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Efficacy of total neoadjuvant therapy for rectal cancer: results of a randomized trial

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ABSTRACT *AIM: to compare the treatment outcomes of rectal cancer patients using two regimens of total neoadjuvant therapy (TNT): short-course radiotherapy with three cycles of consolidating chemotherapy and long-course chemoradiotherapy with three cycles of consolidating chemotherapy.*
PATIENTS AND METHODS: a prospective, Single-Center, Randomized Study. From September 2022 to February 2025, 125 patients were enrolled in the study. Of these, 64 were assigned to Group A and 61 to Group B. In Group A, patients received a short-course radiotherapy (RT) regimen followed by three cycles of consolidating chemotherapy with the XELOX regimen. Treatment response was assessed 10–18 weeks after the completion of radiotherapy. In Group B, patients received a long-course chemoradiotherapy (CRT) regimen followed by three cycles of consolidating chemotherapy with the XELOX regimen. Treatment response was assessed 10–18 weeks after the completion of chemoradiotherapy. The primary endpoint of the study is the rate of complete tumor response (pathological complete response, pCR).
RESULTS: the median tumor size was 50 mm (interquartile range, IQR: 24–123 mm) in Group A and 47 mm (IQR: 27–76 mm) in Group B (p = 0.3). There were no significant differences in the presence or absence of involved circular resection margin (p = 0.9) or extramural vascular invasion (p = 0.8) before treatment initiation. Both groups showed comparable results in terms of compliance (p = 1.0), tolerability (p = 0.7), and toxicity (p = 0.8) of radiotherapy. No statistically significant differences were found in the compliance (p = 1.0), tolerability (p = 0.8), and toxicity (p = 0.2) of chemotherapy. Surgical outcomes were also comparable regarding the rate of negative resection margins (p = 1.0), quality of mesorectal excision (p = 0.5), degree of tumor response to neoadjuvant treatment (p = 0.6), and postoperative complications (p = 0.8). The rate of complete tumor responses (both clinical and pathological) did not differ significantly between the groups. With a follow-up ranging from 3 to 35 months (median 18 months), the clinical complete response rate was 5/61 (8.2%) in Group A and 11/64 (17.2%) in Group B (p = 0.18). The pathological complete response rate was 9/53 (14.7%) vs. 6/51 (9.3%), respectively (p = 0.6). The overall complete response rate was 14/61 (22.9%) in the short-course RT and 17/64 (26.5%) in the long-course CRT group (p = 0.6).
CONCLUSION: the compared TNT regimens are comparable in compliance, tolerability, and toxicity. The combination of SCRT with consolidation chemotherapy in a neoadjuvant regimen is comparable in the frequency of complete responses compared with a CRT with consolidation chemotherapy.

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

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

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INTRODUCTION

Currently, the standard of treatment for locally advanced colorectal cancer is neoadjuvant chemoradiotherapy (CRT), which reduces the size of the primary tumor and also reduces the risk of disease recurrence [1]. A new stage in the development of neoadjuvant therapy has become total neoadjuvant therapy (TNT), which includes both radiation and chemotherapy in a neoadjuvant regimen. An important advantage of TNT is an increase in the rate of complete tumor responses to neoadjuvant

treatment in comparison with the standard regimen of prolonged chemoradiotherapy. So, Kasi A. et al. in 2020conducted a meta-analysis of both randomized and non-randomized trials, which showed that the rate of complete pathomorphological responses in the TNT mode was significantly higher than in the prolonged CRT mode and amounted to 29.9% versus 14.9%, respectively (OR 2.44; 95% CI 1.99–5.98; $p < 0.001$) [2].

It is important to emphasize that TNT can be performed using both induction and consolidating chemotherapy. In the randomized CAO/ARO/AIO-12 study, it was demonstrated that the use of consolidating chemotherapy in comparison with induction is preferable for the occurrence of complete pathomorphological tumor responses. In this study, the rate of complete pathomorphological tumor responses was 25% in the TNT group with consolidating chemotherapy versus 17% in the TNT group with induction chemotherapy ($p < 0.001$) [3]. It should be noted that in both groups, patients underwent a prolonged course of CRT with a total focal dose (TFD) of 50.4 Gy.

A randomized RAPIDO study showed the advantage of TNT, which includes a short course of large-fraction radiation therapy of TFD 25 Gy with consolidating chemotherapy compared with a prolonged course of CRT TFD 50.4 Gy. The rate of complete pathomorphological responses in the TNT group was 28%, while in the prolonged CRT group it was 14% ($p < 0.0001$) [4].

Total neoadjuvant therapy has advantages over the standard preoperative CRT regimen.

However, the question of choosing a radiation therapy regimen within TNT remains open. When searching the literature, no studies were found that compare the results of treatment of locally advanced colorectal cancer in TNT regimens using a short course of RT and an extended course of CRT, and therefore we initiated this study.

PATIENTS AND METHODS

From September 2022 to February 2025, a prospective, single-center, randomized trial was conducted, which included 125 people. The study was a two-group study, 1:1 randomization was performed using a randomizer for numbers and data randomus.ru.

Patients Grouping

In group A, patients underwent a short course of radiation therapy (RT) with three cycles of XELOX consolidating chemotherapy with an assessment of the effect 10–18 weeks after the end of RT.

In group B, patients underwent a prolonged course of chemoradiotherapy (CRT) with three cycles of XELOX consolidating chemotherapy with an assessment of the effect 10–18 weeks after the end of CRT.

A complete clinical response (cCR) was established based on digital examination, colonoscopy, and MRI of the pelvic organs in the absence of macroscopic signs of a tumor in 10–18 weeks after the end of radiation/chemoradiotherapy. In the case of a complete clinical response of the tumor, patients were offered follow-up, according to the “watch and wait” strategy. In the absence of complete clinical regression of the tumor, patients underwent surgical treatment. A complete pathomorphological response (pCR) was established based on a morphological examination of the surgical material with complete regression of adenocarcinoma and the absence of metastatically altered lymph nodes.

The hypothesis of the study is that the combination of a short course of radiation therapy with a course of consolidating chemotherapy in a neoadjuvant regimen is no worse in terms of the rateof complete rectal tumor responses, compared with a prolonged course of chemoradiotherapy with a course of consolidating chemotherapy.

Inclusion criteria:

- Adenocarcinoma of the rectum cT3-T4aN0-2M0.
- Assessment of the general condition of the patient ECOG 0-2
- Signed voluntary informed consent to participate in the study.

Non-inclusion criteria:

- Age less than 18 and over 80 years old
- Recurrence of rectal cancer
- Primary multiple tumors of other localizations
- Previous radiation therapy for pelvic organs
- Pregnancy, breast-feeding
- Presence of distant metastases
- Presence of chronic diseases in the decompensation stage
- Complicated nature of the tumor (paratumoral abscess, anemia Hb < 100 g/l)

Exclusion criteria:

- Patient's refusal to participate in the study.

Primary endpoint: the rate of complete responses (clinical and pathomorphological).

Secondary endpoints:

- Compliance with neoadjuvant therapy using short and prolonged cycles of RT;
- Rate and structure of intra- and postoperative complications according to Clavien-Dindo's classification [5];
- Rate of grade 3–4 complications of radiation therapy according to the RTOG scale [6] and chemotherapy according to the NCI-CTCAE toxicity scale [7];
- Quality of mesorectumectomy;
- Rate of R0 resections.

With a study capacity of 80%, a coincidence interval of 95%, an expected effect value of less than 10% (the use of a short course of RT is no worse than prolonged CRT during TNT), and an expected rate of complete tumor responses of 20–30%, the sample size, according to the hypothesis of no less effectiveness ("non-inferiority trial"), amounts to 250 patients per group. Due to the correspondence of the expected effect value (less than 10%) at the primary endpoint during the interim audit, it was decided to complete the recruitment of patients and stop the study ahead of the schedule.

The protocol of the randomized clinical trial was reviewed and approved at a meeting of the Local Ethics Committee of the RNMRC of Coloproctology of the Ministry of Health of Russia on September 26, 2022.

Statistical Analysis

A statistical analysis was performed using the Statistica 13.3 program (TIBCO, USA) and RStudio (R v. 4.4.1 (R Core Team, Vienna, Austria)). The normal distribution was checked by Kolmogorov-Smirnov's test and by visual evaluation of the histogram of the rate distribution of the feature. Under the condition of Gaussian's distribution, continuous data were described by averages and standard deviations in the form of M ± SD; in the other cases, by the median and interquartile range in the form of Me (IQR). The comparison of groups by quantitative criteria, regardless of the nature of the distribution, was carried out by Mann-Whitney's U-test, by qualitative Pearson'sc^{2}test with expected values of more than 10 for all cells for four-field tables and more than 5 for at least 20% of cells in multi-field tables, in the other cases, a two-sided Fisher's exact test was used. When assessing disease-free survival, the time interval from the start date of the treatment to the date of recurrence or the last control was calculated. Survival was assessed by constructing Kaplan-Mayer's curves, and the groups were compared using a logrank test.

The differences were considered statistically significant at $p < 0.05$.

RESULTS

The study included 125 patients, of whom 61 patients — in the short course RT group and 64 patients — in the prolonged CRT group.

The groups were comparable in gender, age, tumor size, and the presence or absence of involvement of the circular margin of resection or invasion of extramural vessels before treatment (Table 1).

In both groups, comparable results were obtained in terms of compliance, tolerability, and toxicity of radiation therapy (Table 2). All patients underwent a full course of RT/CRT, with grade 3–4 toxicity on the RTOG scale recorded in 2% of patients from each group.

Compliance with chemotherapy did not differ significantly in both groups. For various reasons,

Table 1. *Characteristics of groups*

Parameter		25 Gy + 3 cycles XELOX (N = 61)	50.4 Gy + 3 cycles XELOX (N = 64)	*p*
Gender	Male	36 (59%)	32 (50%)	0.3
	Female	25 (41%)	32 (50%)	
Age, years, M ± SD (Min–Max)		63.4 ± 10.9 (31–80)	62.2 ± 11.4 (29–83)	0.3
Tumor size, mmMe (Q1–Q3)		50 (24–123)	47 (27–76)	0.4
Circular margin of resection before treatment	CRM+	31 (51%)	33 (52%)	0.9
	CRM–	30 (49%)	31 (48%)	
Invasion of extramural vessels before treatment	EMVI+	23 (38%)	23 (36%)	0.8
	EMVI–	38 (62%)	41 (64%)	

Table 2. *Results of radiation therapy*

Criterion	Result	25 Gy + 3 cycles XELOX (N = 61)	50.4 Gy + 3 cycles XELOX (N = 64)	p
Compliance	Satisfactory	61 (100%)	64 (100%)	–
Tolerability	Satisfactory	59 (96%)	60 (94%)	0.7
Toxicity(RTOG)	1–2 grade	1 (2%)	3 (4%)	0.8
	3–4 grade	1 (2%)	1 (2%)	

Table 3. *Compliance with consolidating chemotherapy*

Criterion	Result	25 Gy + 3 cycles XELOX (N = 61)	50.4 Gy + 3 cycles XELOX (N = 64)	p
Compliance	Completed 3 CT cycles	54 (88%)	57 (89%)	1.0
	Completed 1–2 CT cycles	4 (7%)	4 (6%)	
	Refusal of CT	3 (5%)	3 (5%)	

Table 4. *Tolerability and toxicity of consolidating chemotherapy*

Criterion	Result	25 Gy + 3 cycles XELOX (N = 58)	50.4 Gy + 3 cycles XELOX (N = 61)	p
Tolerability	Satisfactory	48 (82%)	52 (85%)	0.8
Toxicity (NCI-CTCAE)	1-2 grade	5 (9%)	8 (13%)	0.19
	3-4 grade	5 (9%)	1 (2%)	

consolidating chemotherapy was not performed in 5% of patients from each group (Table 3).

The tolerability of chemotherapy (CT) was assessed in 119 out of 125 patients who underwent at least 1 cycle of CT: the groups were comparable in terms of CT tolerance. Grade 3–4 toxicity according to the NCI-CTCAE scale was detected in 2% of patients from group B (CRT), while in group A (RT) — in 9% of patients (Table 4).

Among 125 patients included in the study, 25 (20%) were diagnosed with a complete clinical response, of whom, there were 9/61 (15%) patients in Group A and 16/64 (25%) patients in group B (Fig. 1).

With a follow-up period of 3 to 35 months with a median of 18 months, the rate of complete clinical responses was 5/61 (8.2%) in the short-course RT group and 11/64 (17.2%) in the prolonged CRT group ($p = 0.18$). In 9 (36%) of the 25 patients who were diagnosed with cCr and offered “watch and wait” tactics, the progression of the disease was registered ($p = 0.7$).

In group A, disease progression was diagnosed in 4 cases: 2 patients had a local recurrence, and 2 more patients had a local recurrence and distant

metastases. In group B, 5 cases of progression were detected: one patient had lung metastases, and 4 others had local recurrence without distant metastases.

Of 125 patients included in the study, 20 cases of disease progression were registered as of November 2025. So, in the short-course radiation therapy group — 10/61 (16.3%), and in the prolonged CRT group — 10/64 (15.6%) cases. In the analysis of 12-month disease — free survival, the probability of no recurrence in group A was 84.8% (95% CI: 74.5 — 96.4), in group B — 96% (95% CI: 90.7 — 100). The median survival was not reached, and the groups did not significantly differ in disease-free survival (p = 0.54) (Fig. 2).

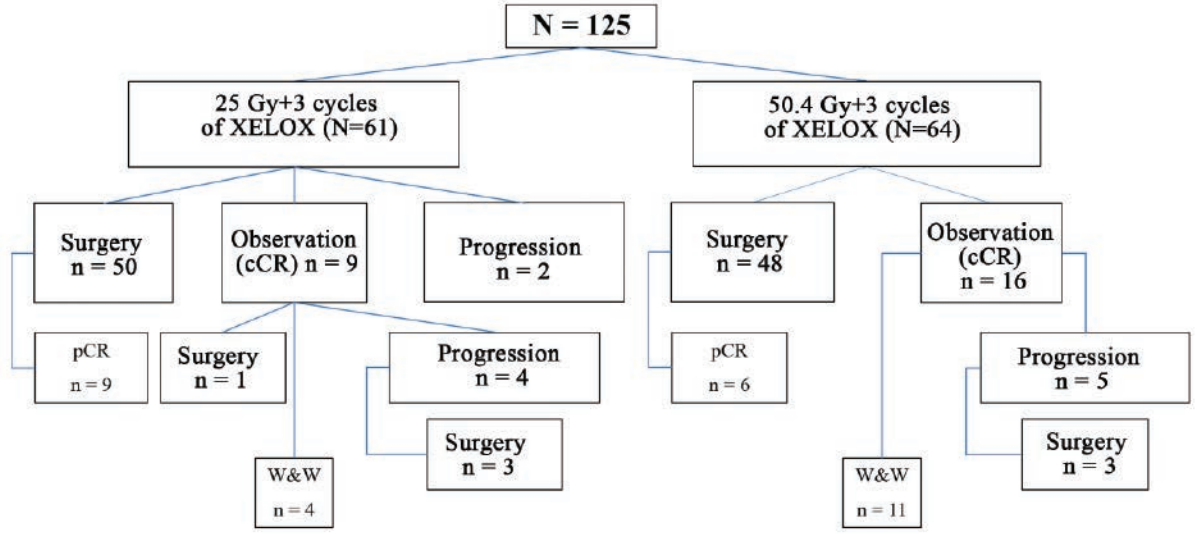

Figure 1. *Patient allocation flow chart of patients with clinical complete response*

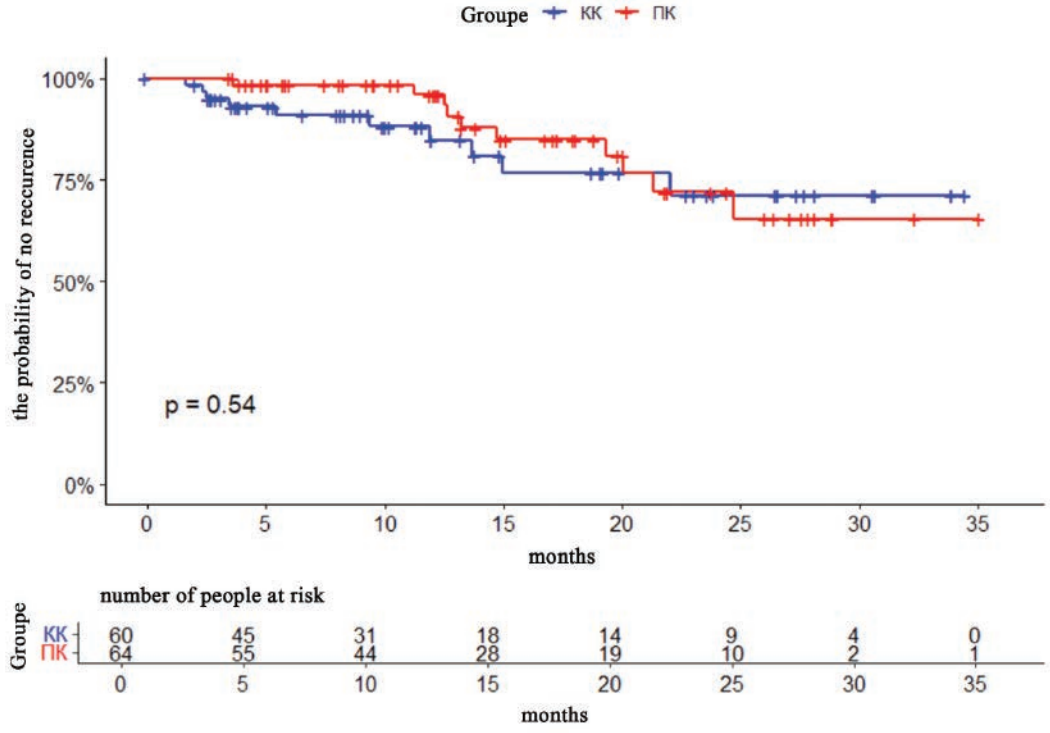

Figure 2. *Kaplan-Mayer curves for three-year disease-free survival among groups with short-course radiation therapy and long-course chemoradiotherapy*

Table 5. *Rate of complete responses*

Parameter	25 Gy + 3 cycles XELOX (N = 61)	50.4 Gy + 3 cycles XELOX (N = 64)	*p*
pCR	9/53 (14.7%)	6/51 (9.3%)	0.6
cCR (mediantraceability, months:18 (3–35))	5 (8.2%)	11 (17.2%)	0.18
Recurrence after a complete clinical response	4/9 (44%)	5/16 (31%)	0.7
Overall rate of complete responses	14 (22.9%)	17 (26.5%)	0.6

Table 6. *Results of surgical treatment*

Parameter		25 Gy + 3 cycles XELOX (N = 54)	50 50.4 Gy + 3 cycles XELOX (N = 51)	*p*
Resection margins	R0	49 (91%)	47 (92%)	1.0
	R1	5 (9%)	4 (8%)	
The quality of mesorectumectomy	Quirke 1	10 (19%)	6 (12%)	0.5
	Quirke 2	8 (15%)	6 (12%)	
	Quirke 3	36 (66%)	39 (76%)	
The grade of tumor response according to Ryan	0	9 (17%)	6 (12%)	0.6
	1	8 (15%)	12 (25%)	
	2	24 (47%)	23 (47%)	
	3	11 (21%)	8 (16%)	
Postoperative complications according to Clavien-Dindo	C-D I-II	16 (30%)	12 (23%)	0.8
	C-D IIIA	1 (2%)	0	
	C-D IIIB	1 (2%)	1 (2%)	

As of November 2025, 5/61 (8.2%) patients from group A and 11/64 (17.2%) patients from group Bwere under dynamic observation with no signs of the disease return.

One patient from group A, who was diagnosed with a complete clinical response, decided to refrain from the "watch and wait" strategy and underwent surgery. He was diagnosed with a complete pathomorphological response.

The rate of complete pathomorphological responses was 9/53 (14.7%) versus 6/51 (9.3%), respectively ($p = 0.6$). The overall rate of complete responses was 14/61 (22.9%) in the short–course RT group and 17/64 (26.5%) in the prolonged CRT group ($p = 0.6$) (Table 5).

The results of surgical treatment were comparable in terms of the rate of negative resection margins, the quality of mesorectomectomy, the grade of tumor response to neoadjuvant treatment, and postoperative complications (Table 6).

In the structure of complications, it should be noted that Clavien-Dindo's grade I-II complications were represented by gastrointestinal paresis and neurogenic bladder dysfunction, while grade III complications should be singled out separately.

In group A, two patients required re-operations. Complication IIIA — gastric bleeding (Forrest 1B) [8] from acute erosion in the area of the stomach body (registered on the 3rd day after surgery) — was stopped by installing an endoscopic clip. Complication IIIB was the colorectal anastomosis leakage on the 6th day after laparoscopically assisted low anterior rectal resection, loop ileostomy.

Re-operation required dissection of the colorectal anastomosis. In group B, complication IIIB as per Clavien-Dindo was registered in one patient — the colonoanal anastomosis leakage after laparoscopic intersphincter resection of the rectum, loop ileostomy. The patient underwent re-operation:

relaparotomy and disconnection of the colonoanal anastomosis on the 8th day after the surgery.

DISCUSSION

One of the criteria for the effectiveness of neoadjuvant therapy is the grade of therapeutic pathomorphosis of the tumor, including the rate of complete clinical responses of the tumor. Thus, according to the results of Habr-Gama, A.'s study, after a prolonged course of neoadjuvant CRT, the 10-year survival rate reached 97.7%, and the recurrence free rate reached 84%. At the same time, the rate of complete clinical responses was 26.8% [9]. The multicenter randomized STELLAR study reflected the results of total neoadjuvant therapy in a short course of large-fraction RT TFD 25 Gy with consolidating chemotherapy: the rate of complete clinical responses was 11.1% in the TNT group, whereas with prolonged CRT TFD 50 Gy it was 4.4% [10].

In order to assess the tumor's response to neoadjuvant treatment and identify a complete clinical response (cCR) of the tumor, digital and endoscopic examinations, as well as magnetic resonance imaging (MRI) of the pelvic organs, are used. The combination of these three research methods makes it possible to predict the absence of a residual tumor in 98% of cases [11]. Thus, the guideline for setting cCR during digital rectal examination is the smooth mucous layer of the rectum or the presence of a soft, elastic cicatrix. The endoscopic criterion for a complete clinical response of a tumor is a flat, whitish cicatrix without ulceration, possibly the presence of telangiectasia [12]. According to MRI data, the complete clinical response is characterized by the presence of a cicatrix in the area of a previously located tumor, which does not limit diffusion to T2, as well as the absence of visually altered lymph nodes in the mesorectal tissue [13].

In this randomized trial, when comparing TNT with short and prolonged cycles of RT, there were no significant differences in the analysis of the rate of complete clinical and pathomorphological responses — the immediate treatment results were comparable in both groups.

Total neoadjuvant therapy opens up opportunities for follow-up of patients with a complete clinical response and, in some cases, avoids surgery by adhering to the watch and wait strategy [14,15]. It should be noted that this strategy is experimental and applicable only in specialized medical institutions, and surgical treatment remains the standard of treatment for rectal cancer, often accompanied by the need for intestinal stoma. Currently, the issue of determining the category of patients who should expect a complete clinical response after TNT remains relevant. According to Guida A.M. et al., the most important prognostic factors used to assess the prognosis of complete tumor regression are: the clinical stage according to the TNM classification, extramural vascular invasion, as well as the potential involvement of the circular margin of resection [16]. It should be noted that in such large randomized trials as RAPIDO [4], Polish II [17], KCSGCO 14-03 [18], WAIT [19], PRODIGE-23 [20], there were no significant differences regarding the clinical stage of the tumor before the treatment and the complete response. The presence of extramural vascular invasion was assessed in the RAPIDO study; however, its relationship to the tumor response to TNT was not studied. When analyzing the data obtained, the depth of invasion of the primary tumor, as well as the status of lymph nodes before the start of the treatment, were identified among the predictors of a complete tumor response. The studied regimens of total neoadjuvant therapy are comparable when evaluating the immediate results of treatment. Therefore, both a short course of RT and prolonged CRT with consolidating chemotherapy can be used to treat patients with rectal cancer, and at least one in five patients can achieve a complete tumor response.

Among the limitations of the study, it is worth highlighting the lack of blindness, which could affect the subjective assessment of the toxicity of radiation and chemotherapy. The study was conducted in a highly specialized center, which may

limit the generalizability of the results to a wider population. It should also be noted that the patient follow-up period is short, which is not sufficient to assess long-term oncological results.

CONCLUSION

A short course of radiation therapy with a course of consolidating chemotherapy is comparable in terms of the rate of complete clinical and pathomorphological tumor responses in comparison with prolonged chemoradiotherapy with a course of consolidating chemotherapy.

AUTHORS CONTRIBUTION

Concept and design of the study: *Mikhail V. Alekseev, Rashid I. Fayzulin*

Collection and processing of the material: *Rashid I. Fayzulin*

Statistical processing: *Rashid I. Fayzulin, Artyom A. Balkarov*

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