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# Neoadjuvant chemotherapy without radiation therapy for rectal cancer with negative prognosis

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**ABSTRACT** *AIM: to assess the effectiveness of neo-CT in the FOLFOX6 regimen in patients with mid- and upper rectal cancer (RC) associated with poor prognosis.*
*PATIENTS AND METHODS: fifty-two patients were included into study. All had neo-CT with subsequent surgical treatment between 2017 and 2021. Of them 94.2% had stage III and 5.8% had stage II. An extramural vascular invasion was detected by MRI in 33 (63.5%) patients. The distance between the tumor and the mesorectal fascia was ⩽ 2 mm in 17%. All patients had 4 cycles of neo-CT in FOLFOX6 regimen followed by surgery.*
*RESULTS: the compliance (⩾ 4 cycles of neo-CT) was 82.7% (n = 43). The overall toxicity rate was 35.6%. Sphincter-saving surgery was performed in 51 (98.1%) patients. Postoperative morbidity was 25.0%. Final pathology revealed stage III in 29 (55.8%) patients, stage 0 — stage II — in 22 (42.3%). In accordance with the degree of pathomorphosis (CAP, 2019), 12 (23.1%) patients showed a partial response. In one patient (1.9%) no signs of residual tumor were detected. Down staging of the T stage compared with MRI data before neo-CT was noted in 23 (44.2%) patients, N stage — in 29 (55.8%). With a mean follow-up of 31 (3-54) months, local recurrences were detected in 5 (9.6%) patients, and distant metastases in 4 (7.7%). The cumulative 3-year recurrence rate was 11.3 ± 4.8%. The three-year overall and recurrence-free survival rate was 88.2 ± 5.8% and 76.4 ± 7.4%, respectively.*
*CONCLUSION: the multimodal approach for RC with adverse prognostic factors using neo-CT in the FOLFOX6 regimen is well tolerated by patients, has a small toxicity and postoperative morbidity as well. It is necessary to develop new pathology criteria for tumor response to neo-CT.*

**KEYWORDS:** *rectal cancer, neoadjuvant chemotherapy, chemoradiotherapy, pathomorphosis*

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

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## INTRODUCTION

Rectal cancer (RC) is one of the most common tumors in the structure of oncological morbidity. Malignant rectal neoplasms affect 5.6% of the male population and 4.4% of the female population in Russia. At the same time, the proportion of RC detected in stage I–II is 51.4%, and another quarter (24.9%) accounts for tumor neoplasms detected in stage III [1].

Neoadjuvant radiation therapy (RT) or chemoradiotherapy (CRT) with further surgery is the standard approach for patients with locally advanced RC [2–4], as it allows to reduce the size of the tumor, which in turn decrease local recurrence rate and increase survival. However, RT and CRT are

accompanied by a significant number of radiation reactions and lesions, most often manifested by an increase in the incidence of genitourinary dysfunction, functional disorders after sphincter-preserving procedures, as well as an increased-postoperative morbidityrate [5,6]. It should also be noted that prolonged RT is associated with systemic chemotherapy up to 15–16 weeks [7], which can potentially negatively affect patients with a high risk of distant metastasis.

In connection with the above, approaches based on the inclusion of systemic therapy in the neoadjuvant treatment in the form of induction [8,9], consolidating [6,10], total neoadjuvant therapy [11,12], as well as only chemotherapy without radiation therapy as such, have become increasingly widespread in recent years. Carrying out neoadjuvant chemotherapy (NCT) instead of RT in RC makes it possible to avoid radiation reactions and lesion, as well as to start systemic treatment earlier, aimed not only at the primary tumor, but also at its possible micrometastases. At the same time, NCT is distinguished by better completion rates compared to adjuvant mode, and in a number of patients with postoperative morbidity and/or decompensation of concomitant diseases, adjuvant chemotherapy is in principle impossible [13–15].

The rate of complete answers, a surrogate indicator of the effectiveness of treatment, when performing NCT with oxaliplatin in combination with 5-fluoropyrimidines, varies widely from 0% to 17.8% [16–25]. In the vast majority of cases, these are data from non-randomized single-center studies. To date, there are results of only one phase III study of FOWARC, in which the results of NCT in FOLFOX6 mode were compared with standard CRT [26]. In patients in the FOLFOX6 group, the incidence of complete pathomorphological regressions was 6.5%, and in the CRT group — 14%. When comparing the recurrence-free and overall survival, as well as the incidence of local recurrences, no significant differences were found.

It should be noted that there are few completed studies in Russia on the use of NCT in the treatment of patients with RC [27,28]. Basically, speaking about this method, we are based on the data of foreign researchers. In this regard, the use of this method in the Russian population of patients is of interest from the point of view of effectiveness and tolerability. For this purpose, in the period from January 2017 to September 2021, the study of NCT effectiveness in FOLFOX6 mode in patients with cancer of the middle and upper RC with unfavorable prognosis.

## PATIENTS AND METHODS

The study included 52 patients with rectal adenocarcinomas, who underwent neoadjuvant chemotherapy (NCT) followed by surgery between 2017 and September 2021 (Table 1).

To assess the prevalence of the tumor, we used magnetic resonance imaging (MRI), according to which we assessed the size of the neoplasm, the distance from the anal verge to the lower pole of the tumor, the depth of invasion, the presence of extramural vascular invasion (EVI), as well as the distance from the tumor to the potential lateral resection margins (LRM), represented by rectal fascia propria. The study included patients who, according to the results of the check-up, revealed one or more negative prognostic factors: the presence of EVI, affected regional lymph nodes (cN1-2) or involvement of LRM (distance to the mesorectal fascia ⩽ 2 mm) with the upper rectum.

The majority of patients had clinical stage III (IIIB — 59.6%, IIIC — 34.6%); 3 (5.8%) patients had clinical stage IIA. Clinical invasion of the tumor into adipose tissue without signs of lesion to adjacent organs was observed in 67.3% of patients ($n$ = 35); invasion of the visceral peritoneum, spread to other organs and structures were detected in 32.7% ($n$ = 17) of patients. The regional lymph nodes involvement was found in 94.2% of patients ($n$ = 49) and was absent in 3 (5.8%) patients.

According to MRI, 33 (63.5%) patients were found to have EVI. The distance from the tumor to the mesorectal fascia ⩽ 2 mm was detected in 17 (32.7%) patients.

All the patients were scheduled to undergo neoadjuvant chemotherapy in FOLFOX6 mode (a two-hour infusion of oxaliplatin 85 mg/m$^2$ on the first day, then leucovorin 400 mg/m$^2$ for two hours, followed by a bolus injection of 400 mg/m$^2$ of 5-fluorouracil, and a 46-hour infusion of 2400 mg/m$^2$ of 5-fluorouracil) in an amount of 4 cycles. The

**Table 1.** *Clinical characteristics of patients (n = 52)*

| Parameters | Data | % |
|---|---|---|
| Gender | | |
| Males | 21 | 40.4 |
| Females | 31 | 59.6 |
| Median age, years | 58 (42–71) | |
| Median body mass index, kg/m$^2$ | 29.2 (18–50) | |
| Distance from the anal verge to the lower pole of the tumor, cm | 10.5 (4–15) | |
| < 6 | 1 | 1.9 |
| 6–10 | 26 | 50.0 |
| 11–15 | 22 | 42.3 |
| > 15 | 3 | 5.8 |
| Median tumor extent, cm | 6 (1.3–13) | |
| MRI EVI | | |
| Yes | 33 | 63.5 |
| No | 19 | 36.5 |
| MRI lateral resection margins | | |
| Positive | 17 | 32.7 |
| Negative | 35 | 67.3 |
| Clinical stage (cTNM) | | |
| II | 3 | 5.8 |
| IIIB | 31 | 59.6 |
| IIIC | 18 | 34.6 |
| Tumor invasion depth (cT) | | |
| T3 | 35 | 67.3 |
| T4a | 10 | 19.2 |
| T4b | 7 | 13.5 |
| Lymph nodes involvement (cN) | | |
| N0 | 3 | 5.8 |
| N1 | 22 | 42.3 |
| N2 | 27 | 51.9 |
| Tumor differentiation grade | | |
| G1 | 21 | 40.4 |
| G2 | 27 | 51.9 |
| G3 | 4 | 7.7 |

**Table 2.** *Toxicities according to CTC AE scoring system (n = 45)*

| Toxicity | Grade 1 | Grade 2 | Grade 3 | Grade 4 | Total |
|---|---|---|---|---|---|
| **Hematological** | | | | | |
| Anemia | – | 2 (4.4%) | – | – | 2 (4.4%) |
| Neutropenia | – | 3 (6.6%) | 2 (4.4%) | 1 (2.2%) | 6 (13.3%) |
| Leukopenia | – | 2 (4.4%) | – | – | 2 (4.4%) |
| Thrombocytopenia | – | 1 (2.2%) | – | – | 1 (2.2%) |
| **Non-hematological** | | | | | |
| Hepatotoxicity | – | 1 (2.2%) | – | – | 1 (2.2%) |
| Nephrotoxicity | – | 2 (4.4%) | – | – | 2 (4.4%) |
| Weightloss | 2 (4.4%) | – | – | – | 2 (4.4%) |
| Intestinal obstruction | – | 1 (2.2%) | – | 1 (2.2%) | 2 (4.4%) |
| Diarrhea | 1 (2.2%) | – | – | – | 1 (2.2%) |
| Nausea | 1 (2.2%) | – | – | – | 1 (2.2%) |
| Impaired glucose tolerance | – | 1 (2.2%) | – | – | 1 (2.2%) |
| Polyneuropathy | – | 1 (2.2%) | – | – | 1 (2.2%) |
| Pneumothorax | – | – | 1 (2.2%) | – | 1 (2.2%) |
| **Total morbidity** | **4 (8.9%)** | **14 (31.1%)** | **3 (6.6%)** | **2 (4.4%)** | **–** |
| **Total patients with morbidity** | **4 (8.9%)** | **11 (24.4%)** | **3 (6.6%)** | **2 (4.4%)** | **–** |

toxicity assessment was carried out according to the criteria of the generally accepted CTC AE scale (version 5.0) [29].

In 3–4 weeks after the completion of chemotherapy, all the patients underwent a control MRI of the grade of tumor regression. The surgery was performed in 4–6 weeks after completion of the neoadjuvant treatment.

Biomedical packages Prism 3.1 and In Stat (Graph Pad Software, Inc., San Diego, USA) were used for statistical processing. The evidence level of the differences between the indicators was assessed using the Pearson $\chi^2$-test. The differences were considered significant at $p < 0.05$. The survival rate of the patients was analyzed using the Kaplan-Meier test. A logarithmic rank test was used to compare the survival curves. The 3-year survival rate was assessed. When calculating the overall survival rate, the death of a patient was considered an 'event'. When calculating recurrence-free survival rate, the 'event' was considered a local recurrence, distant metastasis or death of the patient from any of the causes.

## RESULTS

All the patients underwent NCT in 1–8 cycles (median — 4). In 6 cases, more than 4 cycles were used, which was associated with a good reaction to chemotherapy.

In two cases, there were deviations from the chemotherapy mode. The patients received neoadjuvant treatment in XELOX mode, one of the components of which is also oxaliplatin. In one patient, due to the inability to continue chemotherapy through central venous access, after the second course, FOLFOX6 mode was changed to XELOX.

Chemotherapy in full (≥ 4 cycles) was completed in 43 (82.7%) patients. In 9 (17.3%) patients, due to toxic reactions, a smaller number (1–3) of cycles of NCT were performed.

In total, toxic reactions or morbidity in the process of NCT were registered in 16 (35.6%) of 45 patients (Table 2).

In 7 cases, a reliable assessment of toxicity was not possible. Most often, in 31.1% of cases

**Table 3.** *Surgery results (n = 52)*

| Parameter | Data | % |
|---|---|---|
| Operation time (median), minutes | 225 (90–450) | |
| Median blood loss, ml | 100 (10–2000) | |
| Median postoperative hospital stay, days | 7 (4–42) | |
| Surgical access | | |
| Laparoscopic | 41 | 78.8% |
| Open | 11 | 21.2% |
| Surgery type | | |
| Anterior resection | 48 | 92.3% |
| Hartmann's procedure | 3 | 5.8% |
| APE | 1 | 1.9% |
| Surgery volume | | |
| Standard | 36 | 69.2% |
| Multivisceral | 16 | 30.8% |
| IMA ligature level | | |
| High IMA ligation | 27 | 51.9% |
| more distal than LCA | 22 | 42.3% |
| no data | 3 | 5.8% |
| Mobilization of the splenic bend | | |
| performed | 28 | 53.8% |
| did not perform | 24 | 46.2% |
| Morbidityas per Clavien-Dindo classification | | |
| Absent | 39 | 75.0% |
| I grade | 6 | 11.5% |
| II grade | 4 | 7.7% |
| III grade | 1 | 1.9% |
| IV grade | 2 | 3.8% |

*Note: ARR — anterior rectal resection; APE — abdominal-perineal excision; IMA — inferior mesenteric artery; LCA — left colon artery; n.d. — no data*

(*n* = 14), toxic reactions of the 2nd grade were detected. Grade 3–4 toxicity was observed in 5 (11.1%) patients and was most often represented by neutropenia. Morbidity unrelated to chemotherapy, but affecting the further continuation of the treatment, included intestinal obstruction in a patient with a tumor of the middle rectum, who underwent emergency surgery in the volume of transversostomy, as well as pneumothorax when placing a subclavian catheter before the 3rd cycle of NCT in another case.

According to the results of the control MRI after NCT, a decrease in the stage of the tumor process compared with the clinical one was noted in 15 (28.8%) patients. In these patients, there was a reduction in the extent of the tumor, a decrease in the depth of invasion, the appearance of fibrosis sites and reduction of diffusion restriction sites,

**Table 4.** *The relationship between clinical and pathological staging of the study patients (n = 52)*

| Clinical category | Pathomorphological category | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | ypT0 | ypT1 | ypT2 | ypT3 | ypT4a | ypT4b | ypN0 | ypN1 | ypN2 |
| cT3 (*n* = 35) | 1 | 1 | 9 | **21** | 2 | 1 | | | |
| cT4a (*n* = 10) | | | | 8 | **1** | 1 | | | |
| cT4b (*n* = 7) | | | | 4 | 1 | **2** | | | |
| cN0 (*n* = 3) | | | | | | | **2** | | 1 |
| cN1 (*n* = 22) | | | | | | | 9 | **11** | 2 |
| cN2 (*n* = 27) | | | | | | | 11 | 9 | **7** |
| Total | 1 | 1 | 9 | 33 | 4 | 4 | 22 | 20 | 10 |

as well as a decrease in the number of potentially affected lymph nodes. Progression of the disease was observed in 7 (13.5%) cases. In the remaining patients (*n* = 29; 55.8%), no changes were noted when comparing MRI before and after the treatment. With regard to the remaining factors of negative prognosis, it should be noted that EVI was established in 30 (57.7%) patients, and mesorectal fascia involvement (CRB ⩽ 2 mm) was noted in 15 (28.8%) patients.

All patients included in the study underwent surgery in 3–20 (median 5) weeks after the completion of NCT (Table 3).

In the overwhelming majority of cases (78.8%), laparoscopic approach was used. The operation time ranged from 90 to 450 minutes (median — 225). The mean blood loss was 100 ml (10–2,000). The mean postoperative hospital stay was 7 (4–42) days.

The surgery volume depended on the depth of the tumor invasion, the presence of affected lymph nodes, the growth of the tumor into the visceral peritoneum and surrounding organs, as well as the distance from the anal verge to the lower pole of the tumor. In 51 (98.1%) cases, procedures were sphincter-preserving: in 48 (92.3%) cases, anterior resections were performed, and in 3 (5.8%) patients — Hartmann's procedure due to intestinal obstruction.

Multivisceral procedures were performed in 16 (30.8%) patients, while resections of two or more organs were performed in 10 (19.2%) cases. Most often, hysterectomy was performed in 9 (17.3%) cases, resection of the small intestine in 5 (9.6%) cases, resection of the bladder in 4 (7.7%) cases; and in isolated cases, appendectomy, tubovariectomy, colorectal resection, seminal vesicles, ureter, cervix stump were removed. Also, two patients suspected of having distant metastases, according to the control check-up and intraoperative picture, underwent simultaneous procedures, including resection of the tenth segment of the right lung in one patient, the sixth and eighth segments of the liver in the second. In 83.3% of patients (40 out of 48), a preventive colostomy (90%) or ileostomy (10%) was done.

Postoperative morbidity developed in 13 (25.0%) patients: in most cases, grade I and II according to Clavien-Dindo classification. In 3 (5.8%) patients, morbidity required re-operations. No mortality occurred.

Pathomorphology of the removed specimens showed stage III was most often — in 29 (55.8%) patients, stage 0 — II were detected in 22 (42.3%) patients. In one case, in a patient with simultaneous resection of liver segments, according to histology confirmed the presence of distant metastases of stage IV.

The pathomorphosis was evaluated in accordance with the recommendations of the American Society of Pathomorphologists [CAP 2019]. In 3 (5.8%) cases, it was not possible. In 36 (69.2%) patients, grade 3 pathomorphosis was detected, which corresponded to the absence of a tumor reaction to the treatment. In 12 (23.1%) cases, a minimal tumor reaction (grade 2 pathomorphosis) was registered. In none of the cases was detected grade1 of pathomorphosis, the criteria of which is the predominance of fibrous changes over tumor. Only one (1.9%) patient with clinical stage III

after 4 cycles of NCT did not have a residual tumor during a pathomorphology, which allowed us to confirm a 0-gradepathomorphosis.

A decrease in the category of the extent of the tumor by pathomorphology compared with the data of MRI before NCT was noted in 38 (73.1%) patients. A decrease in category T was observed in 23 (44.2%) patients (Table 4), category N — in 29 (55.8%) patients. At the same time, complete regression of lymph nodes was found in 38.5% (20 patients), partial (from N2 to N1) — in 17.3% (9 patients).

Regression of the tumor extent to ypT0-T2 (stage 0-I) was found in 7 (13.5%) patients.

An increase in the category of the tumor extent compared with the data of MRI before NCT was noted in 6 (11.5%) patients: in 3 (5.8%) patients, an increase in category T was noted, in 3 (5.8%) — category N, a joint increase in categories T and N was not found. In 8 (15.4%) cases, stabilization of the tumor process was noted.

At the same time, in 2 (3.8%) cases, multidirectional changes were observed: during pathomorphology, an increase in the depth of tumor invasion with regression of lymph nodes was noted, which was not verified according to the MRI due to the limit of the diagnostic capability of the method.

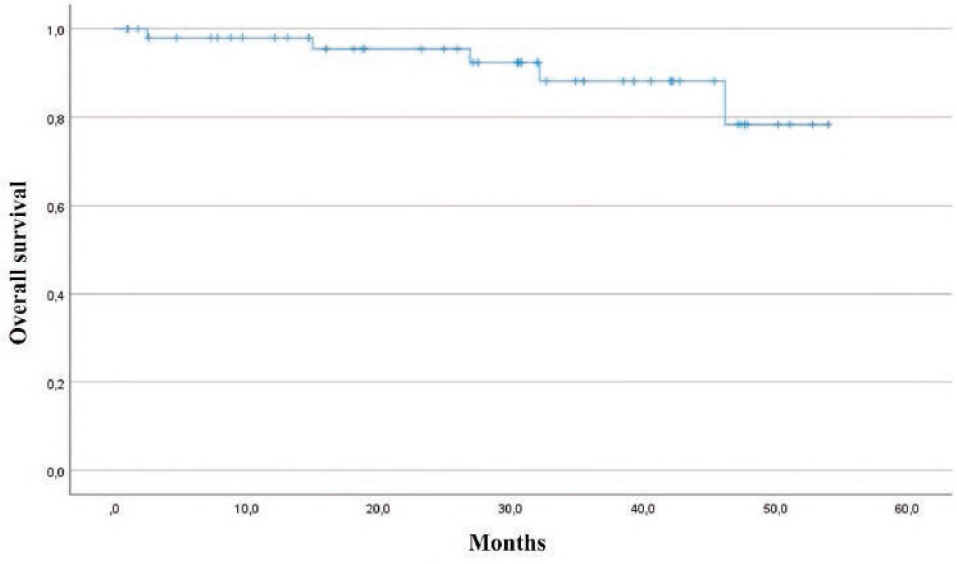


**Figure 1.** *Three-year overall survival*

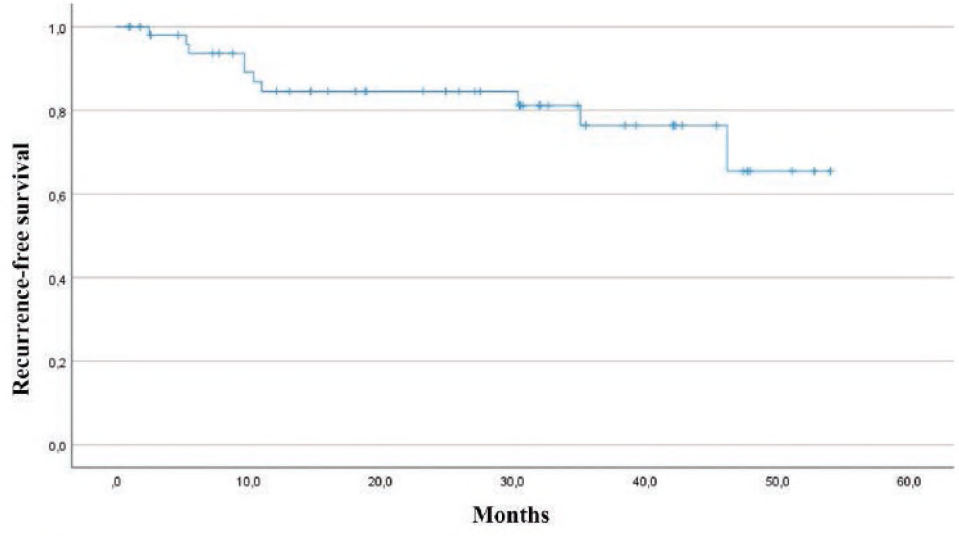


**Figure 2.** *Three-year recurrence-free survival*

**Table 5.** *Prospective clinical research on neoadjuvant two-component chemotherapy based on oxaliplatin drugs in patients with rectal cancer*

| Author, year | N* | Clinical stage | Primary endpoint | Therapy modes | Number of cycles | Resectability | R0-resections | ypCR | LR | DM | CT | Survival |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| ALGizawy S.M. et al. 2015 [18] | 45 | II — 33%<br>III — 67%<br>(exceptT4b) | no data | FOLFOX6 | 6 | 100% | 100% | 17.8% | 8.8% | 17.7% | no data | 3-year OS 80.8%<br>3-year RS 67.9%/ |
| Ueki T. et al. 2016 [17] | 29 | II — 38%<br>III — 62% | R0-resections | XELOX | 3 | 100% | 96.5% | 10.3% | no data | no data | 82.8% | no data |
| Kioke J. et al. 2017 [19] | 52 | II — 20.8%<br>III — 79.2% | pCR, pPR | FOLFOX6 | 4–6 | 98% | 91% | 11.9% | no data | no data | 59.6% | no data |
| Koizumi M. et al. 2018 [31] | 30 | II — 20%<br>III — 80% | R0-resections | FOLFOX6 | 6 | 100% | 100% | 6.7% | 6.7% | 16.6% | no data | 3-year OS 95.7%<br>3-year RS 77.5% |
| Nishimura J. et al. 2018 [21] | 42<br>(45) | II — 57.1%<br>III — 42.9% | 2-year RS | CAPOX | 4 | 91% | 100% | 7.3% | 9.7% | 31.7% | 85.4% | 2-year OS 92.7%<br>2-year RS 71.6% |
| Okuyama T. et al. 2018 [7] | 27<br>(55) | II-III stage | 3-year RS | SOX<br>FOLFOX6<br>XELOX | 2–9 | 100% | no data | 3.7% | 7.4% | 7.4% | 33% | 4-year OS 96.3%<br>3-year RS 85.2% |
| Quezada-Diaz F. et al. 2018 [13] | 12<br>(176) | II-III stage | no data | FOLFOX6<br>CAPOX<br>FLOX | 8<br>5<br>no data | 100% | no data | 25% | no data | no data | no data | no data |
| Cienfuegos J.A. et al. 2019 [32] | 27 | II — 29.6%<br>III — 70.4% | R0-resections<br>pCR, pPR,<br>OS, RS | FOLFOX6 | 6–8 | 100% | 100% | 14.8% | 3,7%<br>3.7% | 11% | no data | 5-year OS 85.0%<br>5-year RS 84.7% |
| Ichikawa N. et al. 2019 [23] | 38<br>(41) | II — 21.1%<br>III — 78.9% | The rate of postoperative morbidity | FOLFOX6 | 4 | 100% | 100% | 0% | no data | no data | no data | no data |
| Shiraishi T. et al. 2019 [39] | 102 | II — 51%<br>III — 49% | no data | FOLFOX — 93%<br>CAPOX — 7% | no data | 100% | no data | no data | 19.6% | 20.6% | no data | 5-year OS 87.0%<br>5-year RS 63.4% |
| Deng Y. et al. 2019 [26] | 163<br>(495) | II — 27.9%<br>III — 72.1% | 3-year RS | FOLFOX6 | 4–6 | 93.3% | no data | 6.5% | 8.3% | no data | no data | 3-year OS 90.7%<br>3-year RS 73.5% |
| Miwa K. et al. 2021[33] | 110 | FOLFOX6<br>II — 32%<br>III — 68%<br>SOX:<br>II — 37.7%<br>III — 62.3% | 3-year RS | FOLFOX6 — 49%<br>SOX — 51% | 6 | 93.6% | 96%<br>100% | 10.4%<br>11.3% | no data | no data | 79,2%<br>79.2%<br>83.0% | 3-year OS 91.8%<br>3-year RS 73.4%<br>3-year OS 92.3%<br>3-year RS 69.4% |
| Our own data | 52 | II — 4%<br>III — 96% | 3-year RS | FOLFOX6<br>XELOX | 4 | 100% | 86.5% | 2% | 9.6% | 7.7% | 53.8% | 3-year OS 88.2%<br>3-year RS 76.4% |

*Note: * The number of patients who received NCT, figures in parentheses — the total number of patients in the study; pCR — complete pathomorphological reaction; pPR — partial pathomorphological reaction; LR — local recurrences; DM — distant metastases; OS — overall survival; RS — recurrence-free survival*

Special staining methods were not used to detect vascular invasion of the tumor. During routine pathomorphology, vascular invasion of the tumor was detected in 4 (7.7%) patients. Perineural invasion was detected in 9 (17.3%) cases. Involvement of LRM was detected in 6 (11.5%) cases.

Subsequently, 28 (53.8%) patients received adjuvant chemotherapy (chemoradiotherapy).

With a median follow-up of 31 (3–54) months, local recurrences were detected in 5 (9.6%) patients (median — 10 months; 5–11), distant metastases — in 4 (7.7%) patients (median — 35 months). 5 (9.6%) patients died: 3 — due to local recurrence of the disease, 1 — due to distant metastasis, 1 — due to another disease.

The overall 3-year survival rate (Fig. 1) was 88.2 ± 5.8%, the recurrence-free 3-year survival rate (Fig. 2) was 76.4 ± 7.4%. The cumulative 3-year rate of local recurrences was 11.3 ± 4.8%.

## DISCUSSION

As a result of improving the surgical technique and methods of preoperative radiation (chemoradiotherapy) treatment of patients with RC, the rate of local recurrences has significantly decreased over the past 20–30 years [5]. Currently, one of the key issues in the treatment of patients with locally advanced RC and the presence of unfavorable prognosis (invasion depth ≥ sT3c, the presence of affected lymph nodes, mrLRM + , EVI + ) remains the prevention of distant metastases that occur during follow-up in about 1/3 of radically operated patients. The use of the standard treatment in the volume of preoperative CRT is associated with an increase in the interval between primary diagnosis and the beginning of systemic drug therapy, which this category of patients so much needs. Adjuvant chemotherapy, which is a standard method of preventing distant metastasis, is not possible in all patients who have received surgical treatment, and is characterized by a low completion rate [30]. At the same time, there are no reliable data that adjuvant chemotherapy in patients with locally advanced tumors who have received CRT contributes to an increase in recurrence-free survival. In this regard, more and more researchers are using NCT in patients with unfavorable prognostic factors instead of CRT [9,11,17,19,20,23].

Two-component oxaliplatin-containing modes are the most studied in the treatment of patients with non-metastatic RC (Table 5).

Despite the differences in the treatment modes used, the number of cycles, the primary endpoints of the studies, a small number of patients and the non-randomized nature of the studies, most authors note the good tolerability of NCT, the absence of influence on the incidence of postoperative morbidity and generally satisfactory results comparable to the effects of CRT. In most cases, the study included patients with resectable forms of stage II-III RC, while the percentage of patients with stage III varied widely (43–80%). However, some authors included patients with T4a and T4b disease categories [17,18,19,31,32,33]. It should be noted that in our study, the number of patients whose cT4 category of tumor was detected during MRI before the treatment was 32.7%, including 13.5% who had cT4b category.

In some studies, the assessment of toxic reactions and morbidity in patients during NCT was carried out. Among them is the study by Miwa et al. [33], according to which the overall rate of toxic reactions was higher in patients in the FOLFOX6 group and amounted to 34.2%. Of these, thrombocytopenia (18.9%) and neutropenia (13.2%) were the most common. It should be noted that in our study, morbidity was present in 35.6% of patients, among whom 11% had morbidity of the third grade or higher. The lower rate of toxic reactions can be explained by the smaller number of PCT cycles in our study — the median was 4 cycles (1–8).

As a rule, the completeness of NCT is higher compared to postoperative [30]. According to Miwa et al.'s studies [33], despite the high rate of toxic reactions, the completeness of NCT was 96%. Koizumi et al. provided similar data on the completion of chemotherapy in their study [31] — 93%. In our study, the completeness of ACT was slightly lower and amounted to 82.7%. It should be noted that the reasons for the incompleteness of the treatment in most cases were due not to the toxicity of chemotherapy as such, but to other factors (obstruction, pneumothorax, etc.), and it is difficult to draw any conclusions based on this indicator.

Postoperative morbidity in patients, who under went NCT, according to the literature, is 18.6% — 33.3% [13,17,31,33]. The results of our study are comparable with them, so the overall morbidity rate was 25%, of which morbidity of the III-IV grade according to the Clavien-Dindo classification were noted in 5.8%.

The incidence of R0 resections in the study was 86.5%, which is lower than in the data of other authors (91% -100%). It should be noted that in most cases, the involvement of LRM by pathomorphology was due to adjacent lymph nodes, in which the prognosis is better than when the resection margins are involved due to the primary tumor [34,35]. It should also be noted that most of these patients had high rectal tumors, in which CRT is associated with an increased risk of radiation lesion.

One of the main criteria for evaluating the effectiveness of NCT is the rate of complete pathomorphological reactions, which ranged widely from 0% in Ichikawa, N. et al.'s study [23], when using 4 cycles of chemotherapy in FOLFOX6 mode, up to 17.8% in the study by ALGizawy S.M. et al. [18], in which 6 cycles of NCT were used in the same mode. A common disadvantage of all studies on NCT is a small number of cases, the lack of uniform criteria for inclusion of patients, which does not allow us to draw any deep conclusions. If we rely on the data of studies with a total number of patients of 110 [33] and 165 [26], the authors obtained complete pathomorphological regressions in 10.4% and 6.5% of cases, respectively. In both studies, the most common FOLFOX6 chemotherapy mode was used (4–6 cycles).

It should be noted that in the study, a complete pathomorphological reaction was achieved only in 1.9% of cases, while 11.5% of patients showed an increase in the tumor category compared to clinical data, which in our opinion may be due to the insufficient effect of NCT in the amount of 4 cycles. Assessing the incidence of cases in which the tumor category increased after chemotherapy, it is also impossible to exclude such a factor as underestimating the extent of the tumor process, which may be due to the imperfection of the MRI method. However, according to Ichikawa, N. et al. [23], performing NCT in more than 4 cycles in patients who do not respond to the treatment can lead to tumor progression. Neoadjuvant chemotherapy in such patients seems to be a useless option, only increasing the interval between primary staging and surgery. Apparently, when planning more than 4 cycles of NCT in patients with prognostically unfavorable RC, it is necessary to conduct a control check-up every 4 cycles to exclude non-responding patients.

The incidence of local recurrences after NCT using oxaliplatin-containing modes (FOLFOX, XELOX, CAPOX) varies widely from 7.1% to 17.4%, and largely depends on the criteria for inclusion of patients in the study, but is generally comparable with the results of the treatment of patients receiving preoperative CRT. In the study, the cumulative 3-year rate of local recurrences with a median follow–up of 30.6 months was 11.3% (5 out of 52 patients), which from our point of view is a satisfactory indicator, taking into account the contingent of the patients (stage III — 94.2%, T4 — 32.7%). When discussing the possible advantages of standard methods of treatment in such patients, it should also be taken into account the fact that in most cases these were patients with upperrectal cancer, in which the benefits of radiation or CRT are not so obvious, and the risks of radiation lesion from normal tissues are quite high.

In many studies devoted to NCT, as the primary endpoint authors use such a criterion as recurrence-free survival, which is somehow associated with a decrease in distant metastasis rate. Thus, the 3-year recurrence-free survival rate according to a number of studies varied from 67.9% to 85.2%, while distant metastases rate also varied widely — 7.4–31.7%. In the research by Deng, Y. et al. [26], Miwa, K. et al. [33], including the largest number of patients with NCT, the 3-year recurrence-free survival rate was identical — 73.5% and 73.4%, respectively. In the study this indicator was 76.4%, and distant metastases rate was 7.7%. At the same time, it should be noted that the majority of patients had unfavorable factors of distant metastasis: 94.2% of patients had clinical stage III, 32.7% had tumor invasion into adjacent organs or visceral peritoneum. Such a good result in patients with an unfavorable prognosis may be due to both the good effect of NCT on micrometastases and insufficient follow-up periods of patients: median 30.6 (1–54) months.

Currently, we have data from only one randomized multicenter phase III study, in which the results of NCT in FOLFOX6 mode were compared with standard methods [26,36]. The study included patients with clinical stages II-III, randomized into three groups: radiation therapy in combination with chemotherapy in de Gramond mode ($n$ = 158), radiation therapy in combination with chemotherapy in FOLFOX6 mode ($n$ = 162), and only NCT in FOLFOX6 mode in the amount of 6 cycles ($n$ = 163). The greatest number of toxic reactions was registered in the group where radiation therapy was used in combination with chemotherapy in the FOLFOX6 mode, the rate of toxic reactions of grade III-IV reached 16.5% for neutropenia and up to 14.5% for diarrhea. After the completion of the preoperative stage of the treatment, all the patients underwent surgery followed by adjuvant chemotherapy in FOLFOX6 mode (6 cycles). A complete pathomorphological reaction was achieved in 14% of the patients who received radiation therapy in combination with monochemotherapy in de Gramond mode, 27.5% of the patients after radiation therapy in combination with FOLFOX6 mode, and 6.5% of the patients who received only chemotherapy [36]. With a median follow-up of 45.2 months, the 3-year overall and recurrence-free survival rates were 91.3% and 72.9%, 89.1% and 77.2%, 90.7% and 73.5%, respectively [26]. There were no significant differences in the rate of local and distant recurrences (29.1%, 24.1%, and 28.2%). Within the framework of this study, functional disorders were assessed in the group of patients after sphincter-preserving procedures, in whom no disease progression was detected during follow-up. Incontinence of gas ($p$ = 0.006), liquid ($p$ < 0.001) and solid ($p$ < 0.001) feces, as well as night incontinence ($p$ = 0.001) were significantly more common in the patients who underwent CRT at the neoadjuvant stage. The number of patients with an average score on the Wexner scale of over 8 in the group of patients with NCT was 18% (16/89), in the group of patients after CRT with FOLFOX6 — 35.7% (25/70), and in the group of patients after CRT with chemotherapy in de Gramond mode — 41% (25/61); the differences are significant ($p$ = 0.005).

It should be noted that the currently available pathomorphological methods for assessing the grade of tumor reaction are imperfect for patients after NCT. This is due to the peculiarities of the systemic effect of NCT on tumor and micrometastases. As a rule, in such patients, the decrease in category T compared to the initial one is less pronounced than category N. Patients who received NCT in comparison with patients who received chemoradiotherapy also have no pronounced fibrous tissue changes. So, in the study by Sakuyama N. et al. [37], when assessing the tumor reaction in the groups with NCT and CRT, a decrease in category T compared to the initial one was found in 25% and 47.7% of cases, respectively, and category N — in 59.1% and 20.5%, respectively ($p$ < 0.05). Grade III fibrotic changes were observed in 6.8% and 59.1% of patients, respectively ($p$ < 0.05). Thus, the traditional scales for assessing the tumor reaction (Mandard, Dworak, CAP, Rayn, Lavnikova, and others), based on determining the ratio of tumor and fibrous changes in the specimen, are ineffective in cases of NCT use.

Discussing further prospects for the use of NCT in the treatment of patients with prognostically unfavorable RC, it is necessary to consider such options as increasing the number of cycles of NCT, the use of three-component modes, as well as a combination of NCT and targeted therapy.

To date, there are data from one prospective phase II study by Zhang, J. et al. [38], in which the use of 4–6 cycles of NCT in the mFOLFOXIRI mode in 101 patients with locally advanced RC (stage III — 85% of patients, cT4b — 21%, mrtCRB + — 31%) allowed to achieve complete therapeutic pathomorphosis in 21% of patients, and tumor regression to stage 0-I in 47% of cases.

## CONCLUSION

Thus, combined treatment using NCT in FOLFOX6 mode is satisfactorily tolerated by patients, is accompanied by a small number of toxic reactions and postoperative morbidity, and is a promising method of treating patients with prognostically unfavorable RC. The 3-year results of treatment of patients are comparable with the results of CRT followed by surgery.

According to the pathomorphological study, 73% of patients showed a decrease in the tumor

category compared to the MRI data before treatment, but this was not reflected in the extent of pathomorphosis, which requires further study, and in the future, the development of other more effective criteria for evaluating the tumor reaction to NCT.

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