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Effectiveness of the total neoadjuvant therapy in rectal cancer treatment. Results of the randomized trial

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ABSTRACT *AIM: to assess effectiveness of total neoadjuvant therapy (TNT) for patients with rectal carcinoma.*
PATIENTS AND METHODS: patients with histologically proven rectal carcinoma were randomly assigned in two groups: in the TNT group after the neoadjuvant CRT 50–54 Gy with capecitabine 3 consolidation courses of XELOX were done, in the CTR group — conventional neoadjuvant CRT 50–54 Gy with capecitabine. At the end of the treatment, effect was assessed by MRI using the mrTRG scale. For patients with a full clinical response, who have refused surgery, «watch&wait» approach was used. For others effect of neoadjuvant therapy was evaluated by pathomorphology using the Ryan scale. The primary endpoint of study was the complete response rate (clinical and pathomorphological). Secondary endpoints of study: frequency and structure of intraoperative and postoperative complications, the rate of grade 3–4 toxicity of radiotherapy and chemotherapy, R0-resection rates. The study was registered on the ClinicalTrials.gov (NCT04747951).
RESULTS: between October 2020 and October 2023, 183 patients were included in the randomized study: 91 patients in the TNT group and 92 patients in the CRT group. At median (Q1, Q3) follow-up period 24 (14; 28) months, complete clinical response occurred in 23% (14/60) of TNT patients and in 7% (5/71) of THL patients (p = 0.008). The pCR rate was 20% (9/45) in the TNT group and 8% (5/66) in the CRT group (p = 0.05). The frequency of development of toxic reactions of degree 3-4, the rate and structure of intra- and postoperative complications, as well as the rate of R0 resection of the group did not differ significantly. The total rate of Grade 3–4 toxicity, rate of intra- and postoperative complications, R0-resections rate did not differ between two groups.
CONCLUSION: preliminary results of a randomized study demonstrated the effectiveness and safety of total neoadjuvant therapy in rectal cancer treatment.

KEYWORDS: *rectal carcinoma, neoadjuvant therapy, total neoadjuvant therapy*

CONFLICT OF INTERESTS: *The authors declare no conflicts of interest*

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INTRODUCTION

Combined treatment is the standard for patients with middle and low rectal cancer stage II-III with a compromised lateral resection margin [1]. The use of this approach reduced the incidence of local recurrences down to 3–5%; however, it did not lead to an increase in overall survival. The leading cause of death in this category of patients is not locoregional recurrence, but distant metastases [2,3]. The systemic chemotherapy in an adjuvant mode in this cohort increases survival. However, its effectiveness is less than in patients with colon cancer. The need for chemoradiotherapy in neoadjuvant mode in patients with rectal cancer affects the tolerability and compliance of adjuvant chemotherapy; and therefore, no more than 70% of patients receive the planned systemic treatment [4,5]. The consolidating or induction chemotherapy in addition to standard CRT in the mode of total neoadjuvant therapy (TNT) is promising. According to the literature, this approach is not only accompanied by better tolerability, but

also increases the chance of obtaining a complete pathomorphological response, which is a favorable prognostic sign in relation to the overall survival [6,7]. Another advantage of TNT is an increase of complete clinical regression rate and possibility of the 'watch-and-wait' approach.

This article is devoted to the results of a randomized trial aimed at analyzing the effectiveness of total neoadjuvant therapy in the treatment of patients with rectal cancer.

PATIENTS AND METHODS

In the period from October 2020 to June 2023, a prospective, single-center, randomized study. The hypothesis of the study is the combination of prolonged chemoradiotherapy with a course of consolidating chemotherapy in the mode of total neoadjuvant therapy increases the rate of complete rectal tumor responses, compared with standard prolonged CRT.

Inclusion criteria:

- signed voluntary informed consent to participate in the study;
- histologically confirmed adenocarcinoma of the middle (cT2-T4N1-2M0) and low rectal cancer (cT2-4N0-2M0);
- ECOG0 scale is 2 points.

Exclusion criteria:

- age under 18 and over 75 years old;
- recurrence of rectal cancer;
- the presence of a synchronous primary multiple tumor of a different sites;
- previous radiation therapy for pelvic organs;
- pregnancy;
- lactation;
- the presence of distant metastases;
- the presence of concomitant diseases in the decompensation stage.

The primary point of the study is the incidence of complete tumor responses (clinical and pathomorphological).

Secondary points of the study are the incidence and structure of intra- and postoperative complications according to the Clavien-Dindo classification, the morbidity rate of radiation therapy as per the RTOG scale and chemotherapy as per the NCI-CTC toxicity scale, the rate of R0 resections. The estimated sample size with a study power of 80% and 0.5% CI was 146 patients in each group.

Complaints and history of the disease were collected at the outpatient stage. The diagnosis was established on the basis of clinical, laboratory and instrumental data, which included proctoscopy and colonoscopy with biopsy. Magnetic resonance imaging (MRI) was used to stage rectal cancer, as well as to study the effect of neoadjuvant therapy using the mrTRG scale [8]. To diagnose distant metastases, multi-spiral computed tomography (CT) of the chest and abdomen with intravenous contrast and/or MRI of the abdominal cavity with intravenous contrast were used.

After receiving voluntary informed consent, each patient who met the inclusion criteria was assigned an individual randomization number using the random number sequence generator of the Internet resource 'www.случайное-число.рф'. According to the assigned individual number, the patients were divided into 2 groups:

1) the CRT group is a standard prolonged course of neoadjuvant chemoradiotherapy of total focal dose (TFD) 50–54 Gy with capecitabine 825 mg/m^2 twice a day *per os* on the days of radiation therapy;
2)– TNT group — a prolonged course of radiation therapy TFD 50-54Gy with capecitabine 825 mg/m^2 twice a day *per os* on the days of radiation therapy and 3 consolidating courses of chemotherapy according to the XELOX scheme in the waiting period after the end of radiation.

Radiation therapy (RT) was performed in the mode of standard fractionation, using the technology of intensive modulated radiation therapy (IMRT), a single dose (SD) of 2 Gy, a total dose (TD) of 50-54Gy.

The RTOG scale [9] was used to evaluate radiation reactions. The NCI-CTC v5.0 scale was used to assess toxic reactions [10].

At the end of neoadjuvant treatment, 7–12 weeks after completion of radiation therapy, a control checkup was performed (MRI of the pelvis, CT of the chest and abdominal organs with intravenous contrast).

In the presence of signs of a complete response (complete regression — mrTRG1 according to pelvic MRI), the checkup was supplemented with endorectal ultrasound, proctoscopy and/or video colonoscopy.

Patients with a complete clinical tumor response were informed about the possibility of an alternative approach within the framework of the 'watch-and-wait' strategy, which includes mandatory checkup every 3 months during the first two years of follow-up. In patients without a confirmed complete clinical response, surgery was performed in the volume of partial or total mesorectumectomy or abdominal-perineal excision of the rectum [11]. The quality of TME was evaluated in accordance with the Quirke P. scale [12]. Cancer staging was carried out according to the classification of TNM of the 8th edition [13]. Therapeutic pathomorphosis was assessed by the Ryan scale [14].

The severity of postoperative complications was assessed by Clavien-Dindo scale [15]. When detecting the colorectal anastomotic leakage, the latter was evaluated in accordance with the classifications of the International Research Group on Rectal Cancer (A, B or C degree) [16]. Follow-up was recommended to all patients after surgery [1].

STATISTICAL ANALYSIS

The patient data was entered into the Microsoft ACCESS 2019 for Windows spreadsheet. Continuous variables with an abnormal distribution of variation series were described using medians and quartiles (Q1, Q3). To analyze the dichotomous variables, the Fisher exact test or the variance analysis based on the χ^2 test were used. Continuous data was evaluated using the Wilcoxon test when comparing the two groups. The results were considered statistically significant at $p < 0.05$. Statistical analysis was performed using the R studio software (version 3.6.1; R studio, Boston, Massachusetts).

RESULTS

In the period from October 2020 to October 2022, 183 patients were included in the study: 91 in the TNT group and 92 in the CRT group. Thirty-one patients were excluded from the TNT group: 10 due to a violation of the protocol (refusal of consolidating chemotherapy, a short course of RT TFD 25 Gy instead of a prolonged course of CRT TFD 50–54 Gy). One patient was excluded due to death from coronavirus infection at the prehospital stage. One patient was diagnosed with synchronous adenocarcinoma of the sigmoid colon. Another 19 patients did not show up for a follow-up control after neoadjuvant therapy. In the CRT group, 21 patients were excluded: 9 due to protocol violations, one patient was diagnosed with a synchronous neuroendocrine rectal tumor, and one patient was diagnosed with cancer on the background of ulcerative colitis. Ten patients did not show up for a follow-up control after neoadjuvant treatment. In total, 52 (28%) patients were excluded from the study. Such a large number of patients who dropped out of the study are largely due to the COVID-19 pandemic in 2020–2022. A significant number of patients suffered from coronavirus pneumonia, which influenced the refusal of consolidating chemotherapy. Logistics was significantly hampered. Another circumstance was the implementation of a short course of RT, which does not require long-term hospital stay, instead of a prolonged course of CRT.

Thus, the analysis included 60 patients who underwent TNT and 71 patients who received a standard course of prolonged CRT (Fig. 1).

Comparison of Groups According to the Main Characteristics of Patients

The groups are completely comparable in terms of the main clinical parameters and characteristics of the tumor (Table 1).

Compliance and Tolerability of Neoadjuvant Therapy
The complete course of neoadjuvant therapy in the TNT group was done by 51/60 (85%) patients versus 70/71 (99%) patients in the CRT group, the differences being statistically significant ($p = 0.006$). In one patient of the control group, CRT was interrupted due to the severe radiation reaction (RTOG 4) — radiation enterocolitis. The overall rate of radiation complications in the groups did not differ significantly and was observed in 35/60 (58%) patients in the TNT group versus 50/71 (70%) patients in the CRT group ($p = 0.2$). The vast majority of 51/60 (85%) patients in the TNT group completed all 3 courses of consolidating chemotherapy, 7 (12%) patients completed 2 courses of chemotherapy and 2 (3%) patients completed only one course. In only one case, chemotherapy was discontinued due to toxic reactions. In the other cases, the reason was non-compliance with the study protocol. The overall rate of chemotherapy complications was 26/60 (43%) cases in the TNT group versus 12/71 (17%) cases in the CRT group, the differences were significant ($p = 0.003$) due to mild toxic reactions by the NCI-CTC v5.0 scale. Severe toxic reactions of 3–4 degrees occurred only in the TNT group in two patients (3%) due to hematological toxicity. There were no significant differences in the incidence of diarrhea, nausea, and peripheral polyneuropathy (Table 2).

The Effectiveness of Neoadjuvant Therap
In total, there were five cases of progression during neoadjuvant treatment. In the TNT group, in 1/60 (2%) patient with low rectal cancer at the end of TNT, there was a complete regression of the primary tumor; however, CT revealed multiple bilobar metastatic lung lesion. In the CRT group, progression was detected in 4/71 (6%) cases. In one patient with locally advanced low rectal cancer after CRT, MRI scan detected metastasis in the S7 liver up to 1.5 cm in diameter. After completion of CRT, a control CT scan of the chest detected metastasis in S6 of the left lung up to 0.6 cm in diameter; therefore, the patient underwent multistage treatment. Solitary metastases were detected intraoperatively in two patients. In both cases, simultaneous surgery with atypical resection of liver segments was performed. Thus,

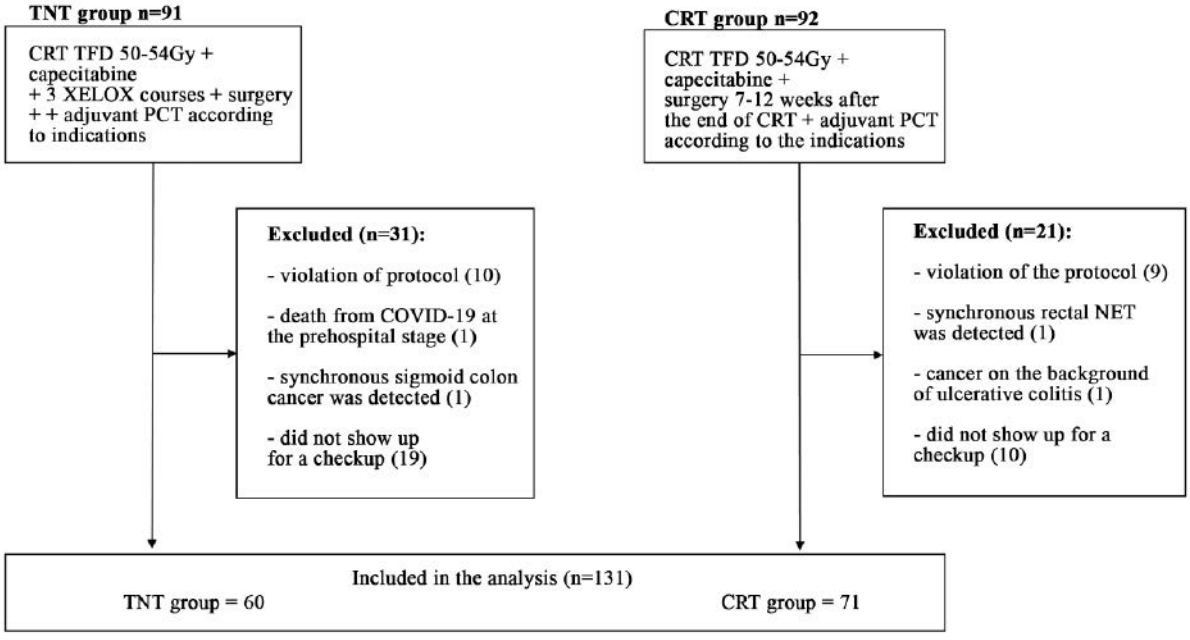

Figure 1. *Block diagram of the study*

Table 1. *Characteristics of patients*

Parameter	TNT Group N = 60 (46%)	CRT Group N = 71 (54%)	P
Age, Me (Q1, Q3)	64 (52, 68)	64 (57, 71)	0.3
Gender *n* (%) Female Male	 25 (42%) 35 (58%)	 25 (35%) 46 (65%)	0.5
BMI, Me(Q1, Q3)	26 (23, 27)	26 (23, 28)	0.8
ASA, *n* (%) ASAI ASAII ASAIII ASA IV Unknown	 7 (16%) 32 (73%) 5 (11%) 0 (0%) 16	 6 (10%) 39 (66%) 13 (22%) 1 (2%) 12	0.6
Abdominal surgery in the anamnesis, *n* (%)	4 (7%)	10 (14%)	0.3
Diabetes mellitus, *n* (%)	6 (10%)	6 (9%)	0.76
Level of cancer markers, Me (Q1, Q3) CEA, ng/ml Unknown CEA 19-9, Units/ml Unknown	 4.4 (2.4, 4.9) 33 4 (0, 16) 33	 3.2 (2.5, 5.4) 44 6 (1, 7) 44	0.9 0.8
cT stage, *n* (%) cT2 cT3 cT4	 18 (30%) 27 (45%) 15 (25%)	 15 (21%) 35 (49%) 21 (30%)	0.3
cN stage, *n* (%) cN0 cN1 cN2	 24 (40%) 17 (28%) 19 (32%)	 19 (27%) 25 (35%) 27 (38%)	0.2
cTNM, *n* (%) I II III	 12 (20%) 12 (20%) 32 (60%)	 9 (12%) 10 (15%) 52 (73%)	0.3
Tumor differentiation, *n* (%) G1 G2 G3 G4	 14 (23%) 39 (65%) 5 (8%) 2 (4%)	 16 (22%) 48 (68%) 5 (7%) 2 (3%)	0.8
CRM + as per MRI data, *n* (%)	25 (42%)	38 (54%)	0.2
Tumor height from the anal edge (mm), Me(Q1, Q3)	51 (28, 62)	54 (37, 65)	0.3
Tumor length (mm), Me (Q1, Q3)	46 (39, 61)	48 (40, 56)	0.9

progression in the TNT group was noted in 1/60 (1%) case compared to 4/71 (6%) cases in the CRT group ($p = 0.4$).

After neoadjuvant treatment and follow-up control, 18 out of 60 (30%) patients from the TNT group and 8 (11%) out of 71 from the CRT group showed complete clinical regression of the tumor. Therefore, these patients refused surgical treatment in favor of 'watch-and-wait' approach ($p = 0.006$). The remaining 41 (68%) out of 60 patients from the TNT group and 63 (89%) out of 71 from the CRT group underwent surgery (Fig. 2, 3).

The Results of Treatment by 'Watch&Wait' Approach

According to the control checkup, complete regression of the tumor developed in 18/60 (30%) patients who received TNT and in 8/71 (11%) patients who received standard CRT. After signing the informed consent, those patients refused surgical treatment in favor of follow-up as part of the 'watch&wait' strategy. The median (Q1, Q3) follow-up time was 24 (14; 28) months. Continued growth was suspected in 4/18 (22%) patients in the TNT group in 6 ($n = 1$), 12 ($n = 2$) and 18 ($n = 1$) months and in 3/8 (37%) patients from the CRT

Table 2. *Compliance and tolerability of neoadjuvant therapy*

Features of neoadjuvant treatment	TNT Group N = 60	CRT Group N = 71	P
Complete course of neoadjuvant treatment	51/60 (85%)	70/71 (99%)	**0.006**
Interruption of radiation therapy	–	1/71 (1%)	1
Total rate of radiation toxicity by RTOG scale, *n* (%) Grade 1–2 Grade 3–4	 35/60 (58%) –	 49/ 71 (69%) 1/71 (1%)	0.2
Total rate of toxic reactions by NCI-CTC scale, *n* (%) Grade 1–2 Grade 3–4	 24/60 (40%) 2/60 (3%)	 12/71 (17%) –	**0.002**
Hematological toxicity, *n* (%) Grade 1–2 Grade 3–4	 6/60 (10%) 2/60 (3%)	 1/71 (1%) –	**0.01**
Diarrhea, *n* (%) Grade 1–2	 14/60 (23%)	 10/71 (14%)	0.2
Peripheralpoly neuropathy, *n* (%) Grade 1–2	 5/60 (8%)	 10/71 (14%)	0.4
Nausea, *n* (%) Grade 1–2	 5/60 (8%)	 1/71 (1%)	0.1

group in 6 (*n* = 1) and 12 (*n* = 2) months after the end of neoadjuvant treatment, in connection with which surgery was performed. Pathomorphology of removed specimens, three patients after TNT and three after CRT showed signs of a residual tumor: ypT2N0cM0 (*n* = 2) and ypT3N0cM0 (after TNT), ypT2N0cM0 (*n* = 2) and ypT3N0cM0 (after CRT). In one case after TNT, according to pathomorphology, a complete tumor response was revealed — ypT0N0cM0. All remaining patients with a complete clinical response remain under control. The median (Q1,Q3) follow-up time is 24 (14; 28) months.

Surgical Results

Surgery was performed in 41 patients in the TNT group and in 63 patients in the CRT group. Within the framework of the 'watch&wait' approach, surgery was performed in 4 more patients in the TNT group and in 3 patients in the CRT group. Thus, in the TNT group, surgery was done in 45 (75%) of 60 patients and in 66 (93%) of 71 patients in the CRT

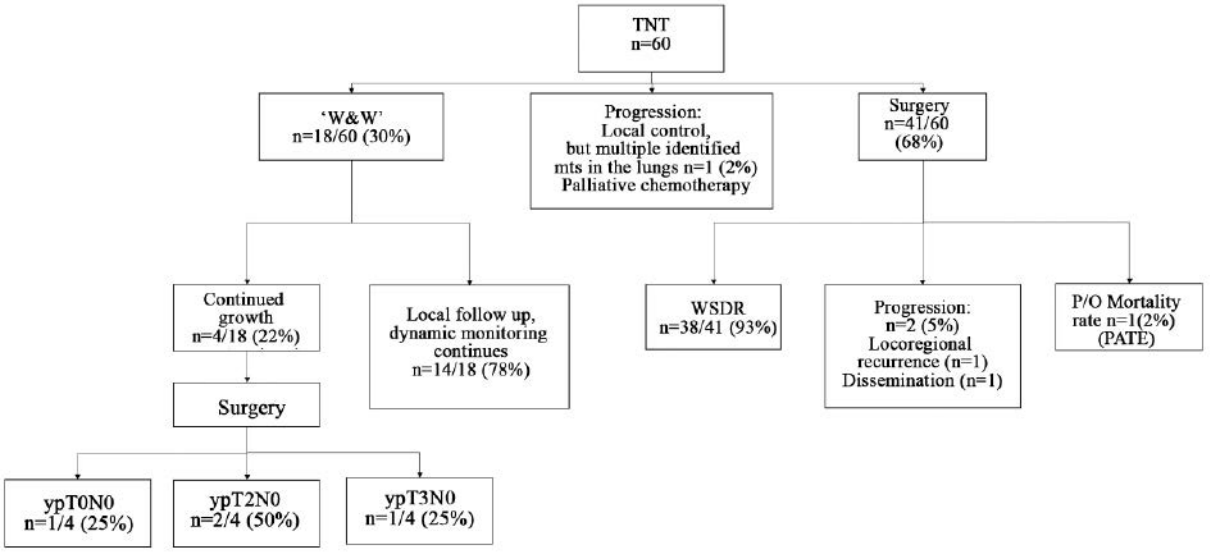

Figure 2. *Flowchart of the results of neoadjuvant treatment of patients in the TNT group: BPVZ — without signs of a return of the disease*

Table 3. *Comparison of data on the immediate results of surgeries*

Parameter	TNT Group N = 45	CRT Group N = 66	P
Operation time (min), Me (Q1, Q3)	180 (148, 195)	180 (156, 208)	0.56
Blood Loss (ml), Me (Q1, Q3)	65 (30, 100)	60 (30, 100)	0.8
Access, *n* (%) laparoscopic open	 33 (73%) 12 (27%)	 39 (59%) 27 (41%)	0.3
Surgery Types, *n* (%) *APE **AAR LAR AR Exenteration	 11 (24%) 10 (22%) 20 (45%) 4 (9%) 0 (0%)	 22 (35%) 12 (19%) 31 (44%) 0 (0%) 1 (2%)	0.3
Sphincter-preserving resections, *n* (%)	34 (75%)	43 (65%)	0.4

*Note: * — APE-abdominal-intermediate extirpation; ** — AAR-abdominal-anal resection*

group. The groups were comparable in operation time, intraoperative blood loss, and type of surgical access (Table 3).

In one patient in the TNT group, the postoperative period was complicated by the pulmonary embolism, which led to the death of the patient. The mortality rate was 2% in the TNT group. Postoperative complications were noted in 33% of patients in the TNT group and in 27% in the CRT group ($p = 0.6$).

The third degree as per the Clavien-Dindo scale occurred in three patients from the TNT group, in two cases the cause of re-operation was perforation of the small bowel, in the other — bleeding. The B degree (anastomotic leakage) developed in two patients (9%) in the TNT group and in one (3%) patient in the CRT group. The median (Q1, Q3) postoperative day in the TNT group was 9 (6, 11) hospital-stay days and 9 (7, 12) days in the CRT group ($p = 0.6$) (Table 4).

The Results of Pathomorphology

The rate of a complete pathomorphological response according to the Ryan scale in the TNT group was 20% (9/45) compared with 8% (5/62) in the CRT group ($p = 0.06$). The rate of R0 resections

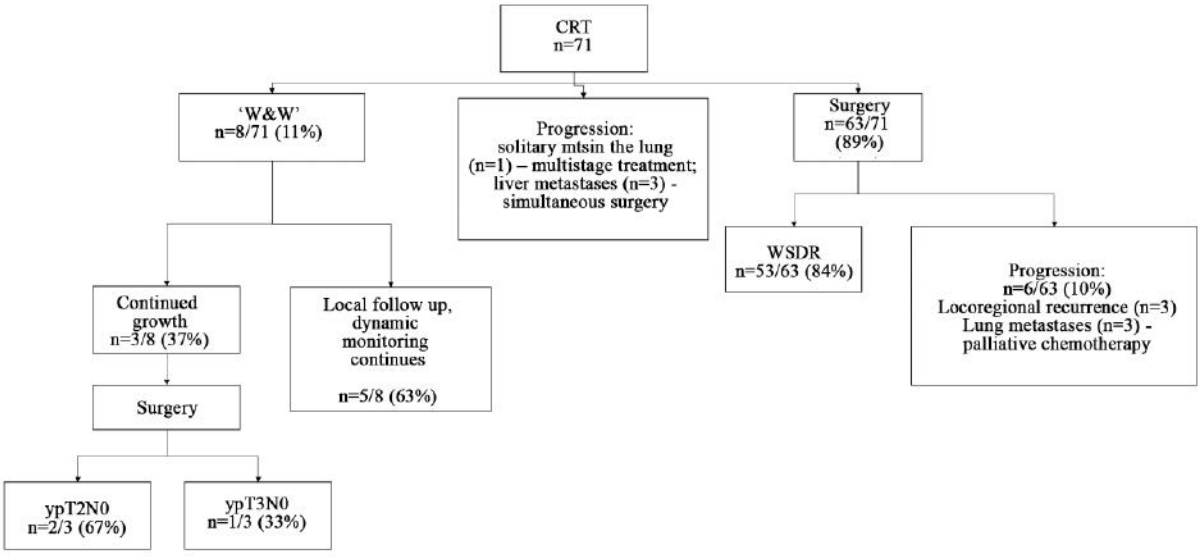

Figure 3. *Flowchart of the results of neo-adjuvant treatment of patients in the CLT group: BPVZ — without signs of a return of the disease*

Table 4. *Rate and structure of postoperative complications*

Parameter	Degree of severity (Clavien-Dindo)	TNT Group N = 45	CRT Group N = 66	P
Wound infection, *n* (%)	I	1 (2%)	1 (2%)	0.9
Bladder atony, *n* (%)	I	3 (7%)	6 (9%)	0.5
paresis of the gastrointestinal tract, *n* (%)	II	5 (11%)	9 (14%)	0.8
Anastomotic leakage, *n* (%) B degree	II	2/23 (9%)	1/30 (3%)	0.7
Perforation of the small intestine, *n* (%)	IIIB	2 (4%)	0	> 0.99
Bleeding, *n* (%)	IIIB	1 (2%)	0	> 0.99
PE, *n* (%)	V	1 (2%)	0	> 0.99
Total, *n* (%)		15 (33%)	17 (26%)	0.6

Table 5. *The results of a pathomorphological study of removed specimens*

Parameter	TNT Group N = 45	CRT Group N = 66	P
stage, *n* (%) ypT0 ypT1 ypT2 ypT3 ypT4	 11 (24%) 3 (7%) 8 (18%) 22 (49%) 1 (2%)	 5 (8%) 3 (5%) 18 (27%) 37 (55%) 3 (5%)	0.2
stage, *n* (%) ypN0 ypN1 ypN2	 33 (73%) 7 (16%) 5 (11%)	 42 (64%) 14 (21%) 10 (15%)	0.5
Perineural invasion (PN), *n* (%)	6 (14%)	16 (24%)	0,2
Lymphovascular invasion (LV), *n* (%)	18 (40%)	39 (59%)	**0.02**
as per Rayn, *n* (%) TRG0 TRG1 TRG2 TRG3 TRG4	 9 (20%) 9 (20%) 18 (40%) 9 (20%) 0 (0%)	 5 (7%) 12 (18%) 40 (61%) 8 (12%) 1 (2)	**0.04**
Complete pathomorphological response (pCR), *n* (%)	9 (20%)	5 (8%)	0.05
R0 resections rate, *n* (%) R0 R1	 41 (91%) 4 (9%)	 59 (89%) 7 (11%)	0.9

Table 6. *Complete responses rate*

Sign	TNT(*n* = 60)	CRT(*n* = 71)	P
Complete clinical response rate, *n* (%)	14 (23%)	5 (7%)	**0.008**
Complete pathomorphological response rate, *n* (%)	9/45 (20%)	5/66 (8%)	0.05
Overall rate of complete responses, *n* (%)	23 (38%)	10 (14%)	**0.001**

in the TNT group was 91% (41/45) versus 89% (57/62) in the CRT group ($p = 0.9$). The groups did not differ in such parameters as ypT and ypN stage, perineural and lymphovascular invasion (Table 5). Thus, the rate of complete clinical response in the TNT group was 17/53 (32%) versus 6/68 (9%) in the CRT group, the differences were significant ($p = 0.001$). The rate of complete pathomorphological response in operated patients was 8/36 (22%) in the TNT group, compared with 4/62 (7%) in the CRT group ($p = 0.02$). Thus, the overall rate of complete responses (pathomorphological and clinical) was 25/53 (47%) in the TNT group, versus 10/68 (15%) in the CRT group ($p = 0.001$) (Table 6).

DISCUSSION

The previously published preliminary results demonstrated the safety of total neoadjuvant therapy for rectal cancer [17]. Upon completion of the

study, it was confirmed that the use of TNT does not lead to a significant increase in the incidence of toxic reactions of III-IV degree, which was noted only in 2/60 (3%) cases in the TNT group, compared with 0/71 (0%) in the CRT group (p = 0.9). Similarly, the use of total neoadjuvant therapy is not followed by significant increase in postoperative morbidity. In this study, an acceptable level of TNT compliance was achieved in 51 out of 60 (85%) patients (3 planned courses of consolidating chemotherapy).Seven (12%) patients completed 2 courses of chemotherapy and 2 (3%) patients completed only one course. However, in only one case, chemotherapy was discontinued due to toxic reactions.

The effectiveness of the neoadjuvant treatment was evaluated by analyzing the incidence of complete clinical and pathomorphological responses. A complete pathomorphological response after neoadjuvant therapy is a favorable prognostic sign. Thus, according to a meta-analysis by Martin, S.T. et al., published in 2012 and combining the results of treatment of more than 3,000 patients, the overall survival rate in patients with a complete pathomorphological response is three times higher (OR = 3.3; 95% CI 1.6–6.5; p = 0.001), and the probability of distant metastases is less by 20% (OR = 0.2; 95% CI 0.1–0.5; p = 0.001) [6].

The use of standard neoadjuvant CRT allows us to expect a complete responsein only one in ten patients [18], while the use of total neoadjuvant therapy allows us to increase the incidence of complete responses, which was also demonstrated in the study. There was a trend to a higher incidence of complete pathomorphological responses, which was 20% (9/45) in the TNT group, compared with 8% (5/66) in the CRT (p = 0.05).

The use of TNT can increase the number of patients with a complete clinical response to rectal cancer for follow-up as part of the 'watch&wait' strategy. The fundamental research in this direction is the publication by Habr-Gama, A. et al., who combined the results of the treatment of 265 patients with rectal cancer. This study convincingly demonstrated the possibility of 'watch-and-wait' approach in patients with a complete clinical tumor response. Upon reaching 10 years of follow-up, a complete clinical response was confirmed in 27% of patients with 97% overall and 84% disease-free survival [19]. When analyzing the rate of complete clinical responses, we faced the problem of the lack of uniform criteria and assessment methods. The generally accepted rule is a minimal two-year follow-up threshold, after which we can talk about a stable clinical response. This conclusion is based on the results of the international database –'International Watch & Wait Database', according to which rectal cancer recurrences occur more often in the first two years [20]. In the study, at the moment, the vast majority of patients have not yet reached the two-year follow-up threshold. However, the preliminary results look optimistic. In 17 (32%) of 53 patients in the TNT group and in 6 (9%) of 68 patients in the CRT group, with a median follow-up of 15 (11, 17) months, signs of a complete clinical response persist, which is significant (p = 0.001). The median (Q1, Q3) follow-up of 15.3 (11.1; 17.4) months limits the reliability of the results obtained. The disadvantage of this study is the large number of patients who dropped out of observation, which was associated with the COVID-19 pandemic. On the other hand, consolidating chemotherapy in a number of patients at their place of residence was associated with a violation of the study protocol, which was inevitable in conditions of excessive burden on healthcare in an unfavorable epidemiological situation.

CONCLUSION

Preliminary results indicate that the use of total neoadjuvant therapy is a safe and effective alternative to standard preoperative CRT due to the higher rate of complete clinical and pathomorphological responses.

AUTHORS CONTRIBUTION

Concept and design of the study: *Sergey I. Sychev, Stanislav V. Chernyshov, Aleksey A. Ponomarenko, Evgeny G. Rybakov*

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