ISSN: 2686-9039 Online

PEER-REVIEWED SCIENTIFIC AND PRACTICAL

# South Russian Journal of Cancer

РЕЦЕНЗИРУЕМЫЙ НАУЧНО-ПРАКТИЧЕСКИЙ

# Южно-Российский онкологический журнал

vol. 2 № 2/2021
том

www.cancersp.com

ISSN: 2686-9039 (Сет.)

РЕЦЕНЗИРУЕМЫЙ НАУЧНО-ПРАКТИЧЕСКИЙ

# 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.




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

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

Журнал зарегистрирован в Роскомнадзоре 28.10.2019 г.,
ПИ № ФС 77-7100 – печатное издание.
С 15.03.2021 г. ЭЛ № ФС 77-80665 – сетевое издание.
Периодичность: 4 раза в год.

Опубликовано 18.06.2021

ISSN: 2686-9039 (Online)

PEER-REVIEWED SCIENTIFIC AND PRACTICAL JOURNAL

# South Russian Journal of Cancer

**"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.




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

Editorial and publisher address:
63, G, room 1, 14 line, Rostov-on-Don 344037, Russia
E-mail: info@cancersp.com
Pfone: +7 (903) 547-04-62, +7 (863) 295-53-62
www.cancersp.com





The journal is registered at the Roskomnadzor on 28.10.2019,
PI № FS 77-77100 – print.
From 15.03.2021 EL № FS 77-80665 of 15.03.2021 – online.
Frequency: 4 issues per year.

Published 18.06.2021

Subscription: the magazine is subscribed to via the electronic editorial system on the website. The price is free.

# СОДЕРЖАНИЕ

# CONTENTS

South Russian Journal of Cancer 2021, v.2, №2, p. 6-14
https://doi.org/10.37748/2686-9039-2021-2-2-1


ORIGINAL ARTICLE

# EVALUATION OF THE CORRECTIVE EFFECT OF THERAPEUTIC PLASMAPHERESIS ON THE STATE OF RENAL FUNCTION IN PATIENTS AFTER SURGICAL TREATMENT OF LOCALIZED KIDNEY CANCER

**S.N.Dimitriadi, N.D.Ushakova, A.V.Velichko*, E.M.Frantsiyants**

National Medical Research Centre for Oncology of the Ministry of Health of Russia, 63 14 line str., Rostov-on-Don 344037, Russian Federation

## ABSTRACT

**Purpose of the study**. To assess the state of renal function in the application of therapeutic plasmapheresis in order to correct the disorders accompanying the development of preclinical stage of AKI in patients after partial nephrectomy under conditions of warm ischemia.

**Patients and methods**. We examined 119 patients (average aged 57.6±7.8 years) from 2018 to 2019, who underwent open or laparoscopic kidney resection for cancer according to elective indications and with the usage of standard WIT technique within 15-21 minutes. Patients with a high risk of developing a clinical stage of AKI ($n$=21) were divided into 2 groups: in group I ($n$=10), patients continued to receive standard nephroprotective therapy, in group II ($n$=11), 24 hours after surgery, therapeutic plasmapheresis was performed according to the TPE (Therapeutic plasma exchange) protocol. During 7 days after the surgery patients in both groups were monitored daily for the rate of hourly diuresis, serum creatinine, and creatinine GFR. The presence of significant differences in the groups was evaluated using the STATISTICA 12.6 software package and the differences between the samples were considered significant at $p$<0.05.

**Results.** The development of the clinical stage of AKI in group I was detected in 80.0 % of cases, in group II in 9.0 % of patients ($p$=0.0019). The rate of diuresis in group II was significantly higher: by more than 2 times by day 3, by 90.0 % on day 4, by 81.4 % on day 5, by 36.8 % on day 6, and by 25.4 % on day 7 ($p$<0.05). The average increase in creatinine in group I was significantly higher: more than 5 times on day 5 and more than 4 times on day 6 and 7 of the study ($p$<0.05). GFR in group II was significantly higher on day 3 (65.3 %), day 5 (54 %), day 6 (39.2 %) and day 7 (50 %) ($p$<0.05).

**Conclusion.** Therapeutic plasmapheresis is highly effective in the correction of renal function disorders after kidney resection under WIT conditions and demonstrates an advantage in reducing the risk of developing a clinical stage of AKI in comparison with preventive measures that include standard nephroprotective infusion therapy.

**Keywords:**
renal cell carcinoma, acute kidney injury, biomarkers of kidney injury, therapeutic plasmapheresis, kidney function, partial nephrectomy.

For correspondence:
Aleksey V. Velichko – oncologist of the Department of Oncohematology, junior researcher of the Department of Drug Treatment of Tumors National Medical Research Centre for Oncology of the Ministry of Health of Russia, Rostov-on-Don, Russian Federation.
Address: 63 14 line str., Rostov-on-Don 344037, Russian Federation
E-mail: lex.vel@mail.ru
SPIN: 2703-7624, AuthorID: 1053682

Information about funding: the research was supported by the grant of the President of the Russian Federation for the support of young Russian scientists MD-5060.2018.7 on the topic: "A new approach to the early diagnosis of acute kidney injury based on the analysis of biomarkers in patients with renal cell carcinoma after kidney resection under conditions of thermal ischemia".
Conflict of interest: authors report no conflict of interest.

For citation:
Dimitriadi S.N., Ushakova N.D., Velichko A.V., Frantsiyants E.M. Evaluation of the corrective effect of therapeutic plasmapheresis on the state of renal function in patients after surgical treatment of localized kidney cancer. South Russian Journal of Cancer. 2021; 2(2): 6-14. https://doi.org/10.37748/2686-9039-2021-2-2-1

Received 16.02.2021, Review (1) 23.03.2021, Review (2) 23.04.2021, Published 18.06.2021

Южно-Российский онкологический журнал 2021, т.2, №2, с. 6-14
https://doi.org/10.37748/2686-9039-2021-2-2-1
ОРИГИНАЛЬНАЯ СТАТЬЯ

# ОЦЕНКА КОРРИГИРУЮЩЕГО ВЛИЯНИЯ ЛЕЧЕБНОГО ПЛАЗМАФЕРЕЗА НА СОСТОЯНИЕ ПОЧЕЧНОЙ ФУНКЦИИ У БОЛЬНЫХ ПОСЛЕ ХИРУРГИЧЕСКОГО ЛЕЧЕНИЯ ЛОКАЛИЗОВАННОГО РАКА ПОЧКИ

**С.Н.Димитриади, Н.Д.Ушакова, А.В.Величко*, Е.М.Франциянц**

ФГБУ «НМИЦ онкологии» Минздрава России, 344037, Российская Федерация, г. Ростов-на-Дону, ул. 14-я линия, д. 63

## РЕЗЮМЕ

**Цель исследования.** Оценить состояние почечной функции на фоне лечебного плазмафереза, применяемого с целью коррекции нарушений, сопровождающих развитие преклинической стадии острого повреждения почек (ОПП) у больных после резекции почки в условиях тепловой ишемии (ТИП).

**Пациенты и методы**. Обследовано 119 больных (средний возраст 57,6±7,8 лет), которым с 2018 по 2019 гг. по элективным показаниям выполнена открытая или лапароскопическая резекция почки по поводу рака с применением стандартной методики ТИП длительностью 15-21 минут. Больные, имеющие высокий риск развития клинической стадии ОПП ($n$=21), были разделены на 2 группы: в группе I ($n$=10) больные продолжили получать стандартную нефропротективную терапию, в группе II ($n$=11) спустя 24 часа после операции проводили лечебный плазмаферез по протоколу TPE (Therapeutic plasma exchange). В течение 7-и суток после операции у больных обеих групп ежедневно осуществляли контроль скорости почасового диуреза, сывороточного креатинина, скорости клубочковой фильтрации (СКФ) по креатинину. Наличие достоверности различий в группах оценивали при помощи программного пакета STATISTICA 12.6, различия между выборками считали достоверными при $p$<0,05.

**Результаты**. Развитие клинической стадии ОПП в группе I выявили в 80,0 % случаев, во II группе в 9,0 % случаев ($p$=0,0019). Скорость диуреза во II группе была значимо выше: более чем в 2 раза к 3-им суткам, на 90,0 % на 4-е сутки, на 81,4 % на 5-е сутки, на 36,8 % на 6-е сутки и на 25,4 % на 7-е сутки ($p$<0,05). Средний прирост креатинина в I группе был значимо выше: более чем в 5 раз на 5-е сутки и более чем в 4 раза на 6-е и 7-е сутки исследования ($p$<0,05). СКФ во II группе была значимо выше на 3-и (на 65,3 %), 5-е (на 54 %), 6-е (на 39,2 %) и 7-е (на 50 %) сутки ($p$<0,05).

**Заключение**. Лечебный плазмаферез обладает высокой эффективностью в коррекции нарушений почечной функции после резекции почки в условиях ТИП и демонстрирует преимущество в снижении рисков развития клинической стадии ОПП в сравнении с профилактическими мероприятиями, включающими в себя проведение стандартной нефропротективной инфузионной терапии.

**Ключевые слова:**
почечно-клеточный рак, острое повреждение почек, биомаркеры почечного повреждения, лечебный плазмаферез, функция почки, резекция почки.

Для корреспонденции:
Величко Алексей Вячеславович – врач-онколог отделения онкогематологии, младший научный сотрудник отдела лекарственного лечения опухолей ФГБУ «НМИЦ онкологии» Минздрава России, г. Ростов-на-Дону, Российская Федерация.
Адрес: 344037, Российская Федерация, г. Ростов-на-Дону, ул. 14-я линия, д. 63
E-mail: lex.vel@mail.ru
SPIN: 2703-7624, AuthorID: 1053682

Информация о финансировании: исследование было поддержано грантом Президента Российской Федерации для поддержки молодых российских ученых МД-5060.2018.7 на тему: «Новый подход к ранней диагностике острого повреждения почек на основе анализа биомаркеров у больных почечно-клеточным раком после резекции почки в условиях тепловой ишемии».
Конфликт интересов: авторы заявляют об отсутствии конфликта интересов.

Для цитирования:
Димитриади С.Н., Ушакова Н.Д., Величко А.В., Франциянц Е.М. Оценка корригирующего влияния лечебного плазмафереза на состояние почечной функции у больных после хирургического лечения локализованного рака почки. Южно-Российский онкологический журнал. 2021; 2(2): 6-14. https://doi.org/10.37748/2686-9039-2021-2-2-1

Получено 16.02.2021, Рецензия (1) 23.03.2021, Рецензия (2) 23.04.2021, Опубликовано 18.06.2021

## RELEVANCE

Renal cell carcinoma is one of the most common oncological diseases, accounting for up to 4.0 % of all malignant neoplasms [1]. The frequency of detection of this pathology is constantly increasing, which is largely due to the technical improvement of modern imaging methods. In accordance with this, the main share of diagnosed nosological forms is represented by localized processes, the standard of treatment of which remains surgical operation: nephrectomy or kidney resection [2, 3].

If it is technically possible to implement it, according to international recommendations, the organ-preserving approach is the most preferable [4]. Resection of the kidney is most often performed using the method of total thermal ischemia (TTI), which consists in temporary clamping of the renal vein and artery. Long-term ischemic exposure in combination with a reperfusion damaging component exerted on a tumor – affected kidney increases the risk of developing a life-threatening condition in the early postoperative period-acute kidney injury (AKI), and subsequently chronic kidney disease [5].

Despite the presence of many well-known methods of anti-ischemic protection, including both surgical approaches (aimed at reducing the time of thermal ischemia, reducing the intensity of energy-dependent metabolic processes in the kidney through hypothermia, increasing the tolerance of the renal parenchyma to hypoxic conditions), and approaches based on the use of pharmacological agents (blood substitutes with oxygen transport function, drugs with anti-ischemic and anti-hypoxic effects), including the use of epidural novocaine blockades, the frequency of the development of the clinical stage of AKI after organ-preserving operations on the kidney remains high (from 5 to 15 % according to different authors) [6-10].

Based on the pathogenetic features of the development of AKI, the main links of which at the initial stages are the immune-mediated development of acute inflammation of the nephron tubules, the use of therapeutic plasmapheresis is pathogenetically justified, since the latter has significant reocorregating, immunocoregating and detoxifying properties [11-13].

Previously, we proposed a method for diagnosing AKI at the preclinical stage [14], which was later supplemented with recommendations for correcting this complication based on the use of therapeutic plasmapheresis [15]. The approach based on extracorporeal detoxification, aimed at correcting complications associated with ischemia-reperfusion syndrome, contributed to a significant reduction in the risk of AKI, which was demonstrated in a number of clinical observations. However, the obtained data should be justified using statistical methods of research with a more detailed assessment of the state of markers of impaired renal function (hourly diuresis rate, serum creatinine, glomerular filtration rate (GFR) for creatinine).

**The purpose of the study**: to evaluate the state of renal function in the context of therapeutic plasmapheresis, used to correct the disorders accompanying the development of preclinical stage of AKI in patients after kidney resection under conditions of thermal ischemia for cancer.

## PATIENTS AND METHODS

A total of 119 patients with localized kidney cancer (72 men and 47 women) were examined, with an average age of 57.6±7.8 years. All patients in the conditions of the FSBI "NMRC of Oncology" of the Ministry of Health of the Russian Federation from 2018 to 2019, according to elective indications, underwent open or laparoscopic kidney resection, during which the standard total TTI technique was used. The criteria for the selection of patients were: normal preoperative creatinine values (in the examined patients they were 83.1±4.6 mmol/L), postoperative verification of localized forms (pT1a-bN0M0) of renal cell carcinoma and the duration of thermal ischemia from 15 to 21 minutes.

Patients with a high risk of developing AKI in the postoperative period were identified using the scale of diagnosis of the preclinical stage of AKI developed earlier [16]. To apply this scale, it is necessary to know the initial and postoperative values of a number of biomarkers of renal damage (cystatin C, L-FABP (Liver Fatty Acid Binding Protein) and NGAL (Neutrophil-Gelatin-Associated Lipokalin) of blood serum), which in patients included in the study were determined using ELISA using standard commercial

test kits: for cystatin C-BioVendor (Czech Republic), for NGAL – BCMDiagnostics (USA), for L – FABP-Hycult Biotechnology (Netherlands).

All patients at high risk of AKI were treated with nephroprotective infusion therapy 16 hours after surgery: albumin 20 % – 100 ml intravenously; sterofundin – 1000 ml + eufillin 2.4 % – 3 ml intravenously; saluretics were prescribed for diuresis of less than 70 ml / hour; oral patients received at least 1 liter of water [17]. Patients who had maintained a ten percent increase from the initial preoperative values of the NGAL and/or L-FABP biomarkers 24 hours after surgery were randomized into 2 groups (I and II). Patients of group I continued to receive conservative therapy, patients of group II were additionally treated with therapeutic plasmapheresis.

Therapeutic plasmapheresis was carried out according to the TPE protocol (Therapeutic plasma exchange) on the MCS+ "Haemonetics" device (USA) with a perfusion rate of 40-60 ml/min, V=4800 rpm; with plasma substitution by intravenous infusions of gelofuzine solutions, 5 % albumin, balanced crystalloid solutions in a total volume exceeding the amount of exfused plasma by 2 times in a ratio of 1 to 1 or 2 to 1, depending on the value of hematocrit and total blood protein levels in the predilution mode. The volume of plasma extraction was 800-1200 ml. Blood stabilization was carried out with 4 % sodium citrate in the ratio of anticoagulant/blood-1 to 12.

Patients of groups I and II were under dynamic observation during the first seven days after the operation. During this period, markers of renal damage (hourly diuresis rate, serum creatinine, and creatinine GFR) were monitored daily, and based on a comparison of their values in the study groups, the effectiveness of therapeutic plasmapheresis in correcting disorders associated with AKI was evaluated. The GFR for creatinine was calculated using the CKD-EPI formula [18]. The presence or absence of a clinical stage of AKI in all patients was confirmed in accordance with the generally accepted classification of KDIGO (Kidney Disease Improving Global Outcomes) 2012 [19].

The presence of significant differences in the groups was assessed using the software package STATISTICA 12.6 (2015). The nonparametric statistical Mann-Whitney U-test was used to compare two independent samples. To identify the significance of differences in the results of correction of homeostasis disorders associated with AKI in groups I and II, the exact Fischer test was used. The differences between the samples were considered significant at the level of statistical significance $p<0.05$.

## RESEARCH RESULTS AND DISCUSSION

The use of a scale for the diagnosis of the preclinical stage of AKI with the calculation of the a-index made it possible to stratify all patients according to the degree of risk of acute kidney injury. According to the data obtained, in 31 (26 %) of the 119 patients, the value of the index a was 3 16 hours after surgery, that is, they had a high risk of developing the clinical stage of this complication, which was the reason for the start of nephroprotective therapy. Taking into account the principle of operation of the scale of diagnostics of the preclinical stage of AKI, which consists in calculating the sum of three indicators (X, Y, Z), two of which are measured in the pre- (Z) and intraoperative (Y) periods, further monitoring of patients should be carried out by measuring the indicator X, which characterizes the dynamic changes in the rate of diuresis and concentrations of biomarkers of AKI (cystatin C, L-FABP and NGAL of blood serum) in the postoperative period. Since the maximum value of each of the parameters can not exceed one, it is obvious that 16 hours after resection, the value of all indicators in each patient with a high risk of developing AKI was 1, and, consequently, all parameters of indicator X responded in 100 % of cases. Repeated measurement of the parameters of the X index in these patients 24 hours after surgical treatment revealed a significant decrease in them against the background of nephroprotective therapy. The data obtained are shown in the figure 1.

Therapeutic treatment, according to the obtained data, has significantly contributed to the restoration of the rate of diuresis of patients: the preservation of values of this parameter less than 70 ml/hour was observed only in 5 (16.1 %) patients. The number of patients in whom the increase in cystatin C values was 10 % or more compared to

the baseline values also significantly decreased: similar dynamics remained in 6 patients (19.3 %). At the same time, it should be noted that the proportion of patients in whom all the parameters of indicator X responded (that is, the rate of diuresis of these patients did not exceed 70 ml/hour, and the one-time increase in cystatin C, L-FABP and NGAL was equal to or greater than 10 %) remained high (67.8 %), most often due to the preservation of the increase in NGAL markers (in 51.6 % of cases) or L-FABP (in 58.1 % of cases). Thus, the above results indicate the need for and at the same time insufficient effectiveness of nephroprotective therapy in patients of this category.

In order to study the corrective effect of therapeutic plasmapheresis, patients at high risk of developing AKI, who 24 hours after surgery revealed the presence of an additional negative prognostic sign, such as the preservation or increase in the increase by 10 % from the preoperative values of the NGAL and/or L-FABP markers ($n$=21), were randomly divided into 2 groups. Group I consisted of 10 patients who continued to receive nephroprotective therapy, group II consisted of 11 patients whose treatment complex included plasmapheresis.

Since, according to studies, the concentration of serum creatinine increases in response to impaired renal function after 24-72 hours, further dynamic monitoring of the functional state of the kidneys of patients in groups I and II was carried out by determining the concentration of serum creatinine and GFR by creatinine, in addition, hourly diuresis was continued (in accordance with the clinical recommendations of KDIGO 2012) [19, 20]. The development of the clinical stage of AKI according to the results of monitoring in group I was detected in 8 patients (in 80 % of cases), which was confirmed by the presence of an increase in serum creatinine by 1.5 times or more from the initial values: in 6 patients (60 %) on day 3 and in 2 (20 %) patients on day 5 after resection. In group II, studies clinically confirmed the presence of AKI in only one (9 %) patient ($p$=0.0019, when compared with the results in group I using the exact Fischer test). The results of comparisons of dynamic changes in the functional markers under study are presented in more detail in the figures 2-4).

As shown in Figure 2, after therapeutic plasmapheresis in group II, the average values of the diuresis rate from the 3rd to the 7th day of the study did not have significant statistical differences in comparison with preoperative ones. At the same time, in the group of patients whose correction of renal function disorders was limited to nephroprotective therapy, a statistically significant decrease in the rate of diuresis compared to the initial values was observed by the 3rd day of the postoperative period (by 55.1 %). It is important to note that the average rate of diuresis from the 3rd to the 7th day of the study in group II was significantly higher: more than 2 times by the 3rd day ($p$<0.05), by 90.0 % on the 4th day ($p$<0.05), by 81.4 % on the 5th day ($p$<0.001), by 36.8 % on the 6th day ($p$<0.05) and by 25.4 % on the 7th day ($p$<0.05). Thus, the obtained results demonstrate a pronounced corrective effect of therapeutic plasmapheresis on the rate of diuresis in patients with a high risk of developing the clinical stage of AKI.

Based on the fact that AKI is usually diagnosed with an increase in the concentration of serum creatinine by 1.5 times from the initial values, it is more informative, from the point of view of this study, to present data comparing not the average values of

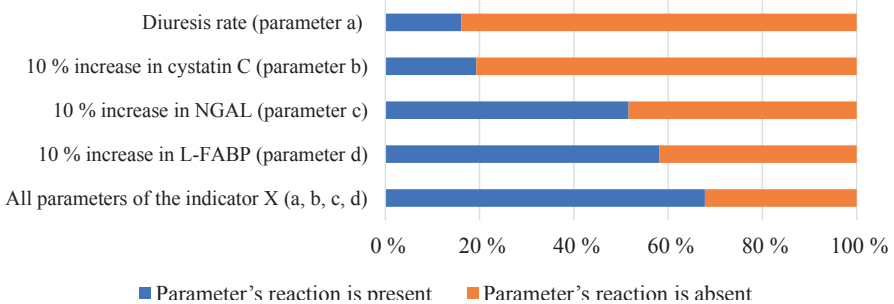



Fig. 1. The occurrence of indicators of the dynamics of the levels of three informative markers of AKI, taking into account the rate of diuresis (indicator X) in patients with a high risk of developing AKI ($n$=31) after the start of infusion therapy (24 hours after surgery), %.

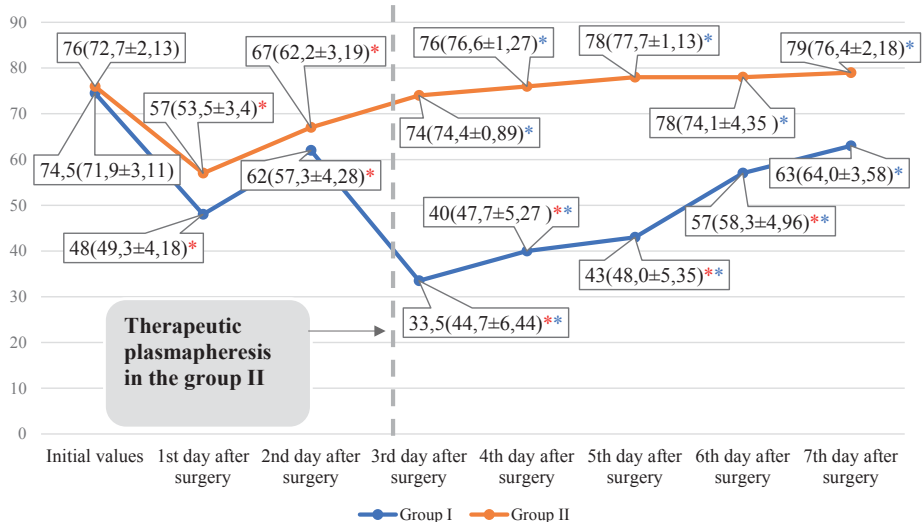



Fig. 2. Dynamics of diuresis rate in patients of group I and II in the perioperative period (Me (M±m)).

Note: * – reliability of differences with the initial values in the subgroup ($p$<0.05); * – reliability of differences between groups I and II ($p$<0.05).

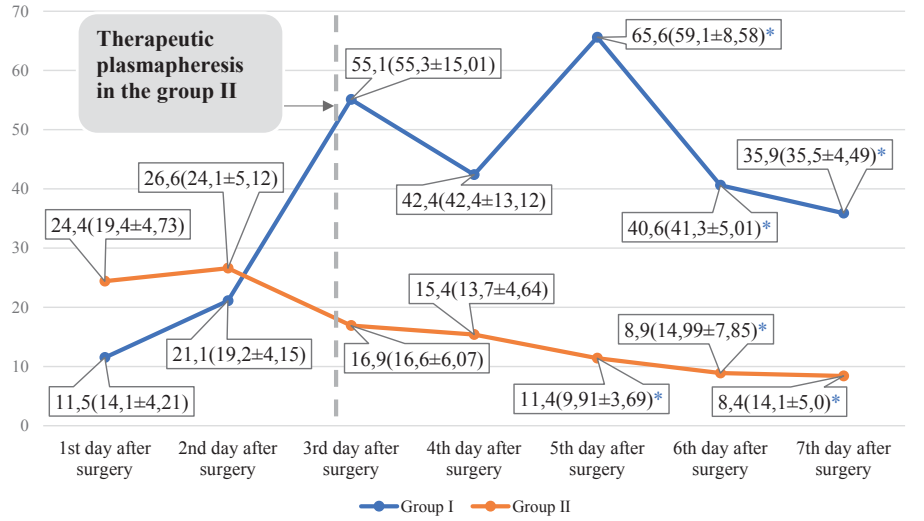



Fig. 3. Average increase in serum creatinine in patients of group I and II in the perioperative period compared to initial values (Me (M±m)).

Note: * – reliability of differences with the initial values in the subgroup ($p$<0.05); * – significance of differences between groups I and II ($p$<0.05).

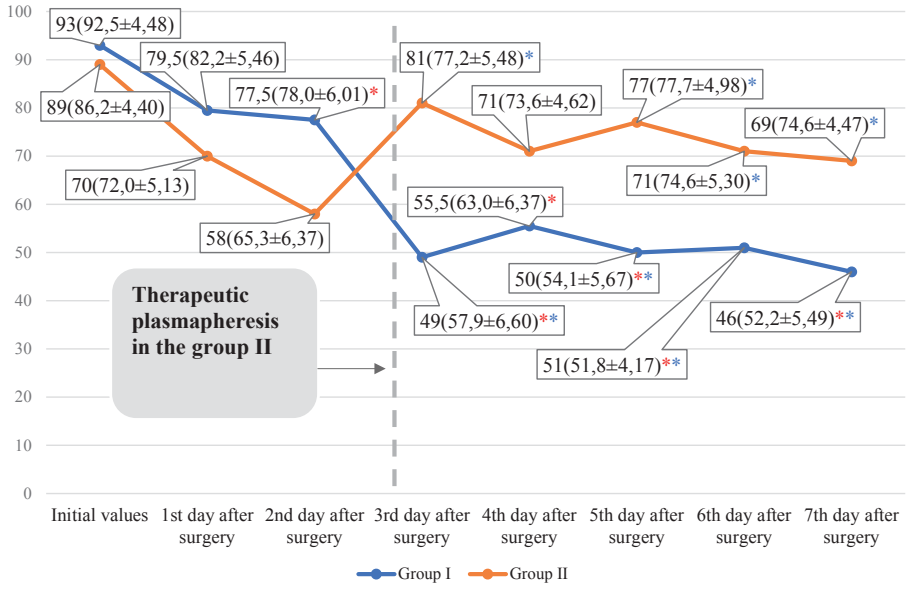



Fig. 4. Dynamics of GFR for creatinine in patients of group I and II in the perioperative period (Me (M±m)).

Note: * – reliability of differences with the initial values in the subgroup ($p$<0.05); * – reliability of differences between groups I and II ($p$<0.05).

serum creatinine, but the average values of its increase per day in relation to its initial values (Fig. 3).

To this end, we calculated the difference in creatinine values for each day of the postoperative period with the initial values in each patient and found the median from the resulting numerical series. The obtained results indicated significant differences in the average values of serum creatinine gain between the subgroups from the 5th to the 7th day of the study. The average increase in creatinine in group I was significantly higher (more than 5 times on day 5 and more than 4 times on day 6 and 7 of the study), which indicated that the majority of patients who received only nephroprotective therapy in comparison with patients who additionally received therapeutic plasmapheresis, more often observed an increase in serum creatinine, which, at the same time, was characterized by greater intensity. Dynamic changes in GFR also indicated statistically significant differences in the functional state of the kidneys in patients of groups I and II (Fig. 4).

When comparing the dynamic changes in GFR in the study subgroups, the latter were characterized by higher values in group II on the 3rd (by 65.3 %), 5th (by 54 %), 6th (by 39.2 %) and 7th (by 50 %) days after resection than in group I (at $p<0.05$ for all comparison cases). Analysis of the results of GFR calculation in group I revealed a significant decrease in the values of this indicator in comparison with the baseline on the 3rd day (by 47.3 %), on the 4th day (by 40.3 %), on the 5th day (by 46.2 %), on the 6th day (by 45.1 %) and on the 7th day (by 50.5 %) of the postoperative period. Consequently, the dynamics of GFR also confirmed the presence of higher functional results of correction of postoperative complications in the group of patients who underwent therapeutic plasmapheresis.

The main direction in the provision of therapeutic and preventive measures at the early stages of AKI development, both in domestic and foreign clinical recommendations, is the conservative correction of complications caused by renal dysfunction [19-24]. The use of combined infusion therapy, the purpose of which is to level protein-energy deficiency, uremic disorders, acid-base and water-electrolyte balance, is a pathogenetically justified, necessary, but insufficiently effective preventive measure, as evidenced by the high rates of morbidity and morbidity associated with AKI. The data presented in this study allow us to recommend the use of therapeutic plasmapheresis in combination with infusion therapy in clinical practice as the most effective approach to reduce the risks of developing and further progressing AKI in patients after kidney resection in conditions of thermal ischemia.

## CONCLUSIONS

Based on the analysis of the dynamics of markers of renal functional impairment (serum creatinine, GFR, and diuresis rate), we can conclude that therapeutic plasmapheresis is highly effective in correcting ischemia-reperfusion syndrome induced by postoperative trauma.

The use of therapeutic plasmapheresis in combination with ifusion nephroprotective therapy, when identifying patients with preclinical stage of AKI, demonstrated an advantage in reducing the risks of progression and development of the clinical stage of this complication in comparison with preventive measures that include an exclusively therapeutic approach.

Authors contribution:

Dimitriadi S.N. – research concept and design, scientific and technical editing.

Ushakova N.D. – data analysis and interpretation, scientific and technical editing.

Velichko A.V. – data collection and statistical analysis, operation assistance, article preparation, text writing, bibliography design, illustration preparation.

Frantsiyants E.M. – scientific and technical editing, material processing.

## References

1. Malignant neoplasms in Russia in 2018 (morbidity and mortality). Edited by A.D. Kaprin, V.V. Starinsky, G.V. Petrova, Moscow: P.A.Hertsen Moscow Oncology Research Institute – Branch of the National Medical Research Radiological Centre, 2019. (In Russian).

2. Matveev VB, Markova AS. Kidney cancer: what's new in 2018. Oncourology 2018; 14(4):48-52. (In Russian). https://doi.org/10.17650/1726-9776-2018-14-4-48-52

3. Rakul S. A. The practice of treating kidney cancer in a modern hospital: the evolution of approaches. Oncourology. 2018;14(2):44–53. (In Russian). https://doi.org/10.17650/1726-9776-2018-14-2-44--53

4. Campbell S, Uzzo RG, Allaf ME, Bass EB, Cadeddu JA, Chang A, et al. Renal Mass and Localized Renal Cancer: AUA Guideline. J Urol. 2017 Sep;198(3):520–529. https://doi.org/10.1016/j.juro.2017.04.100

5. Popov SV, Huseynov RG, Martov AG, Muratov TM, Tabynbaev NB. Molecular and cellular mechanisms of renal parenchyma damage in thermal renal ischemia. Urology. 2017;4:79–84. (In Russian). https://doi.org/10.18565/urol.2017.4.79-84

6. Bratchikov OIPokrovsky MV, Elagin VV, Kostina DA. Correction of endothelial dysfunction in the kidney by distant ischemic and pharmacological preconditioning in thermal ischemia. The Journal of Urology. 2018; 6(2): 5–12. (In Russian). https://doi.org/10.21886/2308-6424-2018-6-2-5-12

7. Shormanov IS, Los MS, Titov KS. Complex anti-ischemic therapy of early postoperative period of organ-preserving surgical treatment of renal cell carcinoma. Russian Biotherapeutic Journal. 2018;17(1):58–63. (In Russian). https://doi.org/10.17650/1726-9784-2018-17-1-58-63

8. Safronova EYu, Krasheninnikov AA, Sergienko SA, Nyushko KM, Alekseev BYa, Kalpinsky AS, et al. Methods of hemostasis in kidney resection. Oncology. P.A.Herzen Magazine. 2016;5(5):55–60. (In Russian). https://doi.org/10.17116/onkolog20165455-60

9. Rospatent. Registered on 06.11.2013. Certificate for computer registration No. 2013149758/14. Kit OI, Dimitriadi SN, Medvedev VL. Method of suturing a kidney wound in laparoscopic organ-preserving treatment of kidney cancer in conditions of warm ischemia.

10. Dimitriadi SN. New opportunities laparoscopic partial nephrectomy for renal cell carcinoma with involvement of the Cup-pelvis-plating system. News of higher educational institutions. The North Caucasus region. Series: Natural Sciences. 2014; 4(182):82–86.

11. Voinov VA, Karchevsky OV, Isaulov OV. Plasmapheresis in nephrology. Nephrology. 2017;21(4):95–101. (In Russian). https://doi.org/10.24884/1561-6274-2017-21-4-95-101

12. Bessmeltsev SS, Kiseleva EA, Zamotina TB, Chechetkin AV. Development of efferent therapy methods at the Russian Research Institute of Hematology and Transfusiology. Bulletin of Nematology. 2017;13(1):40–44. (In Russian).

13. Kutilin DS, Dimitriadi SN, Vodolazhsky DI, Franciyants EM, Kit OI. Influence of warm ischemia-reperfusion on the expression of apoptosis-regulating genes in the renal tissue of patients with renal cell carcinoma. Nephrology. 2017;21(1):80–86.

14. Dimitriadi SN, Franciyants EM, Ushakova ND, Rozenko DA, Velichko AV. Biomarkers in the diagnosis of acute kidney injury after organ-preserving surgical treatment of localized kidney cancer. Medical Bulletin of the South of Russia. 2018;9(3):77–83. (In Russian). https://doi.org/10.21886/2219-8075-2018-9-3-77-83

15. Dimitriadi SN, Ushakova ND, Velichko AV, Franciyants EM, Rozenko DA. The role of biomarkers in the diagnosis of reperfusion-ischemic kidney damage as indications for therapeutic plasmapheresis in patients after renal resection in conditions of thermal ischemia for localized renal cell carcinoma. Modern problems of science and education. 2019;4:57. (In Russian).

16. Rospatent. Registered on 17.08.2018. Certificate for computer registration No. 2018130173. Kit OI, Dimitriadi SN, Franciyants EM, Ushakova ND, Rozenko DA, Velichko AV. Method of diagnosis of acute kidney injury after organ-preserving surgical treatment of localized kidney cancer. (In Russian).

17. Ostermann M. Acute kidney injury during critical illness – a global challenge. Messenger of Anesthesiology and Resuscitation. 2019;16(2):83–95. (In Russian). https://doi.org/10.21292/2078-5658-2019-16-2-83-95

18. Batyushin MM. Methodical bases of estimation of glomerular filtration rate in urological practice. The journal of urology. 2017;5(1):42–51. (In Russian). https://doi.org/10.21886/2306-6424-2017-5-1-42-51

19. Kellum JA, Lameire N, Aspelin P, Barsoum RS, Burdmann EA, Goldstein SL, et al. Kidney disease: Improving global outcomes (KDIGO) acute kidney injury work group. KDIGO clinical practice guideline for acute kidney injury. Kidney International Supplements. 2012 Mar;2(1):1–138.

20. Smirnov AV, Dobronravov VA, Rumyantsev ASh, Shilov EM, Vatazin AV, Kayukov IG, et al. National recommendations. Acute kidney injury: basic principles of diagnosis, prevention and therapy. Part I. Nephrology. 2016;20(1):79–104. (In Russian).

21. Moore PK, Hsu RK, Liu KD. Management of Acute Kidney Injury: Core Curriculum 2018. Am J Kidney Dis. 2018 Jul;72(1):136–148.
https://doi.org/10.1053/j.ajkd.2017.11.021
22. Hassanein M, Thomas G, Taliercio J. Management of acute kidney injury in COVID-19. Cleve Clin J Med. 2020 May 20. https://doi.org/10.3949/ccjm.87a.ccc034
23. Wen Y, Parikh CR. The Aftermath of AKI: Recurrent AKI, Acute Kidney Disease, and CKD Progression. J Am Soc Nephrol. 2021 Jan;32(1):2–4.
https://doi.org/10.1681/ASN.2020091317
24. Gameiro J, Fonseca JA, Marques F, Lopes JA. Management of Acute Kidney Injury Following Major Abdominal Surgery: A Contemporary Review. J Clin Med. 2020 Aug 18;9(8):2679.
https://doi.org/10.3390/jcm9082679

Information about author:

Sergey N. Dimitriadi – Dr. Sci. (Med.), senior researcher of the Department of Oncourology National Medical Research Centre for Oncology of the Ministry of Health of Russia, Rostov-on-Don, Russian Federation. SPIN: 8337-8141, AuthorID: 692389, ResearcherID: P-9273-2017

Natalia D. Ushakova – Dr. Sci. (Med.), professor, anesthesiologist-resuscitator of the Department of Anesthesiology and Resuscitation National Medical Research Centre for Oncology of the Ministry of Health of Russia, Rostov-on-Don, Russian Federation. SPIN: 9715-2250, AuthorID: 571594, ResearcherID: L-6049-2017

Aleksey V. Velichko* – oncologist of the Department of Oncohematology, junior researcher of the Department of Drug Treatment of Tumors National Medical Research Centre for Oncology, Rostov-on-Don, Russian Federation. SPIN: 2703-7624, AuthorID: 1053682

Elena M. Frantsiyants – Dr. Sci. (Biol.), professor, deputy director general for science, head of the Laboratory for the Study of the Pathogenesis of Malignant Tumors National Medical Research Centre for Oncology of the Ministry of Health of Russia, 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

South Russian Journal of Cancer 2021, v.2, №2, p. 15-21
https://doi.org/10.37748/2686-9039-2021-2-2-2


CLINICAL CASE REPORTS

# RADICAL REMOVAL OF ADVANCED CANCER OF THE ORAL CAVITY AND OROPHARYNX

**P.V.Svetitskiy**

National Medical Research Centre for Oncology of the Ministry of Health of Russia, 63 14 line str., Rostov-on-Don 344037, Russian Federation

## ABSTRACT

Surgery for advanced cancer of the oral cavity and oropharynx are among the most difficult. This is due to the topographical and anatomical features that limit the operating field and the proximity of the internal carotid artery, which penetrates into the skull without branches. Her injury and bandaging are fraught with lethality. In the postoperative period, due to a violation of the function of swallowing, there is a stagnation of oral fluid in the oral cavity, which promotes healing by secondary tension. The functions of the oropharynx are impaired: swallowing, chewing, breathing and speech.

**Purpose of the study.** To develop an operation in patients with advanced cancer of the oral cavity and oropharynx, allowing to visualize the area of the tumor with it's radical removal and postoperative healing without suppuration.

**Patients and methods.** We've operated a patient with advanced cancer of the oral cavity and oropharynx with metastases to the cervical lymph nodes (T4 N1 M0 – IV st.). Cervical lymphodessection and removal of the tumor from the oral cavity and oropharynx was performed according to the method developed at the National Medical Research Centre for Oncology of the Ministry of Health of Russia: the tumor was removed after a preliminary modified mandibulotomy. Good visualization allowed for a radical operation, after which a urostoma was formed, which promotes the free flow of oral fluid from the oral cavity, without its stagnation and without suppuration of the tissues. The jaw was restored with two titanium mini-plates.

**Results**. The healing was carried out by primary tension. On the 7th day after the operation, breathing was restored-decanulated. On day 20, epithelialization of the wound surface of the oral cavity and oropharynx occurred. The nasoesophageal probe was removed. Plastic orostoma was produced. By this time, the functions of the oropharyngeal region were partially restored: chewing, swallowing, and speech. Discharged home. Remission for more than 2 years.

**Conclusions.** Previously performed modified mandibulotomy in patients with advanced cancer of the oral cavity and oropharynx, allows you to expand the view of the operating field and provide a radical operation. The formed orostoma, preventing suppuration in the oral cavity, accelerates healing with the restoration of functions: chewing, swallowing, breathing and speech.

**Keywords:**
advanced cancer, oral cavity organs, oropharynx, mandibulotomy, osteonecrosis, orostoma.

For correspondence:
Pavel V. Svetitskiy – Dr. Sci. (Med.), professor, Head of the Department of Head and Neck Tumors National Medical Research Centre for Oncology of the Ministry of Health of Russia, Rostov-on-Don, Russian Federation.
Address: 63 14 line str., Rostov-on-Don 344037, Russian Federation
E-mail: svetitskiy.p@gmail.com
ORCID: https://orcid.org/0000-0001-5198-9873
SPIN: 6856-6020, AuthorID: 735792
Scopus Author ID: 6603343526

Information about funding: no funding of this work has been held.
Conflict of interest: authors report no conflict of interest.

For citation:
Svetitskiy P.V. Radical removal of advanced cancer of the oral cavity and oropharynx. South Russian Journal of Cancer. 2021; 2(2): 15-21.
https://doi.org/10.37748/2686-9039-2021-2-2-2

Received 25.01.2021, Review (1) 09.04.2021, Review (2) 26.04.2021, Published 18.06.2021

Южно-Российский онкологический журнал 2021, т.2, №2, с. 15-21
https://doi.org/10.37748/2686-9039-2021-2-2-2
КЛИНИЧЕСКОЕ НАБЛЮДЕНИЕ

# РАДИКАЛЬНОЕ УДАЛЕНИЕ РАСПРОСТРАНЕННОГО РАКА ПОЛОСТИ РТА И РОТОГЛОТКИ

**П.В.Светицкий**

ФГБУ «НМИЦ онкологии» Минздрава России, 344037, Российская Федерация, г. Ростов-на-Дону, ул. 14-я линия, д. 63

## РЕЗЮМЕ

Операции при распространенном раке органов полости рта и ротоглотки относятся к категории наиболее сложных. Обусловлено это топографо-анатомическими особенностями, ограничивающими операционное поле, и близостью расположения внутренней сонной артерии, которая без ответвлений проникает в череп. Её травма и перевязка чреваты летальностью. В послеоперационном периоде, из-за нарушения функции глотания, возникает застой ротовой жидкости в полости рта, что способствует заживлению вторичным натяжением. Нарушаются функции рото-гортаноглотки: глотание, жевание, дыхание и речь.

**Цель исследования**. Разработать операцию у больных с распространенным раком органов полости рта и ротоглотки, позволяющую визуализировать зону ОП процесса с радикальным его удалением и послеоперационным заживлением без нагноения.

**Пациенты и методы**. Нами прооперирован больной с распространенным раком полости рта и ротоглотки с метастазами в шейные лимфатические узлы (T4 N1 M0 – IV ст.). Проведена шейная лимфодессекция и удаление опухоли из полости рта и ротоглотки по методике, разработанной в ФГБУ «НМИЦ онкологии» Минздрава России: опухоль удалена после предварительной модифицированной мандибулотомии. Хорошая визуализация позволила радикально провести операцию, после которой сформирована оростома, способствующая свободному истечению ротовой жидкости из полости рта, без её застоя и без нагноения тканей. Челюсть восстановлена двумя титановыми мини-пластинами.

**Результаты**. Заживление прошло первичным натяжением. На 7-е сутки после операции дыхание восстановилось – деканулирован. На 20-е сутки произошла эпителизация раневой поверхности полости рта и ротоглотки. Удален носопищеводный зонд. Произведена пластика оростомы. К данному сроку частично восстановились функции орофарингеальной области: жевание, глотание и речь. Выписан домой. Ремиссия более 2-х лет.

**Заключение**. Предварительно проведенная модифицированная мандибулотомия у больных с распространенным раком полости рта и ротоглотки, позволяет расширить обзор операционного поля и обеспечить радикальное проведение операции. Сформированная оростома, предотвращая нагноение в полости рта, ускоряет заживление с восстановлением функций: жевания, глотания, дыхания и речи.

**Ключевые слова:**
распространенный рак, органы полости рта, ротоглотки, мандибулотомия, остеонекроз, оростома.

Для корреспонденции:
Светицкий Павел Викторович – д.м.н., профессор, руководитель отдела опухолей головы и шеи ФГБУ «НМИЦ онкологии» Минздрава России, Ростов-на-Дону, Российская Федерация.
Адрес: 344037, Российская Федерация, г. Ростов-на-Дону, ул. 14-я линия, д. 63
E-mail: svetitskiy.p@gmail.com
ORCID: https://orcid.org/0000-0001-5198-9873
SPIN: 6856-6020, AuthorID: 735792
Scopus Author ID: 6603343526

Информация о финансировании: финансирование данной работы не проводилось.
Конфликт интересов: авторы заявляют об отсутствии конфликта интересов.

Для цитирования:
Светицкий П.В. Радикальное удаление распространенного рака полости рта и ротоглотки. Южно-Российский онкологический журнал. 2021; 2(2): 15-21. https://doi.org/10.37748/2686-9039-2021-2-2-2

Получено 25.01.2021, Рецензия (1) 09.04.2021, Рецензия (2) 26.04.2021, Опубликовано 18.06.2021

## RELEVANCE

Cancer of the oral cavity and oropharynx in the Russian Federation ranks first among head and neck tumors, accounting for 5.5 patients (per 100,000 US) for the oral cavity with an average annual increase of 2.41 %, and the pharynx – 3.28 with an increase of 1.80 % [1]. The number of these patients in 2019 was 29.7 (per 100,000 us). At the same time, 62.8 % already had a common, in the volume of III-IV art.process [2]. A similar situation is observed in the South of Russia, where up to 72.8 % of patients are admitted to an oncologist with an already common process [3]. Despite the treatment, the 5-year survival rate, taking into account all stages, is in the range of 15-35 % [4].

Treatment of patients with advanced cancer of the oral cavity and oropharynx is complex and complex, where surgery is given a leading role. The greatest difficulties arise with a widespread tumor process located in the posterior parts of the tongue and the bottom of the oral cavity, which often passes to the root of the tongue, anatomically related to the oropharynx. In this regard, such a common tumor process in practical work is treated as oropharyngeal cancer.

The anatomical features of the oral cavity and oropharynx are due to the limited space and the proximity of the passage of the internal carotid artery, which runs along the back wall of the pharynx without branches into the skull. Injury to the artery leads to lethality, and restoring its integrity is almost impossible. This makes it difficult to determine the clear boundaries of the tumor and complicates the operation.

Access to the operating field in common processes is usually performed by intraoral, submandibular, and sublingual approaches. A pre-performed mandibulotomy is also used. Difficulties also arise in the postoperative period, especially with radical operations of a crippling nature that violate the functions of the tongue and oropharynx responsible for swallowing. When it is disturbed in the oral cavity, the stagnation of oral fluid occurs: saliva, sloughed epithelium from the salivary ducts, damaged tissues, microbes and their waste products, food residues [5]. This causes suppuration in the oral cavity, complicating the postoperative period. Suppuration is difficult to get rid of physically, and mouthwashes and mouthwashes are usually not used because of the danger of fluid aspiration into the larynx.

**The purpose of the study:** to create an operation in patients with advanced cancer of the oral cavity and oropharynx, allowing to visualize the area of the tumor process with its radical removal and postoperative healing without suppuration.

### Clinical case description

Patient M. 66 years old-a resident of the Republic of Crimea was admitted to the Federal State Medical Institution "NMRC of Oncology" of the Ministry of Health of Russia with a diagnosis of tongue cancer. Complaints of pain in the mouth and throat that increase when swal-

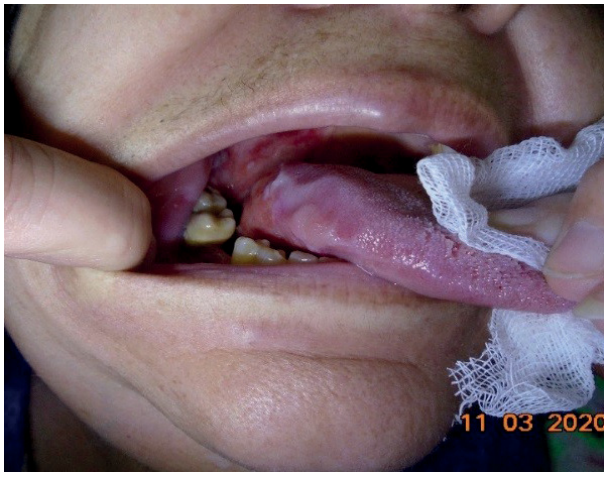



Fig. 1. On the right half of the posterior parts of the tongue, a tumor with a diameter of up to 2.0–2.5 cm is detected descending into the oropharynx.

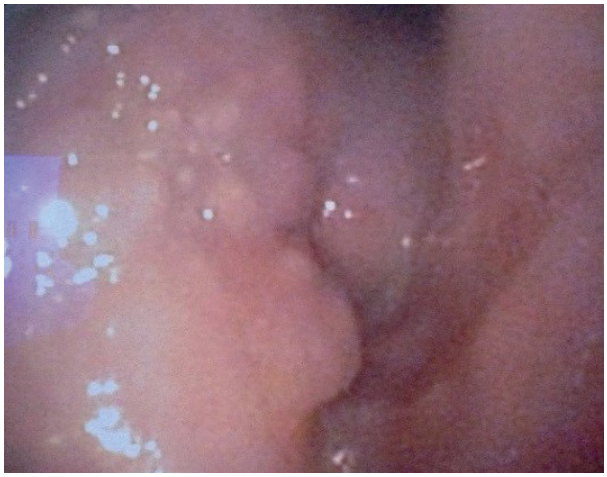


Fig. 2. The tumor spreads from the oral cavity to the right half of the oropharynx to the pear-shaped sinus.

lowing. The cause of the disease is associated with hypothermia. For about 4 months, he was treated by a dentist and an otorhinolaryngologist in Simferopol for pharyngopharyngitis. The pain progressed. There was a tumor in the posterior parts of the tongue. He was referred to an oncologist. A tumor biopsy revealed the presence of squamous cell carcinoma. The patient received a course of radiation therapy (60 Gr.) – without effect. Due to the deterioration of breathing, a tracheostomy was imposed on him at the place of residence and the patient was sent to the National Medical Research Centre for Oncology of the Ministry of Health of Russia, Rostov-on-Don.

The patient was examined in the polyclinic of the National Medical Research Centre for Oncology of the Ministry of Health of Russia. Has a tracheostomy. On the neck and in the submandibular region on the right, a weakly mobile conglomerate of lymph nodes of levels IB, IIA, and III is determined. The mouth, due to soreness, does not open well. When examining the oral cavity, in its posterior parts, a tumor of the tongue is detected with a spread to the oropharynx (fig. 1). Revision of histological preparations confirmed the presence of squamous cell carcinoma.

The endoscopic examination revealed a tumor of the posterior third of the back of the tongue, extend-

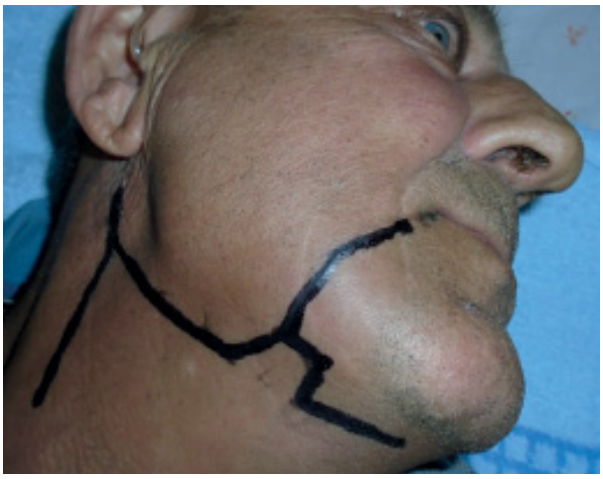


Fig. 3. Skin incisions on the neck and face. Formation of a skin flap for orostoma.

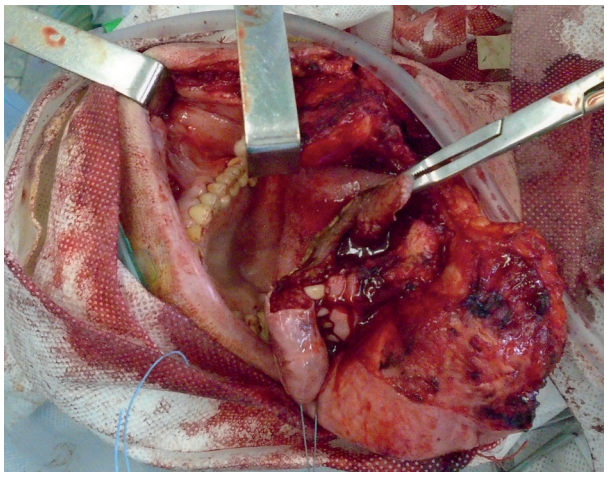


Fig. 4. After the mandibulotomy, the fragments of the lower jaw are separated. The affected part of the tongue, the floor of the oral cavity and the oropharynx are brought out and resected.

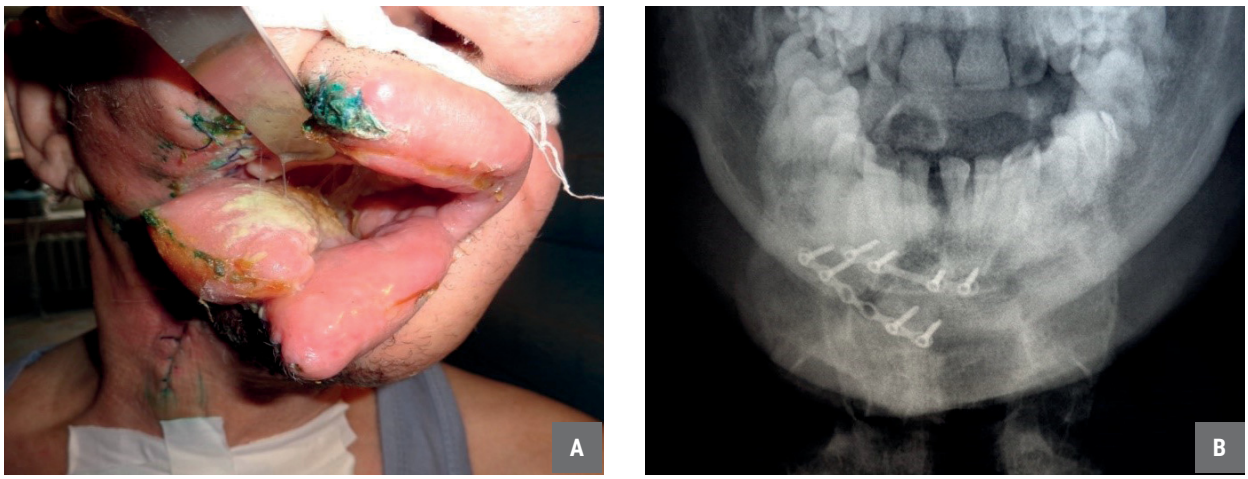



Fig. 5. Destruction of the soft tissues of the oral cavity (A) and osteonecrosis (B) of the attached fragments of the lower jaw subjected to mandibulotomy (observations of patients during the development of the operation).

ing from the oral cavity into the oropharynx to the pear-shaped sinus, covering the entire right half of the oropharynx (Fig. 2).

The diagnosis was established: advanced cancer of the tongue and oropharynx, metastases to the cervical lymph nodes: T4 NI M0 (IV st.).

The patient was offered an operation, for which consent was obtained. The operation under general endotracheal anesthesia through a tracheostomy was performed according to the method developed in the National Medical Research Centre for Oncology of the Ministry of Health of Russia [6, 7].

Initially, the traditional method was performed by cervical lymph node dissection of levels IB, II, III. The cutaneous incision is extended into the submandibular and buccal areas. At the level of the corner of the mouth along the line of incisions, a quadrilateral leather flap is cut out to form, after removal of the tumor and plastic surgery of the oral cavity, orostoma (Fig. 3).

The chin-submandibular skin-muscle flap was separated with the lower jaw exposed. The mandibulotomy was performed according to the developed method, which consists in the following. First, a median cut of the jaw body is carried out along a vertical line from its upper edge down by 1.0 cm (to preserve the roots of the front incisors), and then at an angle of 135° in the

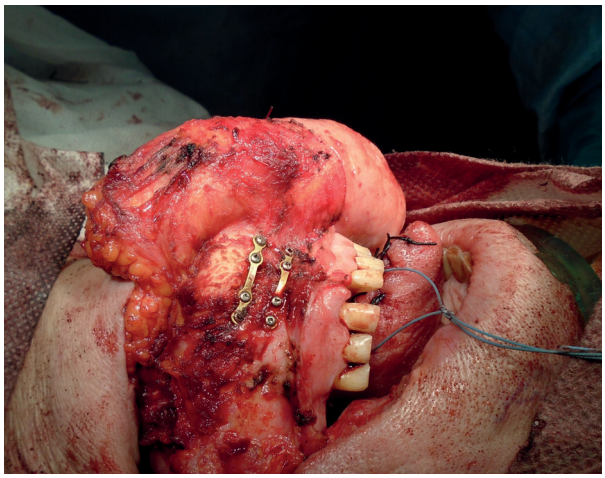


Fig. 6. Osteosynthesis of the lower jaw with 2 titanium mini-plates.

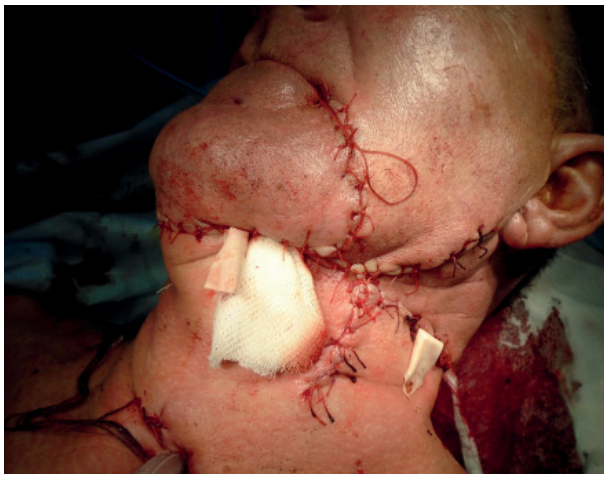


Fig. 7. The operation is finished.

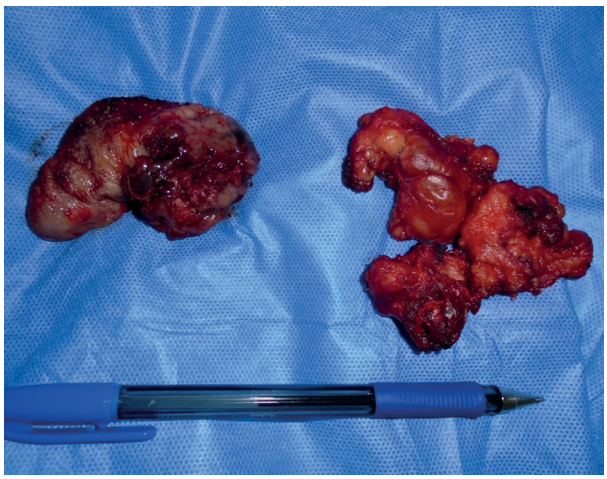


Fig. 8. Removed 2/3 of the tongue with the lateral wall of the oropharynx affected by the cancer process (left), cervical and submandibular metastases (right).

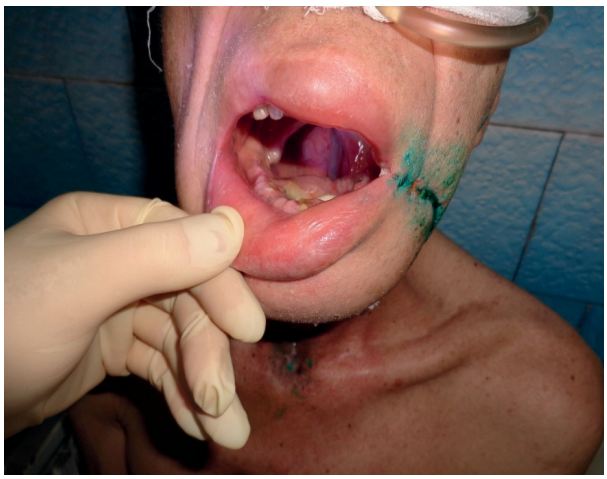


Fig. 9. Oropharyngeal area after surgery on day 20. Epithelization of the resected parts of the oral cavity and oropharynx was achieved.

direction opposite to the tumor process. Two triangular bone fragments are formed. Pushing them apart, on the side of the lesion, the mucosa of the bottom of the oral cavity is dissected, within the healthy tissues to the retromolar level. The tongue on the holder is brought out, which improves the view of the oral cavity and oropharynx, the boundaries of the tumor are clearly defined.

The area and edges of the tumor are evaluated, and the topography of the internal carotid artery passing along the posterolateral wall of the oropharynx is specified. The resection zone is determined, which includes the affected tumor tissues of the tongue (in this case, 2/3 of the tongue and half of its root) and the oropharynx. Resection and removal of the tumor is performed within healthy tissues (Fig. 4).

In the postoperative period, there are difficulties associated with a violation of the act of swallowing and depositing oral fluid in the oral cavity, which leads to suppuration of soft tissues and osteonecrosis of fragments of the lower jaw (Fig. 5).

For spontaneous evacuation of oral fluid from the oral cavity, an orostoma was formed. The most deepened part of the bottom of the oral cavity is chosen as the place of its localization. When creating it, we focused on the topography of the bottom of the oral cavity, the thickness and roughness of which is mainly determined by two muscles: the chin-hyoid (m. geniohyoideus) and maxillohyoid (m. mylohyoideus). The intersection of these two muscles in the anterolateral part of the floor of the oral cavity – its diaphragm, is the most deepened place where the liquid contents spontaneously accumulate. Therefore, this place, in our opinion, is the most suitable for creating an orostome [8]. The walls of the formed orostoma are a quadrilateral skin flap cut out from the submandibular region at the beginning of the operation (Fig. 3).

Osteosynthesis of the lower jaw was performed by bringing together and fastening its fragments with two titanium mini-plates (Fig. 6).

At the end of the operation, a nasoesophageal probe is inserted for nutrition. Layer-by-layer stitched muscles and skin, inserted rubber graduates. The orostoma is slightly tamponized (Fig. 7).

The tumor and metastases (Fig. 8) were sent for morphological examination, which confirmed the presence of squamous cell carcinoma in the removed tongue and cervical lymph nodes.

On the 7th day after the operation, breathing was restored-decanulated. On day 20, epithelialization of the wound surface of the oral cavity and oropharynx occurred (Fig. 9).

The nasoesophageal probe was removed. Plastic orostoma was produced. Discharged home. By the end of the 3rd month, the functions of the oropharyngeal region were restored: chewing, swallowing, and speech. Remission is predicted for more than 2 years.

## DISCUSSION

Topographical and anatomical features of the posterior parts of the oral cavity and oropharynx cause difficulties in identifying, diagnosing and treating tumors of these localizations. The combination of vital organs: the root of the tongue, the entrance to the larynx and esophagus, as well as the limited view limit the activity of the surgeon. The use of endoscopic equipment does not always allow us to accurately determine the features of the tumor process and its boundaries. At the same time, caution is required when operating in the area of the passage of the internal carotid artery, the injury of which is fraught with death. This situation was the basis for the development of an operation that allows you to visualize the area of the tumor process, the safe conduct of radical surgery and postoperative primary healing. To do this, in some cases, a mandibulotomy is performed beforehand. It is carried out mainly in 2 versions: the incision of the jaw is carried out vertically along its center or < figuratively. However, vertical dissection does not provide stable stability of the bonded fragments in the postoperative period. This is due to the sliding of their smooth surfaces, and the < shaped cut injures the roots of the front incisors with their subsequent loss. With extended operations, the act of swallowing is disrupted, which causes accumulation of oral fluid in the oral cavity, followed by suppuration of soft and bone tissues, leading to tissue disintegration, bleeding, osteonecrosis of the lower jaw with a violation of its integrity. All this complicates the post-vaccination period [9]. Mechanical sanitation of the oral cavity during this period is painful, complex and ineffective. In this regard, the goal was set: to develop an operation that provides radicalism with postoperative healing without suppuration. For this purpose, the method of mandibulotomy was modified, in which triangular fragments of the lower jaw were formed, which reduced their mobility

when restoring its integrity. After radical removal of the tumor, an orostoma was formed to avoid stagnation and suppuration of the oral fluid in the oral cavity. The developed method of mandibulotomy provides visualization of all parts of the oral cavity and oropharynx, as well as the ability to control the topography of the internal carotid artery. This allows you to perform a radical removal of the tumor with maximum preservation of healthy tissues. At the end of the operation, the fragments of the jaw are matched and fastened with one or two titanium mini plates, restoring its integrity. The jaw, restored in this way, acquires a stable fixation, since its fragments, fastened in a triangular shape, reduce their mobility: the mobility of the upper fragment is limited to the lower one, and the lower one – to the upper one. The distribution of the load on the jaw, at the same time, is carried out more evenly. This eliminates the need for additional metal fasteners, the number of which is not indifferent if subsequent radiation therapy is necessary.

The formed orostoma accelerates and improves the postoperative period with almost no suppuration. While eating, the orostoma is tamponed by the patient himself. By the end of the month, it usually scars on its own. If necessary, perform its plastic closure.

## CONCLUSION

To improve the effectiveness of surgical treatment of patients with advanced cancer of the posterior parts of the oral cavity and oropharynx, a method of mandibulotomy in the form of a vertically oblique dissection of the jaw was developed. It provides a sufficient overview of the operating field, a radical operation when monitoring the topography of the internal carotid artery, reliable hemostasis and strong fixation of the attached fragments of the jaw. The developed method of orostoma formation allows avoiding the accumulation of oral fluid in the oral cavity and the possibility of suppuration in the postoperative period, which accelerates and improves the postoperative period and the rehabilitation of the functions of the resected organs of the oral cavity and oropharynx.

Authors contribution:
Svetitskiy P.V. – surgery concept and performing, data analysis, manuscript writing.

### References

1. Malignant neoplasms in Russia in 2013. Ed. by A.D.Kaprin, V.V.Starinsky, G.V.Petrov. M.: P.A.Hertsen Moscow Oncology Research Institute – Branch of the National Medical Research Radiological Centre. 2015, 250 p. (In Russian).
2. The state of cancer care in Russia in 2019. Ed. by A.D.Kaprin, V.V.Starinsky, A.O.Shakhzadova. M.: P.A.Hertsen Moscow Oncology Research Institute – Branch of the National Medical Research Radiological Centre. 2020, 239 p. (In Russian). Available at:
https://glavonco.ru/cancer_register/Помощь%202019.pdf
3. Cancer of the oral mucosa. (In Russian). Available at: http://www.oncology.ru/specialist/treatment/references/oral-cavity.pdf. Accessed 18.01.2021
4. Kit OI, Duritskiy MN, Shelyakina TV, Engibaryan MA. Some characteristics of detection of oncological diseases of head and neck organs in cancer institution and institution of general health services. Modern problems of science and education. 2015:(4). (In Russian).
5. Kononenko VI. Optimization of the system of early prediction of the progression of cancer of the oral mucosa. Dissertation. Volgograd, 2017. (In Russian).
6. Rospatent. Registered on 06.12.2013. Certificate of state registration No. 2556604. Svetitsky PV, Aedinova IV, Volkova VL, Nistratov GP. Method of surgical treatment of cancer of the oral cavity and oropharynx. (In Russian).
7. Rospatent. Registered on 22.03.2018. Certificate of state registration No. 2694215. Kit OI, Svetitsky PV, Ganiev AA. Method of surgical treatment of patients with advanced cancer of the oral cavity and oropharynx. (In Russian).
8. Rospatent. Registered on 23.05.2019. Certificate of state registration No. 2704599. Kit OI, Svetitsky PV, Yengibaryan MA, Ganiev AA. A method for improving the effectiveness of surgical treatment of advanced cancer of the oral cavity and oropharynx using orostomy. (In Russian).
9. Kropotov MA. Median mandibulotomy as a means of operative access in patients with locally advanced cancer of the oral and oropharyngeal mucosa. Russian Journal of Oncology. 2002;2:34–37. (In Russian).

Information about author:
Pavel V. Svetitskiy – Dr. Sci. (Med.), professor, Head of the Department of Head and Neck Tumors National Medical Research Centre for Oncology of the Ministry of Health of Russia, Rostov-on-Don, Russian Federation. ORCID: https://orcid.org/0000-0001-5198-9873, SPIN: 6856-6020, AuthorID: 735792, Scopus Author ID: 6603343526

South Russian Journal of Cancer 2021, v.2, №2, p. 22-33
https://doi.org/10.37748/2686-9039-2021-2-2-3


CLINICAL CASE REPORTS

# ORTHOPEDIC TREATMENT IN CANCER PATIENTS WITH MAXILLOFACIAL PATHOLOGY

**I.V.Pustovaya*, M.A.Engibaryan, P.V.Svetitskiy, I.V.Aedinova, V.L.Volkova, N.A.Chertova, Yu.V.Ulianova, M.V.Bauzhadze**

National Medical Research Centre for Oncology of the Ministry of Health of Russia, 63 14 line str., Rostov-on-Don 344037, Russian Federation

## ABSTRACT

**Relevance**. Staged orthopedic treatment was used to improve the quality of life of patients who underwent radical maxillofacial surgeries for cancer.

**Patients and methods.** 197 patients receiving treatment for maxillofacial cancer were observed at the Department of head and neck tumors, National Medical Research Centre for Oncology of the Ministry of Health of Russia, in 1998-2018. All patients underwent radical surgical treatment resulting in postoperative defects of the upper jaw, soft tissues of the zygomatic-buccal-orbital region, nose, or auricle.

**Results**. Removable obturator prostheses with various supporting and retaining elements were made for 159 (80.7 %) patients. Individual facial prostheses were made for 38 (19.3 %) patients: 17 (44.7 %) – external orbital prostheses, 14 (36.8 %) – external nasal prostheses, 6 (15.8 %) – external zygomatic-buccal-orbital prostheses, 1 (2.7 %) – external auricle prosthesis. Combined prostheses were made for 4 patients – removable upper jaw obturator and nose prosthesis; removable upper jaw obturator and eye prosthesis. Combined prostheses were fixed to each other using magnets. The results of maxillofacial prosthetics were evaluated according to the aesthetic requirements of the patients and their quality of life. Maxillofacial prostheses allowed a complete restoration of chewing, swallowing, and speaking, restored facial deformation, and improved the appearance of patients.

**Conclusions.** Timely and comprehensive orthopedic treatment of patients with postoperative maxillofacial defects after radical surgeries for malignant tumors takes the main place in the complex of rehabilitation measures. Early elimination of extensive defects is aimed at maximum restoration of oral dysfunctions and appearance preservation. The apparent advantages of maxillofacial prostheses involve improvement of social adaptation and the quality of life of patients, which promotes complete rehabilitation and a return to socially useful activities.

**Keywords:**
oncology, rehabilitation, maxillofacial defect, combination defects, shaping prosthesis, facial prostheses.

For correspondence:
Irina V. Pustovaya – Cand. Sci. (Med.), maxillofacial surgeon of the Department of Head and Neck Tumors National Medical Research Centre for Oncology of the Ministry of Health of Russia, Rostov-on-Don, Russian Federation.
Address: 63 14 line str., Rostov-on-Don 344037, Russian Federation
E-mail: ivpustovaya@yandex.ru
SPIN: 5913-8360, AuthorID: 416789

Information about funding: no funding of this work has been held.
Conflict of interest: authors report no conflict of interest.

For citation:
Pustovaya I.V., Engibaryan M.A., Svetitskiy P.V., Aedinova I.V., Volkova V.L., Chertova N.A., Ulianova Yu.V., Bauzhadze M.V. Orthopedic treatment in cancer patients with maxillofacial pathology. South Russian Journal of Cancer. 2021; 2(2): 22-33. https://doi.org/10.37748/2686-9039-2021-2-2-3

Received 04.02.2021, Review (1) 21.04.2021, Review (2) 23.04.2021, Published 18.06.2021

Южно-Российский онкологический журнал 2021, т.2, №2, с. 22-33
https://doi.org/10.37748/2686-9039-2021-2-2-3
КЛИНИЧЕСКОЕ НАБЛЮДЕНИЕ

# ОРТОПЕДИЧЕСКОЕ ЛЕЧЕНИЕ У ОНКОЛОГИЧЕСКИХ БОЛЬНЫХ С ЧЕЛЮСТНО-ЛИЦЕВОЙ ПАТОЛОГИЕЙ

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

ФГБУ «НМИЦ онкологии» Минздрава России, 344037, Российская Федерация, г. Ростов-на-Дону, ул. 14-я линия, д. 63

## РЕЗЮМЕ

**Актуальность**. Для улучшения качества жизни пациентов, перенесших расширенные онкологические операции челюстно-лицевой области, применяется этапная методика ортопедического лечения.
**Пациенты и методы**. В отделении опухолей головы и шеи ФГБУ «НМИЦ онкологии» Минздрава России, с 1998 по 2018 гг. под наблюдением находились 197 больных, излеченных по поводу злокачественных опухолей челюстно-лицевой локализации. Всем больным выполнены расширенные радикальные операции, вследствие которых, образовывались послеоперационные дефекты: дефекты верхней челюсти, мягких тканей скуло-щечно-орбитальной области, носа, ушной раковины.
**Обсуждение**. Съёмные протезы с обтуратором на различных опорно-удерживающих элементах изготовлены 159 (80,7 %) больным. Индивидуальные лицевые протезы изготовлены всего 38 (19,3 %) больным. У 17 (44,7 %) – эктопротезы глазничной области, у 14 (36,8 %) – эктопротезы наружного носа, у 6 (15,8 %) – эктопротезы щёчно-скуло-глазничной области, у одного (2,7 %) – эктопротез ушной раковины. У 4 пациентов изготовлены комбинированные протезы: съёмный протез верхней челюсти с обтуратором и протез носа; съёмный протез верхней челюсти с обтуратором и протез глаза. Фиксация комбинированных протезов между собой осуществлялась при помощи магнитов. Результаты челюстно-лицевого протезирования оценивались в соответствии с эстетическими требованиями пациентов и качеством их жизни. Челюстно-лицевые протезы позволили полностью восстановить функцию жевания, глотания, речи, восстановить деформацию лица, улучшить внешний облик пациентов.
**Заключение.** Своевременное и полноценное ортопедическое лечение пациентов с послеоперационными дефектами тканей челюстно-лицевой области после расширенных операций по поводу злокачественных новообразований, занимает ведущее место в комплексе реабилитационных мероприятий. Раннее устранение обширных дефектов направлено на максимальное восстановление нарушенных функций полости рта, сохранение внешнего облика. Несомненным достоинством использования челюстно-лицевых протезов является повышение социальной адаптации больных, улучшение качества их жизни, что в свою очередь способствует полной реабилитации, возвращению к общественно полезному труду.

**Ключевые слова:**
онкология, реабилитация, дефект верхней челюсти, комбинированные дефекты, формирующий протез, лицевые протезы.

Для корреспонденции:
Пустовая Ирина Викторовна – к.м.н., врач-челюстно-лицевой 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: ivpustovaya@yandex.ru
SPIN: 5913-8360, AuthorID: 416789

Информация о финансировании: финансирование данной работы не проводилось.
Конфликт интересов: авторы заявляют об отсутствии конфликта интересов.

Для цитирования:
Пустовая И.В., Енгибарян М.А., Светицкий П.В., Аединова И.В., Волкова В.Л., Чертова Н.А., Ульянова Ю.В., Баужадзе М.В. Ортопедическое лечение у онкологических больных с челюстно-лицевой патологией. Южно-Российский онкологический журнал. 2021; 2(2): 22-33.
https://doi.org/10.37748/2686-9039-2021-2-2-3

Получено 04.02.2021, Рецензия (1) 21.04.2021, Рецензия (2) 23.04.2021, Опубликовано 18.06.2021

## INTRODUCTION

According to epidemiological data, the incidence and mortality from oral cancer have been steadily increasing in Russia over the past decades. The morbidity rate of the Russian population in 2019 was 29.4 per 100 thousand people. In the Rostov region, the incidence rates are slightly lower than in Russia, but continue to remain at a fairly high level, amounting to 16.3 per 100 thousand of the population. The mortality rate from oral cancer in the first year of life from the moment of diagnosis in Russia was 32.4 %, in the Rostov region – 24.9 % [1]. The vast majority of cancer patients are of working age by the time the disease is established. Modern possibilities of surgical, combined and complex methods of treatment allow to save the lives of patients. However, extensive surgical operations, intensive radiation, cytostatic therapy, used by oncologists, lead to significant anatomical and functional disorders and complications that reduce the working capacity of patients [2]. It should be noted that due to disability, oncological diseases occupy the second place after diseases of the circulatory system, and the first place in terms of the severity of disability [3, 4].

The quality of life of cancer patients is equally comparable to its duration. Therefore, simultaneous reconstructive operations have become an integral part of the surgical treatment of patients with locally advanced forms of maxillofacial cancer. Reconstructive and reconstructive operations are associated with numerous difficulties. After radical operations, courses of radiation and chemotherapy, there is an abundant amount of scarring and trophic disorders, which leads to poor tissue engraftment. The elimination of acquired defects of the maxillofacial region in such patients dictates the need for plastic surgery in several stages. For patients, waiting periods for subsequent surgical interventions are quite tedious [2, 4]. In this regard, the rehabilitation of oncostomatological patients over the past decades has not lost its relevance. What can be more important for the patient if he can not fully take food, can not appear in society [5]?

Currently, due to the introduction of implantation technologies, the orthopedic method of treatment in cancer patients with maxillofacial pathology has become more widespread, as it allows to eliminate tissue defects and restore impaired functions in a short time [2-7].

The success of orthopedic treatment largely depends on the coherence and mutual understanding of the surgeon and the orthopedic dentist. When analyzing the literature data, it can be concluded that in the practice of most dental organizations, specialized dental care for cancer patients is not carried out. There is a complete lack of social support and a well-established routing scheme for this category of patients. All this has not only medical, but also social significance [2].

In orthopedic dentistry, there is a fairly extensive selection of materials for the production of jaw and facial prostheses. Until the 50s of the last century, facial prostheses were made of metal, porcelain, ivory, celluloid and rubber [2, 8]. Each material has its own characteristics that allow you to use them for specific tasks. Modern removable jaw structures are made of new polymers (soft, hypoallergenic and durable): acry-fries, nylon, acrylic (plastic). Most often, acrylic is used for removable dentures, as an alternative to the materials of the previous generation. In terms of cost, it is not expensive, it has a wide palette of colors, which allows you to choose natural shades more accurately for each patient.

Over the past decades, great advances have been made in the field of facial prosthetics due to the appearance of materials that better mimic living tissue. Such materials include siloxanes. The results of experimental and clinical studies conducted in CRIDMS showed that silicone prostheses are biologically inert, retain elasticity, strength, and do not change shape [2]. Three-dimensional modeling and rapid prototyping technologies are being actively implemented.

There are two types of prosthetics of defects: direct and sequential. Direct prosthetics consists in the fact that the prosthesis is made before the operation and installed immediately after the surgical intervention. Subsequent prosthetics include such prosthetics, when the prostheses are made 2-3 weeks after the operation (early prosthetics) or 3-4 months later (later prosthetics) [4, 5, 7].

The most important tasks of orthopedic treatment are:

1. Closure of the postoperative defect;
2. Restoration of chewing, swallowing, speech;
3. Maintaining the patient's appearance;
4. Psychocorrective therapy.

## Clinical case description

In the department of head and Neck Tumors of the National Medical Research Centre for Oncology of the Ministry of Health of Russia, from 1998 to 2018, 197 patients were treated for locally common malignant tumors of the maxillofacial localization. All patients underwent extended radical operations, as a result of which postoperative defects were formed: defects of the upper jaw, soft tissues of the zygomatic-buccal-orbital region, nose, and auricle.

The distribution of patients found that among the observed patients, 152 men (77.2 %), 45 women (22.8 %). The age of the patients ranged from 22 to 70 years.

The distribution of patients by gender and age is shown in Table 1.

As can be seen from Table 1, the overwhelming majority of patients (175 (88.9 %) people) were persons of working age, i.e. up to 41-60 years.

In all patients, the diagnosis of a malignant tumor was verified morphologically. According to the histological structure, all tumors were of epithelial origin: squamous cell carcinoma (with/without keratinization) was found in 112 (64 %) patients, basal cell carcinoma – in 24 (14 %), estesioneuroblastoma – in 18 (10 %), cylindroma – in 21 (12 %).

Defects in the tissues of the maxillofacial region formed after surgery were diverse, and depended on the localization of the tumor process, the volume of the operation. Depending on the nature of the defect, the observed patients were divided into four groups (Table 2).

The largest number of patients with postoperative defects of the upper jaw, reported with the nasal cavity and maxillary sinus, was observed in 134 (68 %) patients. The lowest number of patients with combined postoperative defects of the upper jaw, combined with facial defects – in 4 (2 %) patients. Isolated postoperative defects of the face without a combination with defects of the upper jaw (defects of the nose, auricle, orbital, zygomatic-orbital, zygomatic-buccal-orbital region) – in 34 (2.6 %) patients. Postoperative defects without communication with the nasal cavity and maxillary sinus – in 25 (12.7 %) patients.

In patients who had part of the hard palate removed, a message appeared between the oral cavity and the nasal cavity. There were violations

**Table 1. Distribution of the patients by their age and gender**

| Gen-der | Age of patients (years) | | | | | Total | |
|---|---|---|---|---|---|---|---|
| | 20-30 | 31-40 | 41-50 | 51-60 | Above 61 | Abs. number | % |
| Male | 3 | 4 | 30 | 103 | 12 | 152 | 77.2 |
| Fem. | 0 | 0 | 14 | 28 | 3 | 45 | 22.8 |
| Total | 3 | 4 | 44 | 131 | 15 | 197 | 100.0 |
| % | 1.5 | 2.0 | 22.4 | 66.5 | 7.6 | | |

**Table 2. Distribution of the examined patients according to the defect features**

| Defect features | Total | |
|---|---|---|
| | Abs. number | % |
| Postoperative defects of the upper jaw, without communication with the nasal cavity and maxillary sinus | 25 | 12.7 |
| Postoperative defects of the upper jaw, communicating with the nasal cavity and maxillary sinus | 134 | 68 |
| Combined postoperative defects of the upper jaw, combined with facial defects | 4 | 2 |
| Isolated postoperative facial defects without combination with upper jaw defects | 34 | 17.3 |
| Total | 197 | 100 |

of swallowing, speech in the form of nasal voice. There were no cosmetic violations. In cases where resection of the upper jaw was performed (removal of the alveolar process and hard palate), more pronounced functional and cosmetic disorders appeared. In such patients, there was a sinking of the soft tissues of the cheek on the side of the operation, leading to facial asymmetry. The most pronounced facial deformity, chewing, swallowing and speech disorders were observed in those patients who underwent total resection of the upper jaw. When resection of the upper jaw with exenteration of the eye socket, along with pronounced functional disorders, significant cosmetic defects of the face were observed. Pronounced disfigurement was observed in patients who underwent resection of the upper jaw with excision of the surrounding soft tissues of the face (cheek, upper lip, nose, eye socket).

Orthopedic treatment was carried out according to the generally accepted method [6, 7, 9]. At the first stage, before the operation, in the presence of preserved teeth, a protective plate or plate prosthesis was made. Sometimes the old prostheses of this patient were used, after their preliminary correction. At this stage, it was necessary: to ensure the possibility of a full meal through the oral cavity; to fix the tampon in the postoperative cavity, creating a reliable separation between the oral cavity and the wound surface; to preserve speech.

On the 10th-15th day after the operation (the second stage), a jaw structure was made, which formed the bed of the obturating part of the permanent prosthesis during subsequent prosthetics. The forming prosthesis made it possible to reliably eliminate the oronosal and oroantral connections, significantly improve chewing, swallowing, diction, and prevent the development of facial scarring.

A month after the operation (the third stage), the final hollow prosthesis-obturator was made. This design made it possible to completely restore the functions of chewing, swallowing, speech and preserve the appearance of the patient. In each specific case, depending on the specifics of the clinical situation, the production time of the final prosthesis varied from 1.5 to 5 months. The final orthopedic structure with an obturator was made taking into account all the nuances found at the stage of manufacturing the forming prosthesis.

We used the method of manufacturing a post-resection prosthesis with an obturating part according to E.Ya. Vares [5]. It was as follows: the anatomical impression was removed with a standard spoon. A thermoplastic mass was applied to the spoon, over which a two-layer (inner and outer) gauze cloth soaked in 0.9 % sodium chloride solution was applied. The impression spoon was inserted into the oral cavity and pressed against the postoperative defect. With the help of active and passive movements, the edges of the impression were formed along the border of the transition fold, in the area of the defect. The spoon was removed from the oral cavity until the final solidification of the mass. Next, the excess mass and the outer gauze cloth were removed. On the surface of the impression made of thermoplastic mass, covered with an inner layer of gauze, a corrective layer of silicone impression mass was applied. The spoon was inserted into the oral cavity and pressed against the jaw until the mass was completely polymerized. In order to reduce the severity of the pain syndrome and to suppress the gag reflex when taking the impression, the postoperative defect was treated with a local anesthetic solution (a spray of 10 % lidocaine solution). After casting the plaster model, the necessary places of isolation were covered with adhesive plaster, the preserved teeth, and the areas of undercuts were filled with wax. According to the obtained model, a rigid individual tray was made in the laboratory. The tray was adapted on the upper jaw with a thermoplastic material and an individual spoon was made. Occlusal rollers made of thermomass were glued to the rigid base of the spoon. An individual spoon was stored in the oral cavity. A functional impression was taken. Thus, the soft tissue support of the postoperative defect was formed, the height of the lower face was fixed, and the central ratio of the jaws was determined. The model of the upper jaw was cast again from this impression and a plastic base with supporting and retaining clasps was made. In the clinic, the finished structure was stored in the oral cavity. If necessary, its correction was carried out.

It should be noted that when studying working models, it is always important to determine the boundaries of: the scar ring; the prosthesis on the remaining part of the upper jaw and, in the area of the postoperative defect space; the edges of the buccal-labial support. Also, it is necessary to take into account the features of the pliability of the mucous membrane, preserved bridles, cords and formed scar elements.

The hollow obturating part of the replacement prosthesis was made according to the method of Ya. M. Zbarzh [10]. The placement of the teeth made it possible to balance the occlusal contacts as much as possible. The finished removable plate prosthesis with an obturator was adapted in the oral cavity. The design allows you to correct or restore the phonetics, restore or bring the deformed face closer to the "ideal".

According to the literature, intraosseous or magnetic implants allow you to create a reliable fixation of prostheses. In cancer patients with defects of the upper jaw, the formation of scars occurs, a large mass of the bone skeleton of the jaw is lost. The radical doses used in radiation therapy do not allow the use of dental implants for fixing dentures, especially in the first year after the completion of antitumor treatment [5].

To fix the jaw prostheses, the most commonly used support-retaining solid multi-link clamps made of kobolto-chrome alloy and bent wire clamps were used in our patients. Telescopic crowns and attachments were also used. These devices evenly distributed the load, provided a sufficiently high aesthetic and functional effect, and if necessary, radiation and chemotherapy, could be freely removed from the oral cavity. To ensure reliable fixation of the prosthesis and its stabilization under functional loads, tissue areas in the defect area were used, into which the obturating part of the prosthesis made of elastic plastic was inserted.

If the orthopedic method of treatment was carried out late after the resection of the jaw, then the postoperative scars formed prevented full-fledged prosthetics. Massive, non-stretchable scar tissue displaced the prosthesis and contributed to the rapid loosening of the remaining teeth, which were necessary for fixing the prosthesis.

Often, after storing replacement dentures in the oral cavity, as well as in the process of adapting to them, prosthetic stomatitis develops. To prevent inflammatory complications in our patients, we used dental film pads that have antimicrobial, anti-inflammatory and wound-healing effects: adhesive and solcoseryl-containing therapeutic-adhesive pads. These films, which are tasteless and odorless, swelled in the oral cavity and had bilateral adhesion (to the mucous membrane of the prosthetic bed and to the base of the resection prosthesis). The elastic base of the film pads provided cushioning of the chewing pressure on the prosthetic bed, which was the prevention of injury, inflammation and excessive resorption of the bone skeleton.

Prosthetics of the lower jaw was a more complex task and was carried out in 2 patients due to removable (clasp and collapsible with pilots) prostheses. Extensive excision of the soft tissues of the oral cavity during radical surgery is usually accompanied by a reduction in the prosthetic bed. In such clinical situations, for full-fledged prosthetics, it is necessary to perform additional surgical intervention in the volume of plastic surgery of the vestibule of the oral cavity. Patients do not always give their consent to such an operation.

Below are various options for removable orthopedic structures (Fig. 1-5).

In patients with combined postoperative defects, prosthetics began with the elimination of the upper jaw defect. After setting up a post-resection removable jaw structure, defects in the eye socket and soft tissues of the face were compensated with a facial prosthesis. Ectoprosthetics in each individual case was a complex and time-consuming process that required an individual approach. Success was achieved only when all the anatomical features of the face were taken into account.

The replacement of the defect of the external nose presented great difficulties, since the postoperative deformity of the face led to such changes that it was not always possible to restore the former appearance of the patient.

For prosthetics of the defect of the auricle, a wax template was used, which was obtained by making a cast from the opposite auricle or from the auricle of

another person, according to the configuration approximately corresponding to the object of prosthetics.

In our department, in order to eliminate the aesthetic disadvantage, exoprosthesis was performed using the domestic silicone material "Ectosil" [4, 11].

The technique of manufacturing facial prostheses consisted of the following stages:

- Examination and examination of the patient. Attention was paid to: the asymmetry of the face, nasolabial folds; the closing of the lips; the condition of the eye of the defective side and the pupil line; the defeat of the nose; anthropometric landmarks of the face; the color of the skin; the condition and formation of postoperative scars, etc.
- Removing the impression of the face from the elastic material;
- Production of a plaster model based on an impression;
- Sculptural modeling of ectoprosthesis made of wax;
- Supply of a wax template in the clinic;
- In case of eye socket defects, the selection and installation of an eye prosthesis on a wax template;
- Determination of the base color of the prosthesis by the color of the skin of the face;
- Production of painted silicone prosthesis;
- Reproduction of eyebrows, eyelashes, and hair fragments.

For minor facial defects, a spectacle frame, theater glue, and retention points were used for fixation. In the case of combined defects of the face and upper jaw, fixation was performed by connecting the facial prosthesis with the jaw prosthesis using locking devices or magnets.

The results of maxillofacial prosthetics were evaluated in accordance with the aesthetic requirements of the patients and their quality of life. The assessment

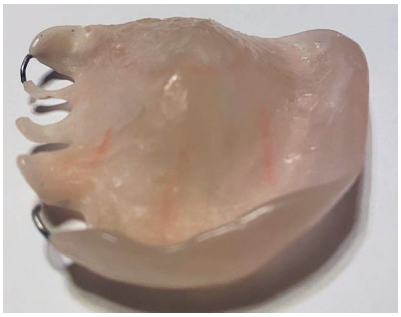


Fig. 1. Protective dividing plate.

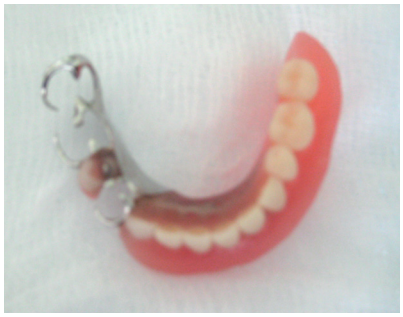


Fig. 2. Clasp prosthesis of the lower jaw with solid multi-link clasps.

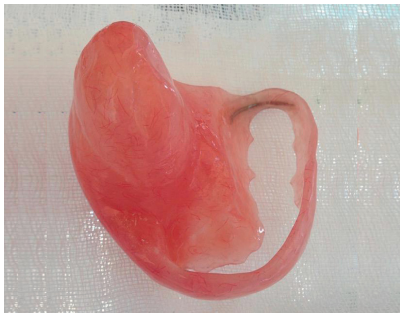
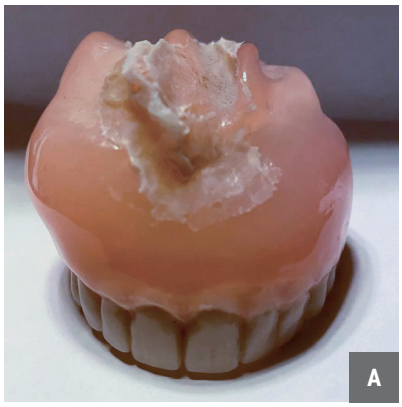
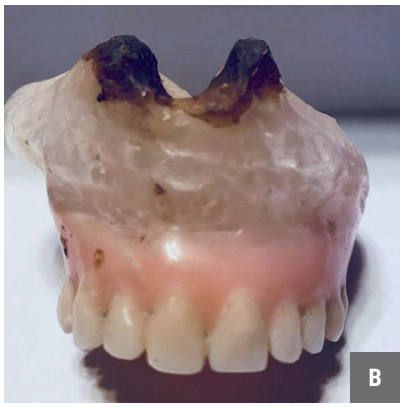


Fig. 3. Removable plate prosthesis with obturator with dentoalveolar plastic clasps to restore the defect of the upper jaw half.



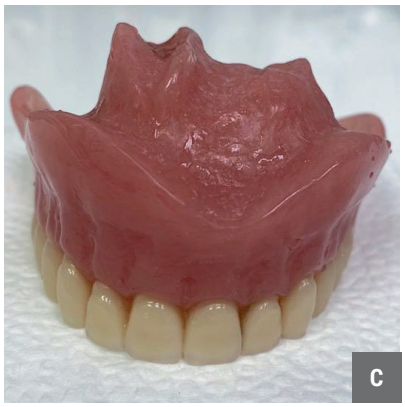




Fig. 4. Removable plate prosthesis with a hollow obturator for the restoration of a total defect of the upper jaw with a missing tooth row.

of the general condition of patients was evaluated by the Karnovsky index (0-100:) or the ECOG scale (0-4 points) (Tables 3-4).

Photos of clinical examples of facial prosthetics (Fig. 6-10). All the patients whose photos are shown in the drawings signed their consent to the processing of personal data and permission to take photos.

The service life of removable dentoalveolar and facial prostheses is limited to 3-4 years, after which they need to be replaced. The need to manufacture new prostheses is dictated by unsatisfactory fixation or violation of the sealing of the oral cavity, the patient's desire to have replacement prostheses, etc.

In 40 patients, at various times after the primary dentofacial prosthetics, orthopedic structures

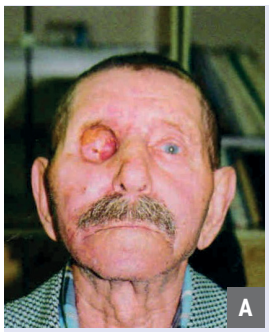
Fig. 5. Removable plate prosthesis with a hollow obturator to restore the defect of the hard palate with the preserved dentition.

**Table 3. Karnovsky index**

| | | |
|---|---|---|
| Normal physical activity, the patient doesn't need special care | 100 % | The condition is normal, there are no complaints and symptoms of diseases |
| | 90 % | Normal activity is maintained, but there are minor symptoms of the disease |
| | 80 % | Normal activity is possible with additional effort, with moderate symptoms of the disease |
| Restriction of normal activity while maintaining complete independence of the patient | 70 % | The patient serves himself independently, but is not capable of normal activity or work |
| | 60 % | The patient sometimes needs help, but mostly serves himself |
| | 50 % | The patient often needs help and medical care |
| The patient can not serve himself independently, care or hospitalization is necessary | 40 % | Most of the time the patient spends in bed, special care and outside help is needed |
| | 30 % | The patient is bedridden, hospitalization is indicated, although a terminal condition is not necessary |
| | 20 % | Severe manifestations of the disease, hospitalization and supportive therapy are necessary |
| | 10 % | Dying patient, rapid progression of the disease |
| | 0 % | Death |

**Table 4. Assessment of the patient's status on the ECOG scale**

| | |
|---|---|
| 0 | The patient is fully active, able to perform everything as before the disease (90–100 % on the Karnovsky scale) |
| 1 | The patient is not able to perform heavy work, but can perform light or sedentary work (for example, light homework or clerical work, 70–80 % on the Karnowski scale) |
| 2 | The patient is treated on an outpatient basis, is capable of self-care, but cannot perform work. More than 50 % of the waking time is spent activelyin an upright position (50–60 % on the Karnowski scale) |
| 3 | The patient is capable of only limited self-care, spends more than 50 % of the waking time in a chair or bed (30–40 % on the Karnowski scale) |
| 4 | Disabled, completely unable to self-serve, confined to a chair or bed (10–20 % on the Karnowski scale) |



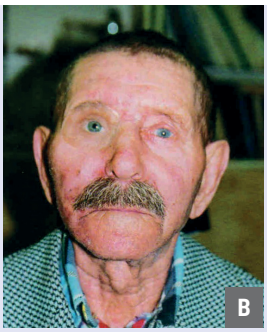
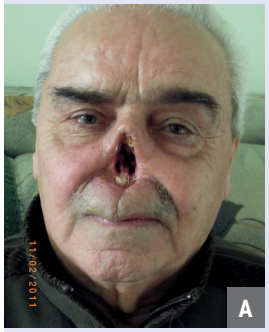




Fig. 6. Patient K., 70 years old. Diagnosis: Skin cancer of the lower eyelid of the right eye, art. III, T3N0M0. The patient underwent surgery – removal of the tumor with exenteration of the orbit on the right. An individual silicone endoprosthesis of the right orbit was made.




Fig. 7. Patient L., 65 years old. Diagnosis: Cancer of the trellis labyrinth on the right, art. IV, T4N0M0. The patient underwent surgery – removal of the tumor with exenteration of the orbit and excision of the soft tissues of the face on the right. An endoprosthesis of the right zygomatic-buccal-orbital complex was made.



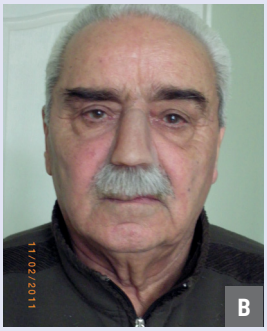
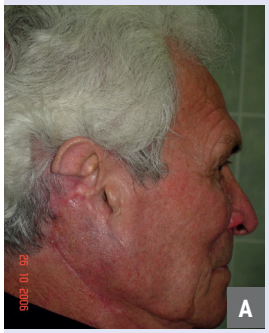





Fig. 8. Patient S., 71 years old. Diagnosis: Nasal skin cancer, art. I, T1N0M0, locally advanced cancer recurrence after radiation therapy. The patient underwent surgery – total resection of the external nose. A prosthetic nose was made.



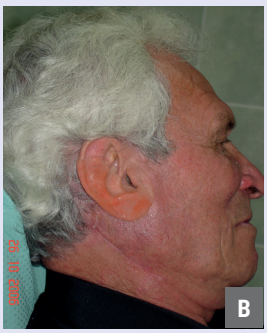
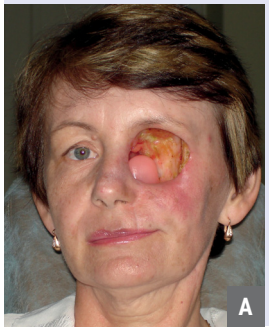




Fig. 9. Patient K., 72 years old. Diagnosis: Skin cancer of the right auricle, art. III, T3N0M0. The patient underwent surgery – resection of the auricle on the right. The prosthesis of the right auricle was made.



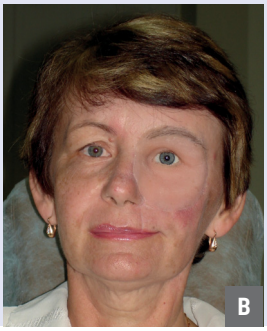





Fig. 10. Patient O., 58 years old. Diagnosis: Cancer of the upper jaw on the left with spread into the orbit, art. IV, T4N0M0. The patient underwent an operation – a half resection of the upper jaw with exenteration of the orbit on the left. The first stage is a removable upper jaw prosthesis with a hollow obturator, the second – an ectoprosthesis of the left orbit.

were re-manufactured. Over time, there was a biological destruction of the material, which led to a change in the configuration and size of the obturating part of the upper jaw prosthesis. As a result, there was a need for a corresponding change in its shape and volume, and the restructuring of the system of supporting and fixing elements.

In 52 patients, the prostheses were relocated according to the method of updating the basis. In these cases, the old prosthesis was used as an individual spoon. From the surface of the base of the prosthesis, which is facing the prosthetic bed, a layer of plastic was removed with a cutter. A uniform layer of elastic correcting mass (speedex, silagum, panasil) was applied to the prosthesis) and under the dosed pressure of the opposite dentition, the impression was taken. Then the prosthesis together with the impression mass was packed in a cuvette with gypsum, and the impression mass was replaced with a base plastic by polymerization. If it was impossible to correct all the shortcomings of the prostheses (the wrong shape of the arch, the unsatisfactory color of the teeth) by one relocation of the prosthesis, then in such cases a new dentoalveolar prosthesis was made.

## DISCUSSION

There were 197 patients under our supervision. As a result of the performed radical operations, isolated and combined postoperative defects of the supporting and soft tissues of the maxillofacial region were formed. Removable prostheses with an obturator on various supporting and retaining elements (clasps, attachments, telescopic crowns) were made in 159 patients.

Individual facial prostheses were made in only 38 patients. In 17 (44.7 %) – ectoprostheses of the orbital region, in 14 (36.8 %) – ectoprostheses of the external nose, in 6 (15.8 %) – ectoprostheses of the buccal-zygomatic-orbital region, in one (2.7 %) – ectoprosthesis of the auricle. Combined prostheses were made in 4 patients: a removable upper jaw prosthesis with an obturator and a nose prosthesis; a removable upper jaw prosthesis with an obturator and an eye prosthesis. The combined prostheses were fixed together using magnets.

Prior to the start of orthopedic treatment, patients had a significant decrease in physical activity with the predominance of the role of physical problems in the restriction of vital activity. There was also a decrease in social activity with an increased role of emotional problems in limiting their life activity. The existing defects of the middle zone of the face led not only to "physical" disability, but also caused a state of pronounced psycho-emotional discomfort in patients. Low indicators on the criteria of general perception of health, vital activity and mental health allowed us to state the moderate nature of the pathological condition and the lack of sufficient compensatory capabilities.

Jaw prostheses with an obturator made it possible to completely restore chewing, swallowing and speech of patients. Separating dentures with a dental row allowed to minimize postoperative psychological and speech therapy disorders, dysfunction of the musculature and temporomandibular joint. Facial prostheses allowed to restore the deformity of the face, improve the appearance of patients. Silicone ectoprostheses are almost invisible on the face, securely fixed, well imitated the color and texture of the skin of the face. Their weight was light, and not felt by the patients.

By the end of orthopedic treatment, the patients showed an increase in the overall perception of health, increased physical and mental performance. Maxillofacial prosthetics had a positive effect on the" psychogenic component " of the pathological condition. I gained confidence in myself, in my abilities. The circle of professional and everyday communication has been restored.

## CONCLUSION

In time and complete orthopedic treatment of patients with postoperative defects of the maxillofacial tissues after extended operations for malignant neoplasms, occupies a leading place in the complex of rehabilitation measures. Early elimination of extensive defects is aimed at the maximum restoration of the disturbed functions of the oral cavity, the preservation of the external appearance. The undoubted advantage of using maxillofacial prostheses is to increase the social adaptation of patients, improve their quality of life. All this has a beneficial effect on the mental health and contributes to full rehabilitation, a return to socially useful work.

Authors contribution:

Pustovaya I.V. – collection, analysis and interpretation of data. Research concept and design, manuscript writing, material processing. Technical editing, bibliography design, preparation of illustrations.

Engibaryan M.A. – technical and scientific editing.

Svetitskiy P.V. – scientific editing.

Aedinova I.V. – surgery assistance, material processing.

Volkova V.L. – surgery assistance, collection and analysis of data.

Chertova N.A. – surgery assistance, material processing.

Ulianova Yu.V. – surgery assistance, analysis and interpretation of data.

Bauzhadze M.V. – surgery assistance, collection of data, preparation of illustrations.

## References

1. The state of cancer care in Russia in 2019. Ed. by A.D.Kaprin, V.V.Starinsky, A.O.Shakhzadova. Moscow: P.A.Hertsen Moscow Oncology Research Institute – Branch of the National Medical Research Radiological Centre, 2020, 239 p. (In Russian).

2. Arutyunov AS. Clinical and organizational basis for increasing the effectiveness of orthopedic dental rehabilitation of cancer patients with acquired defects of the upper jaw. Dissertation. Moscow, 2012. (In Russian).

3. Esirpekov AA. Prosthetic dental care to patients with maxillofacial defects. Vestnik KazNMU. 2014;2(2):142–144. (In Russian).

4. Arutynov AS, Kitsul IS, Sedrakyan AN, Makarechich AA, Arutynov SD. Quality of life of maxillofacial cancer patients after prosthetic dentistry rehabilitation. Bulletin of the N.N.Blokhin Russian Research and Development Center. 2010;21(2):29–37. (In Russian).

5. Abakarov SI, Adzhiev KS, Balandina AS, Shpakovskaya IA, Adzhieva AK, Abakarova SS, et al. Orthopedic treatment of defects and deformities of the maxillofacial region: a tutorial. Moscow: FGBOU DPO RMANPO, 2017, 184 p. (In Russian). Available at: http://irbis.rmapo.ru/UploadsFilesForIrbis/cb-322da64848060691cfc7f6c1aa58d1.pdf.

6. Chuchkov VM, Matyakin EG, Akhundov AA, Mudunov AM, Podvyaznikov SO, Fedotov NN, et al. Orthopedic rehabilitation of cancer patients with defects of the upper jaw. Modern Oncology. 2006;8(3):28–34. (In Russian).

7. Zhulev EN, Arutyunov SD, Lebedenko IYu. Maxillofacial orthopedic dentistry. Moscow: Medical Information Agency. 2008, 160 p. (In Russian).

8. Kulakov AA, Chuchkov VM, Matyakin EG, Azizyan RI, Romanov IS, Mudunov AM, et al. Rehabilitation of cancer patients with a defect and complete secondary adentia after removal of both upper jaws. Tumors of Head and Neck. 2012;(4):34–39. (In Russian)

9. Zbarzh YaM. Fast-hardening plastics in dental and jaw prosthetics. Leningrad: Medgiz, 1963, 112 p. (In Russian).

10. Engibaryan MA, Pustovaya IV. Optimization of prosthetics of the orbit at patients with malignant tumours after liquidating operations. Kuban Scientific Medical Bulletin. 2011;1(124):118–121. (In Russian).

11. Kulakov AA, Chuchkov VM, Matyakin EG, Azizyan RI, Romanov IS, Mudunov AM, et al. Facial prostheses for the closure of postoperative soft tissue defects in cancer patients. Tumors of Head and Neck. 2011;(3):21–25. (In Russian).

Information about author:

Irina V. Pustovaya* – Cand. Sci. (Med.), maxillofacial surgeon of the Department of Head and Neck Tumors National Medical Research Centre for Oncology of the Ministry of Health of Russia, Rostov-on-Don, Russian Federation. SPIN: 5913-8360, AuthorID: 416789

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

Pavel V. Svetitskiy – Dr. Sci. (Med.), professor, scientific director of the Department of Head and Neck Tumors National Medical Research Centre for Oncology of the Ministry of Health of Russia, Rostov-on-Don, Russian Federation. ORCID: https://orcid.org/0000-0001-5198-9873, SPIN: 6856-6020, AuthorID: 735792, Scopus Author ID: 6603343526

Irina V. Aedinova – Cand. Sci. (Med.), oncologist, Department of Head and Neck Tumors National Medical Research Centre for Oncology of the Ministry of Health of Russia, Rostov-on-Don, Russian Federation. SPIN: 9904-0539, AuthorID: 734387

Viktoriya L. Volkova – Cand. Sci. (Med.), oncologist, Department of Head and Neck Tumors National Medical Research Centre for Oncology of the Ministry of Health of Russia, 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 of the Ministry of Health of Russia, Rostov-on-Don, Russian Federation. SPIN: 7051-4574, AuthorID: 473541

Yuliya V. Ulianova – Cand. Sci. (Med.), surgeon, Department of Head and Neck Tumors National Medical Research Centre for Oncology of the Ministry of Health of Russia, Rostov-on-Don, Russian Federation. SPIN: 1276-9063, AuthorID: 457370

Mamuka V. Bauzhadze – Cand. Sci. (Med.), oncologist, Department of Head and Neck Tumors National Medical Research Centre for Oncology of the Ministry of Health of Russia, Rostov-on-Don, Russian Federation. SPIN: 5315-3382, AuthorID: 734578

South Russian Journal of Cancer 2021, v.2, №2, p. 34-41
https://doi.org/10.37748/2686-9039-2021-2-2-4


CLINICAL CASE REPORTS

# THE USE OF IMMUNOTHERAPY FOR THE TREATMENT OF REFRACTORY FORMS OF HODGKIN LYMPHOMA IN REAL CLINICAL PRACTICE

**I.A.Kamaeva*, I.B.Lysenko, N.V.Nikolaeva, T.F.Pushkareva, E.A.Kapuza, Ya.S.Gaisultanova, A.V.Velichko**

National Medical Research Centre for Oncology of the Ministry of Health of Russia, 63 14 line str., Rostov-on-Don 344037, Russian Federation

## ABSTRACT

With a frequency of 2.2 cases per 100,000 population in Russia, Hodgkin's lymphoma (HL) is one of the most common malignant neoplasms in young people. In connection with the predominant spread of HL among young people, the issue of effective treatment of various forms of HL remains relevant. Currently, 70-90 % of patients with HL who have received standard chemotherapy or chemoradiotherapy have a long period of remission. However, 10 % of patients with progressive course, can`t achieve a response, and 30 % of patients subsequently recur. The standard approach of treating recurrent and/or refractory HL after initial treatment is “salvage therapy” followed by consolidation with high-dose chemotherapy and stem cell transplantation. Although there is a model for treating these patients, recent research has focused on improving the effectiveness and tolerability of rescue therapy. The use of anti-PD-1 drugs opens up new possibilities for the treatment of recurrent/refractory HL. The article describes the results of using checkpoint inhibitors for patients with a history of multi-course chemotherapy. Inhibitors of immune check points were supplemented in the 3rd and subsequent lines of ChT. A clinical case with immunotherapy supplementation in a patient with severe comorbidity is also presented.

**Keywords:**
Hodgkin lymphoma, immunotherapy, refractory, relapse, targeted therapy, clinical experience.

For correspondence:
Inna A. Kamaeva – junior researcher at the Department of drug Treatment of Tumors National Medical Research Centre for Oncology of the Ministry of Health of Russia, Rostov-on-Don, Russian Federation.
Address: 63 14 line str., Rostov-on-Don 344037, Russian Federation
E-mail: inkamaeva@yandex.ru
ORCID: https://orcid.org/0000-0003-3001-0675
SPIN: 8953-3351, AuthorID: 937725

Information about funding: no funding of this work has been held.
Conflict of interest: authors report no conflict of interest.

For citation:
Kamaeva I.A., Lysenko I.B., Nikolaeva N.V., Pushkareva T.F., Kapuza E.A., Gaisultanova Ya.S., Velichko A.V. The use of immunotherapy for the treatment of refractory forms of Hodgkin lymphoma in real clinical practice. South Russian Journal of Cancer. 2021; 2(2): 34-41. https://doi.org/10.37748/2686-9039-2021-2-2-4

Received 19.02.2021, Review (1) 07.04.2021, Review (2) 26.04.2021, Published 18.06.2021

Южно-Российский онкологический журнал 2021, т.2, №2, с. 34-41
https://doi.org/10.37748/2686-9039-2021-2-2-4
КЛИНИЧЕСКОЕ НАБЛЮДЕНИЕ

# ПРИМЕНЕНИЕ ИММУНОТЕРАПИИ ДЛЯ ЛЕЧЕНИЯ РЕФРАКТЕРНЫХ ФОРМ ЛИМФОМЫ ХОДЖКИНА В РЕАЛЬНОЙ КЛИНИЧЕСКОЙ ПРАКТИКЕ

**И.А.Камаева*, И.Б.Лысенко, Н.В.Николаева, Т.Ф.Пушкарева, Е.А.Капуза, Я.С.Гайсултанова, А.В.Величко**

ФГБУ «НМИЦ онкологии» Минздрава России, 344037, Российская Федерация, г. Ростов-на-Дону, ул. 14-я линия, д. 63

## РЕЗЮМЕ

Лимфома Ходжкина – это В-клеточное злокачественное лимфопролиферативное заболевание. При частоте встречаемости 2,2 случая на 100 000 населения в России ЛХ является одним из наиболее встречающихся злокачественных новообразований у молодых людей. Заболевание возникает в любом возрасте, зачастую в интервале от 16 до 35 лет, среди заболевших большую часть составляют женщины. В связи с преимущественным распространением ЛХ среди молодежи вопрос эффективного лечения различных форм ЛХ остается актуальным. В настоящее время 70-90 % пациентов с ЛХ, получивших стандартную химиотерапию или химиолучевую терапию, имеют длительный период ремиссии. Однако у 10 % больных с прогрессирующим течением не удается добиться ответа, а 30 % больных впоследствии рецидивируют. Стандартным подходом в лечении рецидивирующей и/или рефрактерной ЛХ после первоначального лечения является «терапия спасения» с последующей консолидацией при помощи высокодозной химиотерапии и трансплантации стволовых клеток. Несмотря на то, что существует модель лечения таких пациентов, исследования последних лет направлены на повышение эффективности и переносимости терапии «спасения». Применение анти-PD-1 препаратов открывает новые возможности лечения рецидивирующих/рефрактерных ЛХ. В статье описаны результаты применения ингибиторов контрольных точек иммунитета у девятерых пациентов, имеющих в анамнезе многокурсовую химиотерапию. Ингибиторы контрольных точек иммунитета назначались при этом в 3 и последующих линиях ХТ. Приведен также клинический случай использования иммунотерапии у пациента с выраженной коморбидностью.

**Ключевые слова:**
лимфома Ходжкина, иммунотерапия, рефрактерность, рецидив, таргетная терапия, клинический опыт.

Для корреспонденции:
Камаева Инна Анатольевна – младший научный сотрудник отдела лекарственного лечения опухолей ФГБУ «НМИЦ онкологии» Минздрава России, г. Ростов-на-Дону, Российская Федерация.
Адрес: 344037, Российская Федерация, г. Ростов-на-Дону, ул. 14-я линия, д. 63
E-mail: inkamaeva@yandex.ru
ORCID: https://orcid.org/0000-0003-3001-0675
SPIN: 8953-3351, AuthorID: 937725

Информация о финансировании: финансирование данной работы не проводилось.
Конфликт интересов: авторы заявляют об отсутствии конфликта интересов.

Для цитирования:
Камаева И.А., Лысенко И.Б., Николаева Н.В., Пушкарева Т.Ф., Капуза Е.А., Гайсултанова Я.С., Величко А.В. Применение иммунотерапии для лечения рефрактерных форм лимфомы Ходжкина в реальной клинической практике. Южно-Российский онкологический журнал. 2021; 2(2): 34-41. https://doi.org/10.37748/2686-9039-2021-2-2-4

Получено 19.02.2021, Рецензия (1) 07.04.2021, Рецензия (2) 26.04.2021, Опубликовано 18.06.2021

## RELEVANCE

Hodgkin's lymphoma (HL) is a B – cell malignant lymphoproliferative disease [1]. The incidence of HL a in Russia is 2.2 cases per 100,000 population per year, and the mortality rate reaches 0.61 cases per 100,000 population per year. The disease occurs at any age, but mainly in the range of 16-35 years, in this age group in Russia, women predominate among the patients [2]. Despite significant success in HL therapy, relapses occur in 10-15 % of patients with local and 20-49 % with generalized stages of the disease (depending on the factors of unfavorable prognosis and treatment). In 40-50 % of cases, relapses are registered within 12 months after the completion of initial polychemotherapy. Line 2 treatment allows achieving remission only in half of the patients [3]. Treatment of patients with relapses and refractory forms of HL remains an urgent problem at the present time. The advent of immunotherapy in the treatment of refractory and recurrent HL has dramatically changed the treatment options for such patients. Classic HL are unique in that they consist of a small number of Reed-Sternberg cells and a large number of dysfunctional reactive immunological cells that make up the majority of the tumor mass. Neoplastic Reed-Sternberg cells secrete various cytokines and chemokines to regulate the microenvironment and evade the immune response [4]. One of the pathways involved in T-cell functional disorders is the programmed cell death – 1 (PD-1) – PD-1 ligand signaling system. Tumor cells that express PD-1 engage the PD-1 receptor on T cells and inhibit cell activation and proliferation. PD-1 expression is markedly increased in tumor-infiltrating T cells of classical HL. This factor has made PD-1/PD-L1 a promising pathway for therapeutic targeted therapy with immune checkpoint inhibitors (CPIs) [5]. However, when CPI is treated, an unusual response to treatment may be observed. Thus, when using CPI, the clinical situation can develop in five main directions: reducing the size of existing foci without the appearance of new ones; long-term stabilization of the tumor size with its subsequent decrease in size; increasing the existing foci with the appearance of new foci; as well as 2 unique options: reducing the size of the tumor after its initial increase and reducing the size of some foci with the appearance of new ones [6]. At the same time, it is necessary to focus on the general well-being of the patient and continue the ongoing immunotherapy.

### Clinical case review description

The patient considers himself ill since March 2015, when he first developed a cough, fever, and treated ARVI without effect. He was examined at the place of residence, an increase in ESR to 65 was revealed. In April 2015, he performed spiral computed tomography (SCT), which revealed: hyperplasia of the intra-thoracic lymph nodes (in the upper mediastinum, conglomerate up to 9.2 cm: retrocaval lymph nodes up to 2.3 cm, bifurcation up to 1.4 cm, anterior to the aorta up to 1.5 cm, bronchopulmonary on the right up to 1.4 cm, left 1.7 cm), subclavian on the left 2.0 cm, right 1.3 cm, axillary on the left 1.2 cm. A biopsy of the right neck lymph node was performed, histological conclusion: the morphological picture corresponds to HL; according to the results of the immunohistochemical study – "Hodgkin's lymphoma, nodular sclerosis". In May 2015, the patient had a myocardial infarction. From May to August, 4 courses of polychemotherapy (PCT) were conducted according to the BEACOPP scheme. In the control SCT, hyperplasia was observed – intra-thoracic lymph nodes in the mediastinum up to 6.4 cm. Incomplete remission was achieved. Then 2 more ChT courses were conducted according to the BEACOPP scheme (a total of 6 ChT courses).

Due to the persistent conglomerate of intrathoracic lymph nodes up to 6.4 cm, the PCT course was changed. In October-November 2015, 2 courses of ChemT were conducted under the MEPD scheme. In March 2016, a course of radiation therapy was performed, with a total dose of 37G on the area of the supraclavicular and subclavian lymph nodes. Complete remission was achieved.

In March 2018, the patient's condition began to deteriorate – there was a fever, weakness. He independently applied to the RNIOI in May 2018, where SCT showed hyperplasia of the upper mediastinal lymph nodes up to 4.8 cm. In May 2018, a video-assisted thoracoscopic biopsy was performed on the right side with the histological conclusion "Hodgkin's lymphoma". The condition is regarded as the first late relapse-activation of the intra-thoracic lymph nodes, stage 2B.

By the decision of the council recommended to conduct anti-relapse courses of ChT. From June to August 2018, 4 anti-relapse PCT courses were conducted under the BEACOPP scheme. In September, he performed SCT of the chest organs, which showed lung tissue without pathology, and fibrous tissue in the upper mediastinum. Complete remission was achieved. In September, the 5th anti-relapse course was conducted under the BEACOPP scheme. It is recommended to perform a PET-CT scan.

The patient did not follow the recommendations for further examination to determine the tactics of further treatment, and appeared with signs of early relapse No. 2. PET-CT was performed only in March 2019: in the right supraclavicular region, a drain focus of pathologically increased accumulation of radiopharmaceutical therapy (RPT) with dimensions of 17 × 18 × 25 mm is determined; in the jugular region with a spread to the right half of the upper floor of the mediastinum, a focus with dimensions of 43 × 43 × 47 mm. Signs of metabolic activity in the right supraclavicular region and mediastinum, 5 points according to Deauville. The condition is regarded as a second early relapse.

From March to July 2019, 4 courses of anti-relapse ChT were conducted according to the GPD-21 scheme. In August 2019, he performed a PET-CT scan: a picture of a tumor conglomerate of the upper mediastinum with dimensions up to 60x55x37mm, a conglomerate of supraclavicular lymph nodes on the right, a parasternal nodular formation of the anterior chest on the right, single axillary lymph nodes (left axillary node 6x5 mm), axillary lymph nodes up to 12 mm, lymph nodes of the right side of the neck with hyperfixation of RPT 5 points according to Deauville. The condition is regarded as continuously progressive, and therefore the patient is recommended to undergo immunotherapy. From October 2019 to February 2020, 7 courses of nivolumab were conducted.

In April 2020, he performed a PET-CT scan, which showed a decrease in the size of single cervical-supraclavicular lymph nodes on the right (up to 8 mm) with an increase in their metabolic activity, 5 points for Deauville; a decrease in the size of the tumor conglomerate in the upper mediastinum (40.5 × 29 mm), 5 points for Deauville; a decrease in the size of the parasternal lymph node on the right and the axillary lymph node on the left with the absence of pathological hyperfixation of RF. It is recommended to continue therapy until the disease progresses, or until unacceptable toxicity occurs.

## DISCUSSION

The table 1 shows retrospective data on 9 patients with refractory HL who received and continued the treatment in the Department of Oncohematology of the National Medical Research Centre for Oncology of the Ministry of Health of Russia. Of all patients: 6 patients (66.6 %) initially had stage IV of the disease, 2 patients had stage II (22.2 %), 1 patient initially had stage I (11.1 %). B-symptoms were observed in the majority of patients (88.8 %). Morphological variants of HL were nodular sclerosis in 7 patients (77.7 %), mixed-cell variant in 2 patients (22.2 %). 6 patients (66.6 %) had concomitant pathology in the form of chronic heart disease. The first-line therapy was mainly the BEACOPP scheme – in 5 patients (55.5 %), which is due to the prevalence of the process. Four patients (44.4 %) who received first-line treatment received remote radiotherapy. The response in the form of partial remission was noted in 4 patients (44.4 %), initially resistant in 3 patients (33.3 %), in 2 patients, according to control examinations, an uncertain complete remission of the disease was registered, but less than 6 months later, these patients had an early relapse. According to the literature data, preference in first-line therapy for localized stages of the process should be given to the ABVD scheme followed by radiation therapy, which gives satisfactory results with a 10-year progression-free survival of 87 % [7]. Early assessment of the response by PET-CT after two ABVD cycles can significantly reduce the toxicity of therapy [8]. For common stages of the disease and the presence of risk factors, the BEACOPP scheme is currently used [1]. However, in the era of PET-CT, more and more research is devoted to finding the optimal balance between the response to therapy and the intensity of treatment. The HD15 test can serve as an example showing that 6 BEACOPP-escalated cycles are equally effective and at the same time less toxic compared to the previous standard consisting of 8

such cycles [9]. All patients received 2-line therapy from 2 to 14 courses. The most common regimens of 2-line therapy were DHAP, MINE, GDP-21, as well as bendamustine therapy in a single mode. Three (33.3 %) patients managed to achieve stabilization after the 2-line therapy, but less than 6 months later they experienced a progression of the process. All cases are considered to be refractory to standard chemotherapy, and patients are recommended to continue treatment with immunotherapy.

During therapy, stabilization of the process was achieved in 7 patients (77.7 %), no adverse events were noted. The median duration of treatment was 4 months (range 1-7). Autotransplantation of stem cells was performed in 1 patient after 8 injections of the drug, the remaining patients continue immunotherapy with nivolumab. In 1 patient, after 14 injections of the drug nivolumab, the progression of the process was noted (after 7 months of treatment with the drug), at the moment the patient receives anti-relapse courses of CT. Interruptions in taking doses of the drug were registered in 1 patient, the duration of the delay in the dose of the drug was 3 weeks. The choice of the BeGeV regimen in combi-

**Table 1. Patient taking Nivolumab as a therapy**

| № | Patient 1, 47 years | Patient 2, 40 years | Patient 3 24 years | Patient 4 51 years | Patient 5, 37 years |
|---|---|---|---|---|---|
| D | Hodgkin's lymphoma, nodular sclerosis, with lesions of the cervical-supraclavicular, axillary, intra-thoracic l/n, v/lobar bronchus on the right st IVB (2018) | Hodgkin's lymphoma, nodular sclerosis with lesions of the cervical l/n on both sides, axillary l/n st IIB (2017) | Hodgkin's lymphoma, nodular sclerosis with lesions of the cervical-supraclavicular axillary, intra-thoracic retroperitoneal l/n, lung st IV B (2019) | Hodgkin's lymphoma, nodular sclerosis, lesion of intra-thoracic l/n, retroperitoneal l/n of the breast, pleura with IVB (2006) | Hodgkin's lymphoma, nodular sclerosis, lesion of the cervical-supraclavicular subclavian l/n on 2 sides, axillary l/n on the left, in/thoracic l/n, soft tissues of the chest wall st IVB (2015) |
| 1st line therapy | 6 courses BEACOPP[1] | 8 courses BEACOPP[2] | 8 courses BEACOPP[1] | 5 courses ABVD[3], 1 course BEACOPP2, DRT 36G, 6 courses BEACOPP[2], 4 courses COPP[4] | 8 courses BEACOPP[2], 2 courses MEPD[5], DRT SLD 37 G |
| Response | PR | PR | Resistant flow | PR | APR (2018) Early relapse (2019) |
| 2nd line therapy | 2 courses ICE[6], 2 courses DHAP[7] | 2 courses GemOx[8], 4 courses MINE[9], 2 courses of bendamustine | 2 courses DHAP[7] | 6 courses GDP-21[10], 4 courses MINE[9], 4 courses bendamustin | 5 courses BEACOPP[2], 4 courses GDP-21[10] |
| Response | Progression after stabilisation | Refractive flow | Progression after stabilisation | Progression after stabilisation | Refractive Flow |
| CPI | Nivolumab therapy 8 administrations | Nivolumab therapy 2 administrations | Nivolumab therapy 11 administrations | Nivolumab therapy 6 administrations | Nivolumab therapy 12 administrations |
| Effects | Stabilisation | Stabilisation | PR | Stabilisation | Stabilisation |
| AE | No AE | No AE | No AE | No AE | No AE |
| Current time | auto-THSC | Observation | Observation | Observation | Observation |

nation with brentuximab-vedotin as an anti-relapse course after progression against the background of nivolumab therapy is not accidental. According to the literature data, the BeGeV scheme shows good results in the treatment of refractory forms of HL with a complete response of 75 % and a total response rate of 83 % [10]. The successful use of brentuximab-vedotin in the treatment of refractory and recurrent (r/r) forms of HL is also confirmed in many clinical studies. This drug was the first approved for the treatment of such a cohort of patients. This is based on the results of a phase II study in patients with p/r HL after auto-THSC or 2 lines of prior therapy. Patients received brentuximab-vedotin at a dose of 1.8 mg/kg every 3 weeks with an overall response rate of 75 % [11]. Its use in combination with chemotherapeutic regimens, such as DHAP, ICE, etc., is also being actively studied [10].

The effectiveness of nivolumab has been evaluated in many clinical trials. According to the literature [12], the response when taking this drug can be achieved in 70 % of patients, the frequency of partial remissions was 34 %, complete remissions-36 %, stabilization of the process in 8 % of patients. In our

**Table 1. Patient taking Nivolumab as a therapy**

| № | Patient 6, 28 years | Patient 7, 22 years | Patient 8, 50 years | Patient 9, 36 years |
|---|---|---|---|---|
| D | Hodgkin's lymphoma, mixed-cell variant, with lesions of the cervical-supraclavicular axillary, inguinal, intra-thoracic retroperitoneal l/n, left lung, st IVB (2015) | Hodgkin's lymphom, mixed-cell variant with lesion of the cervical-supraclavicular l/n on the right st I B (2015) | Hodgkin's lymphoma, nodular sclerosis NSII, with lesions of the supraclavicular axillary intra-thoracic l/n, sternum, st IVB (2018) | Hodgkin's lymphoma, nodular sclerosis involving the cervical-supraclavicular, axillary, and intra-thoracic l/n. st. IIA (2010) |
| 1st line therapy | 8 courses BEACOPP[2] | 7 courses BEACOPP[2] DRT SLD 30 G | 6 courses ABVD[3] | 5 courses BEACOPP[2] DRT SLD 36 G |
| Response | APR (2016) Early relapse (2016) | Resistant flow | Resistant flow | PR |
| 2nd line therapy | 4 courses DHAP[7], 2 courses ViGEPP[11], 6 courses bendamustin, DRT 36 G | 6 courses GDP-21[10], 2 courses ICE[6], 2 courses GemOx[8] | 3 courses MINE[9] | 5 courses ICE[6], 1 courses BEAM[12], Auto-THSC, 1 course BEACOPP esc.[13], 10 course GDP-21[10] |
| Response | Refractive flow | Refractive flow | Refractive flow | Refractive flow |
| CPI | Nivolumab therapy 12 administrations | Nivolumab therapy 3 administrations | Nivolumab therapy 14 administrations | Nivolumab therapy 12 administrations |
| Effects | Stabilisation | Stabilisation | Progression | Stabilisation |
| AE | No AE | No AE | No AE | No AE |
| Current time | Observation | Observation | Anti-relapse courses: BeGeV+ brentuximab vedotin | Observation |

work, stabilization was observed in 77.7 %, partial remission in 11 %, it is necessary to take into account the lines of therapy, in our work, nivolumab was prescribed to patients of the 3rd and subsequent lines. The differences in results seem to be related to a small sample of patients and differences in the duration of treatment. It is also necessary to take into account that the article provides data on the routine use of the drug. And the literature describes the results of clinical trials in which there are certain criteria for the selection of patients, the duration of follow-up.

## CONCLUSIONS

Thus, this clinical observation confirms the validity of the use of immunotherapy in refractory forms of HL after 3 or more lines of systemic therapy, including patients with severe comorbidity and a long history of the disease. In addition, our clinical experience allows us to conclude that earlier use of PD-1 inhibitors in patients with an established refractory course of HL for the possibility of using the option of autologous stem cell transplantation to achieve a long-term response.

Authors contribution:
Kamaeva I.A., Lysenko I.B., Nikolaeva N.V. – research concept and design, text writing, material processing.
Lysenko I.B., Nikolaeva N.V. – scientific editing.
Kamaeva I.A., Pushkareva T.F., Kapuza E.A. – technical editing, bibliography design, preparation of illustrations.
Kamaeva I.A., Gaisultanova Ya.S., Velichko A.V. – data collection, analysis, and interpretation.

### References

1. Russian clinical guidelines for the diagnosis and treatment of malignant lymphoproliferative diseases. Ed. by Demina EA, Poddubnaya IV, Savchenko VG. General principles of lymphoma diagnosis. 2018, 470 p. (In Russian).
2. Malignant neoplasms in Russia in 2017 (morbidity and mortality). Ed. by A.D.Kaprin, V.V.Starinsky, G.V.Petrova. Moscow: P.A.Hertsen Moscow Oncology Research Institute – Branch of the National Medical Research Radiological Centre, 2018, 250 p. (In Russian).
3. Baryakh E.A. treatment of relapse and refractory Hodgkin lymphoma. Oncohematology. 2017;12(2):8–13. (In Russian). https://doi.org/10.17650/1818-8346-2017-12-2-8-13
4. Steidl C, Connors JM, Gascoyne RD. Molecular pathogenesis of Hodgkin's lymphoma: increasing evidence of the importance of the microenvironment. J Clin Oncol. 2011 May 10;29(14):1812–1826.
https://doi.org/10.1200/JCO.2010.32.8401
5. Shanbhag S, Ambinder RF. Hodgkin lymphoma: A review and update on recent progress. CA Cancer J Clin. 2018 Mar;68(2):116–132. https://doi.org/10.3322/caac.21438
6. Yudin DI, Laktionov KK, Sarantseva KA, Breder VV, Reutova EV, Borisova OI, et al. Pseudoprogression in patients on immunotherapy. Medical Council. 2019;(10):10-14. (In Russ.) https://doi.org/10.21518/2079-701X-2019-10-10-14
7. Sasse S, Bröckelmann PJ, Goergen H, Plütschow A, Müller H, Kreissl S, et al. Long-Term Follow-Up of Contemporary Treatment in Early-Stage Hodgkin Lymphoma: Updated Analyses of the German Hodgkin Study Group HD7, HD8, HD10, and HD11 Trials. J Clin Oncol. 2017 Jun 20;35(18):1999–2007. https://doi.org/10.1200/JCO.2016.70.9410
8. Schmitz N, Pfistner B, Sextro M, Sieber M, Carella AM, Haenel M, et al. Aggressive conventional chemotherapy compared with high-dose chemotherapy with autologous haemopoietic stem-cell transplantation for relapsed chemosensitive Hodgkin's disease: a randomised trial. Lancet. 2002 Jun 15;359(9323):2065–2071.
https://doi.org/10.1016/S0140-6736(02)08938-9
9. Engert A, Haverkamp H, Kobe C, Markova J, Renner C, Ho A, et al. Reduced-intensity chemotherapy and PET-guided radiotherapy in patients with advanced stage Hodgkin's lymphoma (HD15 trial): a randomised, open-label, phase 3 non-inferiority trial. Lancet. 2012 May 12;379(9828):1791–1799.
https://doi.org/10.1016/S0140-6736(11)61940-5
10. Voorhees TJ, Beaven AW. Therapeutic Updates for Relapsed and Refractory Classical Hodgkin Lymphoma. Cancers (Basel). 2020 Oct 8;12(10):2887.
https://doi.org/10.3390/cancers12102887
11. Younes A, Gopal AK, Smith SE, Ansell SM, Rosenblatt JD, Savage KJ, et al. Results of a pivotal phase II study of brentuximab vedotin for patients with relapsed or refractory Hodgkin's

lymphoma. J Clin Oncol. 2012 Jun 20;30(18):2183–2189. https://doi.org/10.1200/JCO.2011.38.0410

12. Bekoz, H, Ozbalak M, Karadurmus N, Paydas S, Turker A, Toptas T, et al. Nivolumab for relapsed or refractory Hodgkin lymphoma: real-life experience. Ann Hematol. 2020 Nov;99(11):2565–2576. https://doi.org/10.1007/s00277-020-04077-4

13. Patent for the invention RU 2487727 C1, 20.07.2013. Application No. 2012106961/14 on 27.02.2012. Kit OI, Snezhko TA, Lysenko IB, Ushakova ND, Zlatnik EYu. Method of treatment of patients with refractory and recurrent Hodgkin's lymphoma.

Information about author:

Inna A. Kamaeva* – junior researcher at the Department of drug Treatment of Tumors National Medical Research Centre for Oncology of the Ministry of Health of Russia, Rostov-on-Don, Russian Federation. ORCID: https://orcid.org/0000-0003-3001-0675, SPIN: 8953-3351, AuthorID: 937725

Irina B. Lysenko – Dr. Sci. (Med.), professor, head of the Department of Hematology and Oncology National Medical Research Centre for Oncology of the Ministry of Health of Russia, Rostov-on-Don, Russian Federation. ORCID: https://orcid.org/0000-0003-4457-3815, SPIN: 9510-3504, AuthorID: 794669

Nadezhda V. Nikolaeva – Dr. Sci. (Med.), MD, hematologist of the Department of Oncohematology National Medical Research Centre for Oncology of the Ministry of Health of Russia, Rostov-on-Don, Russian Federation. ORCID: https://orcid.org/0000-0001-7224-3106, SPIN: 4295-5920, AuthorID: 733869

Tatyana F. Pushkareva – MD, oncologist at the Clinical and Diagnostic Department National Medical Research Centre for Oncology of the Ministry of Health of Russia, Rostov-on-Don, Russian Federation. SPIN: 8047-6830, AuthorID: 801681

Elena A. Kapuza – MD, hematologist of the Department of Oncohematology National Medical Research Centre for Oncology of the Ministry of Health of Russia, Rostov-on-Don, Russian Federation. ORCID: https://orcid.org/0000-0002-0761-2486, SPIN: 4430-1151, AuthorID: 794666

Yakha S. Gaisultanova – oncologist at the Department of Antitumor Drug Therapy No. 2 National Medical Research Centre for Oncology of the Ministry of Health of Russia, Rostov-on-Don, Russian Federation.

Alexey V. Velichko – MD, hematologist of the Department of Oncohematology National Medical Research Centre for Oncology of the Ministry of Health of Russia, Rostov-on-Don, Russian Federation. SPIN: 2703-7624, AuthorID: 1053682

South Russian Journal of Cancer 2021, v.2, №2, p. 42-49
https://doi.org/10.37748/2686-9039-2021-2-2-5


CLINICAL CASE REPORTS

# OPTIMIZATION OF ANESTHETIC TACTICS IN THE SURGICAL TREATMENT OF MULTIPLE PRIMARY NON-SMALL CELL LUNG CANCER

**S.N.Tikhonova[1], D.A.Rozenko[1], N.D.Ushakova[1], N.N.Popova[1,2]*, A.M.Skopintsev[1], A.V.Shulga[1], I.A.Ten[1]**

1. National Medical Research Centre for Oncology of the Ministry of Health of Russia, 63 14-line str., Rostov-on-Don 344037, Russian Federation
2. Rostov State Medical University, 29 Nakhichevansky Lane, Rostov-on-Don, 344022, Russian Federation

## ABSTRACT

The article describes a clinical case of surgical treatment of a patient with multiple primary malignant lesions of the lungs (cancer of the left lung, central peribronchial nodular tumor with involvement of the upper lobe and distal parts of the main bronchus; cancer of the right lung, central tumor with involvement of the upper lobar bronchus). Radical treatment became possible due to using the potential of artificial gas exchange of both lungs with two devices with fundamentally different ventilation mechanics. The choice of an optimal tactics for the functional correction of the supposed hypoxemia by volumetric and high-frequency pulmonary ventilation allowed avoiding an imbalance in the ventilation/perfusion ratio and preventing the development of life-threatening complications, as well as ensured an adequate gas exchange for the patient during surgical treatment.

**Keywords:**
multiple primary cancer, lung cancer, surgical treatment, lobectomy, artificial lung ventilation, gas exchange.

For correspondence:
Nataliya N. Popova – anesthesiologist and reanimatologist, National Medical Research Centre for Oncology of the Ministry of Health of Russia, Rostov-on-Don, Russian Federation, assistant at the Department of Oncology, Rostov State Medical University, Rostov-on-Don, Russian Federation.
Address: 63 14 line, Rostov-on-Don 344037, Russian Federation
Address: 29 Nakhichevansky Lane, Rostov-on-Don, 344022, Russian Federation
E-mail: natalyaanest@mail.ru
ORCID: https://orcid.org/0000-0002-3891-863X
SPIN: 5071-5970, AuthorID: 854895
Scopus Author ID: 57215858399

Information about funding: the research was carried out with the support of the National Medical Research Centre for Oncology of the Ministry of Health of Russia.
Conflict of interest: authors report no conflict of interest.

For citation:
Tikhonova S.N., Rozenko D.A., Ushakova N.D., Popova N.N., Skopintsev A.M., Shulga A.V., Ten I.A. Optimization of anesthetic tactics in the surgical treatment of multiple primary non-small cell lung cancer. South Russian Journal of Cancer. 2021; 2(2): 42-49.
https://doi.org/10.37748/2686-9039-2021-2-2-5

Received 03.03.2021, Review (1) 31.03.2021, Review (2) 19.04.2021, Published 18.06.2021

Южно-Российский онкологический журнал 2021, т.2, №2, с. 42-49
https://doi.org/10.37748/2686-9039-2021-2-2-5
КЛИНИЧЕСКОЕ НАБЛЮДЕНИЕ

# ОПТИМИЗАЦИЯ АНЕСТЕЗИОЛОГИЧЕСКОЙ ТАКТИКИ В ХИРУРГИЧЕСКОМ ЛЕЧЕНИИ ПЕРВИЧНО-МНОЖЕСТВЕННОГО НЕМЕЛКОКЛЕТОЧНОГО РАКА ЛЁГКОГО

**С.Н.Тихонова[1], Д.А.Розенко[1], Н.Д.Ушакова[1], Н.Н.Попова[1,2]*, А.М.Скопинцев[1], А.В.Шульга[1], И.А.Тен[1]**

1. ФГБУ «НМИЦ онкологии» Минздрава России, 344037, Российская Федерация, г. Ростов-на-Дону, ул. 14-я линия, д. 63
2. ФГБОУ ВО «РостГМУ» Минздрава России, 344022, Российская Федерация, г. Ростов-на-Дону, пер. Нахичеванский, д. 29

## РЕЗЮМЕ

Описан клинический случай хирургического лечения пациента с первично-множественным злокачественным поражением легких (рак левого лёгкого, центральная перибронхиально-узловая форма с поражением верхнего долевого и дистальных отделов главного бронха, рак правого лёгкого центральная форма с поражением верхнего долевого бронха). Проведение радикального лечения состоялось благодаря использованию потенциала искусственного газообмена обоих лёгких двумя аппаратами с принципиально различной механикой вентиляции. Выбор необходимой тактики функциональной коррекции предполагаемой гипоксемии методом объемной и высокочастотной легочной вентиляции позволил избежать нарушения вентиляционно-перфузионного соотношения и предотвратить развития жизнеугрожающих осложнений, полноценно обеспечил адекватный газообмен данного пациента на этапах хирургического лечения.

**Ключевые слова:**
первично-множественный рак, рак лёгкого, хирургическое лечение, лобэктомия, искусственная вентиляция лёгких, газообмен.

Для корреспонденции:
Попова Наталья Николаевна – врач анестезиолог-реаниматолог отделения анестезиологии и реанимации ФГБУ «НМИЦ онкологии» Минздрава России, г. Ростов-на-Дону, Российская Федерация, ассистент кафедры онкологии ФГБУ ВО «РостГМУ» Минздрава России, г. Ростов-на-Дону, Российская Федерация.
Адрес: 344037, Российская Федерация, г. Ростов-на-Дону, ул. 14-я линия, д. 63
Адрес: 344022, Российская Федерация, г. Ростов-на-Дону, пер. Нахичеванский, д. 29
E-mail: natalyaanest@mail.ru
ORCID: https://orcid.org/0000-0002-3891-863X
SPIN: 5071-5970, AuthorID: 854895
Scopus Author ID: 57215858399

Информация о финансировании: работа проведена при поддержке ФГБУ «НМИЦ онкологии» Минздрава России.
Конфликт интересов: авторы заявляют об отсутствии конфликта интересов.

Для цитирования:
Тихонова С.Н., Розенко Д.А., Ушакова Н.Д., Попова Н.Н., Скопинцев А.М., Шульга А.В., Тен И.А. Оптимизация анестезиологической тактики в хирургическом лечении первично-множественного немелкоклеточного рака лёгкого. Южно-Российский онкологический журнал. 2021; 2(2): 42-49. https://doi.org/10.37748/2686-9039-2021-2-2-5

Получено 03.03.2021, Рецензия (1) 31.03.2021, Рецензия (2) 19.04.2021, Опубликовано 18.06.2021

## RELEVANCE

According to the International Agency for Research on Cancer and the World Health Organization, over the past decade, the number of new cases of cancer in the world has increased up to 14.1 million, and the number of deaths has reached 8.2 million people. The undisputed leader among oncological diseases is lung cancer (LC) – 13 % of cases among all malignant neoplasms in the world [1]. In Russia, according to statistical data, RL ranks first in morbidity and mortality among the male and female population with an annual detection of new cases of about 60,000 people [2]. Bilateral lung damage is detected in 0.08-3.5 % of cases [3]. In 80-85 % of cases, the morphological structure of RL is represented by non-small cell lung cancer (NSCLC): adenocarcinoma, large cell and squamous cell carcinoma. Surgical treatment of NSCLC is basic and involves removal of the organ (pneumonectomy) or anatomical resection of the lung with extended regional lymph node dissection [4, 5].

The improvement of oncosurgical techniques and anesthesiological support determines the feasibility of revising the criteria for functional and surgical operability of patients with common tumor processes [6] and contributes to improving the immediate and long-term results of radical surgical treatment of cancer patients [7, 8]. A specific feature of anesthesia in chest surgery is to ensure optimal and safe operations with the most adequate compensation for functional gas exchange. Standard methods of anesthesia and ventilation in this case may be ineffective. To ensure surgical operation, it is necessary to minimize the volume of the lung and partially or completely "turn it off" from the act of breathing [9]. However, the lack of gas exchange in the lung is extremely unphysiological. Given that the lungs are a bioactive organ, any deformity and / or temporary absence of respiration in one lung during surgery can trigger a cascade of pathological changes in homeostasis. Single-lung ventilation contributes to an increase in operational stress, causing the release of pro-inflammatory cytokines, and a violation of gas supply in the form of a decrease in the partial pressure of oxygen in the blood and cardiac output leads to the development of tissue hypoxemia [10, 11]. These systemic processes are accompanied by a change in the nature of the course of oxidative reactions, a violation of the energy supply of functions and plastic processes in tissues and organs. Destruction of non-cellular structures, cell death and systemic functional destabilization lead to disruption of the vital activity of the body as a whole [12, 13].

The expansion of indications for surgical treatment of a locally advanced lung tumor process encourages the search and development of new methods of anesthesiological aids, the main principles of which are effective protection against surgical aggression, full-fledged pulmonary ventilation with adequate gas exchange, correction of acid-base and water-electrolyte balances.

The purpose of the study: to demonstrate with this clinical example the possibility of performing surgical treatment of patients diagnosed with primary multiple lung cancer using two fundamentally different technologies of artificial ventilation.

### Clinical case

Patient K., 60 years old, went to a doctor in August 2018, complaining of a cough with sputum of a mucopurulent nature, shortness of breath during physical exertion, intermittent pain behind the sternum, weakness and dizziness. He considers himself ill since May 2018, when there were clinical manifestations of the disease. Radiological examination at the place of residence revealed neoplasms in both lungs. The patient was referred to FSBI "Rostov Research Cancer Institute" RFHM for further examination and specialized care. According to the results of the examination, the diagnosis was made – primary multiple cancer: Cancer of the left lung, central peribronchial-nodular form with damage to the upper lobar and distal parts of the main bronchus, cT2NxM0, stage IIA. Right lung cancer is a central form with a lesion of the upper lobar bronchus, cT-1NxM0, stage I, clinical group 2.

Morphological examination: biopsy of a tumor from the anterior segmental bronchus (B3) on the right-foci of squamous cell carcinoma. Histological analysis: 1) from B3 on the right, No. 40978-82 / 18-foci of squamous cell carcinoma; 2) from the up-

per lobar bronchus on the left, No. 40983-88 / 18-foci of squamous cell carcinoma.

Concomitant diseases: chronic obstructive pulmonary disease of the first degree, stage 1, phase of remission; ischemic heart disease: atherosclerotic cardiosclerosis, circulatory insufficiency of the 1st degree; varicose veins of the lower extremities, chronic venous insufficiency of the 2nd degree. From 18.05.2018 to 26.07.2018, as part of the complex treatment, the patient underwent 3 courses of induction polychemotherapy according to the scheme cisplatin 360 mg + gemcitabine 6.0 g + refnot 900.000 IU. In the Department of Thoracic Surgery of the Federal State Budgetary Institution "RNIOI" of the Ministry of Health of the Russian Federation (03.08.2018), an operation was performed in the volume of expanded upper bronchoplastic lobectomy on the left. According to the histological analysis of 03.08.2018: highly differentiated squamous cell carcinoma with keratinization and foci of necrosis. The surgical intervention and the postoperative period were carried out without any special features or complications. The patient was discharged on the 25th day.

Upon re-hospitalization, standard physical, instrumental (external respiration function, computed tomography of the chest, fibrobronchoscopy, esophagoduodenoscopy, electrocardiography, ultrasound examination of the abdominal cavity, ultrasound Dopplerography of the vessels of the neck and lower extremities) and laboratory methods were performed to continue treatment on 26.09.2018.

Instrumental research data from 26.09.2018:

Electrocardiography: irregular rhythm 72 %, atrial fibrillation normal-systolic form, heart rate (HR) 80-85 per minute, slowing of atrial conduction of the myocardium, hypoxia and reduced recovery processes of the myocardium of the anterior-septum region of the left ventricle;

Evaluation of the function of external respiration: vital capacity of the lungs 46.73 %, forced vital capacity of the lungs 43.86 %, volume of forced air when exhaling in 1 second 47.52 %, a pronounced decrease in all indicators;

Fibrobronchoscopy: condition after bronchoplastic upper lobectomy on the left, bronchial anastomosis is stable, without signs of inflammation, peribronchial nodular cancer of the upper lobe of the right lung, deforming the lumen of the bronchus;

Laboratory parameters from 26.09.2018:

1) CBC: Hb 133 g/l, red blood cells $4.4*10^{12}$/l, color index 0.90, Ht 40 %;

2) Indicators of biochemical blood tests: amylase 40.4 U/l, ASTL 18.4 U/l, ALTL 17.3 U/l, creatinine 82.3 mmol/l, urea 6.59 mmol/L, total protein 79.6 g/l, bilirubin 6.5 mmol/l;

3) Acid-base state: $PCO_2$ 40 mmHg, $PO_2$ 81 mmHg, pH 7.401, BE 2.3 mmol/L, HCO3 23.3 mmol/L, $SO_2$ 98 %, $Na^+$ 137.0 mmol/L, $K^+$ 4.8 mmol/L, $Cl^-$ 101.0 mmol/L, $Ca^{2+}$ ion – 1.12 mmol/l.

Taking into account the anamnesis of the disease (complex treatment, condition after 3 courses of induction polychemotherapy and extended upper bronchoplastic lobectomy on the left), concomitant pathology, data from instrumental and laboratory research methods, the doctors ' council of 27.09.2018 decided to perform surgery in the volume of bronchoplastic upper lobectomy on the right. The choice of the concept of functional correction of hypoxemia in this patient was based on the rational use of the potential of artificial ventilation of both lungs in gas exchange. This scheme was provided by the use of separate intubation and ventilation of both lungs with two ventilators (artificial lung ventilation) different in mechanics: volumetric and high-frequency. Ventilation of the left lung (the remaining segments) was performed with the device No. 1 Drager Infinity C 700 in the volume control mode (CMV), the right – high-frequency (HF) (device No. 2 ZisLine JV 100B) in the catheter ventilation mode. In this case, it was impossible to use volumetric ventilation of both lungs as a result of the anatomical location and features of the tumor growth (Fig. 1).

The method of HF ALV (high-frequency artificial lung ventilation) is considered to be lung ventilation performed at a frequency of more than 60 cycles per minute. This mode with a respiratory rate of 100 or more oscillations per minute is achieved by reducing the respiratory volume to 100-150 $cm^3$ (1.5-2.5 $cm^3$ / kg) and shortening the inhalation phase to 0.1-0.01 s. This technique is accompanied by a slight increase in intra-pulmonary pressure with an improvement in hemodynamic parameters

compared to traditional methods of ventilation. The most common option is a jet HF ALV ventilator with a respiratory rate of 100-300 per minute through an adapted catheter.

Surgical intervention in this patient required compliance with all the basic and generally accepted principles of multicomponent balanced anesthesia, with the exception of ventilation. Intraoperative monitoring met the Harvard standard and included cardiomonitoring, monitoring of blood gas composition, assessment and analysis of the bispectral index, and monitoring of neuromuscular conduction.

On the day of the operation (29.09.2018), after standard premedication, patient K. was taken to the operating room at 9:00. Baseline functional parameters: blood pressure (BP) 150/100 mmHg, heart rate 84 per minute, respiratory rate 17 per minute, $SpO_2$ (blood saturation) 94 %. Under ultrasound navigation, the cubital and right subclavian veins were punctured and catheterized according to the Seldinger method. For the purpose of prolonged anesthesia in the Th3-Th4 interval, the epidural space was punctured and catheterized. After the test dose, a continuous infusion of ropivacaine hydrochloride was initiated at a rate of 5-6 ml/hour [14, 15]. At 9:30, after standard induction with propofol at a dose of 2-3 mg/kg, fentanyl 2 mcg/kg, and rocuronium bromide 1 mg/kg, the trachea was intubated with a thermoplastic two-light tube No. 39 Left. The correct position of the endotracheal tube was confirmed by bronchoscopy.

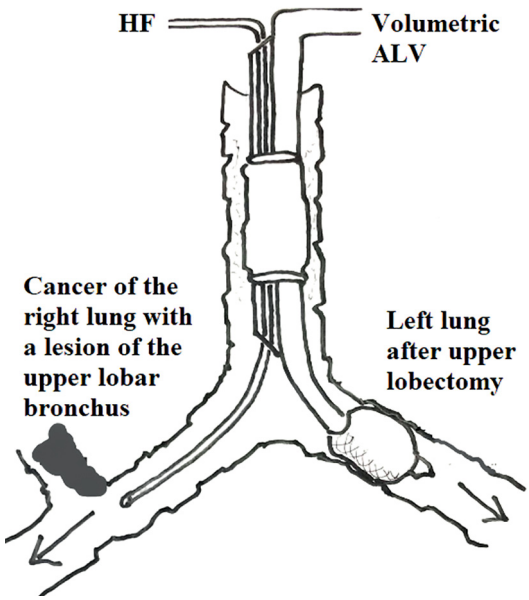



Fig. 1. Separate ventilation of the lungs: the right – high-frequency (HF), the left lung (the remaining segments) in the volume-controlled mode.

Artificial ventilation of the early operated left lung, i.e. the remaining lower lobe after extended upper bronchoplastic lobectomy, was performed with the Drager Infinity C 700 device No. 1 – in the volume control mode (CMV): respiratory volume (RV) 200 ml, minute respiratory volume (MRV) 3.7 l/min, BH 18 per minute, Ppeak (peak airway pressure) +28 cm of water, PEEP (positive end respiratory pressure/ constant positive airway pressure). 0 cm of water, FiO2 (fractional oxygen content in the inhaled air) 80 %. The breathing circuit is partially reversible, sealed.

The right lung, whose tumor was planned to be removed, was ventilated with apparatus No. 2 (high-frequency jet ZisLine JV 100B) in the jet ventilation mode with a catheter inserted into the right main bronchus. ALV parameters: BH 80 per minute, MRV 10 l/min, resulting in a respiratory volume (RV) 140 ml. The ventilation modes of the high-frequency device were changed during the operation. During the revision and rotation of the right lung, the respiratory rate was increased to 120 per minute, with a MRV of 10 l/min, RV 60-80 ml. At the same time, the gas exchange area in the operated lung did not decrease. These regimens did not prevent radical removal of the tumor. The course of anesthesia proceeded without cardio-respiratory disorders. Restrictive infusion therapy according to the standard scheme for such surgical interventions was carried out by dosed administration of a balanced crystalloid solution at a rate of 3-5 ml/kg*h. The average blood pressure was kept at the level of 62-74 mmHg.

At 12:20 after the end of the main stage of the operation, adequate hemostasis and pneumostasis, the patient was transferred to double-lung ventilation in the CMV mode: UP to 450 ml, BH 15 per minute, MRV 6.2 l/min, $FiO_2$ 60 %. Against this background, $SpO_2$ is 97 %. In the control study of the gas state of arterial blood, decompensation of indicators was not observed: $pCO_2$ 42.3 mmHg, $pO_2$ 140 mmHg,

pH 7.370, BE 7.4 mmol/L, $HCO_3$ 31.2 mmol/dL, $SO_2$ 94 %, $Na^+$ 141.0 mmol/dL, $K^+$ 3.8 mmol/dL, $Cl^-$ 103.0 mmol/dL, $Ca^{2+}$ ion –1.26 mmol/l. Vital functions were monitored. Hemodynamic parameters remained stable: blood pressure 127/85 mmHg, heart rate 86 per minute, pulse 81 per minute (pulse deficit 5 beats per minute).

At 13:45, the operation is completed. The duration of the operation was 3 hours and 45 minutes. An extended bronchoplastic upper lobectomy was performed on the right. At 14:10, after full recovery of consciousness and muscle tone, rehabilitation of the tracheobronchial tree, oral cavity, the patient was extubated. The duration of anesthesia was 4 hours and 40 minutes. No episodes of hypoxemia were recorded. After extubation, the patient's oxygen therapy was continued using a high-flow air-oxygen mixture flow generator with parameters: flow 20 l/min, temperature 37 °C, $FiO_2$ 40-50 %. Against this background, the patient's functional indicators were as follows: Blood pressure 126/76 mmHg, heart rate 78 per minute, BH 16 per minute, $SpO_2$ 97-99 %. Respiratory deficiency was absent, which was confirmed by laboratory data on the gas composition of arterial blood: $pCO_2$ 35 mmHg, $pO_2$ 139 mmHg, pH 7.412, BE – 0.5, $HCO_3$ 25.3 mmol/dL, $SO_2$ 97 %, $Na^+$ 142.0 mmol/dL, $K^+$ 4.1 mmol/dL, $Cl^-$ 103.0 mmol/L, $Ca^{2+}$ 1.04 mmol/dL.

In the early postoperative period, the patient received standard drug therapy, which included infusion, antibiotic therapy, prevention of thrombogenic complications, oxygen therapy, inhalation with mucolytics and bronchodilators. Postoperative analgesia was performed by titrated background epidural analgesia (Noel-Brevik type mixture) with periodic anesthetic boluses as indicated. The adequacy of postoperative analgesia was determined using the visual-analog pain scale (VAS). The average indicator of the intensity of the pain syndrome during the first day was 2.6 points, which did not require additional administration of opioids. In the Department of Anesthesiology and resuscitation, patient K. was under observation for 2 days, after which, in a satisfactory condition, he was transferred to the specialized department under the supervision of the attending physician to continue treatment.

## DISCUSSION

Among the methods of respiratory support that provide the necessary oxygenation of patients during anesthesia, the traditional use of volumetric ALV (CMV ventilation mode – volume control) occupies a leading position. The choice of HF ALV takes place in the surgical treatment of pathology of the thoracic cavity. Optimization of ventilation support of HF ALV during operations on the trachea and bronchi, helps to maintain the necessary oxygenation in the absence of airway tightness. The combination of volumetric ALV of the independent lung and HF ALV of the contralateral lung is one of the ways to ensure proper gas exchange in thoracic surgery for pulmonary bleeding, gangrene or lung abscess, bronchopleural fistulas [9]. Among the scientific publications there is evidence of the use of independent separate ventilation as a method of treatment of postoperative complications of lung transplantation and in unilateral diseases of the lung parenchyma. At the same time, in the available scientific literature, we have not seen such clinical observations in the surgical treatment of lung tumor lesions.

It should be noted that the main task facing the anesthesiologist in this clinical case was to prevent the development of hypoxemia and hypercapnia during ventilation of the previously operated lung (bronchoplastic upper lobectomy on the left) due to a decrease in the gas exchange area. This was provided by separate intubation and ventilation with two breathing apparatus with different operating principles (volumetric and high-frequency), which allowed minimizing airway injury and optimizing the patient's oxygen supply. The use of a tactical approach in surgical treatment using two fundamentally different technologies of lung ventilation in a patient with primary multiple lung cancer had no complications. However, it is necessary to take into account the potential risk of HF ALV in the form of an aspiration component by blood and tumor masses, as well as the occurrence of barotrauma in the absence of a sufficiently effective exhalation.

When using high-frequency ALV, the currently operated lung was not collapsed, and, as a result,

there were no newly formed areas of atelectasis. The creation of positive pressure in the airways led to a decrease in the dead space in the lungs and an increase in their gas exchange area, which contributed to adequate oxygenation and mucociliary clearance. The use of this technique made it possible to reduce violations of the ventilation-perfusion ratio, thereby avoiding the development of life-threatening complications.

## CONCLUSIONS

Based on the analysis of clinical and laboratory data, it can be stated that the method of using two fundamentally different lung ventilation technologies is applicable in patients with primary multiple lung cancer. The choice of this anesthetic support provided an opportunity to perform radical surgical treatment in a patient with subcompensated contralateral lung function.

Authors contribution:
Tikhonova S.N. – conducting anesthesia, analysis of the data obtained, writing the text of the manuscript.
Rozenko D.A. – determination of research objectives, study design.
Ushakova N.D. – analysis of the data obtained, consultation.
Popova N.N. – direct conduction of the study.
Skopintsev A.M. – carrying out laboratory research, obtaining data for analysis.
Shulga A.V. – processing and analysis of results.
Ten I.A. – participation in the study.

## References

1. Kaprin AD, Starinskiy VV, Petrova GV. Malignant neoplasms in Russia in 2017 (incidence and morbidity). Moscow: P.A.Hertsen Moscow Oncology Research Institute – Branch of the National Medical Research Radiological Centre, 2018, 250 p. (In Russian).
2. Merabishvili VM, Arseniev AI, Tarkov SA, Barchuk AA, Shcherbakov AM, Demin EV, et al. Lung cancer morbidity and mortality. Siberian Journal of Oncology. 2018;17(6):15-26. (In Russian).
https://doi.org/10.21294/1814-4861-2018-17-6-15-26
3. Borisova TN, Breder VV, Nazarenko AV, Ivanov SM, Tkachev SI, Alekseeva TR. Multiple primary lung cancer. Literature reviews and clinical observations. Journal of Oncology: Diagnostic Radiology and Radiotherapy. 2018;1(2):90–95. (In Russian).
https://doi.org/10.37174/2587-7593-2018-1-2-90-95
4. Gorbunova VA, Artamonova EV, Breder VV, Laktionov KK, Moiseenko FV, Reutova EV, et al. Practical recommendations for the drug treatment of non-small cell lung cancer. Malignant Tumors. (In Russian). 2017;7(3s2):28–42.
https://doi.org/10.18027/2224-5057-20l7-7-3s2-28-42
5. Miller SV, Volkov MYu, Rodionov EO, Tuzikov SA, Yevtushenko VV, Lukyanenok PI, Yevtushenko AV. Experience of angioplastic operations in non-small cell lung cancer. International Journal of Applied and Fundamental Research. 2016;6(2):263–269. https://doi.org/10.17513/mjpfi.9593
6. Kolbanov KI, Trakhtenberg AK, Pikin OV, Glushko VA, Ryabov AB. Surgical treatment of patients with resectable non small cell lung cancer. Research and Practical Medicine Journal. 2014;1(1):16–23. (In Russian).
https://doi.org/10.17709/2409-2231-2014-1-1-16-23
7. Karitsky AP, Chulkova VA, Pestereva EV, Semiglazova TYu. Rehabilitation of a cancer patient as a basis for improving the quality of his life. Problems in Oncology. 2015;61(2):180–184. (In Russian).
8. Dalzell MA, Smirnow N, Sateren W, Sintharaphone A, Ibrahim M, Mastroianni L, et al. Rehabilitation and exercise oncology program: translating research into a model of care. Curr Oncol. 2017 Jun;24(3):e191–198.
https://doi.org/10.3747/co.24.3498
9. Kassil VL, Vyzhigina MA, Leskin GS. Artificial and assisted pulmonary ventilation. Moscow: Meditsina Publishers, 2004, 480 p. (In Russian).
10. Grichnik KP, Clark JA. Pathophysiology and management of one-lung ventilation. Thorac Surg Clin. 2005 Feb;15(1):85–103. https://doi.org/10.1016/j.thorsurg.2004.09.004
11. Razumovskiy AYu, Stepanenko SM, Afukov II, Demakhin AA. Methods of single-lung ventilation in children. Pediatric Surgery. 2014;18(2):20–25. (In Russian).
12. Ovechkin AM. Surgical stress response, its pathophysiological significance and modulation methods. Regional Anesthesia in the Treatment of Acute Pain. 2008;2(2):49–62. (In Russian).

13. Strashnov VI, Zabrodin ON, Mamedov AD, Strashnov AV, Koriachkin VA. Prevention of Intraoperative Stress and Its Consequences. Saint Petersburg: ELBI-SPb, 2015, 160 p. (In Russian).
14. Purohit A, Bhargava S, Mangal V, Parashar VK. Lung isolation, one-lung ventilation and hypoxaemia during lung isolation. Indian J Anaesth. 2015 Sep;59(9):606–617. https://doi.org/10.4103/0019-5049.165855
15. Koriachkin VA. Neuraxial blockade. Saint Petersburg: ELBI-SPb, 2017, 544 p. (In Russian).

Information about author:

Svetlana N. Tikhonova – anesthesiologist and reanimatologist, National Medical Research Centre for Oncology of the Ministry of Health of Russia, Rostov-on-Don, Russian Federation. ORCID: https://orcid.org/0000-0001-6919-3523, SPIN: 5141-1656, AuthorID:1077917

Dmitriy A. Rozenko – Cand. Sci. (Med.), Head of Department of Anesthesiology and Intensive Care, National Medical Research Centre for Oncology of the Ministry of Health of Russia, Rostov-on-Don, Russian Federation. ORCID: https://orcid.org/0000-0002-5563-484X, SPIN: 4658-5058, AuthorID: 917988

Nataliya D. Ushakova – Dr. Sci. (Med.), professor, anesthesiologist and reanimatologist, National Medical Research Centre for Oncology of the Ministry of Health of Russia, Rostov-on-Don, Russian Federation. ORCID: https://orcid.org/0000-0002-0068-0881, SPIN: 9715-2250, AuthorID: 571594, Scopus Author ID: 8210961900, ResearcherID: L-6049-2017

Nataliya N. Popova* – anesthesiologist and reanimatologist, National Medical Research Centre for Oncology of the Ministry of Health of Russia, Rostov-on-Don, Russian Federation, assistant at the Department of Oncology, Rostov State Medical University, Rostov-on-Don, Russian Federation. ORCID: https://orcid.org/0000-0002-3891-863X, SPIN: 5071-5970, AuthorID: 854895, Scopus Author ID: 57215858399

Aleksandr M. Skopintsev – anesthesiologist and reanimatologist, National Medical Research Centre for Oncology of the Ministry of Health of Russia, Rostov-on-Don, Russian Federation. ORCID: https://orcid.org/0000-0001-8834-4817, SPIN: 3635-3780, AuthorID: 1096021

Aleksandr V. Shulga – Cand. Sci. (Med.), anesthesiologist and reanimatologist, National Medical Research Centre for Oncology of the Ministry of Health of Russia, Rostov-on-Don, Russian Federation. ORCID: http://orcid.org/0000-0003-2722-5640, SPIN: 7430-4810, AuthorID: 735049

Igor A. Ten – Cand. Sci. (Med.), anesthesiologist and reanimatologist, National Medical Research Centre for Oncology of the Ministry of Health of Russia, Rostov-on-Don, Russian Federation. ORCID: http://orcid.org/0000-0003-1511-250X, SPIN: 3657-6259, AuthorID: 449613

South Russian Journal of Cancer 2021, v.2, №2, p. 50-56
https://doi.org/10.37748/2686-9039-2021-2-2-6
REVIEW



# MOLECULAR GENETIC CLASSIFICATION OF COLORECTAL CANCER SUBTYPES: CURRENT STATE OF THE PROBLEM

**O.I.Kit, E.A.Dzhenkova, E.A.Mirzoyan*, Yu.A.Gevorkyan, A.B.Sagakyants, N.N.Timoshkina, O.Yu.Kaymakchi, D.O.Kaymakchi, R.E.Tolmakh, A.V.Dashkov, V.E.Kolesnikov, A.G.Milakin, S.I.Poluektov**

National Medical Research Centre for Oncology of the Ministry of Health of Russia, 63 14 line str., Rostov-on-Don 344037, Russian Federation

## ABSTRACT

Today, colorectal cancer (CRC) is the third most common cancer and therefore an urgent problem of oncology. Despite all modern diagnostic capabilities, the rates of advanced cases are growing steadily. CRC was proven to be a result of a phased dysplastic change in the colon mucosa, molecular genetic changes that determine the molecular biology of the tumor, its properties, morphology, disease prognosis and response to therapy. The following mechanisms of CRC tumor progression are distinguished: chromosomal instability, microsatellite instability, "methylator" phenotype, and serrated pathway of adenocarcinoma development. Application of molecular and diagnostic methods has become a promising direction in recent years. This led to the development of a molecular genetic classification with 4 CRC subtypes differing not only in their molecular genetic characteristics, but also in clinical course and response to therapy.

**Keywords:**
colorectal cancer, molecular biology, molecular and genetic subtypes, pattern-recognition receptors, Toll-like receptors, lymphogenous metastasis, surgical treatment.

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

Information about funding: no funding of this work has been held.
Conflict of interest: authors report no conflict of interest.

For citation:
Kit O.I., Dzhenkova E.A., Mirzoyan E.A., Gevorkyan Yu.A., Sagakyants A.B., Timoshkina N.N., Kaymakchi O.Yu., Kaymakchi D.O., Tolmakh R.E., Dashkov A.V., Kolesnikov V.E., Milakin A.G., Poluektov S.I. Molecular genetic classification of colorectal cancer subtypes: current state of the problem. South Russian Journal of Cancer. 2021; 2(2): 50-56. https://doi.org/10.37748/2686-9039-2021-2-2-6

Received 22.01.2021, Review (1) 26.01.2021, Review (2) 24.04.2021, Published 18.06.2021

Южно-Российский онкологический журнал 2021, т.2, №2, с. 50-56
https://doi.org/10.37748/2686-9039-2021-2-2-6
ОБЗОР

# МОЛЕКУЛЯРНО-ГЕНЕТИЧЕСКАЯ КЛАССИФИКАЦИЯ ПОДТИПОВ КОЛОРЕКТАЛЬНОГО РАКА: СОВРЕМЕННОЕ СОСТОЯНИЕ ПРОБЛЕМЫ

**О.И.Кит, Е.А.Дженкова, Э.А.Мирзоян*, Ю.А.Геворкян, А.Б.Сагакянц, Н.Н.Тимошкина, О.Ю.Каймакчи, Д.О.Каймакчи, Р.Е.Толмах, А.В.Дашков, В.Е.Колесников, А.Г.Милакин, С.И.Полуэктов**

ФГБУ «НМИЦ онкологии» Минздрава России, 344037, Российская Федерация, г. Ростов-на-Дону, ул. 14-я линия, д. 63

## РЕЗЮМЕ

На сегодняшний день колоректальный рак (КРР) является актуальной проблемой онкологии, занимая третье место в структуре общей онкологической заболеваемости. Несмотря на все современные диагностические возможности, показатели запущенности неуклонно растут. Доказано, что КРР развивается вследствие поэтапного диспластического изменения слизистой толстой кишки, молекулярно-генетических изменений, которые определяют молекулярную биологию опухоли, её свойства, морфологию, прогноз заболевания и ответ на проводимую терапию. Выделяют следующие механизмы опухолевой прогрессии при КРР: хромосомная нестабильность, микросателлитная нестабильность, «метиляторный» фенотип, зубчатый (serrated) путь развития аденокарцином. В последние годы перспективным направлением стало использование молекулярных методов диагностики. Это привело к разработке молекулярно-генетической классификации, включающей в себя 4 подтипа КРР, которые отличаются между собой не только по молекулярно-генетическим характеристикам, но и по клиническому течению и ответу на проводимую терапию.

**Ключевые слова:**
колоректальный рак, молекулярная биология, молекулярно-генетические подтипы, паттерн-распознающие рецепторы, толл-подобные рецепторы, лимфогенное метастазирование, хирургическое лечение.

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

Информация о финансировании: финансирование данной работы не проводилось.
Конфликт интересов: авторы заявляют об отсутствии конфликта интересов.

Для цитирования:
Кит О.И., Дженкова Е.А., Мирзоян Э.А., Геворкян Ю.А., Сагакянц А.Б., Тимошкина Н.Н., Каймакчи О.Ю., Каймакчи Д.О., Толмах Р.Е., Дашков А.В., Колесников В.Е., Милакин А.Г., Полуэктов С.И. Молекулярно-генетическая классификация подтипов колоректального рака: современное состояние проблемы. Южно-Российский онкологический журнал. 2021; 2(2): 50-56.
https://doi.org/10.37748/2686-9039-2021-2-2-6

Получено 22.01.2021, Рецензия (1) 26.01.2021, Рецензия (2) 24.04.2021, Опубликовано 18.06.2021

Over the past decades, colorectal cancer (CRC) remains an urgent problem of oncology both in Russia and abroad, taking the third place in the structure of morbidity, disability and mortality from malignant neoplasms (MN). Every year, more than 1 million new cases of CRC are registered in the world, with approximately the same prevalence in men and women [1]. Among the male population, the incidence rate reaches 11.4 %, ranking third after malignant neoplasms of the trachea, bronchi, lungs (17.8 %), and prostate (14.4 %). Among the female population, this indicator is 11.7 %, ranking third after breast tumors (20.9 %) and skin tumors (14.6 %). In 2015, more than 68 thousand cases of colon cancer were registered in Russia.

Today, it is proven that CRC develops due to a gradual dysplastic change in the colon mucosa, molecular and genetic changes that determine the molecular biology of the tumor, its properties, morphology, disease prognosis and response to therapy [2, 3].

The following mechanisms of tumor progression in CRC are distinguished:

1. Chromosomal instability (90 %), which leads to aneuploidy and aberration of chromosomes. This mechanism is associated with mutations of the tumor suppressor gene APC (the gene for adenomatous polyposis of the colon) and with mutations of other genes-SMAD2 and SMAD4, involved in the intracellular transmission of the TGF-b signal, as well as the KRAS gene. Clinically associated with an unfavorable prognosis [4, 5].
2. Microsatellite instability (20 %) is associated with a violation of DNA repair during replication as a result of mutations in the genes of one of the proteins of the Mismatch repair system (MRS). To date, there are 7 known genes whose mutations lead to microsatellite instability in CRC-MLH1, MLH3, MSH2, MSH3, MSH6, PMS1 and PMS2 [6].
3. The "methylator" phenotype (CpG island methylator phenotype, CIMP) (15 %) is caused by the presence of hypermethylated promoter sites (CpG island), in which inactivation of tumor suppressor genes is observed and, as a rule, mutations in the KRAS, BRAF and TP53 genes are often detected in patients [7, 8].
4. Serrated pathway of adenocarcinoma development: there are 2 molecular pathways for the development of CRC from a serrated polyp. The first pathway is a sequence of toothed polyp cancers resulting from a BRAF mutation, which leads to inactivation of the MMR genes (mismatch repair system – a system of repair of unpaired DNA bases), to low and high levels of microsatellite instability (MSI-H, MSI-L).

The second pathway involves the emergence of a tumor from a traditional serrated adenoma (TSA), leading to a low level of microsatellite instability (MSI-L) or microsatellite-stable (MSS) dentate formations. These tumors contain KRAS mutations [9, 10].

The first attempts to create a CRR classification were made by several groups. But they did not come to a common opinion and this did not lead to the formation of a single classification [11, 12].

Subsequently, international experts, after analyzing 18 different gene expressions in CRC in more than 4,000 samples, came to an agreement and described four molecular subtypes of CRC (copsepsis molecular subtypes, CMS). Approximately 87 % of the 4,151 samples that were analyzed by the six expert groups were subdivided into 4 molecular subtypes (CMS), and the remaining 13 % of the cases remained "unclassified".

Additional data, including mutations, somatic copyicity, methylation status, and biological characteristics, correlate with CRC subtypes [13, 14] (Table 1).

1. CMS1 (MSI, immune, 14 %) develops due to defective repair by microsatellite instability (MSI) and suppression of MLH1 expression, high methylation (CpG-island methylator phenotype, CIMP-high). They are characterized by mutations in the BRAF gene and a low level of somatic copyability. Patients with early-stage CMS1 tumors (with MSI) have a better prognosis compared to patients with microsatellite stability (MSS) of the tumor. CMS1 has a good prognosis when detected before the disease progresses, in particular due to the presence of specific populations of T-lymphocytes and natural killer cells. However, patients with CMS1 tumors, which are most often right-sided, have very poor survival after relapse detection [15].
2. CMS2 (canonical, 37 %) occurs due to the sequential transition of the colon epithelium to adenoma and later to carcinoma, with the activation of the WNT-β catenin and MYC signaling

pathway. CMS2 is more often left-sided (59 %) and is characterized by the highest five-year overall survival at all stages compared to the other subtypes of CRC [14].

3. CMS3 (metabolic, 13 %) has less somatic copyability (SCNAs)and contains more heterogeneous tumors (MSI) than in CMS2 and CMS4. Although mutations in the KRAS gene are present in all molecular subtypes, they are most common in CMS3 (in 68 %) [11, 13, 14]. The metabolic subtype is characterized by a higher frequency of KRAS mutations, which affects the therapy with anti – epidermal growth factor (EGFR) monoclonal antibodies [15-17].
4. CMS4 tumors (mesenchymal, 23 %) show increased expression of genes involved in the epithelial-mesenchymal transition and indicate activation of transforming growth factor-β, with expression of genes involved in complement-related inflammation, matrix remodeling, stromal invasion, and angiogenesis. CMS4 tumors exhibit very low levels of hypermutation, MSS status, and very high levels of somatic copyability. CRC CMS4 is manifested by a mesenchymal phenotype and an inflammatory microenvironment with innate immune cells [13]. Patients with the CMS4 subtype, often diagnosed at late stages, have worse overall survival and worse relapse-free survival than patients in other CRC groups [11, 14, 15].

As can be seen from the above, the molecular subtypes of CRC differ not only in their molecular features, but also in their clinical course and sensitivity to chemo-radiation therapy.

Along with the development of molecular classification, an attempt was made to introduce it into clinical practice. In Sadanandam et al. the relationship between the molecular subtypes of cancer and the possible response to the prescribed treatment was revealed. In patients with a generalized form of the disease, the response rate to FOLFIRI first-line chemotherapy was 71 %. The response to cetuximab therapy was evaluated in a group of 80 patients by the molecular subtype, which was observed in 54 % of patients. Two groups were identified: sensitive and resistant to cetuximab [18].

Research results from Okita et al. they indicate a relationship between the molecular subtype of CRC and the effectiveness of the therapy. More than 193 patients with generalized CRC were divided into subtypes: CMS1 (N = 21), CMS2 (N = 53), CMS3 (N = 69), and CMS4 (N = 50). Then, the effectiveness of irinotecan and oxaliplatin-based chemotherapy, as well as anti-EGFR therapy in specific molecular subtypes, was analyzed. In the analyzed group, longer progression-free survival and overall survival (S) were observed in patients receiving irinotecan as first-line chemotherapy compared to oxaliplatin therapy ($p$<0.01). The percentage of objective responses was higher in the irinotecan group (for the CMS4 subtype, it was 80 %). The lowest response rate to the therapy was observed in the CMS1 subtype [19].

**Table 1. Molecular subtypes of CRC**

| Characteristics | CMS1 Immune (microsatellite unstable) | CMS2 (canonical) | CMS3 (metabolic rate) | CMS4 (mesenchimal) |
|---|---|---|---|---|
| Frequency of occurrence | 14 % | 37 % | 13 % | 23 % |
| Molecular characteristics: | Increased MSI gene expression | epithelial differentiation; activation of the WNT and MYC signaling pathway; high somatic copyability | heterogeneous by MSI; metabolic dysregulation; low somatic copyability | TGF-b activation; epithelial-mesenchymal transition; high somatic copyability |
| BRAF/KRAS mutations' presence | BRAF mutations | | KRAS mutations | |
| Tumor's localisation | Right-sided localisation | Left-sided localisation | Mixed localisation | Left-sided localisatio |
| Clinical flow, prognosis: | Positive flow | better survival rates after relapse | | worst survival after relapse |

Conclusions of Marta Frąckowiak et al. they correspond to the results presented by Fontan and Sandals at the ASCO GI conference (2018). In the group of patients with "wild type" RAS, the objective response to anti-EGFR therapy was differentiated depending on the subtype: CMS1-20 %, CMS2-76 %, CMS3-23 %, and CMS4-88 % [20].

It is believed that there is a relationship between the molecular subtypes, the localization of the primary tumor, and the prognosis. In the course of the FIRE-3, CRYSTAL study, it was proved that the localization of the primary tumor in the proximal colon is an unfavorable prognostic factor [21].

A retrospective analysis of data from 728 patients participating in the CALGB/SWOG 80405 study (comparing bevacizumab and cetuximab in combination with first-line chemotherapy for metastatic CRC) showed that patients with left-sided localization have a significantly higher survival rate than patients with right-sided localization. The median OS for left-sided localization was 32.9 months compared to 19.6 months for right-sided localization ($p$<0.0001). In patients with the "wild" type of KRAS/BRAF treated with cetuximab, OS was greater in left-sided localization than in right-sided localization (40.3 months and 18.4 months, respectively, $p$=0.003). In the group with the BRAF mutation treated with bevacizumab, the results were more favorable for right-sided localization (23.7 months and 12.0 months, respectively, $p$=0.035). Of the cases of left-sided tumor location, the majority were subtypes CMS2 and CMS4, and of the cases of right-sided location-CMS1 and CMS3 [22].

Results of the study by Sagawa et al. it was shown that in the group of patients treated with cetuximab, OS was better in patients with left-sided tumors (50.6 months and 10.5 months, $p$=0.0004) [23].

An additional analysis conducted in the framework of the FIRE-3 project (AIO KRK-0306), which compared the effectiveness of cetuximab and bevacizumab in combination with FOLFIRI first-line chemotherapy, depending on the subtype, noted an association between OS and the CRC subtype and the type of treatment. In the CMS4 group, this relationship was statistically significant, and the median OS for cetuximab and bevacizumab was 41.3 months and 22.3 months, respectively ($p$=0.016) [24].

The availability of molecular genetic studies currently used in other types of cancer may be a prerequisite for targeted therapy of specific subtypes of CRC. Approximately 3 % of CMS3 and 5 % of CMS4 have high expression of the HER2 receptor protein. In these cases, antibodies against HER2 or tyrosine kinase inhibitors, such as lapatinib and neratinib, may be active. Attempts to use immunotherapy with checkpoint inhibitors (in particular, pembrolizumab and nivolumab) may be most effective in CMS1 [25].

## CONCLUSIONS

The molecular genetic classification of CRC subtypes is of prognostic importance and may influence the selection of optimal treatment. According to the literature analysis, the advantage of bevacizumab in CMS3 and cetuximab in CS4 and CS2 was noted. The benefits of irinotecan therapy were mainly noted in patients with CS3 and CS4, and in CMS2 it is less effective.

The optimal treatment for CMS 1 is a combination of oxaliplatin with bevacizumab, CMS 2-cetuximab in combination with oxaliplatin or irinotecan, CMS3-oxaliplatin with cetuximab, and CMS4-irinotecan with cetuximab.

The molecular genetic classification of CRC subtypes is important for predicting the clinical course of the disease and the adequate selection of drug therapy regimens, and today requires further study.

Authors contribution:

Kit O.I., Dzhenkova E.A., Gevorkyan Yu.A., Sagakyants A.B., Timoshkina N.N. – scientific editing.

Mirzoyan E.A. – text writing, material processing.

Kaymakchi O.Yu., Kaymakchi D.O., Tolmakh R.E., Dashkov A.V., Kolesnikov V.E., Milakin A.G., Poluektov S.I. – data collection, analysis, technical editing, bibliography design.

## References

1. The editional board of the cancer statistics in Japan. Cancer statistics in Japan. 2015. 129 p. Available at: https://ganjoho.jp/data/reg_stat/statistics/brochure/2015/cancer_statistics_2015.pdf. Accessed: 15.01.2021.

2. Al-Hajeili M, Shields AF, Hwang JJ, Wadlow RC, Marshall JL. Molecular Testing to Optimize and Personalize Decision Making in the Management of Colorectal Cancer. Oncology (Williston Park). 2017 Apr 15;31(4):301–312.

3. Sepulveda AR, Hamilton SR, Allegra CJ, Grody W, Cushman-Vokoun AM, Funkhouser WK, et al. Molecular Biomarkers for the Evaluation of Colorectal Cancer: Guideline From the American Society for Clinical Pathology, College of American Pathologists, Association for Molecular Pathology, and American Society of Clinical Oncology. J Mol Diagn. 2017 Mar;19(2):187–225.
https://doi.org/10.1016/j.jmoldx.2016.11.001

4. Muller MF, Ibrahim AEK, Arends MJ. Molecular pathological classification of colorectal cancer. Virchows Arch. 2016 Aug;469(2):125–134.
https://doi.org/10.1007/s00428-016-1956-3

5. Bosman F, Yan P. Molecular pathology of colorectal cancer. Pol J Pathol. 2014 Dec;65(4):257–266.
https://doi.org/10.5114/pjp.2014.48094

6. Setaffy L, Langner C. Microsatellite instability in colorectal cancer: clinicopathological significance. Pol J Pathol. 2015 Sep;66(3):203–218. https://doi.org/10.5114/pjp.2015.54953

7. Nazemalhosseini Mojarad E, Kuppen PJ, Aghdaei HA, Zali MR. The CpG island methylator phenotype (CIMP) in colorectal cancer. Gastroenterol Hepatol Bed Bench. 2013;6(3):120–128.

8. Rhee Y-Y, Kim K-J, Kang GH. CpG Island Methylator Phenotype-High Colorectal Cancers and Their Prognostic Implications and Relationships with the Serrated Neoplasia Pathway. Gut Liver. 2017 Jan 15;11(1):38–46.
https://doi.org/10.5009/gnl15535

9. Ageykina NV, Duvansky VA, Knyazev MV, Malkov PG, Danilova NV, Harlova OA. The alternative way of colorectal cancer developing. the histogenetic and molecular features of serrated lesions. Experimental and Clinical Gastroenterology. 2014:(7(107)):4–12. (In Russian).

10. Mozerov SA, Komin YuA, Novikov NYu, Yuzhakov VV, Pashkin SB, Mozerova ES. Tumor response to neoadjuvant therapy in colorectal cancer. Journal of scientific articles health and education in the XXI century. 2018:20(4):99–108.
http://doi.org/10.26787/nydha-2226-7425-2018-20-4-99-108

11. Muller MF, Ibrahim AEK, Arends MJ. Molecular pathological classification of colorectal cancer. Virchows Arch. 2016 Aug;469(2):125–134.
https://doi.org/10.1007/s00428-016-1956-3

12. Budinska E, Popovici V, Tejpar S, D'Ario G, Lapique N, Sikora KO, et al. Gene expression patterns unveil a new level of molecular heterogeneity in colorectal cancer. J Pathol. 2013 Sep;231(1):63–76. https://doi.org/10.1002/path.4212

13. Guinney J, Dienstmann R, Wang X, de Reyniès A, Schlicker A, Soneson C, et al. The consensus molecular subtypes of colorectal cancer. Nat Med. 2015 Nov;21(11):1350–1356.
https://doi.org/10.1038/nm.3967

14. Thanki K, Nicholls ME, Gajjar A, Senagore AJ, Qiu S, Szabo C, et al. Consensus Molecular Subtypes of Colorectal Cancer and their Clinical Implications. Int Biol Biomed J. 2017;3(3):105–111.

15. Dienstmann R, Vermeulen L, Guinney J, Kopetz S, Tejpar S, Tabernero J. Consensus molecular subtypes and the evolution of precision medicine in colorectal cancer. Nat Rev Cancer. 2017 Feb;17(2):79–92.
https://doi.org/10.1038/nrc.2016.126

16. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. Cell. 2011 Mar 4;144(5):646–674.
https://doi.org/10.1016/j.cell.2011.02.013

17. Zhao Y, Butler EB, Tan M. Targeting cellular metabolism to improve cancer therapeutics. Cell Death Dis. 2013 Mar 7;4:e532. https://doi.org/10.1038/cddis.2013.60

18. Sadanandam A, Lyssiotis CA, Homicsko K, Collisson EA, Gibb WJ, Wullschleger S, et al. A colorectal cancer classification system that associates cellular phenotype and responses to therapy. Nat Med. 2013 May;19(5):619–625.
https://doi.org/10.1038/nm.3175

19. Okita A, Takahashi S, Ouchi K, Inoue M, Watanabe M, Endo M, et al. Consensus molecular subtypes classification of colorectal cancer as a predictive factor for chemotherapeutic efficacy against metastatic colorectal cancer. Oncotarget. 2018 Apr 10;9(27):18698–18711.
https://doi.org/10.18632/oncotarget.24617

20. Fontana E, Nyamundanda G, Cunningham D, Ragulan C, Sclafani F, Eason K, et al. Molecular subtype assay to reveal anti-EGFR response sub-clones in colorectal cancer (CRC). JCO. 2018 Feb 1;36(4_suppl):658–658.
https://doi.org/10.1200/jco.2018.36.4_suppl.658

21. Tejpar S, Stintzing S, Ciardiello F, Tabernero J, Van Cutsem E, Beier F, et al. Prognostic and Predictive Relevance of Primary Tumor Location in Patients with RAS Wild-Type Metastatic Colorectal Cancer: Retrospective Analyses of the CRYSTAL

and FIRE-3 Trials. JAMA Oncol. 2017 Feb 1;3(2):194–201. https://doi.org/10.1001/jamaoncol.2016.3797

22. Venook AP, Ou F-S, Lenz H-J, Kabbarah O, Qu X, Niedzwiecki D, et al. Primary (1°) tumor location as an independent prognostic marker from molecular features for overall survival (OS) in patients (pts) with metastatic colorectal cancer (mCRC): Analysis of CALGB / SWOG 80405 (Alliance). JCO. 2017 May 20;35(15_suppl):3503–3503. https://doi.org/10.1200/jco.2017.35.15_suppl.3503

23. Sagawa T, Hamaguchi K, Sakurada A, Tamura F, Hayashi T, Fujikawa K, et al. Primary tumor location as a prognostic and predictive factor in metastatic colorectal cancer (mCRC) treated with chemotherapy plus cetuximab: A retrospective analysis. JCO. 2017 Feb 1;35(4_suppl):711–711. https://doi.org/10.1200/jco.2017.35.4_suppl.711

24. Stintzing S, Wirapati P, Lenz H-J, Neureiter D, Fischer von Weikersthal L, Decker T, et al. Consensus molecular subgroups (CMS) of colorectal cancer (CRC) and first-line efficacy of FOLFIRI plus cetuximab or bevacizumab in the FIRE3 (AIO KRK-0306) trial. JCO. 2017 May 20;35(15_suppl):3510–3510. https://doi.org/10.1200/jco.2017.35.15_suppl.3510

25. Boland PM, Ma WW. Immunotherapy for Colorectal Cancer. Cancers (Basel). 2017 May 11;9(5). https://doi.org/10.3390/cancers9050050

Information about author:

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

Elena A. Dzhenkova – Dr. Sci. (Med.), Associate Professor, academic secretary of the Academic Council National Medical Research Centre of Oncology of the Russian Ministry of Health, Rostov-on-Don, Russian Federation. ORCID: https://orcid.org/0000-0002-3561-098X, SPIN: 6206-6222, AuthorID: 697354, ResearcherID: K-9622-2014, Scopus Author ID: 6507889745

Ellada A. Mirzoyan* – PhD student National Medical Research Centre of Oncology of the Russian Ministry of Health, Rostov-on-Don, Russian Federation. ORCID: https://orcid.org/0000-0002-0328-9714, SPIN: 2506-8605, AuthorID: 1002948

Yuriy A. Gevorkyan – Dr. Sci. (Med.), professor, Head of the Department of Abdominal Oncology No. 2 National Medical Research Centre of Oncology of the Russian Ministry of Health, Rostov-on-Don, Russian Federation. ORCID: https://orcid.org/0000-0003-1957-7363, SPIN: 8643-2348, AuthorID: 711165

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

Natalia N. Timoshkina – Cand. Sci. (Biol.), head of the Laboratory of Molecular Oncology National Medical Research Centre of Oncology of the Russian Ministry of Health, Rostov-on-Don, Russian Federation. ORCID: https://orcid.org/0000-0001-6358-7361, SPIN: 9483-4330, AuthorID: 633651

Oleg Yu. Kaymakchi – Dr. Sci. (Med.), associate Professor of Oncology Department National Medical Research Centre of Oncology of the Russian Ministry of Health, Rostov-on-Don, Russian Federation. AuthorID: 335064

Dmitriy O. Kaymakchi – MD, surgeon at the Department of Abdominal Oncology No. 2 National Medical Research Centre of Oncology of the Russian Ministry of Health, Rostov-on-Don, Russian Federation. ORCID: https://orcid.org/0000-0002-7556-9897, SPIN: 4803-6558, AuthorID: 793912

Roman E. Tolmakh – Cand. Sci. (Med.), MD, surgeon at the Department of Abdominal Oncology No. 2 National Medical Research Centre of Oncology of the Russian Ministry of Health, Rostov-on-Don, Russian Federation. SPIN: 4559-2047, AuthorID: 733791

Andrey V. Dashkov – Cand. Sci. (Med.), senior Researcher of the Department of Abdominal Oncology No. 2 National Medical Research Centre of Oncology of the Russian Ministry of Health, Rostov-on-Don, Russian Federation. ORCID: https://orcid.org/0000-0002-3867-4532, SPIN: 4364-9459, AuthorID: 308799

Vladimir E. Kolesnikov – Dr. Sci. (Med.), MD, surgeon at the Department of Abdominal Oncology №2 National Medical Research Centre of Oncology of the Russian Ministry of Health, Rostov-on-Don, Russian Federation. SPIN: 9915-0578, AuthorID: 705852

Anton G. Milakin – MD, oncologist of the Department of Thoracic Oncology National Medical Research Centre of Oncology of the Russian Ministry of Health, Rostov-on-Don, Russian Federation. ORCID: https://orcid.org/0000-0001-7661-1340, SPIN: 7737-4737, AuthorID: 794734

Sergey I. Poluektov – MD, surgeon at the Department of Abdominal Oncology No. 2 National Medical Research Centre of Oncology of the Russian Ministry of Health, Rostov-on-Don, Russian Federation. SPIN: 4267-3840, AuthorID: 842869

Федеральное государственное бюджетное учреждение
НАЦИОНАЛЬНЫЙ
МЕДИЦИНСКИЙ ИССЛЕДОВАТЕЛЬСКИЙ ЦЕНТР
ОНКОЛОГИИ
Министерства здравоохранения Российской Федерации

PEER-REVIEWED SCIENTIFIC AND PRACTICAL

# South Russian Journal of Cancer

РЕЦЕНЗИРУЕМЫЙ НАУЧНО-ПРАКТИЧЕСКИЙ

Южно-Российский онкологический журнал

www.cancersp.com