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REVIEW

Modern strategy of metastatic colorectal cancer treatment (literature review)

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ABSTRACT

Metastatic lesions account for about 50–60 % of all cases of colorectal cancer (CRC). Currently, the prognosis for metastatic CRC has significantly improved due to the advent of effective drug therapy and the expansion of surgical treatment options. In this regard, the study of modern directions of treatment of metastatic CRC is of particular interest.

In this study, both literature data and obtained treatment results of patients with metastatic colorectal cancer have been analyzed (PubMed, Scopus, eLibrary databases were used) at the National Medical Research Centre for Oncology.

Currently, many factors should be taken into account when planning therapy for patients with metastatic CRC: the characteristics of the tumor itself (biology and localization of the tumor, tumor burden, RAS, BRAF mutational status), the patient (age, performance status, functional state of organs and systems, comorbidity, patient attitude, expectations and preferences) and the treatment itself (toxicity, flexibility of the treatment program, socio-economic factors, quality of life). With a resectable process, surgical treatment with adjuvant or perioperative chemotherapy, and with potentially resectable liver metastases, with massive prevalence, unfavorable prognosis – to carry out the most active drug therapy taking into account the mutational status of the tumor in order to transfer the process to a resectable one. In case of widespread colorectal cancer, drug therapy lines are consistently carried out, the selection of which is based on the goals of therapy, the type and time of primary therapy, the mutation profile of the tumor, and the toxicity of drugs.

Patients with metastatic liver and/or lung lesions should be considered through the prism of surgical treatment, since it is surgical intervention that can significantly improve the results of treatment of patients. Therefore, patients with potentially resectable metastases should receive the most effective treatment and be operated on as soon as the process becomes resectable. At the same time, modern chemotherapy and targeted therapy are an integral part of the treatment of patients with metastatic colorectal cancer.

Keywords: review, metastatic colorectal cancer, liver resection, chemotherapy, targeted therapy

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3.1.6. Онкология, лучевая терапия
ОБЗОР

Современные хирургические стратегии лечения метастатического колоректального рака (обзор литературы)

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РЕЗЮМЕ

Метастатическое поражение составляет около 50–60 % всех случаев колоректального рака (КРР). В настоящее время прогноз в отношении метастатического КРР значительно улучшил-ся в связи с появлением эффективной лекарственной терапии и расширением возможностей хирургического лечения. В связи с этим особый интерес представляет изучение современных направлений лечения метастатического КРР.

В данном исследовании был проведен анализ данных литературы (использовались базы данных PubMed, Scopus, eLIBRARY) и собственных результатов лечения больных метастатическим колоректальным раком в ФГБУ «Национальный медицинский исследовательский центр онкологии» Министерства здравоохранения Российской Федерации.

В настоящее время при планировании терапии пациентов с метастатическим КРР следует учи-тывать многие факторы: характеристики самой опухоли (биология и локализация опухоли, tumour burden, мутационный статус RAS, BRAF), пациента (возраст, performance status, функ-циональное состояние органов и систем, коморбидность, отношение пациента к различным ме-тодам лечения, ожидания и предпочтения) и самого лечения (токсичность, гибкость програм-мы лечения, социоэкономические факторы, качество жизни). При резектабельном процессе хирургическое лечение с адъювантной или периоперационной химиотерапией, а при потенци-ально резектабельных метастазах в печень, при массивной распространенности, неблагоприят-ном прогнозе – проводить максимально активную лекарственную терапию с учетом мутаци-онного статуса опухоли с целью перевода процесса в резектабельный. При распространенном КРР последовательно проводят линии лекарственной терапии, выбор которой основывается на целях терапии, виде и времени первичной терапии, мутационном профиле опухоли, токсично-сти препаратов.

Пациенты с метастатическим поражением печени и/или легких должны рассматриваться через призму оперативного лечения, поскольку именно хирургическое вмешательство способно зна-чимо улучшить результаты лечения пациентов. Поэтому пациенты с потенциально резекта-бельными метастазами должны получать максимально эффективное лечение и оперироваться, как только процесс станет резектабельным. При этом современная химиотерапия и таргетная терапия являются неотъемлемой частью лечения больных метастатическим КРР.

Ключевые слова: обзор, метастатический колоректальный рак, резекция печени, химиотерапия, таргетная терапия

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INTRODUCTION

Colorectal cancer (CRC) is the third most common type of malignant neoplasm worldwide and the second leading cause of cancer death [1, 2]. In Russia, the incidence of CRC was 124 per 100 thousand population in 2022 [3]. Metastatic lesions are observed in 50–60 % of all CRC cases, while metachronous metastases occur in 20–50 %, and synchronous metastases account for 15–30 % of cases, and there is also a relationship between the latter and the worst prognosis [4, 5]. The most common localization of metastases is the liver, followed by the lungs, peritoneum and distant lymph nodes.

At the same time, metachronous metastases occurring after treatment are most often observed (40 %), synchronous metastases account for 25 % of cases and are associated with a worse prognosis. In 30 % of patients, metastatic lesion is limited only to the liver with a primary resectable process in 1/3 of these patients. In 70 % of patients with metastatic CRC, liver damage is primarily unresectable or there are extrahepatic metastases [6, 7]. These data indicate that the majority of CRC patients will sooner or later have distant metastases, and these will mainly be liver metastases.

Nevertheless, the current situation is not so tragic, since the prognosis for metastatic CRC has improved significantly due to the advent of effective drug therapy and the expansion of surgical treatment options [8, 9].

The purpose of the study was to study modern treatment options for metastatic colorectal cancer.

Metastatic CRC drug therapy

Many studies have been devoted to the choice of drug therapy for metastatic CRC. There are modern chemotherapy and immunotherapy regimens (targeted drugs, immune checkpoint inhibitors), as well as methods of local exposure (radiofrequency thermal ablation, chemoembolization).

The long-term results of using FOLFOX and FOLFIRI schemes turned out to be comparable, but the advantages of the FOLFOX scheme in line 1 in terms of the frequency of liver resections were revealed [10]. A retrospective PRIME study conducted in England among 512 patients showed that the addition of EGFR inhibitors to chemotherapy regimens increases the frequency of R0 liver resections by 60 % in patients with unresectable metastases, and these patients can be cured [11]. This conclusion was also confirmed by a meta-analysis conducted by Petrelli F. and coauthors [12]. The FIRE-3 study conducted among 353 patients compared the use of different therapy regimens for metastatic CRC and found that the best response was achieved in the group of patients receiving cetuximab and FOLFIRI after 3.5 months of treatment [13]. The meta-analysis also confirmed that for patients with metastatic CRC with wild type RAS, the best treatment strategy in the 1st line of therapy is chemotherapy + cetuximab [14]. In wild type RAS/BRAF and left–sided localization of the primary tumor, anti-EGFR should be used, in right-sided – bevacizumab [15]. Achieving resectability of liver metastases increases the 5-year survival rate from 9 to 42 % [16].

Surgical strategies for CRC metastatic liver damage

The requirement for liver resection in CRC metastases is currently beyond doubt and has been proven by LiverMetSurvey International Registry data, according to which, out of 23 thousand patients, the 5-year survival rate in the presence of liver resection was 42 %, without resection – 9 %. In the review by Simmonds R. S. et al. [17], based on the analysis of 30 studies, it was found that the 5-year survival rate of CRC patients with liver metastases with liver resection R0/R1 was 30–32 %, with resection R2 – 7 %, without liver resection – 0 %. A meta-analysis conducted by Kanas G. P. et al. [18] showed that the 5-year survival rate of patients with metastatic CRC undergoing liver resection was 38 %. Therefore, surgery should be the goal for the majority of these patients [6].

The criteria for resectability of liver metastases were determined by Adam R. They were divided into technical and oncological [19]. The technical absolute criteria are the impossibility of R0 resection with less than or 30 % of the remaining liver tissue, as well as the presence of unresectable extrahepatic metastases. The technical relative criteria are the possibility of R0 resection only using other procedures, as well as R1 resection. The oncological criteria are unresectable extrahepatic metastases, 5 or more liver metastases, and tumor progression.

Prognostically unfavorable factors after liver resection for CRC metastases are: R1 resection, ex-

trahepatic metastases, more than 1 metastasis, size more than 5 cm, CEA above 200 ng/ml, metastases in the lymph nodes of the primary tumor, non-event interval less than 12 months, bilateral liver damage [16, 19], BRAF mutation [20].

Oncological and surgical criteria are taken into account when choosing treatment tactics for initially resectable liver metastases. In the absence of surgical difficulties and favorable oncological prognostic factors. Surgical treatment without preoperative chemotherapy is recommended (adjuvant therapy is possible). In case of adverse oncological factors, pre- or perioperative chemotherapy is necessary. In case of surgical difficulties, systemic chemotherapy is recommended regardless of oncological factors [21].

Adam R. suggests determining the tactics of treatment of CRC with liver metastases depending on the presence of symptoms of the primary tumor: with an asymptomatic tumor with resectable metastases, simultaneous resection of the liver and primary focus is possible, however, if there are risk factors, then chemotherapy is performed first, then liver resection, and only then resection of the primary focus is performed; with symptomatic tumors with resectable metastases undergo resection of the primary lesion, followed by chemotherapy followed by liver resection. In case of an asymptomatic tumor with unresectable metastases, chemotherapy is recommended, followed by step-by-step resection of the liver and primary focus when the process is transferred to a resectable one. In case of a symptomatic tumor with unresectable metastases, resection of the primary focus is performed, chemotherapy followed by liver resection when the process is transferred to a resectable one [7].

Aigner F. and co-author. They make their own adjustments to the treatment regimen for metastatic CRC: in an asymptomatic resectable process with the presence of risk factors after neoadjuvant chemotherapy, simultaneous surgical interventions should be performed instead of two-stage ones [22].

The views of oncologists are currently attracted by a group of asymptomatic tumors with conditionally resectable liver metastases, which is recommended to undergo the most active neoadjuvant chemotherapy with the maximum frequency of objective response (duplets, triplets) using targeted drugs (depending on the RAS status) with an assessment of the effect every two months [11, 23].

At the same time, patients with conditionally resectable liver metastases undergoing drug therapy should undergo surgery immediately upon reaching resectability, without waiting for a full response. This position is due to several factors. Firstly, 83 % of metastases that disappeared during chemotherapy will cause the progression of the disease, and secondly, there is also a danger of hepatotoxicity [18, 22], to reduce the development of which it is recommended to limit preoperative therapy to 2–3 months [24].

In addition, the frequency of postoperative complications directly depends on the number of therapy courses performed: 13.6 % – without chemotherapy, 19 % – after 5 courses of therapy, 45.4 % – after 6–9 courses of therapy, 61.5 % – after 10 or more courses of therapy [25, 26]. At the same time, early tumor reduction (≥ 20 % or ≤ 30 %) at 6–8 weeks of therapy is an indicator of sensitivity to treatment and is associated with a high frequency of liver resections and an increase in overall patient survival [11, 27].

The volume of surgical intervention on the liver for CRC metastases

The question of an adequate amount of liver surgery for CRC metastases is a matter of debate. Anatomical and atypical resections are possible here. Previously, the advantage was given to extensive liver resections with a large margin from the edge of metastasis due to the better results of extensive interventions. However, the era of highly effective drug therapy has made it possible to equalize the survival of patients with anatomical and non-anatomical liver resections for CRC metastases [28].

In 2019, a meta-analysis of 18 studies was published, including 7,081 patients, comparing parenchymal-preserving and extensive liver resections [29]. It turned out that the overall and relapse-free survival in these groups of patients was comparable, which allowed the authors to conclude that parenchymal-preserving surgery is an adequate method of treating metastatic CRC. Parenchymal-preserving and anatomical liver resections for metastases were compared with the same results in 12 studies involving 2505 patients [30].

Currently, the attitude towards the negative edge of liver resection has also changed. Thus, Kokudo N. [31] found CRC micrometastases in the liver parenchyma in only 2 % of patients within 5 mm or more of the macroscopic border of the tumor. Fur-

ther studies have shown that there is no significant difference in patient survival when the distance from the resection line is less than and more than 1 cm. Even a clearance of 1 mm did not increase the time before the recurrence of liver metastasis, and the 5-year overall survival rate was 33 % [31]. In addition, with modern chemotherapy, even R1 resection has no prognostic value for patient survival [32].

Parenchymal-preserving liver resections have also opened up wide opportunities for the successful application of laparoscopic techniques in CRC metastases [33–35].

Repeated liver resections for metastatic CRC

The point of preserving the liver parenchyma is not only the possibility of chemotherapy, but also repeated liver resections in the event of new metastases. The expediency of repeated liver resections has been proven in studies, in particular, in the work of Schmidt T. [36], in which, when analyzing the data of 578 patients, it was found that without repeated liver resections with recurrence of metastatic lesion, the 5-year overall survival was 36.7 %, with repeated liver resections – 56.6 %, with resections for the third time – 53.2 %.

At the same time, the established prognostic factors for repeated resections are not applicable, only the pT stage of the primary tumor and the metachronism of the lesion are important [37]. A meta-analysis of 7,200 patients from 27 studies showed that repeated operations benefit patients with a long relapse-free period with solitary, small, unilobar lesion and absence of extrahepatic metastases [36]. Therefore, patients for repeated liver resections should be carefully selected.

In cases of impossibility of resection or RTT of metastatic liver damage, it is possible to use other methods of local exposure such as regional intraarterial chemoinfusion, embolization therapy, which allow achieving a median overall survival of 45.6 months compared with 40.5 months with systemic therapy alone [38].

Metastatic lung and ovarian lesions in CRC

Metastatic lung disease is the second favorite localization of distant CRC metastasis. The importance of active surgical tactics in this case was demonstrated in a study by Onaitis M. W. et al. [39], in which thoracic intervention made it possible to achieve 28 % 3-year recurrence-free and 78 % overall survival when analyzing data from 378 patients. The factors of negative prognosis for lung metastases are: a short recurrence-free interval, metastatic lymph node lesion, the presence of more than 1 metastatic lesion in the lungs, high CEA, lung resection R1, large metastases, liver metastases in the anamnesis [39, 40].

Clinical recommendations for the treatment of metastatic liver damage in CRC are also applicable for metastatic lung damage [39]. Combined and sequential resections of the liver and lungs are possible with encouraging results in a selected group of patients with solitary metastatic lesion [41].

Metastatic ovarian lesions often occur in women, while they are more often detected with damage to other organs, a single lesion occurs only in 24 % of women. The prognosis for ovarian metastases is worse than in the liver, and the median survival is only 23 months [42].

The choice of treatment tactics for metastatic CRC

The ESMO-ASIA 2019 consensus on the treatment of metastatic CRC summarized current views and recommended surgical treatment with adjuvant or perioperative chemotherapy in a resectable process, and with potentially resectable liver metastases, with massive prevalence, and an unfavorable prognosis, to carry out the most active drug therapy taking into account the mutational status of the tumor in order to transfer the process to a resectable one [21]. In case of unresectable CRC, drug therapy lines are consistently carried out, the choice of which is based on the goals, type and time of primary therapy, the mutational profile of the tumor, and the toxicity of the drugs. Studies have found a correlation between an increase in the median survival of metastatic CRC and the use of all three main cytotoxic agents (fluorouracil/leucovorin, oxaliplatin, irinotecan) during therapy [43].

At the same time, many factors should be taken into account when planning therapy for patients with metastatic CRC. These are the characteristics of the tumor itself (biology and localization of the tumor, tumour burden, RAS mutations, BRAF), the patient (age, functional state of organs and systems, comorbidity, patient attitude, expectations and preferences) and the treatment itself (toxicity, flexibility of the treatment program, socio-economic factors, quality

of life) [21]. That is, a balance is needed between the risks and benefits of metastatic CRC therapy, and much attention was paid to this issue at ASCO 2020.

CONCLUSION

Therefore, patients with colorectal cancer with metastatic liver and/or lung damage should be considered through the prism of surgical treatment, since it is surgical intervention that can significantly improve the results of treatment of patients. Therefore, patients with potentially resectable metastases should receive the most effective treatment and be operated on as soon as the process becomes resectable. At the same time, modern chemotherapy and targeted therapy, depending on the mutation status and localization of the tumor, are an integral part of the treatment of patients with metastatic CRC.

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