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Impact of neoadjuvant chemotargeted therapy in patients with colorectal cancer and synchronous liver metastases in perioperative period

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ABSTRACT *AIM: assess the impact of neoadjuvant chemotargeted therapy in patients with colorectal cancer and synchronous liver metastases in perioperative period.*
PATIENTS AND METHODS: a pilot prospective study included 30 patients with colorectal cancer and synchronous liver metastases (mCRC). The combined treatment included 3 cycles of neoadjuvant FOLFOXIRI chemotherapy with the addition of targeted agents: cetuximab (24 patients with wtKRAS) and bevacizumab (6 patients with mtKRAS) followed by radical surgery.
RESULTS: the clinical and radiological response of colorectal cancer liver metastases to neoadjuvant chemotherapy (NACT) was complete in 4 (13.3%) patients and partial in 26 (86.7%) patients. Partial response to NACT in the primary tumor occurred in all patients. Adverse events of NACT were detected in 12 (40%) patients, 1 (3.3%) of them produced grade III toxicity. All patients underwent radical surgery (R0) 3–4 weeks after NACT, 28 (93.3%) of them underwent simultaneous colorectal and liver resection. Postoperative complications occurred in 21 (70%) patients, including grade I and grade IIIa complications (according to Clavien-Dindo classification) — 22 (73.3%) and 2 (6.7%), respectively. Histology revealed pathologic complete response (pCR) of liver metastases in 1 (3.6%) case and pathological grade 3 regression of the primary tumor (TRG3, Mandard A.M.) in 23 (76.7%) patients. Two (6.7%) patients with complete clinical and radiological response of liver metastases, who did not undergo liver resection, had no evidence of disease progression 12 months after the treatment.
CONCLUSION: in mCRC with synchronous liver metastases, NACT according to the FOLFOXIRI regimen in combination with targeted agents with a moderate toxicity profile provide significant carcinocidal effect without having a negative impact in the perioperative period. The study is ongoing to analyze 2-year disease-free and overall survival of patients.

KEYWORDS: *colorectal cancer, liver metastases, neoadjuvant chemotherapy, targeted therapy, surgery*

CONFLICT OF INTEREST: *The authors declare no conflict of interest*

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INTRODUCTION

In 2020, colorectal cancer (CRC) accounts for 10% of all new cases of cancer in the world [1], while advanced stages of the tumor process are quite often diagnosed. The only radical method of treatment for this category of patients is surgery, which allows to achieve a 5-year survival rate in almost 50% of patients. However, the recurrence rate after liver resection remains quite high [2], and therefore neoadjuvant chemotherapy (NACT) has been used, which increases the survival rate of patients by suppressing tumor micrometastases and increasing resectability. At the same time, it is known that NACT has its drawbacks associated with the possibility of disease progression and toxic effects on the liver, including sinusoidal obstruction and steatohepatitis [3].

Currently, chemotherapy regimens in the form of duplets (FOLFOX, XELOX and FOLFIRI) and triplets (FOLFOXIRI) are widely used, supplemented by the appointment of monoclonal antibodies depending on the mutation status of the *KRAS/NRAS* genes (bevacizumab, cetuximab and panitumumab) [4,5]. The results of randomized studies show that the incidence of objective tumor responses, overall and disease-free survival of patients is significantly increased due to the intensification of antitumor drug treatment in the form of triplets and bevacizumab [6–8]. However, chemotherapy using three–component regimens, including bevacizumab, was followed by a significant increase in the rate of adverse events of grade III–IV relative to two–component regimens: neutropenia — 49–50% vs. 21%, diarrhea — 14–17% vs. 5%, respectively [6,8]. Similarly, the combination of FOLFOXIRI with anti-EGFR therapy (cetuximab/panitumumab) led to an increase in the incidence of objective response to 60–95.5% [9–11] and the resectability of liver metastases up to 52.2% with the incidence of R0 resections reaching 35.8% [11]. At the same time, neutropenia (14–31.3%), diarrhea (7.5–33%) and skin toxicity (14.1–20%) prevailed among the adverse events of the III–IV grade [9–11]. In addition, modern chemo-targeted therapy regimens used at the preoperative stage can lead to morphofunctional changes in the hepatic parenchyma, which negatively affect the entire perioperative period. In this regard, a three-level strategy has been proposed for the prevention of postoperative livercomplications [12], assuming: 1) conducting short courses of NACT with an adequate interval between chemotherapy and liver resection; 2) a thorough assessment of liver functional reserves after completion of NACT; 3) performing parenchymal-sparing interventions on the liver with the rejection of anatomical and extended resections, if possible.

Thus, there are currently a number of studies on the treatment of mCRC with liver damage, but questions remain about determining the optimal regimen and the number of courses of neoadjuvant antitumor drug therapy of chemotherapy, taking into account its immediate effectiveness and tolerability.

THE AIM OF THE STUDY

To assess the effect of neoadjuvant chemo-targeted therapy on the perioperative period in patients with colorectal cancer with isolated synchronous metastatic liver damage.

PATIENTS AND METHODS

The pilot prospective study, which has been started 2020, included 30 patients with mCRC with liver involvement. All patients underwent 3 courses of NACT according to the FOLFOXIRI regimen, while in the case of the wild type *KRAS* gene (wtKRAS) cetuximab was additionally used (25 patients), and in the presence of a mutation in the *KRAS* gene (mtKRAS) bevacizumab was used (5 patients). After neoadjuvant chemo-targeted therapy, surgery on the primary tumor and liver was performed in the patients.

Table 1 presents the clinical and morphological characteristics of the patients.

The diagnosis was proved by colonoscopy, biopsy, thoracic and abdominal computed tomography

(SCT) with contrast enhancement, pelvic magnetic resonance imaging (MRI) with contrast enhancement, as well as mutations of the *KRAS, NRAS, BRAF, EGFR* genes and determination of the level of tumor markers (CEA, CA 19–9).

The analysis of the clinical and radiological effect of preoperative treatment was carried out using the RECIST 1.1 scale. Adverse events of NACT and targeted therapy were evaluated according to the criteria of NCI CTCAE (v.4.03). Postoperative complications were described using the Clavien-Dindo scale (2004).

Therapeutic tumor pathomorphosis after chemotargeted therapy was determined according to Mandard, A.M.'s scale (1994).

STATISTICAL ANALYSIS

Statistical processing of the material was carried out using the program STATISTICA v.10 (StatSoft Inc., USA). Quantitative data are given in the form of median and quartiles (Me (Q1–Q3)). The description of qualitative data was performed using absolute and relative values (*n* (%)). The Wilcoxon test was used to compare dependent samples. The differences were considered statistically significant at $p < 0.05$.

RESULTS

Table 1. *Clinical and morphological characteristics of patients*

Parameters	mCRC patients with livermets N = 30
Age of patients, years	50 (40–63)
Gender	
Male	13 (43.3)
Female	17 (56.7)
General condition of patients	
ECOG 0	23 (76.7)
ECOG 1	5 (16.7)
ECOG 2	2 (6.7)
Localization of the primary tumor	
Right colon cancer	4 (13.3)
Left colon cancer	18 (60)
Upper and middle rectum	8 (26.7)
The primary tumor	
T2	4 (13.3)
T3	16 (53.3)
T4a	7 (23.3)
T4b	3 (10)
Lymph nodes	
N0	5 (16.7)
N1	4 (13.3)
N2	21 (70)
The number of liver metastases	
1–3	17 (56.7)
4–6	5 (16.7)
7–9	4 (13.3)
10–11	4 (13.3)
Risk of recurrence (GAME scale)	
0–1 points	14 (46.7)
1–2 points	13 (43.3)
> 2 points	3 (10)
Grade of tumor differentiation	
G1	12 (40)
G2	14 (46.7)
G3	4 (13.3)

Neoadjuvant chemotherapy according to the FOLFIRI + cetuximab/bevacizumab regimen was performed in full in all 30 patients with mCRC, without reducing agent dosages.

Adverse events of NACT were recorded in 12 (40%) patients (Table 2). Of the toxic reactions, nausea/vomiting prevailed — 9 (30%) cases, leuko- and neutropenia — 7 (23.3%) cases each, and diarrhea — 4 (13.3%) cases. The developed adverse events mainly corresponded to grade I–II (96.7%), did not require a reduction in drug dosages or discontinuation of the treatment, and were stopped by the administration of symptomatic therapy. After the end of the 3rd course of NACT, 1 (3.3%) patient had grade III neutropenia — to correct an undesirable phenomenon and prevent inflammatory complications, the hospital stay was increased by 6 days.

When evaluating the direct clinical and radiological effect of neoadjuvant treatment, it was found (Table 3) that the objective response for the primary tumor showed partial regression — 100%, and for metastatic foci in the liver developed complete response in 13.3% and partial regression — in 86.7%.

It should be noted that after 3 courses of NACT, down staging was noted (Table 4) according to the T index (43.3%) and the N index (48%), which manifested itself in a decrease in the depth of

Table 2. *Adverse events of NACT, abs. n (%)*

Parameters	mCRC patients with livermets N = 30
Total patients with complications	12 (40)
Leukopenia	7 (23.3)
Neutropenia	7 (23.3)
Anemia	3 (10)
Hepatotoxicity	3 (10)
Nephrotoxicity	1 (3.3)
Nausea / vomiting	9 (30)
Diarrhea	4 (13.3)
Polyneuropathy	2 (6.7)

Table 3. *Clinical and radiological response to NACT, abs.n (%)*

Treatment effect	Primary tumor N = 30	Liver metastases N = 30
Full regression	0	4 (13.3)
Partial regression	30 (100)	26 (86.7)
Objective response	30 (100)	30 (100)

invasion of the primary tumor, as well as in the normalization of the size of the initially affected lymph nodes.

The clinical and radiological effect of NACT was accompanied by a sharp decrease in the level of CEA.

There was a significant decrease in the initially high level of CEA from 148.4 ng/ml (103.5–180.3) to normal values of 3.6 ng/ml (1.8–5.4) ($p < 0.0001$).

The post-op results are presented in Table 5. The surgical stage of combined treatment was performed after 3–4 weeks from the completion of the NACT. Operations in all 30 (100%) patients were performed in radical volume (R0), of whom 28 (93.3%) patients had simultaneous procedures, while resection of the primary tumor was carried out by laparoscopic access, and liver surgery was performed openly. In 2 (9.7%) of 4 patients with complete clinical and radiological regression of liver metastases, only the removal of the primary tumor without liver resection was performed. This was due to the fact that, taking into account the initial liver lesion (bilobar with the number of metastases from 3 to 5), these patients required extended right-sided hepatectomies with anatomical/atypical resection of the left lobe. However, the residual volume of the liver according to the results of SCT did not exceed 20% and was considered functionally insufficient. At the same time, two-stage liver resections were not shown in patients due to cardiovascular comorbidities. Atypical resections of initially affected liver segments were performed in 2 (9.7%) patients with complete clinical and radiological regression of single hepatic metastases. It should be noted that the complete clinical and radiological regression of liver metastases, detected preoperatively, was confirmed by intraoperative ultrasound. Thus, the rate of 'disappeared' metastases was 13.3%.

When analyzing early postoperative period, it was noted that intestinal peristalsis restored after 7 hours (6–13 hours), the first stool appeared after 26 hours (24–52 hours).

Postoperative complications occurred in 21 (70%) patients. It should be noted that the main share was made up of complications of the I grade (according to Clavien-Dindo). So, in 21 (70%) cases, febrile fever developed to 38°C, which lasted for 3–4 days without leukocytosis and increased levels of C-reactive protein and procalcitonin. Antipyretics were successfully prescribed for the purpose of correction.

In addition, in 1 (3.3%) case, seroma occurred in the projection of the suture of the laparotomy wound after laparoscopic resection of the sigmoid colon and resection of the VI + VII segments of the liver. In this regard, seroma drainage was performed with complete on day 5.

Of the grade IIIa complications, bilomas were detected in 2 (6.7%) patients in 3 months after surgery during a routine follow-up, as a result of which repeated admissions for 3–4 days and drainage under ultrasound control were required. Subsequently, these complications were resolved after 22 and 46 days. There were no intestinal complications.

Pathomorphosis of the tumor was evaluated (Table 6). It was found that in the liver the complete pathomorphological response of metastases was 3.6%, and a good response, including TRG 1 and TRG 2, reached 25%.

Table 4. *Clinical stage before and after NACT*

Before treatment	After preoperative therapy							
	ycT_1	ycT_2	ycT_3	ycT_{4a}	ycT_{4b}	ycN_0	ycN_1	ycN_2
cT_2 (n = 4)	1	3						
cT_3 (n = 16)	1	7	8					
cT_{4a} (n = 7)			3	4				
cT_{4b} (n = 3)				1	2			
cN_0 (n = 5)						5		
cN_1 (n = 21)						9	12	
cN_2 (n = 4)						1	2	1
Total (n = 30)	2	10	11	5	2	15	14	1

At the same time, on the part of the primary tumor, the carcinocidal effect was less significant, since TRG 3 was most often detected up to 76.7%.

DISCUSSION

Recently, antitumor drug therapy in combination with surgery is widely used in patients with mCRC with isolated liver damage. For example, the EPOC study (EORTC 40983) showed a 7% improvement in disease-free survival as a result of perioperative chemotherapy. In addition, targeted agents were actively used in addition to chemotherapy from the standpoint of intensifying treatment for advanced CRC [6–11], which allowed to increase the incidence of objective tumor responses, resectability of liver metastases and patient survival. These data justified for chemo-targeted therapy in patients with mCRC with resectable and conditionally resectable liver metastases. However, the New EPOC study, despite expectations, did not reveal the benefits of supplementing cetuximab with chemotherapy. At the same time, it should be noted a number of key parameters of this study that could affect the results obtained: 1) treatment was carried out in patients with synchronous and metachronous liver metastases; 2) previous treatment with oxaliplatin as adjuvant therapy was allowed; 3) duplets (FOLFOX 6, XELOX and FOLFIRI) were used for chemotherapy and the duration of chemo-targeted therapy was 12 weeks before surgery and 12 weeks after its completion, and the surgical treatment itself included both primary and repeated liver resections. Thus, the literature data demonstrate the different effectiveness of chemo-targeted therapy in mCRC with liver mets, which indicates the relevance of this problem and the need for further research.

Traditionally, during complex multimodal treatment, special attention is paid to assessing its immediate effectiveness and tolerability, since this directly affects the entire perioperative period.

In this study, after 3 courses of preoperative antitumor drug treatment, adverse events developed in 40% of patients and mainly corresponded to grade I-II toxicity: nausea/vomiting (30%), neutropenia (20%) and diarrhea (13.3%). Grade III toxicity was minimal and included neutropenia (3.3%). At the same time, the completion of preoperative treatment was 100%, dose reduction or drug withdrawal was not required. According to literature data [6,8–11], the incidence of adverse events when using FOLFOXIRI in combination with targeted therapy reaches 97–98%, including grade III-IV toxicity as neutropenia (14–50%), diarrhea (7.5–33%) and skin rash (14.1–20%). It should be noted that the higher rate and severity of adverse events in these trials are associated with a large number of courses of chemo-targeted therapy (on average, from 6 to 12).

The clinical and radiological effect of NACT in this study was 100%, partial regression was noted from the primary tumor in all patients, and complete (13.3%) and partial regression (86.7%) were recorded for liver metastases. In turn, according to Falcone A. [13], the objective response of liver metastases to FOLFOXIRI chemotherapy was lower down to 66%, including complete (8%) and partial regression (58%), due to the lack of additional targeted therapy.

Table 5. *Surgery outcomes in patients with mCRC*

Parameters	mCRC patients with livermets N = 30
Operation time, min.	210 (172–410)
Blood loss, ml	345 (200–995)
Surgery option	
Simultaneous procedures	28 (93.3)
Procedures for the primary tumor	2 (6.7)
Surgery type on the primary tumor	
Right hemicolectomy	2 (6.7)
Transverse colon resection	2 (6.7)
Left hemicolectomy	4 (13.3)
Sigmoid colon resection	15 (50)
Anterior rectal resection	7 (23.3)
Surgery type for liver metastases	
Anatomical liver resection	12 (40)
Atypical liver resection	10 (33.3)
Left hepatectomy	3 (10)
Right hepatectomy	2 (6.7)
Right trisectionectomy	1 (3.3)
Complications according to the Clavien-Dindo classification	
The number of patients with complications	21 (70)
Total complications	24 (80)
I grade	22 (73.3)
II grade	0
IIIa grade	2 (6.7)

Table 6. *Pathologic tumor response, abs. n (%)*

TRG	Primary tumor N = 30	Liver metastases N = 30
1 grade (TRG 1)	0	1 (3.6)
2 grade (TRG 2)	3 (10)	6 (21.4)
3 grade (TRG 3)	23 (76.7)	16 (57.1)
4 grade (TRG 4)	4 (13.3)	5 (17.9)
5 grade (TRG 5)	0	0

According to our data, postoperative complications developed in 70% of patients, with grade I complications prevailing, including febrile hyperthermia. We associate an increase in body temperature with the separation of the liver parenchyma using bipolar coagulation, which is confirmed by other studies [14,15].

Despite technological progress and extensive accumulated experience of liver resections in specialized centers, it is known that operations on the liver are still accompanied by high rates of postoperative morbidity (4.1–47.7%) and mortality (0.2–9.7%) [11,16,17].

One of the main types of postoperative complications in liver resection is biliary fistula and biloma, which range from 3.6% to 33% [11,18] and can lead to the development of intraperitoneal septic complications and liver failure.

It should be noted that liver failure refers to life-threatening complications of liver surgery and is closely related to neoadjuvant treatment, active hepatitis, cirrhosis of the liver, small functional volume of remaining liver tissue, massive intraoperative bleeding, type and duration of portal vein occlusion. According to various data, the incidence of liver failure is 0.7–33.83% [19,20].

Bleeding, the level of which ranges from 4.2% to 13.5%, is considered to be an equally formidable complication in liver surgery [11]. The main causes of this complication are bleeding from the wound surface, incomplete intraoperative hemostasis and weakening of vascular sutures, which is associated with increased pressure in the inferior vena cava system and activation of the patient [21].

In this study, despite intensive preoperative antitumor drug therapy and simultaneous surgeries, there were no complications of the IIIb-V grade.

Currently, the literature is actively discussing the effect of increasing the number of NACT courses on the rate of complete pathomorphological tumor response. There is conflicting information that if after 5 courses the complete response of liver metastases is 9% [22], then when using 9 courses it does not exceed 4% [23]. At the same time, it has been shown that 2–4 courses of chemo-targeted therapy is quite effective, and the intensification of preoperative treatment in the form of an increase in the number of courses does not enhance the damaging effect on the tumor, but leads to an increase in the rate of perioperative complications [14,24,25].

We compared the results of clinical, radiological and pathomorphological responses of metastatic foci in the liver. Of the 28 patients who underwent liver resection, 2 (7.1%) patients with established complete clinical and radiological response by histology of removed metastases in 1 (3.6%) case, a complete response (pCR) was confirmed and in 1 (3.6%) case, single remaining tumor cells were detected. It should be noted that of all 30 patients

included in the study, 2 (6.7%) patients with a complete clinical and X-ray response who had not undergone liver resection did not show signs of liver disease progression during follow-up for 12 months.

There are also publications in the literature indicating a discrepancy in the rate of complete clinical, radiological and pathomorphological responses of CRC metastases to the liver [26,27]. According to Adam, R. [23], after liver resection, out of 4% of patients with a complete pathomorphological response, none had a complete clinical and radiological response after completion of preoperative chemotherapy. At the same time, it is known that the rate of detection of a complete clinical and radiological response of liver metastases directly depends on the imaging methods used (SCT, MRI, Ultrasound, including intraoperative), combinations of preoperative chemotherapy and targeted therapy, and currently this indicator ranges from 6% to 37% [28]. In this regard, the question of choosing a treatment strategy for patients with a complete clinical and radiological response to liver metastases is quite acute. According to previous studies, the need to remove all initially affected liver segments was shown [29]. However, there are objective difficulties in detecting lesions both at the stage of pre- and intraoperative diagnosis [14], which partially limits the possibilities of surgical treatment and, in some cases, allows you to abandon the resection stage on the liver when subject to active monitoring.

CONCLUSION

The possibilities of modern oncology make it possible to improve the results of combined treatment in patients with mCRC with synchronous liver metastases through the use of neoadjuvant chemotargeted therapy supplemented by radical surgery. When performing NACT using a three-component FOLFOXIRI regimen in combination with targeted therapy with cetuximab /bevacizumab, depending on the mutation profile of the tumor, high completion of treatment with an acceptable incidence and severity of adverse events is noted. At the same time, when evaluating the clinical, radiological and pathomorphological response, it was shown that the chemo-targeted therapy has a pronounced antitumor effect on the primary tumor and metastatic foci in the liver, without having a negative effect on perioperative period.

The results of the presented combined treatment of mCRC with synchronous liver damage in terms of immediate tolerability and effectiveness are regarded as encouraging, and the study continues to analyze the 2-year disease-free and overall survival of patients.

AUTHORS CONTRIBUTION

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