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Outcomes of multimodal treatment including preoperative chemotherapy for upper rectal cancer

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ABSTRACT *AIM: to analyze outcomes of multimodal treatment including preoperative chemotherapy with FOLFOX 4 regimen in patients with upper rectal cancer.*
PATIENTS AND METHODS: the pilot study included 24 patients. Stages II and III were confirmed in 2 (8.3%) and 22 (91.7%) patients, respectively. All patients underwent 3 cycles of chemotherapy in FOLFOX 4 regimen followed by surgery. In the postoperative period, patients with T4 and N+ underwent adjuvant chemotherapy administered over 6 months including the time of preoperative treatment.
RESULTS: all patients completed preoperative chemotherapy with the FOLFOX 4 regimen. The toxicity of chemotherapy was 38.9%; adverse events did not exceed grades I-II. Partial tumor regression (RECIST 1.1 criteria) was achieved in 18 (75.0%) patients. All patients underwent surgery 4 weeks after chemotherapy. Postoperative complications occurred in 4 (16.7%) patients, 1 (4.2%) had grade IIIb complication (Clavien-Dindo scale), which required re-surgery. Pathological complete response (TRG1 by Mandard scale) was revealed in 1 (4.2%) patient. Thirteen patients (54.2%) received adjuvant chemotherapy. The mean follow-up was 38 (17-54) months. Three patients (12.5%) developed local recurrence and 4 (16.7%) patients — distant metastases. The 3-year overall and disease-free survival rates were 91.7% u 79.2%, respectively.
CONCLUSION: multimodal treatment including preoperative chemotherapy with the FOLFOX 4 regimen was well tolerated and produced tumor regression with high 3-year survival rates in patients with upper rectal cancer.

KEYWORDS: *rectal cancer, preoperative chemotherapy, toxicity, pathomorphosis, survival*

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

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INTRODUCTION

Currently, in local advanced rectal cancer (RC), the use of radiation or chemoradiotherapy (CRT) with subsequent surgical treatment is standard [1,2]. As a result of preoperative CRT, tumor regression is noted (50–60%) and a complete pathomorphological response is recorded (10–30%), which leads to a decrease in the incidence of locoregional recurrences and an improvement in the survival of patients with RC [3,4].

At the same time, according to previously conducted randomized studies [5,6], it was shown that when using a short course of preoperative radiation therapy, radiation reactions and complications (anal incontinence, sexual dysfunction, etc.) develop, leading to a significant decrease in the quality of life of patients. Similar results were recorded during prolonged preoperative CRT [7,8].

Given these circumstances, in recent years, only preoperative chemotherapy without radiation therapy has been used in patients with RC

Table 1. *Clinical characteristics of patients, abs. n (%)*

Criterion		Number of patients (n = 24)
Gender	Males	16 (66.7)
	Females	8 (33.3)
Stage, TNM	mrT3dN0M0	1 (4.2)
	mrT4aN0M0	1 (4.2)
	mrT3–4aN1M0	22 (91.7)

[9–13]. This approach made it possible to eliminate the negative impact of radiation therapy on the anal sphincter and reduce the number of postoperative complications.

Preoperative chemotherapy is performed using oxaliplatin and fluoropyrimidines, the mean number of courses is 4–6, while the completeness of treatment, the frequency of adverse events of III-IV grade, the timing of the start of surgical treatment and the level of postoperative complications vary widely. In addition, the incidence of complete pathomorphological responses of the tumor to preoperative chemotherapy is significantly different, which, combined with the prevalence of the tumor process, directly affects the survival of patients. Thus, within the framework of the combined treatment of RC, it is relevant to search for new options using preoperative chemotherapy.

AIM

to analyze the tolerability and effectiveness of combined treatment with preoperative chemotherapy according to the FOLFOX 4 regimen for cancer of the upper ampullary rectum.

PATIENTS AND METHODS

A pilot prospective study 2018–2020, which included 24 patients with the upper rectal cancer. The general condition of the patients corresponded to ECOG 0-1. The age of patients was 61 (44–75) years. There were 16 men (66.7%), 8 women (33.3%). Twenty-two (91.7%) patients had stage III and 2 (8.3%) patients had stage II clinical stage. In all cases, pathomorphological examination confirmed adenocarcinoma of various degrees of differentiation: G1 — 3 (12.5%), G2 — 20 (83.3%) and G3 — 1 (4.2%). The distance from the anal edge to the lower pole of the tumor was more than 10 cm. The clinical characteristics of patients are presented in Table 1.

The prevalence of RC was determined on the basis of magnetic resonance imaging (MRI) of the pelvic organs, video colonoscopy and multispiral computed tomography of the chest and abdominal cavity.

As part of the combined treatment at the preoperative stage, patients with RC underwent 3 courses of chemotherapy according to the FOLFOX 4 regimen.

The immediate effectiveness of chemotherapy was evaluated on the RECIST 1.1 scale (according to MRI data). The study of the toxicity of chemotherapy was carried out according to the criteria of NCI–CTCAE (v.4.03). Therapeutic pathomorphosis (TP) of the tumor was studied according to the scheme of Mandard, A.M. (1994).

Four weeks after preoperative chemotherapy, surgical treatment (anterior rectal resection) was performed. The anastomosis was formed by stapler. Loop colostomy was performed to protect the anastomosis.

Postoperative complications were analyzed according to the Clavien-Dindo scale (2004).

Table 2. *Postoperative complications according to the Clavien-Dindo scale, abs. n (%)*

Grade	Complication	Number
I	The bladder atony	1 (4.2)
II	Pneumonia	1 (4.2)
	Anastomosis failure	1 (4.2)
IIIb	Bleeding	1 (4.2)
Patients with complications		4 (16.7)

Table 3. *Therapeutic pathomorphosis of the tumor, abs. n (%)*

Therapeutic pathomorphosis grade	Number of patients
TRG 1	1 (4.2)
TRG 2	3 (12.5)
TRG 3	7 (29.2)
TRG 4	8 (33.3)
TRG 5	5 (20.8)
Total	24 (100)

Adjuvant chemotherapy was performed at T4 and/or N+ with a total duration of 6 months, taking into account the time of preoperative chemotherapy.

Statistical analysis of the results obtained was performed using the software package "Statistica for Windows" (version 8.0). Qualitative data were described using absolute and relative values, quantitative data are indicated in the form of median and quartiles (25%; 75%). Survival rate was assessed according to 3-year indicators, including the incidence and timing of recurrences, metastases and deaths. The survival rate of patients was studied in accordance with the Kaplan–Mayer method. A "Log rank test" was used to compare survival curves. The differences were considered statistically significant at $p < 0.05$.

RESULTS

All patients included in the study completed 3 courses of preoperative chemotherapy (100%). The toxicity of chemotherapy was 38.9%. Of the adverse events of chemotherapy, there were: grade I and II leukopenia — 11 (15.3%) and 4 (5.5%) cases, respectively, nausea/vomiting — 10 (13.9%) cases, grade I stomatitis — 3 (4.2%) cases.

When assessing the effect of chemotherapy, a partial tumor response was noted in 18 (75%) patients, stabilization in 5 (20.8%) patients, and progression in the form of an increase in the size of the primary tumor in 1 (4.2%) patient (radical surgery was subsequently performed). There were no cases of a complete radiological response of the tumor.

Surgeries in all 24 (100%) patients were performed in radical volume (R0), of which 18 (75%) were performed by laparoscopic and 6 (25%) by

open access. Combined surgeries were required in 2 (8.3%) patients and included extirpation of the uterus — 1 (4.2%) and resection of the bladder — 1 (4.2%). There were no intraoperative complications due to previous chemotherapy.

Postoperative complications were recorded in 4 (16.7%) patients (Table 2). In 1 (4.2%) case, anastomosis failure developed, which resolved conservatively against the background of a protective colostomy. Grade IIIb complication (bleeding) occurred in 1 (4.2%) patient, which required surgical hemostasis. The other postoperative complications were pneumonia (4.2%) and bladder atony (4.2%).

In assessing the therapeutic pathomorphosis (Table.3) it was found that a complete tumor response (TRGl) obtained in 1 (4.2%) patient. In addition, the minimum number of preserved tumor cells on the background of fibrosis (TRG2) was detected in 3 (12.5%) patients. The absence of signs of tumor regression (TRG5) was noted in 5 (20%) patients.

After surgical treatment, 13 (54.2%) patients received adjuvant chemotherapy.

With a median follow-up of 38 months (17–54), progression was detected in 5 (20.8%) patients: in 3 (12.5%) cases, local recurrences developed (median — 9 months; 8–11), in 4 (16.7%) cases, distant metastases to the liver, lungs and bones (median — 17 months; 11–28). It should be noted that in 2 patients with progression, a combination of local recurrences and distant metastases was noted. During the specified period of time, 2 (8.3%) patients died from progression: 1 — from local recurrence, 1 — from local recurrence and distant metastases (median — 24 months; 17–31).

The three-year overall and disease-free survival rate of patients was 91.7% and 79.2%, respectively (Fig. 1, 2).

Additionally, the disease-free 3-year survival rate of patients was analyzed depending on the degree of therapeutic pathomorphosis and the pathomorphological prevalence of the tumor process (Fig. 3–5).

With a pronounced tumor response to chemotherapy, which corresponds to TRG 1-2, the survival rate of patients was 100%. As the degree of damage to tumor tissue TRG 3, TRG 4 and TRG5 decreased, the survival rate of patients decreased to 85.7%, 75% and 60%, respectively.

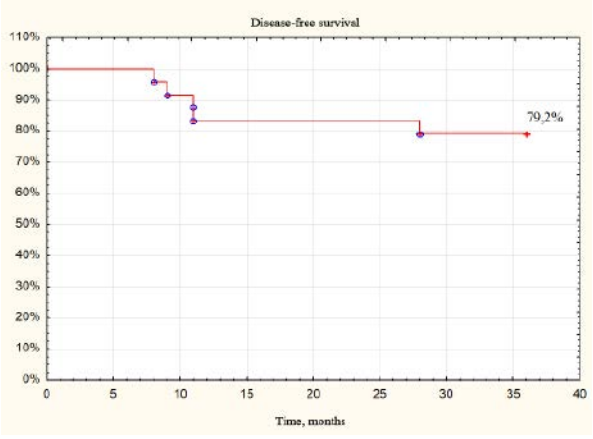

Figure 1. *3-year disease-free survival of rectal cancer patients*

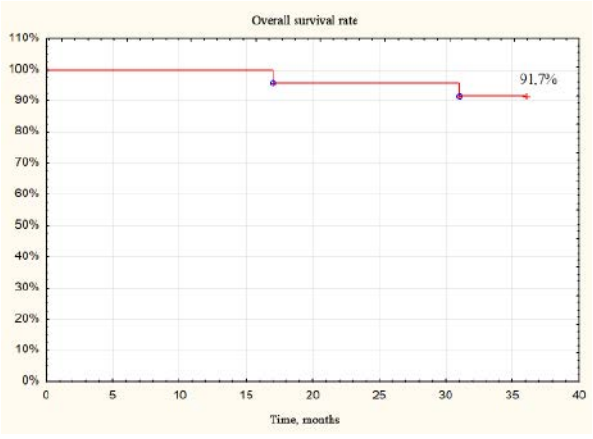

Figure 2. *3-year overall survival of rectal cancer patients*

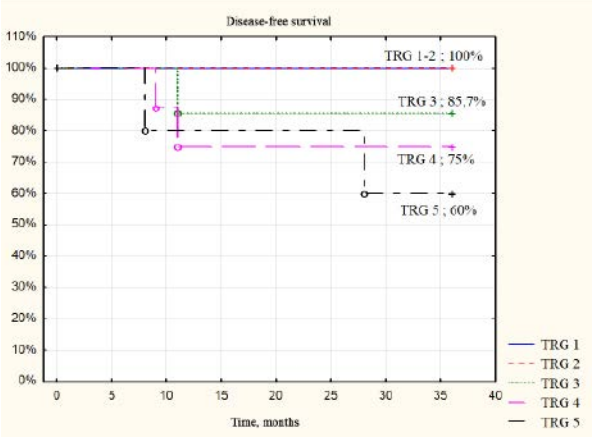

Figure 3. *3-year survival of rectal cancer patients according to the grade of therapeutic pathomorphosis*

With the prevalence of the primary tumor ypT0–3 (ypT0, *n* = 1; ypT1, *n* = 1; ypT2, *n* = 7; ypT3, *n* = 3), the disease-free 3-year survival rate of patients reached 100%. In turn, with ypT4a (*n* = 10) and ypT4b (*n* = 2), the survival rate of patients significantly decreased to 60% and 50%, respectively ($p = 0.014$). Similar results were obtained when analyzing the lymphogenic prevalence of the tumor. So, if at ypN0 (*n* = 16) the survival rate of patients was 100%, then at ypN1 (*n* = 5) and ypN2 (*n* = 3) it significantly decreased to 60% and 0% ($p = 0.0002$).

DISCUSSION

In recent years, the possibility of using preoperative chemotherapy without radiation has been widely discussed in the treatment of RC [1,8–13]. This approach is used in patients with stage II-III of the tumor process, including in the presence of unfavorable prognostic factors (sT3c–4b, N+, CRM+, extramural vascular invasion of the tumor), with lesions of the upper and middle ampullary rectum. Chemotherapy at the preoperative stage is carried out according to the regimen with oxaliplatin and fluoropyrimidines (FOLFOX 6, CAPOX), the number of courses varies in the range of 4–6, while the completion of treatment is 82.7–94.9%. The rate of complete pathomorphological response of the tumor after 4 courses of chemotherapy is at the level of 1.9–11% [9, 10], after 6 courses — 6.7–11.9% [11,12]. At the same time, with an increase in the number of chemotherapy courses from 4 to 6, there is an increase in grade III-IV adverse events from 5.1–12% [9,10,13] to 23.3–24.8% [11,12], respectively.

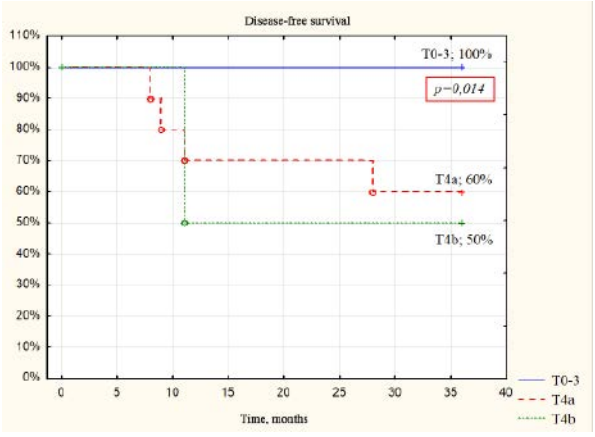

Figure 4. *3-year survival of rectal cancer patients according to the pathomorphological T-criterion*

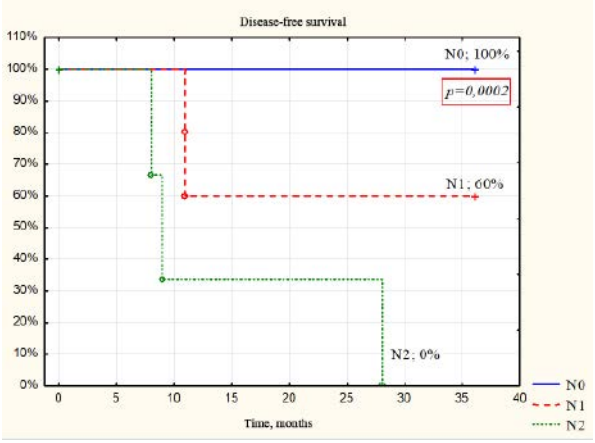

Figure 5. *3-year survival of rectal cancer patients according to the pathomorphological N-criterion*

In our study, at the preoperative stage, 3 courses of chemotherapy according to the FOLFOX 4 regimen were performed in all patients with RC (the completion of treatment was 100%). The tolerability of chemotherapy was regarded as satisfactory, no adverse events of the III–IV degree were recorded. These facts are due to the fact that fewer chemotherapy courses were used compared to other studies [9–13]. At the same time, it was found that after 3 courses of FOLFOX 4, the rate of complete tumor responses, confirmed by pathomorphological examination, was 4.2%. The results obtained by us correlate with the literature data [10,12], according to which after 4–6 courses of FOLFOX 6, the complete tumor response reaches 1.9–6.7%.

A number of studies [9–13] have shown that surgical treatment after completion of preoperative chemotherapy is carried out in 2–6 weeks. Radical surgery (R0) in patients with RC was performed in 86.5–100%. The rate of postoperative complications reaches 17.6–28.9%, including grade III-IV on the Clavien-Dindo scale in 5.8–10.5% [9–11,13], in this connection, in

3.7–5.8%, surgical treatment of the post-op complications was required.

The results of our study are generally comparable with the literature data [9–13]: surgeries were performed 4 weeks after the end of chemotherapy, and in all cases, they were performed to a radical plan (100%). At the same time, it should be noted that the level of postoperative complications was lower than the average, which is explained by fewer courses of preoperative chemotherapy. Thus, the rate of postoperative complications did not exceed 16.7%, including 1 (4.2%) grade IIIb complication (bleeding) with the need for surgical hemostasis.

As it is known, one of the main criteria for evaluating the effectiveness of treatment is the survival rate of patients. According to our study, after combined treatment using 3 courses of preoperative chemotherapy according to the FOLFOX 4 regimen, the overall and disease-free 3-year survival rate (91.7% and 79.2%, respectively) was similar to the results obtained in the study by Koizumi, M. [12], in which 6 courses of chemotherapy were conducted according to them FOLFOX 6 regimen (95.7% and 77.5%, respectively), in Deng Y.'s study [8] when using 4–6 courses of chemotherapy according to the mFOLFOX 6 regimen (90.7% and 73.5%, respectively) and in the study by A.A. Nevolskikh [10], where 4 courses of chemotherapy according to the mFOLFOX6 regimen were used (88.2% and 76.4%, respectively).

At the same time, it was shown that the incidence of local recurrences depended on the number of courses of preoperative chemotherapy. Thus, the minimum rate of locoregional recurrences of 6.7% was recorded after 6 courses of chemotherapy [12] and increased to 8.3% after 4–6 courses [8] and 11.3% after 4 courses of chemotherapy [10]. When analyzing distant metastases, there was no such dependence: the incidence of hematogenous metastases varied in a wide range — from 7.7% (after 4 courses) [10] to 16.6% (after 6 courses) [12]. In comparison with the literature data, similar results were obtained in our study — the incidence of local recurrences and distant metastases was 12.5% and 16.7%, respectively. It should be noted that the risk of disease progression and survival of patients were directly influenced by a number of factors, including the prevalence of the tumor process, the presence of negative prognostic factors and the achievement of a complete pathomorphological response of the tumor to the therapy.

Thus, based on the generalized data [1,8,11,12], the prospects for the development of combined methods of treatment of RC are currently associated with the intensification of preoperative treatment due to an increase in the number of courses of preoperative chemotherapy (due to their transfer from adjuvant treatment), the use of three-component chemotherapy regimens (5-fluorouracil, oxaliplatin, irinotecan) and combined use of chemo- and targeted therapy at the preoperative stage.

CONCLUSION

Combined treatment of upper RC patients, including preoperative chemotherapy according to the FOLFOX 4 regimen, is characterized by good tolerability with a low level of adverse events and postoperative complications, leads to a significant regression of the tumor process, confirmed by pathomorphology, which provides high rates of disease-free and overall 3-year survival, including in the presence of unfavorable prognosis factors. This approach is regarded as promising, its further development follows the path of increasing the effectiveness of preoperative antitumor drug therapy using modern cytostatics and targeted drugs.

AUTHORS CONTRIBUTION

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Writing of the manuscript: *Alexey Yu. Dobrodeev*

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