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ABOUT COVER

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AIMS AND SCOPE

The primary aim of *World Journal of Gastrointestinal Oncology* (*WJGO*, *World J Gastrointest Oncol*) is to provide scholars and readers from various fields of gastrointestinal oncology with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

 WJGO mainly publishes articles reporting research results and findings obtained in the field of gastrointestinal oncology and covering a wide range of topics including liver cell adenoma, gastric neoplasms, appendiceal neoplasms, biliary tract neoplasms, hepatocellular carcinoma, pancreatic carcinoma, cecal neoplasms, colonic neoplasms, colorectal neoplasms, duodenal neoplasms, esophageal neoplasms, gallbladder neoplasms, *etc*.

INDEXING/ABSTRACTING

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RESPONSIBLE EDITORS FOR THIS ISSUE

ORIGINAL ARTICLE

Clinical and Translational Research

Total neoadjuvant therapy *vs* standard therapy of locally advanced rectal cancer with high-risk factors for failure

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Abstract

BACKGROUND

For locally advanced rectal cancer (LARC), standard therapy [consisting of neoadjuvant chemoradiotherapy (CRT), surgery, and adjuvant chemotherapy (ChT)] achieves excellent local control. Unfortunately, survival is still poor due to distant metastases, which remains the leading cause of death among these patients. In recent years, the concept of total neoadjuvant treatment (TNT) has been developed, whereby all systemic ChT-mainly affecting micrometastases-is applied prior to surgery.

AIM

To compare standard therapy and total neoadjuvant therapy for LARC patients with high-risk factors for failure.

METHODS

In a retrospective study, we compared LARC patients with high-risk factors for failure who were treated with standard therapy or with TNT. High-risk for failure was defined according to the presence of at least one of the following factors: T4 stage; N2 stage; positive mesorectal fascia; extramural vascular invasion; positive lateral lymph node. TNT consisted of 12 wk of induction ChT with capecitabine and oxaliplatin or folinic acid, fluorouracil and oxaliplatin, CRT with capecitabine, and 6-8 wk of consolidation ChT with capecitabine and oxaliplatin or folinic acid, fluorouracil and oxaliplatin prior to surgery. The primary endpoint was pathological complete response (pCR). In total, 72 patients treated with standard

therapy and 89 patients treated with TNT were included in the analysis.

RESULTS

Compared to standard therapy, TNT showed a higher proportion of pCR (23% *vs* 7%; $P = 0.01$), a lower neoadjuvant rectal score (median: 8.43 *vs* 14.98; $P < 0.05$), higher T-and N-downstaging (70% and 94% *vs* 51% and 86%), equivalent R0 resection (95% *vs* 93%), shorter time to stoma closure (mean: 20 *vs* 33 wk; $P < 0.05$), higher compliance during systemic ChT (completed all cycles 87% *vs* 76%; $P < 0.05$), lower proportion of acute toxicity grade ≥ 3 during ChT (3% *vs* 14%, $P < 0.05$), and equivalent acute toxicity and compliance during CRT and in the postoperative period. The pCR rate in patients treated with TNT was significantly higher in patients irradiated with intensity-modulated radiotherapy/volumetric-modulated arc radiotherapy than with 3D conformal radiotherapy (32% *vs* 9%; $P < 0.05$).

CONCLUSION

Compared to standard therapy, TNT provides better outcome for LARC patients with high-risk factors for failure, in terms of pCR and neoadjuvant rectal score.

Key Words: Locally advanced rectal cancer; Total neoadjuvant therapy; Pathological complete response; Neoadjuvant rectal cancer score

Core Tip: Our data suggest that treatment of locally advanced rectal cancer (LARC) with high-risk factors for failure using total neoadjuvant therapy (TNT) is more effective than standard therapy, achieving a higher rate of pathological complete response, more favourable survival prognosis, higher proportion of T-and N-downstaging, shorter time to temporary stoma closure, better compliance, and lower toxicity grade 3-5 during systemic chemotherapy. The outcomes of TNT in patients with the most aggressive form of LARC are completely comparable to TNT in all patients with LARC.

INTRODUCTION

Neoadjuvant chemoradiotherapy (CRT), followed by surgery and adjuvant chemotherapy (ChT) is recommended as the standard of care for patients with locally advanced rectal cancer (LARC). While this approach has improved local control, survival remains poor due to distant metastases, which remain the leading cause of death among these patients. The role of adjuvant ChT in the treatment of LARC remains unclear. Adjuvant ChT is often associated with poor tolerance and compliance, the need for dose reduction, and delays in beginning adjuvant treatment due to postoperative complication[1,2]. In recent years, the concept of total neoadjuvant treatment (TNT) has been developed, whereby systemic ChT, which mainly affects micrometastasis, is applied with CRT prior to surgery.

Rectal cancer patients who achieve a pathological complete response (pCR) have better disease-free survival, fewer local recurrences, better distant metastasis-free survival, and better overall survival[3]. This fact has become an important guide in testing different strategies to improve the outcome of patients with LARC. Compared to standard treatment, preoperative systemic ChT shows better compliance with ChT, increased downstaging, more margin-negative resections, and a higher rate of pCR[4-7]. Therefore, in the future, this may represent a non-operative approach to selected patients. The highest risk of systemic and/or local failure is found in patients with the

presence of at least one of the following factors: T4 status; N2 status; positive mesorectal fascia; extramural vascular invasion; and positive lateral lymph node[8-13].

The aim of this study was to compare the outcomes following TNT or standard therapy in LARC patients with high-risk factors for failure in the same time period.

MATERIALS AND METHODS

This retrospective study included all adult patients with newly-diagnosed LARC with high-risk factors for failure who were treated with TNT or standard therapy at the Institute of Oncology, Ljubljana (Slovenia), from 2016 to 2019. The inclusion criteria were: Histologically-proven rectal adenocarcinoma with distal margin of 15 cm or less from the anal verge on magnetic resonance imaging; Clinical stage II or III; and The presence of at least one of the high-risk factors for failure (T4, N2, mesorectal fascia+, extramural vascular invasion+, and/or lateral lymph node+). Patients were excluded from the study if they had distant metastases, concomitant malignancy, inflammatory bowel disease, or malabsorption syndrome. The study was approved by the local institutional review boards and the National Medical Ethics Committee of Slovenia (No. 0120-298/2019/5).

Treatment groups

Standard therapy consists of capecitabine-based CRT, followed by surgery and in patients without pCR adjuvant ChT (Figure 1). As part of the preoperative standard therapy, all patients received external-beam radiotherapy using a three-dimensional conformal radiation therapy technique (3D CRT) to the pelvis (45.0 Gy in 25 fractions and a boost to the tumour at a dose of 50.4 Gy for T3 tumours and 54 Gy for T4 tumours, in three to five fractions) and intensity-modulated radiotherapy (IMRT) or volumetric modulated arc therapy (VMAT) to the pelvis (41.8 Gy and simultaneously integrated boost to the tumour at a dose of 46.2 Gy for T3 tumours or 48.4 Gy to T4 tumours in 22 fractions). Concomitant ChT was performed *via* administration of capecitabine at a daily dose of 825 mg/m^2/12 h per os on irradiation day in 3D CRT or from the first to the last irradiation day in IMRT/VMAT. Surgery was scheduled to take place 6-10 wk after completion of CRT. In cases that did not achieve pCR, adjuvant ChT was started at 4-8 wk after surgery. In cases of microscopic residual disease (R1), adjuvant ChT consisted of eight cycles of capecitabine and oxaliplatin (CAPOX). In cases of poor compliance or heart failure, adjuvant ChT consisted of four cycles of 5-fluorouracil and leucovorin.

TNT consisted of induction ChT with CAPOX or with folinic acid, fluorouracil and oxaliplatin (FOLFOX), capecitabine-based CRT and consolidation ChT with CAPOX/FOLFOX prior to surgery. TNT with the CAPOX regimen was defined as four induction cycles (12 wk) of CAPOX, capecitabine-based CRT and two consolidation cycles (6 wk) of CAPOX before surgery. One cycle of the CAPOX regimen involved capecitabine (1000 mg/m^2/12 h per os on days 1-14) and oxaliplatin (oxaliplatin 130 mg/m^2 intravenous over 2 h on day 1) every 3 wk. In cases with expectation of poorer compliance, patients received the FOLFOX regimen instead of ChT according to the CAPOX regimen. TNT with the FOLFOX regimen was defined as 12 wk of induction ChT and 8 wk of consolidation ChT. The FOLFOX regimen involved 5-fluorouracil (400 mg/m^2 intravenous bolus on day 1, then 1200 mg/m^2/d for 2 d), oxaliplatin (85 mg/m^2 intravenous over 2 h on day 1), and leucovorin (400 mg/m^2 intravenous over 2 h on day 1) every 2 wk, twice. CRT in TNT was the same as in standard therapy. Surgery was scheduled to take place 8-10 wk after completion of CRT or 1-2 wk after completion of consolidation ChT.

The study was based upon a cohort of 161 LARC patients who had high-risk factors for failure and who underwent treatment between the years of 2016 and 2019. A total of 72 patients received standard therapy (standard group) and 89 patients received TNT (TNT group). The baseline characteristics for all evaluable patients are listed in Table 1. All patients treated with TNT were pre-treatment staged with computed tomography (CT) of the chest, abdomen and pelvis. Patients treated with standard therapy were pre-treatment staged with CT of the chest, abdomen and pelvis or positron emission tomography-CT (86%); only a minority of patients (14%) had a chest x-ray or abdominal ultrasound in combination with/without CT.

Endpoints

The primary endpoint was pCR rate, which was defined as ypT0N0. Secondary endpoints were neoadjuvant rectal (NAR) score, proportion of T-and N-downstaging,

Table 1 Patient characteristics

Characteristic		Standard therapy, *n* = 72, (%)	TNT, *n* = 89, (%)	*P* value
Age in year	< 65	29 (40)	66 (74)	< 0.001
	≥ 65	43 (60)	23 (26)	
	Range	40-84	33-79	
	mean [SD]	65.4 [10.5]	57.5 [10.1]	< 0.001
Sex	M	45 (63)	54 (61)	0.813
	F	27 (38)	35 (39)	
PS WHO	0	48 (67)	67 (75)	0.229
	1	24 (33)	22 (25)	
High-risk factors for failure	cT4	15 (21)	33 (37)	0.025
	cN2	49 (68)	62 (70)	0.827
	MRF+	39 (54)	66 (74)	0.008
	EMVI+	27 (38)	65 (73)	< 0.001
	Lateral node	15 (21)	8 (9)	0.033
cTN	T2N2	1 (1)	1 (1)	0.138[1]
	T3N0	1 (1)	0 (0)	
	T3N1	21 (29)	20 (22)	
	T3N2	34 (47)	35 (39)	
	T4N1	1 (1)	7 (8)	
	T4N2	14 (19)	26 (29)	
Distance from anal verge in cm	≤ 5	27 (38)	29 (33)	0.370
	5.1-10	37 (51)	43 (48)	
	≥ 10.1	8 (11)	17 (19)	

[1]Likelihood-ratio test.

EMVI: Extramural vascular invasion; MRF: Mesorectal fascia; PS: Performance status; TNT: Total neoadjuvant treatment; WHO: World Health Organization.
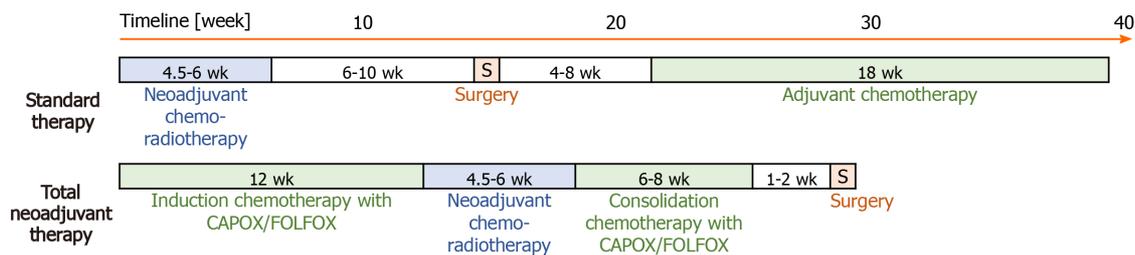
Figure 1 Timeline and protocol of both treatment groups. CAPOX: Chemotherapy with capecitabine and oxaliplatin; FOLFOX: Chemotherapy with folinic acid, fluorouracil and oxaliplatin.

rates of R0 resection, time to stoma closure, acute toxicity, and compliance during treatment. The NAR score was calculated using the equation $[5 \text{ pN} - 3 \times (cT-pT) + 12]^2 / 9.61$ and further classified as low (< 8), intermediate (8-16), or high (< 16)[14,15]. T- or N-downstaging was defined as a reduction in the clinical stage relative to the pathohistological stage. The time to stoma closure was defined as the time from surgery to temporary stoma closure. Treatment-related toxicities were scored according to the National Cancer Institute's Common Terminology Criteria for Adverse Events version 4.0[16].

Statistics analyses

All statistical analyses were performed using the SPSS statistical software, version 26.0 (IBM Corp., Armonk, NY, United States). Patient and treatment parameters were compared with the χ^2 test or Fisher's exact test for categorical variables and with Student's *t*-test for continuous variables. The normality of data distribution was estimated by graphical analysis. In the case of an expected count less than 5 in cells with categorical variables, a likelihood-ratio test was performed, where indicated. A *P* value of < 0.05 was considered statistically significant. Frequencies and percentages are given in the tables presented herein, unless otherwise indicated. The statistical methods of this study were reviewed by a biomedical statistician holding a PhD in statistics (Rho sigma, https://www.rosigma.si/en/rhosigma).

RESULTS

Efficiency

Patients treated with TNT had a statistically significantly higher proportion of pCR compared to those who received the standard treatment (23% *vs* 7%; *P* = 0.007). The odds of achieving pCR were determined to be 3.9-fold higher in the TNT group than in the standard group (odds ratio of 3.92 with a 95% confidence interval of 1.38 to 11.14). The two treatment groups differed significantly in age and in proportion of high-risk factors for failure, but these characteristics alone did not have a significant effect on the rate of pCR. Furthermore, the influence of different characteristics (cT, full dose of systemic ChT, full-dose radiotherapy, all planned preoperative treatment, time from completion of radiotherapy to surgery, presence of acute toxicity, irradiation technique) on the rate of pCR was tested. Among the previously mentioned characteristics, only the irradiation technique showed a statistically significant effect on the rate of pCR in the TNT group, in contrast to the standard therapy group. In detail, we showed a statistically significantly higher proportion of pCR with IMRT/VMAT than with 3D CRT (32% *vs* 9%; *P* = 0.03). Similar to the proportion of pCR achievement, the NAR score showed a more favourable distribution in TNT compared to standard treatment (median: 8.43 *vs* 14.98; *P* < 0.001) (Table 2).

Compliance and toxicity

When comparing compliance and toxicity, we found statistically significant differences between the two treatment groups only during the period of systemic ChT administration (Tables 3 and 4). There were no adverse events experienced by patients with grade 4-5 during systemic ChT nor by those with grade 5 during CRT. The proportion of patients completing all planned cycles of systemic ChT was statistically higher in the TNT group than in the standard group. A statistically significant association was observed between the toxicity and the type of treatment administered during systemic ChT. Specifically, in the TNT group there was a slightly higher proportion of patients who experienced toxicity (82% *vs* 76%) and a higher proportion of patients who experienced adverse events of grades < 3 (79% *vs* 62%). In spite of that, there was a lower proportion of patients who experienced adverse events of grades 3-5 (3% *vs* 14%). The most frequent adverse events during systemic ChT were hand-foot syndrome (40%) in the standard group and paraesthesia (61%) in the TNT group (Table 5). The most frequent adverse events of grade 3 during systemic ChT were hand-foot syndrome (10%) in the standard group and hand-foot syndrome (1%), infection (1%) and thromboembolic event (1%) in the TNT group.

There were no differences between the groups in compliance and acute toxicities during CRT and surgery. In the standard group, 70 (97%) patients underwent surgery, of which 1 patient died a few days after surgery due to septic shock. Two patients who had a clinical complete response refused surgery. In the TNT group, 82 (92%) patients underwent surgery and 6 (7%) patients refused surgery, including 4 patients with clinical complete response among the latter. However, at the end of the first cycle of consolidation ChT, 1 patient developed perineal infection and underwent two non-radical operations at another hospital, dying after the second operation.

DISCUSSION

Through our study, we have confirmed that the treatment of LARC patients with high-risk factors for failure with TNT was statistically significantly better than with

Table 2 Treatment characteristics

Characteristic		Standard therapy, *n* = 70, (%)	TNT, *n* = 82, (%)	*P* value
pCR		5 (7)	19 (23)	0.007
CR		7 (10)	23 (26)	0.009
NAR score	mean [SD]	16.8 [12.9]	10.7 [10.8]	0.002
NAR classes	< 8	9 (13)	35 (43)	< 0.001
	8-16	38 (56)	33 (40)	
	> 16	21 (31)	14 (17)	
Surgery	R0	65 (93)	78 (95)	0.445[1]
	R1	4 (6)	4 (5)	
	R2	1 (1)	0 (0)	
Weeks to stoma closure	mean [SD]	32.8 [18.6]	20.1 [10.9]	< 0.001

[1]Likelihood-ratio test.

CR: Complete response; NAR: Neoadjuvant rectal; pCR: Pathological complete response; TNT: Total neoadjuvant treatment.

Table 3 Treatment compliance during chemoradiotherapy and systemic chemotherapy, *n* (%)

	Standard therapy during CRT	TNT	*P* value
Patients who received CRT	72 (100)	88 (99)	0.275[1]
Patients who received RT	0 (0)	1 (1)	
Full-dose ChT (CAP or 5-FU + LV)	62 (86)	67 (75)	0.087
Modification of concomitant ChT	10 (14)	22 (25)	
Modification of RT	1 (1)	0 (0)	
	During adjuvant ChT	During systemic ChT	
Without ChT due to pCR	5 (7)	0 (0)	
Patients who received ChT	50 (72)	89 (100)	
All planned cycle			
6c of systemic ChT (CAP or CAPOX)	34 (68)	76 (85)	0.048[1]
Other alternative schemes	4 (8)	2 (2)	
No	12 (24)	11 (12)	
Full-dose			
6c of systemic ChT (CAP or CAPOX)	25 (50)	56 (63)	0.158[1]
Other alternative schemes	4 (8)	2 (2)	
No	21 (42)	31 (35)	

[1]Likelihood-ratio test.

5-FU: 5-fluorouracil; c: Cycle; CAP: Capecitabine; CAPOX: Capecitabine and oxaliplatin; ChT: Chemotherapy; CRT: Chemoradiotherapy; LV: Leucovorin; pCR: Pathological complete response; RT: Radiotherapy; TNT: Total neoadjuvant treatment.

standard treatment, in terms of the pCR and NAR score. Despite the fact that the treatment groups differed in age distribution and in the proportions of some high-risk factors for failure, we showed by statistical analysis that these characteristics do not affect achievement of pCR. Moreover, the TNT group had overall greater extent of disease but achieved a higher proportion of pCR. Treatment of LARC patients with high-risk factors for failure by means of TNT is more effective than standard therapy because it achieves a higher rate of pCR, more favourable survival prognosis, higher proportion of T-and N-downstaging, shorter time to temporary stoma closure, better compliance, and lower toxicity grade 3-5 during systemic ChT. To our knowledge, our

Table 4 Acute toxicity in all periods in both treatment groups

Toxicity	Standard therapy, *n* (%)	TNT, *n* (%)	*P* value
During systemic ChT			0.037[1]
Without	12 (24)	16 (18)	
Grade 1-2	31 (62)	70 (79)	
Grade 3	7 (14)	3 (3)	
During CRT			0.553[1]
Without	13 (18)	21 (24)	
Grade 1-2	57 (79)	64 (72)	
Grade 3-4	2 (3)	4 (4)	
Postoperative complications			0.140
Without	43 (61)	62 (76)	
Grade 1-2	18 (26)	15 (18)	
Grade 3-5	9 (13)	5 (6)	

[1]Likelihood-ratio test.

ChT: Chemotherapy; CRT: Chemoradiotherapy; TNT: Total neoadjuvant treatment.

distribution of the NAR prognostic score in the TNT group is the most favourable of all published studies on the treatment of LARC with near TNT, CRT or neoadjuvant radiotherapy[17-21]. Our patients with the most aggressive form of LARC treated with TNT had a similar rate of pCR as all patients with LARC, which speaks in favour of TNT[22,23].

We showed a statistically significant influence of the irradiation technique on the proportion of pCR in the TNT group. This statistically significant influence was not found in the standard group but a similar trend was observed. One of the reasons why we failed to demonstrate the influence of the irradiation technique on the proportion of pCR in standard treatment could be the small sample size. In the standard group, only 17% of patients were irradiated with IMRT/VMAT, whereas in the TNT group, this was 61%. The higher rate of pCR in the TNT group irradiated with IMRT/VMAT is attributed to the fact that shortening of the overall treatment time, accuracy of irradiation technique and hypofractionation (higher dose per fraction, simultaneous integrated boost) were enabled with IMRT/VMAT application[24]. We believe that in the trials of different TNT approaches, greater emphasis should be placed on the choice of optimal radiotherapy.

To the best of our knowledge, this study is one of the first comparing standard therapy and TNT in LARC patients with high-risk factors for failure, in addition to the RAPIDO trial[25]. We achieved a slightly lower rate of pCR with both treatments than that reported for the RAPIDO trial (7% and 23% *vs* 14% and 28% respectively)[26]. Conversely, if we focus only on patients who were irradiated with more advanced irradiation techniques, *i.e.* IMRT/VMAT, we found higher proportions of pCR achievement (17% and 32% *vs* 14% and 28% respectively) compared to the RAPIDO trial. When comparing our study with the RAPIDO trial, it should be noted that patients in the latter were irradiated with a short-course radiotherapy, whereby the rate of tumour regression is lower and the occurrence of pCR is less likely[27]. On the other hand, it should be noted that in the RAPIDO trial, there was a longer interval between the end of radiotherapy and surgery, which may have affected the higher rate of pCR[3,28,29].

After analysing the results of treatment of this high-risk group of patients in two previous Slovenian studies, we reported 10.5% of pCR in 2011-2013 and 20% in 2014-2015[24,30,31]. Preoperative treatment was more intensive than standard treatment in both studies. In our present study, the standard group had 7% of pCR, which is less than in the two previous Slovenian studies, as expected. This fact suggests that the population of patients with LARC with high-risk factors for failure needs a more intensive preoperative treatment regimen as the only standard therapy, in order to achieve a higher rate of pCR. In addition to different treatment regimens, patients in the two previous Slovenian studies were treated with different irradiation techniques.

Table 5 Acute toxicity during systemic chemotherapy in both treatment groups

Toxicity during systemic ChT	Adjuvant ChT (standard therapy), 50 patients						During induction and consolidation ChT (TNT), 89 patients					
	Grade 1-2		Grade 3		Grade 4		Grade 1-2		Grade 3		Grade 4	
Thrombocytopenia	7	14%	0		0		11	12%	0		0	
Anaemia	15	30%	0		0		12	13%	0		0	
Neutropenia	3	6%	0		0		8	9%	0		0	
Diarrhoea	6	12%	1	2%	0		10	11%	0		0	
Nausea	2	4%	1	2%	0		29	33%	0		0	
Vomiting	2	4%	1	2%	0		8	9%	0		0	
Hand foot syndrome	15	30%	5	10%	0		10	11%	1	1%	0	
Paraesthesia	1	2%	0		0		54	61%	0		0	
Acute renal failure	1	2%	0		0		0		0		0	
Rectal fistula	0		1	2%	0		0		0		0	
Stoma site infection	1	2%	1	2%	0		0		0		0	
Hepatotoxicity	0		0		0		3	3	0		0	
Infection	5	10%	0		0		2	2%	1	1%	0	
Chest pain	0		0		0		1	1%	0		0	
Thromboembolism	5	10%	0		0		1	1%	1	1%	0	
Ileus	1	2%	0		0		1	1%	0		0	
Enterocolitis	0		0		0		1	1%	0		0	
Without toxicity	12 (24%)						16 (18%)					

ChT: Chemotherapy; TNT: Total neoadjuvant treatment.

Generally speaking, our TNT with 3D CRT differed from treatment in patients in 2011-2013 in the more aggressive preoperative systemic ChT, which, however, was not clearly reflected in a higher rate of pCR (9% *vs* 10.5%). On the other hand, our TNT with IMRT/VMAT differed from treatment in patients in 2014-2015 in additional preoperative systemic ChT, which was clearly reflected in a higher rate of pCR (32% *vs* 20%). These facts confirm the position of systemic ChT in the preoperative period to achieve more effective downstaging or a high proportion of pCR. In summary, we believe that systemic ChT has a place in the preoperative period but consideration should be given to choosing the more optimal scheme of preoperative systemic ChT. Therefore, the influence of a radiotherapy regimen and of the aggressiveness of systemic ChT on the outcome of treatment must be taken into account when comparing and researching different TNT schemes.

Compliance with all planned cycles of preoperative systemic ChT in the TNT group was statistically significantly better compared to that in the standard group. This is in line with the findings of other randomised studies in LARC patients and LARC patients with high-risk factors for failure[5,25]. Compliance with the systemic ChT of our TNT group is also comparable to compliance in TNT of LARC patients in other studies (86%-100%)[32].

As with compliance, the toxicity between both groups differs most during the period of systemic ChT. Standard treatment showed an 11% higher rate of toxicity grade ≥ 3 compared to TNT (14% *vs* 3%). Studies of the TNT and near TNT regimen in the treatment of LARC patients with high-risk factors have demonstrated a varied spectrum of the most common preoperative adverse reactions of grades ≥ 3. All rates of the most common grade ≥ 3 adverse reactions were higher (range: 9%–42%) than in our TNT group, where radiodermatitis and hand-foot syndrome were the most common (in 2%)[25,33-39]. It should be noted that our scheme of TNT is, according to the aforementioned studies, the least aggressive, but at the same time having a very comparable rate of pCR. We found a markedly lower rate of toxicity of grades 3-5 during TNT when comparing toxicities reported from the RAPIDO trial (7% *vs* 48%)[25]. The lower toxicity in our study could be attributed to the fact that our

patients received ChT separately in two parts, so we believe that there was a lower likelihood of potentiation of adverse effects. Given the fact that in the RAPIDO trial diarrhoea was the most common adverse effect of grades ≥ 3 in TNT, the difference in toxicity was most likely also due to a various radiotherapy regimen. The high rate of diarrhoea may have been exacerbated by larger fields and irradiation with 3D CRT as short-course radiotherapy in the RAPIDO trial. On the other hand, in our long-course CRT with IMRT/VMAT with a simultaneous integrated boost without dose escalation, we had higher accuracy due to the contribution of various factors, such as the higher accuracy of delineation using planned magnetic resonance imaging and daily checking of the patient's position during the radiotherapy administration[24].

The proportion of postoperative complications in both groups (39% for the standard group and 24% for the TNT group) was comparable to that of other studies researching TNT in LARC. These other studies showed 13%-51% of postoperative complications[32]. Comparing the proportions of postoperative complications with the largest randomised study in the field of treatment of LARC patients with high-risk factors, we found a fairly comparable or even a slightly lower proportion of postoperative complications with standard therapy (39% *vs* 47%) and, on the other hand, almost a one-half lower proportion of postoperative complications with TNT (24% *vs* 50%). One reason for this could be a more effective downstaging with our TNT regimen and consequently a lower rate of abdominoperineal excision compared to the RAPIDO trial (17% *vs* 58%), despite the fact that we had more patients with low-lying tumours (33% *vs* 22%)[25]. It is known that the rate of postoperative complications is higher after abdominoperineal excision than after sphincter-preserving surgery[40].

Our study has some limitations that need to be considered when favouring TNT over other treatment options for LARC patients with high-risk factors for failure. First, this study used a retrospective design and, therefore, has a lower level of data reliability than does a prospective or randomised study. Second, patients were followed for up to 3 mo after the end of treatment, which is a short period. A longer follow-up is required to determine the impact on local control, disease-free survival and overall survival. TNT is a relatively new approach in the treatment of LARC, and data on 5-year survival parameters are not yet available.

CONCLUSION

The outcome of TNT is better than that of standard treatment in LARC patients with high-risk factors for failure in terms of the pCR rate and the NAR prognostic score. Our study is one of the first to compare standard treatment and TNT in LARC patients with high-risk factors for failure. With TNT administration, we achieved a statistically significantly higher rate of pCR with IMRT/VMAT compared to 3D CRT. The reasons for the higher pCR are the accuracy of the irradiation technique and the possibility of hypofractionation (higher dose per fraction, simultaneous boost to the tumour) and thus shorter irradiation time.

ARTICLE HIGHLIGHTS

Research background

Distant metastases remain the leading cause of death for patients with locally advanced rectal cancer. Systemic chemotherapy that mainly affects micrometastasis is administered with chemoradiotherapy prior to surgery in total neoadjuvant treatment.

Research motivation

Currently, it is unknown which treatment is better for patients with locally advanced rectal cancer and high-risk factors for treatment failure.

Research objectives

To compare the results of total neoadjuvant therapy and standard therapy in patients with locally advanced rectal cancer and high-risk factors for failure in the same time period.

Research methods

We selected patients with locally advanced rectal cancer and high-risk factors for

failure who were treated with standard therapy or with total neoadjuvant therapy. High-risk for failure were defined by the presence of at least one of the following factors: T4 status; N2 status; positive mesorectal fascia; extramural vascular invasion; and/or positive lateral lymph node.

Research results

This retrospective study showed that total neoadjuvant therapy yielded a higher proportion of pathological complete response (pCR), lower neoadjuvant rectal score, higher T-and N-downstaging, equivalent R0 resection, shorter time to stoma closure, higher compliance during systemic chemotherapy, lower proportion of acute toxicity grades ≥ 3 during chemotherapy, and equivalent acute toxicity and compliance during chemoradiotherapy and in the postoperative period. With total neoadjuvant therapy, we achieved a statistically significantly higher rate of pCR with intensity-modulated radiotherapy/volumetric modulated arc therapy compared to the three-dimensional conformal radiation therapy technique.

Research conclusions

The outcome of total neoadjuvant therapy is better than that of standard treatment of locally advanced rectal cancer with high-risk factors for failure, in terms of the pCR rate and the neoadjuvant rectal prognostic score.

Research perspectives

Randomized studies are needed to more reliably assess the benefits of total neoadjuvant therapy for locally advanced rectal cancer with high-risk factors for failure.

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