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ORIGINAL ARTICLE

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

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ABSTRACT

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

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

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Compliance with ethical standards: the study was carried out in compliance with the ethical principles set forth by the World Medical Association Declaration of Helsinki, 1964, ed. 2013. The study was approved by the Committee on Biomedical Ethics at the V. K. Gusak institute of emergency and reconstructive surgery, Donetsk, Russian Federation (extract from the protocol of meeting No. 2 dated 05/17/2024). Informed consent was received from all participants of the study

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ОРИГИНАЛЬНАЯ СТАТЬЯ

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

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РЕЗЮМЕ

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

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

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Соблюдение этических стандартов: в работе соблюдались этические принципы, предъявляемые Хельсинкской декларацией Всемирной медицинской ассоциации (World Medical Association Declaration of Helsinki, 1964, ред. 2013). Исследование одобрено Комитетом по биомедицинской этике при ФГБУ «Институт неотложной и восстановительной хирургии имени В. К. Гусака» Министерства здравоохранения Российской Федерации (выписка из протокола заседания № 2 от 17.05.2024 г.). Информированное согласие получено от всех участников исследования

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BACKGROUND

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

PATIENTS AND METHODS

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

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

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

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

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

Table 1. Characteristics of the studied patients

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

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

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

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

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

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

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

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

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

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

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

STUDY RESULTS

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

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

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

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

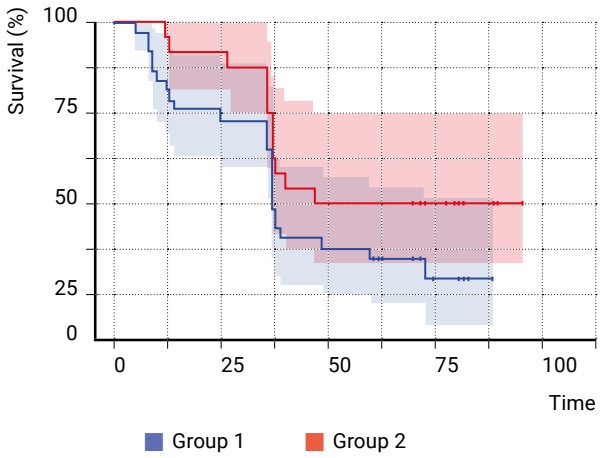

Fig. 1. Overall survival of patients of both groups (1 – group of simultaneous surgical removal of the primary focus and oligometastases, 2 – group of surgical removal of the primary focus followed by chemotherapy)

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

DISCUSSION

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

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

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

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

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

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

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

CONCLUSION

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

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

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

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