The Peerian Journal

Open Access | Peer Reviewed

Volume 48, November 2025
Website: www.peerianjournal.com

ISSN (E): 2788-0303
Email: editor@peerianjournal.com

Modern Targeted Strategies For The Treatment Of Colorectal Cancer With Metastatic Liver Lesions

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The aim of the study was to assess the effectiveness of targeted therapy in the treatment of patients with colorectal cancer with liver metastases.

Objects and methods of the study. aAll patients had morphologically verified adenocarcinoma of the colon. Chemotherapy (CT) based on fluoropyrimidines in combination with oxaliplatin or irinotecan (XELOX/FOLFOX4 regimens) was administered to all patients, supplemented with targeted agents bevacizumab and cetuximab. The effectiveness of chemotherapy was assessed according to RECIST criteria. Follow-up examinations, including computed tomography and ultrasound, were performed every 6-8 weeks from the initiation of therapy in accordance with RECIST. The severity of adverse effects was evaluated using the NCI CTCAE v4.0 (2009) toxicity scale.

Research results. In all patients, adenocarcinoma of the rectum was histologically confirmed. In most cases in 36 patients (48.0%) a moderately differentiated adenocarcinoma was identified. Poorly differentiated adenocarcinoma was detected in 27 patients (36.0%), while well-differentiated adenocarcinoma was observed in 12 patients (16.0%). These findings indicate that the majority of patients presented with an advanced, locally progressive tumor process in which the cells gradually lose their characteristic morphological features.

Keywords: chemotherapy treatment, colorectal cancer.

Official English Translation (Full Text)

Colorectal cancer (CRC) currently occupies one of the leading positions among oncological diseases due to the steady increase in morbidity and mortality rates both worldwide and in the Republic of Uzbekistan. The disease is characterized by high lethality and, according to international epidemiological data, ranks second among the main causes of cancer-related mortality [6].

One of the most important clinical and biological features of CRC is its pronounced tendency toward hematogenous metastasis with predominant involvement of the liver. This phenomenon is explained by the anatomical characteristics of venous blood flow, particularly the drainage of venous blood from the gastrointestinal tract through the portal system, which facilitates the early entry of tumor cells into the liver and the formation of metastatic foci. The presence of hepatic metastases significantly limits the possibilities for surgical intervention and is often associated with an unfavorable prognosis. An additional aggravating factor is the frequent detection of combined distant extrahepatic metastases, which further reduces the likelihood of successful treatment in this category of patients [1,5,11].

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Historically, the main method of systemic treatment for CRC patients with metastatic liver involvement has been chemotherapy (CT), which includes standard cytotoxic agents such as oxaliplatin, irinotecan, 5-fluorouracil (5-FU), and leucovorin. Numerous randomized clinical trials have demonstrated that combining 5-FU with other chemotherapeutic agents leads to a significant increase in the objective response rate and median overall survival. This contributed to the introduction into clinical practice of chemotherapy regimens such as FOLFOX4 (oxaliplatin), XELOX (capecitabine + oxaliplatin), FOLFIRI, and XELIRI (capecitabine + irinotecan), which have become standard treatment approaches for patients with advanced forms of CRC [10,12].

In recent years, therapeutic options in gastrointestinal oncology have expanded significantly due to the development and introduction of targeted agents acting on specific molecular targets of tumor cells. The use of targeted therapy has enabled the personalization of treatment strategies, adapting them to the individual biological characteristics of the tumor. The integration of targeted agents into systemic treatment regimens, as well as modifications of chemotherapy protocols within combined therapeutic strategies, has led to increased objective response rates, improved disease control, and enhanced overall survival outcomes in patients [2,7,8].

Despite the evident progress achieved in CRC treatment, literature data regarding the effectiveness of combining targeted therapy with cytotoxic agents in the setting of metastatic liver involvement remain limited and inconsistent. Currently, there are no unified international standards regulating the optimal choice of treatment regimen for this group of patients, nor is there a single strategy for selecting a targeted agent based on the clinical and molecular characteristics of the tumor. This underscores the need for further clinical studies aimed at evaluating the efficacy and safety of various combinations of targeted and cytotoxic drugs, as well as at developing personalized therapeutic approaches for CRC with distant metastases [3,4,9,11].

The aim of the study was to assess the effectiveness of targeted therapy in the treatment of patients with colorectal cancer with liver metastases.

Objects and methods of the study. Between 2020 and 2024, the study included 75 patients with colorectal cancer (CRC) and metastatic liver involvement who underwent examination and treatment at the Republican Specialized Scientific and Practical Center of Oncology and Radiology of the Ministry of Health of the Republic of Uzbekistan. In all patients, the diagnosis was morphologically confirmed: adenocarcinoma of the colon was identified. As systemic treatment, patients received chemotherapy (CT) based on fluoropyrimidines in combination with oxaliplatin or irinotecan according to the XELOX or FOLFOX4 regimens. Chemotherapy was supplemented with targeted agents bevacizumab or cetuximab.

The effectiveness of the administered treatment was assessed according to RECIST criteria. Follow-up examinations, including computed tomography and ultrasound, were performed every 6-8 weeks from the initiation of therapy. The severity of adverse drug reactions was assessed using the NCI CTCAE version 4.0 (2009) toxicity scale.

The gender distribution of the sample was approximately equal: men constituted 52.6%, and women 47.4%. The mean age of the patients was 62.3 ± 4.9 years, with the majority (52.3%) being older than 60 years.

In accordance with the treatment strategy, the patients were divided into three groups:

1. Group 1 (n=34) patients who received standard preoperative polychemotherapy according to the XELOX or FOLFOX4 regimens;

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2. Group 2 (n=23) patients who underwent preoperative polychemotherapy XELOX / FOLFOX4 in combination with bevacizumab;
3. Group 3 (n=18) patients who received preoperative polychemotherapy XELOX / FOLFOX4 in combination with cetuximab.

Study results. Histological examination confirmed adenocarcinoma of the rectum in all patients. The most common histological type was moderately differentiated adenocarcinoma, identified in 36 cases (48.0%). Poorly differentiated adenocarcinoma was found in 27 patients (36.0%), while well-differentiated adenocarcinoma was diagnosed in 12 patients (16.0%). These findings reflect a tendency toward late presentation and the prevalence of locally advanced disease, in which tumor cells lose their characteristic morphological features.

According to ultrasound examination performed in all 75 patients, an abdominal tumor process was detected in all subjects. In 56 patients (74.7%), the neoplasm demonstrated a heterogeneous structure, whereas in 19 (25.3%) it appeared homogeneous. Clear tumor margins were visualized in 32 patients (42.7%), while indistinct margins were noted in 43 patients (57.3%). During ultrasound evaluation, conglomerates of metastatically altered retroperitoneal lymph nodes were identified in 15 patients (20.0%). Hepatic metastases were present in 63 patients (84.0%). Additionally, enlargement of para-aortic and/or paracaval lymph nodes was detected in 15 patients (20.0%), and signs of ureterohydronephrosis were found in 9 patients (12.0%).

To further clarify the degree of local tumor spread, transrectal ultrasonography was performed in 24 patients (32.0%). This method was primarily used when local tumor extension was suspected, in order to select the most appropriate and radical surgical approach. In all cases, transrectal ultrasonography enabled visualization of the tumor, with longitudinal dimensions ranging from 5.5 to 14 cm. In 18 patients (75.0%), involvement of perirectal tissue was identified, and in 20 patients (83.3%), metastatic involvement of regional lymph nodes was confirmed.

Computed tomography (CT), performed in all patients, demonstrated high diagnostic sensitivity of 95.2%. In only 4.8% of cases was the tumor not detected. Among the visualized tumors, a heterogeneous structure was identified in 78.7% of cases, while indistinct margins with possible extension into pararectal structures were observed in 85.3%. CT analysis revealed multiple liver metastases in the majority of patients in 92.0% of cases. Bilobar hepatic involvement occurred in 81.3% of patients. Unilobar metastases were found in 14.7%, and solitary lesions in only 2.7% of patients.

The results of the study demonstrated that the integration of targeted agents into treatment regimens significantly improved overall survival and time to disease progression (Table 1). The median follow-up duration was 42.3 months. The best outcomes were observed with preoperative chemotherapy XELOX / FOLFOX4 in combination with bevacizumab, whereas the addition of cetuximab resulted in comparatively lower therapeutic efficacy.

Table 1. Survival indicators in patients with colorectal cancer

Survival Indicators	Group 1 (n=34)	Group 2 (n=23)	Group 3 (n=18)

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	95% CI:		
Median Overall Survival	7,4 (6,2-8,6)	11,5 (10,5-12,4)	9,7 (8,8-10,7)
Median Progression-Free Survival	4,9 (4,1-6,4)	6,9 (5,3-8,7)	5,6 (4,1-7,2)

Among 75 patients with metastatic colorectal cancer (CRC) who received 2-4 cycles of palliative chemotherapy (CT) with XELOX/FOLFOX4 regimens, complete disease regression was observed in 14 patients (16.7%), partial regression in 34 patients (40.5%), disease stabilization in 19 patients (22.6%), and disease progression in 17 patients (20.2%).

Based on the conducted studies, a prognostic assessment of individual risk factors influencing long-term treatment outcomes in CRC patients with liver metastases was performed using an integrated data evaluation approach. The likelihood ratio (LR) method was applied, which allows not only for considering the probability of consequences from the influence of each factor but also for identifying the most significant risks. Using this method, overall survival over a 5-year observation period was compared among groups of CRC patients treated with targeted agents and a control group of patients (Table 2).

Likelihood values were calculated using the formula: P1 = pi/n – group with targeted therapy (TT); P2 = pi/n – group with TT + standard chemotherapy (SC); P3 = pi/n – control group without immunotherapy. The likelihood ratio was then calculated as R = (P1 + P2)/P3. Factors where the maximum risk did not exceed the significance threshold of 1 were excluded. These included factors for which the difference between the studied groups did not exceed 1 and, accordingly, did not affect patient survival: presence of solitary liver metastases, liver metastases smaller than 1 cm, monolobar metastatic involvement, well-differentiated tumors, tumor localization in the colon, patient age under 60 years, and homogeneous tumor structure.

Table 2

Prognostic table of risk factors in patients with colorectal cancer

Factors	Gradations of factors	Attitude likelihood (LP)
Number of liver metastases	Single	0,55
	Multiple	1,27
Size of liver metastases	until 1 sm	0,61
	3 sm and higher	1,25
The nature of metastatic liver damage	Monolobular	0,72
	Bilobarnoe	1,18
Poorly differentiated tumor	Highly differentiated	0,60

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	Low-differentiated	1,12
Tumor localization	In the colon	0,67
	In the rectum	1,10
Age	Below 60 years old	0,73
	Over 60 years old	1,07
Tumor structure	Homogeneous	0,74
	Heterogeneous	1,05

The significant factors identified from all those considered in our study, which reflect differences in the 5-year survival outcomes of patients with colorectal cancer (CRC) and metastatic liver involvement, included: the presence of multiple liver metastases (LR=1.27), liver metastases larger than 3 cm (LR=1.25), bilobar metastatic involvement (LR=1.18), poorly differentiated tumors (LR=1.12), tumor localization in the rectum (LR=1.10), patient age over 60 years (LR=1.07), and heterogeneous tumor structure (LR=1.05).

Conclusion. Despite the noticeable improvement in treatment outcomes for patients with colorectal cancer included in recent clinical studies, existing systemic therapy protocols remain limited due to the low predictability of chemotherapy effectiveness. In this context, identifying patient subgroups with a higher-than-average probability of a positive response to therapy becomes particularly important. This approach allows for enhanced treatment efficacy, avoids irrational use of specific drugs, and improves long-term clinical outcomes in patients with metastatic CRC.

In patients with initially resectable liver metastases, the inclusion of targeted agents in standard chemotherapy regimens significantly improves therapeutic outcomes. The highest results were achieved with preoperative chemotherapy using XELOX/FOLFOX4 regimens in combination with bevacizumab, whereas the addition of cetuximab yielded more moderate effects.

Our study identified key factors influencing the 5-year survival of patients with CRC and metastatic liver disease. The most significant were: the presence of multiple liver metastases (relative risk, LR=1.27), metastases larger than 3 cm (LR=1.25), bilobar liver involvement (LR=1.18), poorly differentiated histological tumor structure (LR=1.12), primary tumor localization in the rectum (LR=1.10), patient age over 60 years (LR=1.07), and heterogeneous tumor structure (LR=1.05).

These results emphasize the necessity of an individualized approach to therapeutic strategy selection and confirm the importance of integrating targeted therapy into treatment regimens for patients with resectable liver metastases to improve long-term clinical outcomes.

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