

# Optimal Surgical Treatment Tactics in Patients with Synchronous Metastatic Colorectal Cancer

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## Abstract

**Aim:** The aim of the study is to choose the optimal tactics of surgical treatment in patients with colorectal cancer (CRC) with synchronous intra-abdominal metastases.

**Materials and methods:** The study included 74 patients with CRC with synchronous intra-abdominal metastases (peritoneal carcinomatosis and/or liver metastases), which were divided into 3 groups: I group (25 patients)-Intestinal stoma + neoadjuvant chemotherapy + Cytoreductive Surgery (CRS) + Adjuvant Chemotherapy (ACT); II group (18 patients)-Colon/rectal resection + ACT + CRS + ACT; III group (31 patients)-CRS + ACT.

**Results:** The best oncological results were obtained in III group (median overall survival 46 months vs 27m. in I group and 31m. in II group). In contrast, a higher incidence of postoperative complications was observed also in this group (29%). There is no significant difference in overall survival ( $p > 0.05$  according to Log-Rank test) and the rate of postoperative complications between all groups of patients. The mean length of hospital stay was shorter in III group-9.8 days ( $p < 0.01$ ).

**Conclusions:** All three options could be selected for the treatment of synchronous metastatic CRC. Therefore, the main goal remains the achievement of complete cytoreduction. So, it is necessary to focus on its possibility when choosing the sequence of stages of treatment in such patients. However, if it is possible to achieve complete cytoreduction and in the setting of the oncological center it is recommended cytoreductive surgery as the first step followed by adjuvant chemotherapy as the best treatment tactics for patients with synchronous metastatic CRC.

**Keywords:** Colorectal cancer; Cytoreductive surgery; Peritoneal carcinomatosis; Liver metastases

## Introduction

Colon cancer ranks the third place in the structure of morbidity and the second place in the structure of mortality of patients with oncological diseases [1-3]. About 20-25% of patients with newly diagnosed colon cancer have isolated metastases at the time of diagnosis [4]. Metastases detected before or during the diagnosis of colon cancer are called synchronous. The vast majority of patients with synchron-

ous colon cancer metastases have an intra-abdominal lesion [4]. The prevalence of synchronous liver metastases is 20-25% [4,5] and synchronous peritoneal carcinomatosis is 5.1-20% among patients with newly diagnosed colorectal cancer (CRC) [6-8]. The overall survival of patients with synchronous metastatic colorectal cancer, who do not receive special treatment, usually does not exceed 5.2-7 months [6]. In Ukraine, among patients with newly diagnosed colorectal cancer,



about 30.8% of patients did not survive even a year, according to the data of the National Cancer Registry for 2020 [9]. Such statistics can be observed precisely because of the high number of patients with synchronous metastatic colorectal cancer, who do not receive special treatment. However, such patients may receive a significant advantage in overall survival and quality of life due to combined special treatment (cytoreductive surgery, neo- and adjuvant systemic polychemotherapy, regional chemotherapy) comparing to patients, who receive only best supportive care [5-7].

The issue of choosing a right order and methods of special treatment in patients with intra-abdominal synchronous metastases of colorectal cancer is relevant. According to the NCCN guidelines, there are several possible options for special treatment of synchronous metastatic colon cancer. The first phase of treatment can be surgical (cytoreductive surgery). Its goal is to remove the maximum macroscopically visible tumor mass. Afterwards, patient receives Adjuvant Polychemotherapy (ACT). Another option is to start treatment with Neoadjuvant Polychemotherapy (NACT), followed by cytoreductive surgery and after that ACT. Staged surgical interventions (colon or rectal resection → ACT → cytoreduction (removal of the remaining tumor mass)) may also be a possible option. Anyway, there is a category of patients with synchronous metastatic colorectal cancer, who cannot receive the full amount of neoadjuvant chemotherapy treatment due to the presence of intestinal obstruction, repeated intestinal bleeding from the tumor, risk of colon perforation).

In this connection, the question arises: Does the phasing of special treatment for synchronous metastatic colorectal cancer affect the overall survival and clinical outcomes of patients? Often patients with CRC are examined due to the presence of constipation, abdominal pain, weight loss, and frequent blood in the stool. When CRC is detected in such patients with the presence of synchronous intra-abdominal metastases, there is a high risk of decompensation of intestinal obstruction, perforation of the colon, the occurrence of severe anemia, the development of intestinal bleeding that will not be amenable to conservative treatment during or even as a result of neoadjuvant chemotherapy. The aim of the study is to determine the optimal tactics of surgical treatment in patients with colorectal cancer with synchronous intra-abdominal metastases.

## Materials and Methods

The retrospective cohort single institution study included 74 patients (41 men and 33 women) with colorectal cancer with synchronous intra-abdominal metastases (peritoneal carcinomatosis and/or liver metastases), who underwent cytoreductive surgery at the Center for Reconstructive and Restorative Medicine (University Clinic) of the Odesa National medical university during 2014-2021.

Patients were divided into the following groups:

I group (25 patients)-Intestinal stoma + NACT + Cytoreductive surgery + ACT

II group (18 patients)-Colon/rectal resection + ACT +

Cytoreductive surgery + ACT

III group (31 patients)-Cytoreductive surgery + ACT

The stage of the disease was determined according to the International TNM classifications of the 7th and 8th editions (according to the date of the initial diagnosis). Clinical anamnesis, laboratory and instrumental examination of patients was carried out in accordance with the order of the Ministry of Health of Ukraine No. 554 dated 17.09.2007 and the recommendations of the National Comprehensive Cancer Network, the European Society for Medical Oncology and the European Society of Surgical Oncology in accordance with the order Ministry of Health No. 1422 of December 29, 2016. The diagnosis of all patients was confirmed histologically and immunohistochemically, the spread of the process was determined using intrascopic methods of diagnostics (computed tomography with intravenous contrast and/or magnetic resonance imaging using diffusion-weighted imaging) and intraoperatively. The Peritoneal Cancer Index (PCI) was determined intraoperatively for all patients with peritoneal carcinomatosis.

The Completeness of Cytoreduction (CC), length of stay in hospital, the incidence of early (up to the 7th day after surgery) and late (from the 8th to the 30th day after surgery) postoperative complications of III-IV grade of severity according to Clavien-Dindo classification, overall survival and progression-free period were analyzed for patients of all groups. Comparison of groups of patients according to the criteria represented by numerical variables was carried out using the Kruskal-Wallis test. The  $\chi^2$  criterion was used to compare the frequency of occurrence of features in groups and determine the relationship. Kaplan-Meier curves were constructed to study oncological outcomes, and oncological outcomes in all groups were compared using the log-rank test (Figure 1).

## Results

The average age of patients was  $61.1 \pm 6.4$  years (I group- $60.2 \pm 8.4$  years, II group- $62.3 \pm 6.9$  years, III group- $61.1 \pm 6.2$ ;  $p > 0.05$ ). Patients in all groups were analyzed for nutritional status, family history, presence of anemia and concomitant pathology (mixed concomitant pathology, cardiovascular diseases, diseases of the respiratory and urinary systems, neuroendocrine pathology). Statistical homogeneity of the groups was determined for all indicators ( $p > 0.05$ ). Among patients of all groups, 20.3% (15 patients) had only peritoneal carcinomatosis, 45.9% (34 patients) had only liver metastases, 33.8% (25 patients) were diagnosed with both liver metastases and peritoneal carcinomatosis (data of all groups is presented in (Table 1)). The number of patients with achieved CC-0/CC-1, the average length of stay in hospital, the incidence of postoperative complications of the III-IV degree according to Clavien-Dindo were determined (the results are presented in (Table 1)). The lowest level of CC-0/CC-1 was observed in group III, however, comparing to other groups, the difference is statistically insignificant ( $p > 0.05$ ). The shortest length of stay in hospital was observed in group III, comparing to other groups-the difference is statistically significant ( $p < 0.01$ ).

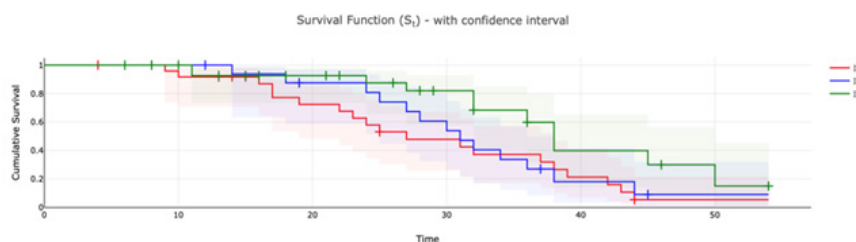


Figure 1: Overall survival Kaplan-Meier curves (I group-red color, II group-blue color, III group-green color).



**Table 1:** Group characteristics and clinical outcomes.

Characteristics	Groups			P-value
	I group (stoma+N-ACT+CRS+ACT), n=25	II group (Colon/rectal resection+ACT+CRS+ACT), n=18	III group (CRS+ACT), n=31	
Liver metastases	10 (40%)	9 (50%)	15 (48.4%)	p>0.05
Peritoneal carcinomatosis	3 (12%)	4 (22.2%)	8 (25.8%)	p>0.05
Liver metastases+ Peritoneal carcinomatosis	12 (48%)	5 (27.8%)	8 (25.8%)	p>0.05
Achieved CC-0/CC-1	22 (88%)	16 (94.4%)	26 (83.9%)	p>0.05
Length of hospital stay	14.9 (9-31) days	18.5 (12-35) days	9.8 (6-28) days	p<0.01
Postoperative complications of the III-IV grade according to Clavien-Dindo	6 (24%)	4 (22.2%)	9 (29%)	p>0.05
- Early	4 (16%)	2 (11.1%)	6 (19.4%)	p>0.05
- Late	3 (12%)	3 (16.6%)	4 (12.9%)	p>0.05

Early postoperative complications (up to 7 days after surgery) included anemia in the postoperative period, ileus, postoperative infection, intraperitoneal bleeding, intestinal anastomosis leak, pleural effusion, pulmonary embolism. Late postoperative complications (from the 8th to the 30th day after surgery) included anemia in the postoperative period, postoperative infection, intestinal anastomosis leak, intestinal fistula formation, evisceration, postoperative hernia formation, pulmonary embolism, acute renal failure, postoperative pneumonia. The highest rate of postoperative complications was observed in the

III group. The significant difference according to the  $\chi^2$  criterion and Fisher's exact test (if the group contained less than five individuals) was not determined (p>0.05). Median overall survival, median progression-free period, 1-year and 3-year survival in all the groups were determined (results are presented in (Table 2)). The highest median overall survival was reached in the III group (46 months). However, according to the results of the Log Rank test, no statistically significant difference was found comparing OS in all groups ( $\chi^2=5.027186$ , p=0.081) (Figure 1).

**Table 2:** Oncological outcomes of all groups.

Characteristics	Groups		
	I group (stoma+N-ACT+CRS+ACT), n=25	II group (Colon/rectal resection+ACT+CRS+ACT), n=18	III group (CRS + ACT), n=31
Median overall survival, months	27	31	46
Median progression free period, months	14	17	25
2-year survival	57.90%	80.80%	92.60%
3-year survival	37.10%	33.70%	68.30%

## Discussion

Improving the oncological results of treatment of patients with colorectal cancer with synchronous intra-abdominal metastases (including peritoneal carcinomatosis and liver metastases) is the main goal of this study. Achieving complete cytoreduction is crucial for prolonging the life expectancy of this category of patients. In this study, the highest rate of CC-0/CC-1 was achieved in the II group (94.4%), but the difference is statistically insignificant, comparing to other groups. The rate of achieving CC-0/CC-1 obtained in this study is similar to the results obtained in the UNICANCER phase III trial Prodiges 7, where the rate of R0/R1 cytoreductions was 91.5% in the group of patients, who underwent cytoreductive surgery and adjuvant chemotherapy [10]. According to the data obtained in the study of Lin EK, et al. [11] the completeness of cytoreduction is reliably correlated with overall survival (patients with CC score  $\geq 2$  have better oncological results

compared to CC score <2 p=0.036) [11]. Although, according to the consensus of the Society of Surgical Oncology Annual Meeting, the achievement of suboptimal cytoreduction also has a positive effect on the life expectancy of patients compared to those who did not undergo surgical treatment at all [12], the main goal remains to achieve complete cytoreduction.

It should be noted that in patients, who were included in the I group, the intestinal stoma was most often formed in an emergency hospital (in case of intestinal obstruction). We consider the choice of symptomatic surgical intervention in patients with colorectal cancer and synchronous metastatic intra-abdominal lesions in the conditions of an emergency hospital to be the most appropriate decision, providing decompensation of the process and the absence of oncological surgeons. Due to the obtained results of our study, the highest level of postoperative complications grade III-IV according to Clavien-Dindo



classification was in patients, who underwent cytoreductive surgery as the primary treatment. The lowest level of postoperative complications was observed in patients, who initially underwent colon/rectal resection, and cytoreductive surgery was performed after systemic chemotherapy. However, the difference is statistically insignificant, so the choice of staging of operative interventions does not have a decisive influence on the incidence of postoperative complications. In the study of Désolneux, et al. [13] 30% of patients, who underwent cytoreductive surgery and systemic chemotherapy, had postoperative complications of grade > III according to the Clavien-Dindo classification [13]. These results are similar to those obtained in the III group. In the phase III trial of Prodigé 7, in patients who underwent cytoreductive surgery followed by systemic chemotherapy, the incidence of grade III-V post-operative complications was 31.1% [10]. Reducing the rate of postoperative complications in this category of patients remains an important task in the future. According to the results of the meta-analysis by Mao F, et al. [14], the introduction of the ERAS protocol allows reducing the level of postoperative complications [13]. Therefore, in our oncological center, the principles of ERAS have been implemented in the perioperative management of patients since 2018, and the study of its feasibility and clinical safety continues.

One of the indicators evaluated in this study was the total length of stay in hospital. The best results were observed in the III group of patients, who underwent surgery in one stage (mean length of hospital stay-9.8 days), comparing to the other groups, where surgical treatment was carried out in two stages ( $p<0.01$ ). Reducing the duration of inpatient treatment allows improving the quality of life of patients, reducing recovery time after surgery, to start systemic chemotherapy faster, and to reduce financial costs. The best oncological results were also obtained in the group of patients, who underwent one-stage cytoreductive intervention followed by systemic chemotherapy (median overall survival 46 months in III group versus 27 in I group and 31 months in II group). However, comparing the groups by Log-Rank test, no statistical difference was obtained. In a study by Désolneux, et al. [13] practically similar to the I group results were obtained: the median overall survival was 48 months in patients with peritoneal carcinomatosis, and 24 months in patients with peritoneal carcinomatosis and liver or lung metastases (the results of patients, who achieved complete cytoreduction were analyzed) [13].

Worse overall survival results were demonstrated by the phase III trial Prodigé 7: the median overall survival in the group of patients, who underwent cytoreductive surgery and systemic chemotherapy, was 41.2 months. Patients with metastases other than peritoneal carcinomatosis were excluded from this study, however, not only synchronous but also metachronous peritoneal carcinomatosis was considered. The obtained results allow us to consider all three options for choosing tactics as possible and expedient in different clinical situations. However, if it is possible to achieve complete cytoreduction, providing the absence of decompensation of the patient's condition, and in the setting of the oncological center, the obtained results allow us to recommend a one-stage cytoreductive surgery followed by adjuvant chemotherapy as the best treatment tactics for patients with colorectal cancer with synchronous intra-abdominal metastases.

## Summary

The best oncological results were obtained in patients, who underwent cytoreductive surgery as the primary treatment. In contrast, a higher incidence of postoperative complications was observed also in this group. However, the obtained results do not show a significant difference in overall survival and the rate of postoperative complications between patients, who underwent cytoreductive surgery as the primary treatment (III group) and those who underwent cytoreductive surgery after the formation of an intestinal stoma and neoadjuvant chemotherapy (I group) and those who underwent colon/rectal resec-

tion followed by adjuvant chemotherapy and cytoreduction (II group). Compared to other patients, the length of hospital stay was shorter in patients who underwent cytoreductive surgery as the primary treatment ( $p<0.01$ ).

Thus, all three options can be selected for the treatment of synchronous metastatic colorectal cancer. And therefore, the main goal remains the achievement of complete cytoreduction. So, it is necessary to focus on its possibility when choosing the sequence of stages of treatment in such patients. However, if it is possible to achieve complete cytoreduction and in the setting of the oncological center it is recommended a one-stage cytoreductive surgery followed by adjuvant chemotherapy as the best treatment tactics for patients with synchronous metastatic colorectal cancer.

The authors declare that there is no conflict of interest regarding the publication of this article.

The study was conducted as a part of the scientific work of the Surgery Department No. 3 at Odessa National Medical University. Compliance with the WMA Code of Ethics of the World Medical Association WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects 2013 (protocol of the meeting of the bioethics commission of the Odessa National Medical University No. 176a of 11/14/2022) was determined. All study participants were informed and agreed to the processing of their clinical data and participation in the research process.

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