https://doi.org/10.33878/2073-7556-2022-21-3-76-84

Safety of the total neo-adjuvant therapy in rectal cancer treatment. Preliminary results of the randomized trial

Sergey I. Sychev[1], Stanislav V. Chernyshov[1], Anna I. Arzamastseva[1], Maria V. Panina[1], Marina V. Chernykh[2,3], Evgeny A. Petukhov[2,4], Evgeny G. Rybakov[1]

[1]Ryzhikh National Medical Research Center of Coloproctology (Salyama Adilya str., 2, Moscow, 123423, Russia)
[2]National Medical Research Center of Oncology named after N.N. Blokhin (Kashirskoe shosse, 23, Moscow, 115478, Russia)
[3]Sechenov First Moscow State Medical University (Trubetskaya str., 8, bild. 2, Moscow, 119991, Russia)
[4]The Burdenko Main Military Clinical Hospital (Hospitalnaya pl., 3, Moscow, 105094, Russia)

ABSTRACT *AIM: assess tolerability and safety of total neoadjuvant therapy (TNT) with three consolidation courses of XELOX 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. The RTOG scale was used to assessed radial reactions, and the NCI-CTC v5.0 scale was used to evaluate toxicity. For selected patients with a complete clinical response «watch and wait» approach was used. Postoperative complications were graded according with the Clavien-Dindo 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 March 2022, 145 patients were enrolled in the randomized study: 72 patients in the TNT group and 73 patients in the CRT group. The full course of neoadjuvant treatment was completed in 90% patients in the TNT group, comparing with 96% in the CRT group ($p = 0.65$). The total rate of severe adverse effects of radiation therapy was 59% in the TNT group, comparing with 67% in the CRT group ($p = 0.48$), with 3–4 grade by RTOG scale were observed only in two cases in the CRT group. During chemotherapy severe adverse effects were observed in 54% in the TNT group comparing with 19% in the CRT group ($p < 0.001$). Grade 3–4 toxicity was 3% in the TNT group comparing with 2% in the CRT group. The rate of intra- and postoperative complications did not differ between two groups.

CONCLUSION: TNT is a safe alternative to conventional CRT.

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

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

FOR CITATION: Sychev S.I., Chernyshov S.V., Arzamastseva A.I., Panina M.V., Chernykh M.V., Petukhov E.A., Rybakov E.G. Safety of the total neo-adjuvant therapy in rectal cancer treatment. Preliminary results of the randomized trial. *Koloproktologia.* 2022;21(3):76–84. (in Russ.). https://doi.org/10.33878/2073-7556-2022-21-3-76-84

ADDRESS FOR CORRESPONDENCE: *Sergey I. Sychev, Ryzhikh National Medical Research Center of Coloproctology, Salyama Adilya str., 2, Moscow, 123423, Russia; e-mail: info@gnck.ru*

Received — 08.06.2022 *Revised — 23.06.2022* *Accepted for publication — 09.08.2022*

INTRODUCTION

Neoadjuvant chemoradiotherapy in the total focal dose of 50–54 Gy on the background of synchronizing doses of fluoropyrimidines followed by surgery is the recommended option for most patients with stage III cancer of the middle and low rectum or with compromised, according to MRI, resection margins.

This approach minimizes the rate of local recurrences within 3–5%, but does not reduce the rate of distant metastases [1,2]. The administration of systemic chemotherapy in adjuvant mode in this cohort of patients does not demonstrate a

significant increase in life expectancy; however, it is associated with higher toxicity due to the pretreatment of patients, and therefore only 70% of the patients receive a full course of postoperative CT [3,4]. A promising approach is total neoadjuvant therapy (TNT), in which systemic chemotherapy is prescribed in the neoadjuvant mode in addition to preoperative CRT. 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 associated with better survival of patients [5,6].

PATIENTS AND METHODS

In October 2020, a prospective, randomized single-center study with "per protocol" analysis was started.

The hypothesis of the study: the combination of chemoradiotherapy with a course of consolidating chemotherapy in the neoadjuvant mode (TNT) increases the rate of complete rectal tumor responses, compared to the standard CRT.

The inclusion criteria were as follows: signed voluntary informed consent to participate in the study, histologically confirmed adenocarcinoma of the low rectum cT2-4N0-2M0 and the cancer of middle rectum cT2-T4N1-2M0, assessment of the patient's general condition on the ECOG scale of no more than 2 points.

The exclusion criteria were as follows: age younger than 18 and older than 75 years; recurrent rectal cancer; primary multiple tumors of other sites; previous radiation therapy for pelvic organs; pregnancy; breast-feeding; distant metastases; severe cardiovascular, respiratory, nervous system, kidneys and liver comorbidities.

The primary point of the study was the rate of complete tumor responses (clinical and pathomorphological).

The secondary points of the study were the rate and the structure of intra- and postoperative complications according to the Clavien-Dindo classification, the rate of complications of the 3^{rd}–4^{th} grade of radiation therapy according to the RTOG scale and chemotherapy according to the NCI-CTC TNT and CRT toxicity scale, the rate of R0 resections.

After receiving voluntary informed consent, the patients were randomized into two groups: 1) the CRT group — the standard prolonged course of neoadjuvant chemoradiotherapy with the TFD of 50-54Gy with capecitabine 825 mg/m^2 twice a day *per os* on the days of the radiation therapy; 2) the TNT group — the prolonged course of the radiation therapy with the TFD of 50-54Gy with capecitabine 825 mg/m^2 twice a day inside on the days of the radiation therapy and 3 consolidating courses of XELOX in the waiting period after the end of the radiation therapy. At the end of the neoadjuvant treatment, a control checkup (pelvic MRI, CT of the chest and abdominal cavity with contrast) was performed, followed by curative surgery.

The operated patients with stage III according to the pathomorphological study and patients with stage I-II risk factors (lymphovascular invasion, R1 resection, mucinous adenocarcinoma, were prescribed adjuvant chemotherapy): in the main group — 5 courses of CAPOX, in the control group 8 courses of CAPOX. The radiation therapy (RT) was performed in the mode of standard fractionation, using the technology of intensive modulated radiation therapy (IMRT). Single Dose (SD) of 2Gy, Total Dose (TD) of 50-54Gy, against the background of taking capecitabine as a modifying agent, in a dose of 825 mg/m^2 twice a day on the RT days. The RTOG scale was used to evaluate radiation reactions [7]. The consolidating chemotherapy in the main group was performed (XELOX), the adjuvant chemotherapy — according to the standard protocols using a doublet of fluoropyrimidines and oxaliplatin. The NCI-CTC v5.0 scale was used to assess toxic reactions [8]. The effect of the neoadjuvant therapy was evaluated according to MRI data on the mrTRG scale [9]. If a complete tumor response was suspected, the examination was supplemented with the data from endorectal ultrasound, proctoscopy and/or video colonoscopy. In patients without a confirmed complete clinical response, the surgery was performed in the volume of total mesorectumectomy or extralevatory abdomino-perineal rectal resection [10].

The quality of TME was evaluated by Quirke P. gradation [11]. Staging — according to the TNM classification of the 8^{th} revision [12]. The degree

of therapeutic pathomorphosis was determined by the Rayn scale [13].

The severity of postoperative complications was assessed on the Clavien-Dindo scale [14]. When detecting the leakage of colorectal anastomosis, the latter was classified in accordance with the recommendations of the International Research Group for the Study of Rectal Cancer (A, B or C grade) [15]. Follow-up was recommended to all operated patients after the treatment [16]. 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 pelvic MRI every 3 months during the first two years of follow-up. The final decision on the choice of treatment approach was made at an oncological MDT.

STATISTICAL ANALYSIS

The patients' data were entered into the Microsoft ACCESS 2019 for Windows. The statistical analysis was carried out using R studio software (version 3.6.1; R studio, Boston, Massachusetts). Continuous variables were described using medians and quartiles (25%:75%). For the analysis of qualitative variables, the exact Fisher's test or χ^2-test was used, the Wilcoxon test was used for the analysis of continuous variables.

RESULTS

In the period from October 2020 to March 2022, 145 patients were included in the study: 72 patients in the TNT group and 73 patients in the CRT

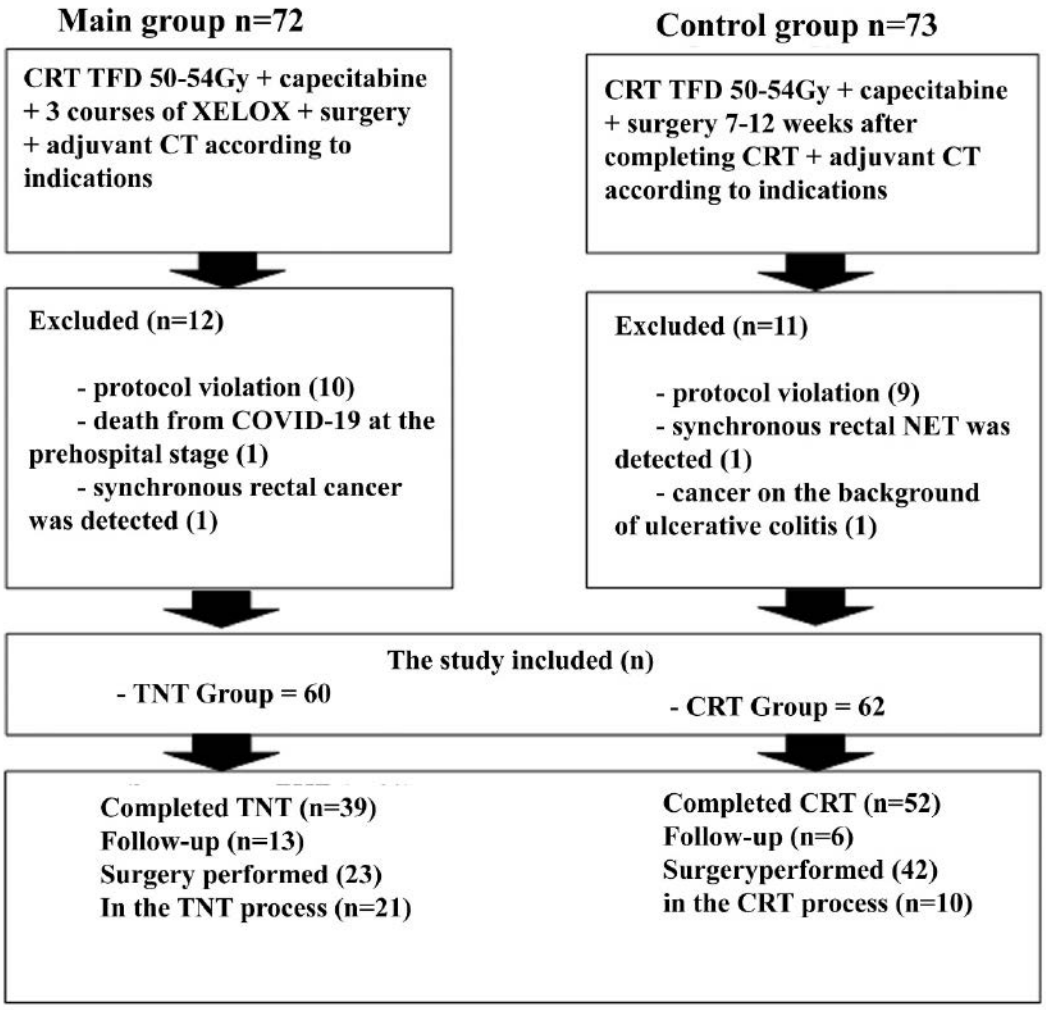

Figure 1. *Research diagram*

Table 1. *Characteristics of patients*

Parameter	TNT	CRT	*P*
Number of patients	60	62	
Age, Me (quartiles)	62 (52:67)	62 (55:69)	0.34
Gender, *n* (%) Female Male	 23 (38%) 37 (62%)	 24 (39%) 38 (61%)	0.97
BMI (kg/m^2) Me (quartiles)	26 (22:28)	26 (22:29)	0.59
ASA, *n* (%) ASAI ASAII ASAIII Unknown	 6 (21%) 18 (64%) 4 (14%) 32	 7 (18%) 25 (62%) 8 (20%) 22	0.8
Abdominal surgery in history, *n* (%)	5 (8%)	7 (11%)	0.6
Diabetes mellitus, *n* (%)	6 (10%)	3 (5%)	0.13
Level of cancer markers, Me (quartiles) REA, ng/ml Unknown	3.1 (1.7: 4.6) 33	2.6 (1.9:4.4) 38	> 0.99
cT, *n* (%) cT2 cT3 cT4	 14 (23%) 29 (48%) 17 (28%)	 12 (19%) 36 (58%) 14 (23%)	0.56
cN, *n* (%) cN0 cN1 cN2	 22 (37%) 20 (33%) 18 (30%)	 20 (32%) 16 (26%) 26 (42%)	0.37
cTNM, *n* (%) I II III	 10 (17%) 11 (18%) 39 (65%)	 7 (13%) 10 (19%) 35 (67%)	0.84
CRM + according to MRI data, *n* (%) By lymph node By tumor	25 (43%) 9 16	31 (51%) 16 15	0.4
Me (quartiles) of tumor height from anal edge (mm)	54 (30:64)	54 (37:68)	0.49
Me (quartiles) tumor extent (mm)	44 (35:56)	48 (40:56)	0.43

group. Twelve patients were excluded from the TNT group: 10 — due to a violation of the protocol (refusal of consolidating chemotherapy, a short course of RT with the TFD of 25 Gr instead of a prolonged course of CRT TFD 50–54 Gr). One patient was excluded due to his death from coronavirus infection at the pre hospital stage, one patient was diagnosed with synchronous adenocarcinoma of the sigmoid colon.

In the CRT group, 11 patients were excluded: 9 — due to a violation of the protocol, one patient revealed a synchronous neuroendocrine tumor of the rectum and one patient had cancer on the background of ulcerative colitis. Currently, 39 out of 60 patients have completed treatment in the TNT group, 13 patients are under follow-up due to the complete clinical response of the tumor, 23 patients underwent surgery. At the time of writing, 52 patients out of 62 completed treatment in the CRT group, 6 patients are under control follow-up due to a complete tumor response, 42 patients underwent surgery. Surgical treatment is planned for the remaining 6 patients from the TNT group and 4 patients from the CRT group (Fig.1).

Table 2. *Compliance and toxicity of neoadjuvant therapy*

	TNT	CRT	*P*
Number of patients who completed the full course of treatment, *n* (%)	35/39 (90%)	50/52 (96%)	0.65
Reduction of radiation therapy dose, *n* (%)	0 (0%)	2 (4%)	> 0.99
Interruption of radiation therapy, *n* (%)	0 (0%)	1 (2%)	> 0.99
Total rate of radiation toxicity on RTOG scale, *n* (%) Grade 1–2 Grade 3-4	23 (59%) 0 (0%)	33 (63%) 2 (4%)	0.48
Total rate of toxic reactions according to NCI-CTC scale, *n* (%) Grade 1–2 Grade 3-4	20 (51%) 1 (3%)	9 (17%) 1 (2%)	**< 0.001**
Hematological toxicity, *n* (%) Grade 1–2 Grade 3-4	6 (15%) 1 (3%)	1 (2%) 1 (2%)	**0.039**
Diarrhea, *n* (%) Grade 1-2	11 (28%)	7 (13%)	0.081
Peripheralpolyneuropathy, *n* (%) Grade 1-2	4 (10%)	2 (4%)	0.4

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

	TNT	CRT	*P*
Number of patients	23	42	
Me (quartiles) surgery time, min	180 (161:188)	180 (151:188)	0.63
Me (quartiles) blood loss, ml	80 (30:100)	50 (20:100)	0.35
Access, *n* (%) Laparoscopic Open	 12 (52%) 11 (48%)	 24 (57%) 18 (43%)	0.76
Intraoperative wound of urethra	0 (0%)	1 (2%)	0.76
Sphincter-saving surgeries, *n* (%)	11 (48%)	23 (55%)	0.59
Preventive stoma, *n* (%)	9 (39%)	20 (47%)	0.51

Comparison of the groups according to the main characteristics of patients

The groups were homogenous in the main clinical parameters and characteristics of the tumor (Table 1).

Compliance and toxicity of neoadjuvant therapy

The full course of the neoadjuvant therapy in the TNT group was completed by 90% (35/39) of patients versus 96% (50/52) in the CRT group, the differences were not significant ($p = 0.65$).

There were no serious problems during the radiation therapy in the TNT group. The vast majority (90.0%) of the patients completed all 3 courses of the consolidating chemotherapy, 2 (5.0%) patients completed 2 courses of the chemotherapy and 2 (5.0%) patients completed only one course. Only in one case, the chemotherapy was discontinued due to the development of toxic reactions. In the other cases, the reason was non-compliance with the study protocol. In the CRT group, two patients (4.0%) required reduction of the radiation therapy with TFD less than 45 Gy due to the severe radiation proctitis. In one patient (2.0%), the neoadjuvant CRT was stopped due to acute respiratory disease.

The overall rate of complications of the radiation therapy in the groups did not differ significantly and was 23 (59.0%) in the TNT group versus 35 (67.0%) in the CRT group ($p = 0.48$), while radiation reactions of the 3rd–4th grade on the RTOG scale were noted only in two cases in the CRT group.

Table 4. *Frequency and structure of postoperative complications**

	Severity grade	TNT	CRT
Wound infection, *n* (%)	I	1 (4.0%)	1 (2.0%)
Urinary retention, *n* (%)	I	2 (9.0%)	4 (10.0%)
Post-op ileus, *n* (%)	II	3 (13.0%)	6 (14.0%)
Anastomosis leakage, *n* (%)	II	0/9 (0%)	1/20 (5%)
Perforation of small intestine, *n* (%)	IIIB	1 (4.0%)	0
Pulmonary embolism, *n* (%)	V	1 (4.0%)	0
Total, *n* (%)		8 (34.0%)	12 (28.0%)

**all differences are not statistically significant*

The overall rate of chemotherapy complications was 54% (21/39) in the TNT group versus 19% (10/52) in the CRT group, the difference was significant ($p < 0.001$). It is worth noting that the differences were due to mild toxic reactions on the NCI-CTC v5.0 scale, while the rate of severe toxic reactions in the TNT group was 3% versus 2% in the CRT group and was due to hematological toxicity. There were no significant differences in the rate of diarrhea and peripheral polyneuropathy (Table 2).

Immediate results of surgical treatment

At the time of writing, in the TNT group of 39 patients who completed the neoadjuvant treatment, surgery was performed in 23 (59.0%), in the CRT group — in 42 (81.0%) of 52 patients. The groups were comparable in median duration of the surgery, intraoperative blood loss and type of surgical access. Intraoperatively, only one patient had a complication: in the CRT group, a patient with a locally advanced tumor had unintentional damage to the urethra ($p = 0.76$) (Table 3).

Postoperative complications were detected in 34% in the TNT group and in 28% in the CRT group ($p = 0.42$). Thus, one patient from the main group had a perforation of the small intestine wall, which was the reason for emergency surgery. The anastomosis leakage was detected in one patient (5.0%) in the CRT group, which corresponded to grade B that required drainage and antibiotics. According to the rate of postoperative urinary retention and ileus, the groups did not differ significantly. In one patient in the TNT group, the postoperative period was complicated by the pulmonary embolism, which led to the death of the patient, thus, the mortality rate was 4% in the TNT group. The median (quartile) of the postoperative day in the TNT group was 10 (8–12) hospital stay days versus 9 (7–12) days in the CRT group, while the differences did not reach significance ($p = 0.5$) (Table 4).

DISCUSSION

Standard protocols for the treatment of patients with rectal cancer of the third stage recommend postoperative systemic chemotherapy.

These recommendations are largely based on the results of clinical trials of adjuvant chemotherapy for colon cancer [17,18]. The role of systemic chemotherapy in the treatment of rectal cancer has not been fully established, and its effectiveness in the postoperative regime has not been proven in most randomized studies [19–21]. Systemic chemotherapy in the mode of total neoadjuvant therapy can potentially improve treatment outcomes by increasing the rate of complete responses, as well as reduce the risk of progression by eliminating micrometastases.

It should be emphasized that the effectiveness of treatment directly depends on the chosen regimen of total neoadjuvant therapy, and the rate of complete pathomorphological responses varies widely from 12% to 28% [22–28]. At the same time, the tolerability and compliance of treatment ultimately determine its practical feasibility.

In the presented randomized study, chemotherapy was prescribed as a consolidating course in the waiting period after completing radiation therapy, while 90% (35/39) of the patients completed the full course of the treatment in the main group,

which is comparable to the control group, where 96% (50/52) of the patients completed the full course of the neoadjuvant therapy (p = 0.65). In the TNT group, 90% (35/39) of the patients completed all 3 courses of consolidating chemotherapy. In a randomized study conducted in 2018 by Kim, S.Y. et al. in a sample of 108 patients, compliance in the TNT group with two consolidating courses according to the XELOX scheme was 87% (48/55). The short interval (on average 7 days) between the end of radiation therapy and the beginning of consolidating chemotherapy, regulated by the study protocol, is indicated by the authors as the most likely reason for refusing to continue treatment in five patients [25]. In this study, the interval between the end of radiation therapy and the beginning of consolidating chemotherapy was not strictly regulated and only one patient refused to continue treatment due to toxic reactions.

The escalation of preoperative treatment was expected to lead to an increase in the overall rate of toxic reactions, which was 51% (20/39) versus 17% (9/52) in the control group, the differences were significant (p < 0.001). At the same time, the addition of chemotherapy did not lead to a critical increase in the rate of severe toxic reactions, and the differences were due to toxic reactions of the 1–2 grade (Table 4). The results obtained correlate with the data of a randomized trial (RAPIDO) published in 2020 by Bahadoer, R. et al. A group of 912 patients demonstrated comparable tolerability of TNT and the standard approach with preoperative prolonged CRT and adjuvant chemotherapy. In the TNT group, where patients underwent consolidating chemotherapy after a short course of RT TFD 25 Gy (6 courses of XELOX / or 9 courses of FOLFOX), the rate of toxic reactions of the 3rd–4th grade was 38% (177/460) compared to the control group, in which the rate of severe toxic reactions during neoadjuvant CRT was 34% (87/254) and 34% (64/187) during adjuvant chemotherapy [24]. In the randomized trial (PRODIGE 23), published in 2021 by Conroy, T. et al. and combining the results of treatment of 461 patients, the rate of severe toxic reactions during TNT with 6 courses of induction CT (FOLFIRINOX) and the standard CRT was 27% (63/231) compared to 22% (50/230) in the control group (the standard course of preoperative CRT), the differences did not reach significance. The authors report a lower rate of severe toxic reactions during adjuvant chemotherapy in the TNT group, where patients received mFOLFOX6 for 3 months, compared to the control group, where patients received similar treatment for 6 months (11% vs 23%, p = 0.0049) [26].

The question of which TNT regime is better tolerated by patients was partially solved in the randomized study published in 2019 by Fokas, E. et al. in a sample of 306 patients. The authors compared two different TNT regimes with induction (group A) and consolidating (group B) chemotherapy with 3 courses of the FOLFOX in combination with a prolonged course of CRT. At the same time, the authors report that the rate of toxic reactions of the 3rd–4th grades during chemotherapy did not differ and amounted to 22% in each group [29].

CONCLUSION

Thus, the transfer of chemotherapy from adjuvant to neoadjuvant regimen in addition to CRT does not negatively affect the tolerability of treatment and its compliance. Also, the rate of intra- and postoperative complications does not increase.

The preliminary results of the presented randomized trial demonstrated that TNT is a safe alternative to the standard neoadjuvant CRT. Further recruitment and analysis of immediate and long-term results will establish the effectiveness of this option.

AUTHORS CONTRIBUTION

Concept and design of the study: *Sergey I. Sychev, Stanislav V. Chernyshov, Anna I. Arzamastseva, Maria V. Panina, Evgeny G. Rybakov*

Collection and processing of the material: *Sergey I. Sychev, Evgeny A. Petukhov*

Statistical processing: *Sergey I. Sychev*

Writing of the text: *Sergey I. Sychev, Stanislav V. Chernyshov, Marina V. Chernykh*

Editing: *Evgeny G. Rybakov*

INFORMATION ABOUT THE AUTHORS (ORCID)

Sergey I. Sychev — 0000-0002-2534-792X

Stanislav V. Chernyshov — 0000-0002-6212-9454

Anna I. Arzamastseva — 0000-0002-1730-3070

Maria V. Panina — 0000-003-4384-3668

Marina V. Chernykh — 0000-0003-4944-4035
Evgeny A. Petukhov — 0000-0001-8444-0158
Evgeny G. Rybakov — 0000-0002-3919-9067

REFERENCES

1. Gollins S, Sebag-Montefiore D. Neoadjuvant Treatment Strategies for Locally Advanced Rectal Cancer. *Clin Oncol*. 2016;28(2):146–151.
2. Bosset J-F, et al. Chemotherapy with Preoperative Radiotherapy in Rectal Cancer. *N Engl J Med*. 2006;355(11):1114–1123.
3. Hattori N, et al. Phase II study of capecitabine plus oxaliplatin (CapOX) as adjuvant chemotherapy for locally advanced rectal cancer (CORONA II). *Int J Clin Oncol*. Springer Singapore. 2020;25(1):118–125.
4. Sandra-Petrescu F, et al. Influence of complete administration of adjuvant chemotherapy cycles on overall and disease-free survival in locally advanced rectal cancer: Post hoc analysis of a randomized, multicenter, non-inferiority, phase 3 trial. *BMC Cancer*. 2018;18(1) 4–11.
5. Martin ST, Heneghan HM, Winter DC. Systematic review and meta-Analysis of outcomes following pathological complete response to neoadjuvant chemoradiotherapy for rectal cancer. *Br J Surg*. 2012;99(7):918–928.
6. Zorcolo L, et al. Complete pathologic response after combined modality treatment for rectal cancer and long-term survival: A meta-analysis. *Ann Surg Oncol*. 2012;19(9):2822–2832.
7. Cox JD, Stetz JA, Pajak TF. Toxicity criteria of the Radiation Therapy Oncology Group (RTOG) and the European organization for research and treatment of cancer (EORTC). *Int J Radiat Oncol Biol Phys*. 1995;31(5):1341–1346.
8. Cancer Therapy Evaluation Program (CTEP). Common Terminology Criteria for Adverse Events (CTCAE).v.5.0 [5x7]. *Cancer Ther Eval Progr*. 2017; p.155.
9. Yoen H, et al. Prognostic value of tumor regression grade on MR in rectal cancer: A large-scale, single-center experience. *Korean J Radiol*. 2020;21(9):1065–1076.
10. Heald RJ, et al. Rectal cancer: the Basingstoke experience of total mesorectal excision, 1978-1997. *Arch Surg United States*. 1998;133(8):894–899.
11. Campa-Thompson M, et al. Pathologic processing of the total mesorectal excision. *Clin Colon Rectal Surg*. 2015;28(1):43–52.
12. Amin MB, et al. The Eighth Edition AJCC Cancer Staging Manual: Continuing to build a bridge from a population-based to a more "personalized" approach to cancer staging. *CA: a cancer journal for clinicians United States*. 2017;67(2):93–99.
13. Ryan JE, et al. Assessing pathological complete response to neoadjuvant chemoradiotherapy in locally advanced rectal cancer: a systematic review. *Color Dis Off J Assoc Coloproctology Gt Britain Irel England*. 2015;17(10):849–861.
14. Dindo D, Demartines N, Clavien P-A. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg*. 2004;240(2):205–213.
15. Rahbari NN, et al. Definition and grading of anastomotic leakage following anterior resection of the rectum: a proposal by the International Study Group of Rectal Cancer. *Surgery United States*. 2010;147(3):339–351.
16. Rectal cancer. Clinical guidelines. Russian Society of Clinical Oncology, Association of Oncologists of Russia, Russian Society of Specialists in Colorectal Cancer, All-Russian Public Organization "Association of Coloproctologists of Russia." 2020; p. 78. (in Russ.).
17. Kuebler JP, et al. Oxaliplatin combined with weekly bolus fluorouracil and leucovorin as surgical adjuvant chemotherapy for stage II and III colon cancer: Results from NSABP C-07. *J Clin Oncol*. 2007;25(16):2198–2204.
18. André T, et al. Improved overall survival with oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment in stage II or III colon cancer in the MOSAIC trial. *J Clin Oncol*. 2009;27(19):3109–3116.
19. Bosset JF, et al. Fluorouracil-based adjuvant chemotherapy after preoperative chemoradiotherapy in rectal cancer: Long-term results of the EORTC 22921 randomised study. *Lancet Oncol*. Elsevier Ltd. 2014;15(2):184–190.
20. Sainato A, et al. No benefit of adjuvant

Fluorouracil Leucovorin chemotherapy after neoadjuvant chemoradiotherapy in locally advanced cancer of the rectum (LARC): Long term results of a randomized trial (I-CNR-RT). *Radiother Oncol Elsevier Ireland Ltd*. 2014;113(2):223–229.
21. Collette L, et al. Patients with curative resection of cT3-4 rectal cancer after preoperative radiotherapy or radiochemotherapy: Does anybody benefit from adjuvant fluorouracil-based chemotherapy? A trial of the European Organisation for Research and Treatment of Cancer Rad. *J Clin Oncol*. 2007;25(28):4379–4386.
22. Chakrabarti D, et al. Short-course radiotherapy with consolidation chemotherapy versus conventionally fractionated long-course chemoradiotherapy for locally advanced rectal cancer: Randomized clinical trial. *Br J Surg*. 2021;108(5):511–520.
23. Maréchal R, et al. Short course chemotherapy followed by concomitant chemoradiotherapy and surgery in locally advanced rectal cancer: A randomized multicentric phase II study. *Ann Oncol*. 2012;23(6):1525–1530.
24. Bahadoer RR, et al. Short-course radiotherapy followed by chemotherapy before total mesorectal excision (TME) versus preoperative chemoradiotherapy, TME, and optional adjuvant chemotherapy in locally advanced rectal cancer (RAPIDO): a randomised, open-label, phase 3 trial. *Lancet Oncol*. 2021;22(1):29–42.
25. Kim SY, et al. A Randomized Phase 2 Trial of Consolidation Chemotherapy After Preoperative Chemoradiation Therapy Versus Chemoradiation Therapy Alone for Locally Advanced Rectal Cancer: KCSG CO 14-03. *Int J Radiat. Oncol Biol Phys Elsevier Inc*. 2018;101(4):889–899.
26. Conroy T, et al. Neoadjuvant chemotherapy with FOLFIRINOX and preoperative chemoradiotherapy for patients with locally advanced rectal cancer (UNICANCER-PRODIGE 23): a multicentre, randomised, open-label, phase 3 trial. *Lancet Oncol*. 2021;22(5):702–715.
27. Moore J, , Price T, Carruthers S, et al. Prospective Randomised Trial Of Neoadjuvant Chemotherapy During The "Wait Period" Following Pre-Operative Chemoradiotherapy For Rectal Cancer; Results of the WAIT trial. *Int J Lab Hematol*. 2017;38(1):42–49.
28. Garcia-Aguilar J, et al. Effect of adding mFOLFOX6 after neoadjuvant chemoradiation in locally advanced rectal cancer: A multicentre, phase 2 trial. *Lancet Oncol Elsevier Ltd*. 2015;16(8):957–966.
29. Fokas E, et al. Randomized phase II trial of chemoradiotherapy plus induction or consolidation chemotherapy as total neoadjuvant therapy for locally advanced rectal cancer: CAO/ArO/AIO-12. *J Clin Oncol*. 2019;37(34):3212–3222.