https://doi.org/10.33878/2073-7556-2025-24-2-76-83

Early outcomes of preoperative chemotherapy combined with targeted therapy for rectal cancer

Aleksey Yu. Dobrodeev[1], Anna S. Tarasova[1], Sergey G. Afanasyev[1], Dmitry N. Kostromitsky[1], Anastasia A. Ponomareva[1], Natalia N. Babyshkina[1,2], Tatyana A. Dronova[1], Irina V. Larionova[1], Natalia V. Yunusova[1,2]

[1]Cancer Research Institute, Tomsk National Research Medical Center of the Russian Academy of Sciences (Kooperativny per., 5, Tomsk, 634009, Russia)
[2]Siberian State Medical University of the Ministry of Health of Russia (Moskovsky trakt, 2, Tomsk, 634050, Russia)

ABSTRACT *AIM: to assess early efficacy and tolerability of preoperative chemotherapy combined with targeted therapy in patients with rectal cancer (RC).*
PATIENTS AND METHODS: a pilot prospective study including 22 RC patients with KRAS wild-type gene is ongoing from 2021. There are 13 (59.1%) females and 9 (40.9%) males. Stage II RC was diagnosed in 2 (9.1%) patients and stage III RC in 20 (90.9%) patients. All patients received 6 cycles of mFOLFOX 6 chemotherapy combined with cetuximab targeted therapy followed by surgery. After completion of surgical treatment, patients with T4 and/or N + received adjuvant chemotherapy for 6 months (taking into account the time of preoperative treatment).
RESULTS: the completion rate of preoperative treatment was 90.9%, and a 15% reduction in drug dosages was required in 9.1% of patients. Adverse events were observed in 45.4% of patients. Grade III toxicity was noted in 13.6% of patients (neutropenia in 9.1% and skin rash in 4.5%). The clinical and radiological response to preoperative chemo-targeted therapy was 77.3%, including complete (9.1%) and partial (68.2%) tumor regression. All patients underwent radical surgery. The rate of postoperative complications was 13.6%. Grade I and grade IIIa complications (according to Clavien-Dindo classification) were observed in 9.1% and 4.5% of cases. Pathological complete response (pCR, according to Mandard TRG 1) was achieved in 13.6% of patients, and good pathological response (TRG 1-2) was observed in 31.8% of patients.
CONCLUSION: preoperative chemotherapy combined with targeted therapy in RC patients with the wild type of the KRAS gene has a pronounced damaging effect on the tumor, and an acceptable toxicity profile does not affect intra- and postoperative period. The short-term outcomes have been found to be encouraging. The study is ongoing to analyze the survival of patients.

KEYWORDS: *rectal cancer, preoperative chemotherapy combined with targeted therapy, objective response, toxicity, surgery*

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

FUNDING: *the study was supported by the Russian Science Foundation grant No. 22-15-00212 dated May 13, 2022 «Transcriptomic and proteomic markers for the prognosis and effectiveness of therapy for metastatic colon cancer»*

FOR CITATION: Dobrodeev A.Yu., Tarasova A.S., Afanasyev S.G., Kostromitsky D.N., Ponomareva A.A., Babyshkina N.N., Dronova T.A., Larionova I.V., Yunusova N.V. Early outcomes of preoperative chemotherapy combined with targeted therapy for rectal cancer. *Koloproktologia.* 2025;24(2):76–83. (in Russ.). https://doi.org/10.33878/2073-7556-2025-24-2-76-83

ADDRESS FOR CORRESPONDENCE: *Alexey Yu. Dobrodeev, Cancer Research Institute, Tomsk National Research Medical Center of the Russian Academy of Sciences, Kooperativny per., 5, Tomsk, 634009, Russia; e-mail: dobrodeev@oncology.tomsk.ru*

Received — 09.12.2024 *Revised — 03.03.2025* *Accepted for publication — 29.04.2025*

INTRODUCTION

Rectal cancer (RC) in Russia and the world occupies a leading position in the structure of morbidity and mortality from malignant neoplasms [1,2]. At the same time, over the past decade, there has been a steady annual increase in the incidence of RC in the country.

Recently, preoperative radiation or chemoradiotherapy (CRT) is the standard approach for locally advanced RC [3,4], which reduces the incidence of locoregional recurrences by 4.7–11% and increases the disease-free survival of patients. However, after completion of the treatment, 20–30% of the disease progresses due to the development of hematogenous metastases. In addition, radiation

therapy used at the preoperative stage is accompanied by the risk of radiation reactions and complications that have a negative impact on anal and genitourinary functions and significantly reduce the quality of life of patients [5–8]. In this regard, new methods of combined treatment of RC have been actively developed in recent years, including preoperative systemic antitumor drug therapy without the use of radiation [3,4,9,10]. According to the literature, preoperative chemotherapy as an alternative to CRT is mainly used in patients with tumor site in the upper and middle rectum. Based on a number of studies, it has been shown [7, 11] that as a result of the rejection of preoperative radiation therapy, it was possible to reduce the toxic effects of treatment and reduce the frequency of postoperative complications. At the same time, randomized trials of FOWARC [7] and PROSPECT [12], devoted to evaluating the effectiveness of FOLFOX preoperative chemotherapy, demonstrated long-term oncological results that were comparable with standard CRT.

At the same time, targeted therapy was applied in addition to chemotherapy at the preoperative stage from the standpoint of intensifying preoperative antitumor drug treatment of RC, depending on the genetic profile of the tumor. It was shown that when combined with chemotherapy and antiVEGF therapy (bevacizumab), there was an increase in the rate of the complete pathomorphological response of the tumor to 20–25% [13,14].

However, this treatment was characterized by greater toxicity in the form of an increase in the level of grade III–IV adverse events to 61%. In patients with wild-type KRAS, NRAS, and BRAF genes, antiEGFR therapy (cetuximab, panitumumab) is used along with preoperative chemotherapy. According to Japanese researchers [15], as a result of chemo-targeted therapy using FOLFOX and cetuximab, 5-year disease-free and overall survival rates in patients with RC (stages cT3-4a or N+) were 67.5% and 79.9%, respectively.

It should be noted that the completeness of preoperative chemo-targeted therapy, its immediate effectiveness and toxicity, as well as the post-op morbidity rate, differ significantly and generally significantly affect the survival of patients [16–18]. Thus, despite a number of studies, there are still questions about choosing the optimal preoperative treatment regimen, taking into account safety criteria and providing maximum damaging effects on the tumor in the framework of combined therapy of patients with RC.

AIM

To evaluate of the immediate efficacy and tolerability of preoperative chemo-targeted therapy in patients with RC.

PATIENTS AND METHODS

Since 2021, a pilot single-center prospective study included 22 patients with cancer of the upper rectum with the wild-type *KRAS* gene (*wtKRAS*).

The clinical and morphological characteristics of RC patients are presented in Table 1. The patients ranged in age from 42 to 76 years, the median was 60 (52–68) years. There were slightly more women in the study (59.1%) than men (40.9%). The general condition of patients on the ECOG scale was 0–1 point.

The prevalence of the tumor process corresponded to clinical stages II (9.1%) and III (90.9%).

Morphologically, adenocarcinoma with a predominance of low grade (77.3%) was confirmed in all patients.

The diagnosis of RC was established on the basis of video colonoscopy with biopsy and pathomorphological study, magnetic resonance imaging (MRI) of the pelvic organs with contrast enhancement, spiral chest and abdominal computed tomography (SCT) with contrast, and identifying *KRAS*, *NRAS*, and *BRAF* gene mutations.

The combined treatment included 6 courses of preoperative chemo-targeting therapy according to the mFOLFOX 6 + cetuximab regimen and radical surgery.

The clinical and radiological effect of preoperative chemo-targeting therapy was assessed using the

RECIST 1.1 scale. Adverse events of preoperative treatment were studied according to the criteria of NCI CTCAE (v.4.03). Therapeutic tumor pathomorphosis as a result of chemo-targeting therapy is presented on Mandard, A.M.'s scale (1994). An analysis of postoperative complications was performed using Clavien-Dindo's classification (2004).

In the postoperative period, patients with T4 and/or N + underwent adjuvant chemotherapy according to the mFOLFOX 6 regimen (up to 6 months, including the time of preoperative treatment).

Statistical Analysis

Statistical processing of the obtained results was carried out using the STATISTICA v.10 program (StatSoft Inc., USA). Qualitative data was described using absolute and relative values (*n* (%)). Quantitative data were presented in the form of medians and quartiles (Me (Q1-Q3)).

RESULTS

Preoperative mFOLFOX6 + cetuximab treatment was completed in the planned volume in 20 (90.9%) patients. Dose reduction of chemo- and targeted drugs by 15% was performed in 2 (9.1%) patients.

Adverse events of preoperative treatment were noted in 12 (45.4%) patients (Table 2). The main toxic reactions were grades I-II, which developed in 9 (40.9%) patients, including skin rash — 7 (31.8%), neutropenia — 5 (22.7%) and peripheral polyneuropathy — 2 (9.1%). Grade III adverse events were reported in 3 (13.6%) patients: neutropenia was present in 2 (9.1%) cases and skin rash in 1 (4.5%) case. In order to correct toxic reactions, symptomatic therapy was performed, and the time of hospitalization of patients was lengthened.

The direct clinical and radiological effect of preoperative chemo-targeted therapy was 77.3%, including complete and partial tumor regression — 2 (9.1%) and 15 (68.2%), respectively. Stabilization was noted in 5 (22.7%) cases, and there was no progression of the tumor process.

Table 1. *Clinical and morphological characteristics of patients*

Parameters	RC patients N = 22
Age of patients, years	60 (52–68)
Gender Male Female	9 (40.9) 13 (59.1)
General condition of patients ECOG 0 ECOG 1	15 (68.2) 7 (31.8)
Stage, TNM mrT3dN0M0 mrT4aN0M0 mrT2N1M0 mrT3-4aN1M0 mrT4bN1M0	1 (4.5) 1 (4.5) 1 (4.5) 17 (77.3) 2 (9.1)
The grade of tumor differentiation Low grade High grade	17 (77.3) 5 (22.7)

Table 2. *Adverse events of preoperative chemotargeted therapy, abs. n (%)*

Parameters	RC Patients N = 22
Total patients with complications	12 (45.5)
Neutropenia	7 (31.8)
Anemia	1 (4.5)
Thrombocytopenia	1 (4.5)
Nausea / vomiting	1 (4.5)
Peripheral polyneuropathy	2 (9.1)
Diarrhea	1 (4.5)
Skin rash	8 (36.4)

After preoperative chemo-targeting therapy, a decrease in the clinical stages of T and N was noted in 14 (63.6%) and 9 (40.9%) patients, respectively (Table 3). An increase in the clinical stage of T occurred in 1 (4.5%) patient.

Surgical treatment was performed in all patients 3–4 weeks after the completion of preoperative chemo-targeted therapy (Table 4). It should be noted that 7 (31.8%) patients had discharge colostomas before the start of combined treatment due to the phenomena of stenosis. The main stage of surgical treatment included anterior rectal resection. In all 22 (100%) patients the surgery was performed in radical volume, of whom 3 (13.6%) patients had laparotomy and

Table 3. *Clinical stage before and after preoperative chemotargeted therapy*

Before treatment	After preoperative therapy						
	ycT0	ycT2	ycT3	ycT4a	ycT4b	ycN_0	ycN_1
cT2 (*n* = 1)			1				
cT3 (*n* = 6)	1	1	4				
cT4a (*n* = 13)	1	2	8	2			
cT4b (*n* = 2)				1	1		
cN0 (*n* = 2)						2	
cN1 (*n* = 20)						9	11
Total (*n* = 22)	2	3	13	3	1	11	11

19 (86.4%) patients had laparoscopic access. In 1 (4.5%) patient, combined surgery, including uterine extirpation, was required due to tumor invasion into the uterus. In order to protect the colorectal anastomosis, preventive colostomy was performed in 15 (68.2%) patients. The median time of surgery and the volume of intraoperative blood loss was 80 minutes and 165 ml, respectively.

Complications in the postoperative period were noted in 3 (13.6%) patients. They mostly corresponded to grade I (as per Clavien-Dindo) and were represented by bladder atony and wound infection in 1 (4.5%) case. Grade IIIa complication in the form of colorectal anastomosis failure was recorded in 1 (4.5%) case and was stopped by conservative measures. The median postoperative hospital stay was 6 days.

The assessment of therapeutic tumor pathomorphosis after preoperative chemo-targeting therapy was performed in all 22 (100%) patients (Table 5). A complete pathomorphological response (pCR) developed in 3 (13.6%) patients, and a good response combining TRG 1 (Fig. 1) and TRG 2 (Fig. 2) was confirmed in 7 (31.8%) patients.

DISCUSSION

When conducting combined treatment of locally advanced RC, traditionally close attention is paid to its safety and immediate effectiveness, which significantly affect the course of the intra- and postoperative period, as well as the survival of patients.

Recently, there are several publications in the world literature on preoperative chemo-targeting

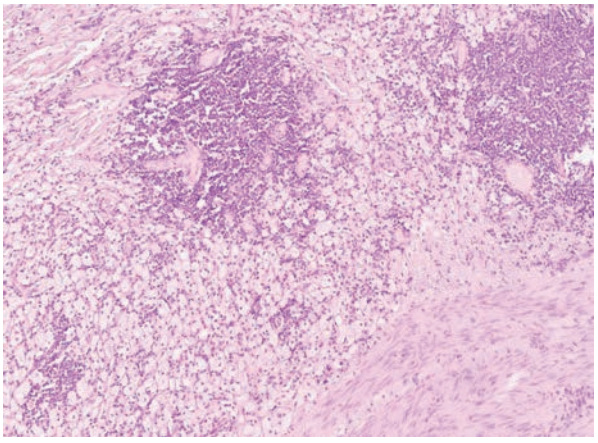

Figure 1. *Microphoto. Therapeutic pathomorphosis of tumor TRG 1 according to Mandard. Fields of connective tissue of varying degrees of maturity with focal clusters of xanthomatous cells. Tumor cells are not detected. Hematoxylin and eosin staining. Magnification ×100.*

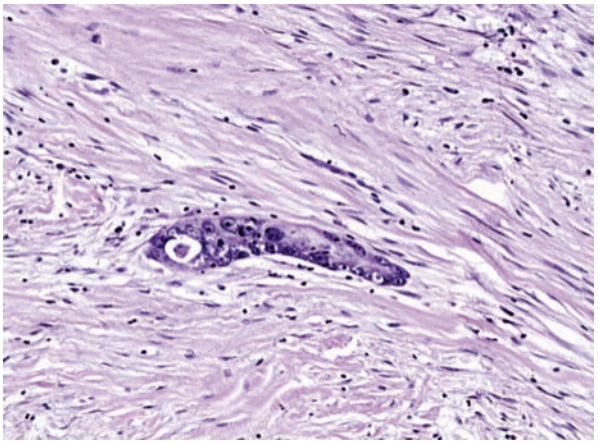

Figure 2. *Microphoto. Therapeutic pathomorphosis of tumor TRG 2 according to Mandard. Solitary tumors glands in massive fibrous stroma. Hematoxylin and eosin staining. Magnification ×200.*

Table 4. *Surgery outcomes*

Parameters	RC Patients N = 22
Surgery duration, min.	80 (54–122)
Volume of blood loss, ml	165 (50–305)
Postoperative hospital-stay, days	6 (4–9)
Surgery type Discharge colostomy Anterior rectal resection Preventive colostomy	7 (31.8) 22 (100) 15 (68.2)
Surgical access Laparotomic Laparoscopic	3 (13.6) 19 (86.4)
Surgery volume Standard Combined	 21 (95.5) 1 (4.5)
Surgery radicality R0 R1 R2	 22 (100) 0 0
Complications as per Clavien-Dindo's classification Number of patients with complications I Grade IIIa Grade	3 (13.6) 2 (9.1) 1 (4.5)

Table 5. *Pathologic tumor response, abs. n (%)*

TRG	CR Patients N = 22
1 Grade(TRG 1)	3 (13.6)
2 Grade(TRG 2)	4 (18.2)
3 Grade(TRG 3)	5 (22.7)
4 Grade(TRG 4)	10 (45.5)
5 Grade(TRG 5)	0

therapy in patients with RC with the wild type of *KRAS* gene [15–18]. Chemotherapy is performed using 5-fluorouracil in combination with oxaliplatin (mFOLFOX 6), of the targeted drugs cetuximab or panitumumab are used (the mean number of courses of preoperative chemo-targeted therapy is 6). It should be noted that the completeness of chemo-targeting therapy ranges from 87.5–88% [16,18] to 96% [17], which is generally lower than with the use of chemotherapy alone. At the same time, chemo-targeting therapy is often accompanied by an increase in the level of adverse events. Thus, in Hasegawa, S.'s study [16], 6 courses of mFOLFOX 6 + cetuximab showed an increase in grade III toxicity, including neutropenia (55%), leukopenia (20%), loss of appetite (12.5%), and skin rash (7.5%). According to C. Fernandez-Martos [18], in the GEMCAD 1601 study, as a result of using 6 courses of mFOLFOX 6 + panitumumab, grade III-IV toxicity reached 54%.

In this study, the completion of preoperative chemo-targeted therapy was 90.9%, and 9.1% of patients required a 15% reduction in doses of chemo- and targeted drugs. Adverse events of chemo-targeted therapywereconfirmed in 45.4% of patients, while grade III toxicity did not exceed 13.6%, including neutropenia and skin rash — 9.1% and 4.5%, respectively. Our results indicate an acceptable toxicity profile, satisfactory tolerability and safety of the combination of mFOLFOX 6 + cetuximab used in patients with stage II-III RC at the preoperative stage. In most cases, the adverse events corresponded to grade I-II (31.9%), were short-term and unstable, and were resolved by drug symptomatic therapy.

According to the literature [15–18], the clinical and radiological effect of preoperative chemo-targeted therapy varies from 50% to 88%, while complete tumor regression is 0–2%, and partial regression reaches 82.5–86%. In this study, the objective tumor response was at the level of 77.3%, including complete regression in 9.1% of patients and partial regression in 68.2% of patients, which is generally consistent with global indicators.

As a result of the pronounced clinical and radiological response of the tumor to preoperative chemo-targeting therapy, the rate of radical surgery in patients with locally advanced RC increases to 100%, which is confirmed by our and literature data [15–18]. However, the analysis of the course of the postoperative period revealed some differences. For example, in a study by Hasegawa, S. [16] postoperative complications mainly corresponded to grade II and grade IIIa — 20% and 10%, respectively, while anastomosis failure was noted in 10% of patients (in some cases, repeated surgery was required — grade IIIb). According to Toritani K. [17], postoperative complications were presented as follows: grade I — 14%, grade II and IIIa — 22% each, and grade IIIb — 2%, anastomosis

failure was established in 6% of patients (in all cases, grade IIIa was conservatively resolved).

In the GEMCAD 1601 study [18], grade III-IV postoperative complications accounted for 19%, of which grade IIIb was 2.9%. According to our study, postoperative complications developed in 13.6% of patients, including grade I and IIIa — 9.1% and 4.5%, respectively; at the same time, the failure of the anastomosis did not exceed 4.5%. The differences we obtained in the level and severity of postoperative complications compared to the presented studies [16,17] may partly be due to the large volume and traumatic nature of surgeries performed in them, such as abdominoperineal resection (10–20%), combined resections (10–14%) and pelvic exenteration (2%).

The rate of complete pathomorphological tumor responses is a surrogate indicator of the effectiveness of preoperative treatment. According to various authors [15–18], in patients with locally advanced RC treated with mFOLFOX 6 chemotherapy in combination with targeted therapy with cetuximab or panitumumab, the complete pathomorphological response ranged from 8% to 32.3%, and a good response (Mandard, TRG 1-2) reached 52.9%. In this study, when evaluating therapeutic pathomorphosis, similar results were obtained: a complete pathomorphological response of the tumor was recorded in 13.6% of patients, and a good response (Mandard, TRG 1-2) was noted in 31.8% of patients.

Thus, the strategy of combined RC therapy is currently developing along the path of intensification of antitumor drug treatment at the preoperative stage with the abandonment of radiation therapy and is used mainly for lesions of the upper and middle rectum and unfavorable prognostic factors such as the prevalence of the cT3–4 or N + tumor process, involvement of the circular resection border (CRM +) and the presence of extramural vascular invasion (EMVI +). This is most often realized in the form of an increase in the number of courses of preoperative chemotherapy using two- or three-component regimens, as well as a combination of chemo- and targeted therapy, depending on the genetic profile of the tumor. Based on generalized data [15–18] and our own experience, it has been shown that the use of preoperative chemo-targeting therapy mFOLFOX 6 + cetuximab is effective and safe, and provides satisfactory long-term results in terms of 3- and 5-year patient survival [15,17].

CONCLUSION

The combination of preoperative chemo-and targeted therapy is a promising direction in the treatment of locally advanced RC. Conducting chemo-targeted therapy with mFOLFOX6 + cetuximab as part of combined treatment in patients with the wild type of *KRAS* gene has a significant damaging effect on the tumor, which is confirmed by clinical, radiological and pathomorphological research methods. At the same time, preoperative chemo-targeting therapy according to this regimen is characterized by high completeness of treatment. The rate and severity of the adverse events as a result of chemo-targeted therapy are regarded as satisfactory and do not affect the course of the intra- and postoperative period. The early results of the use of preoperative chemo-targeting therapy in stage II–III RCare considered promising according to the criteria of efficacy and tolerability. The study continues to analyze the 2-year disease-free and overall survival of patients.

AUTHORS CONTRIBUTION

Study conception and design: *Alexey Yu. Dobrodeev, Anna S. Tarasova*

Data collection and analysis: *Anna S. Tarasova, Dmitry N. Kostromitsky, Anastasia A. Ponomareva*

Writing of the manuscript: *Alexey Yu. Dobrodeev*

Statistical analysis: *Natalia N. Babyshkina, Tatyana A. Dronova*

Editing of the manuscript: *Sergey G. Afanasiev, Natalia V. Yunusova, Irina V. Larionova*

INFORMATION ABOUT THE AUTHORS (ORCID)

Aleksey Yu. Dobrodeev — 0000-0002-2748-0644

Anna S. Tarasova — 0000-0001-6247-3434

Sergey G. Afanasyev — 0000-0002-4701-0375
Dmitry N. Kostromitsky — 0000-0001-5691-2349
Anastasia A. Ponomareva — 0000-0003-2060-4840
Natalia N. Babyshkina — 0000-0002-0562-3878
Tatyana A. Dronova — 0000-0003-3009-2404
Irina V. Larionova — 0000-0001-5758-7330
Natalia V. Yunusova — 0000-0003-4595-4177

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