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Short course radiotherapy with consolidation chemotherapy for rectal cancer: a meta-analysis of randomized trials

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ABSTRACT *AIM: to study the effect of total neoadjuvant therapy with consolidation chemotherapy for rectal cancer.*
MATERIALS AND METHODS: the meta-analysis performed in accordance with PRISMA practices and guidelines.
RESULTS: short-course radiotherapy with consolidation chemotherapy compared to chemoradiotherapy (CRT) improves the rate of complete pathological responses (OR = 1.88; CI 1.47–2.42; p < 0.00001); does not affect the rate of local relapses (OR = 0.95; CI 0.72–1.24; p = 0.69), three-year disease-free survival (OR = 1.19; CI 0.99–1.44; p = 0.06) and overall survival (OR = 1.09; CI 0.88–1.35; p = 0.45). TNT increases the incidence of grade ⩾ 3 toxicity (OR = 1.87; CI 1.10–3.18; p = 0.02), and does not affect treatment compliance (OR = 0.57; CI 0.17–1.95; p = 0.37).
CONCLUSION: the use of TNT can improve the oncological results of treatment of patients with rectal cancer by increasing the frequency of complete pathological responses.

KEYWORDS: *total neoadjuvant therapy, rectal cancer, TNT, locally advanced rectal cancer*

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

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INTRODUCTION

Recently, the main approach to local advanced rectal cancer is neoadjuvant chemoradiotherapy (CRT) followed by surgery with mesorectumectomy [1].

'Total neoadjuvant therapy' (TNT) has been gaining interest, which implies early systemic treatment of rectal cancer, that is, it includes radiation and chemotherapy before surgery, which allows to increase the rate of complete clinical and pathomorphological responses [2]. In the CAO/ARO/AIO-12 trial, two main types of TNT were compared: with induction and consolidating chemotherapy. In both groups, patients underwent CRT with a total focal dose (TFD) of 50.4 G. The rate of complete pathomorphological responses was higher in the consolidating CT group compared with induction CT (25% vs. 17%, respectively, $p < 0.001$); CRT-associated toxicity was lower in the consolidating CT group than with induction CT (27% vs. 37%, respectively) [3]. When assessing late results, there were no differences in 3-year disease-free survival — it was 73% in both groups ($p = 0.82$), as well as in the rate of local recurrences (5% and 6%, respectively). According to the results of the trial, TNT with consolidating chemotherapy turned out to be more preferable.

So, the question of choosing a radiation therapy regimen remains relevant: a short course of large-fraction RT or prolonged CRT.

AIM

To reveal the effect of total neoadjuvant therapy with a consolidating chemotherapy for rectal cancer.

MATERIALS AND METHODS

The meta-analysis was performed in accordance with the preferred reporting items for systematic reviews and meta-analyses (PRISMA) [4]. The search for scientific papers was done in the electronic database of medical literature PubMed. Search keywords were as follows: total neoadjuvant therapy, rectal cancer, TNT, LARC. When searching for literature in the electronic database eLibrary, no randomized studies on this topic were found. We also did an additional search for bibliographic data among the studies included in the meta-analysis in order to identify articles that were missed during the initial search. The meta-analysis includes full-text articles in English, which reflect the results of treatment of patients with local advanced rectal cancer using various modes of total neoadjuvant therapy.

When searching for literature in PubMed, 25,394 publications were found. After screening, 22 full-text articles were selected for this meta-analysis. Then, literature reviews and interim results of randomized clinical trials were excluded. As a result of the literature selection, the meta-analysis included 4 randomized studies comparing the effectiveness of short RT with consolidating chemotherapy and prolonged CRT in the treatment of rectal cancer (Fig. 1).

The endpoints of the meta-analysis were: the rate of complete pathomorphological responses, the rate of local recurrences, the overall and disease-free survival of patients, toxicity and compliance with treatment.

Statistical Analysis

For statistical analysis, the Review Manager 5.4.1 program was used. The total value of the dichotomous data was described as a ratio of odds (OR) with a coincidence interval (CI) equal to 95%. The OR was calculated using the Peto method if one of the values of the bipartite table was 0. Continuous data was described by a non-standardized weighted average with a CI of 95%. Statistical heterogeneity among the included studies was assessed using the χ^2-test.

Heterogeneity was assessed using I^2. Thus, with $I^2 < 50\%$, the heterogeneity was insignificant or moderate, in connection with which models with a fixed effect were built; on the contrary, with $I^2 > 50\%$, there was a high heterogeneity of studies. Therefore, models with a random effect were used. The differences were considered significant at $p < 0.05$.

RESULTS

The meta–analysis included 2,162 patients with rectal cancer, of whom 1,094 patients underwent neoadjuvant CRT in the standard mode (TFD 50.4 G), and 1,068 patients underwent total neoadjuvant therapy (Table 1).

According to the results of the meta-analysis, the rate of complete pathomorphological responses to neoadjuvant treatment was significantly higher in the TNT group (20.5%) compared with standard CRT (12%) (OR = 1.88; CI 1.47–2.42; $p < 0.00001$) (Fig. 2).

When assessing the rate of local recurrences within three years after surgery, no significant differences were obtained (OR = 0.95; CI 0.72–1.24; $p = 0.69$) (Fig. 3). The rate of local recurrences in the TNT group was 12%, whereas in the standard neoadjuvant therapy group it was 12.7%.

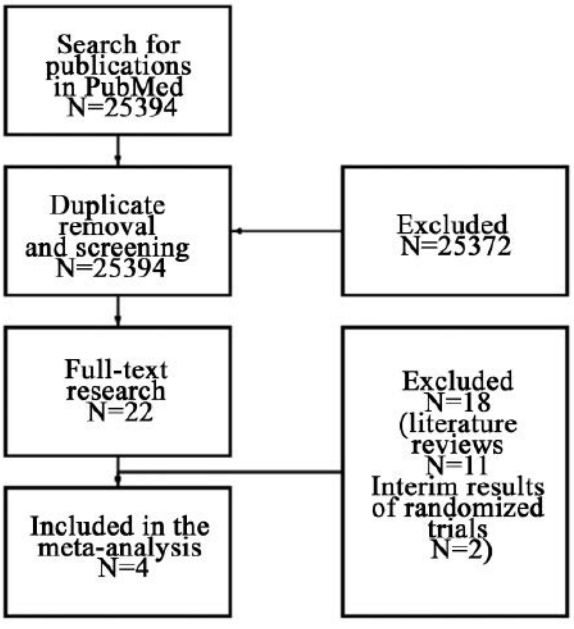

Figure 1. *Block diagram of literature search*

Table 1. *Characteristics of the included studies*

Author	Year	Groups (patients)	Neoadjuvant treatment	Complete patho-morphological response rate, %	Local recurrence rate after 3 years, %	Disease free 3-year survival rate, months	Overall 3-year survival rate, months
Bahadoer et al. RAPIDO [5]	2021	TNT (462)	RT (25 G) + 6 Capoxor 9 Folfox	28	8,3	–	89,1
		Standard (450)	CRT (50.4 G)	14*	6	–	88,8
Bujko et al. POLISH II [6]	2016	TNT (261)	RT (25 G) + 3 Folfox	16	22	53	73
		Standard (254)	CRT (50.4 G)	12	21	52	65
Chakrabarti D. et al. [7]	2021	TNT (69)	RT (25 G) + 2 Xelox	12	–	–	–
		Standard (71)	CRT (50.4 G)	10	–	–	–
Jin et al. STELLAR [8]	2022	TNT (302)	RT (25 G) + 4 Capox	21,8	8,4	64,5	86,5
		Standard (293)	CRT (50.4 G)	12,3	11	62,3	75,1

*Note: * p < 0,05*

There were also no significant differences in 3-year disease free survival among patients of both groups (OR = 1.19; CI 0.99–1.44; p = 0.06) (Fig. 4). The disease free 3-year survival rate reached 66.7% of patients in the TNT group and 62.9% — in the standard neoadjuvant CRT group. According to the data of the three studies included in the meta-analysis, the overall 3-year survival rate had no significant differences with a short course of RT with a course of consolidating CT and traditional CRT (OR = 1.09; CI 0.88–1.35; p = 0.45) (Fig. 5). Thus, with TNT, the overall 3-year survival rate was 63.1%, whereas with standard neoadjuvant therapy it was 61.7%.

The postoperative morbidity rate as per the Clavien-Dindo scale did not differ in both groups both when analyzing all morbidities (OR = 1.17; CI 0.95–1.45; p = 0.14) (Fig. 6) and morbidity of

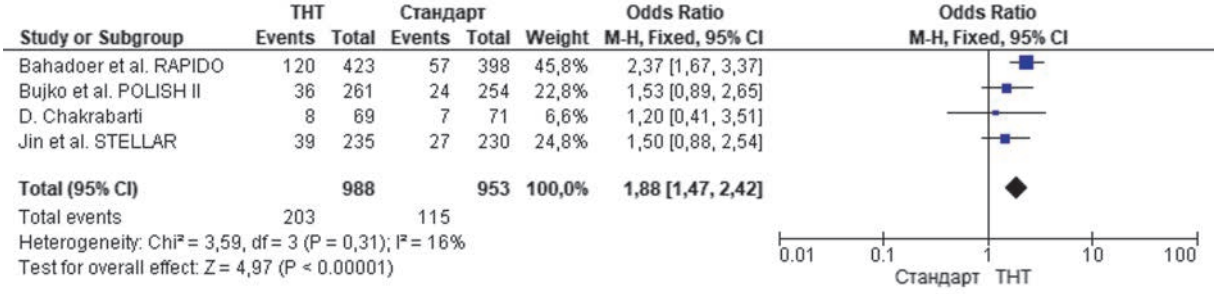

Figure 2. *Frequency of complete pathomorphological responses*

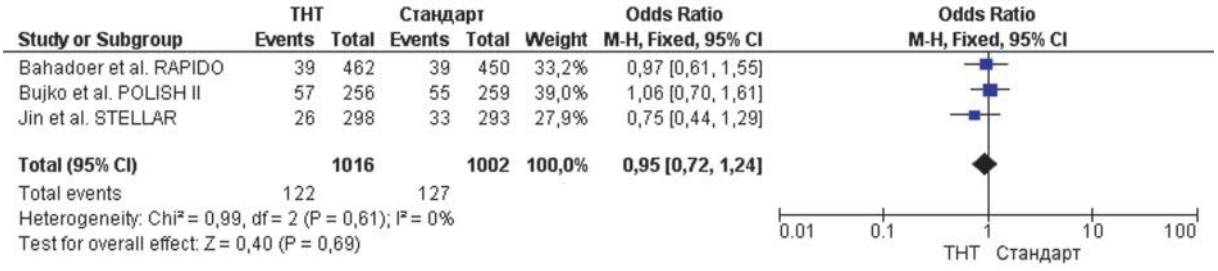

Figure 3. *Frequency of local relapses*

grade 3 or more (OR = 1.00; CI 0.76–1.32; $p = 0.99$) (Fig. 7).

Toxicity of grade 3 or more turned out to be significantly lower in the group of standard CRT in comparison with TNT group (OR = 1.87; CI 1.10–3.18; $p = 0.02$) (Fig. 8).

Compliance was calculated on the results of the three studies, and it turned out that it had no differences in both groups (OR = 0.57; CI 0.17–1.95; $p = 0.37$) (Fig. 9).

It is important to emphasize that in assessing toxicity and compliance, a high heterogeneity of studies was noted (I^2 — 79% and 94%, respectively).

Among the randomized trials included in the meta-analysis, the risk of bias was checked, the diagram was compiled using the Review Manager 5.4.1 program (Fig. 10).

When checking the risk of bias, 3 out of 4 studies met all the criteria of randomized trials, in the study by Chakrabarti D. there was incomplete. Heterogeneity in the analysis of complete

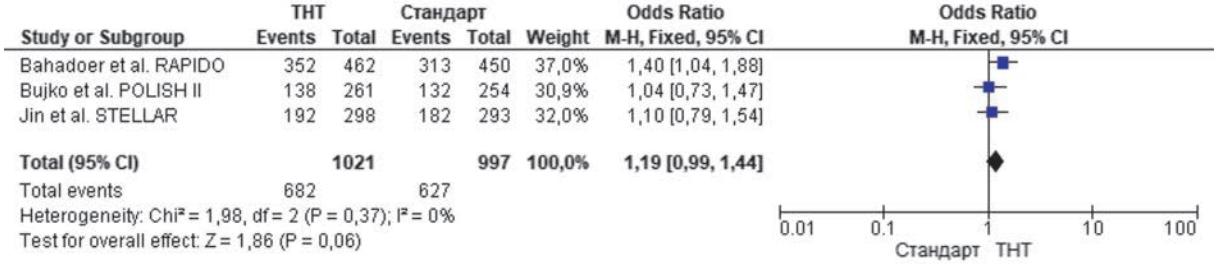

Figure 4. *Relapse-free three-year survival rate*

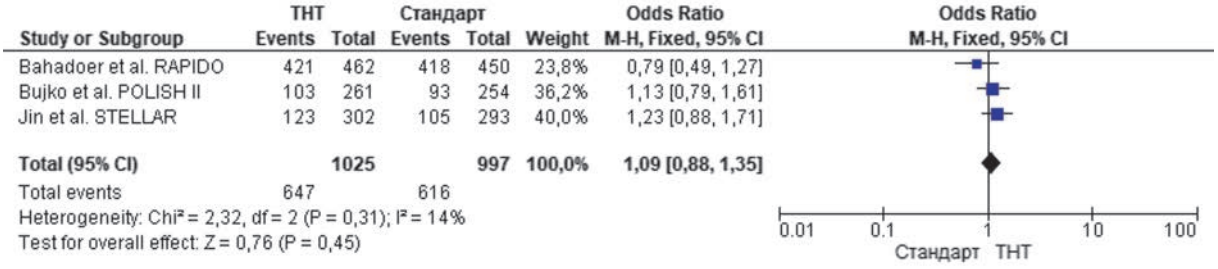

Figure 5. *Total three-year survival rate*

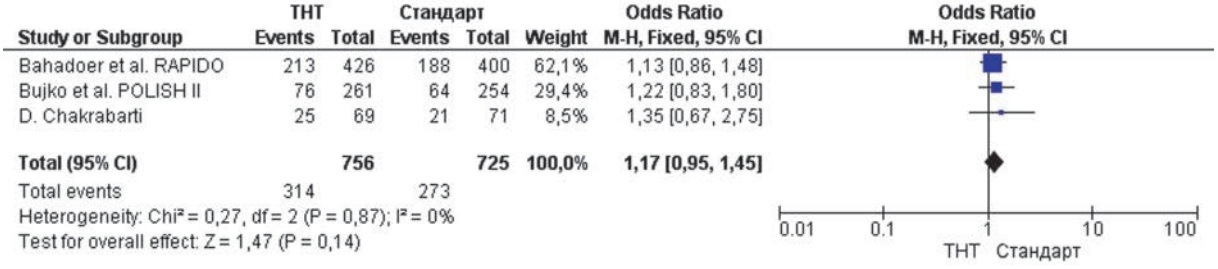

Figure 6. *Postoperative complications*

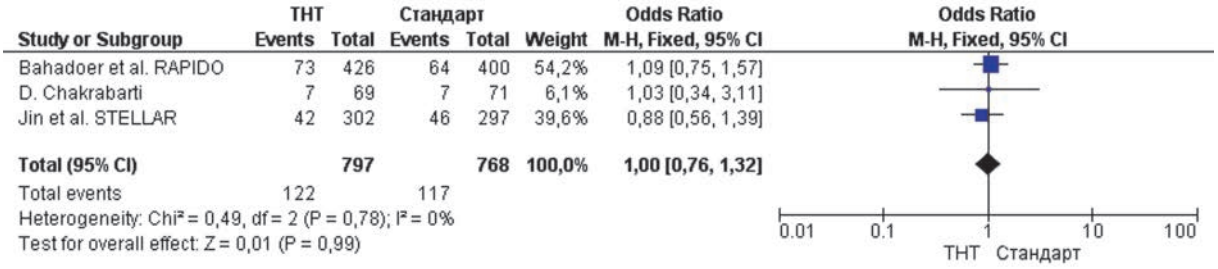

Figure 7. *Postoperative complications of 3 or more degrees according to CD*

pathomorphological responses, overall and disease-free survival was no more than 16%, which indicates the absence of heterogeneity of studies.

DISCUSSION

The results of combined treatment of patients with rectal cancer were first demonstrated in 1985 in a study by the Gastrointestinal Tumor Study Group, which assessed the rate of local recurrences over 80 months: in the group of patients who underwent only surgical treatment, the disease relapsed in 55% of cases; with postoperative radiotherapy (RT) — in 48%; with postoperative chemotherapy (CT) — in 46%; with a combination of radiation and chemotherapy — in 33%, $p < 0.04$. However, this study failed to identify significant differences in overall survival rates [9].

The starting point for conducting a short course of large-fraction RT was the Uppsalatrial trial in 1980–1985, which demonstrated the advantage of a short course of RT in comparison with

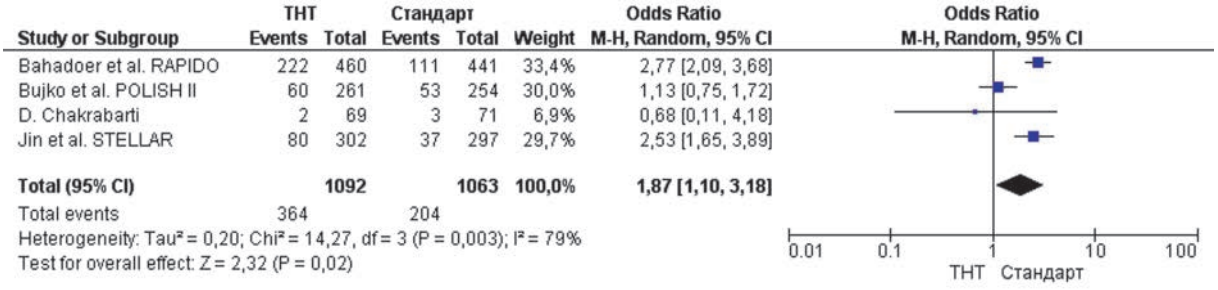

Figure 8. *Toxicity ≥ 3 degrees*

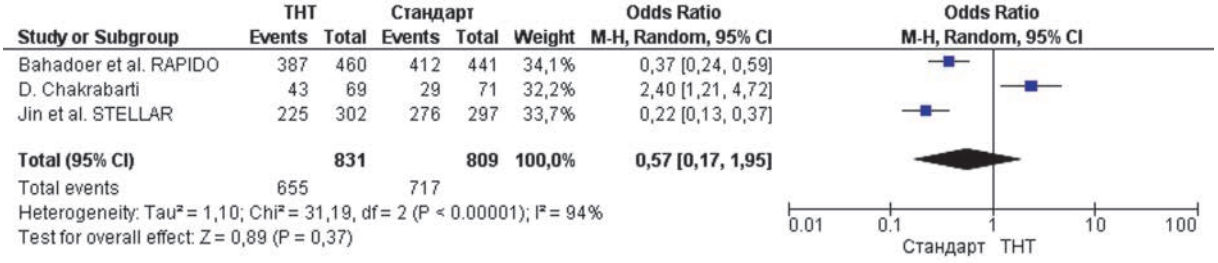

Figure 9. *Compliance with chemoradiotherapy*

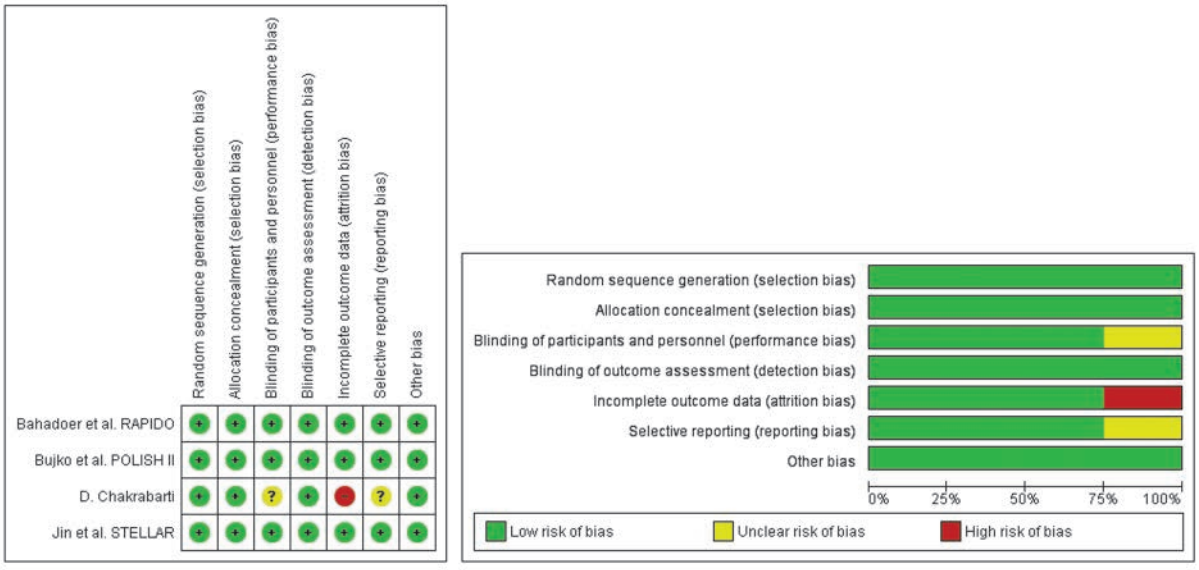

Figure 10. *Assessment of bias risk in randomized trials*

a prolonged course of postoperative RT TFD 60 G: the rate of local recurrences with a minimum follow-up period of 5 years turned out to be significantly lower in the preoperative RT group (13% vs. 22%, $p = 0.02$) [10].

In 1997, the results of a randomized Swedish Rectal Cancer Trial were published. In this work, the authors demonstrated that the use of a short course of radiation therapy in the preoperative period reduces the rate of local recurrences, and also increases overall survival in patients with resectable rectal cancer compared with patients who immediately underwent surgery (11% and 27% of local recurrences, $p < 0.001$). There was also an advantage in the overall 5-year survival rate: 58% in the group of patients who underwent combined treatment versus 48% in the group of patients who underwent only surgical treatment ($p = 0.004$) [11].

The results of another large randomized Dutch Trial study were published in 2001. From January 1996 to December 1999, 1,861 patients participated in the study, who were randomized into two groups: in the main group, patients underwent a short course of RT TFD 25 G followed by surgery in the volume of total mesorectumectomy, whereas in the control group, patients immediately underwent surgical treatment in the volume of total mesorectumectomy. As it turned out, the rate of local recurrences over two years was significantly lower in the group of patients who received combined treatment compared with the group of patients who received only surgical treatment — 2.4% versus 8.2% ($p < 0.001$) [12].

It should be noted that until 2004, there were no studies comparing the two main approaches to the combined treatment of rectal cancer: with the use of preoperative and postoperative CRT. Sauer, R. and co-authors published the results of a randomized trial: preoperative CRT was more preferable than postoperative. Thus, the rate of local recurrences after 5 years was 6% in the preoperative CRT group and 13% in the postoperative CRT group, $p = 0.006$. Acute and delayed toxic reactions were also significantly less common in the preoperative CRT group: 27% and 40%, respectively, $p = 0.001$; 14% and 24%, respectively, $p = 0.01$. There were no differences in the overall 5-year survival rate: 76% versus 74%, respectively, $p = 0.8$ [13]. Thus, the use of CRT as the first stage of the combined treatment of rectal cancer turned out to be more effective than postoperative CRT.

In the Stockholm III trial in 1998–2013, it was noted that, regardless of the neoadjuvant RT regimen, the local recurrence rate does not differ significantly [14]. Thus, local recurrences during a short course of RT (TFD 25 G) followed by surgical treatment within a week were detected in 8 out of 357 (2.2%) patients; with delayed surgery for 4–8 weeks — in 10 out of 355 (2.8%) patients; with prolonged RT (TFD 50 G) — in 7 out of 128 (5.5%) patients ($p = 0.48$). In the 2019 meta-analysis, Qiaoli, W. et al. compared a short course of preoperative RT (TFD 25 G) with prolonged CRT and showed no differences in overall (OR 1.3; CI 0.58–2.89; $p = 0.52$) and disease-free survival (OR 1.1; CI 0.73–1.66; $p = 0.64$). The subanalysis demonstrated differences in the complete pathomorphological response rate: it turned out to be significantly higher in the group of prolonged CRT compared with a short course of RT without the addition of chemotherapy (OR 0.42; CI 0.30–0.60, $p < 0.01$). When consolidating chemotherapy was added to a short course of RT, the difference in the complete pathomorphological response rate was leveled (OR 0.42; CI 0.9–2.09; $p = 0.14$) [15].

Socha J. et al. conducted a meta-analysis of randomized trials in 2020, in which they studied the effectiveness of a short course of RT in comparison with prolonged CRT. According to the results of the meta-analysis, the local recurrence rate was the same (OR 0.87; CI 0.53–1.44; $p = 0.59$) [16].

Thus, the question of choosing a neoadjuvant RT mode remains open.

In the RAPIDO study published in 2021, in the group with a short course of radiotherapy and subsequent consolidating chemotherapy, the complete pathomorphological response rate was significantly higher than in the CRT group: 28% vs. 14% (OR 2.37; CI 1.67–3.37; $p < 0.0001$). The three-year

overall survival rate did not differ and amounted to 89.1% in the TNT group and 88.8% in the control group (OR0.92; CI 0.67–1.25;p = 0.59) [5]. In 2020, data on treatment compliance and toxicity were published: in the TNT group, all patients received a short course of RT, 84% of whom received at least 75% of the volume of neoadjuvant CT. Whereas in the standard treatment group, 93% of patients completed CRT, and 58% completed postoperative chemotherapy. Toxicity of grade 3 or more was detected in 48% of patients in the TNT group, while in the CRT group — in 25% during preoperative treatment and in 35% of patients during adjuvant CT. Postoperative complications were comparable and amounted to 50% and 47% in the TNT and CRT groups, respectively (p = 0.411), as well as the postoperative morbidity rate of grade 3 and higher as per the Clavien-Dindo (CD) scale did not differ: 15% and 14%, respectively (p = 0.67) [17].

Between 2015 and 2018, a randomized STELLAR trial was published [8], the primary point of which was to reveal the effect of neoadjuvant therapy on 3-year disease free survival in patients with local advanced rectal cancer.

3-year disease free (64.5% and 62.3%, p < 0.001) and overall survival (86.5% and 75.1%, p = 0.033) in patients in the TNT group was significantly higher than in patients of the CRT group. The complete pathomorphological response rate was also higher in the TNT group than in the CRT group (21.8% and 12.3%, respectively, p = 0.002). In the TNT group, radiation was completed by 100% of patients, and in the CRT group — 97.6%. The complete volume of combined treatment was received by 74.8% in the TNT group and 93.2% in the CRT group (p < 0.001). Toxicity of grade 3 and higher developed in 26.5% of patients in the TNT group and in 12.6% in the CRT group (p < 0.001). There were no differences in the postoperative morbidity rate of grade 3 and higher as per the CD scale — 14% versus 15.7% in the TNT and CRT groups, respectively (p = 0.625).

Bujko K. et al. compared the effectiveness of TNT and CRT in a randomized Polish II study [6]. The complete pathomorphological response rate did not differ significantly in both groups and amounted to 16% in the TNT group and 12% in the CRT group (p = 0.17). At the same time, the 3-year overall survival rate was higher in the TNT group than in the CRT group (73% vs. 65%, respectively, p = 0.046). 3-year disease free survival was comparable in both groups (53% and 52%, respectively, p = 0.85). Dose reduction of radiation or chemotherapy due to toxicity was 37% and 34% in the TNT and CRT groups, respectively (p = 0.4), which indicates comparable compliance with treatment in both groups. Toxicity of grade 3 or more was detected in 23% and 21% of patients in the TNT and CRT groups, respectively. The postoperative morbidity rate did not differ: 29% in the TNT group and 25% in the CRT group (p = 0.18). When analyzing the long-term results of the Polish II study, it turned out that the 8-year overall survival rate was 49% in both groups and did not differ significantly (p = 0.38). There were also no differences in 8-year diseasefree survival: in the TNT group it was 43%, whereas in the CRT group it was 41% (p = 0.65) [18].

Wisniowska K. and co-authors per formed a subanalysis of the randomized Polish II trial and the effectiveness of oxaliplatin and 5-fluorouracil (5-FU) as part of a course of consolidating chemotherapy after a short course of chemoradiotherapy in comparison with the use of only 5-fluorouracil in tumors with T3-T4 invasion among 272 patients (136 patients in each group). When evaluating complete pathomorphological responses, the use of a combination of oxaliplatin and 5-FU led to a twofold increase in the tumor response to the treatment. However, no significant differences were obtained (14% vs. 7%, respectively, p = 0.1) [19].

Chakrabarti D. et al., in 2021, published data from a randomized trial comparing the results of treatment with a short course of radiation with two courses of consolidating chemotherapy and a prolonged course of chemoradiotherapy. When analyzing the data obtained, it was revealed that the complete pathomorphological response rate did not differ statistically significantly: in the group of a short course of radiation, a complete

pathomorphological response was detected in 8 out of 69 patients, whereas in the group of a prolonged course of chemoradiotherapy, a complete pathomorphological response was detected in 7 out of 71 patients (12% vs. 10%, respectively, $p = 0.74$). It should be noted that data on overall and disease-free survival have not been published at present. Compliance with treatment was higher in the TNT group — 63% compared with 41% in the CRT group ($p = 0.005$). Toxicity of 3–4 grades was noted in 2% and 4% in the TNT and CRT groups, respectively ($p = 1.0$). Complications as per the CD scale were recorded in 36% of patients in the TNT group and in 29% in the CRT group ($p = 0.838$), postoperative complications of Grade 3 and higher were 9% and 10%, respectively [7].

The results of our meta-analysis indicate the advantages of total neoadjuvant therapy in comparison with standard neoadjuvant chemoradiotherapy: the use of TNT significantly increases the complete pathomorphological response rate (OR = 1.88; CI 1.47–2.42; $p < 0.00001$), but has no significant advantages in relation to the total (OR = 1.09; CI 0.88–1.35; $p = 0.45$) and disease-free survival (OR = 1.19; CI 0.99–1.44; $p = 0.06$). The randomized trials included in the meta-analysis combine the results of treatment of 2,162 patients, which demonstrates the need for further study.

Also, randomized trials included in the meta-analysis studied the complete clinical tumor response rate (diagnosed according to objective and instrumental studies). Thus, in the STELLAR study, complete clinical responses after total neoadjuvant therapy were obtained in 9.4% of patients [8]. In cases where, after neoadjuvant therapy, the complete clinical response of the tumor is detected in patients, the question arises about the need for surgical treatment, which entails the postoperative morbidity risk, as well as a violation of the function of anal continence. Thus, according to Paun B.C. et al., low anterior resection syndrome develops in 90% of patients who underwent total mesorectomectomy, and urination difficulties and genitourinary problems occur in 33% and 50% of patients, respectively [20]. According to Russian authors, the site of the anastomosis below 5 cm from the anal verge increases the risk of low anterior resection syndrome by 2.6 times (95% CI: 1.47–4.62), $p = 0.001$) [21]. At the same time, the overall complete clinical and pathomorphological response rate after a short course of radiation with a course of consolidating chemotherapy can be 30%, which in the group of total neoadjuvant therapy opens up opportunities for using an experimental 'watch-and-wait' strategy. Thus, Habr-Gama et al., back in 2004, demonstrated the effectiveness of this approach: patients with rectal cancer underwent a prolonged course of chemoradiotherapy in neoadjuvant mode. Three-hundred sixty-five patients were included in the study. According to the results of neoadjuvant therapy, 71 (26.7%) patients were diagnosed with a complete clinical response — they were offered follow-up, and 194 patients showed an incomplete clinical response — those patients were operated on.

It turned out that 22 (11.3%) of the 194 patients in the resection group had a complete pathomorphological response by morphology of the removed specimen. Further follow-up of patients with complete clinical and pathomorphological responses revealed that in the resection group, the 5-year overall survival and disease free survival were 88% and 83%, whereas in the follow-up group — 100% and 92%, respectively. This trial demonstrates the effectiveness and safety of the 'watch and wait' strategy [22].

CONCLUSION

The use of a short course of radiation with a course of consolidating chemotherapy can improve the oncological results of treatment of patients with rectal cancer by increasing the complete pathomorphological response rate of the tumor, while increasing the toxic reaction rate.

AUTHORS CONTRIBUTION

Concept and design of the study: *Mikhail V. Alekseev, Evgeny G. Rybakov*

Collection and processing of the material: *Rashid I. Fayzulin*
Statistical processing: *Rashid I. Fayzulin*
Writing of the text: *Rashid I. Fayzulin*
Editing: *Mikhail V. Alekseev, Evgeny G. Rybakov*

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