research article

Total neoadjuvant treatment of locally advanced rectal cancer with high risk factors in Slovenia

Mojca Tuta[1], Nina Boc[1], Erik Brecelj[2], Mirko Omejc[4], Franc Anderluh[3], Ajra Secerov Ermenc[3], Ana Jeromen Peressutti[3], Irena Oblak[3], Bojan Krebs[5], Vaneja Velenik[3]

[1] Division of Radiology, Institute of Oncology, Ljubljana, Slovenia
[2] Division of Surgery, Institute of Oncology, Ljubljana, Slovenia
[3] Division of Radiotherapy, Institute of Oncology, Ljubljana, Slovenia
[4] Division of Surgery, University Medical Centre Lubljana, Ljubljana, Slovenia
[5] Division of Surgery University Medical Centre Maribor, Maribor, Slovenia

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Correspondence to: Asst. Prof. Vaneja Velenik, M.D., Ph.D., Institute of Oncology Ljubljana, Zaloška cesta 2, SI-1000 Ljubljana, Slovenia.
E-mail: vvelenik@onko-i.si

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Background. In the light of a high rate of distant recurrence and poor compliance of adjuvant chemotherapy in high risk rectal cancer patients the total neoadjuvant treatment was logical approach to gaining acceptance. We aimed to evaluate toxicity and efficiency of this treatment in patients with rectal cancer and high risk factors for local or distant recurrence.

Patients and methods. Patients with rectal cancer stage II and III and with at least one high risk factor: T4, presence of extramural vein invasion (EMVI), positive extramesorectal lymph nodes or mesorectal fascia (MRF) involvement were treated with four cycles of induction CAPOX/FOLFOX, followed by capecitabine-based radiochemotherapy (CRT) and two consolidation cycles of CAPOX/FOLFOX before the operation. Surgery was scheduled 8–10 weeks after completition of CRT.

Results. From November 2016 to July 2018 66 patients were evaluable. All patients had stage III disease, 24 (36.4%) had T4 tumors, in 46 (69.7%) EMVI was present and in 47 (71.2%) MRF was involved. After induction chemotherapy, which was completed by 61 (92.4%) of patients, radiologic downstaging of T, N, stage, absence of EMVI or MRF involvement was observed in 42.4%, 62.1%, 36.4%, 69.7% and 68.2%, respectively. All patients completed radiation and 54 (81.8%) patients received both cycles of consolidation chemotherapy. Grade 3 adverse events of neoadjuvant treatment was observed in 4 (6%) patients. Five patients rejected surgery, 3 of them with radiologic complete clinical remissions. One patient did not have definitive surgery of primary tumor due to unexpected cardiac arrest few days after sigmoid colostomy formation. Among 60 operated patients pathological complete response rate was 23.3%, the rate of near complete response was 20% and in 96.7% radical resection was achieved. Pathological T, N and stage downstaging was 65%, 96.7% and 83.4%, respectively. Grade ≥ 3 perioperative complications were anastomotic leakage in 3, pelvic abscess in 1 and paralytic ileus in 2 patients. The rate of pathologic complete response (pCR) in patients irradiated with 3D conformal technique was 12.1% while with IMRT and VMAT it was 37% ($p < 0.05$). Hypofractionation with larger dose per fraction and simultaneous integrated boost used in the latest two was the only factor associated with pCR.

Conclusions. Total neoadjuvant treatment of high risk rectal cancer is well tolerated and highly effective with excellent tumor and node regression rate and with low toxicity rate. Longer follow up will show if this strategy will improve distant disease control and survival.

Key words: total neoadjuvant treatment; radiochemotherapy; rectal cancer; capox

Introduction

More than half of the patients with rectal cancer present with locally advanced stage of disease and are treated with combination of preoperative chemoradiotherapy (CRT) followed by total mesorectal excision (TME) and adjuvant chemotherapy with 5-fluorouracil or capecitabine with or without oxaliplatin. With this approach decreased 5 year local recurrence rates to approximately 5–10% has been observed. However, good local control did not result in better survival due to high, more than 30% rate of distant recurrence, which remains the leading cause of rectal cancer-related death.[1,2] The reason probably lies in insufficient dose of chemotherapy (ChT) prior the operation and poor compliance of patients to recieve remaining postoperative ChT needed to influence on micrometastases and prevent distant spread of the disease. Randomised trials testing intensification of preoperative treatment by adding oxaliplatin to capecitabine based CRT failed to prove significant benefit over the gold standard. Oxaliplatin significantly decreased distant failure, but did not improve overall survival (OS), disease free survival (DFS) and local failure (LF) compared to 5-fluorouracyl CRT.[3]

In the light of these unfavorable facts shifting adjuvant ChT into preoperative setting, so called the total neoadjuvant treatment (TNT), was the next logical step. In comparison with standard treatment, TNT is more effective regarding tumor regression rate, the rate of radical resections, sphincter sparing proceadures, patological complete remissions (pCR) and offers a good platform for less radical surgery or potential non-operative management in selected patients. Further, more favorable compliance and lower toxicity rate if ChT is deliverd preoperatively, allows more patients to complete the treatment according to the protocol.[4-6] Currently, there are two slightly different TNT approaches in the treatment of locally advanced rectal cancer (LARC) with high risk of local recurrence. While American National Comprehensive Cancer Network (NCCN) guidelines recommend induction 5-fluorouracyl, leucovorin and oxaliplatin (FOLFOX) or capecitabine and oxaliplatin (CAPOX) ChT followed by CRT and operation, in the northern Europe the same ChT given after short course RT as a consolidation therapy before surgery, is more prefered treatment option according to the latest guidelines from European Society for Medical Oncology (ESMO).[7-9]

In Slovenia, the TNT was introduced in 2016. The treatment scheme consists of four induction cycles of FOLFOX/CAPOX, capecitabine or 5-FU-based CRT and two additional cycles of FOLFOX/CAPOX as a consolidation therapy before the TME surgery. With this regimen the interval between conclusion of CRT and surgery at 8–10 weeks is preserved. At first, only the patients with T4 tumors or with the presence of EMVI or extramesorectal lymph nodes involvement on magnetic resonance imaging (MRI) were considered candidates for TNT. Later on two more indications for this treatment selection were added: N2 disease and the distance £ 1 mm of tumor or lymph nodes from mesorectal fascia (MRF).

The main objective of the present study is to evaluate efficiency and toxicity of TNT treatment in LARC with high risk factors for local or distant recurrence in Slovenia.

Patients and methods

Patient selection

This prospective observational study included all patients with newly diagnosed LARC, treated with TNT from November 2016 to July 2018. Inclusion criteria for the treatment were as follows: histologically proven rectal adenocarcinoma situated up to 15 cm from the anal verge; locally advanced disease (T3/T4 or N+) confirmed by MRI; no evidence of distant metastases on pretreatment workout; the presence of at least one high risk factor: T4, extramural vascular invasion (EMVI), positive extramesorectal lymph nodes or MRF involvement. Patients with second primary or history of carcinoma other than nonmelanoma skin cancer or cervical carcinoma in situ, inflammatory bowel disease and malabsorbtion syndrome were excluded from the analysis. The study was performed with the approval of the Ethics Committee of the Institute of Oncology Ljubljana, number ERIDEK-0014/2019 and ERID-KSOPKR-0009/2019, the National Medical Ethics Committee of the Republic of Slovenia, number 0120-298/2019/5, and in accordance with the principles of the Declaration of Helsinki. All the patients signed informed consent form before treatment.

Pretreatment evaluation

Pretreatment evaluation included the patient's medical history, physical examination, laboratory test (complete blood count, serum biochemistry, carcinoembryonic antigen), colonoscopy with biopsy, computed tomography of the chest and

abdomen and MRI of the pelvis for local staging. All patients were evaluated on a multidisciplinary meeting.

Treatment regimen

All protocol-mandated preoperative treatment was delivered at the Institute of Oncology in Ljubljana. Induction chemotherapy consisted of four cycles of capecitabine (1000 mg/m2/12h per os on days 1-14) and oxaliplatin (oxaliplatin 130 mg/m2 IV over 2h on day 1) (CAPOX regimen) every three weeks or in patients with difficulties of swallowing pills 5-fluorouracil (400 mg/m2 IV bolus on day 1 then 1200 mg/m2/day for 2 days), oxaliplatin (85 mg/m2 IV over 2 h on day 1), and leucovorin (400 mg/m2 IV over 2 h on day 1) (mFOLFOX6 regimen) every 2 weeks.

Radiotherapy was scheduled 1 week after the completion of induction chemotherapy. CT simulation and treatment were performed with the patient in the supine position with full bladder protocol. Fusion with planning MRI carried out with the patient in the treatment position was used for contouring assistance when planning MRI was available. Three-dimensional conformal radiation therapy (3D-CRT), intensity-modulated radiotherapy using simultaneously integrated boost (IMRT SIB) or volumetric modulated arc therapy (VMAT SIB) were administered. 3D-CRT included 45 Gy to the pelvis in 25 fractions followed by the boost to the tumor to the dose 50.4 Gy for T3 and to 54 Gy for T4 tumors in 3–5 fractions. IMRT SIB or VMAT SIB included pelvic dose of 41.8 Gy with SIB to the tumor to the dose 46.2 Gy for T3 and 48.4 Gy for T4 tumors in 22 fractions.[10] Concomitant chemotherapy with capecitabine was administered from the first to the last day of the radiation treatment (including weekends) at a daily dose of 825 mg/m2/12 hours if IMRT/VMAT SIB technique was used and only on RT days in case of 3D conformal RT.

During radiotherapy the patients were evaluated weekly to check out acute toxicity according to the Common Toxicity Criteria for Adverse Events (CTCAE) version 4.0 and compliance with the intended treatment plan during CRT.[11] Two cycles of consolidation ChT with CAPOX were delivered after completion of CRT. Surgery was scheduled 8–10 weeks after the end of CRT. The choice between abdominoperineal and sphincter preserving surgery was at the surgeon's discretion. No additional treatment was administered after surgery.

Endpoints

The primary endpoint was pCR. The secondary endpoints included clinical and pathological downstaging, neoadjuvant rectal (NAR) score, toxicity profile, time to stoma closure and compliance during treatment. Pathologic stage was recorded according to the American Joint Committee on Cancer (AJCC) 7th edition.[12] Tumor regression grade was recorded according to the criteria by Dworak *et al.*[13] We defined pCR as ypT0N0 (Dworak tumor regression grade 4) – the absence of residual viable tumor cells in the surgical specimen.

Statistical analysis

The clinical tumor response was analyzed by comparison of the baseline clinical MRI stage with the one obtained on restaging before the CRT and 8 weeks from the end of CRT (if it was performed). For pathological tumor response the baseline MRI was compared with pathological record of surgical specimen. Each staging component (*T, N, stage, absence of EMVI or MRF involvement*) was analyzed separately. All pre- and postreatment MRI scans were reviewed independently by one radiologist.

Statistical analysis was performed using the Statistical Package for the Social Sciences, version 26.0. (SPSS Inc, Chicago, IL).[14] Descriptive statistics were used for presenting preoperative, surgical and pathological results. Possible associations between disease or treatment negative factors and pCR were determined with the Fisher exact test. All results with a p value of < 0.05 were considered statistically significant.

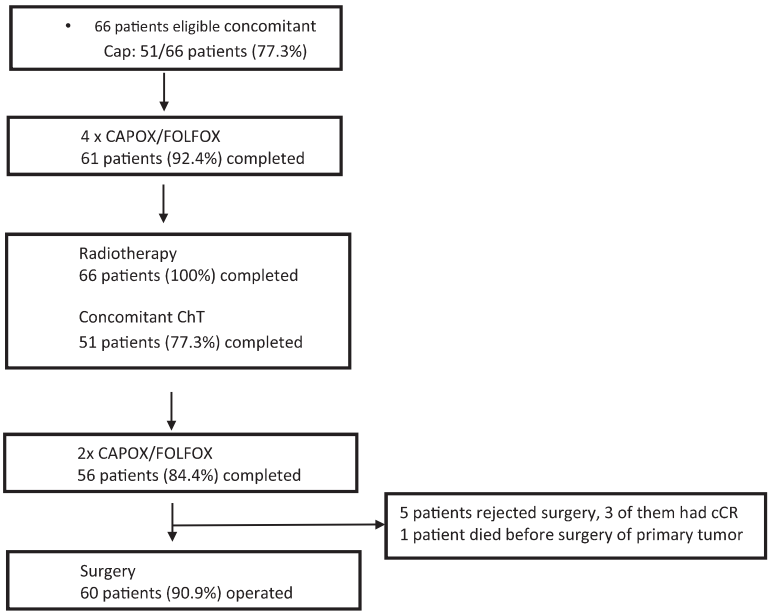
Results

Patient characteristics

Between November 2016 and July 2018, 66 patients with LARC with high risk factors (LARC-HR) were included. Table 1 describes patient's demographic and baseline clinical characteristics. Median age was 59 years (range 33–74), two thirds were men. All patients had stage III disease, 24 (36.4%) had T4 tumors, in 46 (69.7%) EMVI was present and in 47 (71.2%) MRF was involved.

Treatment delivery and toxicity

Figure 1 shows patients' progress through the treatment. Induction chemotherapy was com-



Cap = capecitabine; cCR = clinical coplete response; ChT = chemotherapy

FIGURE 1. Patients' progress through the treatment.

TABLE 1. Patient's demographic and baseline clinical characteristics (N = 66)

Characteristic	No. (66)	%
Gender		
Male	41	62.1
Female	25	37.9
Age, years		
Median, range	59, 33–74	
ECOG performance status		
0	50	75.8
1	16	24.2
Distance from the anal verge		
< 5 cm	25	37.9
5–10 cm	30	45.4
>10 cm	11	16.7
High risk factors		
cT4	24	36.4
EMVI+	46	69.7
Positive extramesorectal lgl	3	4.5
MRF+	47	71.2
cTN stage		
T2N2	1	1.5
T3N1	17	25.8
T3N2	24	36.4
T4N1	3	4.5
T4N2	21	31.8

c = clinical; ECOG = Eastern Cooperative Oncology Group; EMVI = ekstramesorectal vein invasion; MRF = mesorectal fascia; N = node; No. = number; T = tumor

TABLE 2. Acute toxicity during TNT

	Toxicity	Grade 1		Grade 2		Grade 3		Grade 5	
		N	%	N	%	N	%	N	%
During ChT	Thrombocytopenia	4	6.1	4	6.1				
	Anemia	8	12.1	2	3.0				
	Neutropenia	1	1.5	3	4.5				
	Diarrhea	4	6.1	3	4.5				
	Nausea	21	31.8	1	1.5				
	Vomiting	4	6.1	1	1.5				
	Hand-foot syndrome	7	10.6	1	1.5	1	1.5		
	Parasthesia	36	54.5	1	1.5				
During CRT	Thrombocytopenia	9	13.6	2	3.0				
	Anemia	5	7.6	3	4.5				
	Neutropenia	2	3.0	3	4.5				
	Diarrhea	22	33.3	4	6.1	1	1.5		
	Nausea	7	10.6						
	Cystitis	22	33.3	3	4.5				
	Proctitis	8	12.1	3	4.5				
	Dermatitis	5	7.6	5	7.6	2	3.0		
	Hand-foot syndrome	5	7.6	3	4.5				

ChT = chemotherapy; CRT = chemoradiotherapy

pleted by 61 (92.4%) of patients. All patients completed radiation and 77.3% received a full dose of concomitant capecitabine. In others the dose of capecitabine was modified, mainly due to hematological toxicities. Fifty-six (84.8%) patients received both cycles of consolidation chemotherapy. All 6 cycles of CAPOX/FOLFOX were given to 55 (83.3%) patients. Among them only 5/55 patients recevied ChT at modified dose. All planned doses of neoadjuvant ChT and TNT according to the protocol received 77.2% and 60.6% of patients, respectively.

Acute toxicity was assessed in all 66 patients. Data are shown in Table 2. During TNT, 22.7% of patients did not report any toxicity or it was not observed. The most frequent all-grade toxicities during induction and consolidation ChT were neurotoxicity and nausea, observed in 56% and 33.3% of patients, respectively. The most common haematological toxicity was anemia presented in 10 (15.1%) patients. Hematological and other gastrointestinal toxicities were mainly gradus 1. There was only one grade 3 toxicity, hand-foot syndrome.

All patients completed radiation therapy with the median interruption of 2 days due to hollidays and machine maintenance in 36 (54.5%) of them. The 3D conformal, IMRT SIB or VMAT SIB tech-

nique was used in 36 (54.5%), 17 (25.8%) and 13 (19.7%) patients, respectively. The most frequent all-grade CRT-related toxicities were diarrhea (39.4%) and radiation cystitis (37.8%). Similar to that observed during ChT period, gastrointestinal and hematological toxicities were mainly grade 1. Only three grade 3 toxicities were recorded (diarrhea in one and radiation dermatitis in two patients). During CRT thrombocytopenia (16.6%) was the most common adverse hematological event.

Surgery

Sixty (90.9%) patients underwent standard TME surgery or surgery beyond the TME planes. One patient underwent transanal TME, 40 patients underwent low anterior resection, 5 patients underwent anterior resection, 13 patients underwent abdominoperineal excision (APE) and 1 patient underwent total pelvic exenteration. Median time from the end of CRT to operation was 11 weeks (range 7–19). In 76.7% of them sphincter preserving procedure was performed. For the tumors in the lower third of rectum the rate of abdominoperineal amputations was 33%. Among 3 patients with clinically positive extramesorectal lymph nodes 1 patient, who underwent APE, had cancer cells present microscopically at the resection margin (R1), 1 patient who underwent anterior resection had pCR and 1 patient who underwent low anterior resection had pT3N2. One patient did not have definitive surgery of primary tumor due to unexpected cardiac arrest after one cycle of consolidation ChT and three days after sigmoid colostomy formation because of perineal infection in peripheral hospital. Five patients refused surgery, 3 of them with radiologic cCR of the tumor.

In 75% of patients no perioperative complications were noticed. The most common grade ≥ 3 perioperative complications were anastomotic leakage in 3, pelvic abscess in 1 and paralytic ileus in 2 patients. The most frequent all-grade-surgery-related toxicity was wound dehiscence (8.3%). Data on time to stoma closure was available for 29/37 patients with sphincter sparing procedure. Median time was 134 days (range 49–233). Time to stoma closure was nearly doubled in a female patient after TME with posterior vaginal wall excision because of the higher risk for delayed anastomotic-vagina fistula formation. The second longest delay to stoma closure of 200 days after surgery was in a female patients because of the chronic pelvic pain after low anterior resection without anastomotic leakage confirmation.

TABLE 3. Distribution of the initial clinical and pathologic stage, (N = 60)

Clinical stage	Pathological stage							
	pT0	pT1	pT2	pT3	pT4	pN0	pN1	pN2
cT2	1	/	/	/	/			
cT3	7	5	6	17	1			
cT4	6	0	6	8	3			
cN1						17	1	/
cN2						33	8	1

C = clinical; N = node; p = pathological; T = tumor

Efficacy of the treatment

After induction ChT radiologic (evaluation with MRI) downstaging of T, N, stage, absence of EMVI or MRF involvement was observed in 42.4%, 62.1%, 36.4%, 69.7% and 68.2% of patients, respectivelly. We recorded cCR in 6 (9%) patients.

MRI of pelvis after the consolidation ChT was performed in 27 patients, among them only 1 patient was operated outside our institution. Five more (7.6%) cCR were recorded.

Among 60 operated patients pCR rate was 23.3% (Dworak tumor regression grade 4), the rate of near complete response (Dworak tumor regression grade 3) was 20%. Radical resection rate was 96.7% and pathological T, N and stage downstaging was 65%, 96.7% and 83.4%, respectively (Table 3). Upstaging was observed in 1 patient after induction ChT (from T3N2 to T4N2), but after the TNT and surgery pCR has been reported. After operation was tumor upstaging observed in 1 patient (from T3N1 to pT4N0).

The mean neoadjuvant rectal (NAR) score was 10.7. It was low in 24 (40%), intermediate in 26 (43.3%) and high in 10 (16.7%) patients.

There was no association between pCR and disease stage, tumor grade, presence of EMVI, chemotherapy dose, treatment or chemotherapy interruption, total radiation dose received and time to operation on the Fisher exact test. Both radiotherapy techniques using hypofractionation (*i.e.* higher doses per fractions with concomitant boost) was the only variable associated with pCR. The rate of pCR in patients irradiated with 3D conformal technique and standard fractionation was 12.1% while with IMRT SIB and VMAT SIB and hypofractionation it was 37% ($p < 0.05$).

Discussion

Optimal therapy for patients with LARC is still controversial, but TNT is gaining acceptance in the treatment of a high risk group. The goal of the present analysis was to evaluate this approach for patients with LARC-HR in Slovenia. Compared to our previous study with intensified neoadjuvant capecitabine based treatment with one induction cycle of capecitabine before CRT and two consolidation cycles before the operation, TNT achieved better pCR (17.5% *vs.* 23.3%), T (55.5% *vs.* 65%) , N (77.7% *vs.* 96.7%) and stage (79.3% *vs.* 83.4%) downstaging with comparable toxicity and compliance of patients.[15] Direct comparison with the results of these near TNT study and other TNT studies is limited because in majority of them patients with stage II and III LARC were included. It is known that patients with clinical stage II tumors had higher response to treatment and pCR rate than patients with clinical stage III tumors.[6] Taking into account only the high risk group of patients in the study of Golo *et al.*, the greater efficacy of our TNT approach is even more prominent. The difference in pCR rate is 13.8% (10.5% *vs.* 23.3%).[15]

Another difficulty in comparison with other studies presents our scheme of TNT approach which is rather unique with combination of induction ChT before CRT and consolidation ChT after it. We found only one Chinese study reporting results on TNT in LARC-HR only with similar approach: 3 cycles of induction and 3 cycles of consolidation CAPOX, but even more intensified by oxaliplatin added to CRT.[16] Studies with different TNT schemes than our in LARC reported pCR rate ranging from 14% to 36%.[4-6,16,17] Our pCR rate of 23.3% is consistent with most of them. We achieved similar pCR than study from Chau *et al.* (24%) and slightly lower than Chinese study (31.7%).[4,16] Still, our downstaging data appear to be encouraging. We observed slightly higher proportion of low pathological T stage (ypT0-2; 51.7%) than in Chinese study (42.6%).[16] On the other side we observed slightly lower proportion of high pathological T stage (ypT3 and ypT4; 41.7% and 6.7%) than in Chinese study (ypT3 40.4%). In the only TNT-based randomized trial including both (II and III) stages of LARC T downstaging was observed in 43% of patients.[5]

We reported recently that preoperative IMRT-SIB can achieve a high rate of pCR and T or N downstaging.[18] Radiotherapy techniques used in the Chinese study were IMRT or VMAT[16] with standard fractionaction. The possible explanation for lower pCR rate in our study than in Chinese is that more than half of the patients were irradiated with 3D-CRT (54.5%) technique with standard fractionation. If we calculate CR (cCR+pCR) rate in subset of our patients (n = 30) who were irradiated with IMRT SIB or VMAT SIB with higher dose per fraction in shorter time (*i.e.* hypofractionation) with the biological equivalent total dose as with standard fractionation, we get an excellent CR rate of 36.7% (1 patient with cCR and 10 patients with pCR). The result is as good as the result of the Chinese study even without intensification of CRT with oxaliplatin and is better also for the subset of patients with HR in the study of But *et al.* in which pCR was 20%. Compared to this group we also achieved better N (85% *vs.* 96. 7%) downstaging.[18] Moreover, our results are comparable even to other studies involving also favorable stage II LARC.

Further, our interval from completion of CRT to surgery (mean and SD, 11.3 weeks ± 2.5 weeks) was shorter than in Chinese study (mean 20.1 weeks).[16] Time from completing neoadjuvant therapy to surgery is one of important determinant for achieving complete response.[19] Compared to the study from Cercek *et al.*, we had similar interval between completion of CRT and surgery but shorter time from completing neoadjuvant therapy to surgery (most frequent 2–4 weeks versus 8–12 weeks) due to different TNT regimens.[6] In the contrast with us, Cercek *et al.* reported higher rate of pCR (32.8%), but we also have to take into consideration that they reported result for LARC stage III with or without risk factors. To date, there is no consensus about optimal time for surgery after CRT. A lot of studies reported that long interval between preoperative radiotherapy and surgery was associated with a significantly better clinical tumor response and pathologic downstaging.[6,20,21] On the other side, longer interval to surgery was associated with increased risk of death and could have impact on surgical complication due to potential fibrosis development.[21] However, it is difficult to determine the point where the benefit is greater than the risk because time to surgery is not the only factors affecting pCR.

We also evaluated neoadjuvant rectal score (NAR). NAR was developed as a composite short-term endpoint for clinical trials involving neoadjuvant therapy for rectal cancer.[22] It's calculation is based on downstaging data (cT, pT, pN) and has greater predictive validity for overall survival than does ypCR.[23] In the NSABP R-04 randomised trial, the NAR score calculation was divided into three classes. Low (NAR < 8), intermediate (NAR = 8–16),

and high score (NAR > 16) were associated with 92%, 89% and 68% 5 year OS, respectively.[23] In our study 83.3% of patients had NAR in low and intermediate class. Direct comparison with other TNT studies was not possible as we did not find any reports on predictive NAR score. Taking into account the data from NSABP R-04 trial and from randomized trials with near TNT-based regimens for LARC reporting 5 year OS between 67–77%[5,24,25], we can consider results of current study as promising.

Compliance within TNT protocol in our study was in the range of 83% to 100% and is consistent with others who have studied TNT approach.[26] In the largest randomized study of the adjuvant ChT in rectal cancer poor adherence with all planned dose in only 43% of patients was reported.[27] The rates of compliance in TNT-based regimen are promising including our compliance rate for all planned dose ChT (60.6%).

Toxicities were acceptable with minimal life-threatening side effects. Grade 3 adverse event developed only in 6% of patients who recevied TNT and 1 unexplained death occured. Postoperative morbidity rate was 25% which is comparable to postoperative morbidity of TNT-based studies in which ranged from 13 to 51%.[26] In addition, most surgical complications were associated with operative wound healing and not with other serious complications. Compared to other TNT-based regimen in LARC-HR, no relevant differences in terms of treatment outcome and toxicity were observed.

One of the important factors in assessing the quality of life is also the time to temporary stoma closure and the presence of a temporary or permanent stoma due to negative impact on social functioning and gastrointestinal symptoms.[28] There is a lack of studies reporting the time to stoma closure. Cercek *et al.* reported that stoma closure was earlier in the TNT group (89 days in TNT group *vs.* 192 days in group with standard therapy).[6] There are two major reasons for prolonged interval in our study: first, complexity of surgery with prolonged recovery and second, too long waiting time to admission for stoma closure. As pointed out previously our result can not be compared with the control group or another group with similar characteristics, but in relation to the previously mentioned result we consider median time of 134 days in our study as acceptable.

Limitations of our study are lack of control arm and limited number of patients from a single institution. Further, long-term data for our TNT approach are not available yet. Moreover, it should be emphasized that the NAR calculation does not reflect direct clinical benefits but it predicts overall survival. All of the above mentioned facts will bet taken into consideration when designing future studies.

Conclusions

TNT of high risk LARC is well tolerated and highly effective with excellent tumor and node regression rate and with low toxicity rate. Treatment according to the protocol is achievable in a great proportion of patients. Regarding short term outcomes TNT seems to be better option for patients with LARC with high risk for local or systemic recurrence than standard preoperative CRT and adjuvant ChT. Longer follow up will show if this strategy will improve distant disease control and survival.

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