography from 07/04/2019: lesion of both lobes of the prostate gland without the tumor leaving the capsule, internal iliac lymph nodes on the right side up to 3 cm. Osteoscintigraphy dated 07/15/2019 showed no scintigraphic signs of osteodestructive changes in the bones of the skeleton. Hormonal therapy in the amount of maximum androgenic blockade for 12 months was administered. PSA on 07/12/20 was 0.230 ng/ml. From 08/10/2020 to 09/04/2020, the course of conformal remote radiation therapy to a total focal dose (TFD) of 75 Gy per area of the prostate gland and seminal vesicles, up to TFD 50 Gy per pelvic area. MRI from 04/22/2021 showed MR-signs of hyperplasia of the prostate gland transitional zone. The presence of index foci was not revealed. The focus in S1 of the sacrum (possibly mts) requires dynamic

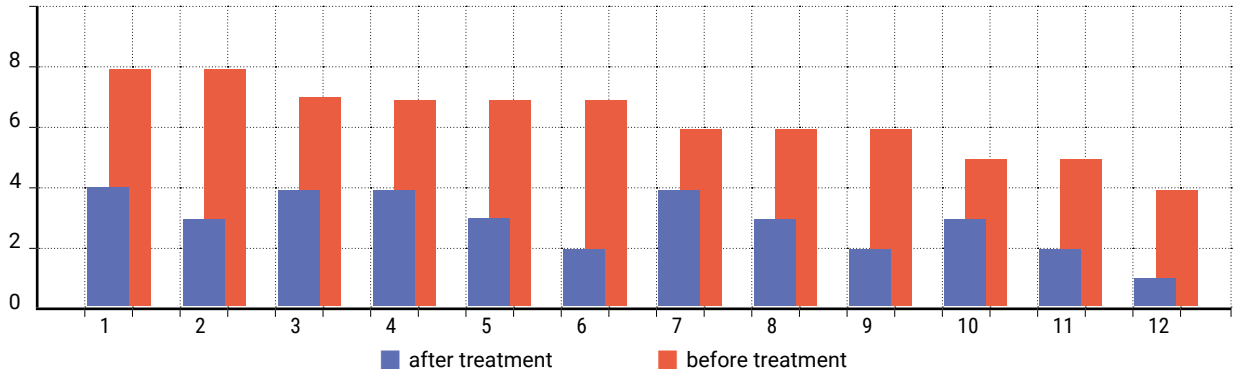


Fig. 1. Results of pain intensity assessment before and after 6 courses of intravenous radiotherapy with radium chloride [223Ra]

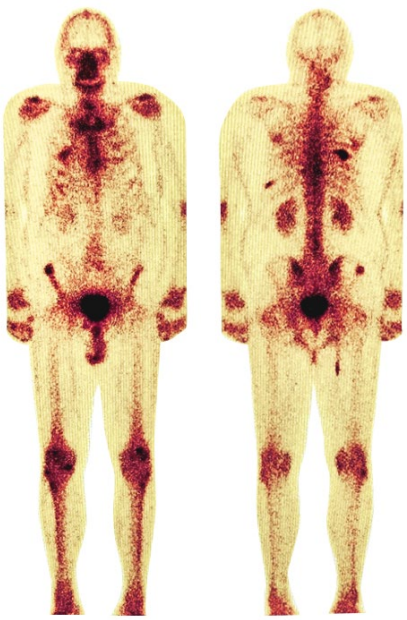


Fig. 2. Bone scintigraphy before the treatment

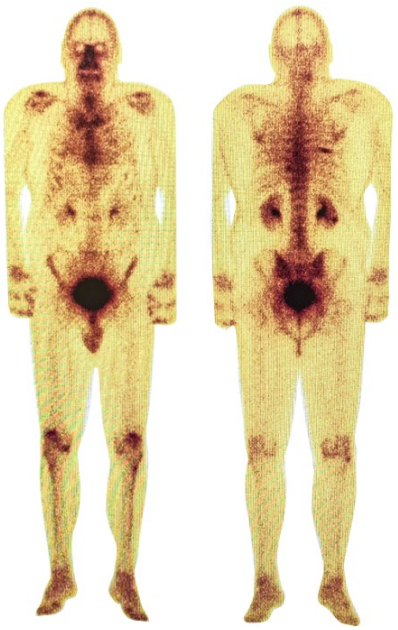


Fig. 3. Bone scintigraphy after the treatment

control. Osteoscintigraphy (05/07/2021): there is a pronounced uneven distribution of radiopharmaceutical (RPT) with signs of focal lesion: 7 ribs on the right – 45 %, 9 ribs on the left – 55 %, iliac root 70 %. Hormonal therapy and bisphosphonates were prescribed. SCT (06/02/2022) showed lung tissue without foci. The intrathoracic lymph nodes were not enlarged. There is no data for visceral metastases. There is no ascites. Retroperitoneal lymph nodes are not enlarged. Metastatic lesion of the 7th rib on the right. Osteoscintigraphy (06/07/2022) revealed signs of local osteodestructive changes in the projection of 7 ribs on the right – 48 %, 9 ribs on the left – 35 %, right iliac bone – 64 % (Fig. 2.). There was a complaint of pain in the pelvic bones. From 07/28/2022 to 12/13/2022, at the National Medical Research Centre for Oncology, the patient underwent 6 courses of systemic radionuclide therapy sessions with radium chloride [223Ra]. The patient tolerated treatment adequately, no toxic reactions from the treatment were observed. According to laboratory studies, there was an increase in PSA throughout the course.

Total PSA on 07/25/2022 was 2.07 ng/ml; on 08/23/2022–3.65 ng/ml; on 09/19/2022–6.55 ng/ml; on 10/14/2022–8.03 ng/ml; on 11/11/2022–8.5 ng/ml; on 12/9/2022–9.54 ng/ml. After the third administration, there was a significant decrease in the severity of the pain syndrome, after the sixth administration, only minor discomfort was noted. Osteoscintigraphy dated 01/26/2023 showed scintigraphic signs of local osteodestructive changes in the bones of the skeleton, in projection of the 7th rib on the right (18 %), and the right ilium (16 %) (Fig. 3).

As we can clearly see there is a pronounced positive shift.

CONCLUSION

Even though it is too early to talk about statistically significant conclusions, a number of positive aspects related to radium chloride 223Ra therapy can already be noted. First, a decrease in the severity of pain syndrome and, as a result, an improvement in the quality of life in patients with bone metastases of castration-resistant prostate cancer. A low degree of severity of adverse and toxic reactions was noted, which is important, since most patients are elderly people with severe concomitant pathology. The results obtained using objective research methods are comparable with the data of domestic and foreign authors and indicate the prospects of this therapeutic technique.

References

1. Malignant neoplasms in Russia in 2021 (morbidity and mortality). Ed. by A. D. Kaprin, V. V. Starinsky, A. O. Shakhzadova. Moscow: P. A. Herzen MNIOI – Branch of the National Medical Research Radiological Center, 2022, 252 p. (In Russ.)
2. Andreev DA, Zavyalov AA, Govorov AV, Kokushkin KA, Davydovskaya MV. Castration-resistant prostate cancer: new perspectives in pharmacological treatment. Russian Medical Journal. 2019;25(1):49–58. (In Russ.). https://doi.org/10.18821/0869-2106-2019-25-1-49-58, EDN: VPCCJR
3. Markova AS. Current possibilities of drug therapy for castration-resistant prostate cancer. Cancer Urology. 2013;9(2):73–77. (In Russ.). https://doi.org/10.17650/1726-9776-2013-9-2-73-77, EDN: RAMIBL
4. Gallaher J, Cook LM, Gupta S, Araujo A, Dhillon J, Park JY, et al. Improving treatment strategies for patients with metastatic castrate resistant prostate cancer through personalized computational modeling. Clin Exp Metastasis. 2014 Dec;31(8):991–999. https://doi.org/10.1007/s10585-014-9674-1
5. Kirby M, Hirst C, Crawford ED. Characterising the castration-resistant prostate cancer population: a systematic review. Int J Clin Pract. 2011 Nov;65(11):1180–1192. https://doi.org/10.1111/j.1742-1241.2011.02799.x
6. Matveev VB, Markova AS. Efficacy and safety of radium-223 in routine clinical practice. Cancer Urology. 2020;16(4):129–135. (In Russ.). https://doi.org/10.17650/1726-9776-2020-16-4-129-135, EDN: OVEGET
7. Mottet N, van den Bergh RCN, Briers E, Van den Broeck T, Cumberbatch MG, De Santis M, et al. EAU-EANM-ESTRO-ESUR-SIOG Guidelines on Prostate Cancer-2020 Update. Part 1: Screening, Diagnosis, and Local Treatment with Curative Intent. Eur Urol. 2021 Feb;79(2):243–262. https://doi.org/10.1016/j.eururo.2020.09.042

8. Keizman D, Fosboel MO, Reichegger H, Peer A, Rosenbaum E, Desax MC, et al. Imaging response during therapy with radium-223 for castration-resistant prostate cancer with bone metastases-analysis of an international multicenter database. Prostate Cancer Prostatic Dis. 2017 Sep;20(3):289–293. https://doi.org/10.1038/pcan.2017.6
9. Maksimova NA, Gusareva MA, Zinkovich MS, Faenson AV, Ilchenko MG, Kosheleva NG, et al. The first case of radium-223 use in patients with bone metastases of castration-resistant prostate cancer is a question of oncology. 2023;69(3S):232–233. (In Russ.). https://doi.org/10.37469/0507-3758-2023-69-3s1, EDN: SBQKBK
10. Kochetova TYu, Krylov VV, Petrosyan KM, Karyakin OB, Biryukov VA, Alekseev BYa, et al. Radium chloride [223Ra] for patients with prostate cancer and skeletal metastases. Clinical recommendations. Cancer Urology. 2020;16(1):114–123. (In Russ.). https://doi.org/10.17650/1726-9776-2020-16-1-114-123, EDN: UPRLFX
11. Kairemo K, Joensuu T, Rasulova N, Kiljunen T, Kangasmäki A. Evaluation of Alpha-Therapy with Radium-223-Dichloride in Castration Resistant Metastatic Prostate Cancer-the Role of Gamma Scintigraphy in Dosimetry and Pharmacokinetics. Diagnostics (Basel). 2015 Jul 30;5(3):358–368. https://doi.org/10.3390/diagnostics5030358
12. Xofigo (radium-223 dichloride). Summary of Product Characteristics. Bayer Inc., 2022. https://www.bayer.com/sites/default/files/xofigo-pm-en.pdf
13. Basch E, Loblaw DA, Oliver TK, Carducci M, Chen RC, Frame JN, et al. Systemic therapy in men with metastatic castration-resistant prostate cancer: American Society of Clinical Oncology and Cancer Care Ontario clinical practice guideline. J Clin Oncol. 2014 Oct 20;32(30):3436–3448. https://doi.org/10.1200/JCO.2013.54.8404

Information about authors:

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

Natalia A. Maksimova – Dr. Sci. (Med.), MD, Professor, Head of Department of Radionuclide Therapy and Diagnostics, National Medical Research Centre for Oncology, Rostov-on-Don, Russian Federation
ORCID: https://orcid.org/0000-0002-0400-0302, SPIN: 1785-9046, AuthorID: 375005, ResearcherID: AAT-9775-2020, Scopus Author ID: 57211495326

Marina A. Gusareva – Cand. Sci. (Med.), MD, Head of Department of Radiology No. 1, National Medical Research Centre for Oncology, Rostov-on-Don, Russian Federation
ORCID: https://orcid.org/0000-0002-9426-9662, SPIN: 9040-5476, AuthorID: 705242

Alexey N. Shevchenko – Dr. Sci. (Med.), MD, Head of Department of Oncourology, National Medical Research Centre for Oncology, Rostov-on-Don, Russian Federation
ORCID: https://orcid.org/0000-0002-9468-134X, SPIN: 2748-2638, AuthorID: 735424, ResearcherID: Y-5387-2018, Scopus Author ID: 57192283096

Mikhail S. Zinkovich – Cand. Sci. (Med.), MD, radiotherapist, National Medical Research Centre for Oncology, Rostov-on-Don, Russian Federation
ORCID: https://orcid.org/0000-0003-2460-0038, SPIN: 1072-9674, AuthorID: 735168, ResearcherID: JGE-4158-2023

Maria G. Ilchenko ✉ – Cand. Sci. (Med.), MD, Researcher at the Department of Tumor Diagnostics, National Medical Research Centre for Oncology, Rostov-on-Don, Russian Federation
ORCID: https://orcid.org/0000-0002-9126-0646, SPIN: 2856-7946, AuthorID: 734046, ResearcherID: AAT-9807-2020

Konstantin P. Boyko – Cand. Sci. (Med.), MD, radiologist, Department of Radionuclide Therapy and Diagnostics, National Medical Research Centre for Oncology, Rostov-on-Don, Russian Federation
ORCID: https://orcid.org/0000-0003-1694-1385, SPIN: 4536-4073, AuthorID: 734382

Aleksandr V. Faenson – Cand. Sci. (Med.), MD, oncologist, National Medical Research Centre for Oncology, Rostov-on-Don, Russian Federation
ORCID: https://orcid.org/0000-0002-3386-0491, SPIN: 4012-6345, AuthorID: 735389

Sergey N. Dimitriadi – Dr. Sci. (Med.), MD, senior researcher, Section of Urology, National Medical Research Centre for Oncology, Rostov-on-Don, Russian Federation
ORCID: https://orcid.org/0000-0002-2565-1518, SPIN: 8337-8141, AuthorID: 692389, Scopus Author ID: 57076760200

Lyudmila Ya. Rozenko – Dr. Sci. (Med.), MD, Professor, radiotherapist, Department of Radiology No. 2, National Medical Research Centre for Oncology, Rostov-on-Don, Russian Federation
ORCID: https://orcid.org/0000-0001-7032-8595, SPIN: 8879-2251, AuthorID: 421802, Scopus Author ID: 55397560100

Contribution of the authors:

Kit O. I. – scientific guidance, scientific editing;
Maksimova N. A. – study concept, scientific editing;
Gusareva M. A. – text editing, material collection;
Shevchenko A. N. – material collection and analysis;
Zinkovich M. S. – material analysis, manuscript writing;
Ilchenko M. G. – material analysis, text design;
Boyko K. P. – material collection;
Faenson A. V. – material collection;
Dimitriadi S. N. – material collection and analysis;
Rozenko L. Ya. – material collection and analysis.

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

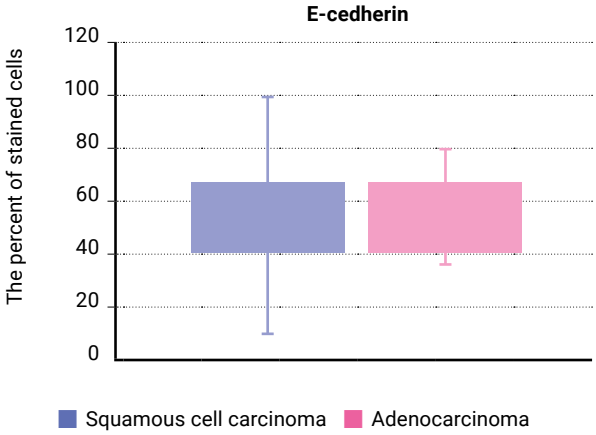


Fig. 1. Expression of E-cadherin in tumor samples taken from NSCLC patients

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)

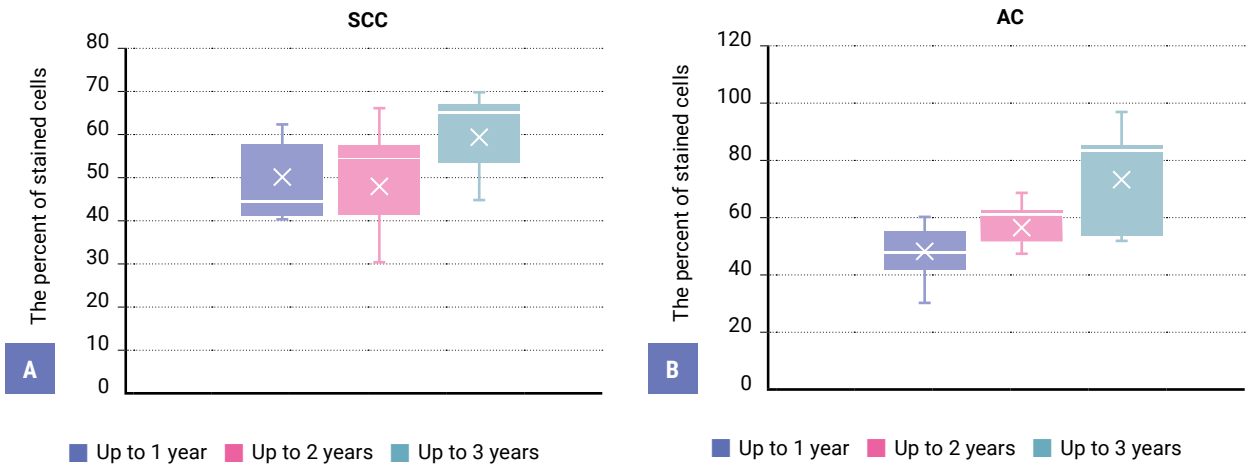


Fig. 2. Expression of E-cadherin in patients with NSCLC with varying survival rates. A – SCC; B – AC

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.

South Russian Journal of Cancer. 2024. Vol. 5, No. 4. P. 20-28
https://doi.org/10.37748/2686-9039-2024-5-4-3
https://elibrary.ru/cctlum
ORIGINAL ARTICLE

Improvement of long-term treatment results in oligometastatic colorectal cancer patients by using a combined approach

E. O. Kalmykova[1]✉, R. V. Ishchenko[1,2], O. Yu. Stukalova[3], D. A. Filimonov[2]

[1] Lomonosov Moscow State University, Moscow, Russian Federation
[2] V. K. Gusak institute of emergency and reconstructive surgery, Donetsk, Russian Federation
[3] ALLORO Medical Center, Fryazino, Russian Federation
✉ elja479@mail.ru

ABSTRACT

Purpose of the study. To improve the treatment results of patients suffering from CRC with oligometastatic lesion by determining the most effective combination of treatment methods.
Patients and methods. The results of treatment of 71 patients with oligometastases of colorectal cancer were analyzed. All patients were divided into 2 groups depending on the treatment methods. The first group included 35 patients who underwent simultaneous removal of the primary tumor and metastatic foci at the first stage of complex treatment. The second group includes clinical data on 36 patients who underwent primary lesion removal at the first stage of complex treatment followed by drug antitumor therapy.
Results. In the primary tumor removal group, the response was received in 3 (8.3 %) cases, stabilization was achieved in 14 (38.9 %) cases, and progression of the tumor process was detected in 19 (52.8 %) cases. The median disease-free survival was 9.2 ± 3.2 months. One-year, two- and three-year survival rates in the group of simultaneous removal of the primary tumor and oligometastases and in the group of primary tumor removal were 97.1 %, 88.6 %, 77.1 % and 100 %, 80.5 %, 72.2 %, respectively. The overall survival rate in the group of simultaneous removal of the primary tumor and oligometastases was 63 ± 3.9 months, in the group of primary tumor removal – 58 ± 3.8 months.
Conclusion. In the presented clinical study, a comparative assessment of the effectiveness of the treatment of patients with colorectal cancer with oligometastases was carried out, depending on the option of an integrated approach. The results obtained turned out to be multidirectional – the response to treatment and progression were obtained in 54.3 % and 45.7 % of cases in the group of simultaneous removal of the primary tumor and oligometastases versus 47.2 % and 52.8 % of cases in the group of removal of the primary tumor without oligometastases, respectively. The median recurrence-free survival was shorter in the group of primary tumor removal without metastases. Complete removal of the primary tumor and oligometastases can significantly increase the overall survival rates of patients.

Keywords: colorectal cancer, oligometastases, chemotherapy, lung metastases, liver metastases

For citation: Kalmykova E. O., Ishchenko R. V., Stukalova O. Yu., Filimonov D. A. Improvement of long-term treatment results in oligometastatic colorectal cancer patients by using a combined approach. South Russian Journal of Cancer. 2024; 5(4): 20-28. https://doi.org/10.37748/2686-9039-2024-5-4-3, https://elibrary.ru/cctlum

For correspondence: Elmira O. Kalmykova – MD, oncologist, Department of Antitumor Drug Therapy, Lomonosov Moscow State University, Moscow, Russian Federation
Address: 27 Lomonosovsky Prospekt, bldg. 10, Moscow 119992, Russian Federation
E-mail: elja479@mail.ru

Compliance with ethical standards: the study was carried 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 V. K. Gusak institute of emergency and reconstructive surgery, Donetsk, Russian Federation (extract from the protocol of meeting No. 2 dated 05/17/2024). Informed consent was received from all participants of the study

Acknowledgement: the authors consider it their duty to express gratitude to Irina Ivanovna Selezneva, PhD., Head of the Department of antitumor Drug therapy at the Central Research Hospital "RZD-Medicine" for valuable comments in the process of carrying out the scientific and practical part of the work and comprehensive support

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 26.05.2024; approved after reviewing 01.11.2024; accepted for publication 14.11.2024

Южно-Российский онкологический журнал. 2024. Т. 5, № 4. С. 20-28
https://doi.org/10.37748/2686-9039-2024-5-4-3
https://elibrary.ru/cctlum
3.1.6. Онкология, лучевая терапия
ОРИГИНАЛЬНАЯ СТАТЬЯ

Улучшение отдаленных результатов лечения больных олигометастатическим колоректальным раком путем применения комбинированного подхода

Э. О. Калмыкова[1]✉, Р. В. Ищенко[1,2], О. Ю. Стукалова[3], Д. А. Филимонов[2]

[1] Московский государственный университет имени М. В. Ломоносова, г. Москва, Российская Федерация
[2] ФГБУ «Институт неотложной и восстановительной хирургии имени В. К. Гусака» Министерства здравоохранения Российской Федерации, г. Донецк, Российская Федерация
[3] Медицинский центр «АЛЛОРО», г. Фрязино, Российская Федерация
✉ elja479@mail.ru

РЕЗЮМЕ

Цель исследования. Улучшить результаты лечения больных, страдающих колоректальным раком (КРР) с олигометастатическим поражением, за счет определения наиболее эффективной комбинации методов лечения.
Пациенты и методы. Проведен анализ результатов лечения 71 пациента с олигометастазами КРР. Все больные были разделены на 2 группы в зависимости от методов лечения. В первую группу включены 35 больных, которым на первом этапе комплексного лечения проводилось одномоментное удаление первичной опухоли и метастатических очагов, с последующим проведением химиотерапии. Во вторую группу включены клинические данные о 36 больных, которым на первом этапе комплексного лечения проводилось удаление первичного очага с последующим проведением лекарственной противоопухолевой терапии.
Результаты. В группе удаления первичной опухоли ответ получен в 3 (8,3 %) случаях, стабилизация достигнута в 14 (38,9 %) случаях, в 19 (52,8 %) случаях выявлено прогрессирование опухолевого процесса. Медиана безрецидивной выживаемости составила 9,2 ± 3,2 мес. Годичная, двух- и трехлетняя выживаемость в группе одномоментного удаления первичной опухоли и олигометастазов и в группе удаления первичной опухоли составила 97,1, 88,6, 77,1 и 100, 80,5, 72,2 % соответственно. Общая выживаемость в группе одномоментного удаления первичной опухоли и олигометастазов составила 63 ± 3,9 мес., в группе удаления первичной опухоли – 58 ± 3,8 мес.
Заключение. В представленном клиническом исследовании проводилась сравнительная оценка эффективности проводимого лечения больных КРР с олигометастазами в зависимости от варианта комплексного подхода. Полученные результаты оказались разнонаправленными – ответ на лечение и прогрессирование получены в 54,3 и 45,7 % случаях в группе одномоментного удаления первичной опухоли и олигометастазов против 47,2 и 52,8 % случаев в группе удаления первичной опухоли без олигометастазов соответственно. Медиана безрецидивной выживаемости оказалась короче в группе удаления первичной опухоли без метастазов. Удаление олигометастазов увеличивает общую выживаемость, но результаты не достигают статистической значимости.

Ключевые слова: колоректальный рак, олигометастазы, химиотерапия, метастазы в легком, метастазы в печени

Для цитирования: Калмыкова Э. О., Ищенко Р. В., Стукалова О. Ю., Филимонов Д. А. Улучшение отдаленных результатов лечения больных олигометастатическим колоректальным раком путем применения комбинированного подхода. Южно-Российский онкологический журнал. 2024; 5(4): 20-28. https://doi.org/10.37748/2686-9039-2024-5-4-3, https://elibrary.ru/cctlum

Для корреспонденции: Калмыкова Эльмира Олеговна – врач-онколог отделения противоопухолевой лекарственной терапии, Московский государственный университет имени М. В. Ломоносова, г. Москва, Российская Федерация
Адрес: 119992, Российская Федерация, г. Москва, Ломоносовский проспект, д. 27, корп. 10
E- mail: elja479@mail.ru
ORCID: https://orcid.org/0009-0008-5842-1250

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 «Институт неотложной и восстановительной хирургии имени В. К. Гусака» Министерства здравоохранения Российской Федерации (выписка из протокола заседания № 2 от 17.05.2024 г.). Информированное согласие получено от всех участников исследования

Благодарности: авторы считают своим долгом выразить слова благодарности к.м.н., заведующей отделением противоопухолевой лекарственной терапии ЧУЗ ЦКБ «РЖД- Медицина» Селезневой Ирине Ивановне за ценные замечания в процессе осуществления научной и практической части работы и всестороннюю поддержку

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 26.05.2024; одобрена после рецензирования 01.11.2024; принята к публикации 14.11.2024

BACKGROUND

Colon cancer (CC) is one of the leading oncological diseases not only in the Russian Federation but in worldwide as well. According to GLOBOCAN 2020 data, colorectal cancer ranks third among the male and second among the female population in terms of the number of cases [1]. Of the 100 new cases of colon cancer, more than 70 % of deaths from this disease are recorded, mainly due to the late treatment of patients to a doctor. Since the tumor is located in a hollow organ, the formation should be of significant size before the first symptoms appear. This occurs mainly when the tumor grows deeply into the surrounding tissues [2].

The most common localization of oligometastases of colorectal cancer are liver, lung, abdominal lymph nodes, ovaries, peritoneum. According to the literature, there are isolated cases of metastasis to the spleen, adrenal glands and thyroid gland [3–8]. Metachronous metastases in distant organs are found in 50 % of patients who underwent surgery for locally advanced CRC, and synchronous secondary lesions are noted in 25 % of patients [9].

More than 40 years ago, the diagnosis of stage IV colorectal cancer, even in the presence of single metastatic foci, served as a reason for patients to refuse specialized treatment, and the median life expectancy was no more than 12.5 months [10].

However, advances in chemotherapy, surgical techniques, and assistive surgery have significantly expanded treatment options and improved outcomes. The division of metastatic lesions of distant organs into oligo- and poly-metastases is of great importance in achieving positive results in the treatment of colorectal cancer. Since 2020, oligometastases should be understood as the presence of a secondary lesion in the amount from 1 to 5 in one or more organs [11]. Analyzing the literature data, it is possible to trace the paradigm shift in the treatment of oligometastatic cancer.

Considering that surgical interventions in patients with metastatic colorectal cancer were performed only for vital indications and, as a rule, were limited only to the formation of unloading colostomies or bypass anastomoses, the main and only treatment of these patients for a long time was palliative chemotherapy. The five-year survival rate did not exceed 10 % [12]. In this connection, in recent years, a surgical treatment method has been actively introduced, thanks to which the 5-year survival rate has increased to 58 % [13].

For a long time, specialists have been faced with the question of whether to remove the primary tumor in the presence of distant metastases or to limit themselves only to chemotherapeutic treatment. M.Karoui noted in his work that the removal of the primary focus is very important, since this leads to an improvement in the quality of life of patients, preventing possible complications such as intestinal obstruction, bleeding, peritonitis. Subsequent chemotherapy courses are more targeted [14]. However, according to a study that compared patients who underwent first-line primary tumor resection followed by chemotherapy (144 patients, resection group) or those who underwent first-line chemotherapy (83 patients, chemotherapy group). In the resection group, the incidence of intestinal obstruction, peritonitis, fistula and intestinal bleeding was 14.6 %, 0 %, 0.7 % and 4.8 %, respectively. In the chemotherapy group, these cases were 15.2 %, 1.2 %, 0 % and 3.5 %, respectively. There were no significant differences between the two groups regarding intestinal complications [15].

Equally important in the treatment of patients with CRC oligometastases is the question of simultaneous or phased removal of the primary focus and secondary changes. Some surgeons believe that simultaneous removal of the primary lesion and metastases allows to increase the proportion of radical operations, contribute to a more guaranteed continuous adjuvant chemotherapy. Others advocate gradual removal, which in turn leads to a decrease in postoperative complications and mortality [16–18].

In recent years, there have been more and more works describing the algorithm of treatment of these patients, which includes preoperative CT followed by liver resection, adjuvant CT and resection of the primary tumor, explaining this by the fact that the most common cause of death of these patients is precisely a focus in the liver, and not the primary focus [19].

Studies were conducted in which FOLFOX and FOLFIRI schemes were compared with each other, the analysis of the study showed the same effectiveness. These regimens can be used both in the first and in the second line of chemotherapy for the treatment of mCRC. It is also worth noting that the

best survival rates were achieved in patients who received all three chemotherapy drugs, i. e. infusion of 5-FU in combination with irinotecan and oxaliplatin in the first and second lines [20].

The addition of targeted drugs to chemotherapeutic treatment significantly increased the life expectancy of patients with metastatic colon cancer up to 22–25 months [21, 22].

The combination of chemoembolization of the hepatic artery with systemic treatment of patients with unresectable liver metastases leads to an increase in average survival [23, 24]. Taking into account the results of a randomized study, the median survival with systemic chemotherapy alone was 17.5, and in combination with chemoembolization – 28.4 months, and in 30 % of patients metastasis resectability was achieved [25].

In addition to surgical methods, ablation therapy [such as radiofrequency ablation (RFA), cryosurgery, or microwave ablation] can be used as potentially curative treatments for liver and lung metastases. In several studies, the 5-year OS ranged from 20–30 % in patients with progressive CRC who had undergone RFA [26, 27].

Thus, metastatic CRC is one of the most common causes of death in patients from cancer, however, the presence of oligometastatic lesions is a positive prognostic factor. Advances in the treatment of oligometastatic CRC are crucial for increasing life expectancy, therefore, treatment strategies for these patients should be discussed by a multidisciplinary team of experts in this field, taking into account various oncological factors. It should be noted that despite all the variety of options that have appeared in the treatment of these patients, there are no clear recommendations and algorithms for the treatment of patients with CRC oligometastases.

The study purpose is to improve the treatment results of patients suffering from CRC with oligometastatic lesion by determining the most effective combination of treatment methods for this cohort of patients.

PATIENTS AND METHODS

A retrospective analysis of the medical histories of 71 patients with synchronous and metachronous oligometastases of CRC, who were treated in the conditions of the department of antitumor drug therapy of the PHI "CCH "RZD-Medicine" from December 2001 to March 2023, the total median follow-up was 38.2 ± 8.7 months.

There were 36 (50.7 %) male and 35 (49.3 %) female patients with a morphologically verified diagnosis of colon cancer (Table 1). The study included patients with initial stages II and III, due to the appearance of metachronous metastases.

The main criterion for inclusion in the study was the presence of no more than 5 secondary foci of CRC in one or more organs.

Taking into account the retrospective design of the study, the mutational status of the primary tumor was excluded from the list of studied indicators due to the lack of data on a number of observations.

Depending on the treatment methods, the patients are divided into 2 groups. The first group

Table 1. Characteristics of the studied patients

Parameter	Patients' count
Stage of the disease	*n (%)*
II	16 (22.5 %)
III	15 (21.1 %)
IV	40 (56.4 %)
Grade of tumor differentiation	
G1	21 (29.6 %)
G2	38 (53.5 %)
G3	12 (16.9 %)

included 35 patients who, at the first stage of complex treatment, underwent simultaneous removal of the primary tumor and metastatic foci followed by chemotherapy. The second group includes clinical data on 36 patients who underwent primary lesion removal at the first stage of complex treatment followed by drug antitumor therapy. Patients in this group underwent surgery for urgent indications due to the threat of massive bleeding from the primary tumor, as well as in conditions of developing intestinal obstruction.

The first group included clinical data on 35 patients with colorectal cancer with oligometastases, of which 15 (42.9 %) men and 20 (57.1 %) women. The average age of the patients was 58 ± 3.4 years. Primary colorectal carcinoma was located in the rectum – in 15 (42.8 %) patients, in the sigmoid colon – in 13 (37.1 %) patients, in the rectosigmoid department – in 4 (11.4 %) patients and in the transverse colon – in 2 (5.7 %) patients, in the caecum – in 1 (2.6 %) of the patient.

The location of oligometastases in the liver was diagnosed in 18 (45 %) cases, lungs were detected in 7 (13.8 %) cases, simultaneous lung and liver damage – in 6 (11.6 %) cases, damage to the right iliac region – in 1 (2 %) case, metastasis of the anterior abdominal wall – in 1 (2 % in the ovary – in 2 (11.6 %) cases. The number of metastatic nodes in each patient varied from 1 to 5 and averaged 3.4 ± 1.2 foci. The average sum of the diameters of metastatic nodes in the largest dimension was 4.1 ± 1.2 cm.

In the second group, clinical data included 36 patients with colorectal cancer with oligometastatic lesion, of whom 15 were women and 21 were men. The average age of the patients was 59.3 ± 2.1 years.

The primary tumor was located in the rectum – in 15 (41.2 %) patients, in the sigmoid colon – in 10 (33.3 %) patients, in the rectosigmoid section – in 5 (9.8 %) patients and in the transverse colon – in 4 (13.7 %) patients, in the caecum – in 2 (2 %) of the patient.

The location of oligometastases in the liver was diagnosed in 16 (45 %) cases, lungs were detected in 9 (13.8 %) cases, simultaneous damage to the lungs and liver – in 8 (11.6 %) cases, simultaneous damage to the ovary and rectovaginal septum – in 1 (2 %) case, in the lymph node of the left axillary region – in 1 (2 %) of cases, simultaneous lesion of the inguinal l/a on the left, adrenal gland and lungs – in 1 (2 %) of cases. The number of metastatic nodes in each patient varied from 1 to 5 and averaged 3.7 ± 1.1 foci. The average sum of the diameters of metastatic nodes in the largest dimension was 4.4 ± 0.9 cm. A comparative analysis of the studied groups of patients revealed no statistically significant differences in gender, age, number of metastatic foci and the prevalence of the tumor process.

As a result of the analysis of the data obtained in the group of patients with simultaneous surgical treatment, it was revealed that at the first stage of complex treatment, abdominal perineal extirpation of the rectum (APER) + liver resection was performed in 4 (11.4 %) cases, in 1 (2.8 %) case – APER + removal of metastasis of the right iliac region, in 4 (11.4 %) cases – anterior rectal resection + lung resection + liver resection, in 3 (8.6 %) cases – anterior rectal resection + lung resection, anterior rectal resection + liver resection was performed in 5 (14.3 %) cases. Sigmoid colon resection + liver resection + lung resection was performed in 2 (5.7 %) cases, sigmoid colon resection + lung resection – in 4 (11.4 %) cases, sigmoid colon resection + ovarian resection – in 1 (2.8 %) case, sigmoid colon resection + liver resection – in 2 (5.7 %) cases. Hartmann type surgery + anterior abdominal wall metastasectomy was performed in 1 (2.8 %) cases, in 5 (14.3 %) cases, Hartmann type surgery + liver resection was performed. Surgical intervention in the volume of right–sided hemicolectomy + liver resection was performed in 1 (2.8 %) case, right-sided hemicolectomy + ovarian resection – in 1 (2.8 %) case. Left-sided hemicolectomy + liver resection was performed in 1 (2.8 %) case.

At the second stage of complex treatment, the patient of the first group underwent systemic chemotherapy according to the following regimens: XELOX – in 13 (37.1 %) cases, FOLFOX-6 – in 11 (31.4 %) cases, XELIRI – in 3 (8.6 %) cases, capecitabine in monorode – in 5 (14.3 %) cases, Mayo – in 2 (5.7 %) cases, FOLFIRI – in 1 (2.8 %) case.

In the group of surgical treatment of the primary focus followed by chemotherapy at the first stage of complex treatment, APER was performed in 6 (16.7 %) cases, anterior rectal resection in 13 (36.1 %) cases, Hartmann–type surgery in 5 (13.9 %) cases, sigmoid colon resection in 6 (16.7 %) cases, in 2 (5.5 %) cases – resection of the transverse colon, in 3 (8.3 %) cases – right-sided hemicolectomy, in 1 (2.8 %) case – left-sided hemicolectomy.

At the second stage of complex treatment, the patient of the second group underwent systemic chemotherapy according to the following regimens: XELOX – in 12 (33.3 %) cases, FOLFOX-6 – in 10 (27.8 %) cases, XELIRI – in 2 (5.5 %) cases, capecitabine in mono-mode – in 3 (8.3 %) cases, Mayo – in 5 (13.9 %) cases, FOLFIRI – 3 (8.3 %) cases, irinotecan in mono mode – in 1 (2.8 %) case.

STUDY RESULTS

As a result of an objective assessment of the effectiveness of the treatment based on a comprehensive examination, it was revealed in the group of simultaneous surgical treatment of patients that the response was achieved in 19 (54.3 %) cases, progression was diagnosed in 16 (45.7 %) cases. The median disease-free survival was 17.8 ± 6.3 months.

In the primary tumor removal group, the response was received in 3 (8.3 %) cases, stabilization was achieved in 14 (38.9 %) cases, and progression of the tumor process was detected in 19 (52.8 %) cases. The median disease-free survival was 9.2 ± 3.2 months.

One-year, two- and three-year survival rates in the group of simultaneous removal of the primary tumor and oligometastases and in the group of primary tumor removal were 97.1 %, 88.6 %, 77.1 % and 100 %, 80.5 %, 72.2 %, respectively.

The overall survival rate in the group of simultaneous removal of the primary tumor and oligometastases was 63 ± 3.9 months, in the group of primary tumor removal – 58 ± 3.8 months, $p > 0.05$ (Fig. 1).

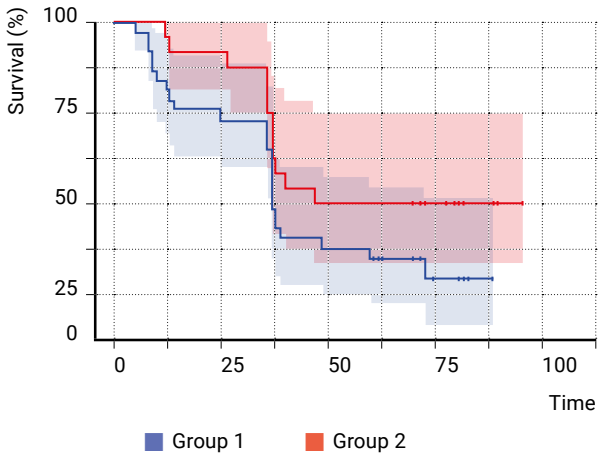


Fig. 1. Overall survival of patients of both groups (1 – group of simultaneous surgical removal of the primary focus and oligometastases, 2 – group of surgical removal of the primary focus followed by chemotherapy)

High CEA, the presence of stage IIIC (at the time of diagnosis), and group (simultaneous removal of the primary tumor and metastatic foci followed by chemotherapy or removal of the primary tumor + CT) were independent predictors affecting survival in the Cox regression model (Table 2).

DISCUSSION

Despite significant progress in modern oncology, surgical management remains the main method of treating patients with oligometastases of colorectal cancer. The most favorable option for synchronous metastases is simultaneous surgery, i. e. simultaneous removal of the primary focus and oligometastases. Patyutko Yu. I. et al. conducted a study in which they compared the results of simultaneous removal of the primary tumor and oligometastases, and sequential removals. The 3-year and 5-year survival rates for simultaneous operations were 48 % and 35 %, with phased operations – 55 % and 38 % [28].

When oligometastases are localized in the lungs, simultaneous interventions are preferred in the choice of surgical tactics [29].

Systemic treatment of patients with CRC oligometastases includes chemotherapy based on fluoropyrimidines, oxaliplatin, irinotecan, as well as treatment with targeted drugs. Combined fluorouracil-based schemes with oxaliplatin (FOLFOX, XELOX, FLOX) or irinotecan (FOLFIRI, XELIRI) are used as the 1st line in unresectable metastatic CRC [30], as well as a triple combination of oxaliplatin, fluoropyrimidines, calcium folinate and irinotecan (FOLFOXIRI).

In the presented clinical study, a comparative assessment of the effectiveness of the treatment of patients with colorectal cancer with oligometastases was carried out, depending on the option of an integrated approach. The results obtained turned out to be multidirectional – the response to treatment and progression were obtained in 54.3 % and 45.7 % of cases in the group of simultaneous removal of the primary tumor and oligometastases versus 47.2 % and 52.8 % of cases in the group of removal of the primary tumor without oligometastases, respectively. The median recurrence-free survival was shorter in

the group of primary tumor removal without metastases (Table 2). The total annual survival of patients was achieved by 100 % in the group of primary tumor removal without metastases, compared with 97.1 % in the group of simultaneous surgical treatment. Such a result is associated with a high risk of mortality during the first year against the background of postoperative complications during extensive surgical interventions in the group of simultaneous removal of the primary tumor and oligometastases.

The three-year survival rate is higher in the group of simultaneous surgical treatment – 77.1 % versus 72.2 % in the group of surgical removal of the primary tumor.

Thus, when choosing the treatment of patients with oligometastatic CRC lesion, it is important to correctly assess all the risks of complications and adopt the only treatment option for a particular patient, with the participation of oncologists, surgeons, radiologists and chemotherapists.

CONCLUSION

In recent years, significant changes have occurred in the treatment of patients with CRC oligometastases. It should be noted that the final management tactics for these patients has not been determined even today. The choice of treatment tactics depends primarily on the localization and prevalence of the tumor process, the number of metastases and the organs affected by them, and therefore the approach to the treatment of patients with CRC oligometastases should be individual. Removal of oligometastases was associated with a slight increase in overall survival, although the difference did not reach statistical significance. High CEA, the presence of stage IIIC (at the time of diagnosis), and group of chemotherapy (simultaneous removal of the primary tumor and metastatic foci followed by or removal of the primary tumor + CT) were independent predictors affecting survival in the Cox model. Further research is needed to increase the sample size.

Table 2. Factors affecting patient survival (Cox regression model)

Predictors	Coeff.	CI	*p*
Groups (main, control)	2.49	1.02 – 6.06	**0.045**
Max. metastasis diameter	1.24	1.01 – 1.51	**0.040**
The sum of metastases diameters	1.03	0.96 – 1.11	0.417
Age	0.98	0.94 – 1.02	0.388
Stage IIA	1.88	0.18 – 19.11	0.595
Stage IIB	0.00	0.00 – Inf	0.998
Stage IIIB	0.30	0.02 – 4.10	0.364
Stage IIIC	13.81	1.13 – 168.96	**0.040**
Stage IIIA	4.54	0.18 – 115.29	0.359
Stage IIIB	0.30	0.01 – 6.84	0.450
Stage IIB	16.64	0.83 – 332.56	0.066
Stage IV	1.55	0.16 – 15.16	0.708
Stage IVa	0.00	0.00 – Inf	0.998
High APA	0.89	0.10 – 7.78	0.917
High CEA	2.75	1.13 – 6.67	**0.025**
High Ca19-9	1.27	0.41 – 3.93	0.679
Number of observations		71	
R^2 Nagelkerke		0.493	

References

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin. 2021 May;71(3):209–249. https://doi.org/10.3322/caac.21660
2. The state of cancer care for the Russian population in 2019. Ed. by A. D. Kaprin, V. V. Starinsky, A. O. Shakhzadova. Moscow: P. A. Herzen MNIOI – Branch of the National Medical Research Radiological Center, 2020, 236 p. (In Russ.).
3. Acciuffi S, Meyer F, Bauschke A, Croner R, Settmacher U, Altendorf-Hofmann A. Solitary colorectal liver metastasis: overview of treatment strategies and role of prognostic factors. J Cancer Res Clin Oncol. 2022 Mar;148(3):657–665. https://doi.org/10.1007/s00432-021-03880-4
4. Al Battal M, Kanaan C, Labaied N, Breuskin I, Leboulleux S, Soufan R, et al. Colon Cancer Metastasis Within a NIFTP: A Case Report and Review of the Literature. Head Neck Pathol. 2020 Sep;14(3):833–836. https://doi.org/10.1007/s12105-019-01089-z
5. Miura T, Mitsunori Y, Takeuchi M, Wada Y, Ishihara S, Nakajima Y, et al. A Case of Synchronous Solitary Splenic Metastasis of Sigmoid Colon Cancer Treated with Laparoscopic Resection. Gan To Kagaku Ryoho. 2022 Apr;49(4):441–443.
6. Gkikas A, Kakos C, Lampridis S, Godolphin PJ, Patrini D. Preoperative prognostic factors for 5-year survival following pulmonary metastasectomy from colorectal cancer: a systematic review and meta-analysis. Eur J Cardiothorac Surg. 2023 Mar 1;63(3):ezad059. https://doi.org/10.1093/ejcts/ezad059
7. Xu J, He Y, Cai Y, Huang Y, He Y. Isolated splenic metastases from rectal carcinoma 5 years after surgery: Case report. Medicine (Baltimore). 2023 Jan 13;102(2):e32493. https://doi.org/10.1097/MD.0000000000032493
8. Chen L, Wang D, Mao W, Huang X, He C. A Case of Long-term Survival after Curative Resection for Synchronous Solitary Adrenal Metastasis from Rectal Cancer. Pak J Med Sci. 2014 Jan;30(1):216–219. https://doi.org/10.12669/pjms.301.4341
9. Van der Geest LGM, Lam-Boer J, Koopman M, Verhoef C, Elferink MAG, de Wilt JHW. Nationwide trends in incidence, treatment and survival of colorectal cancer patients with synchronous metastases. Clin Exp Metastasis. 2015 Jun;32(5):457–465. https://doi.org/10.1007/s10585-015-9719-0
10. Steele G. Natural History Studies and the Evolution of Regional Treatment Modalities for Patients With Isolated Liver Metastases From Primary Colon and Rectum Carcinoma. Cancer Control. 1996 Jan;3(1):34–41. https://doi.org/10.1177/107327489600300104
11. Lievens Y, Guckenberger M, Gomez D, Hoyer M, Iyengar P, Kindts I, et al. Defining oligometastatic disease from a radiation oncology perspective: An ESTRO-ASTRO consensus document. Radiother Oncol. 2020 Jul;148:157–166. https://doi.org/10.1016/j.radonc.2020.04.003
12. Kuipers EJ, Grady WM, Lieberman D, Seufferlein T, Sung JJ, Boelens PG, et al. Colorectal cancer. Nat Rev Dis Primers. 2015 Nov 5;1:15065. https://doi.org/10.1038/nrdp.2015.65
13. Norén A, Eriksson HG, Olsson LI. Selection for surgery and survival of synchronous colorectal liver metastases; a nationwide study. Eur J Cancer. 2016 Jan;53:105–114. https://doi.org/10.1016/j.ejca.2015.10.055
14. Karoui M, Roudot-Thoraval F, Mesli F, Mitry E, Aparicio T, Des Guetz G, et al. Primary colectomy in patients with stage IV colon cancer and unresectable distant metastases improves overall survival: results of a multicentric study. Dis Colon Rectum. 2011 Aug;54(8):930–938. https://doi.org/10.1097/DCR.0b013e31821cced0
15. Seo GJ, Park JW, Yoo SB, Kim SY, Choi HS, Chang HJ, et al. Intestinal complications after palliative treatment for asymptomatic patients with unresectable stage IV colorectal cancer. J Surg Oncol. 2010 Jul 1;102(1):94–99. https://doi.org/10.1002/jso.21577
16. Zeyara A, Torén W, Søreide K, Andersson R. The liver-first approach for synchronous colorectal liver metastases: A systematic review and meta-analysis of completion rates and effects on survival. Scand J Surg. 2022;111(1):14574969211030131. https://doi.org/10.1177/14574969211030131
17. Wang SH, Song L, Tang JY, Sun WP, Li Z. Safety and long-term prognosis of simultaneous versus staged resection in synchronous colorectal cancer with liver metastasis: a systematic review and meta-analysis. Eur J Med Res. 2022 Dec 19;27(1):297. https://doi.org/10.1186/s40001-022-00937-z
18. Hopt UT, Drognitz O, Neeff H. Timing of resection in patients with colorectal carcinoma and synchronous liver metastases. Zentralbl Chir. 2009 Sep;134(5):425–429. https://doi.org/10.1055/s-0029-1224612
19. Mentha G, Majno PE, Andres A, Rubbia-Brandt L, Morel P, Roth AD. Neoadjuvant chemotherapy and resection of advanced synchronous liver metastases before treatment of the colorectal primary. Br J Surg. 2006 Jul;93(7):872–878. https://doi.org/10.1002/bjs.5346

20. Méndez Romero A, de Man RA. Stereotactic body radiation therapy for primary and metastatic liver tumors: From technological evolution to improved patient care. Best Pract Res Clin Gastroenterol. 2016 Aug;30(4):603–616. https://doi.org/10.1016/j.bpg.2016.06.003
21. Folprecht G, Martinelli E, Mazard T, Modest DP, Tsuji A, Esser R, et al. Triplet chemotherapy in combination with anti-EGFR agents for the treatment of metastatic colorectal cancer: Current evidence, advances, and future perspectives. Cancer Treat Rev. 2022 Jan;102:102301. https://doi.org/10.1016/j.ctrv.2021.102301
22. Symonds LK, Cohen SA. Use of perioperative chemotherapy in colorectal cancer metastatic to the liver. Gastroenterol Rep (Oxf). 2019 Oct;7(5):301–311. https://doi.org/10.1093/gastro/goz035
23. Stukalova OYu, Polikarpov AA, Ischenko RV. Chemoembolization of the hepatic artery in the treatment of patients with chemoresistant metastases of colorectal cancer. Review. Surgical practice. 2021;(3):61–68. (In Russ.). https://doi.org/10.38181/2223-2427-2021-3-61-68, EDN: UIXOVJ
24. Karanicolas P, Beecroft JR, Cosby R, David E, Kalyvas M, Kennedy E, et al. Regional Therapies for Colorectal Liver Metastases: Systematic Review and Clinical Practice Guideline. Clin Colorectal Cancer. 2021 Mar;20(1):20–28. https://doi.org/10.1016/j.clcc.2020.09.008
25. Yu Q, Zhang L, Fan S, Huang L, Wang X, Xindun C. The significance of transarterial chemoembolization combined with systemic chemotherapy for patients with KRAS wild-type unresectable metachronous colorectal carcinoma with liver metastases. J Cancer Res Ther. 2016 Dec;12(Supplement):C205–C211. https://doi.org/10.4103/0973-1482.200603
26. Lin YM, Paolucci I, Brock KK, Odisio BC. Image-Guided Ablation for Colorectal Liver Metastasis: Principles, Current Evidence, and the Path Forward. Cancers (Basel). 2021 Aug 4;13(16):3926. https://doi.org/10.3390/cancers13163926
27. Matsui Y, Tomita K, Uka M, Umakoshi N, Kawabata T, Munetomo K, et al. Up-to-date evidence on image-guided thermal ablation for metastatic lung tumors: a review. Jpn J Radiol. 2022 Oct;40(10):1024–1034. https://doi.org/10.1007/s11604-022-01302-0
28. Patyutko YuI, Chuchuev ES, Podluzhny DV, Polyakov AN, Agafonova MG. Surgical tactics in the treatment of patients with colorectal cancer with synchronous liver metastases. Oncological Coloproctology. 2011;2:13–19. (In Russ.).
29. Ryabov AB, Pikin OV, Kolbanov KI, Glushko VA, Vursol DA, Aleksandrov OA. Current approaches to treating patients with colorectal lung metastases. P. A. Herzen Journal of Oncology. 2018;7(6):52–59. https://doi.org/10.17116/onkolog2018705152, EDN: YVRHLN
30. Sadot E, Groot Koerkamp B, Leal JN, Shia J, Gonen M, Allen PJ, et al. Resection margin and survival in 2368 patients undergoing hepatic resection for metastatic colorectal cancer: surgical technique or biologic surrogate? Ann Surg. 2015 Sep;262(3):476–485. https://doi.org/10.1097/SLA.0000000000001427

Information about authors:

Elmira O. Kalmykova ✉ – MD, oncologist, Department of Antitumor Drug Therapy, Lomonosov Moscow State University, Moscow, Russian Federation
ORCID: https://orcid.org/0009-0008-5842-1250

Roman V. Ishchenko – Dr. Sci. (Med.), director, V. K. Gusak institute of emergency and reconstructive surgery, Donetsk, Russian Federation; professor at the Department of Surgical Diseases, Faculty of Fundamental Medicine of Lomonosov Moscow State University, Moscow, Russian Federation
ORCID: https://orcid.org/0000-0003-0260-6922, SPIN: 9021-7370, AuthorID: 1045336

Oksana Yu. Stukalova – MD, coloproctologist, oncologist, ALLORO Medical Center, Fryazino, Russian Federation
ORCID: https://orcid.org/0000-0003-3748-4750, SPIN: 4109-2387, AuthorID: 934990

Dmitry A. Filimonov – Dr. Sci. (Med.), Deputy Director for Scientific Work, V. K. Gusak institute of emergency and reconstructive surgery, Donetsk, Russian Federation
ORCID: https://orcid.org/0000-0002-4542-6860, SPIN: 1491-8262, AuthorID: 786590, Scopus Author ID: 58385159700

Contribution of the authors:

Kalmykova E. O. – concept and design of the study, collection and processing of material, statistical data processing, writing the text;
Ishchenko R. V. – scientific guidance, editing, approval of the final version of the article;
Stukalova O. Yu. – concept and design of the study, editing;
Filimonov D. A. – concept and design of the study, editing, revision of the text.

South Russian Journal of Cancer. 2024. Vol. 5, No. 4. P. 29-37
https://doi.org/10.37748/2686-9039-2024-5-4-4
https://elibrary.ru/cfoldg
ORIGINAL ARTICLE

Main aspects of personalized approach to the treatment of patients with chemotherapy resistant metastatic colorectal cancer

O. Yu. Stukalova[1]✉, R. V. Ishchenko[2,3], A. A. Polikarpov[4], A. I. Farmonkulova[3]

[1] ALLORO Medical Center, Fryazino, Russian Federation
[2] V. K. Gusak institute of emergency and reconstructive surgery, Donetsk, Russian Federation
[3] Lomonosov Moscow State University, Moscow, Russian Federation
[4] Russian Scientific Center of Radiology and Surgical Technologies named after Academician A. M. Granov, St. Petersburg, Russian Federation
✉ docstukalova@mail.ru

ABSTRACT

Purpose of the study. To improve the results of treatment of patients with unresectable metastases of colorectal cancer in the liver that are not controlled by systemic chemotherapy.

Materials and methods. The study includes clinical data on the treatment of 76 patients with metachronous metastases of colorectal cancer in the liver that are not controlled by systemic chemotherapy. Patients underwent removal of the primary tumor according to urgent indications at the first stage of complex treatment, followed by systemic chemotherapy in an adjuvant mode. After 24.5 ± 0.2 months, patients were diagnosed with metastatic liver damage, and therefore systemic chemotherapy was initiated. After changing two lines of drug therapy with a registered progression of the oncological process, liver metastases were recognized as uncontrolled by systemic chemotherapy. After that patients were included in the given study and divided into two groups. The study group included 40 patients who underwent regional chemotherapy. The control group included 36 patients who continued systemic chemotherapy with subsequent line changes. The effectiveness was evaluated according to the RECIST 1.1 and mRECIST scales, as well as the overall one-year, two- and three-year survival rates.

Results. The median overall survival of patients in the control and study groups was 30.0 ± 0.8 and 41.5 ± 0.5 months, respectively, $p < 0.05$. The total one-year, two- and three-year survival of patients in the control and study groups was 94.4 %, 69.4 %, 33.3 % and 100 %, 82.5 %, 57.5 %, respectively, $p < 0.05$. The median life expectancy of deceased patients in the control and study groups was 22.5 ± 0.4 and 27.0 ± 0.4 months.

Conclusions. As a result of a comparative analysis of the detection of adverse events and complications of the treatment, patients of the study group underwent treatment much easier than patients of the control group – in patients in the group of systemic chemotherapy, moderate and severe complications were detected in 44.4 % of cases, in the study group – in 2.5 % of cases. According to the results of a clinical study, regional chemotherapy is an effective method of treating patients with colon cancer metastases in the liver that are not controlled by systemic chemotherapy and is associated with a statistically significant increase in overall survival ($p < 0.05$). For a more detailed study of the benefits of regional chemotherapy in this category of patients, further prospective clinical studies are necessary.

Keywords: colorectal cancer, liver metastases, hepatic artery chemoembolization, chemotherapy resistant metastases

For citation: Stukalova O. Yu., Ishchenko R. V., Polikarpov A. A., Farmankulova A. I. Main aspects of personalized approach to the treatment of patients with chemotherapy resistant metastatic colorectal cancer. South Russian Journal of Cancer. 2024; 5(4): 29-37. https://doi.org/10.37748/2686-9039-2024-5-4-4, https://elibrary.ru/cfoldg

For correspondence: Oksana Yu. Stukalova – MD, coloproctologist, oncologist, ALLORO Medical Center, Fryazino, Russian Federation
Address: 9 Oktyabrskaya str., Fryazino 141195, Russian Federation
E-mail: docstukalova@mail.ru
ORCID: https://orcid.org/0000-0003-3748-4750
SPIN: 4109-2387, AuthorID: 934990

Compliance with ethical standards: the study was carried out in compliance with the ethical principles set forth in the Declaration of the World Medical Association of Helsinki, 1964, ed. 2013. The study was approved by the Committee on Biomedical Ethics at the 4Russian Scientific Center of Radiology and Surgical Technologies named after Academician A. M. Granov (extract from the minutes of the meeting No. 01-04/2024 dated 04/04/2024). Informed consents were 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 07.06.2024; approved after reviewing 11.11.2024; accepted for publication 17.11.2024

Южно-Российский онкологический журнал. 2024. Т. 5, № 4. С. 29-37
https://doi.org/10.37748/2686-9039-2024-5-4-4
https://elibrary.ru/cfoldg
3.1.6. Онкология, лучевая терапия
ОРИГИНАЛЬНАЯ СТАТЬЯ

Роль регионарной химиотерапии в лечении больных с метахронными метастазами колоректального рака в печени, не контролируемыми системной химиотерапией

О. Ю. Стукалова[1]✉, Р. В. Ищенко[2,3], А. А. Поликарпов[4], А. И. Фармонкулова[3]

[1] Медицинский центр «АЛЛОРО», г. Фрязино, Российская Федерация
[2] ФГБУ «Институт неотложной и восстановительной хирургии имени В. К. Гусака» Министерства здравоохранения Российской Федерации, г. Донецк, Российская Федерация
[3] ФГБОУ ВО «Московский государственный университет имени М. В. Ломоносова», г. Москва, Российская Федерация
[4] ФГБУ «Российский научный центр радиологии и хирургических технологий имени академика А. М. Гранова» Министерства здравоохранения Российской Федерации, г. Санкт-Петербург, Российская Федерация
✉ docstukalova@mail.ru

РЕЗЮМЕ

Цель исследования. Улучшить результаты лечения больных с нерезектабельными метастазами колоректального рака в печени, не контролируемыми системной химиотерапией.

Пациенты и методы. В настоящее исследование включены клинические данные о лечении 76 пациентов с метахронными метастазами колоректального рака в печени, не контролируемыми системной химиотерапией. На первом этапе комплексного лечения пациентам проведено удаление первичной опухоли по срочным показаниям с последующим проведением системной химиотерапии в адъювантном режиме. Через 24,5 ± 0,2 месяцев у пациентов диагностировано метастатическое поражение печени, в связи с чем начата системная химиотерапия. После смены двух линий лекарственной терапии с зарегистрированной прогрессией онкологического процесса, метастазы в печени были признаны не контролируемыми системной химиотерапией, после чего больные были включены в настоящее исследование и разделены на две группы. В исследуемую группу включены 40 пациентов, которым проводилась регионарная химиотерапия. В контрольную группы включены 36 пациентов, которым продолжена системная химиотерапия с последующей сменой линий. Оценка эффективности проводилась согласно шкалам RECIST 1.1 и mRECIST, а также оценивалась общая годичная, двух- и трехлетняя выживаемость.

Результаты. Медиана общей выживаемости больных контрольной и исследуемой групп составила 30,0 ± 0,8 и 41,5 ± 0,5 месяцев соответственно, $p < 0,05$. Общая годичная, двух- и трехлетняя выживаемость больных контрольной и исследуемой групп составила 94,4, 69,4, 33,3 и 100, 82,5, 57,5 % соответственно, $p < 0,05$. Медиана продолжительности жизни умерших больных контрольной и исследуемой группы составила 22,5 ± 0,4 и 27,0 ± 0,4 месяцев.

Заключение. В результате сравнительного анализа выявления нежелательных явлений и осложнений проводимого лечения выяснили, что больные исследуемой группы перенесли лечение значительно легче, нежели больные контрольной группы – у больных в группе системной химиотерапии осложнения средней и тяжелой степени выявлены в 44,4 % случаях, в исследуемой группе – в 2,5 % случаях. По результатам проведенного клинического исследования, регионарная химиотерапия является эффективным методом лечения больных с метастазами рака толстой кишки в печени, не контролируемыми системной химиотерапией и ассоциирована со статистически значимым увеличением общей выживаемости ($p < 0,05$). Для более детального изучения преимуществ регионарной химиотерапии в данной категории больных необходимо дальнейшее проведение проспективных клинических исследований.

Ключевые слова: колоректальный рак, метастазы в печень, химиоэмболизация печеночной артерии, химиорезистентные метастазы

Для цитирования: Стукалова О. Ю., Ищенко Р. В., Поликарпов А. А., Фармонкулова А. И. Роль регионарной химиотерапии в лечении больных с метахронными метастазами колоректального рака в печени, не контролируемыми системной химиотерапией. Южно-Российский онкологический журнал. 2024; 5 (4):29-37. https://doi.org/10.37748/2686-9039-2024-5-4-4, https://elibrary.ru/cfoldg

Для корреспонденции: Стукалова Оксана Юрьевна – врач-колопроктолог, онколог, Медицинский центр «АЛЛОРО», г. Фрязино, Российская Федерация
Адрес: 141195, Российская Федерация, г. Фрязино, ул. Октябрьская, д. 9
E-mail: docstukalova@mail.ru
ORCID: https://orcid.org/0000-0003-3748-4750
SPIN: 4109-2387, AuthorID: 934990

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 «Российский научный центр радиологии и хирургических технологий им. акад. А. М. Гранова» Министерства здравоохранения Российской Федерации (выписка из протокола заседания № 01-04/2024 от 04.04.2024 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 07.06.2024; одобрена после рецензирования 11.11.2024; принята к публикации 17.11.2024

INTRODUCTION

Currently, colon cancer occupies one of the leading positions among all oncological diseases [1–3]. One of the main causes of death in patients with malignant tumors of the colon is the prevalence of the oncological process, which in 20–60 % of patients manifests itself in the form of metastatic liver damage [4–6]. Without special antitumor treatment of patients with metastatic liver damage, life expectancy does not exceed one year [3].

The progressive development of oncology led to a deep understanding of the biology of colon tumors and determined the need for immunohistochemical and molecular genetic studies, which made it possible to apply a personalized therapeutic approach [7, 8]. However, systemic chemotherapy (SCT) remains the main method of treating patients with advanced forms of colorectal cancer (CRC) today [9–11].

There is an extensive group of patients with bilobar metastatic liver damage who need to stop CT due to the development of chemoresistance or adverse events [12, 13]. The question of possible treatment options for these patients remains open today.

The study purpose was to improve the results of treatment of patients with unresectable metastases of colorectal cancer in the liver that are not controlled by systemic chemotherapy

PATIENTS AND METHODS

The study included 76 patients aged 40 to 81 years with a morphologically confirmed diagnosis of colon cancer. The average age was 63.6 ± 8.7 years. The primary tumor is represented by adenocarcinoma of various degrees of malignancy – in 23 (30.3 %) cases, highly differentiated adenocarcinoma (G1) was diagnosed, in 48 (63.1 %) cases and in 5 (6.6 %) cases, moderate (G2) and low-differentiated (G3) adenocarcinoma, respectively.

All patients at the first stage of complex treatment underwent surgical treatment for urgent indications due to the development of intestinal obstruction (88.2 %) and the threat of massive bleeding (11,8 %), aimed at removing the primary tumor of the colon. Right-sided hemicolectomy was performed in 25 (32.9 %) cases, sigmoid colon resection was performed in 17 (22.4 %) cases, anterior rectal resection was performed in 19 (25.0 %) cases, left-sided hemicolectomy was performed in 6 (7.9 %) cases and transverse colon resection was performed in 9 (11.8 %) cases. After the surgical intervention, a histological examination of the surgical material was performed, followed by the determination of the final stage according to the TNM classification (8th edition).

Stage T1 was detected in 11 (14.5 %) cases, stage T2 was diagnosed in 29 (38.2 %) cases, stages T3 and T4 were detected in 27 (35.5 %) and 9 (11.8 %) cases, respectively. When assessing regional metastasis, stage N0 was established in 32 (42.1) cases, N1 in 29 (38.2 %) cases, and N2 in 15 (19.7 %) cases (Table 1). No distant metastasis was detected in any patient.

As can be seen from Table 1, stage I was diagnosed in 19 (25 %) patients, stage II was diagnosed in 11 (14.5 %) patients, and stage III in 46 (60.5 %) patients (Fig. 1).

In all cases, patients underwent radical resection of the primary tumor R0.

It was mandatory for all patients to undergo a molecular genetic study determining mutations in the KRAS, NRAS, and BRAF genes. KRAS mutations were detected in 19 (25.0 %) patients. Wild types of KRAS and NRAS were diagnosed in 57 (75.0 %) patients. Given the unfavorable prognosis and the need for more aggressive treatment of patients with mutations in the BRAF gene, the latter were not included in this study.

In 51 (67.1 %) cases, patients underwent systemic chemotherapy in adjuvant mode – in 48 (63.1 %)

Table 1. Distribution of patients according to T and N categories

Category	N0	N1	N2
T1	8 (10.5 %)	3 (3.9 %)	0
T2	11 (14.5 %)	13 (17.1 %)	5 (6.6 %)
T3	9 (11.8 %)	11 (14.5 %)	7 (9.2 %)
T4	2 (2.6 %)	4 (5.3 %)	3 (3.9 %)

cases in patients with the spread of the pT1–4N+ tumor process and in 3 (3.9 %) cases in patients with pT3N0M0 who had negative prognosis factors (high degree of malignancy of the primary tumor, perineural and lymphovascular invasion). In 39 (51.3 %) cases, patients underwent drug therapy in the XELOX mode, in 37 (48.7 %) cases the FOLFOX mode was used. On average, each patient underwent 6.4 ± 1.4 courses of CT (Fig. 2).

As can be seen from Figure 2, in two cases, systemic chemotherapy is limited to one and two courses. The treatment of patients was interrupted due to the development of adverse events. In one case, on the 7th day after the first course of drug therapy in XELOX mode, a myocardial infarction was diagnosed. In the second case, after the second course of CT in FOLFOX mode, an acute stomach ulcer was detected.

All patients whose clinical data are included in this study underwent regular follow-up examinations according to clinical recommendations. The median before the progression of the tumor process was 24.5 ± 0.2 months. All patients were diagnosed with bilobar metastatic liver disease. On average, 5.1 ± 1.4 metastatic foci were diagnosed in each patient. The average sum of the diameters in the largest measurement of liver formations in each patient was 49.9 ± 12.7 mm (Fig. 3).

After the liver formations were detected, according to computed tomography with intravenous contrast, a percutaneous transhepatic trepan biopsy was performed under ultrasound guidance. In all cases, the morphological picture of metastatic foci corresponded to the primary tumor.

After receiving histological confirmation of secondary liver foci, a collegial discussion of further therapeutic tactics was conducted with the participation of an oncologist, surgeon, chemotherapist, radiologist. As a result, patients were prescribed chemotherapy in the following regimens: modified FOLFOX6 – in 22 (28.9 %) cases, XELOX – in 14 (18.4 %) cases, FOLFIRI – in 24 (31.6 %) cases, XELIRI – in 11 (14.5 %) cases, capecitabine in monotherapy in 5 (6.6 %) cases. Chemotherapy courses were conducted against the background of biotherapy. Taking into account the data of the molecular genetic study, bevacizumab was prescribed to patients in 19 (25.0 %) cases, and erbitux was prescribed in 57 (75.0 %) cases. The effectiveness of the drug treatment was evaluated after the fourth course.

When performing a control examination after the fourth course of PCT, 66 (86.8 %) patients showed progression of the tumor process, in 10 (13.2 %) cases, adverse events were detected, and therefore chemotherapeutic treatment was interrupted. In patients with the progression of the tumor process, an increase in targeted foci was diagnosed in 46 (60.5 %) cases, the appearance of new foci was registered in 17 (22.4 %) cases, and in 28 (36.8 %) cases, an increase in blood cancer markers (CA 19–9,

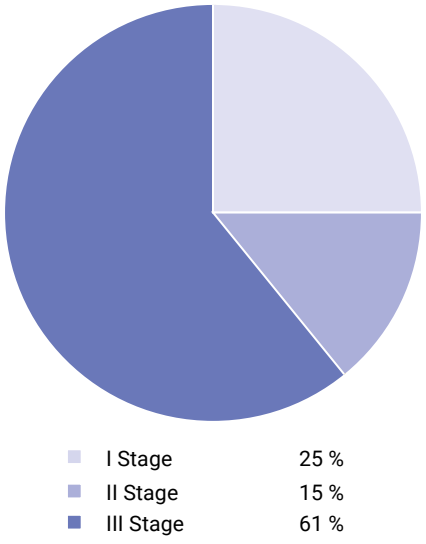


Fig. 1. Distribution of patients by tumor process stages according to TNM classification

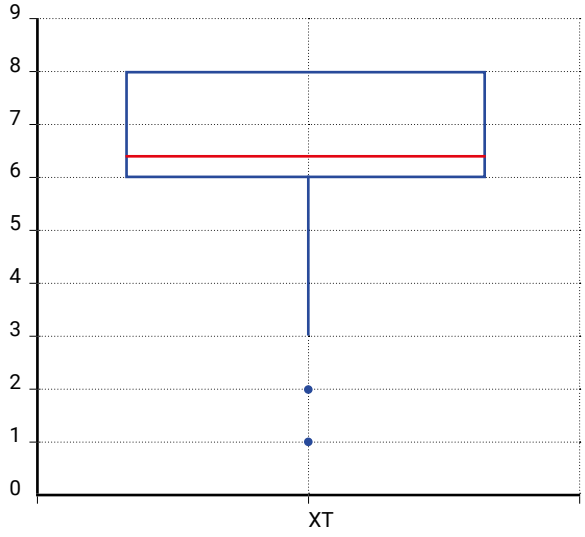


Fig. 2. Distribution of patients by the number of SCT courses performed

cancer-embryonic antigen, alpha-fetoprotein) was revealed in comparison with the baseline level. The patients underwent a change of the chemotherapy line. FOLFIRI CT was prescribed in 26 (34.2 %) cases, FOLFOXIRI in 27 (35.5 %) cases, irinotecan monotherapy was performed in 12 (15.8 %) cases, and XELIRI in 11 (14.5 %) cases. After the control examination, further progression of the tumor process was revealed in 59 (77.6 %) patients, in 17 (22.4 %) cases, adverse events were diagnosed. Given the ineffectiveness of two lines of systemic chemotherapy, metastatic foci are recognized as chemo resistant. Considering the chemo resistant nature of metastatic liver damage, a molecular genetic study of biopsies of liver foci was performed. As a result, 5 (6.6 %) patients showed heterogeneity of metastatic foci in comparison with the primary tumor, which consisted in the detection of the mutant KRAS gene in the wild type of KRAS primary tumor. In this regard, the patients underwent correction of biotherapy.

In patients with a pronounced degree of toxic manifestations of drug therapy, metastatic foci are recognized as uncontrolled by systemic chemotherapy. All the patients presented above are included in this study and divided into two groups.

The first study group included 40 patients with chemo resistant liver metastases, including 17 patients with moderate and severe toxicity on the background of CT. The second, control group included 36 patients with chemo resistant liver metastases.

Patients of the study group underwent regional chemotherapy of secondary foci of the liver, i. e. the hepatic artery chemoembolization (HACE) using Biosphere microspheres 50–100 μm. Irinotecan was used as a cytostatic agent in the first line of RCT, with the ineffectiveness of the latter, doxorubicin was used as a line 2 drug.

HACE was performed in the following mode for all patients – the first two cycles were performed at intervals of 3 weeks, then 1 month after the second cycle, a control computed tomography was performed to assess the effectiveness of the treatment and then decide whether it was advisable to continue the RCT cycles when stabilization/response was obtained or a cytostatic change was detected with the progression of the tumor process (Fig. 4).

Patients in the control group underwent a change of systemic chemotherapy lines. The effectiveness of treatment was evaluated after the fourth course of SCT. The following regimens were used as 3 SCT lines: FOLFIRI, XELIRI, irinotecan in monotherapy, capecitabine in monotherapy. Irinotecan in monorode, capecitabine in monorode and FOLFOXIRI were used as the 4th line of SCT.

The obtained results of the study in both groups were subjected to a comparative analysis. The effectiveness of treatment in the study group was assessed using the response evaluation criteria in solid tumors (RECIST 1.1, 2009) and modified RECIST (mRECIST) scales, in the control group – on the RECIST 1. 1 scale.

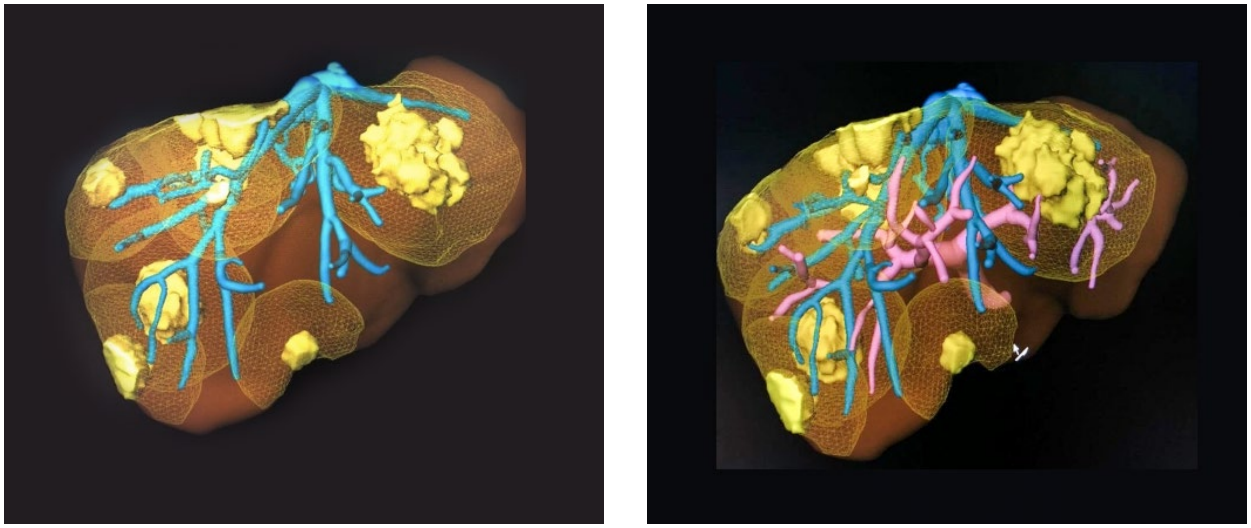


Fig. 3. 3D reconstruction of the liver in patients with CRC metastatic lesions

When simultaneous progression on the RECIST 1.1 scale and stabilization or response on the recist scale were detected, that is, with local extrahepatic metastasis was diagnosed in the response, patients continued to undergo HACE against the background of resumption of systemic chemotherapy.

STUDY RESULTS

A year after the start of RCT in patients of the study group, a partial response on the RECIST 1.1 scale was detected in 8 (20.0 %) patients, stabilization of the tumor process in the liver in patients was diagnosed in 18 (45.0 %) patients, progression of the metastatic process was detected in 8 (20.0 %) patients. In 6 (15.0 %) cases, the appearance of a new metastatic lesion in the liver was registered, despite the local response of the observed foci, and therefore the result was regarded as progression according to the RECIST 1.1 scale and stabilization according to the mRECIST scale. There were no deaths within 12 months after the HACE.

In the control group, one year after inclusion in the present study, stabilization was noted in 16 (44.4 %) patients after CT on the RECIST 1.1 scale, and 20 (56.6 %) patients were diagnosed with progression of the tumor process, including extrahepatic metastasis.

It is worth noting that 5 (13.9 %) patients included in the control group with heterogeneous mutational KRAS status of primary and metastatic tumors showed stabilization of the tumor process against the background of a change in targeted therapy.

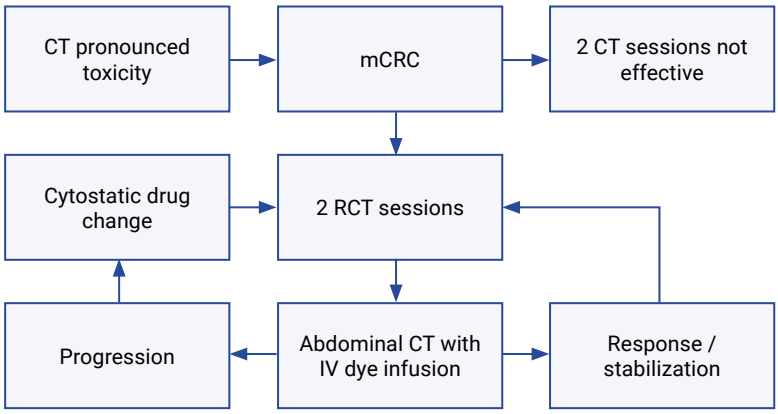


Fig. 4. Algorithm of regional chemotherapy in patients of the research group

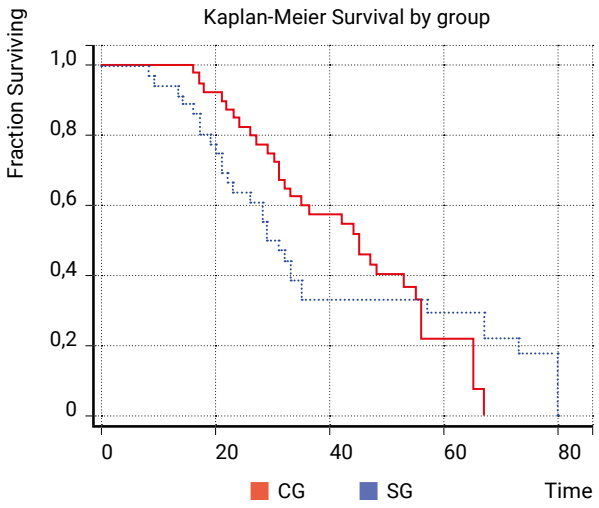


Fig. 5. Overall survival of patients in the study group (SG) and the control group (CG)

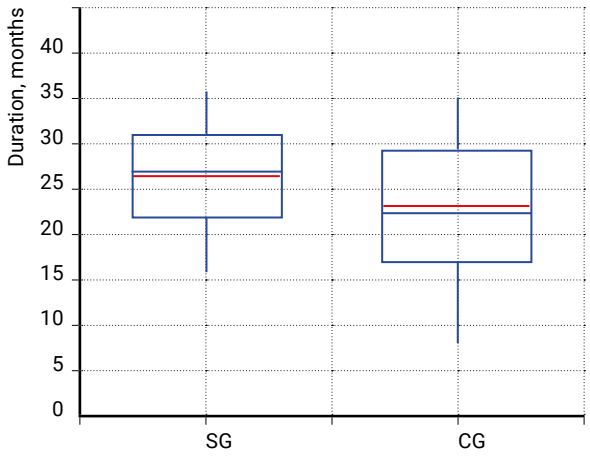


Fig. 6. Life expectancy of deceased patients of the study group (SG) and the control group (CG)

The median overall survival of patients in the control and study groups was 30.0 ± 0.8 and 41.5 ± 0.5 months, respectively, $p < 0.05$ (Fig. 5).

The total one-year, two- and three-year survival of patients in the control and study groups was 94.4 %, 69.4 %, 33.3 % and 100 %, 82.5 %, 57.5 %, respectively, $p < 0.05$.

The median life expectancy of deceased patients in the control and study groups was 22.5 ± 0.4 and 27.0 ± 0.4 months (Fig. 6).

The indicators of cancer markers were monitored: in the case of HACE, there was a decrease in the indicators of cancer markers in 57.5 % of cases, and an increase in their level was noted in 42.5 % of cases.

In the case of CT, 72.2 % of the subjects had an increase in cancer markers and only 27.8 % had stabilization. There were no pronounced phenomena of systemic toxicity, liver and kidney failure after HACE: 6 (15.0 %) patients had a change in Child-Pugh scores (an increase of maximum 1 point from the initial 3–5 points). Postembolization hepatotoxicity (increased activity of gamma-glutamyltraspeptidase (GGTP), alkaline phosphatase, aspartate aminotransferase (AST), alanine aminotransferase (ALT)) was noted in 9 (22.5 %) patients.

In the control group, toxic reactions and complications of varying severity were detected after systemic chemotherapy. Hepatotoxicity was detected in 22 (61.1 %) patients, 8 (22.2 %) of whom had a deterioration in the functional state of the liver according to the Child-Pugh scale. Neurotoxicity was detected in 10 (27.8 %) cases, which manifested itself in the form of the development of peripheral polyneuropathy. The development of acute cardiovascular insufficiency against the background of systemic chemotherapy was detected in one patient (2.8 %), this complication led to a fatal outcome.

In the study group, an assessment and analysis of the developed complications were also carried out. All patients had a manifestation of postembolization syndrome (PES), which manifested itself as a moderate intensity pain syndrome and hyperthermia up to 37.4 °C for three days after HACE was performed. The pain syndrome was completely stopped by a single intramuscular injection with NSAID drugs. One patient treated by us had a case of extrahepatic embolizate injection into the cystic artery. In this regard, the patient was treated conservatively with a positive effect. No surgical intervention was required.

DISCUSSION

A common form of colorectal cancer is one of the leading causes of death among patients with malignant tumors worldwide. The main organ of CRC metastasis is the liver [14].

Currently, methods of a personalized therapeutic approach have been developed and introduced into clinical practice, developed based on an understanding of carcinogenesis and tumor biology. According to clinical recommendations, surgical intervention is the main method of choosing treatment for patients with metastatic colorectal liver cancer. However, liver resection is possible in no more than 30 % of cases due to the prevalence of the tumor process, technical features or the burdened comorbid status of patients. Therefore, chemotherapy remains the main method of treatment for patients of the presented cohort [15].

Systemic chemotherapy is associated with a high risk of toxicity and chemoresistance, which requires discontinuation of drug treatment in the first case or a change of the SCT session in the second case. Thus, the treatment of colon cancer patients with chemoresistant or uncontrolled chemotherapy liver metastases is an urgent topic of discussion [15–17].

In the presented clinical study, a comparative analysis was carried out between treatment with systemic and regional chemotherapy in patients with multiple unresectable chemoresistant liver metastases. Before inclusion in the present study, patients underwent at least two lines of CT. As a result of the conducted clinical study, HACE showed high effectiveness – in 26 (65.0 %) cases, a result was achieved according to the RECIST 1.1 scale and in 32 (80.0 %) cases according to the mRECIST scale, compared with 16 (44.4 %) cases of positive results in patients of the control group. It is worth noting that the evaluation of the results of regional chemotherapy separately on the RECIST 1.1 scale or on the mRECIST scale does not reliably reflect the effectiveness of the treatment. Thus, the appearance of new extrahepatic metastases (progression according to the RECIST 1.1 scale) does not correlate with the ineffectiveness of HACE due to the limited local effect of the latter, which may be accompanied by a response according to the mRECIST scale, which was recorded in 6 cases in patients of the study group. In this regard, the presented patients need to undergo both

systemic chemotherapy and influence extrahepatic foci and continue regional chemotherapy.

As a result of a comparative analysis of the detection of adverse events and complications of the treatment, patients of the study group underwent treatment much easier than patients of the control group – in patients in the group of systemic chemotherapy, moderate and severe complications were detected in 44.4 % of cases, in the study group – in 2.5 % of cases.

CONCLUSION

Thanks to a personalized approach, which includes an assessment of the prevalence of the tumor process, the degree of malignancy of the primary tumor, the results of histological and molecular genetic research methods, as well as the severity of adverse events of chemotoxicity and individual reactions, it is possible to develop an individual treatment plan that will increase the overall and relapse-free survival of patients with uncontrolled systemic chemotherapy metastases of colorectal cancer in the liver. According to the results of a clinical study, regional chemotherapy is an effective method of treating patients with chemo resistant metastases of colon cancer in the liver and is associated with a statistically significant increase in the overall survival of patients compared with systemic chemotherapy ($p < 0.05$). For a more detailed study of the benefits of regional chemotherapy in this category of patients, it is necessary to further conduct prospective clinical studies.

References

1. Abdulaev MA, Napolskaya EV, Tsikoridze MYu. The current state of the problem of minimally invasive methods of local treatment of colorectal cancer metastases in the liver. Surgery and Oncology. 2016;6:43–47. (In Russ.). https://doi.org/10.17650/2220-3478-2016-6-1-43-47, EDN: WAHYVF
2. Ionkin DA, Zhavoronkova OI, Stepanova YuA, Gavrilov YaYa, Vishnevsky VA, Zhao AV. Thermal methods of local destruction (rfa, cryodestruction, microwave ablation) in metastatic liver cancer. Postgraduate Bulletin of the Volga region. 2018;(5-6):127–145. (In Russ.). https://doi.org/10.17816/2072-2354.2018.18.3.127-145, EDN: BUCJUG
3. The state of cancer care for the Russian population in 2018. Ed. by A. D. Kaprin, V. V. Starinsky, G. V. Petrova. Moscow: P. A. Herzen MNIOI – Branch of the National Medical Research Radiological Center, 2019, 236 p. (In Russ.).
4. Oskombaev MSh, Abdurasulov KD, Dzhekshenov MD. Immediate results of surgical treatment of colorectal cancer with synchronous liver metastases. Healthcare in Kyrgyzstan. 2022;(4):163–167. https://doi.org/10.51350/zdravkg2022.4.10.23.163, EDN: MYZKHQ
5. Stukalova OYu, Polikarpov AA, Ishchenko RV, Shugushev ZKh. X-ray-endovascular interventions in the treatment of patients with liver metastases of colorectal cancer after the termination of systemic chemotherapy. Journal of Clinical Practice. 2022;13(2):59–65. (In Russ.). https://doi.org/10.17816/CLINPRACT108552, EDN: UYGVHW
6. Shubin VP, Achkasov SI, Sushkov OI, Tsukanov AS. Molecular-genetic features of colorectal tumors in peritoneal carcinomatosis and liver metastases (review). Coloproctology. 2020;19 (4):177-87. 2020;19(4(74)):177–187. (In Russ.). https://doi.org/10.33878/2073-7556-2020-19-4-177-187, EDN: XGMLSX
7. Fedyanin MYu, Tyulyandin SA. Optimal sequences and combination of chemotherapy and monoclonal antibodies in the treatment of patients with metastatic colorectal cancer. Malignant tumors. 2018;8 (2):50–59. (In Russ.). https://doi.org/10.18027/2224-5057-2018-8-2-50-59, EDN: BSITYS
8. Grozinsky-Glasberg S, Bloom AI, Lev-Cohain N, Klimov A, Besiso H, Gross DJ. The role of hepatic trans-arterial chemoembolization in metastatic medullary thyroid carcinoma: a specialist center experience and review of the literature. European Journal of Endocrinology. 2017 Apr 1;176(4):463–470. https://doi.org/10.1530/EJE-16-0960
9. Martin J, Petrillo A, Smyth EC, Shaida N, Khwaja S, Cheow HK, et al. Colorectal liver metastases: Current management and future perspectives. World J Clin Oncol. 2020 Oct 24;11(10):761–808. https://doi.org/10.5306/WJCO.V11.I10.761
10. Shubin VP, Ponomarenko AA, Tsukanov AS, Maynovskaya OA, Rybakov EG, Panina MV, et al. Heterogeneity in Colorectal Primary Tumor and Synchronous Liver Metastases. Russian Journal of Genetics. 2018;54(6):698–702. https://doi.org/10.1134/S1022795418060091, EDN: YCHHAL

11. Dobrodeev AYu, Kostromitsky DN, Tarasova AS, Afanasyev SG, Babyshkina NN, Ponomaryeva AA, Larionova IV, et al. Multimodal therapy for metastatic colorectal cancer: a case of complete clinical and radiological response of liver metastases. Siberian journal of oncology. 2024;23(1):162–169. (In Russ.). https://doi.org/10.21294/1814-4861-2024-23-1-162-169, EDN: JSQZJV
12. Adenis A, de la Fouchardiere C, Paule B, Burtin P, Tougeron D, Wallet J, et al. Survival, safety, and prognostic factors for outcome with Regorafenib in patients with metastatic colorectal cancer refractory to standard therapies: results from a multicenter study (REBECCA) nested within a compassionate use program. BMC Cancer. 2016 Jul 7;16:412. https://doi.org/10.1186/S12885-016-2440-9
13. Metastatic colorectal cancer is a guide for doctors. Ed. by O. G. Skipenko, Yu. A. Shelygin, S. I. Achkasov. Moscow: Delta Plus, 2020, 421 p.
14. Practical recommendations for the treatment of malignant tumors of the Russian Society of Clinical Oncology. 2021. (In Russ.). Available at: https://www.rosoncoweb.ru/standarts/RUSSCO/2021/, Accessed: 12.11.2024.
15. Ishchenko RV, Dzhansyz IN, Fesak IV. Surgical technology catheterization hepatic arteri under selective intra-arterial chemotherapy. Malignant tumours. 2016;(3):60–66. (In Russ.). https://doi.org/10.18027/2224-5057-2016-3-60-66
16. Ishchenko RV. Selective intraarterial chemotherapy for liver metastases of colorectal cancer. Bulletin of Emergency and Reconstructive Surgery. 2016;1(1):43–47. EDN: XICNWL
17. Polikarpov AA, Tarazov PG, Kagacheva TI, Granov DA. Regional chemotherapy of unresectable liver metastases of colorectal cancer resistant to systemic chemotherapy. Questions of Oncology. 2018;64(4):499–503. (In Russ.). https://doi.org/10.37469/0507-3758-2018-64-4-499-503, EDN: VKVTEQ

Information about authors:

Oksana Yu. Stukalova ✉ – MD, coloproctologist, oncologist, ALLORO Medical Center, Fryazino, Russian Federation
ORCID: https://orcid.org/0000-0003-3748-4750, SPIN: 4109-2387, AuthorID: 934990

Roman V. Ishchenko – Dr. Sci. (Med.), MD, Director, V. K. Gusak institute of emergency and reconstructive surgery, Donetsk, Russian Federation; Professor of the Department of Surgical Diseases, Faculty of Fundamental Medicine of Lomonosov Moscow State University, Moscow, Russian Federation
ORCID: https://orcid.org/0000-0003-0260-6922, SPIN: 9021-7370, AuthorID: 1045336

Alexey A. Polikarpov – Dr. Sci. (Med.), MD, Leading Researcher of the Department of Interventional Radiology and Operative Surgery, Professor of the Department of Radiology and Surgical Technologies, Russian Scientific Center of Radiology and Surgical Technologies named after Academician A. M. Granov, St. Petersburg, Russian Federation
ORCID: https://orcid.org/0000-0002-7683-5042, SPIN: 4641-0720, AuthorID: 690524

Amira I. Farmonkulova – student, Faculty of Fundamental Medicine of Lomonosov Moscow State University, Moscow, Russian Federation
ORCID: https://orcid.org/0009-0007-2851-2226

Contribution of the authors:

Stukalova O. Yu. – participation in the concept of clinical research, writing the source text, final conclusions;
Ishchenko R. V. – scientific guidance, development of the concept of clinical research, revision of the text, final conclusions;
Polikarpov A. A. – scientific guidance, development of the concept of clinical research, revision of the text, final conclusions;
Farmankulova A. I. – writing the source text.

South Russian Journal of Cancer. 2024. Vol. 5, No. 4. P. 38-45
https://doi.org/10.37748/2686-9039-2024-5-4-5
https://elibrary.ru/cxjghi

CLINICAL CASE REPORT

A case of a fifteen-year-old patient suffering from rare adenocystic lung carcinoma bronchoplastic surgery

D. A. Kharagezov, E. A. Mirzoyan✉, Yu. Yu. Kozel, G. A. Mkrtchyan, A. A. Antonyan, T. G. Ayrapetova, I. A. Leyman, A. G. Milakin, O. N. Stateshny

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

ABSTRACT

Adenoid cystic carcinoma of the lung is a relatively rare malignant tumor, accounting for 0.04–0.2 % of all primary malignant tumors of the respiratory system. This carcinoma can occur at any age, but it is more common in the 40–60 age group and usually in women. The main treatment method for adenoid cystic carcinoma is surgical. Since tumors of this histological form are often centrally located, options for bronchoplastic operations are considered. In childhood, adenoid cystic carcinoma is extremely rare, and performing bronchoplastic lobectomies in children is associated with several difficulties, such as the smaller diameter of the bronchi compared to adult patients, complicating surgical intervention and subsequent rehabilitation.
This clinical case demonstrates the experience of performing a bronchoplastic operation on a 15-year-old patient at the Department of Thoracic Oncology of the National Medical Research Centre for Oncology, Rostov-on-Don, Russian Federation. The patient was hospitalized complaining of prolonged cough, shortness of breath, and chest pain. Adenoid cystic carcinoma of the central type was identified during diagnostics, which included bronchoscopy, computed tomography, and biopsy.
The surgical intervention involved performing a bronchoplastic lobectomy, during which the affected lobe of the lung was removed with resection and reconstruction of the bronchus. The operation was performed taking into account the anatomical features of the child's body, which required high precision and surgical skills. The postoperative period proceeded without significant complications, and the patient was under the supervision of a multidisciplinary team of specialists.
This clinical case provides a detailed description of the results of preoperative diagnostic measures, the stages of the operation, and the postoperative follow-up results. Special attention was paid to the difficulties associated with the small diameter of the bronchi in children, which required the use of specialized instruments and techniques. The importance of using modern diagnostic and treatment methods, as well as close interdisciplinary interaction, is emphasized for a successful treatment outcome.
The experience of performing such operations in childhood is extremely important for improving the quality and safety of surgical treatment of adenoid cystic carcinoma and other rare tumors in children. Further observations will be described in stages.

Keywords: lung cancer, adenocystic carcinoma, bronchoplastic lobectomy in children

For citation: Kharagezov D. A., Mirzoyan E. A., Kozel Yu. Yu., Mkrtchyan G. A., Antonyan A. A., Airapetova T. G., Leyman I. A., Milakin A. G., Stateshny O. N. A case of a fifteen-year-old patient suffering from rare adenocystic lung carcinoma bronchoplastic surgery. South Russian Journal of Cancer. 2024; 5(4): 38-45. https://doi.org/10.37748/2686-9039-2024-5-4-5, https://elibrary.ru/cxjghi

For correspondence: Ellada A. Mirzoyan – Cand. Sci. (Med.), MD, oncologist, researcher 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: this study followed the ethical principles outlined in the World Medical Association Declaration of Helsinki (1964, revised in 2013). The research was approved by the Ethics Committee of the National Medical Research Centre for Oncology, Rostov-on-Don, Russian Federation (protocol No. 16 dated 12.10.2021). Informed consent was obtained from all study participants

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 17.05.2024; approved after reviewing 06.09.2024; accepted for publication 28.10.2024

Южно-Российский онкологический журнал. 2024. Т. 5, № 4. С. 38-45
https://doi.org/10.37748/2686-9039-2024-5-4-5
https://elibrary.ru/cxjghi
3.1.6. Онкология, лучевая терапия
КЛИНИЧЕСКОЕ НАБЛЮДЕНИЕ

Случай выполнения бронхопластической операции пациентке пятнадцати лет с редкой аденокистозной карциномой легкого

Д. А. Харагезов, Э. А. Мирзоян✉, Ю. Ю. Козель, Г. А. Мкртчян, А. А. Антонян, Т. Г. Айрапетова, И. А. Лейман, А. Г. Милакин, О. Н. Статешный

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

РЕЗЮМЕ

Аденокистозная карцинома легкого является относительно редкой злокачественной опухолью, на долю которой приходится 0,04–0,2 % всех первичных злокачественных опухолей органов дыхательной системы. Эта карцинома может возникнуть в любом возрасте, однако чаще встречается в возрастной группе 40–60 лет и, как правило, у женщин. Основным методом лечения аденокистозной карциномы является хирургический. Поскольку опухоль данной гистологической формы часто располагается центрально, рассматриваются варианты выполнения бронхопластических операций. В детском возрасте аденокистозная карцинома встречается очень редко, а выполнение бронхопластических лобэктомий у детей сопровождается рядом трудностей, таких как меньший диаметр бронхов по сравнению со взрослыми пациентами, что усложняет оперативное вмешательство и последующую реабилитацию. Настоящий клинический случай демонстрирует опыт выполнения бронхопластической операции 15-летней пациентке на базе отделения торакальной онкологии ФГБУ «Национальный медицинский исследовательский центр онкологии» Министерства здравоохранения Российской Федерации, г. Ростова-на-Дону. Пациентка была госпитализирована с жалобами на длительный кашель, одышку и боли в грудной клетке. В ходе диагностики, включающей бронхоскопию, компьютерную томографию и биопсию, была выявлена аденокистозная карцинома центрального типа.

Хирургическое вмешательство включало проведение бронхопластической лобэктомии, при которой была удалена пораженная доля легкого с резекцией и восстановлением бронха. Операция была выполнена с учетом анатомических особенностей детского организма, что требовало высокой точности и навыков хирурга. Послеоперационный период протекал без значительных осложнений, пациентка находилась под наблюдением мультидисциплинарной команды специалистов.

В данном клиническом случае были подробно описаны результаты предоперационных диагностических мероприятий, этапы проведения операции, а также результаты послеоперационного наблюдения. Отдельное внимание было уделено сложностям, связанным с малым диаметром бронхов у детей, что требовало использования специализированных инструментов и техники. Подчеркивается важность использования современных методов диагностики и лечения, а также тесного междисциплинарного взаимодействия для успешного исхода лечения.

Опыт проведения подобных операций в детском возрасте крайне важен для повышения качества и безопасности хирургического лечения аденокистозной карциномы и других редких опухолей у детей.

Ключевые слова: рак легкого, аденокистозная карцинома, бронхопластическая лобэктомия у детей

Для цитирования: Харагезов Д. А., Мирзоян Э. А., Козель Ю. Ю., Мкртчян Г. А., Антонян А. А., Айрапетова Т. Г., Лейман И. А., Милакин А. Г., Статешный О. Н. Случай выполнения бронхопластической операции пациентке пятнадцати лет с редкой аденокистозной карциномой легкого. Южно-Российский онкологический журнал. 2024; 5(4): 38-45. https://doi.org/10.37748/2686-9039-2024-5-4-5, https://elibrary.ru/cxjghi

Для корреспонденции: Мирзоян Эллада Арменовна – к.м.н., врач-онколог, научный сотрудник 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 этическим комитетом ФГБУ «Национальный медицинский исследовательский центр онкологии» Министерства здравоохранения Российской Федерации (протокол № 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 17.05.2024; одобрена после рецензирования 06.09.2024; принята к публикации 28.10.2024

INTRODUCTION

Lung cancers occupy the first place in the structure of morbidity and mortality from cancer among the male population [1–3].

Adenocystic carcinoma (ACC) of the lung is a relatively rare malignant tumor, which accounts for 0.04– 0.2 % of all primary malignant tumors of the respiratory system [4]. ACC can occur at any age, but it is more common in the age group of 40–60 years and is usually found in women [5–6]. The main method of treatment of ACC is surgical, and since the tumor of this histological form is often centrally located, options for performing bronchoplastic operations are being considered [7, 8].

Bronchoplastic lobectomy with systematic mediastinal lymphodissection is a good choice for the treatment of endobronchial tumors in both children and adult patients in order to preserve lung parenchyma [9]. Primary lung tumors in childhood are very rare, and performing bronchoplastic lobectomies in children is accompanied by a number of difficulties, in particular, the diameter of the bronchi is much smaller than in adults [10].

The purpose of the study was to present a clinical case of a 15-year-old patient with rare adenocystic lung carcinoma who underwent bronchoplastic surgery with a good long-term treatment result.

Clinical observation report

A patient born in 2006 applied to the National Medical Research Center for Oncology, Rostov-on-Don in February 2022 with complaints of periodic cough, shortness of breath, feeling of lack of air, hemoptysis. According to him, he has been ill since 2021, with a history of repeatedly suffering from pneumonia.

Since June, after suffering a new coronavirus infection, there have been frequent attacks of shortness of breath. In November, the condition has worsened, followed by hemoptysis, increased shortness of breath, feeling of lack of air. He went to the doctor at the place of residence. SCT performed on 12/02/2021 showed: a volumetric formation of an irregular shape of 1.3 × 0.7 × 1.2 cm of a heterogeneous structure is determined in the lumen of the left main bronchus.

12/28/22 SCT in the lumen of the main bronchus on the left showed a multi-node formation of 1.3 × 1.2 cm narrows its lumen, the remaining bronchi are passable in the visible extent (bronchial lumen of the 3rd-4th order is visualized), their walls are not thickened, without signs of bronchiectasis, on the left in the lower lobe there are areas of pneumosclerosis, on the right along the interlobular pleura a single dense focus requiring dynamic observation (Fig. 1).

SCT scan with angiography from 01/24/2022. The CT picture is more consistent with the endobronchial formation (carcinoid) of the left main bronchus.

FBS dated 12/28/2021: the larynx is mobile, the trachea, carina and bronchi of the right lung are without features. On the left: the main bronchus is 3/4 encircled by a tuberous exophyte about 1.5 × 1.2 cm in size. The exophyte originates from the interlobular spur and is located on a narrowed base. The spur at the exophyte outlet was expanded due to the sub-

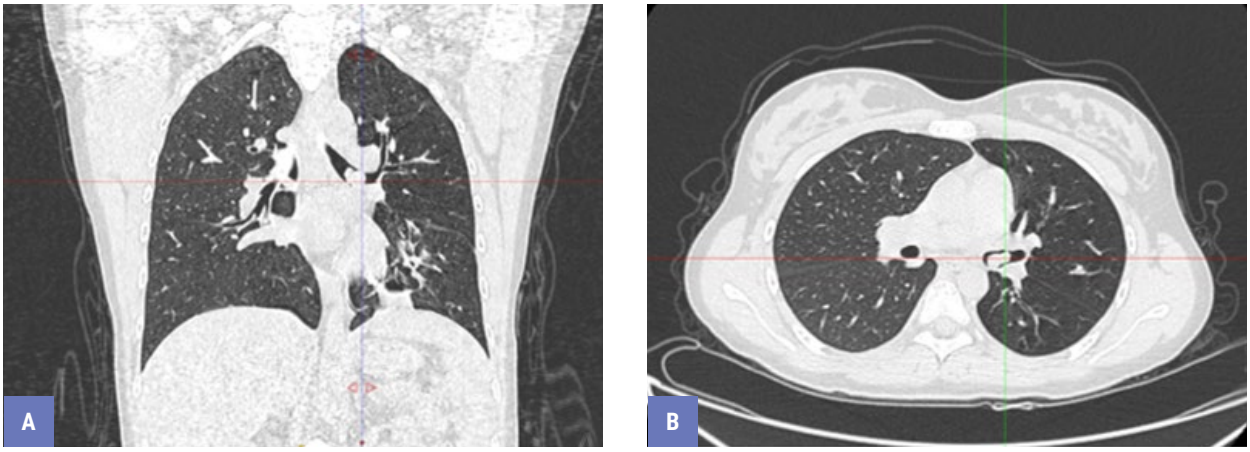


Fig. 1. Chest CT scan of the patient G.: A – frontal section; B – sagittal section

mucosal component of the tumor, and a biopsy was taken. Conclusion: exophytic tumor of the upper lobe spur of the left lung with signs of invasion of the interlobular spur. Subcompensated stenosis of the left main bronchus (carcinoid?) (Fig. 2).

Histological analysis 145380–81 /21 dated 01/13/2022: The morphological picture in the volume of biopsies is more typical for a typical carcinoid/ neuroendocrine tumor. To clarify the immunophenotype of tumor cells, an IHC study is recommended.

IHC dated 01/21/2022: morphological picture and immunophenotype of tumor cells in the volume of biopsies (PanCK+, CK7+, CD117+, p63+ in the myoepithelial layer) are characteristic of adenocystic carcinoma.

Upon admission to the Department of Pediatric Oncology No. 1 02.02.2022, the PCR test for SARS-CoV-2 is negative, PS ECOG (Eastern Cooperative Oncology Group scale, designed to assess the general condition of cancer patients) 1 point. The superficial lymph nodes are not enlarged. The chest is not deformed, both halves of it are evenly involved in the act of breathing. The breathing rate is 15 per 1 minute at rest. Percussive clear pulmonary sound, the same on the right and on the left. Auscultatively vesicular breathing on the right, and weakened on the left. Spirometric parameters are normal. On the ECG: Sinus rhythm with a heart rate of 68 beats /min, an ECG variant of the age norm. The clinical diagnosis was made: (C34.1) Adenocystic carcinoma of the left upper lobe bronchus T1bNxM0, stage IA, cl. gr. 2.

The patient was taken to the operating room on 02/07/2022. The patient was positioned lying on her right flank. An anterolateral thoracotomy was performed in the 5th intercostal space on the left. According to a comprehensive examination, the patient has a central malignant tumor of the distal part of the left main bronchus of 1.3 × 1.0 cm, spreading to the upper lobe bronchus. It was decided to perform an upper bronchoplastic lobectomy on the left with wedge-shaped resection of the main, lower lobar bronchus, mediastinal lymphadenectomy. The pulmonary ligament is excised. A posterior mediastinotomy was performed. Bifurcation lymphodissection was performed using an electrosurgical instrument. Anterior mediastinotomy was performed, the diaphragmatic nerve was visualized, isolated, and placed on a turnstile. With the help of Thunderbeat, the superior pulmonary vein is mobilized and crossed by a suturing device. The anterior mediastinal fiber and a group of 4L-6 lymph nodes were removed in a single block. Hemostasis was performed. The visceral pleura was dissected in the projection of the interstitial fissure. A2, A1–3, A4–5 were isolated, sequentially ligated and crossed. The lower lobe is mobilized from the upper lobe by a linear stitching device. Using the Thunderbeat electrosurgical instrument, the lymph nodes of the lung root were removed with the removal of the l/nodes of the root of the lower lobe with the exposure of the upper lobe, lower lobe bronchus, interlobular spur, distal part of the left main bronchus, where a tumor formation up to 1.5 cm in diameter is contoured. Wedge-shaped resection of the distal part of the main, interlobular spur, and proximal part of the inferior lobe bronchus was performed, with suturing of the defect with separate nodular sutures with atraumatic monofilament thread. The drug has been removed. The line of tantalum sutures on the lung parenchyma is additionally coagulated with bipolar tweezers. Hemostasis was performed. Control of pneumostasis by underwater breakdown: pneumostasis was stable. Drainage of the left pleural cavity at 7 and 9 i/c 2. Layered suturing of a thoracotomy wound.

The result of a planned histological examination: 11136–37/22: The morphological picture (taking into account IHCNo.83/22) is characteristic of bronchial adenocystic carcinoma (salivary gland-type tumor), with an exophytic growth pattern, invasion of the submucosal layer, the presence of foci of carcinoma in the adventitial layer. There were no signs of

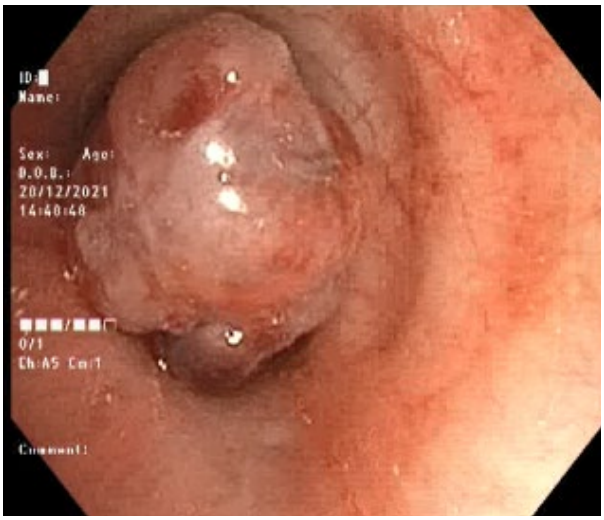


Fig. 2. FBS from 28/12/2021

perineural and lymphovascular invasion. No tumor cell resection lines were found in the adjacent bronchopulmonary 4L-7, 10–14 lymph nodes.

The postoperative period was uneventful. On the control fibrobronchoscopy from 02/14/2022: a wide interbronchial suture was determined. The seam line was consistent. Its mucous membrane was edematous, hyperemic, and there was a fibrin plaque on the anterior and posterior walls. The bronchi of the lower lobe were not deformed, freely passable. The mucous membrane was smooth, pale, shiny (Fig. 3).

The FBS dated 02/21/2022 showed: on the left, an anastomosis of the main and lower lobe bronchi in the form of an annular roller narrowing the lumen by 1/3, with suture ligatures, four red spots and one spot of fibrin. Bronchi of the lower lobe of the usual type. The anastomosis is in the resolution stage (Fig. 4.).

On the 15th day after surgery, the patient was discharged from the hospital in a satisfactory condition with the diagnosis: C34.1 Adenocystic carcinoma of the left upper lobe bronchus pT1bN0M0, stage IA, condition after thoracotomy, combined upper bron-

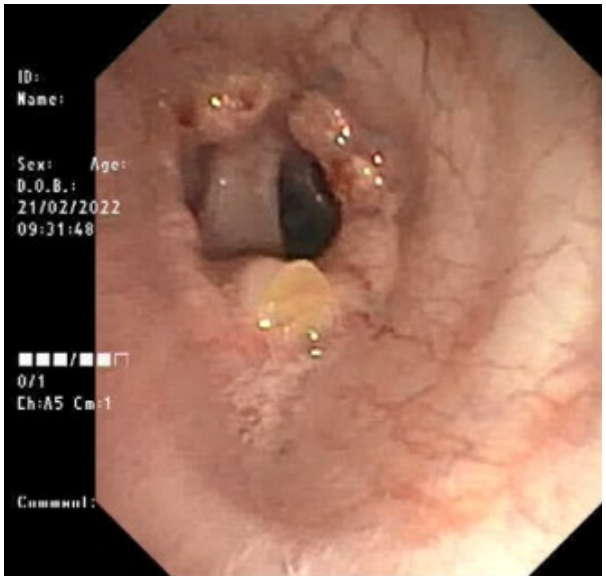


Fig. 3. FBS patient G. from 02/14/2022 on the 7th day after surgery

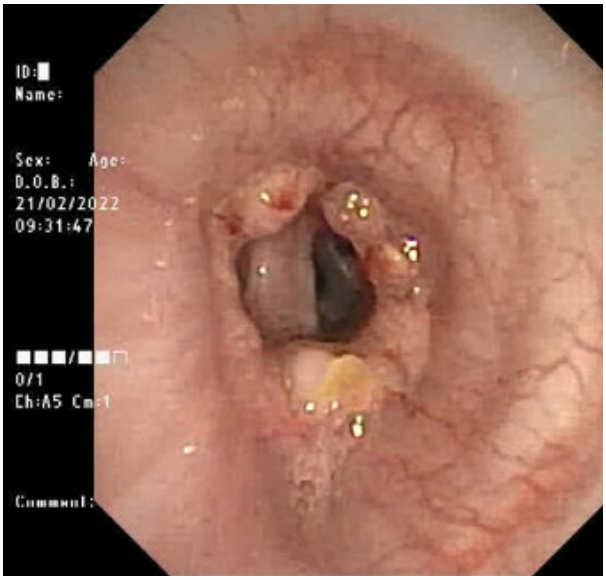


Fig. 4. FBS patient G. dated 02/21/2022 on the 14th day after surgery

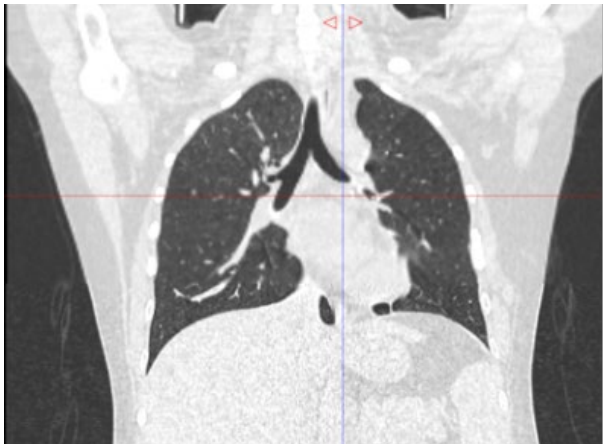


Fig. 5. Chest CT scan of patient G. from 28/11/2023, 1 year 9 months after surgery: frontal section

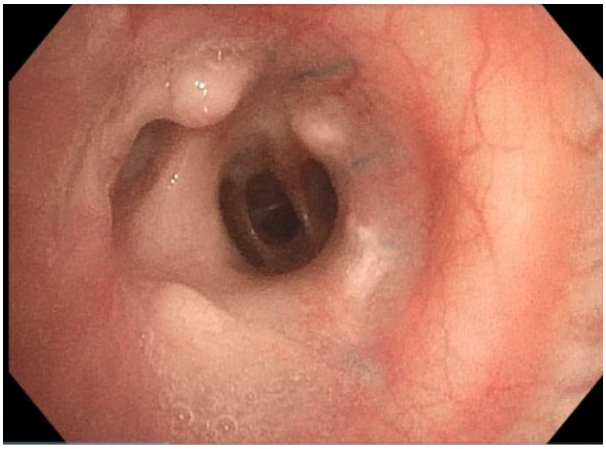


Fig. 6. FBS patient G. from 11.28.2023, 1 year 9 months after surgery

choplastic lobectomy on the left with wedge-shaped resection of the main, lower lobe bronchus, mediastinal lymphadenectomy from 02/07/2022, cl. gr. 3.

At the control visit on 11/28/2023, 1 year and 9 months after the operation, the patient does not complain, feels healthy, and leads an active lifestyle. PS ECOG 0 points, no pathology was detected during physical examination. On CT of the chest organs and FBS without signs of progression of the process (Fig. 5, 6).

DISCUSSION

Improvements in surgical techniques and anesthetic aids have led to the introduction of broncho- and angioplasty operations, which demonstrate better immediate and long-term treatment results compared to the pneumonectomies [11–14].

In the paperwork of E. V. Levchenko et al. A comparative analysis of the long-term results of surgical treatment of 198 patients with stage I–III non-small cell LC was carried out: bronchoplastic operations were performed in 99 patients, pneumonectomies – 99. The median overall and recurrence-free survival was 51.4 and 55.2 months after bronchoplastic lobectomies, and in patients after pneumonectomies 46.2 and 41.0 months, respectively. One-year, 3- and 5-year recurrence-free survival in the group of bronchoplastic resections was 87.9 %, 64.2 % and 52.3 %, respectively, versus 88.1 %, 61.6 % and 37.9 % in the group after pneumonectomies [15].

The results of bronchoplastic surgeries and pneumonectomies are considered in detail in the meta-analysis of Z. Li with co-authors, which presents the results of treatment of 14194 patients: 4145 performed bronchoplastic operations, 10049 – pneumonectomies. Overall survival was higher in the group of patients who underwent bronchoplastic lobectomies (OR: 1.53; 95 % CI: 1.31–1.80; $p < 0.00001$), and in the group of patients after pneumonectomies, there was a higher level of postoperative and 30-day mortality, as well as the frequency of distant metastases (5.86 % and 2.78 %, respectively) [16].

Various variants of bronchoplastic surgeries have also been used in pediatric practice, where the preservation of maximum lung tissue is also an important aspect [17]. Yu et al. presented the largest study evaluating the effectiveness of bronchoplastic interventions in children and adults. The authors found that this technique has a good prognosis in the pediatric population [18]. However, there are few reports in the literature about performed bronchoplastic surgeries for lung cancer in children [19].

CONCLUSION

A clinical case of a 15-year-old patient with a rather rare adenocystic lung carcinoma who underwent bronchoplastic lobectomy has been presented in this article. There is no data for the progression and recurrence of the process, the patient is currently under dynamic observation.

References

1. Kit OI, Kharagezov DA, Lazutin YuN, Mirzoyan EA, Leyman IA, Tikhonova SN. Sequential bronchoplastic lobectomies in complex treatment for synchronous bilateral multiple primary non-small cell lung cancer: a rare clinical case. South Russian Journal of Cancer. 2022;3(4):67–73. (In Russ.). https://doi.org/10.37748/2686-9039-2022-3-4-7, EDN: NIGIFS
2. Kharagezov DA, Lazutin YuN, Mirzoyan EA, Milakin AG, Stateshny ON, Leiman IA, et al. Клинический случай легочной формы мукормикоза у ребенка с острым лимфобластным лейкозом. South Russian Journal of Cancer. 2021;2(4):38–47. (In Russ.). https://doi.org/10.37748/2686-9039-2021-2-4-5, EDN: PLFQUY
3. Kharagezov DA, Lazutin YuN, Mirzoyan EA, Milakin AG, Stateshny ON, Leyman IA. Neoadjuvant and adjuvant immunotherapy of non-small cell lung cancer (literature review). Environmental issues. 2022;68(2):159–168. (In Russ.). https://doi.org/10.37469/0507-3758-2022-68-2-159-168, EDN: VYYGNS
4. Krifa M, Bdioui A, Lajmi Z, Missaoui N, Hmissa S, Mokni M. Primary adenoid cystic carcinoma of the lung: A case report and literature review. Heliyon. 2021 Feb;7(2):e06206. https://doi.org/10.1016/j.heliyon.2021.e06206
5. Li M, Zhao BR, Liu SQ, An J, Deng PB, Han-Zhang H, et al. Mutational landscape and clonal diversity of pulmonary adenoid cystic carcinoma. Cancer Biol Ther. 2018;19(10):898–903. https://doi.org/10.1080/15384047.2018.1480296

6. Elnayal A, Moran CA, Fox PS, Mawlawi O, Swisher SG, Marom EM. Primary salivary gland-type lung cancer: imaging and clinical predictors of outcome. AJR Am J Roentgenol. 2013 Jul;201(1):W57–63. https://doi.org/10.2214/AJR.12.9579
7. Yokouchi H, Otsuka Y, Otoguro Y, Takemoto N, Ito K, Uchida Y, et al. Primary peripheral adenoid cystic carcinoma of the lung and literature comparison of features. Intern Med. 2007;46(21):1799–1803. https://doi.org/10.2169/internalmedicine.46.0331
8. Grillo HC, Mathisen DJ. Primary tracheal tumors: treatment and results. Ann Thorac Surg. 1990 Jan;49(1):69–77. https://doi.org/10.1016/0003-4975(90)90358-D
9. Tang J, Cao M, Qian L, Fu Y, Tang J, Zhao X. The pure distal left main bronchial sleeve resection with total lung parenchymal preservation: report of two cases and literature review. J Thorac Dis. 2014 Dec;6(12):E294–298. https://doi.org/10.3978/j.issn.2072-1439.2014.12.14
10. Gaissert HA, Mathisen DJ, Grillo HC, Vacanti JP, Wain JC. Tracheobronchial sleeve resection in children and adolescents. J Pediatr Surg. 1994 Feb;29(2):192–197. https://doi.org/10.1016/0022-3468(94)90316-6
11. Kharagezov DA, Mirzoyan EA, Turkin IN, Lazutin YuN, Milakin AG, Stateshny ON, et al. Comparative analysis of the results of bronchoplastic surgical interventions and pneumonectomies. The journal Chief physician of the South of Russia. 2022;(1(82)):10–13. (In Russ.). EDN: HQJKHD
12. Presley CJ, Gross CP, Lilenbaum RC. Optimizing Treatment Risk and Benefit for Elderly Patients With Advanced Non-Small-Cell Lung Cancer: The Right Treatment for the Right Patient. J Clin Oncol. 2016 May 1;34(13):1438–1442. https://doi.org/10.1200/JCO.2015.65.9599
13. Tikhonova SN, Rozenko DA, Ushakova ND, Popova NN, Skopintsev AM, Shulga AV, et al. Optimization of anesthetic tactics in the surgical treatment of multiple primary non-small cell lung cancer. South Russian Journal of Cancer. 2021;2(2):42–49. https://doi.org/10.37748/2686-9039-2021-2-2-5, EDN: MGRWDV
14. Reshetov AV, Elkin AV, Nikolaev GV, Stepanov SS. Broncho- and angioplasty lobectomy as an alternative to pneumonectomy in treatment of non-small-cell lung cancer. Grekov's Bulletin of Surgery. 2018;177(3):19–24. (In Russ.). https://doi.org/10.24884/0042-4625-2018-177-3-19-24, EDN: XRSVVB
15. Levchenko EV, Levchenko NE, Yurin RI, Mikhnin AE, Ergnian SM, Barchuk AS. Long-term results of bronchoplastic surgical interventions compared with pneumonectomies in lung cancer. Questions of Oncology. 2017;63(2):234–239. (In Russ.). https://doi.org/10.37469/0507-3758-2017-63-2-234-239, EDN: YNCXYX
16. Li Z, Chen W, Xia M, Liu H, Liu Y, Inci I, et al. Sleeve lobectomy compared with pneumonectomy for operable centrally located non-small cell lung cancer: a meta-analysis. Transl Lung Cancer Res. 2019 Dec;8(6):775–786. https://doi.org/10.21037/tlcr.2019.10.11
17. Gaissert HA, Mathisen DJ, Grillo HC, Vacanti JP, Wain JC. Tracheobronchial sleeve resection in children and adolescents. J Pediatr Surg. 1994 Feb;29(2):192–197. https://doi.org/10.1016/0022-3468(94)90316-6
18. Yu Y, Song Z, Chen Z, Jian H, Lu S. Chinese pediatric and adolescent primary tracheobronchial tumors: a hospital-based study. Pediatr Surg Int. 2011 Jul;27(7):721–726. https://doi.org/10.1007/s00383-011-2858-8
19. Toker A, Bayrak Y, Dilege S, Kalayci G. Bronchial sleeve resections for carcinoid tumor in the first decade of life. Interact Cardiovasc Thorac Surg. 2004 Jun;3(2):280–282. https://doi.org/10.1016/j.icvts.2003.12.006

Information about authors:

Dmitrii 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, oncologist, researcher at the Department of Thoracic Oncology, of 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

Yulia Yu. Kozel – Dr. Sci. (Med.), MD, Head of the Department of Pediatric Oncology, National Medical Research Centre for Oncology, Rostov-on-Don, Russian Federation
ORCID: https://orcid.org/0000-0002-6681-3253, SPIN: 6923-7360, AuthorID: 732882, ResearcherID: AAZ-2780-2021, Scopus Author ID: 57221118516

Gulnara A. Mkrtchyan – MD, pediatric surgeon at the Department of Pediatric Oncology No. 2, National Medical Research Centre for Oncology, Rostov-on-Don, Russian Federation
ORCID: https://orcid.org/0000-0002-5202-7681, SPIN: 1861-5165, AuthorID: 794720

Artur A. Antonyan – PhD student, National Medical Research Centre for Oncology, Rostov-on-Don, Russian Federation
ORCID: https://orcid.org/0000-0001-6449-7026, ResearcherID: JWQ-0734-2024

Tamara G. Ayrapetova – Cand. Sci. (Med.), 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

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

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, Scopus Author ID: 57192109933

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

Contribution of the authors:

Kharagezov D. A., Kozel Yu.Yu. – scientific editing.
Mirzoyan E. A., Antonyan A. A. – writing the draft; data processing.
Mkrtchyan G. A., Ayrapetova T. G., Leyman I. A., Milakin A. G., Stateshny O. N. – data collection, analysis, technical editing, reference list arrangement.

South Russian Journal of Cancer. 2024. Vol. 5, No. 4. P. 46-57
https://doi.org/10.37748/2686-9039-2024-5-4-6
https://elibrary.ru/hfikew

REVIEW

Prospects for the use of flavonoid substances in pulmonary fibrosis (review of experimental studies)

E. A. Gubareva✉, A. L. Semenov

N. N. Petrov National Medicine Research Center of Oncology, St. Petersburg, Russian Federation
✉ gubareva1984@gmail.com

ABSTRACT

Pulmonary fibrosis develops both spontaneously and as a result of lung damage by radiotherapy and chemotherapy, infectious diseases, and inhalation of harmful substances and particulate matter. In this case, normal tissue repair is disturbed: instead of regeneration of normal lung cells, the damaged tissue is replaced by fibrotic one consisting of dense collagen fibers. This leads to loss of lung tissue elasticity and impairment of its function, which significantly reduces the quality of patients' lives. The search for drugs for interstitial fibrotic lung diseases remains an urgent task, since the existing antifibrotic drugs only slow down disease progression and have side effects that significantly reduce the patients' quality of life. It is believed that natural polyphenolic substances, in particular flavonoids, can be used for the treatment of pulmonary fibrosis. Flavonoids present in various fruits, vegetables, tea and wine show a wide range of biological activities. They have antioxidant, anti-inflammatory and immunomodulatory properties, making them promising for the treatment of various diseases, including pulmonary fibrosis. Some studies have shown that flavonoids can inhibit myofibroblast activation and collagen production, which is directly related to the fibrotic process. Flavonoids are safe and can influence the hallmarks of fibrosis: oxidative stress, inflammation, cell proliferation and differentiation. To date, a large amount of experimental data confirming the antifibrotic effect of flavonoids has been accumulated. In recent years, clinical studies have been conducted to investigate the efficacy and safety of flavonoids in patients with pulmonary fibrosis. For example, quercetin and curcumin are being explored and have shown encouraging results in reducing markers of inflammation and fibrosis in the lung. However, the main obstacle to the widespread introduction of flavonoid substances into clinical practice remains their low oral bioavailability and rapid metabolism. The experimental data on the effect of flavonoids on the development of pulmonary fibrosis is analyzed in this review. The perspectives for improving their bioavailability using modern delivery systems (nanoparticles, liposomes, etc.), as well as dosage forms for topical application, are discussed in this paperwork.

Keywords: pulmonary fibrosis, flavonoids, experimental models

For citation: Gubareva E. A., Semenov A. L. Prospects for the use of flavonoid substances in pulmonary fibrosis (review of experimental studies). South Russian Journal of Cancer. 2024; 5(4): 46-57. https://doi.org/10.37748/2686-9039-2024-5-4-6, https://elibrary.ru/hfikew

For correspondence: Ekaterina A. Gubareva – Cand. Sci. (Biol.), senior researcher, N. N. Petrov National Medicine Research Center for Oncology, St. Petersburg, Russian Federation
Address: 68 Leningradskaya str., Pesochny settlement, Saint Petersburg 197758, Russian Federation
E-mail: gubareva1984@gmail.com
ORCID: https://orcid.org/ 0000-0002-9212-6086
SPIN: 5556-8242, AuthorID: 895429
ResearcherID: AAD-2072-2020
Scopus Author ID: 56909987000

Funding: the project was supported by RSF grant No. 22-25-20177 and RSF (St. Petersburg Science Foundation) grant No. 50/2022

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 07.11.2023; approved after reviewing 20.07.2024; accepted for publication 28.10.2024

Южно-Российский онкологический журнал. 2024. Т. 5, № 4. С. 46-57
https://doi.org/10.37748/2686-9039-2024-5-4-6
https://elibrary.ru/hfikew
3.1.6. Онкология, лучевая терапия

ОБЗОР

Перспективы применения веществ флавоноидного ряда при фиброзе легкого (обзор экспериментальных исследований)

Е. А. Губарева✉, А. Л. Семенов

ФГБУ «Национальный медицинский исследовательский центр онкологии им. Н. Н. Петрова» Министерства здравоохранения Российской Федерации, г. Санкт-Петербург, Российская Федерация
✉ gubareva1984@gmail.com

РЕЗЮМЕ

Фиброз легкого развивается как спонтанно, так и вследствие воздействия повреждающих факторов, включая лучевую и химиотерапию, инфекционные заболевания, вдыхание вредных веществ и твердых частиц. При этом происходит нарушение нормальной репарации тканей: вместо регенерации нормальных клеток легкого происходит замещение поврежденной ткани фиброзной, состоящей из плотных коллагеновых волокон. Этот процесс ведет к утрате эластичности легочной ткани и нарушению ее функции, что существенно снижает качество жизни пациентов. Поиск средств для лечения интерстициальных фиброзирующих заболеваний легкого остается актуальной задачей, т. к. существующие антифибротические препараты лишь замедляют их прогрессирование и обладают побочными эффектами, существенно снижающими качество жизни пациентов. Считается, что природные вещества полифенольной природы, в частности, флавоноиды, могут применяться для лечения фиброза легкого. Флавоноиды, присутствующие в различных фруктах, овощах, чае и вине, демонстрируют широкий спектр биологических активностей. Они обладают антиоксидантными, противовоспалительными и иммуномодулирующими свойствами, что делает их перспективными для лечения различных заболеваний, включая фиброз легкого. Некоторые исследования показали, что флавоноиды могут ингибировать активацию миофибробластов и продукцию коллагена, что непосредственно связано с процессом фиброзирования. Флавоноиды нетоксичны и способны регулировать процессы, связанные с развитием фиброза: окислительный стресс, воспаление, пролиферацию и дифференцировку клеток. На сегодняшний день накоплено большое количество экспериментальных данных, подтверждающих антифибротическое действие флавоноидов. В последние годы проводятся клинические исследования, направленные на изучение эффективности и безопасности флавоноидов у пациентов с фиброзом легкого. Например, исследуются кверцетин и куркумин, которые показали обнадеживающие результаты в снижении маркеров воспаления и фиброза в легких. Однако основным препятствием для широкого внедрения флавоноидных веществ в клиническую практику остается их низкая биодоступность при пероральном применении и быстрый метаболизм. В данной работе проанализированы данные литературы о влиянии флавоноидов на развитие фиброза легкого в экспериментах и в клинических исследованиях, обсуждаются перспективы улучшения их биодоступности с помощью современных систем доставки (наночастицы, липосомы и др.), или использования лекарственных форм для местного применения.

Ключевые слова: фиброз легкого, флавоноиды, экспериментальные модели

Для цитирования: Губарева Е. А., Семенов А. Л. Перспективы применения веществ флавоноидного ряда при фиброзе легкого (обзор экспериментальных исследований). Южно-Российский онкологический журнал. 2024; 5(4): 46-57. https://doi.org/10.37748/2686-9039-2024-5-4-6, https://elibrary.ru/hfikew

Для корреспонденции: Губарева Екатерина Александровна – к.б.н., старший научный сотрудник, ФГБУ «Национальный медицинский исследовательский центр онкологии имени Н. Н. Петрова» Министерства здравоохранения Российской Федерации, г. Санкт-Петербург, Российская Федерация
Адрес: 197758, Российская Федерация, г. Санкт-Петербург, п. Песочный, ул. Ленинградская, д. 68
E-mail: gubareva1984@gmail.com
ORCID: https://orcid.org/0000-0002-9212-6086
SPIN: 5556-8242, AuthorID: 895429
ResearcherID: AAD-2072-2020
Scopus Author ID: 56909987000

Финансирование: финансирование работа была поддержана грантом РНФ № 22-25-20177 и грантом РНФ (Санкт-Петербургский научный фонд) № 50/2022

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

Статья поступила в редакцию 07.11.2023; одобрена после рецензирования 20.07.2024; принята к публикации 28.10.2024

INTRODUCTION

The spectrum of interstitial fibrotic lung diseases is quite wide, but all of them lead to a gradual decrease in respiratory function, a significant decrease in the quality of patients' life and premature death [1]. Life expectancy after diagnosis in idiopathic pulmonary fibrosis (IPF) is on average 3–5 years [2], and the average five-year survival rate for this disease is 45.6 % [3]. Existing treatment methods and registered antifibrotic drugs somewhat slow down the progression of the disease and reduce the mortality rate, but have contraindications and side effects, so their long-term use is not always possible [4, 5]. Since the disease can occur for several years, finding drugs that can slow down or stop the progression of pulmonary fibrosis (PF) and are safe with long-term use, is an urgent task. In recent years, much attention has been paid in this regard to natural substances of polyphenolic nature, in particular, flavonoids.

These substances are found in various parts of plants and are an important component of traditional medicine and functional nutrition [6]. Flavonoids are nontoxic and are able to regulate the processes involved in the development of fibrosis: oxidative stress, inflammation, cell proliferation and differentiation (in particular, epithelial-mesenchymal transition), intercellular interactions [7, 8]. To the date, a substantial experimental evidence base has been accumulated justifying the use of flavonoids as antifibrotic agents. In addition, several pilot clinical trials have been conducted on patients with IPF [9, 10]. However, their low bioavailability prevents the widespread introduction of flavonoid substances into clinical practice. In this regard, the prospects of using dosage forms for topical use are being considered.

The purpose of the study was to analyze the literature data on the effect of flavonoid substances on the development of lung fibrosis in experiments with laboratory animals and in clinical studies, to identify prospects for increasing their bioavailability using modern delivery systems.

Pulmonary fibrosis: risk factors, occurrence, main mechanisms of pathogenesis

PF can occur as a manifestation of certain systemic diseases (systemic sclerosis, rheumatoid arthritis, etc.), interstitial lung diseases (nonspecific interstitial pneumonia, chronic pneumonitis on the background of hypersensitivity), because of viral and bacterial infections. These diseases are designated as chronic interstitial fibrotic lung diseases with a progressive course [11]. IPF, interstitial pneumonia, is isolated as a separate disease without clarified etiological factors [1]. Risk factors for the development of IPF include smoking, inhalation of particulate substances, viral infections, gastroesophageal reflux syndrome, genetic predisposition, the use of certain medications, ionizing radiation [2, 12].

In this paperwork, we will use the term "pulmonary fibrosis" in relation to all progressive fibrotic interstitial lung diseases, with clarifications if necessary.

The incidence of diseases in which PF occurs is relatively low. According to a 2021 study, the incidence of IPF (per 100,000 population per year) ranged from 3.5 to 13 in the Asia-Pacific region, from 0.9 to 4.9 in Europe and from 7.5 to 9.3 in North America [11]. In Russia, during 2018, an average of 7 new cases of IPF per 100,000 people per year were registered in women and 11 in men [2].

The incidence of other fibrosing interstitial lung diseases in the United States is about 52 patients per 100,000 people per year, of which 33 cases are with a progressive phenotype [14]. It is assumed that after the SARS-CoV19 epidemic, these figures may increase: after the coronavirus infection is cured, some patients experience a decrease in respiratory function and changes in the X-ray picture of the lungs, similar to that of PF [15].

Normally, epithelial damage is repaired by type II alveolocytes, capable of proliferating and differentiating into type I alveolocytes, which line most of the surface of the alveoli and carry out gas exchange. At the same time, in the places of damage, epithelial cells secrete profibrotic factors that cause the activation of resident fibroblasts and their differentiation into myofibroblasts [16]. Myofibroblasts are also formed from circulating bone marrow precursors, epithelial and endothelial cells [17]. The main function of these cells is the synthesis of the intercellular matrix, which is necessary for tissue repair at the site of injury, after which they normally undergo apoptosis, and the excess extracellular matrix is cleaved [18]. The literature describes several mechanisms that can interfere with the normal resolution of the reparative process.

Many authors consider excessive activation of the immune system and chronic inflammation to be the main factors in the development of PF [2, 19]. It has been shown that various cells of the immune system, e. g. neutrophils, macrophages, lymphocytes, contribute to the development of PF due to the activation of oxidative stress and the production of profibrotic growth factors, cytokines and chemokines [2, 20]. It is assumed that activation of the immune response makes a significant contribution to the development of PF associated with COVID-19 [15].

The mechanism of PF development is also described, in which the main role is given to the chronic epithelial damage, leading to an increase in the level of reactive oxygen species, apoptosis, activation of cellular aging, depletion of the stem cell pool and the so-called "phenotypic reprogramming" of the type II alveolocytes [16, 21], i. e. aberrant activation of normal repair pathways and the release of mediators activating fibroblasts [22, 23].

Another mechanism of tissue fibrotization is being considered due to positive feedback from the extracellular matrix [24]. It has been shown that with excessive deposition of the matrix, its densification occurs, which leads to tissue hypoxia and epithelial damage; the compacted matrix creates a profibrotic environment and promotes cellular aging [25, 26]. Thus, a so-called "fibrogenic niche" is created, and the fibrotic process is self-sustaining [24]. Shochet et al. [27] showed that while culturing normal fibroblasts on a "fibrotic" matrix obtained after culturing fibroblasts of patients with IPF (IPF), the expression of genes associated with the HIF1 signaling pathway is activated, which contributes to the differentiation of myofibroblasts and the progression of fibrosis.

Pulmonary fibrosis treatment

Medicinal and non-medicinal methods are used to treat PF. The latest ones include lung transplantation and the use of palliative methods (oxygen therapy, physical exercises, etc.) [28].

Initially, anti-inflammatory drugs, corticosteroids and immunosuppressive drugs were used to treat IPF, based on the hypothesis that chronic inflammation is the main mechanism of development of this disease. These drugs did not improve survival and pulmonary function, and combined therapy with prednisone, azathioprine and N-acetylcysteine increased mortality and hospitalization rates [4]. Two drugs have been registered for the treatment of IPF – nintedanib, an oral inhibitor of intracellular tyrosine kinases, and pirfenidone, a pyridone compound with anti-inflammatory, antifibrotic and antioxidant properties [4]. Both drugs reduce the risk of mortality by almost 2 times, and quintedanib also significantly reduces the risk of acute complications compared with patients who do not take drugs [29]. Nintedanib and pirfenidone have been recognized as effective for other fibrotizing lung diseases [1, 11]. Nevertheless, the long-term use of these drugs often becomes impossible due to the refusal of treatment due to the lack of effect and/or side effects [4, 5, 28].

To date, antibodies to the connective tissue growth factor (CTGF), pentraxin-2, an endothelin receptor antagonist, new small molecules (inhibitors of autotaxin phosphodiesterase, integrins, etc.), and others are being studied as potential antifibrotic drugs (check reviews [4, 30] for details).

The prospects for the use of substances of natural origin, in particular, flavonoids, are discussed, since such compounds have anti-inflammatory, antiproliferative and immunomodulatory effects, as well as low toxicity and can be used long-term. In addition, flavonoids (and polyphenols in general) reduce the toxicity of cytostatics, for example, cyclophosphamide, which is used in patients with PF as an immunosuppressant.

In a pilot study carried out on patients with IPF, it was shown that after 14 days of EGCG (epigallocatechin gallate, the most common catechin found in tea), the content of two biomarkers produced by fibroblasts, cartilage oligomeric matrixprotein (COMP) and periostin, was reduced in serum, as well as collagen I in lung biopsies, SNAI1, phosphorylated SMAD3 [9]. The same team of authors showed that in *ex vivo* lung tissue obtained from patients undergoing lung transplantation, EGCG suppresses the TGF-β1 signaling cascade and collagen accumulation, as well as activates its MMP-dependent decay [31].

In pilot trials on patients with IPF, it was shown that physical performance improved in the group of people taking a combination of dasatinib and quercitin. In addition, a decrease in the level of some markers of cellular aging in the blood was noted [10].

The use of flavonoids in experiments on laboratory animals

To study PF using laboratory animals, a wide range of models are used that reproduce the effect of the main etiological factors of disease development, i. e. genetic predisposition, drug use, radiation, inhalation of solid particles [19, 32]. If experiments with genetically modified or immunodeficient mice help to better understand the molecular genetic mechanisms of PF development, then cheaper and more convenient models of fibrosis induction using tissue-damaging light chemical agents, solid particles or irradiation are most often chosen for screening potential antifibrotic drugs [32]. The most commonly used well–characterized PF model using bleomycin, systemic administration of which leads to damage to the lung endothelium, inflammation, apoptosis of epithelial cells and the launch of reparative processes, and local – directly into the respiratory tract causes direct damage to the alveolar and bronchial epithelium, followed by pronounced inflammation and tissue fibrosing [33].

The relevance of these models is being discussed, however, they reproduce the main aspects of fibrotizing lung diseases in humans at the tissue (excessive deposition of extracellular matrix, decrease in respiratory volume), cellular (epithelial damage, fibroblast proliferation, epithelial-mesenchymal transition) and molecular (oxidative stress, secretion of profibrotic factors) levels.

Table 1 shows studies over the past 5 years that studied the effect of individual flavonoid compounds on the development of experimental lung fibrosis in mice and rats. In almost all the analyzed studies, it was shown that the use of flavonoid-type substances reduces the severity of PF at the morphological level; in two studies, no statistically significant decrease in the histopathological index [34] and relative lung mass [35] was revealed when quercetin was used, however, the drug influenced other studied indicators.

Compared with untreated animals, the use of flavonoids in the lungs reduces the synthesis of extracellular matrix proteins such as collagen and fibronectin [34, 36–38], the content of the myofibroblast marker α-SMA and markers of the epithelial-mesenchymal transition [37, 39, 40]. It was also revealed in experiments that flavonoid preparations contribute to a decrease in the production of profibrotic cytokines in the lung: TGF-β [41–43] and proinflammatory cytokines [35, 39, 42, 44]. The positive effect of the studied substances on the activity of enzymes of the antioxidant defense system and a decrease in markers of oxidative stress were found [35, 36, 43, 44]. Despite the fact that the antifibrotic effect of flavonoids has been studied in several experimental models, and the range of techniques used and the estimated indicators differed, the results of these studies show that flavonoids are able to affect the main mechanisms/aspects of fibrogenesis *in vivo*. The results of animal experiments are supported by data obtained in experiments using flavonoids *in vitro*. Thus, baicalin has been shown to reduce the proliferation of rat pulmonary fibroblasts induced by bleomycin [45].

Flavonoids also have a protective effect on models of chronic obstructive pulmonary disease induced by cigarette smoke or its components. The observed effects of flavonoids are consistent with the results obtained in lung fibrosis models: these substances reduce inflammation, activate antioxidant defense mechanisms, and prevent cellular aging and cell death of the alveolar epithelium [46].

Nevertheless, such experimental studies have been conducted for more than 10 years, and clinical studies remain isolated.

Thus, there is a significant gap between the stages of preclinical development and clinical trials for this class of compounds.

Prospects for the use of flavonoids for the treatment of lung fibrosis

The probable reason for the slow introduction of flavonoid preparations into clinical practice, in addition to the difficulties of standardization and commercial component, may be the limited bioavailability of flavonoids.

Unlike other molecules included in the composition of drugs, flavonoids in unchanged form do not reach target organs when administered orally. When ingested in the form of aglycones, flavonoids undergo metabolic transformation in the intestine (including with the participation of microorganisms) and the liver; the initial forms are practically not detected in blood plasma [54]. The antioxidant activity of conjugated products entering the systemic circulation after methylation, sulfation and

Table 1. Flavonoid-type substances with proven *in vivo* antifibrotic activity

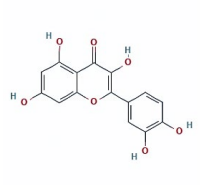
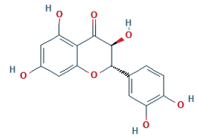
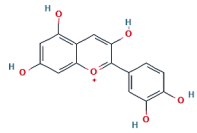
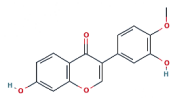
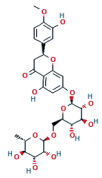
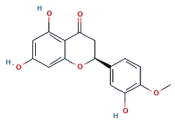
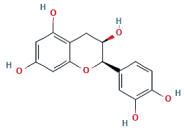
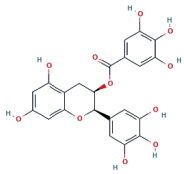
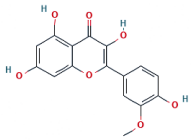
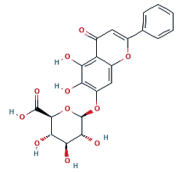
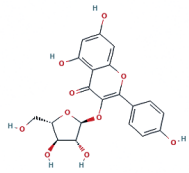
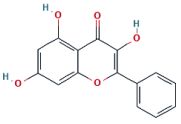
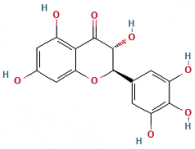
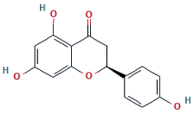
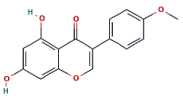
Substance formula	Substance	Model	Reference
	Quercetin	C57BL/6 mice; IT bleomycin	[34]
		Mice, SiO_2	[47]
		Wistar rats; IT bleomycin	[35]
	Dihydroquercetin	C57BL/6 rats; IT SiO_2	[48]
	Cyanidine	C57BL/6 mice; IT SiO_2	[49]
	Calicosin	C57BL/6 mice, IT bleomycin	[36]
	Hesperidin	Sprague-Dawley Rats; IP bleomycin	[42]
	Hesperidin	Wistar rats; IT SiO_2	[44]
	Epicatechin	NMRI mice; IT bleomycin	[43]
	Epigallocatechin gallate	C57BL/6 mice; solid particles intranasally	[50]
		Wistar rats; IT SiO_2	[51]

Table 1. Flavonoid-type substances with proven *in vivo* antifibrotic activity

Substance formula	Substance	Model	Reference
	Isoramnetin	C57BL/6 mice; IP bleomycin	[37]
	Baikal	Wistar rats; IT bleomycin	[45]
	Yuglanin	C57BL/6 mice; IT bleomycin	[40]
	Galangin	C57BL/6 mice; IT bleomycin	[52]
	Dihydromyricetin	C57BL/6 mice; IT bleomycin	[39]
	Naringenin	Balb/c mice; Mycoplasma infection	[53]
	Biochanin A	Wistar rats; IT bleomycin	[38]

Notes: IT stands for intratracheal, IP stands for intraperitoneal

glucuronidation is significantly reduced compared to that of the corresponding aglycones [7]; metabolites are rapidly excreted from the body. It is more likely that flavonoids, more precisely, the products of their metabolism, are able to activate the antioxidant defense system through the KEAP1-NRF2 pathway, which regulates the adaptive response to cellular stress [8].

Obviously, in order to increase the activity of flavonoids, it is necessary to provide ways and forms of administration that will avoid or minimize metabolic transformation in the intestine and liver. For the treatment of PF, these may be options for inhalation use or taking flavonoids in complexes with carriers. Such delivery systems include phytosomes (complexes of plant substances with phospholipids), lipid nanoparticles, polymer nanoparticles, and inorganic nanoparticles [7].

In particular, after administration of quercetin to mice as part of cationic lipid carriers, its higher content was observed in the lung, liver and kidneys compared with the control group that received free quercetin [55]. It was shown that apigenin more effectively inhibited the development of bleomycin-induced lung fibrosis in rats when it was administered to animals as part of polymer nanoparticles, compared with the substance in free form [56]

The use of dosage forms for inhalation has a number of advantages, such as the delivery of active substances directly to the lung, a relatively low content of substances in the systemic circulation, and ease of use [57]. In rats with induced PF, inhalation of pirfenidone or quintedanib gave the same therapeutic effect as oral administration, while the dose with topical application and, accordingly, the manifestations of side effects were significantly lower Rasooli et al. 2018; Surber et al. 2020, cit. according to [57]).

The bioavailability of naringenin complexes with hydroxypropyl-β-cyclodextrin was studied *in vivo*. It was found that the solubility of the flavonoid in the complex increases, and with intratracheal application, naringenin accumulates mainly in the lung [58]. It has also been shown that the bioavailability of naringenin in solid lipid particles is 2.5 times higher than in free form when administered intratracheal [59]. The effectiveness of naringenin-loaded phytoses based on the surfactant component dipalmitoyl phosphatidylcholine was demonstrated in a model of acute lung injury in rats [60].

Thus, the use of flavonoids in the composition of nanoparticles, liposomes and other carriers, including in the form of inhaled dosage forms, makes it possible to improve their bioavailability, as well as ensure the delivery of starting substances to the lung, rather than products of their metabolism.

CONCLUSION

Treatment of PF remains an urgent problem, because existing drugs only slow down the progression of this deadly disease, and their long-term use is often associated with serious side effects. In recent years, natural substances, in particular, flavonoids, have been studied as an alternative or accompanying therapy. Numerous animal and *in vitro* studies prove that flavonoids have antifibrotic properties. At the same time, due to the peculiarities of the metabolism of these substances in the mammalian body, with oral administration of flavonoids, they enter the lung only in small amounts in the form of secondary metabolites. The solution to this problem may be the development of delivery systems such as liposomes, as well as dosage forms for topical use.

References

1. Wijsenbeek M, Cottin V. Spectrum of Fibrotic Lung Diseases. N Engl J Med. 2020 Sep 3;383(10):958–968. https://doi.org/10.1056/nejmra2005230
2. Dygai AM, Skurikhin EG, Krupin VA. Pulmonary fibrosis and stem cells: new treatment approaches. Moscow: Publishing House of the Russian Academy of Sciences, 2018, 200 p. (In Russ.).
3. Zheng Q, Cox IA, Campbell JA, Xia Q, Otahal P, de Graaff B, et al. Mortality and survival in idiopathic pulmonary fibrosis: a systematic review and meta-analysis. ERJ Open Res. 2022 Jan;8(1):00591–2021. https://doi.org/10.1183/23120541.00591-2021
4. Thong L, McElduff EJ, Henry MT. Trials and Treatments: An Update on Pharmacotherapy for Idiopathic Pulmonary Fibrosis. Life (Basel). 2023 Feb 10;13(2):486. https://doi.org/10.3390/LIFE13020486

5. Kato M, Sasaki S, Tateyama M, Arai Y, Motomura H, Sumiyoshi I, et al. Clinical Significance of Continuable Treatment with Nintedanib Over 12 Months for Idiopathic Pulmonary Fibrosis in a Real-World Setting. Drug Des Devel Ther. 2021;15:223–230. https://doi.org/10.2147/DDDT.S284819
6. Zhou F, Gu K, Zhou Y. Flavonoid intake is associated with lower all-cause and disease-specific mortality: The National Health and Nutrition Examination Survey 2007-2010 and 2017-2018. Front Nutr. 2023;10:1046998. https://doi.org/10.3389/fnut.2023.1046998
7. Zverev YF, Rykunova AY. Modern Nanocarriers as a Factor in Increasing the Bioavailability and Pharmacological Activity of Flavonoids. Appl Biochem Microbiol. 2022;58(9):1002–1020. https://doi.org/10.1134/S0003683822090149
8. Golubev AG, Gubareva EA, Anisimov VN, Fedoros EI. Polyphenols of natural origin against age-related disorders of tissue homeostasis. Advances in Gerontology. 2023;36(4):555–568. (In Russ.). https://doi.org/10.34922/AE.2023.36.4.014, EDN: UKTAJY
9. Chapman HA, Wei Y, Montas G, Leong D, Golden JA, Trinh BN, et al. Reversal of TGFβ1-Driven Profibrotic State in Patients with Pulmonary Fibrosis. N Engl J Med. 2020 Mar 12;382(11):1068–1070. https://doi.org/10.1056/NEJMC1915189
10. Justice JN, Nambiar AM, Tchkonia T, LeBrasseur NK, Pascual R, Hashmi SK, et al. Senolytics in idiopathic pulmonary fibrosis: Results from a first-in-human, open-label, pilot study. EBioMedicine. 2019 Feb;40:554–563. https://doi.org/10.1016/j.ebiom.2018.12.052
11. Avdeev SN, Chikina SYu, Tyurin IE, Belevskiy AS, Terpigorev SA, Anan'yeva LP, et al. Chronic fibrosing progressing interstitial lung disease: a decision of Multidisciplinary Expert Board. Pulmonologiya. 2021;31(4):505–510. (In Russ.). https://doi.org/10.18093/0869-0189-2021-31-4-505-510, EDN: OKQQCQ
12. Sauleda J, Núñez B, Sala E, Soriano JB. Idiopathic Pulmonary Fibrosis: Epidemiology, Natural History, Phenotypes. Med Sci (Basel). 2018 Nov 29;6(4):110. https://doi.org/10.3390/MEDSCI6040110
13. Maher TM, Bendstrup E, Dron L, Langley J, Smith G, Khalid JM, et al. Global incidence and prevalence of idiopathic pulmonary fibrosis. Respir Res. 2021 Jul 7;22(1):197. https://doi.org/10.1186/S12931-021-01791-Z
14. Olson AL, Patnaik P, Hartmann N, Bohn RL, Garry EM, Wallace L. Prevalence and Incidence of Chronic Fibrosing Interstitial Lung Diseases with a Progressive Phenotype in the United States Estimated in a Large Claims Database Analysis. Adv Ther. 2021 Jul;38(7):4100–4114. https://doi.org/10.1007/s12325-021-01786-8
15. Duong-Quy S, Vo-Pham-Minh T, Tran-Xuan Q, Huynh-Anh T, Vo-Van T, Vu-Tran-Thien Q, et al. Post-COVID-19 Pulmonary Fibrosis: Facts-Challenges and Futures: A Narrative Review. Pulm Ther. 2023 Sep;9(3):295–307. https://doi.org/10.1007/s41030-023-00226-y
16. Parimon T, Yao C, Stripp BR, Noble PW, Chen P. Alveolar Epithelial Type II Cells as Drivers of Lung Fibrosis in Idiopathic Pulmonary Fibrosis. Int J Mol Sci. 2020 Mar 25;21(7):2269. https://doi.org/10.3390/IJMS21072269
17. Hung C. Origin of Myofibroblasts in Lung Fibrosis. Curr Tissue Microenviron Rep. 2020 Dec 1;1(4):155–162. https://doi.org/10.1007/s43152-020-00022-9
18. Hinz B, Lagares D. Evasion of apoptosis by myofibroblasts: a hallmark of fibrotic diseases. Nat Rev Rheumatol. 2020 Jan;16(1):11–31. https://doi.org/10.1038/s41584-019-0324-5
19. Miles T, Hoyne GF, Knight DA, Fear MW, Mutsaers SE, Prêle CM. The contribution of animal models to understanding the role of the immune system in human idiopathic pulmonary fibrosis. Clin Transl Immunology. 2020;9(7):e1153. https://doi.org/10.1002/CTI2.1153
20. Liu T, De Los Santos FG, Phan SH. The Bleomycin Model of Pulmonary Fibrosis. Methods Mol Biol. 2017;1627:27–42. https://doi.org/10.1007/978-1-4939-7113-8_2
21. Confalonieri P, Volpe MC, Jacob J, Maiocchi S, Salton F, Ruaro B, et al. Regeneration or Repair? The Role of Alveolar Epithelial Cells in the Pathogenesis of Idiopathic Pulmonary Fibrosis (IPF). Cells. 2022 Jun 30;11(13):2095. https://doi.org/10.3390/CELLS11132095
22. Chanda D, Otoupalova E, Smith SR, Volckaert T, De Langhe SP, Thannickal VJ. Developmental pathways in the pathogenesis of lung fibrosis. Mol Aspects Med. 2019 Feb;65:56–69. https://doi.org/10.1016/J.MAM.2018.08.004
23. Parimon T, Yao C, Habiel DM, Ge L, Bora SA, Brauer R, et al. Syndecan-1 promotes lung fibrosis by regulating epithelial reprogramming through extracellular vesicles. JCI Insight. 2019 Aug 8;5(17):e129359. https://doi.org/10.1172/jci.insight.129359
24. Herrera J, Henke CA, Bitterman PB. Extracellular matrix as a driver of progressive fibrosis. J Clin Invest. 2018 Jan 2;128(1):45–53. https://doi.org/10.1172/JCI93557

25. Selman M, Pardo A. Fibroageing: An ageing pathological feature driven by dysregulated extracellular matrix-cell mechanobiology. Ageing Res Rev. 2021 Sep;70:101393. https://doi.org/https://doi.org/10.1016/j.arr.2021.101393
26. Mebratu YA, Soni S, Rosas L, Rojas M, Horowitz JC, Nho R. The aged extracellular matrix and the profibrotic role of senescence-associated secretory phenotype. Am J Physiol Cell Physiol. 2023 Sep 1;325(3):C565– C579. https://doi.org/10.1152/AJPCELL.00124.2023
27. Shochet G, Bardenstein-Wald B, McElroy M, Kukuy A, Surber M, Edelstein E, et al. Hypoxia Inducible Factor 1A Supports a Pro-Fibrotic Phenotype Loop in Idiopathic Pulmonary Fibrosis. Int J Mol Sci. 2021 Mar 24;22(7):3331. https://doi.org/10.3390/ijms22073331
28. Saito S, Alkhatib A, Kolls JK, Kondoh Y, Lasky JA. Pharmacotherapy and adjunctive treatment for idiopathic pulmonary fibrosis (IPF). J Thorac Dis. 2019 Sep;11(Suppl 14):S1740–S1754. https://doi.org/10.21037/jtd.2019.04.62
29. Petnak T, Lertjitbanjong P, Thongprayoon C, Moua T. Impact of Antifibrotic Therapy on Mortality and Acute Exacerbation in Idiopathic Pulmonary Fibrosis: A Systematic Review and Meta-Analysis. Chest. 2021 Nov;160(5):1751–1763. https://doi.org/10.1016/J.CHEST.2021.06.049
30. Pitre T, Mah J, Helmeczi W, Khalid MF, Cui S, Zhang M, et al. Medical treatments for idiopathic pulmonary fibrosis: a systematic review and network meta-analysis. Thorax. 2022 Dec;77(12):1243–1250. https://doi.org/10.1136/THORAXJNL-2021-217976
31. Wei Y, Dong W, Jackson J, Ho TC, Le Saux CJ, Brumwell A, et al. Blocking LOXL2 and TGFβ1 signalling induces collagen I turnover in precision-cut lung slices derived from patients with idiopathic pulmonary fibrosis. Thorax. 2021 Jul;76(7):729–732. https://doi.org/10.1136/THORAXJNL-2020-215745
32. Moore BB, Lawson WE, Oury TD, Sisson TH, Raghavendran K, Hogaboam CM. Animal models of fibrotic lung disease. Am J Respir Cell Mol Biol. 2013 Aug;49(2):167–117. https://doi.org/10.1165/RCMB.2013-0094TR
33. Gul A, Yang F, Xie C, Du W, Mohammadtursun N, Wang B, et al. Pulmonary fibrosis model of mice induced by different administration methods of bleomycin. BMC Pulm Med. 2023 Mar 21;23(1):91. https://doi.org/10.1186/s12890-023-02349-z
34. Boots AW, Veith C, Albrecht C, Bartholome R, Drittij MJ, Claessen SMH, et al. The dietary antioxidant quercetin reduces hallmarks of bleomycin-induced lung fibrogenesis in mice. BMC Pulm Med. 2020 Apr 29;20(1):112. https://doi.org/10.1186/S12890-020-1142-X
35. Mehrzadi S, Hosseini P, Mehrabani M, Siahpoosh A, Goudarzi M, Khalili H, et al. Attenuation of Bleomycin-Induced Pulmonary Fibrosis in Wistar Rats by Combination Treatment of Two Natural Phenolic Compounds: Quercetin and Gallic Acid. Nutr Cancer. 2021;73(10):2039–2049. https://doi.org/10.1080/01635581.2020.1820053
36. Liu H, Bai X, Wei W, Li Z, Zhang Z, Tan W, et al. Calycosin Ameliorates Bleomycin-Induced Pulmonary Fibrosis via Suppressing Oxidative Stress, Apoptosis, and Enhancing Autophagy. Evid Based Complement Alternat Med. 2022;2022:9969729. https://doi.org/10.1155/2022/9969729
37. Zheng Q, Tong M, Ou B, Liu C, Hu C, Yang Y. Isorhamnetin protects against bleomycin-induced pulmonary fibrosis by inhibiting endoplasmic reticulum stress and epithelial-mesenchymal transition. Int J Mol Med. 2019 Jan;43(1):117–126. https://doi.org/10.3892/IJMM.2018.3965
38. Andugulapati SB, Gourishetti K, Tirunavalli SK, Shaikh TB, Sistla R. Biochanin-A ameliorates pulmonary fibrosis by suppressing the TGF-β mediated EMT, myofibroblasts differentiation and collagen deposition in in vitro and in vivo systems. Phytomedicine. 2020 Nov;78:153298. https://doi.org/10.1016/J.PHYMED.2020.153298
39. Xiao T, Wei Y, Cui M, Li X, Ruan H, Zhang L, et al. Effect of dihydromyricetin on SARS-CoV-2 viral replication and pulmonary inflammation and fibrosis. Phytomedicine. 2021 Oct;91:153704. https://doi.org/10.1016/J.PHYMED.2021.153704
40. Sun SC, Han R, Hou SS, Yi HQ, Chi SJ, Zhang AH. Juglanin alleviates bleomycin-induced lung injury by suppressing inflammation and fibrosis via targeting sting signaling. Biomed Pharmacother. 2020 Jul;127:110119. https://doi.org/10.1016/J.BIOPHA.2020.110119
41. Ma C, Lyu M, Deng C, Liu X, Cui Y, Shen Y, et al. Cyanidin-3-galactoside ameliorates silica-induced pulmonary fibrosis by inhibiting fibroblast differentiation via Nrf2/p38/Akt/NOX4. Journal of Functional Foods. 2022 May 1;92:105034. https://doi.org/10.1016/j.jff.2022.105034
42. Zhou Z, Kandhare AD, Kandhare AA, Bodhankar SL. Hesperidin ameliorates bleomycin-induced experimental pulmonary fibrosis via inhibition of TGF-beta1/Smad3/AMPK and IkappaBalpha/NF-kappaB pathways. EXCLI J. 2019;18:723–745. https://doi.org/10.17179/excli2019-1094

43. Shariati S, Kalantar H, Pashmforoosh M, Mansouri E, Khodayar MJ. Epicatechin protective effects on bleomycin-induced pulmonary oxidative stress and fibrosis in mice. Biomed Pharmacother. 2019 Jun;114:108776. https://doi.org/10.1016/J.BIOPHA.2019.108776
44. Li S, Shao L, Fang J, Zhang J, Chen Y, Yeo AJ, et al. Hesperetin attenuates silica-induced lung injury by reducing oxidative damage and inflammatory response. Exp Ther Med. 2021 Apr;21(4):297. https://doi.org/10.3892/ETM.2021.9728
45. Zhao H, Li C, Li L, Liu J, Gao Y, Mu K, et al. Baicalin alleviates bleomycin induced pulmonary fibrosis and fibroblast proliferation in rats via the PI3K/AKT signaling pathway. Mol Med Rep. 2020 Jun;21(6):2321–2334. https://doi.org/10.3892/MMR.2020.11046
46. Yang Y, Jin X, Jiao X, Li J, Liang L, Ma Y, et al. Advances in Pharmacological Actions and Mechanisms of Flavonoids from Traditional Chinese Medicine in Treating Chronic Obstructive Pulmonary Disease. Evid Based Complement Alternat Med. 2020;2020:8871105. https://doi.org/10.1155/2020/8871105
47. Geng F, Xu M, Zhao L, Zhang H, Li J, Jin F, et al. Quercetin Alleviates Pulmonary Fibrosis in Mice Exposed to Silica by Inhibiting Macrophage Senescence. Front Pharmacol. 2022;13:912029. https://doi.org/10.3389/fphar.2022.912029
48. Yuan L, Sun Y, Zhou N, Wu W, Zheng W, Wang Y. Dihydroquercetin Attenuates Silica-Induced Pulmonary Fibrosis by Inhibiting Ferroptosis Signaling Pathway. Front Pharmacol. 2022;13:845600. https://doi.org/10.3389/fphar.2022.845600
49. Cui Y, Zhao J, Chen J, Kong Y, Wang M, Ma Y, et al. Cyanidin-3-galactoside from Aronia melanocarpa ameliorates silica-induced pulmonary fibrosis by modulating the TGF-β/mTOR and NRF2/HO-1 pathways. Food Sci Nutr. 2022 Aug;10(8):2558–2567. https://doi.org/10.1002/FSN3.2861
50. Zhongyin Z, Wei W, Juan X, Guohua F. Epigallocatechin Gallate Relieved PM2.5-Induced Lung Fibrosis by Inhibiting Oxidative Damage and Epithelial-Mesenchymal Transition through AKT/mTOR Pathway. Oxid Med Cell Longev. 2022;2022:7291774. https://doi.org/10.1155/2022/7291774
51. Adamcakova J, Balentova S, Barosova R, Hanusrichterova J, Mikolka P, Prso K, et al. Effects of Green Tea Polyphenol Epigallocatechin-3-Gallate on Markers of Inflammation and Fibrosis in a Rat Model of Pulmonary Silicosis. Int J Mol Sci. 2023 Jan 17;24(3):1857. https://doi.org/10.3390/ijms24031857
52. Wang L, Liu H, He Q, Gan C, Li Y, Zhang Q, et al. Galangin ameliorated pulmonary fibrosis in vivo and in vitro by regulating epithelial-mesenchymal transition. Bioorg Med Chem. 2020 Oct 1;28(19):115663. https://doi.org/10.1016/J.BMC.2020.115663
53. Lin Y, Tan D, Kan Q, Xiao Z, Jiang Z. The Protective Effect of Naringenin on Airway Remodeling after Mycoplasma Pneumoniae Infection by Inhibiting Autophagy-Mediated Lung Inflammation and Fibrosis. Mediators Inflamm. 2018;2018:8753894. https://doi.org/10.1155/2018/8753894
54. Thilakarathna SH, Rupasinghe HPV. Flavonoid bioavailability and attempts for bioavailability enhancement. Nutrients. 2013 Aug 28;5(9):3367–3387. https://doi.org/10.3390/NU5093367
55. Liu L, Tang Y, Gao C, Li Y, Chen S, Xiong T, et al. Characterization and biodistribution in vivo of quercetin-loaded cationic nanostructured lipid carriers. Colloids Surf B Biointerfaces. 2014 Mar 1;115:125–131. https://doi.org/10.1016/j.colsurfb.2013.11.029
56. Zhang J, Chao L, Liu X, Shi Y, Zhang C, Kong L, et al. The potential application of strategic released apigenin from polymeric carrier in pulmonary fibrosis. Exp Lung Res. 2017;43(9–10):359–369. https://doi.org/10.1080/01902148.2017.1380086
57. Xie X-F, Lu Y, Chen X-S, Muhetaer G, Tao H, Li H, Liu H-J. Inhalation therapy for pulmonary fibrosis: chemical medicines and herbal medicines. TMR Modern Herb Med. 2023;6(3):14. https://doi.org/10.53388/MHM2023014
58. Guan M, Shi R, Zheng Y, Zeng X, Fan W, Wang Y, et al. Characterization, in Vitro and in Vivo Evaluation of Naringenin-Hydroxypropyl-ß-Cyclodextrin Inclusion for Pulmonary Delivery. Molecules. 2020 Jan 28;25(3):554. https://doi.org/10.3390/MOLECULES25030554
59. Ji P, Yu T, Liu Y, Jiang J, Xu J, Zhao Y, et al. Naringenin-loaded solid lipid nanoparticles: preparation, controlled delivery, cellular uptake, and pulmonary pharmacokinetics. Drug Des Devel Ther. 2016;10:911–925. https://doi.org/10.2147/DDDT.S97738
60. Yu Z, Liu X, Chen H, Zhu L. Naringenin-Loaded Dipalmitoylphosphatidylcholine Phytosome Dry Powders for Inhaled Treatment of Acute Lung Injury. J Aerosol Med Pulm Drug Deliv. 2020 Aug;33(4):194–204. https://doi.org/10.1089/jamp.2019.1569

Information about authors:

Ekaterina A. Gubareva ✉ – Cand. Sci. (Biol.), senior researcher, N. N. Petrov National Medicine Research Center of Oncology, St. Petersburg, Russian Federation
ORCID: https://orcid.org/0000-0002-9212-6086, SPIN: 5556-8242, AuthorID: 895429, ResearcherID: AAD-2072-2020, Scopus Author ID: 56909987000

Alexander L. Semenov – Cand. Sci. (Med.), MD, senior researcher, N. N. Petrov National Medicine Research Center of Oncology, St. Petersburg, Russian Federation
ORCID: https://orcid.org/0000-0002-5190-0629, SPIN: 4301-8679, AuthorID: 900704, ResearcherID: S-1484-2016, Scopus Author ID: 16307589600

Contribution of the authors:

Gubareva E. A. – article concept, writing source text, collecting material, article design;
Semenov A. L. – text revision, scientific and technical editing.

South Russian Journal of Cancer. 2024. Vol. 5, No. 4. P. 58-70
https://doi.org/10.37748/2686-9039-2024-5-4-7
https://elibrary.ru/jbckse
REVIEW

The role of tumor stem cells and the immune microenvironment in the pathogenesis of lung cancer: mechanisms of interaction and research prospects

D. A. Kharagezov, A. A. Antonyan✉, E. Yu. Zlatnik, A. B. Sagakyants, E. A. Mirzoyan, T. G. Ayrapetova, I. A. Leyman, A. G. Milakin, O. N. Stateshny, K. D. Iozefi, M. A. Homidov, E. A. Alekseev

National Medical Research Centre for Oncology, Rostov-on-Don, Russian Federation
✉ arturantonyan12@gmail.com

ABSTRACT

Despite significant advances in the treatment of malignant neoplasms, the issue of therapy resistance mediated by cancer stem cells (CSCs) necessitates the development of new treatment strategies. Studying the role of CSCs and the immune microenvironment in the pathogenesis of cancer, particularly non-small cell lung cancer (NSCLC), is a pressing issue in modern oncology. This paper is based on an extensive analysis of recent research and aims to study the mechanisms underlying the development of NSCLC.

The origin of CSCs, their markers, and the main signaling pathways involved in regulating their activity are considered. Special attention is paid to the influence of CSCs on the progression of lung cancer and the mechanisms underlying their therapy-mediated resistance. Various approaches to treating lung cancer targeting CSCs, focusing on targeted therapy aimed at specific molecular targets, are highlighted.

The important role of the tumor immune microenvironment in the pathogenesis of lung cancer and its impact on CSCs is emphasized. Mechanisms of immune response regulation in tumors and the potential use of immunotherapy to improve lung cancer treatment outcomes are discussed. The article also reviews modern diagnostic and treatment methods, including molecular-genetic and immunohistochemical approaches.

This paper work represents a review of current knowledge on the mechanisms of lung cancer development and is significant for understanding tumor biology and developing new treatment methods. The need for an interdisciplinary approach and comprehensive use of modern diagnostic and therapeutic methods to improve the prognosis and survival rates of NSCLC patients is emphasized. Special attention is given to the prospects of using combined therapeutic approaches, including targeted drugs and immunotherapy, aimed at suppressing CSC activity and modifying the tumor microenvironment.

In conclusion, a deep understanding of the molecular mechanisms regulating CSC activity and their interaction with the tumor microenvironment opens new opportunities for developing effective treatment strategies. This review underscores the need for further research in this area to ensure more successful treatment and improved quality of life for lung cancer patients.

Keywords: cancer stem cells, immune microenvironment, lung cancer, non-small cell lung cancer, therapy resistance, targeted therapy, immunotherapy

For citation: Kharagezov D. A., Antonyan A. A., Zlatnik E. Yu., Sagakyants A. B., Mirzoyan E. A., Ayrapetova T. G., Leyman I. A., Milakin A. G., Stateshny O. N., Iozefi K. D., Homidov M. A., Alekseev E. A. The role of tumor stem cells and the immune microenvironment in the pathogenesis of lung cancer: mechanisms of interaction and research prospects. South Russian Journal of Cancer. 2024; 5(4): 58-70. https://doi.org/10.37748/2686-9039-2024-5-4-7, https://elibrary.ru/jbckse

For correspondence: Artur A. Antonyan – PhD student of the 1st year, National Medical Research Centre for Oncology, Rostov-on-Don, Russian Federation
Address: 63 14 line str., Rostov-on-Don 344037, Russian Federation
E-mail: arturantonyan12@gmail.com
ORCID: https://orcid.org/0000-0001-6449-7026
ResearcherID: JWQ-0734-2024

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 08.06.2024; approved after reviewing 30.10.2024; accepted for publication 13.11.2024

Южно-Российский онкологический журнал. 2024. Т. 5, № 4. С. 58-70
https://doi.org/10.37748/2686-9039-2024-5-4-7
https://elibrary.ru/jbckse
3.1.6. Онкология, лучевая терапия
ОБЗОР

Роль опухолевых стволовых клеток и иммунного микроокружения в патогенезе рака легкого: механизмы взаимодействия и перспективы исследований

Д. А. Харагезов, А. А. Антонян✉, Е. Ю. Златник, А. Б. Сагакянц, Э. А. Мирзоян, Т. Г. Айрапетова, И. А. Лейман, А. Г. Милакин, О. Н. Статешный, К. Д. Иозефи, М. А. Хомидов, Э. А. Алексеев

ФГБУ «Национальный медицинский исследовательский центр онкологии» Министерства здравоохранения Российской Федерации, г. Ростов-на-Дону, Российская Федерация
✉ arturantonyan12@gmail.com

РЕЗЮМЕ

Несмотря на значительные успехи в лечении злокачественных новообразований, проблема резистентности к терапии, опосредованной опухолевыми стволовыми клетками (ОСК), диктует необходимость разработки новых стратегий лечения. Изучение роли ОСК и иммунного микроокружения в патогенезе рака, особенно немелкоклеточного рака легкого (НМРЛ), является актуальным вопросом современной онкологии. Настоящая работа основана на обширном анализе последних исследований и направлена на изучение механизмов, лежащих в основе развития НМРЛ. Рассматривается происхождение ОСК, их маркеры и основные сигнальные пути, участвующие в регуляции активности данного пула клеток. Особое внимание уделяется влиянию ОСК на прогрессирование рака легкого и механизмам, обусловливающим устойчивость к терапии. Освещаются различные подходы к лечению рака легкого, ориентированные на ОСК, с акцентом на таргетную терапию, направленную на специфические молекулярные мишени.

Отмечается важная роль иммунного микроокружения опухоли в патогенезе рака легкого и его влияния на ОСК. Обсуждаются механизмы регуляции иммунных реакций в опухоли и потенциал использования иммунотерапии для улучшения результатов лечения рака легкого. В статье также рассматриваются современные методы диагностики и лечения, включающие молекулярно-генетические и иммуногистохимические подходы.

Работа представляет собой обзор современных знаний о механизмах развития рака легкого и имеет важное значение для понимания биологии опухолей и разработки новых методов лечения. Подчеркивается необходимость междисциплинарного подхода и комплексного использования современных диагностических и терапевтических методов для улучшения прогнозов и выживаемости пациентов с НМРЛ. Особое внимание уделено перспективам использования комбинированных терапевтических подходов, включающих таргетные препараты и иммунотерапию, направленные на подавление активности ОСК и модификацию опухолевого микроокружения.

В заключение, глубокое понимание молекулярных механизмов, регулирующих деятельность ОСК, и их взаимодействие с микроокружением опухоли открывает новые возможности для разработки эффективных стратегий лечения. Данный обзор подчеркивает необходимость дальнейших исследований в этой области, чтобы обеспечить более успешное лечение и повышение качества жизни пациентов с раком легкого.

Ключевые слова: опухолевые стволовые клетки, иммунное микроокружение, рак легкого, немелкоклеточный рак легкого, резистентность к терапии, таргетная терапия, иммунотерапия

Для цитирования: Харагезов Д. А., Антонян А. А., Златник Е. Ю., Сагакянц А. Б., Мирзоян Э. А., Айрапетова Т. Г., Лейман И. А., Милакин А. Г., Статешный О. Н., Иозефи К. Д., Хомидов М. А., Алексеев Э. А. Роль опухолевых стволовых клеток и иммунного микроокружения в патогенезе рака легкого: механизмы взаимодействия и перспективы исследований. Южно-Российский онкологический журнал. 2024; 5(4): 58-70. https://doi.org/10.37748/2686-9039-2024-5-4-7, https://elibrary.ru/jbckse

Для корреспонденции: Антонян Артур Андрясович – аспирант 1-го года обучения, 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: arturantonyan12@gmail.com
ORCID: https://orcid.org/0000-0001-6449-7026
ResearcherID: JWQ-0734-2024

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 08.06.2024; одобрена после рецензирования 30.10.2024; принята к публикации 13.11.2024

INTRODUCTION

Lung cancer is one of the main problems of modern oncology, and it is hoped that progress in treatment can be achieved by improving our understanding of the molecular basis and biology of the tumor, especially at the level of cells that initiate the tumor process. The most common type of lung cancer is its non–small cell variants (NSCLC), which account for about 90 % of lung cancers, the rest are small cell lung cancer (SCLC). NSCLC includes three histological subtypes: adenocarcinoma, squamous cell carcinoma and large cell carcinoma. In most patients with NSCLC, the diagnosis is made at a late stage, when various treatment methods are ineffective [1].

In 2015, a new classification of lung tumors was proposed by the World Health Organization [2], which includes appropriate histopathological and immunohistochemical data, which can be obtained not only from surgical material, but also from biopsies and cytological material [1, 2]. This is especially important due to the fact that about 70 % of patients with lung cancer are in the late stages of the disease, when the process is considered inoperable [1, 2]. For resectable lung tumors, it is important to diagnose tumors *in situ* and minimally invasive operations, in which the probability of recurrence-free survival after complete resection is 100 % [2].

However, in most cases, clinicians are dealing with locally advanced NSCLC, the recurrence and generalization of which, even after the successful surgical stage of treatment, is the main cause of death. These processes, as well as the development of chemo- and radioresistance, according to modern concepts, are not least associated with the presence of stem cells (CSC) in the tumor, a minor subpopulation that ensures their preservation and survival. Since CSC biomarkers can be used for diagnosis, targeted therapy and prediction of the course of the disease, assessing the significance of known ones and searching for new ones seems relevant. Potential markers for NSCLC include surface markers (CD44, CD133, EpCAM, ABCG2), as well as intracellular markers (ALDH, SOX2). The literature discusses not only their diagnostic and prognostic significance in NSCLC, but also the most informative methods of determination, including molecular genetic and immunohistochemical [3, 4], as well as the possibility of using them as targets for therapy [5, 6]. Currently, the noticeable increase in the number of publications on CSC research indicates the relevance of this topic in the scientific community. The valuable scientific data provided by the literature on the mechanisms of oncogenesis and the prospects for the treatment of lung cancer based on them determine the need for a more in-depth scientific analysis of the role of CSC in the pathogenesis of NSCLC. The modern literature provides numerous data on the biology of CSC, their role in the progression of NSCLC, and the development of its resistance to various treatment methods [5, 6].

The purpose of the review is to analyze the current level of scientific knowledge about the role of CSC in NSCLC and the clinical use of these data. The main focus is on identifying the key mechanisms of these cells' involvement in oncogenesis, their interaction with the immune microenvironment of the tumor, as well as developing treatment strategies aimed at CSC in NSCLC. The data obtained as a result of the review, in our opinion, can serve as a foundation for further research and development of promising treatments for NSCLC.

CSC in NSCLC: origin, markers, signaling pathways, role in progression

According to modern concepts, cancer stem cells (CSC) arise from normal tissue-specific stem cells of the original tissues; their main function is to maintain and regulate the processes of growth, development and repair of tissues in the body. CSC are capable of self-renewal, differentiation [7] and proliferation [8] and cause such adverse properties as: chemoresistance, recurrence and metastasis [7]. As a rule, a high number of CSC is associated with aggressive tumor growth and unfavorable clinical outcomes [8], although CSC themselves have low proliferative activity. Reviews of CSC note their common characteristics for various malignant tumors involved in the development of resistance to therapy and are devoted to the development of new therapeutic strategies [7–10].

Inducing epithelial-mesenchymal transition transcription factors (EMF-FT), including SNAIL and SLUG, and induced by signaling pathways such as TGFß, Wnt and Notch, tumor cells begin to show

distinctive signs of CSC: oncogenicity, invasiveness and resistance to basic treatments [11]. Other common signaling pathways involved in CSC include Hedgehog (Hh), PI3K/Akt/mTOR, and NF-κβ [12]. Although many of these pathways are also observed in normal cells and non-stem cancer cells [13], their altered activity, along with certain membrane markers and transcription factors, is a distinctive feature of CSC. Some of these characteristics, such as the high expression of CD44+, CD133+, ATP-binding cassette transporters (ABC), epithelial cell adhesion molecules (EpCAM), aldehyde dehydrogenase 1 (ALDH1), and transcription factors Oct4 and Sox2, are common to CSC in many forms of cancer [11]. Recognition of such similarities may reveal new therapeutic possibilities for influencing common markers or pathways, and thus contribute to the development of effective treatments targeting CSC.

Identification of the origin of tumor stem cells (CSC) in the lungs is a difficult task, since the epithelium of the trachea and bronchioles is at rest and has low proliferative activity [11]. The most common hypothesis states that CSC arise from normal tissue-specific stem cells. Squamous cell lung cancer originates from the basal cells of the proximal respiratory tract (trachea and bronchi) [12]. Clara cells in squamous cell lung cancer are also able to exhibit stem properties, and adenocarcinoma is associated with normal stem cells from the junction of bronchoalveolar ducts [12].

Although the available knowledge about the functions of lung CSC is limited, a number of CSC markers belonging to differentiation clusters (CD) have been proposed. Many studies have confirmed the presence of the following molecules on lung CSC: CD133, CD44, CD90, EpCAM, CXCR4 [14, 15]. However, it should be noted that impaired expression of these markers is characteristic not only of NSCLC, but also of many types of cancers.

EpCAM is a transmembrane glycoprotein expressed in most human carcinomas; high expression is noted in rapidly proliferating tumors of epithelial origin [12].

CD133 is a marker widely used to identify stem cells in both tumor and normal tissues. The CD133 transcription process is regulated by five promoters, and the 5P5 promoter plays a crucial role in CD133 expression in the CSC [16]. Some studies have characterized CD133+ cells in NSCLC [11, 15]. For example, Eramo et al. The presence of CD133 in NSCLC was detected in a small amount of less than 1 % [16]. CD133+ cells were able to form tumor spheroids *in vitro* in about 30 % of cases when grown in a serum-free medium; CD133+ cells derived from tumor spheroids are capable of inducing tumors with histological signs similar to those of the original tumor when inoculated to immunodeficient mice [16]. Moreover, CD133+ cells show resistance to chemotherapy due to the expression of high levels of ATP-binding G2 [17].

CD44 (P-glycoprotein 1), a transmembrane type I glycoprotein, belongs to the family of cell adhesion molecules, is a receptor for hyaluronic acid, when interacting with which cell detachment, metastasis and invasion can occur. CD44 is responsible for various functions such as cell differentiation, survival, migration, proliferation. Studies have demonstrated that CD44 plays a crucial role in ensuring self-renewal and resistance to apoptosis of CSC [11, 18]. Mutations in the key regulator of apoptosis, the p53 gene, may be associated with high CD44 expression in pancreatic cancer [19]. CD44+ adenocarcinoma and squamous cell lung cancer cells demonstrate the ability to form spheroid bodies *in vitro* [20] and lead to tumor formation *in vivo* when administered to mice with immunodeficiency [14, 21].

Studies have shown that in lung cancer, CD44 expression in NSCLC cells is higher than in SCLC, and in squamous cell lung cancer its highest level was observed [22]. CD44 regulates several signaling pathways contributing to cancer progression, including Notch, Hedgehog (HH), Wnt, STAT3, Hippo, JNK and RhoGTPase, and It is a co-receptor involved in the signaling pathways of tyrosine kinase receptors [23, 24]. In addition, CD44 is a key mediator of adhesion between endothelial cells, while playing an important role in pathological angiogenesis [25]. CD44 can also promote tumor proliferation and evasion of immunity by stimulating PD-L1 expression on the surface of tumor cells [26]. Cells coexpressing CD44 and ALDH, which is typical for squamous cell lung cancer, always exhibit a high ability for self-renewal, increased migration and tumorigenicity [27].

CD90 is a glycoprotein anchored by glycosylphosphatidylinositol, expressed mainly in leukocytes and participates in cell-matrix and cell-cell interactions.

Although CD90 is known as a marker for various types of CSC, its potential role as a marker for NSCLC has not yet been fully described [11, 28]. It has been reported that CD44 and CD90 coexpressed CSC can be detected in primary pancreatic cancer cell lines [19]. Mutations activating CD90 expression are not described in the literature, however, in a mouse model it has been shown that DNA methylation plays a role in stimulating the expression of this molecule. Serial xenotransplantation of EpCAM+CD90+ NSCLC cells (adenocarcinoma and squamous cell carcinoma) to mice with immunodeficiency revealed rapid growth of these cells during heterotopic grafting [14].

CXCR4 is a chemokine receptor present on the surface of hematopoietic stem cells involved in the formation of premetastatic niches in the bone marrow [29]. The CXCR4/CXCL12 pathway plays a role in tumor metastasis, induction of angiogenesis, and development of resistance to apoptosis. Moreover, CXCR4 is present on circulating tumor cells released from tumors into peripheral blood, which induces their spread to distant CXCL12-positive sites [30]. The expression of CXCR4 is regulated by the nuclear respiratory factor NRF, a mutation in which can lead to higher expression of CXCR4 [31]. CXCR4+ cells isolated from NSCLC lines exhibited the properties of CSC *in vitro*: they formed tumor spheroids, had the ability to self-renew, and demonstrated radiation resistance [32].

Taking into account the described properties of CSC, their determination in tumors, in particular lung tumors, is an urgent scientific and clinical task [11, 33].

Due to the fact that CSC markers can also be expressed on normal stem cells necessary for self-renewal and tissue regeneration, the belonging of stem cells to tumor cells can be determined not only by the expression of membrane markers, transcription factors and signaling pathways, but also by the results of some functional tests, which, despite their certain complexity, They are informative, especially for research purposes, as well as for conducting preclinical trials of potential drugs aimed at CSC. In addition to the mentioned spheroid formation test, organoids obtained from patients with NSCLC can become a tool for such studies, due to their ability to recreate the tissue architecture and maintain genomic changes in primary tumors during long-term *in vitro* growth [34]. The organoid culture method allows CSC to be propagated *in vitro*, reflecting the complexity of tumor formation using tumor tissues. Moreover, the culture of organoids allows for the functional analysis of CSC, including their genetic engineering using CRISPR/Cas9-mediated genome editing [35]. Organoids obtained from the patient can be used to identify signs of CSC resistance to treatment. Most organoid models for cancer research are applicable to adenocarcinomas of different localizations [36]. However, as the understanding of the mechanisms of tumor development expands, organoids may become a more widely used tool [36]. Thus, in combination with other *in vivo* experiments, such as xenotransplantation of CSC, organoid cultures, human CSC have high potential to improve understanding of cancer biology [37].

CSC-mediated resistance to treatment and the possibility of overcoming it

Drug resistance has been described as one of the most serious problems in the treatment of cancer, while the multidrug resistance of CSC, which ensures the chemoresistance of the tumor as a whole, is considered the main reason for the ineffectiveness of chemotherapy [38]. The mechanisms that cause chemoresistance include ABC transporters, pumps for efflux of chemotherapy drugs and ALDH1 [38].

CSC radioresistance develops due to the inhibition of apoptosis through the synthesis of antiapoptotic proteins, increased DNA repair and the ability to remove free radicals, slowing down the kinetics of the cell cycle, and transformation of non-stem tumor cells into CSC [39].

It is believed that the resistance of CSC to traditional radiation therapy and chemotherapy is associated with the activation of various signaling pathways in them, such as: Wnt, Notch and Hedgehog, which are involved in increasing oncogenicity and tumor invasiveness [40]. Currently, there is increasing evidence that these pathways are being deregulated and mutated in the CSC [41]. Aberrant Wnt signaling is found in many cancers, including NSCLC, especially adenocarcinomas [42], in which Wnt-reactive cells demonstrated proliferative potential and progression, which suggests that they possess the characteristics of CSC [42]. A growing number of publications confirm the association of abnormal regulation of Notch signaling with vari-

ous types of malignant neoplasms, including NSCLC. The Notch signaling pathway plays a role in stem cell maintenance in NSCLC; aberration in this pathway may lead to an increase in the number of CSC resistant to platinum drug therapy [42]. It was reported that the increased activity of Notch was associated with the formation of tumor spheroids *in vivo* [40]. The same authors associate Notch activity with a worse prognosis in patients with adenocarcinoma, which suggests a potential role of inhibition of Notch activity as a new therapeutic approach [41]. In NSCLC, the Hedgehog pathway is closely related to CSC [41, 42] and is involved in the formation of tumor drug resistance to targeted, chemo- and radiation therapy [42].

Some approaches to overcoming resistance mediated by OSC are also described in the literature. Some combinations of chemo- and targeted drugs have the property of inhibiting OSC in NSCLC, for example, the combination of trifluorperazine with gefitinib or cisplatin reduces the regulation of CD133 and CD44, reducing drug resistance and increasing the response to therapy [43].

It was found that the miR-29c tumor suppressor is significantly suppressed in radioresistant NSCLC CSC, but this resistance was overcome by restoring its expression, activating apoptosis, and suppressing the regulation of Bcl-2 and Mcl-1 target genes by this suppressor [44].

Yin and colleagues [45] conducted a study in which they found that certain cells in the lungs, called bronchoalveolar stem cells, transform into tumor stem cells due to two factors: the lack of a protein that usually protects the cell from becoming a tumor (Gprc5a), and exposure to nicotine-derived substances. These cells have a set of special markers (SPA+, CC10+, EGFR+, Abcg2+), thanks to which they can be updated. The researchers also found that cancer can develop not only from these stem cells, which underscores the need to study different cell types to understand the mechanisms of lung cancer development [45].

Approaches to the treatment of NSCLC targeted at CSC

The development of drugs for targeted therapy of oncological diseases is a consequence of the discovery of specific molecular genetic targets and receptors responsible for progression and chemoresistance. The CSC associated with these processes are considered in the literature as a promising target [46].

Three main approaches to CSC targeting have been proposed: identification of new CSC biomarkers, modification of their microenvironment, and sensitization to traditional medicines [8]. Combined treatment methods have been found to be the most effective [8, 9, 13–15]. Makena et al. Other therapeutic approaches have been investigated, including therapies that target dormant CSC and immunotherapy, but noted that additional research is needed in these new areas [8]. Dongre and Weinberg proposed inducing reverse EMF as a potential therapeutic strategy, representing promising approaches to reduce the number of CSC inside tumors and increase their sensitivity to various types of treatment, including chemotherapy, radiotherapy and immunotherapy [10].

It is known that chelation of intracellular iron is one of the targets of exposure to CSC, due to its ability to successfully restrain cell proliferation, as has been demonstrated in studies on models of breast and pancreatic cancer. However, despite these encouraging data, the efficacy and mechanisms of action of iron chelation in the context of squamous cell lung cancer remain poorly understood, emphasizing the need for further research in this area [47].

In the literature, increasing attention is being paid to the role of miRNAs and long non-coding RNAs (lncRNAs) in the regulation of transcription factors and pathways present in CSC [48]. It is known that the miR-17–92 cluster, acting as a stimulator of tumor growth, also has a noticeable effect on the development of lung cancer, which leads to the study of the relationship between microRNAs and tumor development, definitely emphasizing their important role in cancer biology. lncRNAs control gene expression and are involved in the maintenance and reproduction of CSC by activation of the Wnt/β-catenin and IL6/STAT3 signaling pathways. Consequently, lncRNAs can be used as predictors of an unfavorable prognosis for cancer patients and, thus, can play a major role in the eradication of CSC [48].

It has been repeatedly noted in the literature that the acquisition of "stemness" by NSCLC tumors is a negative prognostic factor of survival. Loss of PTEN expression, for example, has important consequences for the NSCLC, and is also an inde-

pendent prognostic factor for the overall survival of patients with NSCLC [49]. Similarly, patients with stage IIIB/IV NSCLC with tumors enriched with CD133+ lung cancer stem cells tend to have a shorter progression-free survival after platinum chemotherapy [16].

Nevertheless, a serious problem is the identification of "silent" CSC, i. e., those that do not express well-known markers by which they can be identified. Conversely, many surface markers of CSC, such as r2R4 and CD34, are also expressed by normal embryonic or adult stem cells, while others, such as CD44 variants, are widely expressed even in normal cells of various tissues [16]. Thus, the identification of more specific markers of OSC remains a key goal for the development of more effective treatment strategies [16].

CSC and the tumor microenvironment

The tumor microenvironment consists of a variety of non-malignant cells, including tumor-associated macrophages (M1/M2), tumor-infiltrating lymphocytes, including regulatory T cells (Tregs), dendritic cells (DC), natural killer cells (NK) and myeloid suppressor cells (MDSC). These cells interact with each other and with tumor cells, organizing an immune response, and can influence the behavior of other cells in the tumor microenvironment either by direct regulation or with the help of produced mediators (cytokines, chemokines) interacting with receptors. These interactions can be mediated by both paracrine and autocrine pathways, as well as activation of co-inhibition or coactivation receptors. Cells are able to modulate the secretion of chemokines and cytokines with an imbalance between those that perform suppressive and activating immune functions. The source of intercellular communication is a complex network of cytokines, chemokines, growth factors, inflammatory mediators and enzymes. In general, the suppressive function of the immune system prevails in the tumor microenvironment, and the process of its formation is called "tumor immunoredition" [50, 51].

Some studies have also shown that CSC can activate mechanisms that allow tumors to avoid attacks from immune cells, for example, loss of cancer antigen expression and activation of oncogenic pathways leading to the development of tolerance [52]. CSC can also contribute to the creation of an immunosuppressive environment. Some studies have demonstrated that CSC derived from various solid tumors, including glioblastoma multiforme and melanoma, secrete various immunosuppressive cytokines such as IL-13, IL-10, TGF-β, GDF-15, PGE2 and galectin-3. These cytokines can protect the tumor microenvironment from effector immune cells. CSC can induce differentiation of mature DC or Treg by transforming growth factor beta (TGF-β) [51]. The tumor microenvironment (MO, TME) is an area that can simultaneously regulate tumor development and cell self-renewal. CSC can contribute to the development of the local vascular network and angiogenesis due to their production of vascular endothelial growth factor (VEGF) [52]. MO actively interacts with CSC, providing a basis for the induction or differentiation of immune cells that suppress tumor growth, including suppressive macrophages (M2-type) or regulatory T cells (Tregs) [51, 52]. In addition, the population of tumor-associated macrophages (TAMs) increases the activity of transcription factors such as Sox, Oct-4 and Nanog, which support the CSC in a state of proliferation and self-renewal. MDSCs are a heterogeneous group of immature myeloid cells that play a role in immune response and tissue remodeling. It has been shown that MDSCs have proangiogenic activity and induce the production of metalloproteinases, which can contribute to the formation of "metastatic" niches that facilitate the colonization of tissues by tumor cells. The tumor microenvironment induces differentiation of CD4+ T cells into various subpopulations of T cells, such as Tregs and T-17 cells (Th17). The exact role of Th17 cells in tumor immunity remains unclear, apparently depending on the tumor stage and histological subtype. Interestingly, recent reports suggest that Tregs, under certain conditions, express IL-17, which, together with hypoxia, plays a crucial role in the regulation of cancer stem cells. However, the interactions between CSC and Treg, which significantly contribute to the suppression of immunity in the tumor microenvironment, are still poorly understood.

The location, type, density and functional status of immune cells (T cells, B cells, NK cells, DC cells, macrophages, neutrophils, monocytes and

mast cells) in the immune microenvironment of a tumor characterize its heterogeneity. Using single-cell RNA sequencing technology, significant differences between the immune microenvironment of adenocarcinoma and squamous cell lung cancer were confirmed [53]. This diversity affects the occurrence, growth of tumors, as well as the response to treatment. Therefore, many studies have focused on studying the immune microenvironment of the tumor. Patients receiving neoadjuvant chemotherapy had higher levels of PD-L1 expression and T-cell subpopulations than those who did not receive neoadjuvant chemotherapy for NSCLC [54]. In a study by Peng et al. [55] analysis of 26 types of immune cells in the immunological microenvironment of the tumor in 681 NSCLC samples showed that patients with low levels of immune cells and a predominance of macrophages in the tumor had a shorter recurrence-free survival. The total proportion and characteristics of T cells in a tumor are the main factors determining the development of tumor progression. Depletion of T cells occurs immediately after oncogene initiation and is the cause of patients' insensitivity to anti-PD-1/PD-L1 therapy. During the depletion of T cells, inhibitory receptors such as CTLA-4, TIM-3, LAG-3 and PD-1 are usually overexpressed on T cells, and effector cytokines such as IFN-γ decrease [55].

It is known that the immune microenvironment of a tumor can be altered by epigenetic immune editing. Epigenetic changes can be caused by inflammation [56]. The hypoxia-adapted cellular phenotype is maintained in the tumor microenvironment due to the synergistic effect of epigenetic factors and hypoxia-induced transcription factors (HIF). Under conditions of hypoxia, intensive DNA methylation and histone modification occur, which promotes tumor growth, increases invasiveness and supports the stemness of cancer cells [56].

Currently, tumor-associated macrophages (TAM) are the most widely studied immunosuppressive cells [55]. TAMs are collected at the site of injury after identification of chemokines, cytokines, inflammatory mediators, pathogens, or damage-related molecular structures (damps). There are TAM phenotypes: M1 and M2. The M1 phenotype is characterized by antitumor activity and, as a rule, is represented by activated macrophages. After epigenetic reprogramming, M2 phenotype macrophages are formed by differentiation and polarization, which can potentially contribute to the development of tumors [55]. Phenotypic M2 supports tumor stem cell populations by secreting chemokines and ligands that activate stem cell development pathways [57]. Enhanced methylation modifications and decreased chemokine expression in TAMs under hypoxic conditions alter the immune landscape in TME [57]. It was found that NEAT1 is highly expressed in lung cancer and interacts with DNA methyltransferase DNMT1, regulating the infiltration of lung cancer by cytotoxic T cells by inhibiting the cGAS/STING pathway [58]. The proliferation, differentiation and survival of T cells depend on the activity of EZH2 enhancers, which are important epigenetic regulators of gene expression. It is noteworthy that GSK126, an EZH2 inhibitor, can stimulate the synthesis of Th1 chemokines CXCL9 and CXCL10 in tumors and enhance their infiltration by CD8+ T cells [59]. The presence of tumor-infiltrating B lymphocytes can be observed at all stages of lung cancer development, and it has been found that histone modification can also increase B cell infiltration [56]. Epigenetic suppression of NKG2DL in SCLC leads to the absence of stimulating signals for activation of NK cells, thereby increasing the aggressiveness and metastasis of SCLC [60].

These studies show that the tumor microenvironment plays an important role in the progression of lung cancer. In particular, the condition of lung cancer stem cells, which is influenced by epigenetic and immune changes in the tumor microenvironment, is an important cause of treatment resistance and the development of cancer recurrence. Potential targets for antitumor effects may be not only molecules present in tumor cells, but also the tumor microenvironment, primarily immune and cytokine.

CONCLUSION

Understanding the biology of tumor stem cells is one of the most important tasks in clinical oncology. Recent studies have shown that these cells play a significant role in the development of solid tumors, such as lung cancer, which is becoming more common.

The importance of tumor stem cells in lung cancer is manifested not only through their ability to form tumors, but also through interaction with the tumor microenvironment, which plays a critical role in tumor development and its response to therapy. The tumor microenvironment, consisting of immune cells, fibroblasts, vascular network and extracellular matrix, creates conditions that support the growth and survival of tumor stem cells, and also contributes to the development of resistance to chemotherapy and radiation therapy.

The integration of knowledge about the behavior of tumor stem cells and interaction with their microenvironment in the context of lung cancer in clinical practice opens up new prospects for improving treatment and prognosis of patients. Understanding the molecular mechanisms that regulate the activity and functionality of these cells, as well as their interaction with the microenvironment, offers new opportunities for developing treatments aimed at both suppressing the activity of tumor stem cells and modifying the microenvironment to fight the tumor. Successful research in this area may be the key to more effective control of lung tumors and improving the quality of life of patients.

References

1. Travis WD, Brambilla E, Burke AP, Marx A, Nicholson AG. Introduction to The 2015 World Health Organization Classification of Tumors of the Lung, Pleura, Thymus, and Heart. J Thorac Oncol. 2015 Sep;10(9):1240–1242. https://doi.org/10.1097/JTO.0000000000000663
2. Travis WD, Brambilla E, Riely GJ. New pathologic classification of lung cancer: relevance for clinical practice and clinical trials. J Clin Oncol. 2013 Mar 10;31(8):992–1001. https://doi.org/10.1200/JCO.2012.46.9270
3. Dietel M, Bubendorf L, Dingemans AMC, Dooms C, Elmberger G, García RC, et al. Diagnostic procedures for non-small-cell lung cancer (NSCLC): recommendations of the European Expert Group. Thorax. 2016 Feb;71(2):177–184. https://doi.org/10.1136/thoraxjnl-2014-206677
4. Kerr KM, Bibeau F, Thunnissen E, Botling J, Ryška A, Wolf J, et al. The evolving landscape of biomarker testing for non-small cell lung cancer in Europe. Lung Cancer. 2021 Apr;154:161–175. https://doi.org/10.1016/j.lungcan.2021.02.026
5. Giroux-Leprieur E, Costantini A, Ding VW, He B. Hedgehog Signaling in Lung Cancer: From Oncogenesis to Cancer Treatment Resistance. Int J Mol Sci. 2018 Sep 19;19(9):2835. https://doi.org/10.3390/ijms19092835
6. Ahmad A, Maitah MY, Ginnebaugh KR, Li Y, Bao B, Gadgeel SM, et al. Inhibition of Hedgehog signaling sensitizes NSCLC cells to standard therapies through modulation of EMT-regulating miRNAs. J Hematol Oncol. 2013 Oct 7;6(1):77. https://doi.org/10.1186/1756-8722-6-77
7. Li F, Zhou K, Gao L, Zhang B, Li W, Yan W, et al. Radiation induces the generation of cancer stem cells: A novel mechanism for cancer radioresistance. Oncol Lett. 2016 Nov;12(5):3059–3065. https://doi.org/10.3892/ol.2016.5124
8. Makena MR, Ranjan A, Thirumala V, Reddy AP. Cancer stem cells: Road to therapeutic resistance and strategies to overcome resistance. Biochim Biophys Acta Mol Basis Dis. 2020 Apr 1;1866(4):165339. https://doi.org/10.1016/j.bbadis.2018.11.015
9. Ahmed M, Chaudhari K, Babaei-Jadidi R, Dekker LV, Shams Nateri A. Concise Review: Emerging Drugs Targeting Epithelial Cancer Stem-Like Cells. Stem Cells. 2017 Apr;35(4):839–850. https://doi.org/10.1002/stem.2579
10. Dongre A, Weinberg RA. New insights into the mechanisms of epithelial-mesenchymal transition and implications for cancer. Nat Rev Mol Cell Biol. 2019 Feb;20(2):69–84. https://doi.org/10.1038/s41580-018-0080-4
11. Testa U, Castelli G, Pelosi E. Lung Cancers: Molecular Characterization, Clonal Heterogeneity and Evolution, and Cancer Stem Cells. Cancers (Basel). 2018 Jul 27;10(8):248. https://doi.org/10.3390/cancers10080248
12. Barr MP, Gray SG, Hoffmann AC, Hilger RA, Thomale J, O'Flaherty JD, et al. Generation and characterisation of cisplatin-resistant non-small cell lung cancer cell lines displaying a stem-like signature. PLoS One. 2013;8(1):e54193. https://doi.org/10.1371/journal.pone.0054193
13. Kim WT, Ryu CJ. Cancer stem cell surface markers on normal stem cells. BMB Rep. 2017 Jun;50(6):285–298. https://doi.org/10.5483/bmbrep.2017.50.6.039
14. Zhang WC, Shyh-Chang N, Yang H, Rai A, Umashankar S, Ma S, et al. Glycine decarboxylase activity drives non-small cell lung cancer tumor-initiating cells and tumorigenesis. Cell. 2012 Jan 20;148(1–2):259–272. https://doi.org/10.1016/j.cell.2011.11.050

15. Herreros-Pomares A, de-Maya-Girones JD, Calabuig-Fariñas S, Lucas R, Martínez A, Pardo-Sánchez JM, et al. Lung tumorspheres reveal cancer stem cell-like properties and a score with prognostic impact in resected non-small-cell lung cancer. Cell Death Dis. 2019 Sep 10;10(9):660. https://doi.org/10.1038/s41419-019-1898-1
16. Ohnishi S, Maehara O, Nakagawa K, Kameya A, Otaki K, Fujita H, et al. hypoxia-inducible factors activate CD133 promoter through ETS family transcription factors. PLoS One. 2013;8(6):e66255. https://doi.org/10.1371/journal.pone.0066255
17. Eramo A, Lotti F, Sette G, Pilozzi E, Biffoni M, Di Virgilio A, et al. Identification and expansion of the tumorigenic lung cancer stem cell population. Cell Death Differ. 2008 Mar;15(3):504–514. https://doi.org/10.1038/sj.cdd.4402283
18. Alamgeer M, Peacock CD, Matsui W, Ganju V, Watkins DN. Cancer stem cells in lung cancer: Evidence and controversies. Respirology. 2013 Jul;18(5):757–764. https://doi.org/10.1111/resp.12094
19. Hou YC, Chao YJ, Hsieh MH, Tung HL, Wang HC, Shan YS. Low CD8+ T Cell Infiltration and High PD-L1 Expression Are Associated with Level of CD44+/CD133+ Cancer Stem Cells and Predict an Unfavorable Prognosis in Pancreatic Cancer. Cancers (Basel). 2019 Apr 15;11(4):541. https://doi.org/10.3390/cancers11040541
20. Godar S, Ince TA, Bell GW, Feldser D, Donaher JL, Bergh J, et al. Growth-inhibitory and tumor- suppressive functions of p53 depend on its repression of CD44 expression. Cell. 2008 Jul 11;134(1):62–73. https://doi.org/10.1016/j.cell.2008.06.006
21. Leung ELH, Fiscus RR, Tung JW, Tin VPC, Cheng LC, Sihoe ADL, et al. Non-small cell lung cancer cells expressing CD44 are enriched for stem cell-like properties. PLoS One. 2010 Nov 19;5(11):e14062. https://doi.org/10.1371/journal.pone.0014062
22. Roudi R, Madjd Z, Korourian A, Mehrazma M, Molanae S, Sabet MN, et al. Clinical significance of putative cancer stem cell marker CD44 in different histological subtypes of lung cancer. Cancer Biomark. 2014;14(6):457–467. https://doi.org/10.3233/cbm-140424
23. Bourguignon LYW. Hyaluronan-mediated CD44 activation of RhoGTPase signaling and cytoskeleton function promotes tumor progression. Semin Cancer Biol. 2008 Aug;18(4):251–259. https://doi.org/10.1016/j.semcancer.2008.03.007
24. Orian-Rousseau , Sleeman J. CD44 is a multidomain signaling platform that integrates extracellular matrix cues with growth factor and cytokine signals. Adv Cancer Res. 2014;123:231–254. https://doi.org/10.1016/B978-0-12-800092-2.00009-5
25. Ludwig N, Szczepanski MJ, Gluszko A, Szafarowski T, Azambuja JH, Dolg L, et al. CD44(+) tumor cells promote early angiogenesis in head and neck squamous cell carcinoma. Cancer Lett. 2019 Dec 28;467:85–95. https://doi.org/10.1016/j.canlet.2019.10.010
26. Kong T, Ahn R, Yang K, Zhu X, Fu Z, Morin G, et al. CD44 Promotes PD-L1 Expression and Its Tumor-Intrinsic Function in Breast and Lung Cancers. Cancer Res. 2020 Feb 1;80(3):444–457. https://doi.org/10.1158/0008-5472.CAN-19-1108
27. Masciale V, Grisendi G, Banchelli F, D'Amico R, Maiorana A, Sighinolfi P, et al. CD44+/EPCAM+ cells detect a subpopulation of ALDHhigh cells in human non-small cell lung cancer: A chance for targeting cancer stem cells? Oncotarget. 2020 Apr 28;11(17):1545–1555. https://doi.org/10.18632/oncotarget.27568
28. Hardavella G, George R, Sethi T. Lung cancer stem cells-characteristics, phenotype. Transl Lung Cancer Res. 2016 Jun;5(3):272–279. https://doi.org/10.21037/tlcr.2016.02.01
29. Eckert F, Schilbach K, Klumpp L, Bardoscia L, Sezgin EC, Schwab M, et al. Potential Role of CXCR4 Targeting in the Context of Radiotherapy and Immunotherapy of Cancer. Front Immunol. 2018;9:3018. https://doi.org/10.3389/fimmu.2018.03018
30. Trautmann F, Cojoc M, Kurth I, Melin N, Bouchez LC, Dubrovska A, et al. CXCR4 as biomarker for radioresistant cancer stem cells. Int J Radiat Biol. 2014 Aug;90(8):687–699. https://doi.org/10.3109/09553002.2014.906766
31. Gzil A, Zarębska I, Bursiewicz W, Antosik P, Grzanka D, Szylberg Ł. Markers of pancreatic cancer stem cells and their clinical and therapeutic implications. Mol Biol Rep. 2019 Dec;46(6):6629–6645. https://doi.org/10.1007/s11033-019-05058-1
32. Jung MJ, Rho JK, Kim YM, Jung JE, Jin YB, Ko YG, et al. Upregulation of CXCR4 is functionally crucial for maintenance of stemness in drug-resistant non-small cell lung cancer cells. Oncogene. 2013 Jan 10;32(2):209–221. https://doi.org/10.1038/onc.2012.37
33. De Francesco EM, Sotgia F, Lisanti MP. Cancer stem cells (CSCs): metabolic strategies for their identification and eradication. Biochem J. 2018 May 9;475(9):1611–1634. https://doi.org/10.1042/BCJ20170164
34. Barkauskas CE, Chung MI, Fioret B, Gao X, Katsura H, Hogan BLM. Lung organoids: current uses and future promise. Development. 2017 Mar 15;144(6):986–997. https://doi.org/10.1242/dev.140103
35. Matano M, Date S, Shimokawa M, Takano A, Fujii M, Ohta Y, et al. Modeling colorectal cancer using CRISPR-Cas9-mediated engineering of human intestinal organoids. Nat Med. 2015 Mar;21(3):256–262. https://doi.org/10.1038/nm.3802

36. Nagle PW, Plukker JTM, Muijs CT, van Luijk P, Coppes RP. Patient-derived tumor organoids for prediction of cancer treatment response. Semin Cancer Biol. 2018 Dec;53:258–264. https://doi.org/10.1016/j.semcancer.2018.06.005
37. Shimono Y, Mukohyama J, Isobe T, Johnston DM, Dalerba P, Suzuki A. Organoid Culture of Human Cancer Stem Cells. Methods Mol Biol. 2019;1576:23–31. https://doi.org/10.1007/7651_2016_13
38. Kusumbe AP, Bapat SA. Cancer stem cells and aneuploid populations within developing tumors are the major determinants of tumor dormancy. Cancer Res. 2009 Dec 15;69(24):9245–9453. https://doi.org/10.1158/0008-5472.CAN-09-2802
39. Arnold CR, Mangesius J, Skvortsova II, Ganswindt U. The Role of Cancer Stem Cells in Radiation Resistance. Front Oncol. 2020;10:164. https://doi.org/10.3389/fonc.2020.00164
40. Kumar V, Vashishta M, Kong L, Wu X, Lu JJ, Guha C, et al. The Role of Notch, Hedgehog, and Wnt Signaling Pathways in the Resistance of Tumors to Anticancer Therapies. Front Cell Dev Biol. 2021;9:650772. https://doi.org/10.3389/fcell.2021.650772
41. Yang L, Shi P, Zhao G, Xu J, Peng W, Zhang J, et al. Targeting cancer stem cell pathways for cancer therapy. Signal Transduct Target Ther. 2020 Feb 7;5(1):8. https://doi.org/10.1038/s41392-020-0110-5
42. Vasileva MV, Khromova NV, Boichuk SV, Kopnin PB. The effect of NOTCH1 knockdown on the phenotype of human lung and colon cancer stem cells. Advances in Molecular Oncology. 2024;11(2):97–105. (In Russ.). https://doi.org/10.17650/2313-805X-2024-11-2-97-105, EDN: RXXWTD
43. Yeh CT, Wu ATH, Chang PMH, Chen KY, Yang CN, Yang SC, et al. Trifluoperazine, an antipsychotic agent, inhibits cancer stem cell growth and overcomes drug resistance of lung cancer. Am J Respir Crit Care Med. 2012 Dec 1;186(11):1180–1188. https://doi.org/10.1164/rccm.201207-1180OC
44. Arechaga-Ocampo E, Lopez-Camarillo C, Villegas-Sepulveda N, Gonzalez-De la Rosa CH, Perez-Añorve IX, Roldan-Perez R, et al. Tumor suppressor miR-29c regulates radioresistance in lung cancer cells. Tumour Biol. 2017 Mar;39(3):1010428317695010. https://doi.org/10.1177/1010428317695010
45. Yin H, Jing B, Xu D, Guo W, Sun B, Zhang J, et al. Identification of Active Bronchioalveolar Stem Cells as the Cell of Origin in Lung Adenocarcinoma. Cancer Res. 2022 Mar 15;82(6):1025–1037. https://doi.org/10.1158/0008-5472.CAN-21-2445
46. Saygin C, Matei D, Majeti R, Reizes O, Lathia JD. Targeting Cancer Stemness in the Clinic: From Hype to Hope. Cell Stem Cell. 2019 Jan 3;24(1):25–40. https://doi.org/10.1016/j.stem.2018.11.017
47. Lang J, Zhao X, Wang X, Zhao Y, Li Y, Zhao R, et al. Targeted Co-delivery of the Iron Chelator Deferoxamine and a HIF1α Inhibitor Impairs Pancreatic Tumor Growth. ACS Nano. 2019 Feb 26;13(2):2176–2189. https://doi.org/10.1021/acsnano.8b08823
48. Dong L, Lyu X, Faleti OD, He ML. The special stemness functions of Tbx3 in stem cells and cancer development. Semin Cancer Biol. 2019 Aug;57:105–110. https://doi.org/10.1016/j.semcancer.2018.09.010
49. Tang JM, He QY, Guo RX, Chang XJ. Phosphorylated Akt overexpression and loss of PTEN expression in non-small cell lung cancer confers poor prognosis. Lung Cancer. 2006 Feb;51(2):181–191. https://doi.org/10.1016/j.lungcan.2005.10.003
50. Zou W. Immune regulation in the tumor microenvironment and its relevance in cancer therapy. Cell Mol Immunol. 2022 Jan;19(1):1–2. https://doi.org/10.1038/s41423-021-00738-0
51. Oh SA, Wu DC, Cheung J, Navarro A, Xiong H, Cubas R, et al. PD-L1 expression by dendritic cells is a key regulator of T-cell immunity in cancer. Nat Cancer. 2020 Jul;1(7):681–691. https://doi.org/10.1038/s43018-020-0075-x
52. Zhang D, Tang DG, Rycaj K. Cancer stem cells: Regulation programs, immunological properties and immunotherapy. Semin Cancer Biol. 2018 Oct;52(Pt 2):94–106. https://doi.org/10.1016/j.semcancer.2018.05.001
53. Wang C, Yu Q, Song T, Wang Z, Song L, Yang Y, et al. The heterogeneous immune landscape between lung adenocarcinoma and squamous carcinoma revealed by single-cell RNA sequencing. Signal Transduct Target Ther. 2022 Aug 26;7(1):289. https://doi.org/10.1038/s41392-022-01130-8
54. Shestopalov AV, Kit OI, Zabolotneva AA, Zlatnik EY, Maksimov AYu, Novikova IA et al. Alkylresorcinols as a New Type of Gut Microbiota Regulators Influencing Immune Therapy Efficiency in Lung Cancer Treatment. Advanced Gut & Microbiome Research. 2023. https://doi.org/10.1155/2023/2333767, EDN: ZIVEKT
55. Sagakyants AB, Teplyakova MA, Vladimirova LYu, Bondarenko ES, Zlatnik EYu, Novikova IA, et al. Features of the population remaining of peripheral blood immune cells in patients with non-small cell lung cancer during immunotherapy with different effectiveness. Modern problems of science and education. 2023;2:87. (In Russ.). https://doi.org/10.17513/spno.32545, EDN: EWBINE

56. Karin M, Shalapour S. Regulation of antitumor immunity by inflammation-induced epigenetic alterations. Cell Mol Immunol. 2022 Jan;19(1):59–66. https://doi.org/10.1038/s41423-021-00756-y
57. Teplyakova MA, Vladimirova LYU, Popova IL, Lyanova AA, Abramova NA, Storozhakova AE, et al. Cytokine profiles of peripheral blood in patients with non-small cell lung cancer receiving anti-PD1 therapy. Journal of Clinical Oncology. 2022;40(16). https://doi.org/10.1200/JCO.2022.40.16_suppl.e21068, EDN: RDAZOV
58. Ma F, Lei YY, Ding MG, Luo LH, Xie YC, Liu XL. LncRNA NEAT1 Interacted With DNMT1 to Regulate Malignant Phenotype of Cancer Cell and Cytotoxic T Cell Infiltration via Epigenetic Inhibition of p53, cGAS, and STING in Lung Cancer. Front Genet. 2020;11:250. https://doi.org/10.3389/fgene.2020.00250
59. Huang S, Wang Z, Zhou J, Huang J, Zhou L, Luo J, et al. EZH2 Inhibitor GSK126 Suppresses Antitumor Immunity by Driving Production of Myeloid-Derived Suppressor Cells. Cancer Res. 2019 Apr 15;79(8):2009–2020. https://doi.org/10.1158/0008-5472.CAN-18-2395
60. Zhu M, Huang Y, Bender ME, Girard L, Kollipara R, Eglenen-Polat B, et al. Evasion of Innate Immunity Contributes to Small Cell Lung Cancer Progression and Metastasis. Cancer Res. 2021 Apr 1;81(7):1813–1826. https://doi.org/10.1158/0008-5472.CAN-20-2808

Information about authors:

Dmitrii 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

Artur A. Antonyan ✉ – PhD student of the 1st year, National Medical Research Centre for Oncology, Rostov-on-Don, Russian Federation
ORCID: https://orcid.org/0000-0001-6449-7026, ResearcherID: JWQ-0734-2024

Elena Yu. Zlatnik – Dr. Sci. (Med.), MD, Professor, Chief Researcher, Laboratory of Immunophenotyping of Tumors, National Medical Research Centre for Oncology, Rostov-on-Don, Russian Federation
ORCID: https://orcid.org/0000-0002-1410-122X, SPIN: 4137-7410, AuthorID: 327457, ResearcherID: AAI-1311-2020, Scopus Author ID: 6603160432

Alexander B. Sagakyants – Cand. Sci. (Biol.), head of the Laboratory of Immunophenotyping of Tumors, National Medical Research Centre for Oncology, Rostov-on-Don, Russian Federation
ORCID: https://orcid.org/0000-0003-0874-5261, SPIN: 7272-1408, AuthorID: 426904, ResearcherID: M-8378-2019, Scopus Author ID: 24329773900

Ellada A. Mirzoyan – Cand. Sci. (Med.), MD, oncologist, researcher 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.), 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

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

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, Scopus Author ID: 57192109933

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

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

Mekhrullokhodzha A. Homidov – PhD student, National Medical Research Centre for Oncology, Rostov-on-Don, Russian Federation
ORCID: https://orcid.org/0000-0003-0645-0937, SPIN: 1950-8737, AuthorID: 1067071, ResearcherID: JFK-3888-2023

Eduard K. Alekseev – MD, resident doctor, National Medical Research Centre for Oncology, Rostov-on-Don, Russian Federation
ORCID: https://orcid.org/0009-0007-4982-5491, ResearcherID: JWP-6340-2024

Contribution of the authors:

Kharagezov D. A., Zlatnik E. Yu. – scientific management;
Antonyan A. A. – writing the draft; material processing;
Sagakyants A. B., Mirzoyan E. A., Ayrapetova T. G., Leyman I. A., Milakin A. G., Stateshny O. N. Iozefi K. D., Homidov M. A., Alekseev E. K. – data collection, analysis, technical editing, bibliography design.

South Russian Journal of Cancer. 2024. Vol. 5, No. 4. P. 71
https://elibrary.ru/kcgjmy

ANNIVERSARY

YURI S. SIDORENKO

RAS academician
Doctor of Medical Sciences
Professor
Honored Scientist of the Russian Federation
Laureate of the RSFSR State Prize in the field of science and technology
Honored Innovator of the RSFSR
Laureate of the I. I. Mechnikov Prize of the Russian Academy of Sciences

Awarded with: the Order of the Badge of Honor, the Order of Friendship, the Medal of the Russian Federation Ministry of Health "For Serving to National Healthcare"

Yu. S. Sidorenko is a well-known oncological gynecologist and specialist in the field of clinical oncology and pathophysiology, an author of more than 800 scientific paper works, including 30 monographs, ha has 398 copyright certificates and patents for inventions.

Dr. Sidorenko was born on November 8, 1939 in Kherson city. After graduation from Uzhhorod State University, he was working in various medical institutions in the Transcarpathian region and in Novocherkassk, Rostov region, in the period from 1968 to 1972. He was a clinical resident since 1972, then a postgraduate student at the Rostov Research Institute of Oncology. In 1978, Sidorenko Yu. S. defended his PhD work on the topic of "Endolymphatic polychemotherapy in the treatment of cervical cancer." Sir Yuri Sidorenko was the chief physician of the city hospital No. 20 in Rostov-on-Don in the period from 1979 to 1982.

From March 1982 to August 2010, he was the director of the Rostov Cancer Research Institute. Dr. Sidorenko defended his doctoral dissertation called "Some aspects of diagnosis, treatment and medical examination of oncogynecological patients" in 1988.

In the period from 1986 to 2001, the Institute has hosted the III All-Russian Congress of Oncologists (1986), the meeting of directors of research Institutes of Oncology and Radiology of the USSR (1989), IV (1995) and VI (2005) congresses of oncologists of Russia, the Plenum of the Board of the Scientific Oncological Society (1999) and the II All-Russian Congress of pediatric oncologists (2001).

The scientific research conducted by academician Sidorenko Yu. S. included the development of new, non-traditional approaches to the complex treatment of malignant diseases, in particular, to the chemotherapy with auto-biological solvents, i.e. autohemochemotherapy, autolymphochemotherapy, homohemochemotherapy and homolymphochemotherapy, endolymphatic chemotherapy, intraperitoneal permanent and interstitial chemotherapy. The implication of these biological components at that time made it possible to increase the effectiveness of chemotherapy. For this cycle of works Academician Sidorenko Yu. S. was awarded the I. I. Mechnikov Prize in Physiology at the Russian Academy of Sciences (2008).

Dr. Sidorenko introduced an original cancer screening system in non-manifested form and proposed a number of organ-preserving and functionally sparing operations, for the development of which the author was awarded the State Prize of the RSFSR. He also created a model of original population-based cancer screening based on the psychological principle of self-formation of groups with increased cancer risk through patient self-observation and self-control.

In 1997 Sidorenko Yu. S. was elected to the Russian Academy of Medical Sciences as a corresponding member of the Russian Academy of Medical Sciences. He became the Academician of the Russian Academy of Medical Sciences in 1999, and since 2006 an Academician of the Russian Academy of Sciences.

Dr. Sidorenko is a man of encyclopedic knowledge and erudition. He is a fine connoisseur and an expert in painting, literature and the national culture of the country. Sidorenko Yu. S. is outstanding for a holistic perception of life, his personality combines refined intelligence and broad-spectrum education, benevolence and dedication of the true teacher, intuition and experience of a practical surgeon, fundamental knowledge and precise scientific foresight of a natural scientist, wisdom and confidence of the true leader.

The staff of the National Medical Research Center of Oncology wholeheartedly congratulates Dr. Sidorenko on his anniversary. We sincerely wish him happiness, great health, never-ending creativity, and lots of love from his loved ones.

The staff of the National Medical Research Center for Oncology, the Russian Federation Ministry of Health

ФГБУ "НМИЦ ОНКОЛОГИИ"
МИНЗДРАВА РОССИИ

South Russian Journal of Cancer

PEER-REVIEWED SCIENTIFIC AND PRACTICAL

Южно-Российский
онкологический журнал

РЕЦЕНЗИРУЕМЫЙ НАУЧНО-ПРАКТИЧЕСКИЙ

www.cancersp.com