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Южно-Российский онкологический журнал

«Южно-Российский онкологический журнал»: профессиональное медицинское издание. В нем публикуются новости медицинского и фармацевтического сообществ, научно-практические статьи для целевой аудитории – врачей-онкологов. Редакция журнала ставит своей задачей популяризацию научно-исследовательских работ и достижений онкологов Южного федерального округа, анализ процесса глубокой реорганизации здравоохранения в России. Редакция приглашает в качестве авторов всех, кто ищет и находит интересные решения многогранных задач, стоящих перед современной медициной, и хочет поделиться своими мыслями и наблюдениями с коллегами.

Цель: способствовать развитию онкологической медицины Юга России и внедрению её достижений в практику.

Задачи: освещать современные достижения онкологической службы Юга России; содействовать обмену опытом и передовыми знаниями между специалистами; информировать читателей об итогах крупных медицинских форумов.

В журнале размещаются публикации различных рубрик: обзоры литературы, мета-анализы, клинические исследования, наблюдения клинических случаев, обсуждения, анонсы и описания новых методов лечения.

Журнал принимает к публикации: оригинальные статьи, организации здравоохранения, лучевой диагностики, обмен опытом, обзоры, клинические наблюдения.

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Адрес редакции и издателя:
344037, Россия, Ростов-на-Дону, 14-я линия, д. 63, литер Г, комната 1
E-mail: info@cancersp.com
Телефон: +7 (903) 547-04-62, +7 (863) 295-53-62
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"South-Russian Oncological Journal": professional medical publication. It publishes news from the medical and pharmaceutical communities, scientific and practical articles for the target audience-oncologists. The editorial board of the journal aims to popularize the research works and achievements of oncologists of the Southern Federal District, to analyze the process of deep reorganization of healthcare in Russia. The editorial board invites as authors all those who are looking for and find interesting solutions to the multifaceted problems facing modern medicine and want to share their thoughts and observations with colleagues.

Purpose: to promote the development of cancer medicine in the South of Russia and the introduction of its achievements into practice.
Tasks: to highlight the current achievements of the oncology service in the South of Russia; to promote the exchange of experience and advanced knowledge between specialists; to inform readers about the results of major medical forums.
The journal contains publications of various categories: literature reviews, meta-analyses, clinical studies, observations of clinical cases, discussions, announcements and descriptions of new treatment methods.
The journal accepts for publication: original articles, health organizations, radiation diagnostics, exchange of experience, reviews, clinical case reviews.

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E-mail: info@cancersp.com
Pfone: +7 (903) 547-04-62, +7 (863) 295-53-62
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ORIGINAL ARTICLE

PRESEPSIN AS A MARKER OF SEPSIS IN ONCOLOGICAL PATIENTS AFTER SURGICAL INTERVENTIONS

N. K. Guskova[1]✉, A. A. Morozova[1], D. A. Rozenko[1], A. V. Alyoshkina[1], A. M. Skopintsev[1], O. N. Selyutina[1], N. V. Golomeeva[1], E. A. Guskova[2], A. K. Donskaya[1], I. V. Tselishcheva[1], A. S. Nozdricheva[1]

1. National Medical Research Centre for Oncology, Rostov-on-Don, Russian Federation
2. Da Vinci Clinical and Diagnostic Center, Rostov-on-Don, Russian Federation
✉ guskova.nailya@mail.ru

ABSTRACT

Purpose of the study. Analysis of the possibility of using presepsin in the early diagnosis of sepsis in cancer patients after extensive surgical interventions for tumors of the thoraco-abdominal localization.

Materials and methods. The study included 27 people: 10 healthy individuals (control) and 17 patients who received surgical treatment at the National Medical Research Center of Oncology for malignant neoplasms of thoraco-abdominal localization. In the blood of all patients, studies of sepsis markers were performed: presepsin (P-SEP), highly sensitive CRP (hsCRP) (PATHFAST, Japan), procalcitonin (PCT), interleukin-6 (IL6) (Cobas e 411, Germany), as well as lactate, total leukocyte count (WBC) with a leukocyte formula, a blood culture test for suspected septic complications included in a routine examination. The studies were carried out before and on the 2nd day after the operation. Data were assessed by comparing P-SEP levels with hsCRP, PCT, IL6, lactate, WBC, blood culture test results, and the clinical status of patients. Depending on the data obtained, 2 groups were distinguished: I – patients with confirmed sepsis (3 people), II – without sepsis (14 people). Statistical processing was performed using STATISTICA 13.0.

Results. In the control group, the level of P-SEP was 182.7 ± 11.9 pg/ml. In patients before surgery, the marker values were 213.7 ± 47.7 pg/ml, which did not differ statistically from the control data and did not go beyond the reference values, as did the content of PCT, hsCRP, IL6. On the 2nd day after surgery, all patients showed unidirectional changes, characterized by an increase in the levels of the studied parameters, but with varying degrees of intensity. The most significant was the increase in the concentration of presepsin. At the same time, it was noted that the level of presepsin on the 2nd day after surgery in patients of group I patients with confirmed sepsis averaged 2577.5 ± 1762.5 pg/ml with a maximum level 4340.0 pg/ml, and in group II with In the absence of confirmed bacteremia, there was an increase in the level of presepsin 1205.0 pg/ml. The data obtained correlated with the dynamics of changes in the concentration of other sepsis markers – hsCRP, PCT, IL6. Thus, the study of the level of presepsin, along with widely used markers – hsCRP, PCT, IL6, allows diagnosing sepsis in the early postoperative period in cancer patients.

Conclusion. In patients with malignant neoplasms of thoracoabdominal localization, changes in the levels of sepsis markers in the early postoperative period can be used as a basis for prescribing antibiotic therapy. Presepsin may be recommended for use as an early marker of sepsis in patients with oncological pathology.

Keywords:
sepsis, sepsis markers, presepsin, surgical interventions, malignant neoplasms of thoraco-abdominal localization

For correspondence:
Nailya K. Guskova – Cand. Sci. (Biol.), head of clinical diagnostic laboratory, National Medical Research Centre for Oncology of the Ministry of Health of Russia, Rostov-on-Don, Russian Federation.
Address: 63 14 line, Rostov-on-Don 344037, Russian Federation
E-mail: guskova.nailya@mail.ru
ORCID: https://orcid.org/0000-0002-4222-1579
SPIN: 5407-6285, AuthorID: 306979
Scopus Author ID: 6506703993

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ОРИГИНАЛЬНАЯ СТАТЬЯ

ПРЕСЕПСИН КАК МАРКЕР СЕПСИСА У ОНКОЛОГИЧЕСКИХ БОЛЬНЫХ ПОСЛЕ ХИРУРГИЧЕСКИХ ВМЕШАТЕЛЬСТВ

Н. К. Гуськова[1]✉, А. А. Морозова[1], Д. А. Розенко[1], А. В. Алешкина[1], А. М. Скопинцев[1], О. Н. Селютина[1], Н. В. Голомеева[1], Е. А. Гуськова[2], А. К. Донская[1], И. В. Целищева[1], А. С. Ноздричева[1]

1. НМИЦ онкологии, г. Ростов-на-Дону, Российская Федерация
2. Клинико-диагностический центр «ДА ВИНЧИ», г. Ростов-на-Дону, Российская Федерация
✉ guskova.nailya@mail.ru

РЕЗЮМЕ

Цель исследования. Анализ возможности применения пресепсина в ранней диагностике сепсиса у онкологических пациентов после проведения обширных оперативных вмешательств по поводу опухолей торако-абдоминальной локализации.
Материалы и методы. В исследование включены 27 человек: 10 здоровых лиц (контроль) и 17 пациентов, пролеченных хирургическим методом по поводу злокачественных новообразований торако-абдоминальной локализации в ФГБУ «НМИЦ онкологии» Минздрава России. Всем пациентам в крови выполнены исследования маркеров сепсиса: пресепсина (P-SEP), высокочувствительного СРБ (hsCRP) (PATHFAST, Япония), прокальцитонина (PCT), интерлейкина-6 (IL6) (Cobas e 411, Германия), а также лактата, суммарного показателя лейкоцитов (WBC) с лейкоцитарной формулой, исследование крови на гемокультуру при подозрении на септические осложнения, входящие в плановое обследование. Исследования проводились до- и на 2-е сутки после операции. Данные оценивались путем сопоставления уровня P-SEP со значениями hsCRP, PCT, IL6, лактата, WBC, результатами теста на гемокультуру и клиническим состоянием больных. В зависимости от полученных данных выделено 2 группы: I – больные с подтвержденным сепсисом (3 человека), II – без сепсиса (14 человек). Статистическая обработка выполнялась с использованием STATISTICA 13.0.
Результаты. В контрольной группе уровень P-SEP составил 182,7 ± 11,9 pg/ml. У больных до операции значения маркера составили 213,7 ± 47,7 pg/ml, что статистически не отличалось от данных контроля и не выходило за пределы референтных значений, как и содержание PCT, hsCRP, IL6. На 2-е сутки после операции у всех больных отмечены однонаправленные изменения, характеризующиеся повышением уровней исследуемых показателей, но с разной степенью интенсивности. Наиболее значимым было увеличение концентрации пресепсина. При этом обращало на себя внимание, что на 2-е сутки после операции у больных I группы с подтвержденным сепсисом уровень пресепсина составил в среднем 2577,5 ± 1762,5 pg/ml с максимальным значением 4340,0 pg/ml, а во II группе, при отсутствии подтвержденной бактериемии, отмечалось повышение уровня пресепсина до 1205,0 pg/ml. Полученные данные соотносились с динамикой изменения концентрации других маркеров сепсиса – hsCRP, PCT, IL6. Таким образом, исследование уровня пресепсина, наряду с широко используемыми маркерами – hsCRP, PCT, IL6 позволяет диагностировать сепсис в раннем послеоперационном периоде у онкологических пациентов.
Заключение. У больных со злокачественными новообразованиями торако-абдоминальной локализации изменение уровней маркеров сепсиса в раннем послеоперационном периоде можно использовать как основание для назначения антибиотикотерапии. Пресепсин может быть рекомендован к применению в качестве раннего маркера сепсиса у больных с онкологической патологией.

Ключевые слова:
сепсис, маркеры сепсиса, пресепсин, хирургические вмешательства, злокачественные новообразования торако-абдоминальной локализации

Для корреспонденции:
Гуськова Наиля Катифовна – к.б.н., заведующая клинико-диагностической лабораторией ФГБУ «НМИЦ онкологии» Минздрава России, г. Ростов-на-Дону, Российская Федерация.
Адрес: 344037, Российская Федерация, г. Ростов-на-Дону, ул. 14-я линия, д. 63
E-mail: guskova.nailya@mail.ru
ORCID: https://orcid.org/0000-0002-4222-1579
SPIN: 5407–6285, AuthorID: 306979
Scopus Author ID: 6506703993

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RELEVANCE

Sepsis is a life threatening organ dysfunction caused by the body's dysregulatory response to infection. According to WHO, mortality from sepsis is caused by the development of septic shock and multiple organ failure and amounts to 11 million people annually. Of the surviving patients, only half recover completely, and the rest either die within 1 year or live with acquired chronic pathology. The most susceptible to septic complications are newborns, pregnant women, the elderly, people with weakened immunity, as well as cancer patients [1]. In the presence of oncological pathology, aggravating factors are both the tumor itself and the implementation of a complex of specific treatment methods i.e. chemo and radiation therapy, surgical interventions [2]. When conducting extensive surgical interventions, the urgent task of surgery is to reduce the frequency of purulent-septic complications [3]. The development of septic complications and high mortality are usually caused by untimely diagnosis and late onset of pathogenetic treatment. The concept of sepsis itself has been repeatedly revised and changed in recent years, which has given the medical community a clearer prediction of the course and outcomes of this pathology. Nevertheless, the problems of early diagnosis have not been solved definitively [1; 4]. Hemoculture, a very specific and accessible method in routine practice, is recognized as the "gold standard" for the diagnosis of infection. However, the duration of the study (more than 48 hours), the low sensitivity of the method (25–42 %) and the negative result of blood culture do not guarantee the absence of bacteremia. At the same time, the inability to assess the effect of uncultivated forms of microorganisms on the infectious and inflammatory process limits the diagnostic capabilities of the method [4] and, as a consequence, prevents the timely initiation of pathogenetic treatment.

Currently, various biochemical markers are used to diagnose sepsis: procalcitonin, C-reactive protein, cytokines. Procalcitonin – glycoprotein, which is a precursor of calcitonin, is synthesized by pancreatic C-cells. In the inflammatory process of bacterial or fungal nature, when stimulated by endotoxins or proinflammatory cytokines, the level of procalcitonin increases within 6–12 hours. However, there are limitations in the use of procalcitonin as a marker of sepsis, since an increase in the level of the indicator is known due to injuries, extensive damage to organs and tissues of a non-infectious nature [4; 5]. Much earlier than the increase in procalcitonin, there is an increase in the level of interleukin-6 with a peak after 2–4 hours, which is associated with a severe course of the disease or the volume of surgical intervention, which also makes it difficult to establish the nature of the inflammatory process [4]. C-reactive protein (CRP) belongs to the group of proteins of the acute phase of inflammation and is synthesized mainly in hepatocytes. The synthesis of CRP is initiated by antigens, immune complexes, infectious agents and particles of necrotic tissue. The concentration of CRP increases after 4–6 hours from the beginning of the pathological process and continues to increase for 24–48 hours, increasing hundreds of times. The marker is most often used to diagnose acute inflammatory conditions and necrotic processes, as well as to evaluate the effectiveness of therapeutic measures. In some cases, an increase in the level of CRP may be due to non-specific causes, such as necrotic tissues formed during burns, necrosis, which reduces its diagnostic significance and does not allow it to be used to confirm the infectious etiology of inflammatory processes [5; 6].

There are data on the use of presepsin in the diagnosis of acute inflammatory reactions. Presepsin is a circulating protein whose concentration in the blood increases rapidly with the development of systemic infections, sepsis, severe sepsis and septic shock. It was first described in 2005 by a group of researchers from Iwate Medical University, Japan [7]. The mechanism of increasing presepsin levels is fundamentally different from the mechanism of increasing other pro-inflammatory markers – interleukin-6, interleukin-10, procalcitonin, CRP, since immune mechanisms aimed at activating phagocytosis participate in its production. The increase in presepsin level is registered earlier due to a short half-life (0.5–1.0 hours) [8; 9]. The reference values of presepsin in healthy people do not exceed 320 pg/ml, however, the manufacturer of test systems LSI Medience Corporation, Japan [10], shows the threshold values of the marker recommended for use in the early diagnosis of septic reactions (Table 1).

However, according to the literature, the level of presepsin increases with varying degrees of intensity during surgical interventions, injuries and burns both in the absence of an infectious component, and

with the development of septic reactions in patients without oncological pathology [11–15]. In this regard, the study of presepsin levels in oncological practice in patients after extensive surgical interventions is very relevant.

The purpose of the study: to analyze the possibility of using presepsin in the early diagnosis of sepsis in cancer patients after extensive surgical interventions for tumors of the thoraco-abdominal localization.

MATERIALS AND METHODS

The study included 27 people: 10 healthy individuals (control) and 17 patients who received surgical treatment at the National Medical Research Center of Oncology for malignant neoplasms of thoraco-abdominal localization. There is informed consent of patients for the study. Sepsis markers were studied in the blood of all patients: presepsin (P-SEP), highly sensitive CRP (hsCRP) (PATHFAST, Japan), procalcitonin (PCT), interleukin-6 (IL6) (Cobas e 411, Germany), as well as lactate, total leukocyte count (WBC) with leukocyte formula, blood testing for hemoculture in case of suspected septic complications included in the routine examination. The studies were conducted before and on the 2nd day after the operation. The data were evaluated by comparing the P-SEP level with the values of hsCRP, PCT, IL6, lactate, WBC, the results of the hemoculture test and the clinical condition of patients. Depending on the data obtained, 2 groups were identified: I – patients with confirmed sepsis (3 people), II – without sepsis (14 people). Statistical processing was performed using STATISTICA 13.0.

RESEARCH RESULTS AND DISCUSSION

In the control group of individuals, the P-SUP level averaged 182.7 ± 11.9 pg/ml. In the examined group of patients before surgery, the marker values were in the range of 166.0–261.5 pg/ml and averaged 213.7 ± 47.7 pg/ml, which did not statistically differ from the data of the control group ($p > 0.001$) and did not exceed the reference values (< 320 pg/ ml) recommended by the manufacturer of the test systems (Table 1). The content in the blood of patients before surgery of other markers of inflammation – PCT, hsCRP, IL6 was also within the reference boundaries (Table 2).

On the 2nd day after surgery, unidirectional changes were noted in all patients included in the study, characterized by an increase in the levels of the studied indicators, but with varying degrees of intensity. At the same time, the most significant was the increase in presepsin concentration. Thus, in group I (with sepsis), the P-SEP level averaged 2577.5 ± 1762.5 pg/ml, 8.1 times higher than the reference values proposed by the manufacturer, 14.1 times higher than the data of the control group and 12.1 times higher than the values before surgery ($p < 0.001$). The content of other markers in this group of patients also increased and averaged: PCT – 328.3 ± 284.0 ng/ml ($p < 0.001$), hsCRP – 211.68 ± 153.52 mg/l ($p < 0.001$), IL6–982.4 ± 128.3 pg/ml ($p < 0.001$), which is in accordance with the literature data indicated the development of sepsis [11]. At the same time, the lactate level in this group of patients (I) increased and amounted to 6.31 ± 0.4 mmol/l ($p < 0.05$), which, in turn, reflected the fact of bacteremia with the development of metabolic

Table 1. Interpretation of presepsin level results

Presepsin Level* (pg/ml)	Diagnosis
< 200	Sepsis excluded
200–299	Low chance of systemic infection
300–499	Possible systemic infection
500–999	Moderate risk of sepsis, increased risk of adverse outcome
≥ 1000	High risk of systemic infection (severe sepsis/septic shock). High risk of 30-day mortality, comparable to the risk on the APACHE scale ≥ 25

Note: presepsin values are recommended by the manufacturer of test systems LSI Medience Corporation, Japan, 2013.

acidosis characteristic of the septic process. The WBC level also increased to 13.15 ± 2.55 × 10^9/L ($p < 0.05$). This, along with lymphopenia observed in almost all patients, the appearance of immature granulocytes in the blood and a significant number of rod-shaped forms of neutrophils (more than 25.0 %), reflected the presence of an inflammatory process caused by both the body's reaction to surgery and bacteremia. The development of sepsis in this group of patients was confirmed by positive results of blood culture for hemoculture.

In the II group of patients (without sepsis) after surgery, the degree of increase in the concentration of the studied parameters was less pronounced and had a short-term character. Thus, the P-SEP level averaged 657.5 ± 547.5 pg/ml in the group, 2.1 times higher than the reference data ($p < 0.001$), 3.6 times higher than the control values ($p < 0.001$), 3.2 times higher than the results obtained before surgery ($p < 0.001$) and 3.9 times It was lower than the values in group I patients (with sepsis) ($p < 0.001$), which is extremely important in assessing the role

Table 2. Dynamics of changes in the level of sepsis markers in cancer patients

Indicators, reference values, units of measurement	Groups				
	Control	Group I (n = 3)		Group II (n = 14)	
		Before surgery	After surgery	Before surgery	After surgery
P-SEP, < 320 pg/ml	182.7 ± 11.9 (170.8–194.6)	213.7 ± 47.7 (166.0–261.5)	2577.5 ± 1762.5 (815.0–4340.0) $p_1 < 0.001$ $p_2 < 0.001$	206.4 ± 39.6 (166.8–246)	657.5 ± 547.5 (110.0–1205.0) $p_1 < 0.001$ $p_2 < 0.001$ $p_3 < 0.001$
hsCRP, < 5.0 mg/l	1.24 ± 0.77 (0.47–2.01)	2.4 ± 0.3 (2.0–3.1) $p_1 < 0.05$	211.68 ± 153.52 (58.16–365.2) $p_1 < 0.001$ $p_2 < 0.001$	2.1 ± 0.2 (1.9–3.3) $p_1 < 0.05$	32.2 ± 21.4 (10.8–53.6) $p_1 < 0.001$ $p_2 < 0.001$ $p_3 < 0.001$
PCT, < 0.05 ng/ml	0.015 ± 0.015 (0.00–0.03)	0.025 ± 0.015 (0.01–0.04)	328.3 ± 284.0 (44.24–612.33) $p_1 < 0.001$ $p_2 < 0.001$	0.01 ± 0.01 (0.00–0.02)	2.6 ± 0.5 (2.10–3.05) $p_1 < 0.05$ $p_2 < 0.05$ $p_3 < 0.001$
IL6, < 7.0 pg/ml	2.85 ± 1.75 (1.1–4.6)	4.0 ± 0.2 (3.3–4.7)	982.4 ± 128.3 (45.46–1127.7) $p_1 < 0.001$ $p_2 < 0.001$	3.6 ± 0.3 (3.3–3.9)	10.1 ± 1.5 (8.6–11.6) $p_1 < 0.05$ $p_2 < 0.05$ $p_3 < 0.001$
Lactate, 0.5–2.2 mmol/l	1.56 ± 0.48 (1.08–2.04)	1.66 ± 0.22 (1.44–1.88)	6.31 ± 0.4 (5.91–6.71) $p_1 < 0.05$ $p_2 < 0.001$	1.59 ± 0.27 (1.32–1.86)	2.06 ± 0.68 (1.38–2.74) $p_3 < 0.001$
WBC, 4.0–10.0 × 10^9/L	7.4 ± 2.1 (5.3–9.5)	10.95 ± 2.55 (8.4–13.5)	13.15 ± 2.55 (10.60–15.7) $p_1 < 0.05$	10.15 ± 2.25 (7.9–12.4)	15.2 ± 5.6 (9.6–20.8) $p_1 < 0.05$

Note: values are statistically significant if $p < 0.05$ – $p < 0.001$
p_1 – in comparison with control group;
p_2 – in comparison with indicators before the surgery;
p_3 – in comparison with indicators in the group I.

of presepsin as an early marker of sepsis. The PCT content increased on average to 2.6 ± 0.5 ng/ml ($p < 0.05$), hsCRP – 32.2 ± 21.4 mg/l ($p < 0.05$), IL6–10.1 ± 1.5 pg/ml ($p < 0.05$) (Table 2). The lactate level remained within the reference values. The totality of laboratory data, the clinical condition of patients, and the negative results of hemoculture made it possible to exclude the development of the septic process in this group of patients. We believe that the marked increase in the level of acute phase proteins and WBC (14.2 × 10^9/L) in group II patients is due to the peculiarities of the immune response of cancer patients to extensive surgery. The level of the studied markers began to decrease already on 3–4 days, which was expected and typical for this group of patients (without sepsis).

Thus, changes in the presepsin level seemed to be the most significant. The results obtained confirm the data of other studies, which note that P-SEP is an effective biomarker of sepsis, which complements the clinical assessment, and is also significant in diagnosing the severity of sepsis and the effectiveness of therapy [11–13]. It has been shown that with the development of systemic infections, presepsin increases earlier than other markers of sepsis, and regardless of their increase or decrease, with 100 % reliability, subsequently confirmed by a positive test for hemocultures, diagnoses sepsis before the manifestation of clinical symptoms, which allows timely initiation of therapy, predicts favorable and unfavorable outcomes [14]. In a study by M. Behnes et al. (2014), the diagnostic level of P-SEP ≥ 530 pg/ml was established in sepsis, and in severe sepsis – ≥ 600 pg/ml [12]. In a study by T. Shozushima et al. (2011) the following levels of P-SEP were established: local infection – 721.0 ± 611.3 pg/ml; sepsis – 817.9 ± 572.7 pg/ml; severe sepsis – 1992.9 ± 1509.2 pg/ml [15]. In other studies in patients with sepsis and severe sepsis, the optimal borderline level of P-SEP for detecting the development of sepsis with artificial lung ventilation was 1,965 pg/ml, in the absence of sepsis – < 1600 pg/ml [13].

According to our data, in patients with malignant tumors of thoraco-abdominal localization in the absence of confirmed bacteremia, there is an increase in presepsin levels on the 2nd day after surgery with a maximum level 1205.0 pg/ml, and in a similar group of patients with confirmed sepsis, presepsin values averaged 2577.5 ± 1762.5 pg/ml with a maximum level 4340.0 pg/ml, which correlated with the dynamics of changes in the concentration of other markers of sepsis – hsCRP, PCT, IL6. According to the results of the study, this category of cancer patients after undergoing surgery has a moderate risk of sepsis and an increased risk of its adverse outcome, which serves as the basis for starting antibiotic therapy in accordance with the protocols for the treatment of septic conditions. In this regard, the study of presepsin levels, along with widely used markers – hsCRP, PCT, IL6, will make it possible to diagnose sepsis in the early postoperative period in cancer patients.

CONCLUSION

Changes in the levels of sepsis markers in early postoperative period can be used as a basis for prescribing antibiotic therapy in patients with malignant neoplasms of thoracoabdominal localization. Presepsin may be recommended as an early marker of sepsis in patients with oncological pathology.

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Information about authors:

Nailya K. Guskova ✉ – Cand. Sci. (Biol.), head of clinical diagnostic laboratory, National Medical Research Centre for Oncology, Rostov-on-Don, Russian Federation. ORCID: https://orcid.org/0000-0002-4222-1579, SPIN: 5407-6285 AuthorID: 306979, Scopus Author ID: 6506703993

Antonina A. Morozova – biologist, clinical and diagnostic laboratory, National Medical Research Centre for Oncology, Rostov-on-Don, Russian Federation. ORCID: https://orcid.org/0000-0003-3443-4694

Dmitriy A. Rozenko – Cand. Sci. (Med.), head of department of anesthesiology and intensive care, National Medical Research Centre for Oncology, Rostov-on-Don, Russian Federation. ORCID: https://orcid.org/0000-0002-5563-484X, SPIN: 4658-5058, AuthorID: 917988

Alexandra V. Alyoshkina – MD, anesthesiologist-resuscitator, department of anesthesiology and intensive care, National Medical Research Centre for Oncology, Rostov-on-Don, Russian Federation. ORCID: https://orcid.org/0000-0002-1532-2761

Aleksandr M. Skopintsev – MD, anesthesiologist-resuscitator, department of anesthesiology and intensive care, National Medical Research Centre for Oncology, Rostov-on-Don, Russian Federation. ORCID: https://orcid.org/0000-0001-8834-4817, SPIN: 3635-3780, AuthorID: 1096021

Olesya N. Selyutina – biologist, clinical and diagnostic laboratory, National Medical Research Centre for Oncology, Rostov-on-Don, Russian Federation. ORCID: https://orcid.org/0000-0001-6762-0835, SPIN: 4347-0302, AuthorID: 759134, Scopus Author ID: 57194276434

Nadezhda V. Golomeeva – biologist, clinical and diagnostic laboratory, National Medical Research Centre for Oncology, Rostov-on-Don, Russian Federation. ORCID: https://orcid.org/0000-0001-5009-5560

Ekaterina A. Guskova – Cand. Sci. (Med.), obstetrician-gynecologist Clinical and Diagnostic Center «DA VINCI», Rostov-on-Don, Russian Federation. SPIN: 6776-4011, AuthorID: 812913

Aliya K. Donskaya – MD, radiotherapist, radiotherapy department, National Medical Research Centre for Oncology, Rostov-on-Don, Russian Federation. SPIN: 9764-9563, AuthorID: 734505

Irina V. Tselishcheva – biologist, clinical and diagnostic laboratory, National Medical Research Centre for Oncology, Rostov-on-Don, Russian Federation. ORCID: https://orcid.org/0000-0002-9096-0173

Anastasiya S. Nozdricheva – biologist, clinical and diagnostic laboratory, National Medical Research Centre for Oncology, Rostov-on-Don, Russian Federation. ORCID: https://orcid.org/0000-0003-3336-9202

Contribution of the authors:

Guskova N. K. – development of research design, systematization and analysis of the data obtained, writing the text of the manuscript, consultation;
Morozova A. A. – performing laboratory research, collecting, systematization and analysis of the data obtained, writing the text of the manuscript;
Rozenko D. A. – analysis of the received data, consultation;
Alyoshkina A. V. – analysis of the received data, consultation;
Skopintsev A. M. – analysis of the received data, consultation;
Selyutina O. N. – systematization and analysis of the data obtained, review of publications on the topic of the article, writing the text of the manuscript;
Golomeeva N. V. – performing laboratory tests, analyzing the data obtained;
Guskova E. A. – analysis of the received data, consultation;
Donskaya A. K. – analysis of the received data, consultation;
Tselishcheva I. V. – collection of clinical material;
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ORIGINAL ARTICLE

MODELING OF MULTIPLE PRIMARY MALIGNANT TUMORS IN EXPERIMENT

E. M. Frantsiyants, I. V. Kaplieva, V. A. Bondovkina, E. I. Surikova, I. V. Neskubina, L. K. Trepitaki, Yu. A. Pogorelova, N. D. Cheryarina, E. A. Sheiko✉, I. M. Kotieva, K. A. Shumarin

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

ABSTRACT

Purpose of the study. Creation and study of models of primary multiple malignant tumors (MMPT model) under experimental conditions.

Materials and methods. The study was carried out involving male and female BALB/c Nude mice (n = 42). Experimental groups of mice: with melanoma B16/F10 (B16/F10), males (control 1) and females (control 3) by n = 7; control 2 – with sarcoma 45 (C45), males n = 7; control 4 – with Guerin carcinoma (KG), females n = 7; basic: MMPT model No. 1 – B16/F10 and S45, males n = 7, and MMPT model No. 2 – B16/F10 and GC, females n = 7. 0.5 ml suspension of murine B16/F10 melanoma tumor cells diluted in the saline proportions 1:20 was injected under the skin of the left dorsal side to all animals with MMPT model, as well as 0.5 ml of a suspension containing 0.50×10^6 S45 or GC tumor cells in the saline under the skin on the right dorsum. Control groups received the same amount of tumors as the MMPT model.

Results. Tumors in male mice in MMPT model No. 1 appeared simultaneously and significantly earlier than in controls: B16/F10 melanoma by 3 times, S45 by 2 times. Tumor zises in MMPT model No. 1 were larger than in the corresponding controls: by 8.5 times at the area of B16/F10 melanoma inoculation and by 2.2 times at the area of S45 inoculation. Melanoma metastasized under the S45 capsule. Tumor at the area of GC transplantation in MMPT model No. 2 grew 5 times faster than at the area of B16/F10 melanoma injection; both tumors appeared on average 3 times earlier than in control groups 3 and 4. Tumor volumes in MMPT model No. 2 were larger than in the corresponding controls: by 7.5 times at the area of B16/F10 melanoma inoculation and by 2.2 times at the area of GC inoculation. However, almost the entire volume of the tumor node in the area of B16/F10 melanoma transplantation was represented by GC tumor tissue due to metastasis from the primary GC tumor. Melanoma remained as a small black spot with a diameter of 5–6 mm at the area of its inoculation under the skin. The average survival of mice in MMPT models No. 1 and No. 2 was 1.5–2 times ($p < 0.05$) lower than in the corresponding controls.

Conclusions. Sequential subcutaneous transplantation of mouse B16/F10 melanoma and rat sarcoma 45 to BALB/c Nude mice increased the malignant potential of each tumor: the time of their onset was shorter, and the growth rate of tumors increased which decreased the survival of animals. Sequential subcutaneous transplantation of mouse B16/F10 melanoma and Guerin's rat carcinoma to female BALB/c Nude mice suppressed tumor growth of B16/F10 melanoma and increased the malignant potential of rat GC.

Keywords:
BALB/c Nude mice, sarcoma 45, Guerin's carcinoma, B16/F10 melanoma, multiple primary tumors, males, females

For correspondence:
Elena A. Sheiko – Cand. Sci. (Biol.), junior research fellow of the laboratory of Malignant Tumor Pathogenesis Study National Medical Research Centre for Oncology, Rostov-on-Don, Russian Federation.
Address: 63 14 line str., Rostov-on-Don 344037, Russian Federation
E-mail: esheiko@inbox.ru
ORCID: https://orcid.org/0000-0002-9616-8996
SPIN: 7293-3480, AuthorID: 479978

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ОРИГИНАЛЬНАЯ СТАТЬЯ

МОДЕЛИРОВАНИЕ ПЕРВИЧНО-МНОЖЕСТВЕННЫХ ЗЛОКАЧЕСТВЕННЫХ ОПУХОЛЕЙ В ЭКСПЕРИМЕНТЕ

Е. М. Франциянц, И. В. Каплиева, В. А. Бандовкина, Е. И. Сурикова, И. В. Нескубина, Л. К. Трепитаки, Ю. А. Погорелова, Н. Д. Черярина, Е. А. Шейко✉, И. М. Котиева, К. А. Шумарин

НМИЦ онкологии, г. Ростов-на-Дону, Российская Федерация
✉ esheiko@inbox.ru

РЕЗЮМЕ

Цель исследования. Создание и изучение моделей первично-множественных злокачественных опухолей (модель ПМЗО) в условиях эксперимента.

Материалы и методы. Работа выполнена на мышах обоего пола линии BALB/c Nude (*n* = 42). Экспериментальные группы мышей: с меланомой B16/F10 (B16/F10), самцы (контроль 1) и самки (контроль 3) по *n* = 7; контроль 2 – с саркомой 45 (С45), самцы *n* = 7; контроль 4 – с карциномой Герена (КГ), самки *n* = 7; основные: модель ПМЗО № 1 – B16/F10 и С45, самцы *n* = 7 и модель ПМЗО № 2 – B16/F10 и КГ, самки *n* = 7. Каждому животному с моделью ПМЗО под кожу спины слева перевивали по 0,5 мл взвеси клеток B16/F10 в физ. растворе в разведении 1:20, справа – по 0,5 мл взвеси, содержащей 0,5 × 10^6 клеток С45 или КГ в физ. растворе. Контрольным мышам перевивали опухоли в том же количестве и объёме, что и в модели ПМЗО.

Результаты. В модели ПМЗО № 1 опухоли появлялись одновременно, быстрее, чем в контроле: B16/F10 – в 3 раза, С45 – в 2 раза. Объём каждой опухоли в модели ПМЗО № 1 превышал объём опухолей в соответствующих контролях: B16/F10 – в 8,5 раза, С45 – в 2,2 раза. B16/F10 метастазировала под капсулу опухоли С45. В модели ПМЗО № 2 опухоль в месте перевивки КГ вырастала в 5 раз быстрее, чем в месте перевивки B16/F10, при этом, обе опухоли появлялись в среднем в 3 раза раньше, чем в контролях 3 и 4. Объём опухолей в модели ПМЗО № 2 превышал объём опухолей в соответствующих контролях: B16/F10 – в 7,5 раза, КГ – в 2,1 раза. Однако, большую часть опухоли в зоне введения B16/F10 занимала ткань КГ вследствие её метастатического отсева из первичной опухоли. Ткань B16/F10 сохранялась в виде небольшого чёрного пятна в месте её введения под кожей. Средняя продолжительность жизни мышей в моделях ПМЗО № 1 и № 2 была в 1,5–2 раза ($p < 0,05$) меньше, чем в соответствующих контролях.

Заключение. Последовательная подкожная перевивка мышиной B16/F10 и крысиной С45 самцам мышей BALB/c Nude увеличивала злокачественный потенциал каждой из опухолей: опухоли появлялись раньше и росли активнее, что способствовало уменьшению продолжительности жизни животных. Последовательная подкожная перевивка мышиной B16/F10 и крысиной КГ самкам мышей линии BALB/c Nude способствовала подавлению опухолевого роста мышиной B16/F10 и увеличивала злокачественный потенциал крысиной КГ.

Ключевые слова:
мыши линии BALB/c Nude, саркома 45, карцинома Герена, меланома B16/F10, полинеоплазии, самцы, самки

Для корреспонденции:
Шейко Елена Александровна – к.б.н., младший научный сотрудник лаборатории изучения патогенеза злокачественных опухолей ФГБУ «НМИЦ онкологии» Минздрава России, г. Ростов-на-Дону, Российская Федерация.
Адрес: 344037, Российская Федерация, г. Ростов-на-Дону, ул. 14 линия, д. 63
E-mail: esheiko@inbox.ru
ORCID: https://orcid.org/0000-0002-9616-8996
SPIN: 7293-3480, AuthorID: 479978

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RELEVANCE

Despite the fact that malignant tumors, as a disease, have been known for a long time, their experimental reproduction has not been possible for a long time. That is why the creation of this pathological process in an experiment became a major scientific achievement at the beginning of the last century. Experimental models of tumors make it possible to find out the causes, study the pathogenesis of the tumor process, and develop methods for its prevention and treatment [1]. Animal models are a powerful tool for studying the biology of neoplasms and the mechanisms of influence of various pathogenic factors on them [2–5], assessing the toxicity and effectiveness of new antitumor agents in preclinical studies [4–8]. For these purposes, mouse and rat models are most often used [9; 10]. Primary multiple malignant tumors (MMPT) were first described by Billroth T. and Reimer G. in 1889 and studied in details by Warren S., Gates O. in 1932. Based on the criteria proposed by these authors, the diagnosis of MMPT can be made if each tumor during histological examination has clear evidence of malignancy, is located separately from another tumor and is not a metastatic dropout. Experimental models of multiple homogeneous tumors-multiple myeloma (MMBD) in NSG mice have been developed, which allow us to investigate the mechanism of oncogenesis of this pathology [11; 12]. In this study, it was found that, compared with single, multiple homogeneous tumors progress more slowly, but subsequently a more severe form of MMBD develops. Since the number of cases of MMPT increases every year, the issue of developing experimental models to assess the pathogenesis of this oncological disease in several tumors of different genesis in one animal remains relevant. Experimental oncology has a sufficiently large number of models that can be used to solve many problems, but one of the unresolved ones is the problem of the development of malignant growth in various immunodeficiency conditions. Primary immunodeficiency states are a group of heterogeneous diseases characterized by recurrent infections, autoimmunity, the course of which is determined by lymphoproliferative diseases and other malignant neoplasms. Immunodeficiency has prognostic and practical consequences [13; 14]. Thus, the increasing incidence of MMPT on the background of primary immunodeficiency dictates the need to study the pathogenesis of this oncological pathology.

The purpose of the study: to create and study models of primary multiple malignant tumors in experimental conditions.

MATERIALS AND METHODS

The work was performed on BALB/c Nude mice with genetically determined thymus aplasia (*n* = 42), of which males (*n* = 21) and females (*n* = 21). Experimental groups of mice: with melanoma B16/F10 (B16/F10) – males, control 1, and females, control 3, *n* = 7; with sarcoma 45 (S45) – males, control 2, *n* = 7; with Guerin carcinoma (GC) – females, control 4, *n* = 7 and the MMPT models: MMPT model No. 1 (B16/F10 and S45), *n* = 7 and MMPT model No. 2 (B16/F10 and GC), *n* = 7. Work with animals was carried out in accordance with the rules of the "European Convention for the Protection of Animals Used in Experiments" (Directive 86/609/EEC).

Reproduction of MT No. 1 consisted in successive subcutaneous inoculation of B16/F10 and S45 to male mice: 0.5 ml of suspension of B16/F10 at a dilution of 1:20 in phys. the solution was injected below the angle of the left scapula, 0.5 ml of suspension S45 containing 0.5×10^6 cells was injected below the angle of the right scapula. The control was male mice with either B16/F10 or S45 in the same dose and volume as in MMPT model No. 1. To reproduce MMPT model No. 2, female mice were used, which were sequentially transplanted with B16/F10 and GC. The method of re-grafting was carried out, as in MMPT model No. 1. However, if below the angle of the left shoulder blade, 0.5 ml of suspension B16/F10 was still injected into the physical. In a dilution solution of 1:20, then 0.5 ml of a GC suspension containing 0.5×10^6 cells was injected below the angle of the right scapula. The control was female mice with either B16/F10 or GC in the same dose and volume as mice with MMPT model No. 2.

Statistical processing of the obtained results was carried out using the Student's parametric criterion on a personal computer using the STATISTICA 10.0 program and the nonparametric Wilcoxon-Mann-Whitney criterion. All the results obtained were checked for compliance with the law on normal distribution. Some of the indicators corresponded to the law, some did not. For those indicators that corresponded to the normal distribution, we used parametric statistics, for those indicators whose distribution did not cor-

respond to the normal distribution, we used nonparametric statistics. The differences between the two samples were considered statistically significant at $p < 0.05$.

RESEARCH RESULTS AND DISCUSSION

When reproducing MMPT model No. 1, the following results were obtained, which are presented in Table 1.

As follows from Table 1, tumors B16/F10 and S45, transplanted in an independent version, appeared approximately at the same time. At the same time, after B16/F10 transplantation, tumors began to be palpated from 11 days (3 mice, 42.8 %), from 45 – from 7 days (1 mouse, 14.3 %) and 10 days (2 mice, 28.6 %). The term of the end of the appearance of tumors in male mice with B16 / F10 is 14 days (1 mouse, 14.3 %) and 15 days (1 mouse, 14.3 %), in male mice with S45–13 days (1 mouse, 14.3 %). In all mice with MMPT model No. 1, tumors appeared earlier, already 1 week after transplantation. At the same time, the tumor B16/F10 began to be determined in the form of a black millet grain starting from 3 days after the transfer (2 mice, 28.6 %), and S45 – in the form of a white string 4–5 mm long from 4 days after the transfer (3 mice, 42.8 %). The deadline for the appearance of both tumors is 7 days after the transfer (1 mouse, 14.3 %). Thus, in MMPT model No. 1, with sequential grafting of tumors, tumors B16/F10 appeared 3 times faster, and S45 2 times faster than with independent grafting (Table 1). There was no statistically significant difference in the timing of the appearance of tumors of various histological structures, either in an independent or combined variant.

The volume of tumors in all animals was measured before the death of the first mice with MMPT model No. 1 – on the 20th day after transplantation. It was found that the volume of each tumor transplanted sequentially into one mouse exceeded the volume of the corresponding tumors transplanted in the standard isolated variant: B16/F10 – by 2.2 times, S45 – by 3.2 times (Table 1).

Table 1. Features of growth of mouse B16/F10 melanoma and rat sarcoma 45 in the MMPT model No. 1 in male mice of the BALB/c Nude line, (M ± m)

Study object	Control 1 (B16/F10), *n* = 7	Control 2 (C45), *n* = 7	MMPT model No. 1, *n* = 7	
			B16/F10	C45
Date of appearance of the tumor, day	11.3 ± 0.6	10.9 ± 0.8	4.3 ± 0.4[1]	5.4 ± 0.6[2]
The volume of the tumor 3 weeks after the transfer, cm^3	1.3 ± 0.1	1.1 ± 0.1	2.9 ± 0.3[1]	3.5 ± 0.3[2]
Life length, days	30.4 ± 2.3	43.0 ± 2.9	22.0 ± 0.6[1,2]	

Note: statistically significant difference is revealed in comparison with [1] – isolated B16/F10 melanoma growth; [2] – isolated sarcoma 45 growth ($p < 0,05$). B16/F10, i.e B16/F10 melanoma, S45, i.e. sarcoma 45.

Table 2. Features of the growth of mouse melanoma B16/F10 and rat GC in the MMPT model No. 2 in female mice of the BALB/c Nude line, (M ± m)

Study object	Control 3 (B16/F10), *n* = 7	Control 4 (GC), *n* = 7	MMPT model No. 2, *n* = 7	
			B16/F10	GC
Date of appearance of the tumor, day	12.3 ± 0.5	7.6 ± 0.4[1]	4.0 ± 0.6[1]	2.7 ± 0.5[2]
The volume of the tumor 2 weeks after the transfer, cm^3	0.2 ± 0.09	3.8 ± 0.2[1]	1.7 ± 0.1[1]	8.4 ± 0.9[2]
Life length, days	33.3 ± 2.4	24.9 ± 1.0[1]	16.6 ± 0.8[1,2]	

Note: statistically significant difference is revealed in comparison with [1] – isolated B16/F10 melanoma growth; [2] – with isolated growth of GC ($p < 0,05$). B16/F10 – melanoma B16/F10, GC is Guerin's carcinoma.

It was found that B16/F10 in MMPT model No. 1, in addition to typical places (lungs, spleen, liver), metastasized to S45 from the side adjacent to the chest – under the capsule of the tumor node.

The life expectancy of the mice depended on the histological type of tumor and the variant of grafting: isolated or combined. Mice with isolated growth of rat S45 lived for the longest time: their minimum life expectancy was 35 days (2 mice, 28.6 %), maximum – 56 days (1 mouse, 14.3 %), average – 43 days (Table 1). Mice with isolated B16/F10 growth lived on average 10 days less than mice with S45, while their minimum life expectancy was 27 days (3 mice, 42.8 %), the maximum was 42 days (1 mouse, 14.3 %). Mice with MMPT model No. 1 lived the least: their average life expectancy was 1.5 times ($p < 0.05$) less than in mice with isolated growth B16/F10, and 2.0 times less than in mice with isolated growth S45 (Table 1); their minimum life expectancy was 21 days (3 mice, 42.8 %), the maximum is 25 days (1 mouse, 14.3 %).

Thus, with successive subcutaneous grafting of mouse B16/F10 and rat S45 to male mice of the BALB/c Nude line, the malignant potential of each of the tumors increased, which manifested itself in shortening the time of their appearance and increasing the rate of tumor growth and contributed to a decrease in the life expectancy of animals with MMPT model No. 1.

When reproducing MMPT model No. 2, the following results were obtained, which are presented in Table 2.

In female mice of the BALB/c Nude line, rat GC, with subcutaneous grafting, appeared on average 5 days earlier ($p < 0.05$) than mouse B16/F10, also grafted under the skin. The period of the appearance of the GC tumor is from 6 to 9 days from the moment of transplantation, B16/F10 from 11 to 15 days. In female mice with sequential grafting of two strains, both tumors appeared almost immediately: GC in the first mouse (14.3 %) the day after grafting, B16 /F10 two days later in 2 mice (28.6 %); the end date of the appearance of GC 4–5 days (1 mouse, 14.3 %), B16/F10 5 (3 mice, 42.8 %) – 6 (1 mouse, 14.3 %) days. The tumor B16/F10 had the appearance of a black millet grain, the tumor GC was a white rounded formation with a diameter of 3.2 ± 0.03 mm. Thus, in MMPT model No. 2, both tumors appeared, on average, three times faster than with isolated grafting, while there was no statistically significant difference in the timing of the appearance of combined tumors (Table 2). The volume of tumors in mice in all groups was measured before the death of the first mice with MMPT model No. 2 on 14 days from the moment of the transfer. Figure 1 shows a photograph of a female with two tumor nodes after successive transplantation of mouse B16/F10 (left) and rat GC (on the right).

The volume of each tumor sequentially transplanted into one mouse exceeded the volume of the corresponding tumors transplanted in an independent variant: the tumor on the left (in the area of B16/F10 grafting) compared with a single tumor B16/F10 7.5 times, the tumor on the right (in the area of GC grafting) compared with a single tumor GC – 2.2 times (Table 2). The subcutaneous tumor located at the site of the B16/F10 grafting had an atypical appearance for melanoma: rounded shape, soft-elastic elastic consistency, light color (with the exception of a small spot, i.e. the grafting point, 3.4 ± 0.2 mm in diameter, which was black in color, and a pronounced venous network on the skin (Fig. 2).

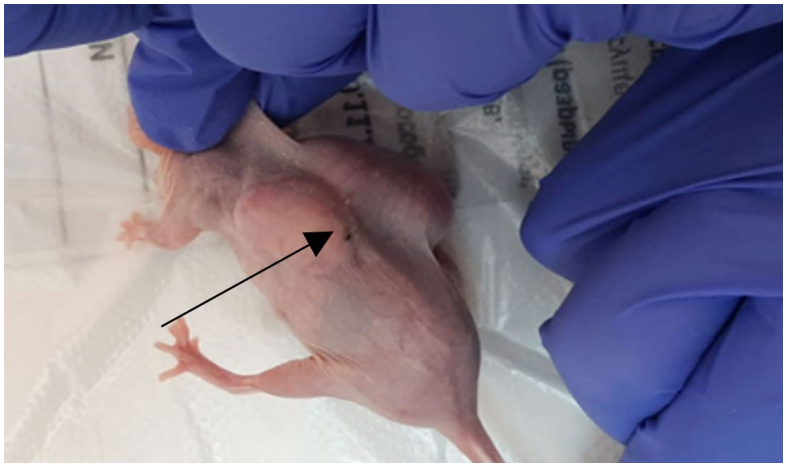

Fig. 1. Type of subcutaneous tumors: melanoma B16/F10 (left) and GC (right) in a female of the BALB/c Nude line in the experimental MMPT model No. 2; a black spot is the place of melanoma grafting (arrow).

Upon autopsy, it was found that GC in all mice metastasized to B16/F10 and almost completely suppressed its growth. Most of the subcutaneous tumor located on the left was occupied by GC tissue. Melanoma B16/F10 was represented by a small "island" of tissue of uneven color, located "on top" of the tumor tissue GC. Immediately under the skin at the injection site of B16/F10 cells, a tumor site with a diameter of 3.3 ± 0.2 mm of black color was visualized. Around the dark "center" there was a light part B16/F10 of the same loose pasty consistency as the dark part, with a diameter of 6.5 ± 0.3 mm. For the rest, the tumor on the left had the appearance of an elongated node of grayish-pink color, dense elastic consistency – just like the tumor on the right, which was much larger in volume. The right and left tumors did not merge with each other, there was a small distance between them of at least 2–3 mm. A small focus of caseous necrosis with a diameter of 6.8 ± 0.2 mm was registered in the center of the right tumor of the GC, there was no necrosis on the left. The smaller size, absence of necrosis, and visually more "young" tissue of the GC on the left testified to its later occurrence than on the right, which, combined with the remnants of B16/F10 soldered to the left tumor, indicated the metastatic nature of the tissue of the GC on the left. B16/F10 did not metastasize even to typical sites, including lungs. The rounded formation under the skin, located below the left tumor, turned out to be the end of the sternum, deployed by the right tumor node.

The life expectancy of female mice with MMPT model No. 2 was minimal, a little more than 2 weeks (Table 2). Female mice with isolated GC growth lived a week longer. The life expectancy of female mice with B16/F10 turned out to be maximum, more than 4 weeks (Table 2).

Thus, successive subcutaneous inoculation of mouse B16/F10 and rat GC to female mice of the BALB/c Nude line contributed to the suppression of tumor growth of B16/F10 and increased the malignant potential of GC.

CONCLUSION

Summarizing the results obtained from the developed and studied experimental MMPT model No. 1 and MMPT model No. 2 in animals with congenital, genetically determined immunodeficiency, it can be concluded that with successive grafting of heterogeneous tumor material, the "manifests itself" of each tumor depends on the histological structure, and, consequently, the biological activity of both tumors. With different combinations, the same tumor in the MMPT model "behaves" differently. In one case, its aggressiveness may increase (B16/F10 with simultaneous growth with S45 in MMPT model No. 1 in males), which manifests itself not only in an increase in its growth rate, but also in active metastasis, including to another tumor (S45). In another case, its growth is almost completely suppressed by the second tumor (B16/F10 with simultaneous growth with GC in MMPT model No. 2 in females).

In general, successive subcutaneous inoculation of mouse B16/F10 and rat S45 to male mice of the BALB/c Nude line increased the malignant potential of each tumor: the period of their appearance accelerated and the rate of tumor growth increased, which contributed to a decrease in the life expectancy of animals. Successive subcutaneous inoculation of mouse B16/F10 and rat GC to female BALB/c Nude mice contributed to the suppression of tumor growth in B16/F10 and increased the malignant potential of GC.

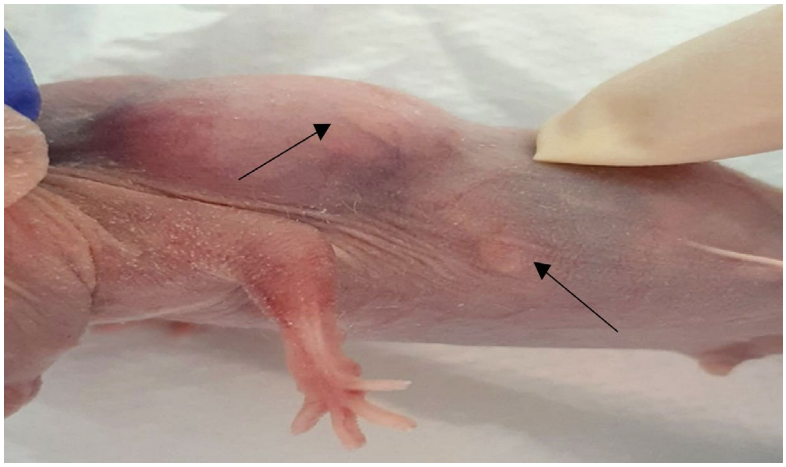

Fig. 2. View of the subcutaneous tumor located on the left – the side of the melanoma B16/F10 grafting in a female of the BALB/c Nude line in the MMPT model No. 2, with a pronounced venous network (arrow); below the tumor is a rounded cartilaginous formation with a diameter of about 5–6 mm.

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Information about authors:

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

Irina V. Kaplieva – Dr. Sci. (Med.), senior researcher of the laboratory for the study of pathogenesis of malignant tumors of National Medical Research Centre for Oncology, Rostov-on-Don, Russian Federation. ORCID: http://orcid.org/0000-0002-3972-2452, SPIN: 5047-1541, AuthorID: 734116

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

Ekaterina I. Surikova – Cand. Sci. (Biol.), senior researcher of the laboratory for the study of pathogenesis of malignant tumors of National Medical Research Centre for Oncology, Rostov-on-Don, Russian Federation. ORCID: http://orcid.org/0000-0002-4318-7587, SPIN: 2401-4115, AuthorID: 301537

Irina V. Neskubina – Cand. Sci. (Biol.), senior researcher at the laboratory for the study of the pathogenesis of malignant tumors National Medical Research Centre for Oncology, Rostov-on-Don, Russian Federation. ORCID: https://orcid.org/0000-0002-7395-3086, SPIN: 3581-8531, AuthorID: 794688

Lidiya K. Trepitaki – assistant researcher at the laboratory for the study of pathogenesis of malignant tumors of National Medical Research Centre for Oncology, Rostov-on-Don, Russian Federation. ORCID: http://orcid.org/0000-0002-9749-2747, SPIN: 2052-1248, AuthorID: 734359

Yuliya A. Pogorelova – Cand. Sci. (Biol.), senior researcher at Laboratory of Malignant Tumor Pathogenesis Study, National Medical Research Centre for Oncology, Rostov-on-Don, Russian Federation. ORCID: http://orcid.org/0000-0002-2674-9832, SPIN: 2168-8737, AuthorID: 558241

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

Elena A. Sheiko ✉ – Cand. Sci. (Biol.), junior research fellow of the laboratory of Malignant Tumor Pathogenesis Study National Medical Research Centre for Oncology, Rostov-on-Don, Russian Federation. ORCID: https://orcid.org/0000-0002-9616-8996, SPIN: 7293-3480, AuthorID: 479978

Inga M. Kotieva – Dr. Sci. (Med.), senior researcher of the laboratory for the study of pathogenesis of malignant tumors of National Medical Research Centre for Oncology, Rostov-on-Don, Russian Federation. ORCID: https://orcid.org/0000-0003-0252-4708, SPIN: 3478-5811, AuthorID: 637665

Konstantin A. Shumarin – PhD student of the National Medical Research Centre for Oncology, Rostov-on-Don, Russian Federation. ORCID: https://orcid.org/0000-0003-4362-9303, SPIN: 5042-4897, AuthorID: 1090463

Contribution of the authors:

Frantsyants E. M. – research concept and design, text writing, data analysis and interpretation;
Kaplieva I. V. – research concept and design;
Bandovkina V. A. – assistance in operations;
Surikova E. I. – technical editing, material processing;
Neskubina I. V. – scientific editing;
Trepitaki L. K. – assistance in operations;
Pogorelova Yu. A. – assistance in operations;
Cheryarina N. D. – technical editing, material processing;
Sheiko E. A. – technical editing;
Kotieva I. M. – scientific editing;
Shumarin K. A. – collection, analysis and interpretation of data.

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ORIGINAL ARTICLE

POST-RADIATION COMPLICATIONS IN CHILDREN WITH ACUTE LYMPHOBLASTIC LEUKEMIA WHO UNDERWENT A COURSE OF CRANIAL RADIATION

T. S. Rogova[1]✉, P. G. Sakun[1], V. I. Voshedskii[1], S. G. Vlasov[1], Yu. Yu. Kozel[1], V. V. Dmitrieva[1], O. V. Kozyuk[1], K. S. Aslanyan[2], E. V. Vasileva[2]

1. National Medical Research Centre for Oncology, Rostov-on-Don, Russian Federation
2. Regional Children's Clinical Hospital, Rostov-on-Don, Russian Federation
✉ coffeecreeps@yahoo.com

ABSTRACT

Purpose of the study. To analyze the physical and neuropsychiatric development of pediatric patients who underwent cranial irradiation in the period from 2015 to 2020 in the radiotherapy department of the National Research Center of Oncology and to assess the risk of post-radiation complications.

Materials and methods. 17 children aged from 3 to 17 years were hospitalized under medical supervision in the department of pediatric oncology of the National Medical Research Centre for Oncology. All the children underwent a course of conformal radiation therapy totally on the brain area and the first two cervical vertebrae in the radiotherapy department of the National Medical Research Centre for Oncology. 13 patients (76.7 %) underwent radiation therapy due to the prevention of neuroleukemia with a total dose of 12 Gy (a dose per fraction was 2 Gy), 2 patients with a confirmed relapse of acute lymphoblastic leukaemia (ALL) (11.65 %), 1 patient with a confirmed diagnosis of neuroleukemia (5.8 %) and 1 patient from the high-risk group (5.8 %) – with a total dose of 18 Gy (a dose per fraction was 2 Gy). Further 75 month regular medical checkup was carried out on the basis of the Regional Children's Clinical Hospital for.

Results. None of the surviving patients showed growth retardation. Two patients (11.65 %) complained of increased fatigue, decreased concentration; one patient (5.8 %) showed unmotivated irritability and aggression during the examination. Intellectual development corresponded to age in all patients (100 %). One patient (5.8 %) experienced episodes of nausea and vomiting (grade 1 on the CTCAE scale), three patients (17.7 %) suffered from headache (grade 2 on the CTCAE scale), three patients (17.7 %) complained of fever up to 38 °C (1 degree on the CTCAE scale). Two out of 17 ALL patients died due to disease progression.

Conclusion. Taking into account the different time intervals between treatment and the moment of the study (from 9 to 75 months), cranial irradiation demonstrates relative safety for patients undergoing treatment during critical periods of development of both physical and neuropsychic spheres. However, an objective assessment of the development prospects is difficult due to the relatively short time after undergoing therapy (from 9 to 75 months) and a small sample of patients.

Keywords:
acute lymphoblastic leukemia, hemoblastoses, conformal radiation therapy, cranial irradiation, neuroleukosis, post-radiation complications

For correspondence:
Tatyana S. Rogova – resident at the National Medical Research Centre for Oncology, Rostov-on-Don, Russian Federation.
Address: 63 14 line str., Rostov-on-Don 344037, Russian Federation
E-mail: coffeecreeps@yahoo.com
ORCID: https://orcid.org/0000-0003-0074-0044
SPIN: 8280-9470, AuhtorID: 1113449
ResearcherID: AAG-1260-2021

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ОРИГИНАЛЬНАЯ СТАТЬЯ

ПОСТЛУЧЕВЫЕ ОСЛОЖНЕНИЯ У ДЕТЕЙ С ОСТРЫМ ЛИМФОБЛАСТНЫМ ЛЕЙКОЗОМ, ПРОШЕДШИХ КУРС КРАНИАЛЬНОГО ОБЛУЧЕНИЯ

Т. С. Рогова[1]✉, П. Г. Сакун[1], В. И. Вошедский[1], С. Г. Власов[1], Ю. Ю. Козель[1], В. В. Дмитриева[1], О. В. Козюк[1], К. С. Асланян[2], Е. В. Васильева[2]

1. НМИЦ онкологии, г. Ростов-на-Дону, Российская Федерация
2. Областная детская клиническая больница, г. Ростов-на-Дону, Российская Федерация
✉ coffeecreeps@yahoo.com

РЕЗЮМЕ

Цель исследования. Провести анализ физического и нервно-психического развития пациентов детского возраста, прошедших курс краниального облучения в период с 2015 по 2020 гг. в отделении радиотерапии ФГБУ «НМИЦ онкологии» Минздрава России и оценить риск развития постлучевых осложнений.

Материалы и методы. Под наблюдение в отделение детской онкологии ФГБУ «НМИЦ онкологии» Минздрава России было госпитализировано 17 детей в возрасте от 3 до 17 лет. Все дети прошли курс конформной лучевой терапии тотально на область головного мозга и первых двух шейных позвонков в отделении радиотерапии ФГБУ «НМИЦ онкологии» Минздрава России. 13 пациентов (76,7 %) прошли курс лучевой терапии ввиду профилактики нейролейкоза с суммарной очаговой дозой 12 Гр (разовая очаговая доза составила 2 Гр), 2 пациента с подтвержденным рецидивом острого лимфобластного лейкоза (ОЛЛ) (11,65 %), 1 пациент с подтвержденным диагнозом нейролейкоза (5,8 %) и 1 пациент из группы высокого риска (5,8 %) – с суммарной очаговой дозой 18 Гр (разовая очаговая доза составила 2 Гр). Дальнейшее диспансерное наблюдение проводилось на базе ГБУ РО «Областная детская клиническая больница» в течение 75 мес.

Результаты. Ни у одного из выживших пациентов не было выявлено задержки физического развития. У двух пациентов (11,65 %) были жалобы на повышенную утомляемость, снижение концентрации внимания; один пациент (5,8 %) проявлял немотивированные раздражительность и агрессию во время осмотра. Интеллектуальное развитие соответствовало возрасту у всех пациентов (100 %). Один пациент (5,8 %) испытывал эпизоды тошноты и рвоты (1 степень по шкале CTCAE), три пациента (17,7 %) страдали от головной боли (2 степень по шкале CTCAE), три пациента (17,7 %) предъявляли жалобы на подъем температуры тела до 38 °С (1 степень по шкале CTCAE). Из 17 пациентов с ОЛЛ погибло двое детей в связи с прогрессированием болезни.

Заключение. Учитывая разные временные промежутки между лечением и моментом проведения исследования (от 9 до 75 мес.), краниальное облучение демонстрирует относительную безопасность для пациентов, проходящих лечение в критические периоды развития как физической, так и нервно-психической сферы. Однако, объективная оценка перспективы развития затруднена ввиду относительно маленького срока после прохождения терапии (от 9 до 75 мес.) и небольшой выборки пациентов.

Ключевые слова:
острый лимфобластный лейкоз, гемобластозы, конформная лучевая терапия, краниальное облучение, нейролейкоз, постлучевые осложнения

Для корреспонденции:
Рогова Татьяна Сергеевна – ординатор ФГБУ «НМИЦ онкологии» Минздрава России, г. Ростов-на-Дону, Российская Федерация.
Адрес: 344037, Российская Федерация, г. Ростов-на-Дону, ул. 14-я линия, д. 63
E-mail: coffeecreeps@yahoo.com
ORCID: https://orcid.org/0000-0003-0074-0044
SPIN: 8280-9470, AuhtorID: 1113449
ResearcherID: AAG-1260-2021

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INTRODUCTION

Acute lymphoblastic leukemia (ALL) is a malignant disease of the hematopoietic system, consisting in the appearance of a tumor clone from cells – hematopoietic precursors of lymphoid differentiation lines [1]. ALL is the most frequent oncological disease of childhood: pathology occupies 80 % among hemoblastoses [2; 3] and 25 % of all tumors [1]. The disease occurs in 3–4 cases per 100,000 children in Russia. Over the past 10 years in the Russian Federation, the incidence of acute lymphoblastic leukemia (ALL) in children from 0 to 17 years has increased by 34 % [4], which justifies the need for regular revision of diagnostic and treatment protocols to develop safer therapy strategies while maintaining the level of therapeutic effect. One of the stages of ALL treatment is radiation therapy, in particular, cranial irradiation, but this therapy is associated with the risk of developing immediate and long-term side effects [1; 5]. ALL in children is characterized by a relatively high percentage of five-year event-free survival (> 80 %) [1; 2]. However, an integrated approach to treatment, including radiation therapy, is associated with the risk of radiation complications (pathological changes in the body, organs and tissues developing as a result of exposure to ionizing radiation [5; 6]).

Radiation therapy as one of the stages of treatment of acute lymphoblastic leukemia

Cranial irradiation (CI) is a standard component of many ALL treatment protocols. This preventive approach is aimed at destroying blast cells located in the brain that do not respond to chemotherapy. Of great importance is the coverage of the irradiation area of the entire cerebral part of the skull and necessarily the first two cervical vertebrae. Particular attention should be paid to covering the retroorbital areas, the base of the skull, as well as deep-lying areas in the area of the middle cranial fossa [1]. Cranial irradiation up to a total focal dose of 12 Gy is indicated in patients of intermediate and high risk groups as a prevention of CNS damage, the indication for increasing the total dose to 18 Gy is the detection of relapse of ALL or the diagnosis of neuroleukosis [1; 5].

Changes in bone tissue, which can manifest themselves in the interval from several months to several years, are different: from a slight short-term violation of osteoblastic function to osteonecrosis, osteomyelitis, pathological fracture. Radiation lesions of bones, as a rule, develop after 3 months or more. The clinic of radiation injuries of bones in children is diverse, so a dose of 1.5 to 10 Gy in the area of bone growth zones is sufficient to cause a temporary delay in bone growth [1].

Given the high survival rate after complex treatment, it can be assumed that irradiation of the brain in childhood with ALL may contribute to the development of secondary tumors in the long term, various types of neurological deficits, including neuropsychiatric development delay, endocrine disorders and other consequences [5; 7].

Areas of growth of skull bones

Sphenooccipital (or sphenobasilar) synchondrosis determines the shape of the skull and spine. It is formed by the posterior surface of the sphenoid bone and the basilar part of the occipital bone. This connection can be compared with two vertebrae, located in the middle part of the base of the skull. Synchondrosis persists until the age of 20–25; later it ossifies, maintaining its mobility. Kinetic dysfunction of synchondrosis generates adaptation of the state of the wedge-shaped and occipital bones, which affects the formation of the facial bones of the skull, physiological bends and the structure of the spine, which in the future may form a scoliotic deformity in a child. Dysfunction of the sphenobasilar junction changes the shape of the skull, resulting in an asymmetric face in developmental pathology [8].

During the first year of life, another growth center appears in the nasal septum – the sphenomezoethmoid. The duration of the growth zone activity is not exactly known. According to various authors, the fusion of this growth center with the center located in the main bone occurs at the age of 12 to 25 years. The cartilaginous layers between the mesoethmoidal growth center and the nearby bones of the facial and cerebral skull (frontal, lateral masses of the latticed bone) begin to ossify gradually in 2–6 years [8].

There is a definite connection between the growth of the cerebral part of the skull and the appearance of finger depressions on the inner surface of its bones, although the mechanism of their occurrence is still unclear. They are first detected at the age of 1.5–2 years in the parietal bones, then in the occipital zone and only by 7–8 years – in the frontal. Finger depres-

sions reach their maximum severity in the puberty period, and then begin to gradually smooth out. After 15 years, the severity of these anatomical formations in various areas of the cerebral part of the skull is as follows: occipital, temporal, parietal, frontal (ratio 10:7:7:7, respectively). Some data suggest that finger indentations are more pronounced in children with delayed mental development, and their absence is an important symptom of a violation of osteogenesis processes and is usually accompanied by cortical atrophy [8].

The purpose of the study: to analyze the physical and neuropsychiatric development of children who underwent cranial irradiation in the period from

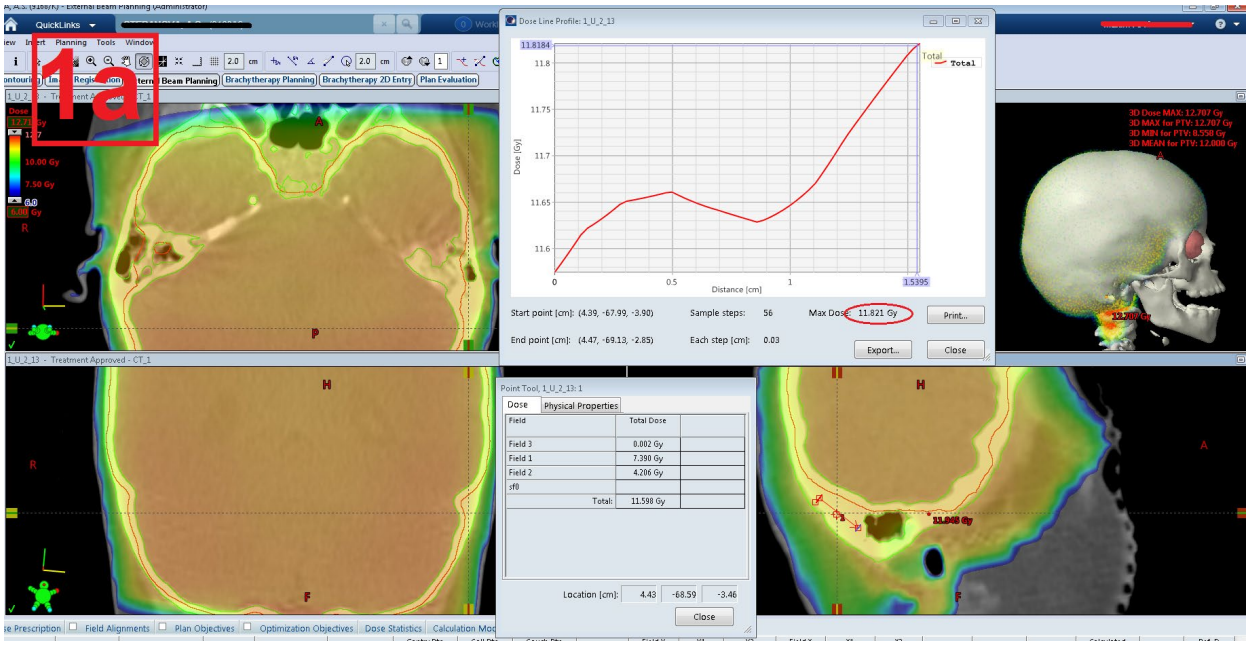

Fig. 1a. Dose load on the sphenooccipital growth zone of patient M., 4 years old. The maximum dose is 11.821 Gy.

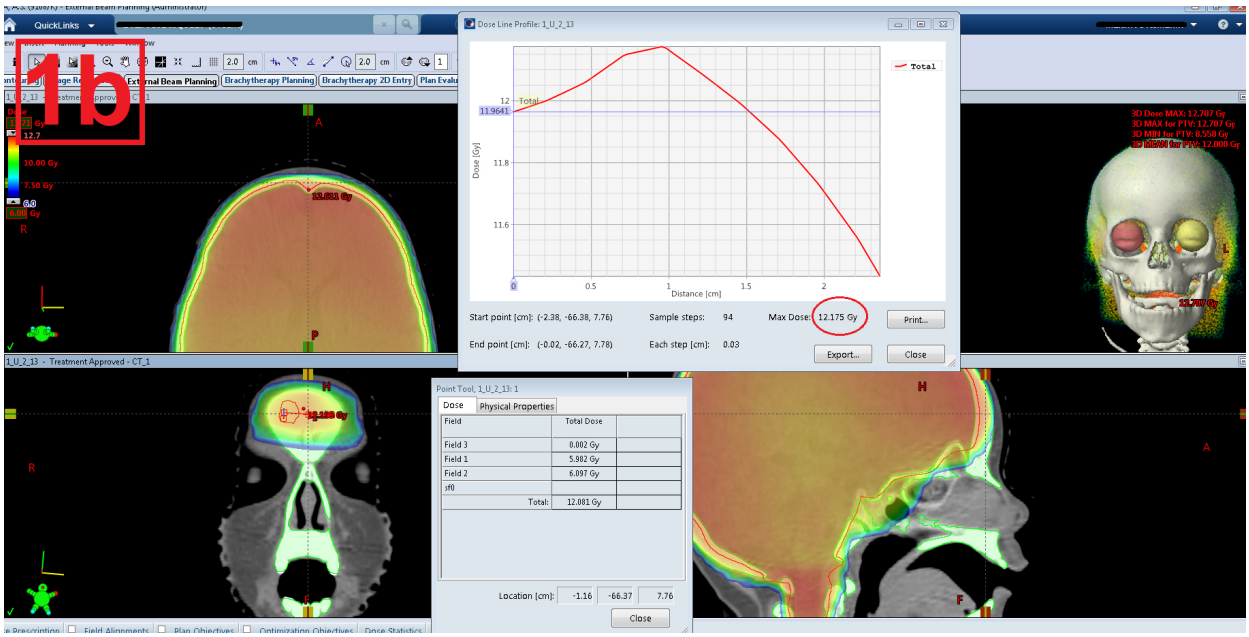

Fig. 1b. Dose load on the growth zone in the area of finger-shaped indentations of the frontal bone of patient M., 4 years old. The maximum dose is 12.175 Gy.

2015 to 2020 in the radiotherapy department of the National Medical Research Centre for Oncology and to assess the risk of post-radiation complications.

MATERIALS AND METHODS

During the period from 2015 to 2020, 17 children and adolescents aged 3 to 17 years were hospitalized under observation in the Department of Pediatric Oncology of the National Medical Research Centre for Oncology; the average age of patients was 10 years 1 month, the median age was 10 years. To conduct a course of cranial irradiation according to the protocol for the treatment of acute lymphoblastic leukemia ALL–MB-2015: 10 patients (59 %) of preschool and primary school age (3–10 years)

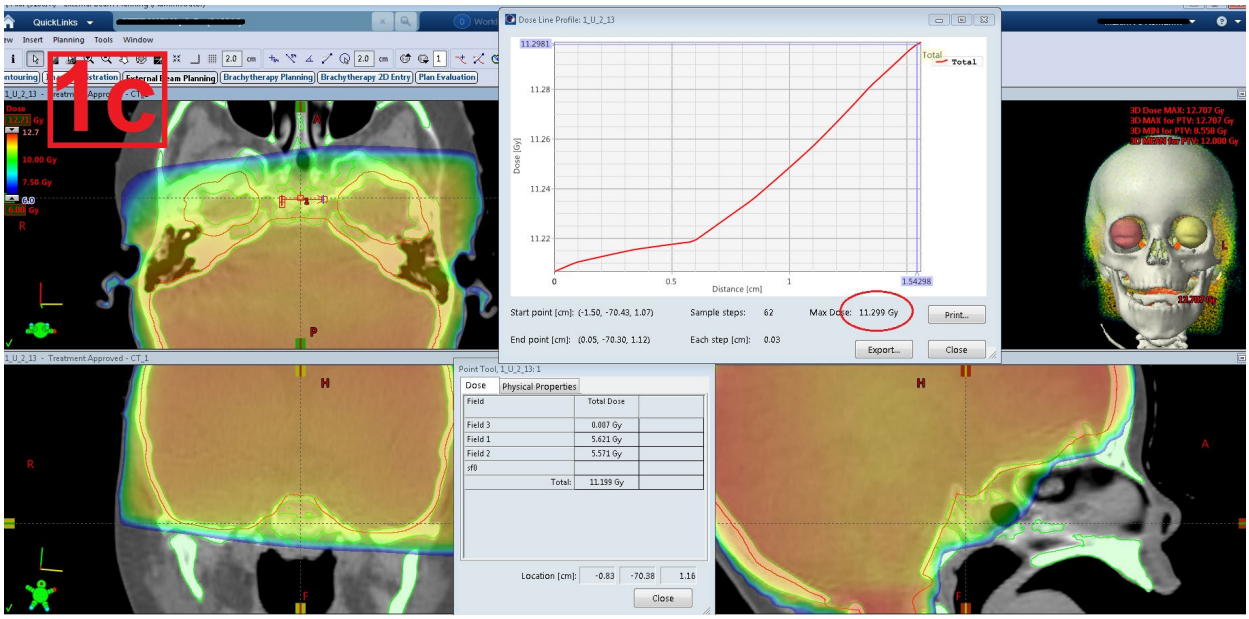

Fig. 1c. Dose load on the growth zone in the area of cartilaginous layers between the latticed and frontal bone of patient M., 4 years old. The maximum dose is 11.415 Gy.

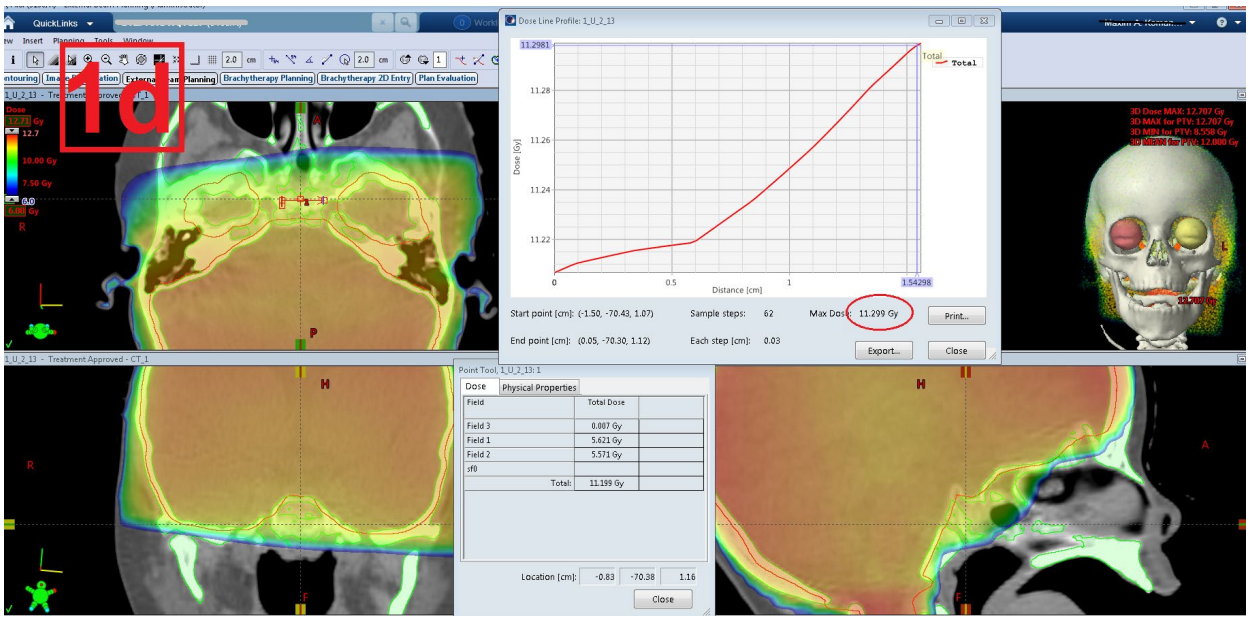

Fig. 1d. Dose load on the sphenomesoethmoidal growth zone of patient M., 4 years old. The maximum dose is 11.299 Gy.

and 7 patients (41 %) of middle and high school age (11–17 years). The ratio of boys and girls was 1:2.5, respectively. The patients underwent the stage of chemotherapy in the Department of Pediatric Oncology. The calculation and verification of the radiation therapy plan were carried out individually for each patient in the radiotherapy department. All patients underwent a course of conformal radiation therapy in the IGRT mode (Image Guided Radiation Therapy, image-controlled radiation therapy) using the Exactrac positioning system (Brainlab) totally on the brain area and the first two cervical vertebrae on the NovalisTx (Varian) device using the VMAT technique. Volumetric Modulated Arc Therapy, rotational therapy with volumetric intensity modulation) with an irradiation energy of 6 MeV and the following target coating parameters: V95 % ≥ 98 %, Dmean = 100 %, D2 % ≤ 107 % Fixation was carried out using individually manufactured devices – a thermoplastic mask with shoulders and a vacuum mattress. Subsequently, the children underwent dispensary observation on the basis of the GBU RO "Regional Children's Clinical Hospital" for 75 months. The assessment of physical development was carried out on the basis of physical examination, anthropometric parameters in accordance with the data of the WHO centile tables. The assessment of neuropsychiatric development was carried out on the basis of anamnesis collection, which includes a survey concerning the emotional-vegetative and psychomotor spheres, behavior analysis, as well as neurological examination and tests evaluating memory, thinking and attention. Adverse events were assessed on the basis of the CTCAE 5.0 toxicity scale [9].

Table 1. The ratio of the facial and cerebral parts of the skull

The ratio of the facial part of the skull to the brain	Age at the time of therapy	Age related normal values	Period after radiation therapy
2015 y. patients			
1:2	17 years	1:2	75 months
1:2	15 years	1:2	72 months
1:3	10 years	1:3	71 months
1:3	9 years	1:3	69 months
2017 y. patients			
1:3	8 years	1:3	44 months
1:4	6 years	1:4	41 months
2019 y. patients			
1:3	10 years	1:3	38 months
1:2.5	13 years	1:3	19 months
1:3	8 years	1:3	18 months
2020 y. patients			
1:2	16 years	1:2	13 months
1:2	17 years	1:2	13 months
1:3	10 years	1:3	11 months
1:4	4 years	1:4	10 months
1:4	6 years	1:4	10 months
1:5	3 years	1:5	9 months

Dose load

Of 17 patients, 13 patients (75.4 %) underwent radiation therapy with a total focal dose of 12 Gy (a single focal dose was 2 Gy), 4 patients (24.6 %) – with a total focal dose of 18 Gy (a single focal dose was 2 Gy). The indicators of dose loads on the growth zones of the skull bones were calculated: the sphenooccipital growth zone – 11.760 Gy (95 % CI 11.673–11.847), the growth zone in the area of finger–shaped depressions of the frontal bone – 11.967 Gy (95 % CI 11.835–12.098), the growth zone in the area of cartilaginous layers between the latticed and frontal bone – 11.276 Gy (95 % CI 11.199–11.354), sphenomesoethmoid growth zone – 11.276 Gy (95 % CI 11.199–11.354). An example of a dose load distribution plan is shown in Fig. 1a, 1b, 1c, 1d.

RESEARCH RESULTS AND DISCUSSION

The anamnesis data of 17 patients were analyzed, the average follow-up period after irradiation was 42 months (from 9 to 75 months). The development of early or late complications in the course of dispensary follow-up in patients was not noted. Despite the predominance of patients of preschool and primary school age groups who undergo critical periods of development, none of the surviving patients showed a delay in physical development (Table. 1, 2): the ratios of the facial and cerebral parts of the skull [8] corresponded to normal proportions in 15 (100 %) patients. The ratio of head circumference by age [7] also corresponded to the norm in 100 % of patients: the indicators of all children were between 25 and 75 percentiles.

Table 2. Distribution of head circumference (cm) by age

Distribution of head circumference (cm) by age	Age	Age related normal values (cm)	Period after radiation therapy
2015 y. patients			
55	17 year	55–57	75 months
56	15 year	54–56	72 months
53	10 year	51–54	71 months
54	9 year	50–54	69 month.
2017 y. patients			
53	8 year	50–53	44 months
51.5	6 year	50–52	41 months
2019 y. patients			
54	10 year	51–54	38 months
55	13 year	52–55	19 months
54	8 year	50–53	18 months
2020 y. patients			
56	16 year	54–56	13 months
57	17 year	55–57	13 months
55	10 year	51–54	11 months
51	4 year	49–51	10 months
53	6 year	50–52	10 months
50	3 year	48–50	9 months

Changes in the emotional-vegetative sphere were detected in two patients (11.65 %) aged 10 and 16 years, which were manifested by complaints of increased fatigue, decreased concentration of attention; in the psychomotor sphere and in behavior there were deviations in one 13-year-old patient (5.8 %), who showed unmotivated irritability and aggression during the examination. Intellectual development corresponded to the age of all patients (100 %).

Adverse events were also observed in a small part of patients. One patient aged 6 years (6.7 %) experienced episodes of nausea and vomiting (1–2 episodes (with an interval of at least 5 minutes) for 24 hours, which corresponds to 1 degree of toxicity) for two weeks a month after the end of the course of radiation therapy. Three patients (20 %) suffered from headache limiting daily activity (corresponding to grade 2 toxicity): the patient is 8 years old for three months, the patient is 10 years old for two months and the patient is 6 years old for two weeks. All three patients complained of headaches a month and a half after the course of radiation therapy. Three patients aged 6, 10 and 8 years (20 %) complained of a rise in body temperature to 38 °C (which corresponds to 1 degree of toxicity) for one and a half months. a month after the end of the course of radiation therapy. No other types of toxicity were observed in any of the patients. Of 17 patients with ALL, two children died due to the progression of the disease 4 years after undergoing radiation therapy.

CONCLUSION

The analysis of the data of the catamnesis of patients who underwent a course of radiation, taking into account the different time intervals between treatment and the moment of the study, demonstrates the relative safety of radiation therapy standards against the background of its effectiveness. Despite the fact that with ALL, patients are exposed to brain radiation during critical periods of development of both the physical and neuropsychic spheres, no significant deviations and undesirable reactions were detected. The results of these examinations and physical research methods confirm the presence of only minor and short-term changes that do not affect the quality of life of children at the moment, however, an objective assessment of the prospects for physical and neuropsychic development is difficult due to the relatively short period after therapy and a small sample of patients, as well as the absence of such studies in Russia and abroad.

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Information about authors:

Tatyana S. Rogova ✉ – resident at the National Medical Research Centre for Oncology, Rostov-on-Don, Russian Federation. ORCID: https://orcid.org/0000-0003-0074-0044, SPIN: 8280-9470, AuhtorID: 1113449, ResearcherID: AAG-1260-2021

Pavel G. Sakun – Cand. (Med.) Sci., radiation therapy doctor, National Medical Research Centre for Oncology, Rostov-on-Don, Russian Federation. SPIN: 3790-9852, AuthorID: 734600, Scopus Author ID: 56531945400

Vitalii I. Voshedskii – MD, radiation therapy doctor National Medical Research Centre for Oncology, Rostov-on-Don, Russian Federation. ORCID: https://orcid.org/0000-0003-1405-8329, SPIN: 4732-4005, AuthorID: 1032685, ResearcherID: Q-6122-2019

Stanislav G. Vlasov – PhD student, National Medical Research Centre for Oncology, Rostov-on-Don, Russian Federation. ORCID: https://orcid.org/0000-0002-4680-8991, SPIN: 3001-7426, AuthorID: 1087319

Yuliya Yu. Kozel – Dr. (Med.) Sci., professor, paediatric oncology department chief doctor, paediatric oncologist, National Medical Research Centre for Oncology, Rostov-on-Don, Russian Federation. ORCID: https://orcid.org/0000-0002-6681-3253, SPIN: 6923-7360, AuthorID: 732882

Viktoriya V. Dmitrieva – Cand. (Med.) Sci., paediatric oncologist National Medical Research Centre for Oncology, Rostov-on-Don, Russian Federation. SPIN: 4416-7947, AuthorID: 312405

Olga V. Kozyuk – paediatric oncologist National Medical Research Centre for Oncology, Rostov-on-Don, Russian Federation. ORCID: https://orcid.org/0000-0002-0676-7398, SPIN: 1962-1920, AuthorID: 734366

Karapet S. Aslanyan – Cand. (Med.) Sci., head of the department of pediatric oncology and hematology with chemotherapy, hematologist, pediatric oncologist, Regional Children's Clinical Hospital, Rostov-on-Don, Russian Federation.

Elena V. Vasileva – hematologist, pediatric oncologist, Regional Children's Clinical Hospital, Rostov-on-Don, Russian Federation. SPIN: 2595-1838, AuthorID: 731952

Contribution of the authors:

Rogova T. S. – research concept and design, text writing, material processing;
Sakun P. G. – data collection, analysis and interpretation, article preparation, technical editing;
Voshedskii V. I. – data collection, analysis and interpretation, article preparation, technical editing;
Vlasov S. G. – data collection, analysis and interpretation, article preparation;
Kozel Yu. Yu. – data collection, analysis and interpretation, scientific editing;
Dmitrieva V. V. – data collection, analysis and interpretation, scientific editing;
Kozyuk O. V. – data collection, analysis and interpretation;
Aslanyan K. S. – data collection, analysis and interpretation, article preparation;
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REVIEW

MODERN DIAGNOSTIC AND TREATMENT METHODS IN PARANASAL SINUS MALIGNANT TUMORS

Yu. V. Ulyanova✉, M. A. Engibaryan, V. L. Volkova, N. A. Chertova, I. V. Aedinova, M. V. Bauzhadze, I. V. Pustovaya

National Medical Research Centre for Oncology, Rostov-on-Don, Russian Federation
✉ 2014_ulia@mail.ru

ABSTRACT

Malignant tumors of the head and neck are still one of the most challenging problems of treatment in modern oncology. The disease affects mainly the capable people (from 30 to 60 years old). Tumor lesions of the paranasal sinuses lead to disability and have a high mortality rate. Head and neck tumors comprise of 20–30 % of all cancer cases. People with early paranasal sinus cancer have minor complaints, their general condition doesn't get affected so they don't seek for medical care in a while. As a result, patients start on treatment at tumor grades III–IV. This article provides the most complete information about the causes, frequency and special features of the course of paranasal sinus cancer, as well as about modern methods of it's diagnosis and combination treatment. Despite the great advances in the treatment of these malignant tumors the three and five year survival rates remain unsatisfactory, which requires a research for new effective treatments. Currently the main treatment methods for these malignant tumors are combination and complex (involving surgery, radiotherapy and chemotherapy) treatments. The standard treatment approach includes radical surgical removal of the primary tumor and metastatic lymph nodes followed by radiation or chemoradiation therapy. Chemotherapy as monotherapy is administered in non-resectable primary or recurrent tumors, distant metastases or when a patient refuses the radical surgery. Improvement of existing treatment methods and development of new ones are an essential need. Earlier detection of the disease requires primary care physicians to be trained to diagnose tumor lesions of the paranasal sinuses, and highly specialized physicians (dentists, otorhinolaryngologists, maxillofacial surgeons, dermatologists) to express their cancer alertness.

Keywords:
malignant neoplasms of the paranasal sinuses, diagnostics of tumors of the malignant nature of the paranasal sinuses, etiological factors of development, methods of treating malignant formations of the paranasal sinuses, chronic inflammatory diseases of the paranasal sinuses, benign neoplasms of the paranasal sinuses

For correspondence:
Yuliya V. Ulyanova – Cand. Sci. (Med.), surgeon, department of head and neck tumors National Medical Research Centre for Oncology, Rostov-on-Don, Russian Federation.
Address: 63 14 line str., Rostov-on-Don 344037, Russian Federation
E-mail: 2014_ulia@mail.ru
SPIN: 1276-9063, AuthorID: 457370

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ОБЗОР

СОВРЕМЕННЫЕ МЕТОДЫ ДИАГНОСТИКИ И ЛЕЧЕНИЯ ЗЛОКАЧЕСТВЕННЫХ ОПУХОЛЕЙ ОКОЛОНОСОВЫХ ПАЗУХ

Ю. В. Ульянова✉, М. А. Енгибарян, В. Л. Волкова, Н. А. Чертова, И. В. Аединова, М. В. Баужадзе, И. В. Пустовая

НМИЦ онкологии, г. Ростов-на-Дону, Российская Федерация
✉ 2014_ulia@mail.ru

РЕЗЮМЕ

Опухоли злокачественной природы, локализующиеся в области головы и шеи, остаются одной из сложнейших проблем при лечении в современной онкологии. Заболеванию подвержена преимущественно трудоспособная часть населения (от 30 до 60 лет). Опухолевые поражения околоносовых пазух приводят к инвалидизации, а также к высокой смертности населения. В общей структуре онкологической заболеваемости опухоли головы и шеи составляют 20–30 %. Жалобы при наличии злокачественной опухоли околоносовых пазухах в начальных стадиях незначительные, общее состояние больных не страдает и продолжительное время они не обращаются к врачу. В итоге, пациенты начинают лечение, когда опухолевый процесс достигает III–IV стадии заболевания. В нашей статье представлена наиболее полная информация о причинах возникновения, частоте встречаемости, особенностях течения злокачественных новообразований околоносовых пазух, современных методах диагностики и комплексного лечения этой категории пациентов. Несмотря на большие достижения в лечении злокачественных опухолей представленной локализации, показатели трех- и пятилетней выживаемости остаются неудовлетворительными, в связи с чем, необходим поиск новых эффективных методов лечения. В настоящее время основными методами лечения злокачественных образований данной локализации являются комбинированный и комплексный (сочетание хирургических вмешательств, лучевой терапии и химиотерапии). Стандартным подходом в лечении является радикальное хирургическое удаление первичной опухоли и метастатически-измененных лимфоузлов с последующей лучевой или одномоментной химиолучевой терапией. Химиотерапия в моноварианте используется при наличии нерезектабельных первичных или рецидивных опухолей, отдаленных метастазов или отказе пациента от радикальной хирургической операции. Неоспоримой является необходимость поиска путей совершенствования существующих и разработки новых методов лечения. Также с целью повышения выявляемости болезни на ранних стадиях необходимо обучение врачей первичного звена диагностике опухолевого поражения околоносовых пазух, проявлению онконастороженности узких специалистов (стоматологов, оториноларингологов, челюстно-лицевых хирургов, дерматологов).

Ключевые слова:
злокачественные новообразования придаточных пазух носа, диагностика опухолей злокачественной природы околоносовых пазух, этиологические факторы развития, методы лечения злокачественных образований околоносовых пазух, хронические воспалительные заболевания околоносовых пазух, доброкачественные новообразования придаточных пазух носа

Для корреспонденции:
Ульянова Юлия Викторовна – к.м.н., врач-хирург отделения опухолей головы и шеи ФГБУ «НМИЦ онкологии» Минздрава России, г. Ростов-на-Дону, Российская Федерация.
Адрес: 344037, Российская Федерация, г. Ростов-на-Дону, ул. 14-я линия, д. 63
E-mail: 2014_ulia@mail.ru
SPIN: 1276-9063, AuthorID: 457370

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RELEVANCE

Approximately 8.8 million people die a year from malignant neoplasms (World Health Organization). The incidence in Russia per 100,000 population in 2020 was 0.65 people [1].

Tumors of the nasal cavity and paranasal sinuses account for 0.2 to 1.4 % of cancerous tumors of other organs and 10 to 20 % of neoplasms of ENT organs [2; 3]. Women get sick with a frequency of 42.9 %, men – 57.1 % [2–4]. Tumors with epithelial origin account for 70–80 %. Esthesioneuroblastoma (as a non-epithelial tumor) accounts for 50–60 % [2]. The asymptomatic course in the early stages of the development of tumors of this localization is the reason for patients to go to an oncologist with advanced processes [5].

Chronic inflammatory diseases such as sinusitis, ethmoiditis, frontitis, rhinosinusitis (catarrhal, polypous) play an important role in the etiology of the development of tumor processes in the nasal cavity and paranasal sinuses. Adverse natural factors, chemical and physical carcinogenic substances also have a great influence on changes in the mucous membrane [6–8].

Inflammatory diseases that occur for a long time, with periodic remissions and exacerbations, lead to various hyperplastic processes in the epithelium of the paranasal sinuses, which may precede the onset of malignancy.

A complex of specific and non-specific mechanisms of local and general immunity provides protection of the mucous membrane of the paranasal sinuses and nasal cavity. Factors of local protection play a leading role. Non-specific factors are the primary link in the protection of the epithelium of the mucous membrane. The secretion of products with bactericidal properties, such as interferon, lysozyme, etc., as well as mucociliary transport carried out by macrophages and monocytes phagocytosis are non-specific protection factors. Lymphocytes of the pharyngeal tonsil and its own epithelial plate provide specific protection of the mucous membrane [9–12]. Secretory immunoglobulin A (SIg A) is the main component of the immune protection of the nasal mucosa and paranasal sinuses from foreign influences. It's production is provided by mucosoassociated lymphoid tissue, which participates in the formation and ensures the functioning of mucosal immunity.

Damage to the epithelium contributes to the penetration of pathogens into the mucous membrane and disrupts the constant immune regulation. Venous congestion, swelling and thickening of the mucous membrane, leading to a violation of blood supply, are constant companions of inflammatory processes in the paranasal sinuses and nasal cavity [12]. Under conditions of oxygen starvation, anaerobic processes begin to prevail in the mucous membrane, which leads to the accumulation of under-oxidized metabolic products. Due to changes in the acid-base balance and slowing of mucociliary clearance, mucosal secretion stagnates. Also, due to the products of metabolic acidosis, the protective effect of lysozyme stops. All these processes provide the most favorable conditions for the suppression of obligate non-pathogenic microflora of the upper respiratory tract and the development of pathogenic anaerobes.

Chronic minor injuries of the mucous membrane play a great role in the etiology of malignant neoplasms of the sinuses. They can occur due to the impact of sharp edges of destroyed teeth, improperly installed fillings or dentures. In the area of chronic minor injuries of the mucous membrane, tumors develop in 5.2–5.7 %.

The source of tumor development may be dystopian foci formed as a result of embryonic disorders during the fusion of various tissue rudiments, which is accompanied by the formation of teeth and the transition of the flat outer epithelium to the atrial fibrillation. Sometimes epithelial rudiments associated with the formation of teeth are preserved in the area of the alveolar process of the upper jaw, which can also give rise to tumor degeneration.

Leukoplakia of the mucous membrane, as one of the types of dyskeratosis, is an optional precancerous disease. According to that, patients are subject to dynamic monitoring and active treatment of foci of leukoplakia. Tumors can develop against the background of polypous rhinosinusitis and various sinus papillomas (especially inverted papilloma). Oncological alertness of primary care physicians, timely histological examination of pathological formations of the paranasal sinuses allows to identify malignant degeneration and to begin timely treatment in the early stages of the disease.

Tumors of the paranasal sinuses can originate from the mucous membrane of the alveolar and

palatine processes of the upper jaw, nasal cavity and sinuses, as well as from cartilage and bone tissue. Most often (70–80 %) there are tumors of epithelial origin, up to 50 % are squamous cell carcinoma, 10 % are transitional cell carcinoma, 5–7 % of patients are diagnosed with adenocarcinomas.

As a result of prolonged inflammatory processes, metaplasia of the cylindrical epithelium occurs. This explains the development in most cases of squamous cell cancers from the mucous membrane lining the oral cavity, sinuses, and nasal cavity. Adenocarcinomas, adenocystic cancers, and cylindrical cell cancers are associated with malignant degeneration of the glandular epithelium.

The most common representative of non-epithelial sinus tumors, occurring in 15–20 %, is esthesioneuroblastoma or neuroendocrine tumor (50–60 %), which develops from the neuroepithelium of olfactory bulbs. The tumor has a high potential for malignancy, intensive growth (often into the cranial cavity), and often recurs after treatment [13; 14].

Sarcomas of the upper jaw, which are connective tissue tumors that originate mainly from the maxillary bone (especially in the area of connective tissue sutures) and are much less common than epithelial neoplasms [14–16].

Also, tumors of the upper jaw in 0.9 % of cases may be secondary or metastatic in thyroid, breast, kidney, and melanoma cancers [14]. The clinical picture of metastatic tumors has no specific signs, the diagnosis is made with a comprehensive examination and histological examination of the biopsy material.

According to the international histological classification of malignant tumors of the nose and sinuses, the following types of formations are distinguished:

Epithelial tumors, which include cancers – squamous, verrucous (squamous), spinocellular, transitional cell, adenocystic, mucoepidermoid, undifferentiated, adenocarcinoma, mucosal adenocarcinoma, others.

II. Soft tissue tumors, which include malignant hemangiopericytoma, fibrosarcoma, rhabdomyosarcoma, neurogenic sarcoma, malignant fibroxanthoma and others.

III. Bone and cartilage tumors are isolated separately, which include chondrosarcomas, osteogenic sarcomas and others.

IV. Tumors of hematopoietic and lymphoid tissue include lymphomas (lymphosarcomas; reticulosarcomas; plasmocytomas; Hodgkin's disease).

V. There are mixed tumors, which include malignant melanoma, esthesioneuroblastoma and others.

Also in this classification, secondary tumors (metastatic) and unclassifiable tumors are singled out separately.

Treatment and diagnosis (especially early) of tumors of the nasal cavity and sinuses is a complex task and does not depend on the histological structure. To date, the search for ways to improve the unsatisfactory results of diagnosis and treatment has not stopped [17–19].

The purpose of the study: was to highlight the relevance of the problem of treating tumors of the paranasal sinuses, the need to develop clear algorithms for diagnosis (especially early), treatment and rehabilitation.

Despite the huge achievements in the field of radiation therapy, surgical technologies, chemotherapy, the prognosis for the treatment of tumors of the paranasal sinuses and nasal cavity remains unfavorable. This is due to the fact that mostly patients with advanced advanced tumor processes get to the oncologist. In the initial stages, the clinical manifestations of these tumors are extremely scarce and, for a long time, patients do not attach importance to them and do not seek medical help. The reasons for the neglect of cancer of these localizations are the late treatment of patients, insufficient oncological alertness of primary care doctors, and, accordingly, incorrect diagnosis and incorrect treatment tactics. Symptoms such as toothache, bleeding from the nasal cavity, purulent discharge, unilateral nasal congestion do not alarm doctors in terms of tumor development. As a result, long-term treatment with antibacterial drugs, physiotherapy, etc. is prescribed [2; 6]. The patient goes to the oncologist when the tumor reaches a large size, deforms the face and there is no doubt about the diagnosis of a malignant tumor.

In the early stages of the development of the disease, it is possible to establish the primary affected area. Most often, tumors begin their development in the area of the ethmoidal labyrinth or the maxil-

lary sinus. It is extremely rare that the primary and frontal sinuses are affected. Unilateral difficulty in nasal breathing may be one of the first symptoms of damage to the maxillary sinus, then local pain, bulging of the eyeball, purulent discharge, repeated bleeding may join. The asymptomatic or latent period of the course of the disease can last up to one year [2; 20; 21].

In the course of clinical observations, the frequency of occurrence of certain symptoms of cancer of the paranasal sinuses and nasal cavity was established. Unilateral difficulty breathing through the nose is noted in 21 % of cases. Discharge from the nasal cavity, which can be mucous, purulent and hemorrhagic, is observed in 14.3 % of cases. Recurrent and non-severe nosebleeds occur in approximately 5 % of patients. Localized in the area of teeth, jaws, ears and eyes, pain of varying intensity is noted by 20.4 % of patients. In 1.1 % of cases, manifestations of paresthesia, anesthesia of individual areas of the face are possible. As the first sign of the disease, 21 % of patients report facial deformity (swelling in the cheeks, eyelids, cheekbones, alveolar and palatine processes of the jaws). 6.9 % of patients have symptoms such as loss, displacement or loosening of teeth. On the part of the organ of vision, symptoms such as lacrimation, swelling of the eyelids, protrusion of the eyeball and its displacement in various directions, impaired mobility of the eyeball and decreased visual acuity are also possible (6.3 % of cases) [2].

Metastatic lesion of the lymph nodes of the neck occurs in 20 % of cases. Mainly the postaryngeal lymph nodes and nodes under the base of the skull are affected, then metastases are found in the submandibular and deep cervical lymph nodes. Distant metastasis to other organs (lungs, brain, liver) is not typical for tumors of these localizations and manifests late [22].

The algorithm of examination of patients with malignant tumors of the paranasal sinuses has been developed. It includes physical examination, X-ray examination of the facial skeleton and chest organs, video endoscopic examination of the nasal cavity and pharynx, tumor biopsy with histological examination, fine needle aspiration biopsy of enlarged lymph nodes, ultrasound examination of the lymph nodes of the neck and abdominal organs, computed tomography of the head with contrast enhancement, etc. [2; 23].

Various types of X-ray examinations (radiography, computed tomography) are the main diagnostic measures that allow to establish the localization and prevalence of the pathological process [24; 25]. SCT and MRI are used for differential diagnosis of inflammatory and cancerous diseases of the adnexal sinuses. During these studies, a detailed assessment of the zone of perifocal edema, the density and size of the tumor in anatomically complex structures of the skull is possible. It is possible to accurately assess destructive processes in the bones of the facial skeleton, the presence or absence of tumor germination into the cranial cavity, damage to vital structures. Magnetic resonance imaging allows you to optimally determine the size of the soft tissue component of the tumor, and computed tomography allows you to more accurately assess the integrity of bone structures. Also, with small-sized neoplasms, it is possible to use positron emission tomography for diagnosis [20; 26].

A necessary and mandatory stage of diagnosis is a biopsy of the pathological formation of the paranasal sinuses. In the histological conclusion, it is necessary to indicate the histotype and the degree of differentiation of tumor cells, which largely affects the choice of the optimal treatment method.

A fine needle aspiration biopsy of enlarged neck lymph nodes under ultrasound control is also a mandatory diagnostic measure. The presence of a metastatic lesion of the cervical lymphocollector largely determines the tactics and choice of treatment method.

Due to the presence of a number of reasons, the treatment of malignant neoplasms of the paranasal sinuses and nasal cavity is considered difficult for both the doctor and the patient. Anatomically complex area, the occurrence of extensive postoperative defects and functional disorders, are the reason for the refusal of patients from active surgical treatment. The surgical method in the monovariant provides a five-year survival rate of 18–35 %, a combination of surgical and radiation methods – 77.5 %. Most often (in 50 % of patients), the disease recurs within the first 2 years from the start of treatment [2].

The leading component of the combined and complex treatment of cancer of the paranasal sinuses is surgical [2; 23]. According to historical sources, one of the first operations in oncology is

resection of the upper jaw for a tumor. There are many options for surgical interventions for neoplasms of the upper jaw (including rhinotomy). Contraindications and indications for surgical interventions on the upper jaw are described in the literature, the disadvantages and advantages of certain approaches are identified, and complications are also analyzed [2; 27–30]. The volume and types of operations depend on the prevalence and localization of the tumor process, the general status of the patient, and the predicted complications. Due to the high risk of recurrence, the surgical method in monovariant is not used in stage 3–4 tumor processes. To date, the search for ways to optimize surgical interventions, increase their radicality, plastic elimination of postoperative defects, complex prosthetics, as well as professional and social rehabilitation has not stopped.

Radiation monotherapy is also ineffective in the treatment of tumors of the paranasal sinuses [31]. A permanent cure is possible in rare cases in the early stages of tumor development. However, if there are contraindications to surgical treatment, radiation therapy is the leading method of treatment. Radiation therapy helps to reduce the size of the tumor, the disappearance of pain, the restoration of nasal breathing, which accordingly leads to an improvement in the patient's well-being. Unfortunately, radiation therapy does not lead to a complete cure, but only helps to slow down the growth of the tumor.

The combined method, which consists in a combination of surgical and radiation methods, is the gold standard in the treatment of locally common tumors of the paranasal sinuses [2; 22; 30]. Postoperative irradiation is more effective than preoperative due to significantly greater targeting, based on determining the true size and prevalence of the tumor during surgery [32]. However, even the use of a combination of radiation and surgical methods in the treatment of malignant tumors of the paranasal sinuses and cavities does not prevent the development of relapses of the disease at a relatively early time, which occur in 30–60 % of cases.

Since the mid-70s of the last century, systemic chemotherapy has been actively used in the treatment of common tumors. Chemotherapy is used as a component of complex treatment (including chemoradiotherapy). It is also possible to use polychemotherapy as an independent palliative method when the possibilities of surgical and radiation treatment have already been exhausted. The most effective use of chemotherapy is for tumors of epithelial origin (squamous cell cancers). Most often, stabilization of the tumor process is achieved. At the same time, tumor regression of varying severity is observed in 10–75 % of cases. Analyzing the experience of our department, the use of chemotherapy as a neoadjuvant component has not been widely used in the treatment of cancer of the paranasal sinuses. Currently, thanks to advances in the study of biology and immunology of malignant tumors, cellular technologies, pharmacodynamics and pharmacokinetics of drugs, as well as a detailed study of the mechanisms of their action, the possibilities of chemotherapy are significantly expanding. However, polychemotherapy in a monovariant never leads to the cure of patients and is mainly used as a palliative effect on the tumor in the late stages of the development of the malignant process.

Currently, the treatment of cancer of the paranasal sinuses depends on the size of the primary focus (symbol T), the sequence of therapeutic measures is reflected in clinical recommendations [23].

Surgical intervention or independent radiation treatment is indicated for patients with cancer of the nasal cavity and the trellis labyrinth T1-T2N0. If the histological examination of the surgical material determines unfavorable prognostic factors, such as intracranial spread and tumor cells at the edges of resection, patients are prescribed postoperative radiation or chemoradiotherapy. This tactic aims to increase overall survival and reduce the number of relapses of the disease.

With the prevalence of the tumor corresponding to the symbols T3-T4a, surgical intervention is also recommended as the first stage of treatment. In case of refusal of the operation, the use of chemoradiotherapy is possible. Radiation or competitive chemoradiotherapy is used as an adjuvant component of treatment.

If there are unresectable tumors (T4b) or if the patient refuses to perform extensive surgery, chemoradiotherapy or independent radiation therapy is performed. With non-radical surgical treatment and the presence of a residual tumor of the lattice labyrinth, patients undergo surgery or chemoradiotherapy. With the prevalence of the primary tumor corresponding to the T1 symbol, the

presence of negative resection edges, high differentiation of tumor cells, dynamic observation is shown in the postoperative period. Dynamic observation in the postoperative period is also indicated for cancer of the maxillary sinus (T1-T2, N0). Adjuvant radiation treatment is indicated in the case of determining unfavorable prognostic factors, such as perivascular, perineural and lymphatic invasion, as well as in the detection of adenocystic cancer. If tumor cells are detected at the edges of the resection, a repeated surgical operation is performed, followed by radiation or chemoradiotherapy.

Patients with locally advanced cancers of the maxillary sinus corresponding to T3-T4a undergo radical surgery with a postoperative course of radiation therapy. In case of detection of tumor cells in the edges of resection, simultaneous chemoradiotherapy is performed, and repeated surgical intervention may also be recommended.

In case of unresectable tumors (T4b) of the maxillary sinus, chemoradiotherapy or independent radiation therapy is performed.

If patients are diagnosed with metastatic lesion of the lymph nodes of the neck, cervical lymph dissection is performed simultaneously with the operation on the primary focus. The volume of surgical intervention in this case is determined by the number and size of metastatic foci. If the histological examination reveals unfavorable prognostic factors, such as extracapsular spread of metastases, positive resection margins, perineural, perivascular, lymphatic invasion, adjuvant radiation or simultaneous chemoradiotherapy is indicated.

Radical surgical intervention is performed in patients with local recurrences of maxillary sinus cancer, the presence of a residual tumor after non-radical removal. Subsequently, the issue of the expediency of adjuvant radiation treatment or competitive chemoradiotherapy is being resolved.

In case of detection of unresectable tumors, repeated radiation therapy, simultaneous chemoradiotherapy, or symptomatic treatment is possible.

Modes of independent radiation therapy for cancer of the paranasal sinuses have been developed: a dose of 66–70 Gy is applied daily to the area of the primary focus and clinically determined metastases to the lymph nodes of the neck in fractions of 1.8–2.0 Gy for 6–7 weeks.

Independent simultaneous chemoradiotherapy is also performed daily for 7 weeks. A dose of 70 Gy is applied to the area of the primary focus and lymphatic collector. At the same time, on the 1st, 22nd and 43rd days of radiation therapy, cisplatin is administered at a dose of 100 mg/m² against the background of hyperhydration and forced diuresis. The total dose of cisplatin for the entire period of treatment is 300 mg/m^2. It is possible to replace cisplatin with carboplatin in the AUC 1.5–2.0 mode in the form of weekly injections from the first day of radiation treatment.

After performing surgical interventions, adjuvant radiation (chemoradiotherapy) should be carried out in the interval from 6 weeks to 3 months. Prolongation of this interval is unfavorable in terms of the appearance of continued tumor growth or relapse of the disease. The total radiation dose during postoperative radiation therapy is 66 Gy per primary focus area and 50–54 Gy per regional lymphatic collector area. In the presence of recurrent unresectable tumors, as well as with the appearance of distant metastases, mono- or polychemotherapy with first-line drugs, which include cisplatin (carboplatin), paclitaxel, cetuximab, is used to increase overall survival [22; 31].

The results of treatment of malignant tumors of the paranasal sinuses and nasal cavity, despite great achievements in oncology, remain unsatisfactory. Combined treatment (a combination of surgical and radiological methods) allows achieving five–year survival in stage I–II cancer in 73.6 % of patients, stage III – in 54.9 % of patients, stage IV – in 24.2 % of patients. When regional metastases to the neck lymph nodes are detected, the five-year survival rate decreases to 37.5 %. In the presence of a widespread tumor lesion with a low degree of cell differentiation, chemoradiotherapy will be used, which allows achieving a positive clinical result in 74 % of patients. However, the stabilization of the tumor process is not long-term. The use of surgical or radiation method in monovariants allows to achieve a five-year survival rate in 18–35 % of patients, which demonstrates the need for combined treatment. If the tumor is detected early and combined treatment is started in a timely manner, it is possible to achieve the values of the overall three- and five-year survival of 87.3 % and 83.5 %, respectively. With the complex treatment of locally widespread tumor processes of the paranasal sinuses, the three-year survival rate is 37.1 %.

CONCLUSION

Our analysis of the literature data, as well as our own experience in the treatment of limited and widespread tumors of the paranasal sinuses and nasal cavity, indicate the need to improve existing and develop new methods of treatment. The training of primary care physicians in the diagnosis of tumor lesions of the paranasal sinuses in the early stages, the oncological alertness of narrow specialists (dentists, otorhinolaryngologists, maxillofacial surgeons, dermatologists) will contribute to the early and timely detection, and accordingly the timely treatment of malignant neoplasms of tumors of the head and neck organs.

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Information about authors:

Yuliya V. Ulyanova ✉ – Cand. Sci. (Med.), surgeon, department of head and neck tumors National Medical Research Centre for Oncology, Rostov-on-Don, Russian Federation. SPIN: 1276-9063, AuthorID: 457370

Marina A. Engibaryan – Dr. Sci. (Med.), head of the department of head and neck tumors National Medical Research Centre for Oncology, Rostov-on-Don, Russian Federation. ORCID: https://orcid.org/0000-0001-7293-2358, SPIN: 1764-0276, AuthorID: 318503, Scopus Author ID: 57046075800

Viktoria L. Volkova – Cand. Sci. (Med.), senior researcher, department of head and neck tumors National Medical Research Centre for Oncology, Rostov-on-Don, Russian Federation. ORCID: https://orcid.org/0000-0003-2674-0755, SPIN: 8289-6300, AuthorID: 290072

Nataliya A. Chertova – Cand. Sci. (Med.), surgeon, department of head and neck tumors National Medical Research Centre for Oncology, Rostov-on-Don, Russian Federation. ORCID: https://orcid.org/0000-0002-9279-9408, SPIN: 7051-4574, AuthorID: 473541

Irina V. Aedinova – Cand. Sci. (Med.), senior researcher, department of head and neck tumors National Medical Research Centre for Oncology, Rostov-on-Don, Russian Federation. SPIN: 9904-0539, AuthorID: 734387

Mamuka V. Bauzhadze – Cand. Sci. (Med.), oncologist, department of head and neck tumors National Medical Research Centre for Oncology, Rostov-on-Don, Russian Federation. SPIN: 5315-3382, AuthorID: 734578

Irina V. Pustovaya – Cand. Sci. (Med.), maxillofacial surgeon of the department of head and neck tumors National Medical Research Centre for Oncology, Rostov-on-Don, Russian Federation. SPIN: 5913-8360, AuthorID: 416789

Contribution of the authors:

Ulianova Yu. V. – writing the draft, final conclusions, writing the article;
Engibaryan M. A. – scientific management, research concept, scientific editing;
Volkova V. L. – material collection, material processing;
Chertova N. A. – material collection, material processing;
Aedinova I. V. – analysis of the material, refining of the text;
Bauzhadze M. V. – material collection, material processing;
Pustovaya I. V. – material collection, analysis of the material.
The authors contributed equally to this article.

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REVIEW

MODERN TREATMENT OF ALK-POSITIVE NON-SMALL CELL LUNG CANCER

D. A. Kharagezov, Yu. N. Lazutin, E. A. Mirzoyan✉, A. G. Milakin, O. N. Stateshny, I. A. Leyman, M. A. Gappoeva, V. N. Vitkovskaya, K. D. Iozefi

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

ABSTRACT

Lung cancer (LC) takes the first place in the structure of overall oncology in males. More than 1.8 million of new cases of lung cancer (LC) are registered each year worldwide. LC is the leading cause of cancer death in both developing and developed countries, and the 5-years survival rate is as low as 19 %. Many factors explain such unsatisfactory outcomes, including the LC diagnosis at an advanced stage, when the currently available treatments can rarely provide cure. Non-small cell lung cancer (NSCLC) with chromosomal rearrangement of anaplastic lymphoma kinase (ALK) is sensitive to targeted therapy with tyrosine kinase inhibitors (TKIs). Tumor cells containing ALK fusion are sensitive to TKIs – targeted drugs that have significantly improved the results of treatment of patients with ALK-positive NSCLC, half of whom survive more than 6.8 years after diagnosis. The number of patients with ALK-positive NSCLC varies, so ALK rearrangements are detected in about 3–7 % of lung adenocarcinomas, which accounts for up to 60.000 new cases of the disease annually worldwide. ALK-positive NSCLC is observed almost exclusively in adenocarcinomas associated with persons of younger age, male and never smoked or smoked a little. Patients with ALK-positive stage I–III NSCLC are shown treatment similar to patients with wild-type NSCLC, including surgery, radiation therapy, chemotherapy or multimodal treatment, depending on the stage of the tumor process. Numerous ALK TKIs have been developed in recent years, including alectinib, which is the current preferred first-line agent for patients who haven't received therapy. The study of the mechanisms of resistance has led to the development of next-generation ALK inhibitors that better penetrate the central nervous system, actively affecting brain metastases. This review highlights the current state and prospects for the development of ALK-positive NSCLC therapy.

Keywords:
non-small cell lung cancer, anaplastic lymphoma kinase (ALK), alectinib, brigatinib, crizotinib, lorlatinib, ceritinib

For correspondence:
Ellada A. Mirzoyan – PhD student 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

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ОБЗОР

СОВРЕМЕННОЕ ЛЕЧЕНИЕ ALK-ПОЗИТИВНОГО НЕМЕЛКОКЛЕТОЧНОГО РАКА ЛЕГКОГО

Д. А. Харагезов, Ю. Н. Лазутин, Э. А. Мирзоян✉, А. Г. Милакин, О. Н. Статешный, И. А. Лейман, М. А. Гаппоева, В. Н. Витковская, К. Д. Иозефи

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

РЕЗЮМЕ

Рак легкого (РЛ) занимает первое место в структуре общей онкологической заболеваемости мужского населения. Ежегодно в мире РЛ диагностируется более чем у 1,8 миллиона человек и остается основной причиной смертности от злокачественных новообразований как в развивающихся, так и в развитых странах, а 5-летняя выживаемость, достигающая 19 % вызывает разочарование. Подобные неудовлетворительные исходы объясняются многими факторами, включая диагностику РЛ на поздней стадии, когда излечение остается редким при доступных на сегодняшний день методах лечения. Немелкоклеточный рак легкого (НМРЛ) с хромосомной перестройкой киназы анапластической лимфомы (ALK) чувствителен к таргетной терапии ингибиторами тирозинкиназы (ТКИ). Опухолевые клетки, содержащие слияние ALK, чувствительны к ингибиторам ТКИ – таргетным препаратам, которые существенно улучшили результаты лечения больных ALK-позитивным НМРЛ, половина из которых выживают более 6,8 года после установления диагноза. Количество пациентов с ALK-позитивным НМРЛ варьируется, так ALK реаранжировки обнаруживаются примерно в 3–7 % аденокарцином легкого, что составляет до 60 000 новых случаев заболевания ежегодно во всем мире. ALK-позитивный НМРЛ наблюдается почти исключительно при аденокарциномах, ассоциированных с лицами более молодого возраста, мужского пола и никогда не курившими или курившими мало. Больным ALK-позитивным НМРЛ I–III стадии показано лечение аналогичное пациентам с НМРЛ дикого типа, включая хирургическое вмешательство, лучевую терапию, химиотерапию или мультимодальное лечение в зависимости от стадии опухолевого процесса. В последние десятилетие разработано несколько ALK ТКИ и среди них алектиниб, который в настоящее время является препаратом выбора первой линии терапии больных, не получавших лечения. Изучение механизмов резистентности привело к разработке ингибиторов ALK следующего поколения, которые лучше проникают в центральную нервную систему, активно воздействуя на метастазы в головном мозге. Данный обзор освещает современное состояние и перспективы развития терапии ALK-позитивного НМРЛ.

Ключевые слова:
немелкоклеточный рак легкого, киназа анапластической лимфомы (ALK) алектиниб, бригатиниб, кризотиниб, лорлатиниб, церитиниб

Для корреспонденции:
Мирзоян Эллада Арменовна – аспирант ФГБУ «НМИЦ онкологии» Минздрава России, г. Ростов-на-Дону, Российская Федерация.
Адрес: 344037, Российская Федерация, г. Ростов-на-Дону, ул. 14-я линия, д. 63
E-mail: 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

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INTRODUCTION

The fusion of the EML4 gene (echinoderm microtubule associated protein-like 4) with the ALK gene (anaplastic lymphoma kinase), first described in 2007, represents chromosomal inversions leading to constitutive oncogenic activation. It was found that a small percentage of NSCLC tumors (3–7 %) have EML4-ALK translocation [1]. Tumor cells containing ALK fusion are sensitive to tyrosine kinase inhibitors (TKI), targeted drugs that have significantly improved the results of treatment of patients with ALK-positive non-small cell lung cancer (NSCLC), half of whom survive more than 6.8 years after diagnosis [2].

The number of patients with ALK-positive NSCLC varies [3], so ALK rearrangements are detected in about 3–7 % of lung adenocarcinomas, which accounts for up to 60,000 new cases of the disease annually worldwide [4]. This indicator is the same among the population of the West (3.4 %), and the East. ALK-positive NSCLC is observed almost exclusively in adenocarcinomas associated with younger people (average age 52), male and never smoked or smoked a little [3].

Patients with ALK-positive stage I–III NSCLC are shown treatment similar to patients with wild-type NSCLC, including surgery, radiation therapy, chemotherapy or multimodal treatment, depending on the stage of the tumor process. What role tyrosine kinase inhibitors (TKI) will play in patients in the early stages of the disease has yet to be established. A variety of TKI are available for patients with previously untreated metastatic ALK-mutant NSCLC (Table 1). Over time, drug resistance inevitably arises, which led to the development of more potent ALK TKI of the next generation (Table 2).

Diagnostics of ALK fusion

All patients with metastatic lung adenocarcinoma should be tested for the presence of ALK fusion [5] using in situ fluorescent hybridization (FISH), immunohistochemical assay (IHCA) or next-generation sequencing (NGS) [6]. FISH is the gold standard for detecting ALK rearrangement and uses red and green probes for hybridization on either side of the ALK translocation breakpoint. These probes are either superimposed on each other, forming a yellow signal for wild-type samples, or appear as independent red and green signals if a fusion mutation is present [6].

An alternative to FISH is IHCA, which uses monoclonal antibodies to the ALK fusion oncogene. NGS is performed by extracting genomic DNA from tumor cells using probes targeting tumor–specific genes using either plasma or tumor tissue [7]. Comparing the three methods with each other, it should be noted that IHCA has the highest positive indicator – 94.5 %, NGS – 92.7 %, followed by FISH – 82.4 % [6].

Tyrosine kinase inhibitors. Krizotinib

Krizotinib is the first developed TKI ALK fusion. The PROFILE 1007 protocol is a Phase 3 clinical trial involving 347 patients with ALK-mutant NSCLC, which compared krizotinib with chemotherapy in patients who had previously received chemotherapy (Table 1). Krizotinib demonstrated an improvement in the level of objective response rate (ORR): 65 % vs. 20 % ($p < 0.001$), survival progression-free (PFS): 7.7 months vs. 3 months ($p < 0.001$) and quality of life [4]. In a Phase 3 PROFILE 1014 study comparing crizotinib with first-line chemotherapy in 343 patients, crizotinib demonstrated an improvement in ORR to 74 % vs. 45 % ($p < 0.001$) and PFS to 10.9 months vs. 7.0 months ($p < 0.001$) [8]. There was no difference in overall survival(s) in both studies [4; 8]. These studies have determined the role of crizotinib as the standard of first-line therapy.

Gastrointestinal toxicity is the most common adverse adverse reaction to crizotinib with diarrhea of any degree in 61 % of cases, and 3 or 4 degrees in 22 %; vomiting in 46 % and constipation in 43 % of patients. Liver dysfunction of grade 3 or 4, monitored every 2 weeks for the first 2 months and then periodically observed in 14 % of patients. Cardiotoxicity was manifested by bradycardia and prolongation of the QT interval. Visual impairment was observed in 71 % of patients, but only 1 % had grade 3 or higher [9].

Crizotinib is practically ineffective in lung adenocarcinoma metastases to the central nervous system (CNS), with a response rate barely reaching 7 % [10]. The brain is the most common site of disease progression in patients receiving crizotinib. Krizotinib is a well-known substrate of the p-glycoprotein pump of drug outflow, limiting its accumulation in the central nervous system [11]. The lack of effective exposure to CNS damage stimulated the development of a new generation of inhibitors.

Ceritinib

Ceritinib is a second-generation ALK inhibitor with activity against IGF-R1, IR and ROS-1. The drug has activity against crizotinib-resistant NSCLC, as it targets resistance mutations such as L119M and G1269A, as well as I1171T and S1206Y. Ceritinib penetrates the blood-brain barrier better [12].

Ceritinib is approved for both untreated and crizotinib-resistant patients. The ASCEND-5 protocol study demonstrated the advantage of prescribing ceritinib compared to third-line chemotherapy in 231 patients who previously received platinum-based chemotherapy and crizotinib [13]. The ASCEND-4 protocol compared ceritinib with chemotherapy in 376 untreated patients, including those with asymptomatic brain metastases. Median PFS in the ceritinib group was 16.6 months versus 8.1 months in the chemotherapy group ($p < 0.00001$) (Table. 1) [14]. Neither the ASCEND-4 protocol nor ASCEND-5 showed an improvement in the indicators of S. The poor tolerability of ceritinib and the higher efficacy of alectinib prevented its widespread use [15].

What is the role of ceritinib in the treatment of ALK-positive NSCLC resistant to alectinib remains to be seen. The ASCEND-9 clinical study examining the efficacy of prescribing ceritinib to patients who progressed on alectinib demonstrates an ORR of 25 % and a disease control level (DCR) of –70 % [16].

Ceritinib has excellent activity against CNS metastases with a response rate to therapy reaching 72 % [17]. Despite the high activity, the median PFS of patients with brain metastases treated with ceritinib was shorter than patients who did not receive this drug: 10.7 months versus 26.3 months, respectively [14]. Nevertheless, the study of the efficacy and safety of ceritinib in patients with brain metastases continues within the framework of the ASCEND-7 Phase 2 study [NCT01828112] [18].

When treated with ceritinib, toxicity of the 3rd or 4th degree is observed in 78 % of patients [14]. Gastrointestinal toxicity of varying severity is noted most often, namely: diarrhea in 85 %, nausea in 69 %, vomiting in 66 % and abdominal pain in 25 % of cases. More than 70 % of patients have a violation of the functional parameters of the liver of the

Table 1. ALK TKI in targeted first-line therapy of ALK-mutant NSCLC

Protocol.	Drug.	Groups.	*N*	ORR, %	*p*	PFS month	*p*	OS month	*p*
PROFILE 1014 [9]	Crizotinib	Crizotinib	172	74	< 0.001	10.9	< 0.001	-	0.097
		CT	171	45		7.0		47.5	
ASCEND-4 [14]	Peritinib	Ceritinib	189	72.5	< 0.01	16.6	< 0.00001	-	0.056
		CT	187	26.7		8.1		26.2	
J-ALEX [22]	Alectinib	Alectinib	103	92	0.072	34.1	< 0.0001	НД	-
		Crizotinib	104	79		10.2		НД	
ALEX [20]	Alectinib	Alectinib	152	83	0.0936	34.8	< 0.001	-	-
		Crizotinib	151	75.5		10.9		-	
ALESIA [23]	Alectinib	Alectinib	125	91	< 0.01	НД	< 0.0001	-	-
		Crizotinib	62	77		11.1		-	
ALTA-1L [25]	Brigatinib	Brigatinib	137	71	-	НД	-	-	-
		Crizotinib	138	60		9.8		-	

Note: *N* – number of patients enrolled in the study; ORR – objective response rate; PFS – progression-free survival; OS – overall survival; NA – not achieved.

3rd or higher degree, clinically manifested by severe anorexia, asthenia and fatigue [14]. Poor tolerability of the recommended dose of ceritinib 750 mg once a day on an empty stomach prevented its intake [15]. A new lower dose approved by the FDA, equal to 450 mg taken with meals, improved the tolerability of this adverse reaction [19].

Alectinib

Alectinib is a second-generation ALK inhibitor, which, due to its high efficacy and excellent safety profile, has become the drug of choice for the first-line targeted therapy of metastatic ALK-positive NSCLC. Not being a substrate of the outflow transporter of p-glycoprotein, alectinib is able to penetrate into the central nervous system [20].

In a worldwide phase 3 clinical trial of ALEX, 303 untreated patients were randomized for targeted first-line therapy with alectinib or crizotinib [20]. Median PFS in the alectinib group reached 35 months versus 11 months in the crizotinib group (HR = 0.43, $p < 0.001$) [21]. Similar results were obtained in 207 Japanese patients included in the J-ALEX protocol [22], as well as in the third later phase 3 study of ALESIA [23], which compared the effectiveness of alectinib with crizotinib in patients from Asian countries. These studies have made alectinib the drug of choice for targeted first-line therapy (Table 1).

In addition, alectinib plays an important role in the treatment of patients whose disease has progressed while taking crizotinib or intolerance to the latter drug has been noted. In the ALUR Phase 3 study, 107 patients who had previously received chemotherapy and crizotinib were assigned to groups for alectinib therapy or chemotherapy. Median PFS in the targeted therapy group was 7.1 months. compared with 1.6 months in the chemotherapy group (HR = 0.32, $p < 0.01$) [24].

The excellent activity of alectinib in CNS metastases has been consistently demonstrated in all studies. In the ALEX protocol, the time to progression of metastases in the central nervous system was significantly longer in the alectinib group compared to the crizotinib group (HR = 0.16, $p < 0.001$) [20]. In 16 patients with initial metastatic CNS lesion treated with alectinib, responses to targeted therapy were

Table 2. ALK TKI in subsequent lines of targeted therapy of previously treated ALK-positive NSCLC

Protocol.	Drug.	Previous treatment.	Groups.	*N*	ORR, %	*p*	PFS Mec.	*p*
PROFILE 1007 [4]	Crizotinib	CT	Crizotinib	173	65	< 0.001	7.7	< 0.001
			CT	174	20		3.0	
ASCEND 5 [38]	Ceritinib	Crizotinib or/and CT	Ceritinib	115	39	< 0.01	5.4	< 0.01
			CT	116	7		1.6	
ALUR [24]	Alectinib	CT and Crizotinib	Alectinib	72	37.5	< 0.01	7.1	< 0.001
			CT	35	3		1.6	
ALTA [26]	Brigatinib	Crizotinib	H Dose	112	48	-	9.2	-
			B Dose	110	53		16.7	
Solomon et al. 2018 [31]	Lorlatinib	Crizotinib 2 TKI ALK 3 TKI ALK	Lorlatinib	59	НД	-	-	-
			Lorlatinib	198	7.3		-	
ASCEND 9 [16]	Ceritinib	Alectinib ± Crizotinib	Lorlatinib	111	6.9	-	-	-
			Ceritinib	20	25		3.7	

Note: *N* – the number of patients included in the study; ORR (objective response rate) – the level of objective response; PFS (progression-free survival) – progression-free survival; NA – not achieved.

achieved in 75 % of cases. Consequently, many patients with brain metastases can only be treated with TKI without local exposure: surgery and/or radiation therapy.

As noted above, alectinib is much better tolerated than krizotinib, with a toxicity of 3–5 degrees in about 40 % of patients [20; 24]. The profile of adverse side effects includes: anemia in 20 %, nausea in 14 %, diarrhea in 12 %, vomiting in 7 % and elevated bilirubin levels in 15 %. Alectinib causes myalgia in 16 % of cases, and therefore creatine kinase (CK) levels are monitored every 2 weeks during the first month of therapy. Photosensitization is less frequent in 5 % [20].

Brigatinib

Brigatinib is a second-generation oral TKI that is able to overcome several mutations of resistance to crizotinib. Brigatinib is indicated for targeted therapy of ALK-positive NSCLC in patients with disease progression while taking crizotinib, in addition, studies on its first-line appointment are continuing

In the ALTA-1L study, 275 untreated patients were divided into groups for therapy with brigatinib or krizotinib. After 12 months of follow-up, PFS in the brigatinib group was 67 % versus 43 % in the crizotinib group (HR = 0.49, $p < 0.001$) [25]. OV in the protocols of targeted first-line therapy has not yet been studied. There are no studies comparing the effectiveness of brigatinib with alectinib in untreated patients. At the same time, the use of brigatinib is considered promising in patients refractory to crizotinib with a median PFS of 16.7 months in a recent phase 2 study [26]. There is evidence that the use of brigatinib during progression on alectinib improves the median PFS from 4.4 to 6.6 months [27; 28].

Brigatinib showed excellent activity in 78 % of patients with measurable brain metastases with targeted first-line therapy. Updated results of the phase 2 study showed that patients refractory to crizotinib with measurable CNS lesions achieved an objective response rate of 67 % with a median PFS of 18.4 months [29].

In the ALTA-1L protocol, adverse side effects of the 3rd and higher degree occurred in 61 % of observations of 136 patients receiving brigatinib [25]. Like other ALK inhibitors, brigatinib is characterized by the most frequent gastrointestinal adverse side effects of any severity in 49 %, increased creatinine kinase in 39 % and alanine aminotransferase (ALT) in 19 % [25]. There is also an increase in the level of amylase in 19 % and lipase in 14 % of observations, and cardiotoxicity in the form of bradycardia [25]. Blood pressure should be monitored before taking brigatinib and then monthly, since arterial hypertension is observed in 23 % of patients [30].

A distinctive feature of brigatinib is the possibility of acute development of severe pulmonary toxicity. An undesirable side effect, as a rule, occurs within 24–48 hours after the start of therapy, clinically manifests itself by shortness of breath, decreased oxygen saturation, and radiologically manifests itself by turbidity in the form of "frosted glass" and interstitial darkening [12]. The described reaction develops in 3–6 % of patients and is probably more common in patients previously treated with crizotinib, and depends on the dose [12; 25; 26]. In patients with newly emerging or worsening respiratory symptoms, urgent diagnosis should be carried out to exclude pneumonitis, and if it is confirmed, brigatinib should be discontinued [30].

Lorlatinib

Lorlatinib is a selective inhibitor of ALK and ROS1 of the third generation [1], which demonstrates ORR in 57 % in patients with the G1202R mutation, usually detected after the use of second-generation ALK inhibitors.

A modern phase 2 study was conducted in a group of 228 patients with ALK-positive NSCLC who had previously undergone multicomponent treatment. The clinical status varied depending on the previous therapy of TCI. Patients receiving only crizotinib demonstrated an ORR of 69 %. The median PFS was not reached. Patients who received targeted therapy with two or more ALK TKI had an ORR equal to 39 % with a median PFS of 6.9 months [31].

An ongoing phase 3 trial using the CROWN protocol [NCT03052608] randomizes patients with untreated ALK-positive NSCLC either to the lorlatinib therapy group or to the first-line crizotinib therapy group [32]. The French study LORLATU [NCT 02327477] studies the sequence of therapy in patients receiving lorlatinib [33]. Studies comparing lorlatinib with chemotherapy for alectinib-resistant NSCLC have not yet been conducted.

The ratio of lorlatinib concentration in cerebrospinal fluid and blood plasma in early studies was 0.75, which confirms the significant penetration of the drug into the central nervous system. In patients

with initial brain metastases who had previously taken at least one ALK TKI, the objective response rate was 63 %, and the median duration of response to treatment was 14.5 months [33].

Severe hyperlipidemia of 3–4 degrees is observed in 31 % of patients, in which 81 % of patients need hypolipidemic therapy [34]. Peripheral edema was observed in 43 % of patients in combination with peripheral neuropathy in 30 %. Neurological disorders occur in 39 % of patients, including changes in cognitive functions in 23 %, mood in 22 % and speech in 8 %. Most cognitive disorders were moderate and easily reversible with dose reduction [34].

Ensartinib (X-396) is a novel TCI with activity against ALK and ROS1 mutations of resistance to crizotinib, such as L1196M and C1156Y [35]. In a recent study, the ORR was 60 % with a median PFS of 26.2 months [35]. The drug is active in patients who previously received second-generation ALK TKI with ORR = 23 %, as well as in patients who previously received from 2 to 5 different targeted ALK TKI therapy regimens. The level of response of brain metastases reaching 64 % and the level of disease control equal to 92.9 % should be recognized as particularly promising [35]. A phase 3 clinical trial using the eXalt3 protocol [NCT02767804], currently compares ensartinib with crizotinib [36].

Entrectinib is another new ALK inhibitor. A modern phase 1 study has shown that entrectinib is highly effective in patients with NSCLC carrying NTRK, ROS1 and ALK rearrangements. However, in patients previously treated with ALK inhibitors, the drug did not cause any reactions [37].

Repotrectinib – ROS, a next-generation TRK-A and ALK inhibitor, demonstrates significant preliminary results in the Trident-1 clinical trial [NCT03093116], which is still ongoing [38].

Mechanisms of resistance

Mutations in the ALK kinase domain are the most well-described mechanism of resistance to TKI, occurring in 20–36 % of patients treated with crizotinib and 50 % of patients receiving second-generation ALK TKI [39]. Each TCI is associated with an individual spectrum of mutations. Genetic analysis of 103 biopsies of ALK-positive tumors from patients treated with various ALK inhibitors revealed that L1196M is the most common mutation found in resistance to crizotinib [39]. G1202R resistance mutation is often found after the use of second-generation drugs, including: ceritinib in 21 %, alectinib in 29 % and brigatinib in 43 % [24,30]. Despite the fact that the G1202R mutation creates high resistance, it is overcome by lorlatinib [39]. Little is known about resistance to lorlatinib.

Resistance mechanisms also arise outside the domain of ALK kinase. Amplification of ALK occurs in approximately 10 % of samples resistant to crizotinib, either in isolation or with other mutations. Activation of the bypass signaling pathway is another mechanism of resistance with activation of the EGFR receptor [40].

After the possibilities of targeted therapy are exhausted, chemotherapy is used with or without immunotherapy. The use of combined chemoimmunotherapy is confirmed by the study of a subgroup of 111 patients with NSCLC carrying EGFR and ALK mutations from the IMpower150 study. The combination of carboplatin, paclitaxel, bevacizumab and atezolizumab demonstrated an improvement in PFS up to 9.7 months. compared only with chemotherapy for 6.1 months [41].

In addition to the IMpower150 study, data confirming the effectiveness of immunotherapy in patients with ALK-mutant NSCLC are clearly insufficient. In studies on immuno- and chemoimmunotherapy in patients with ALK-mutant NSCLC, unsatisfactory results are observed [42; 43]. In addition, extrapolation of EGFR data [44] leads to safety problems of either TCI or immunotherapy [45]. Testing for ALK should be performed before starting chemoimmunotherapy to avoid an increased risk of toxicity.

Summing up, it should be emphasized that alectinib is currently the drug of choice for targeted first-line therapy of ALK-positive metastatic NSCLC [5]. This preference is based on high efficacy, acceptable profile of adverse toxic events and activity against metastases in the central nervous system compared with krizotinib [20]. Brigatinib, ceritinib and crizotinib remain first-line targeted therapy options and are considered in the context of specific clinical circumstances. Lorlatinib should be prescribed to patients with disease progression during treatment with alectinib.

The excellent activity of alectinib and brigatinib is able to treat metastases in the central nervous system with targeted therapy, thereby allowing to delay or even avoid the use of radiation therapy or surgery [17; 20; 26; 29]. In patients with progression of brain metastases during treatment with alectinib, the appointment of lorlatinib is rational [33].

The results of targeted therapy with brigatinib require continued monitoring for a reliable assessment. Ensartinib, entrectinib and repotrectinib continue to be studied in clinical trials, their role in targeted therapy of ALK-mutant NSCLC has also yet to be determined. Additional data are needed regarding the optimal treatment after ALK TC therapy, whether it is chemotherapy or chemoimmunotherapy.

Currently, the possibilities of perioperative use of TKI ALK are being investigated. Krizotinib is being studied in neoadjuvant [NCT03088930] [46], as well as in adjuvant mode as part of a large, multicenter ALCHEMIST study (Adjuvant Lung Cancer Enrichment Marker Identification and Sequencing Trial) [NCT02201992] [NCT02201992] [47; 48].

The ongoing phase 3 study of ALINA is studying the efficacy and safety of the administration of alectinib compared with platinum-based chemotherapy in radically operated patients with stage IB-IIIA ALK-positive NSCLC as adjuvant therapy [49].

CONCLUSION

The progress made in the treatment of ALK-positive NSCLC over the past decade is obvious. Four ALK inhibitors have been developed, which are currently approved both for first-line targeted therapy and as additional options available during disease progression. ALK inhibitors of the new generation demonstrate excellent activity against metastatic damage to the central nervous system. Current research areas include the development of next-generation ALK inhibitors, the study of their role in neo- and/or adjuvant therapy and optimal drug treatment tactics when the available options for targeted therapy have already been exhausted.

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Information about authors:

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

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

Ellada A. Mirzoyan ✉ – PhD student 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

Anton G. Milakin – MD, oncologist of 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

Oleg N. Stateshny – MD, oncologist of 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

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

Madina A. Gappoeva – oncologist of the clinical and diagnostic department National Medical Research Centre for Oncology, Rostov-on-Don, Russian Federation. ORCID: https://orcid.org/0000-0003-0783-8626

Viktoriia N. Vitkovskaya – oncologist of the clinical and diagnostic department National Medical Research Centre for Oncology, Rostov-on-Don, Russian Federation. ORCID: https://orcid.org/0000-0002-9603-1607

Kristian D. Iozefi – PhD student 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:

Kharagezov D. A. – scientific editing;

Lazutin Yu. N. – text writing, data processing;

Mirzoyan E. A., Milakin A. G., Stateshny O. N., Leyman I. A., Chubaryan A. V., Gappoeva M. A., Vitkovskaya V. N., Iozefi K. D. – data collection, analysis, technical editing, bibliography design.

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REVIEW

GENES COPY NUMBER VARIATION IN COLORECTAL CANCER PATIENTS AS A MARKER OF THE DISEASE CLINICAL OUTCOME AND RESPONSE TO THERAPY

A. A. Maslov, L. Kh. Chalkhakhyan✉, S. A. Malinin, G. V. Kaminsky, E. A. Mirzoyan

National Medical Research Centre for Oncology, Rostov-on-Don, Russian Federation
✉ gabo80.80@inbox.ru

ABSTRACT

Abnormal gene copies, a special type of genetic polymorphism, is a hallmark of most solid tumors, including colorectal cancer. Abnormal copy number of genes leads to tumor-specific genomic imbalance, which manifests itself already in precancerous precursor lesions. The aim of this review was to systematize the scattered data on changes in gene copy number observed in colorectal cancer and their impact on the outcome of the disease and response to therapy. The data from 58 studies was analyzed on gene copy number changes and their expression in primary carcinomas, cell lines and experimental models. This review examines the spectrum of genetic changes that lead to colorectal cancer, describes the most frequent changes in the number of gene copies at different stages of the disease, and changes in the number of gene copies that can potentially affect the outcome of the disease of individual patients or their response to therapy. In fact, aberrant gene copy number as a form of chromosomal imbalance affects a number of genes that provide a metabolic selective advantage for a tumor cell. Changes in the genes copy number in colorectal cancer patients not only positively correlate with changes in their expression, but also affect the levels of gene transcription at the genome-wide scale. Aberrant gene copy numbers are closely related to disease outcome and response to treatment with 5-fluorouracil, irinotecan, cetuximab and bevacizumab. Nevertheless, the possibility of translating the genes copy number index into clinical practice requires further research.

Keywords:
colorectal cancer, gene copy number, gene expression, biomarkers, overall survival, response to therapy

For correspondence:
Lusegen Kh. Chalkhakhyan – Cand. Sci. (Med.), surgeon at the abdominal oncology department No. 2, National Medical Research Centre for Oncology, Rostov-on-Don, Russian Federation.
Address: 63 14 line str., Rostov-on-Don 344037, Russian Federation
E-mail: gabo80.80@inbox.ru
ORCID: https://orcid.org/0000-0001-8397-4393
SPIN: 6534-5911, AuthorID: 794696

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ОБЗОР

ПОКАЗАТЕЛЬ КОПИЙНОСТИ ГЕНОВ У БОЛЬНЫХ КОЛОРЕКТАЛЬНЫМ РАКОМ КАК МАРКЕР КЛИНИЧЕСКОГО ИСХОДА ЗАБОЛЕВАНИЯ И ОТВЕТА НА ТЕРАПИЮ

А. А. Маслов, Л. Х. Чалхахян✉, С. А. Малинин, Г. В. Каминский, Э. А. Мирзоян

НМИЦ онкологии, г. Ростов-на-Дону, Российская Федерация
✉ gabo80.80@inbox.ru

РЕЗЮМЕ

Аномальная копийность генов – особый типом генетических полиморфизмов, является отличительной чертой большинства солидных опухолей, включая колоректальный рак.
Аномальная копийность генов приводит к специфическому для опухоли геномному дисбалансу, который проявляется уже в предраковых поражениях-предшественниках. Целью данного обзора стала систематизация разобщенных данных о наблюдаемых при колоректальном раке изменениях копийности генов и их влиянии на исход заболевания и ответ на терапию. Были проанализированы данные 58 исследований по изменению числа копий генов и их экспрессии в первичных карциномах, клеточных линиях и экспериментальных моделях. В данном обзоре рассмотрен спектр генетических изменений, которые приводят к колоректальному раку, описаны наиболее частые изменения количества копий генов на разных стадиях заболевания, и изменения количества копий генов, которые потенциально могут повлиять на исход болезни отдельных пациентов или их ответ на проводимую терапию. Фактически, аберрантная копийность генов как форма хромосомного дисбаланса затрагивает целый ряд генов, обеспечивающих метаболическое избирательное преимущество для опухолевой клетки. Изменения числа копий генов у больных колоректальным раком не только положительно коррелируют с изменениями их экспрессии, но также влияют на уровни транскрипции генов в масштабе всего генома. Аберрантная копийность генов тесно связана с исходом заболевания и ответом на лечение 5-фторурацилом, иринотеканом, цетуксимабом и бевацизумабом. Тем не менее, возможность трансляции показателя копийности генов в клиническую практику требует дальнейших исследований.

Ключевые слова:
колоректальный рак, показатель копийности генов, экспрессия генов, биомаркеры, общая выживаемость, ответ на терапию

Для корреспонденции:
Чалхахян Лусеген Хачатурович – к.м.н., хирург отделения абдоминальной онкологии № 2, ФГБУ «НМИЦ онкологии» Минздрава России, г. Ростов-на-Дону, Российская Федерация.
Адрес: 344037, Российская Федерация, г. Ростов-на-Дону, ул. 14-я линия, д. 63
E-mail: gabo80.80@inbox.ru
ORCID: https://orcid.org/0000-0001-8397-4393
SPIN: 6534-5911, AuthorID: 794696

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INTRODUCTION

Colorectal cancer (CRC) is one of the most common oncological diseases in the world. According to WHO, about 1 million new cases are registered every year. In terms of the number of diagnosed cases and the number of deceased patients, this pathology is second only to lung, stomach and breast cancer. Currently, despite the successes achieved in the diagnosis of these tumors, they are often detected at late stages [1].

CRC is characterized by aberrant behavior of cells that destroy already existing tissues, both locally in the organ of origin and at a distance, in the niches of metastasis. The aberrant behavior of tumor cells is caused by changes in cell biology and affects critical processes such as proliferation, invasion, avoidance of apoptosis and the immune system [2]. These changes in cell biology, in turn, are the result of an evolutionary process whereby gene mutations and copy number changes (CNVs) accumulate and lead to the selective advantage of cell clones carrying these changes.

There are different types of genetic changes in cancer: small nucleotide variations (SNV), small insertions or deletions (Indels), structural variants (SV) and variations in the number of copies of genes (CNV). The role of CNV in oncogenesis has long been underestimated. Fogelstein's pioneering work with collaborators in the early 90s of the 20th century showed that the accumulation of changes in genes involved in key signaling pathways leads to neoplastic changes in normal epithelial cells of the colon, eventually transforming into cancer [3]. Accordingly, an early decisive event in the development of CRC is a violation of the functioning of the WNT signaling pathway, leading to the formation of an adenoma, and this occurs in most cases due to changes in the APC gene. Further, there is an accumulation of mutations in the *KRAS* gene (involved in the MAPK signaling pathway), large deletions on the long arm of chromosome 18 (affecting the TGF-β signaling pathway), and deletion of the short arm of chromosome 17 (17p), where *TP53* is located, which eventually leads to the formation of cancer [4].

Variations in the number of copies of genes (CNV) are a special type of genetic polymorphisms that lead to a change in the number of copies of a certain gene and, consequently, to a change in the expression level of the product of this gene – protein or non-coding RNA [5]. With the advent of comparative genomic hybridization (CGH), it became possible to analyze CNV throughout the genome. This molecular approach confirmed and refined the results obtained by karyotype analysis [6], allowed us to thoroughly characterize the CNVs observed in microsatellite stable CRC – mainly amplifications of chromosomes 7, 8q, 13 and 20q, as well as deletions of 8p, 17p and 18 [7]. In 2012, information on the number of gene copies in 276 CRC samples was entered into the TCGA. It has been confirmed that CNVs in CRC affect regions of chromosomes 1q, 7, 8q, 13q and 20q and 1p, 4, 5q, 8p, 14q, 15q, 17p and 18q [8].

A great contribution to the study of the role of CNV in the malignancy of various tissues, the response to therapy, including radiation, predicting the course of the disease and the survival of patients, was made by employees of the National Medical Research Centre for Oncology in a series of works performed in 2014–2021. Thus, data were obtained indicating the important role of changes in the copyicity of the genes *BAX, CASP3, CASP8, OCT4, C–MYC, SOX2, BCL2, NANOG, CASP9, NFKB1, HV2, ACTB, MKI67, IL-10, GSTP1* and *P53* in gastric tissue malignancy [9], the copyicity of genetic loci was investigated, responsible for the regulation of apoptosis (*BAX, BCL2, C-FLAR, P53, MDM2, BFAR, SEMA3B, RASSF1A, CASP9, CASP3, CASP8*), proliferation (*SOX2, OCT4, NANOG, PIK3* and *MKI67*), oxidative phosphorylation (*HV2*), response to hypoxia (*HIF1A1*), DNA repair (*XRCC1*), destruction of the intercellular matrix (MMP1), maintenance of telomere length (*TERT*), regulation of adhesive intercellular contacts (CTNNB1) and angiogenesis (*VEGFA*), functioning of the EGFR signaling pathway (*KRAS, EGFR, GRB2, SOS1, MAPK1, STAT1, BRAF*) in normal and tumor lung cells in 90 patients with lung adenocarcinoma[10]. There was also a study of the features of the copyicity of the genes *BAX, BCL2, TP53, MDM2, CASP9, CASP3, CASP7, CASP8, PRKCI, SOX2, OCT4, PIK3, PTEN, C–MYC, SOX18, AKT1, NOTCH1, BRCA1, BRCA2, EXO1, SCNN1A, KRAS, EGFR, BRAF, CYP1A1, CYP1A2, CYP1B1, CYP19A, ESR1, ESR2, GPER, STS, SULT1A, SULT1E1* in tumor and normal cells of serous ovarian adenocarcinoma of high and low malignancy [11]. The role of the replication of a number of genes (*RBBP8, BRCA2, H2AX* and *BCL2*) in the response of malignant tumors of the prostate and rectum to radiation therapy has been established [12].

Thus, the important role of the gene copy index as biomarkers of oncological diseases and the effectiveness of their therapy becomes obvious. The NCBI database contains information on a large number of studies on changes in gene copyness in CRC and their association with certain clinical characteristics, however, all the data presented are extremely heterogeneous and require generalization to form a unified understanding of the role of CNV in CRC.

Therefore, the purpose of this review was to systematize the disjointed data on changes in gene replication observed in colorectal cancer and their impact on the outcome of the disease and response to therapy.

Molecular classification of colorectal cancer

In CRC, two main pathways of genomic instability are observed: chromosomal instability (CIN) – 85 % of cases, and microsatellite instability (MSI) – 15 % of cases [4; 13]. CINS are characterized by large chromosomal aberrations, while MSI are characterized by mutations at the level of one nucleotide in repeating regions (microsatellites) [14].

CRC can also be classified based on data on the level of hypermethylation of the promoter (CpG Island Methylator Phenotype; CIMP) into CRC with high and low levels of CIMP. There is a strong association of the MSI phenotype with CIMP due to hypermethylation of the hMLH1 gene [15]. Another classification based on the transcriptome is also proposed, including 4 subtypes of CRC (CMS) [16], which are not completely discrete classes, since there is some degree of overlap reflecting the continuity of CRC transcriptomes [17]. With the exception of CMS1 (MSI CRC), all other 3 CMS groups (CMS2–4) represent to a certain extent a higher/lower degree of CIN-CRC [17]. The transfer of the CMS classification system to preclinical models and clinical practice opens up prospects for targeted therapy [18].

Formation of CNV during oncogenesis

Disruption in the functioning of the WNT signaling pathway and the acquisition of chromosomal aneuploidy (for example, an additional copy of chromosome 7) can lead to the formation of adenoma, which progresses into carcinoma due to the accumulation of additional genetic and epigenetic changes. Different lesions with different morphology can lead to the development of CRC. These can be ordinary (polypoid, flat) adenomas or toothed polyps. Although the total amount of CNV in adenomas is low compared to carcinomas, it is necessary to take into account the presence of chromosomal aneuploidies and genomic changes in such precancerous lesions, which contributes to achieving relatively high levels of genetic heterogeneity [19]. In addition, differences in CNV patterns can be observed between different morphologies, namely polypoid and non-polypoid adenomas. When comparing a large series of non-polypoid adenomas with polypoid adenomas, it was shown that the former have 5q deletions more often and 1p, 10q, 17p and 18q deletions less often than the latter [20]. Other precursors of CRC, such as dentate polyps [21], progress to a malignant tumor along the MSI pathway and, therefore, do not show common CNVs with tumors arising from polypoid adenomas [22].

Despite the fact that chromosomal aneuploidies can be observed in precancerous lesions, their appearance is more common at later stages of the transition to a malignant neoplasm [23]. Several studies have shown that CNVs are associated with this transition in certain regions of chromosomes – 8q, 13q, 20q, 8p, 15q, 17p and 18q [24].

Colorectal adenomas are a very common finding in the elderly (prevalence 35 %) [4]. However, it is believed that only about 5 % of colon polyps removed during endoscopy could develop into cancer. Indeed, histopathological features associated with the presence of focal cancer in adenomas include a size of ≥ 10 mm, high degree dysplasia and villi histology. The presence of at least one of these histopathological features leads to the progression of adenoma into cancer [4]. However, the accuracy of these indicators for detecting adenomas that can progress to cancer is low [25]. New markers are needed that more accurately reflect the natural course of the disease and more specifically identify adenomas with a high risk of cancer [26].

Strategies and approaches to the analysis of changes in the number of copies of genes in cancer

Molecular cytogenetic methods, including approaches related to FISH and CGH, have improved the analysis of chromosomal aberrations in tumors of various localizations [4]. CGH allowed mapping the genomic imbalance in tumors to an unprecedent-

ed level by comparing genomic DNA isolated from a tumor sample with a reference genome without the need for metaphase chromosome preparations. This made it possible to use formalin-fixed and paraffin-filled material (FFPE blocks) for cytogenetic analyses. The use of CGH has provided evidence that genomic imbalance is responsible for tumor progression from dysplastic lesions to invasive disease. Later, DNA microarrays made it possible to simultaneously measure the number of copies of many polymorphic loci in the genome, which led to the high-resolution detection of LOH, a common phenomenon in oncogenesis [27].

The development of mass parallel sequencing with has led to the development of many tools for analyzing the CNV of the entire exome (WES) or the complete genome (WGS). Consistent analysis of sequencing data was made possible partly thanks to the Genome Analysis Toolkit (GATK) [28]. 4 computational genome sequencing approaches have been described to detect structural variants:

1) paired reading (the distance between the mapped reads and the average size of the genomic insert is compared);

2) split reading (detection of small insertions and deletions by means of alignment analysis on the reference genome);

3) assembly method (a reference-free reconstruction of the entire genome from a set of readings is calculated and compared with the reference genome using several programs)

4) counting the number of reads or the depth of coverage (the most recent approach, which takes into account the number of reads displayed for each region in the genome, and assumes a uniform sequencing process, so the number of reads in a particular region will be proportional to the number of copies of it) [29].

Next, we attempted to compare several methods, further emphasizing the differences between the tools [30–34]. Tools such as GISTIC 2.0 [35], ConVaQ [36] or CNApp [37] allow researchers to

Table 1. Bioinformatic tools and methods for CNV detection using mass parallel sequencing platforms

Name	Sequencing platform	Programming language
CNVkit	WES/WGS	Python
ExomeDepth	WES	R
VarScan2	WES/WGS	Java
ControlFreeC	WES/WGS	C++
ExomeCNV	WES	R
XHMM	WES	C++
CoNIFER	WES	Python
Delly	WGS	C++
XCAVATOR	WGS	Perl, bash, R, Fortran
CNVnator	WGS	C++
CNV-seq	WGS	R, perl
Pindel	WGS	C++
CONTRA	WES	Python/R

Note: WES is whole exome sequencing; WGS is whole genome sequencing.

integrate CNV genomic data with additional molecular and clinical characteristics and uncover new functionality and implications for these genomic events (Table 1).

CNV signatures

To a certain extent, SNV and CNV in the genome of malignant cells represent a trace of uncorrected genetic changes that have accumulated during the life of the tumor. SNV studies have revealed mutational patterns resulting from various types of nucleotide changes in this type of tumor, and defined as mutational signatures [38]. Unlike SNV, only the presence or absence of a specific chromosome in tumor cells has been well described in the literature, but the mechanisms underlying such patterns have not been described. Attempts have been made to identify the signatures of the number of copies of genes taking into account various approaches. Thus, using non-negative matrix factorization models, 6 signatures were extracted to 32 ranked subclasses of breast cancer data obtained by sequencing the entire genome, based on their association with homologous recombination mediated by microhomology [39]. Similarly, 8 gene copy number signatures based on structural features were identified by whole genome sequencing in serous ovarian cancer [40]. These authors showed the correlation of CNV signatures with prognosis and response to treatment, and showed their importance as clinical biomarkers. Finally, "pan-cancer" studies have identified 9 signatures that determine the etiology of structural variants, suggesting that mechanisms based on DNA replication generate different chromosomal structures in different types of tumors, including CRC [41].

Changes in the number of copies of genes and their transcriptional activity

In the work of Ried and co-authors [42], it was found that for each type of tumor there is a specific CNV landscape reflecting genomic imbalance. As mentioned earlier, the following CNV profile is observed in CRC-an increase in copyness in the region of chromosomes 7, 8q, 13, 20q and a decrease in copyness in the region of 8p, 17p and 18. Such observations raise the question of what their effect is on the levels of gene transcription in the affected areas of chromosomes. In fact, among several hypotheses as to why transcription programs are affected by CNVs, the bulk of the literature indicates that CNVs directly affect the expression of most genes in the altered genomic segment; however, the extent to which genes other than oncogenes and tumor suppressors contribute to malignant transformation or preservation of the transformed state remains unclear. The biological consequences of such aneuploidy are not limited to the affected chromosomal region, but may be associated with the effect on the transcriptional activity of genes located in other regions of the genome. Naturally, the third possibility is that these aneuploidies target only a limited number of genes that give a selective advantage to the cancer cell [4].

Cell lines derived from primary carcinomas are widely used to measure the effect of genomic CNVs on gene expression. Analysis of 15 CRC cell lines, including lines with effective and defective repair systems, showed a positive correlation throughout the genome between CNV and the corresponding gene expression [4]. Such correlations have been confirmed for many other types of tumors, for example, prostate cancer and cervical cancer [43].

The correlation of the number of copies of genes and the average level of gene expression is also applicable to primary tumors. In fact, several authors have shown the effect of CNV on gene expression levels in precancerous lesions and carcinomas of various origins [44; 45] In these studies, the authors examined several groups of rectal and colon cancer samples and compared the normal mucosa, and determined that the increased expression was in those genes that are located on chromosomes 7, 13 and 20, that is, chromosomes on which amplifications are observed, while the genes with reduced expression were located on chromosomes 18, 14 and 15, in which CNV deletions are usually observed in CRC. The data obtained by genome-wide sequencing and presented by the Cancer Genome Atlas consortium were used to map somatic structural changes, including CNV, in 600 tumors of various origins, and showed their contribution to altered gene expression in CRC [46].

The positive correlation between CNV and gene expression has led to the discovery of new cancer-related genes. In particular, in CRC, the amplification of chromosome 13 regions and the associated overexpression of multiple genes provided a unique chance to uncover several genes associated with on-

Table 2. Changes in the gene copy index and the outcome of the disease

Chromosome locus	CNV type	Genes	Sample Size, *n*	Clinical significance	Link
1p36.33 – p36.32	Amplification	*SKI*	159	Patients with *SKI* amplification had worse OS and RFS	[52]
5p14.3 – p13.3	Amplification	*RNASEN, C5orf22, GOLPH3, MTMR12, ZFR, SUB1* and *TARS*	111	Amplification was associated with a shorter PFS	[53]
5q12.1 – q12.3	Deletion	*SFRS12IP1, SDCCAG10, CENPK, PPWD1* and *SFRS12*	105	Deletion was associated with a shorter PFS	[53]
5q34	Deletion	*CCNG1*	133	Deletion was associated with a shorter PFS	[53]
6q16.1 – q16.3	Amplification	*KIAA0776, C6orf66, C6orf167, FBXL4, SFRS18, CCNC, ASCC3, ATG5, QRSL1, 6orf203, PDSS2, LACE1, CD164, SMPD2* and *ZBTB24*	111	Amplification was associated with a shorter PFS	[53]
7p11.2	Amplification	*EGFR*	44	Patients with *EGFR* amplification achieved a high percentage of partial remission, while patients without increased *EGFR* replication had progressive disease. In addition, patients with a high *EGFR* copy count had a longer period of time before progression.	[4]
7q22.1	Amplification	*GAEC1*	79	Associated with tumor perforation and later stage T	[53]
17q21 – q21.3	Deletion	*PSMB3, PIP4K2B, CCDC49, RPL23, LASP1, RPL19, FBXL20, MED1, CRKRS, NEUROD2, STARD3, TOP2A, SMARCE1, TMEM99, KRTAP3-3, KRTAP1-1, EIF1, NT5C3L, KLHL11, ACLY2 MLX, EZH1, VPS25, CCDC56, BECN1, PSME3, RUNDC1, RPL27, BRCA1, NBR2, NBR1, DUSP3, TMEM101, LSM12, TMUB2, GPATCH8, CCDC43, EFTUD2, NMT1* and *MAP3K14*	133	Deletion was associated with a shorter PFS	[53]
18p11.32	Deletion	*USP14, THOC1, C18orf56, TYMS, ENOSF1* and *YES1*	111	Deletion was associated with a shorter PFS	[53]
18p11.32 – p11.21	Deletion	*METTL4, NDC80, SMCHD1, EMILIN2, LPIN2, MRCL3, MRLC2, ZFP161, RAB12, KIAA0802, NDUFV2, ANKRD12, TWSG1, RALBP1, PPP4R1, VAPA* and *NAPG*	133	Deletion was associated with a shorter PFS	[53]

Table 2. Changes in the gene copy index and the outcome of the disease

Chromosome locus	CNV type	Genes	Sample Size, *n*	Clinical significance	Link
18p11.21	Deletion	*CHMP1B, MPPE1, IMPA2, TUBB6, AFG3L2, CEP76, PSMG2, PTPN2, SEH1L, CEP192, C18orf19* and *RNMT*	133	Deletion was associated with a shorter PFS	[53]
18q11.2	Deletion	*LAMA3*	133	Deletion was associated with a shorter PFS	[53]
18q21.2	Deletion	*SMAD4*	147	Associated with tumor developement	[4]
18q21.33 – q22	Deletion	*MYO5B, MBD1, CXXC1, C18orf24, ME2, ELAC1, SMAD4, MEX3C, MBD2, POLI, RAB27B, CCDC68, TXNL1, WDR7, FECH, NARS, ATP8B1, ALPK2, MALT1, SEC11C, KIP2A, PF2A1, PF2A14, PF2A1, PF2A1, PF2A1 TNFRSF11A, ZCCHC2, PHLPP, BCL2, KDSR, VPS4B, SERPINB8, TMX3, RTTN, SOCS6, C18orf55* and *CNDP2*	111	Deletion was associated with a shorter PFS	[53]
20q11 – q13.3	Amplification	*BCL2L1, ASXL1, SRC, DNMT3b, Gnas, TOP1, AURKA, PTPRT,* and *NCOA3*	354	Amplification was associated with better OS	[55]
20q11.21 – q13.33	Amplification	*PTK6* and *EEFIA2*	269	Significantly associated with improved overall survival in grade III tumors	[4]
20q13.2	Amplification	*CSE1L, NABC1, ZNF217* and *STK15*	146	An increase in the number of copies is associated with poorer overall survival and faster tumor progression	[4]

Note: RFS – relapse–free survival; OS – overall survival; PFS – progression free survival.

cogenesis, including CDK8, CDX2 and LNX2, for which overexpression was *associated with WNT activity and oncogenic functions [46]. In addition, several other cancer-related genes (AHCY, TPX2, POFUT1, Rpn2, AURKA, TH1L, MTUS1, PPP2CB, ARGLU1, UGGT2, CES2, FUT10, PAOX,* and *PRPF6*) showed a significant linear correlation between the dose of the gene (CNV) and its expression [48; 49].

To study the effect of CNV on gene expression, several models of cell lines or animals have been developed. These studies have also shown that CNVs affect the expression not only of genes located on the aneuploid site, but also of many other genes throughout the genome, which in turn affect protein expression [50].

CNV as biomarkers of clinical outcome and response to therapy

Only a few genetic biomarkers are currently used in clinical practice related to CRC. These include mutations in RAS genes, which are commonly used in patients with CRC to prescribe therapy against EGFR. Similarly, the BRAF V600E mutation is a biomarker of poor prognosis in patients with metastatic CRC. Another prognostic marker used in the clinic is the status of MSI [4].

To date, the needs of oncologists in certain areas of CRC treatment are still unsatisfied, in particular, it concerns the prediction of the likelihood of recurrence in patients with stage II colon cancer [51]. In fact, most modern prognostic biomarkers are applied

only to patients with stage IV CRC. CRC still lacks adequate prognostic biomarkers compared to other cancers, such as melanoma, leukemia, breast, ovarian, prostate and lung cancers [4]. Since molecular cytogenetic methodologies, as well as next-generation sequencing methods for CNV assessment can be applied to archived formalin-fixed material (FFPE), the analysis of large series of CRC with well-annotated clinical data has become possible, which allowed the analysis of the prognostic value of certain CNVs. Candidate biomarkers with their respective clinical significance are shown in table 2.

With advanced CRC, an increased number of *EGFR* copies is associated with poor survival and may be an independent prognostic variable [4]. As for *PTEN*, more thorough research is needed here [4]. An increase in the copyicity of the *STRAP* gene was shown in 22 % of cases of stage II and III CRC [52]. This gene is located on chromosome 12 and encodes a protein associated with the serine/threonine kinase receptor. Interestingly, patients who did not receive adjuvant therapy showed a better prognosis with an increase in the copy of the STRAP gene. In another cohort of 354 patients with CRC (stage IV) as an increase in the copyicity of the *SRC, AURKA, TPX2* and *BCL2L1* genes [55].

A decrease in the number of copies of the *CD226* gene located on chromosome 18q, which encodes a glycoprotein expressed on the surface of NK cells, platelets, monocytes and a subpopulation of T cells, is a biomarker of poor prognosis for 5-year overall and relapse-free survival [55]. In the same CDR cohort, a decrease in the number of CDH-7 copies was a biomarker of a good result with respect to 5-year overall and relapse-free survival [55].

Recently, Lee and his colleagues have shown that *GAEC1*, a putative oncogene located on chromosome 7, was amplified in 24 % of a cohort of CRC patients [54]. Moreover, an increase in the number of copies was associated with a worse prognosis due to the increased aggressiveness of the tumor. Another predictive CNV is *SKI*, located on chromosome 1. In a cohort of 533 cases of stage II and III CRC, the number of copies of the SKI gene could be successfully measured in 159 patients [52]. *SKI* amplification was associated with worse overall and relapse-free survival compared to patients without an increase in the number of copies or deletions of this gene [52].

In 2002, a study of an early-stage CRC cohort (*n* = 180) studied the allelic imbalance of chromosomes 8p and 18q in relation to relapse of the disease. Patients with stage A tumors (according to Dukes) showing an allele imbalance in both chromosomal arms were more likely to have a relapse compared to Dukes B patients without an allele imbalance. Focal chromosomal CNVs can also be used in predicting metastases in patients with CRC. Thus, it was shown that both amplifications in the 8q and 20q regions are more often present in tumors with metastases [4].

A number of CNVs are associated with the response to treatment in CRC. An increase in the copyicity of the *TYMS* gene was shown in a sample of patients with CRC resistant to therapy based on 5-fluorouracil (5-FU) [56]. On the contrary, a decrease in the number of copies of the negative prognostic marker *CD226* is associated with better overall survival after therapy based on 5-FU [4]. Bess and his colleagues [52] reported on a study of patients with stage II and III CRC and demonstrated that *STRAP* amplification leads to a worse response to 5-FU-based therapy, which was observed in patients who had a higher rate of relapse and mortality compared to patients without amplification of this gene. Among CRC patients with wild type *KRAS*, only 17 % benefit from monotherapy against *EGFR* [57]. At the same time, in these patients, an increased number of *EGFR* copies is associated with an improved response to irinotecan-cetuximab therapy and a longer time to progression [4]. In 2013, Jiang and his colleagues conducted a meta-analysis of 13 studies involving 1,174 patients with CRC treated with cetuximab or panitumumab. Their results showed that an increase in the number of *EGFR* copies in this sample was associated with an improvement in overall and relapse-free survival [58].

In a comprehensive analysis of CNV in 349 tumors removed from patients participating in the CAIRO and CAIRO2 clinical trials, it was found that changes in certain chromosomal regions, mainly an increase in gene copy in the 6q region and deletions in the 18q region, were associated with a significant difference in progression-free survival between the irinotecan and non-irinotecan treatment groups. him [53]. In addition, van Dijk and his colleagues showed that the loss of a section of chromosome 18q11.2 – q12.1 in patients with CRC is an indicator of a good prognosis, since these patients were characterized by better overall survival and a better response to bevacizumab therapy [59].

CONCLUSION

Thus, this review shows a positive correlation between CNV levels and gene expression in CRC, leading to massive deregulation of cellular signaling pathways. However, modern literature has not allowed us to answer a number of questions: 1) Are all genes affected by such a positive correlation, or do some genes avoid this dependence? 2) Do the transcription networks of genes identified in CRC function in precancerous lesions? That is, it is necessary to find out exactly how CNVs form the transcriptome of tumor cells and why these cells need such specific deregulated transcription networks.

From the point of view of the translation of the CNV indicator into clinical practice, further research is required. In the end, an in-depth understanding of the role of CNV in CRC will allow stratifying patients based on biological and genetic characteristics to improve the prognosis of the disease and determine therapeutic strategies.

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Information about authors:

Andrey A. Maslov – Dr. Sci. (Med.), professor, chief doctor National Medical Research Centre for Oncology, Rostov-on-Don, Russian Federation. ORCID: https://orcid.org/0000-0001-7328-8074, SPIN: 5963-5915, AuthorID: 817983

Lusegen Kh. Chalkhakhyan ✉ – Cand. Sci. (Med.), surgeon at the abdominal oncology department No.2, National Medical Research Centre for Oncology, Rostov-on-Don, Russian Federation. ORCID: https://orcid.org/0000-0001-8397-4393, SPIN: 6534-5911, AuthorID: 794696

Sergey A. Malinin – Cand. Sci. (Med.), oncologist at the abdominal oncology department No. 2, National Medical Research Centre for Oncology, Rostov-on-Don, Russian Federation. ORCID: https://orcid.org/0000-0002-1220-7143, SPIN: 7229-1610, AuthorID: 794691

Gennadii V. Kaminsky – Cand. Sci. (Med.), surgeon at the abdominal oncology department No.2, National Medical Research Centre for Oncology, Rostov-on-Don, Russian Federation. ORCID: https://orcid.org/0000-0003-4905-4977, SPIN: 3308-4107, AuthorID: 794670

Ellada A. Mirzoyan – PhD student 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

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