



Effect of prolonged interval between neoadjuvant chemoradiotherapy and surgery on pathological and oncological outcomes in locally advanced rectal cancer: a randomized controlled trial

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Abstract

Background The optimal interval between neoadjuvant chemoradiotherapy (nCRT) and total mesorectal excision (TME) in locally advanced rectal cancer (LARC) remains controversial. This randomized controlled trial evaluated whether prolonging the interval between nCRT and surgery improves pathological response and oncological outcomes.

Methods Adult patients with histologically confirmed, MRI-staged II–III rectal adenocarcinoma located within 12 cm of the anal verge were randomized to undergo surgery at 8 weeks or 12 weeks after completion of long-course nCRT (50 Gy with concurrent 5-fluorouracil). The primary endpoint was pathological complete response (pCR; Dworak grade 4). Secondary endpoints included postoperative complications, surgical quality, disease-free survival (DFS), overall survival (OS), and patterns of recurrence.

Results A total of 124 patients were analyzed (61 in the 8-week group and 63 in the 12-week group). Median time to surgery was 72 days (10.3 weeks) and 93 days (13.3 weeks), respectively. pCR was achieved in 14.8% vs 14.5% ($p = 0.904$). There were no significant differences in ypT stage, ypN stage, CRM positivity, or TME quality. Anastomotic leakage was numerically higher in the 12-week group (15.9% vs 4.9%). Three-year OS (76.3% vs 80.0%, $p = 0.657$) and DFS (62.9% vs 62.2%, $p = 0.838$) were comparable. Adjuvant chemotherapy was administered more frequently in the 8-week group (61.7% vs 39.7%, $p = 0.015$).

Conclusion Extending the surgical interval from 8 to 12 weeks did not improve pathological response or oncological outcomes. These results should be interpreted cautiously in the context of evolving total neoadjuvant therapy (TNT) strategies.

Trial registration Clinicaltrials.gov No. NCT03607370.

Keywords Rectal cancer · Neoadjuvant chemoradiotherapy · Pathological complete response · Dworak tumor regression grade · Carcinoembryonic antigen

Introduction

According to the most recent GLOBOCAN estimates, colorectal cancer (CRC) is the third most commonly diagnosed cancer worldwide, with approximately 2.2 million new cases and 1.1 million deaths projected in 2024, making it the second leading cause of cancer-related mortality globally [1, 2]. According to the literature, the CRC population is shifting to younger ages as the median age at the time of the CRC diagnosis is decreasing [3] rectal cancer accounts for approximately 30% of the CRC cases [3]. Locally advanced rectal cancer (LARC) refers to a rectal tumor with a clinical-stage II to III (T3–4 and/or local lymph node involvement).

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National Comprehensive Cancer Network (NCCN), as well as the European Society of Surgical Oncology (ESMO), recommend a tailored concept with different pathways for stage II and III rectal cancer [4, 5]. The Dutch Colorectal Cancer group showed that preoperative radiotherapy reduces the 10-year local recurrence rate by more than 50% vs. surgery alone [6]. Neoadjuvant CRT (nCRT) has been implemented into LARC treatment to downsize and downstage the tumor, prevent or eradicate micrometastases, and reduce the pelvic recurrence rate. nCRT is associated with a potential to increase rectal sphincter preservation rate in patients with low-lying rectal tumors [7]. nCRT followed by a low anterior resection (LAR) with total mesorectal excision (TME) and sphincter preservation, and adjuvant chemotherapy is a standard treatment for LARC. In recent years, the concept of LARC treatment has been developed. The standard LARC treatment approach has several limitations, including a high tumor metastasis rate as well as a low pathological complete response (pCR) rate, and inconsistent compliance with adjuvant chemotherapy [8]. One of the new concepts is that the length between nCRT and LAR with TME and sphincter preservation or abdominoperineal resection (APR) may be associated with a better tumor response to the treatment. Traditionally, this length was recommended to be from 6 to 8 weeks after nCRT to achieve better results [9].

It has been suggested that extending the time more than 6–8 weeks may increase the tumor response rate, including local tumor regression rate, pathological complete response, and complete tumor resection rate, as well as improve the overall survival rate [10–12]. In the GRECCAR-6 randomized controlled trial, the LAR with TME and sphincter preservation was delayed 7 or 11 weeks after nCRT, and it was found that waiting 11 weeks after nCRT did not increase the rate of pCR and it was associated with a higher morbidity rate [8]. The research made by Mei SW et al. in 2020 found that LAR with TME and sphincter preservation delayed by more than 9 weeks may improve the pCR rate and disease-free survival and has little effect on postoperative complications and sphincter preservation [13]. The time between nCRT and LAR with TME and sphincter preservation or APR is still debatable.

Following the ongoing discussion on this subject, our study aimed to evaluate the optimal time interval (8 weeks versus 12 weeks) between nCRT and LAR with TME and sphincter preservation or APR to increase the rate of pCR.

Patients and methods

The primary aim was to determine if lengthening the time interval between neoadjuvant chemoradiotherapy (nCRT) and surgery increases pathological response (pathological complete response) in patients with locally advanced

rectal cancer (LARC). Secondary outcomes were possible complications and differences in oncological outcomes between the groups.

Study design and ethics

This randomized controlled trial was conducted and reported in accordance with the CONSORT 2025 statement. The CONSORT checklist is provided as Supplementary Material.

This two-arm randomized single-center prospective, parallel-group, 1:1-controlled trial (RCT) was conducted at the National Cancer Institute, Vilnius, Lithuania, between October 17, 2017, and February 14, 2022. Patients with locally advanced rectal cancer (LARC—a tumor with a clinical-stage II–III (T3–4 and/or lymph-node-positive)) were randomized. The protocol was approved by the Vilnius Regional Biomedical Research Ethics Committee (No. 2017/6–1133–631) and registered in the *clinicaltrials.gov* (NCT03607370) registry (permission granted 2018).

This study was conducted by the ethical standards of the Helsinki Declaration of 1975. All patients provided written informed consent before participating in the study.

Inclusion/exclusion

All patients over 18 years old provided written informed consent before inclusion in the trial. Patients with stage II and III rectal cancer located within 12 cm from the anal verge were included in the trial. Tumor height was initially measured by rigid rectoscopy and subsequently confirmed on pelvic MRI, in accordance with UICC staging principles, to account for anatomical landmarks relevant to oncological staging and treatment planning. In case of discrepancy, MRI-based localization was used for staging and therapeutic decision-making. All patients had histologically confirmed rectal adenocarcinoma. Other histologic subtypes were excluded. Microsatellite instability (MSI) status was not routinely available at study initiation and was therefore not analyzed. Eastern Cooperative Oncology Group (ECOG) scores were 0 to 1. Before the treatment, all patients underwent a full colonoscopy if possible, a computed tomography (CT) scan of the chest, abdomen and pelvis, and complete blood tests. The local staging was performed by pelvic magnetic resonance imaging (MRI). Carcinoembryonic antigen (CEA) was also evaluated before and after patients received nCRT. Patients unwilling to participate in the trial or refusing the surgery were excluded from the study. All the inclusion/exclusion criteria are summarized in Table 1. The radiotherapist determined patient eligibility for the trial before prescribing RCT.

Table 1 Patient inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
• Over 18 years old • Eastern Cooperative Oncology Group 0–1, • American Society of Anesthesiologists score I–III • Histological confirmation of adenocarcinoma of the rectum • T3 or T4 N0, T any N positive cancer on MRI, without metastasis on CT scan • Undergoing preoperative radiotherapy/chemotherapy • Curative TME intended • Written informed consent • Patients undergoing preoperative radiotherapy should not be excluded	• Patients with distant metastasis • T1 or T2, N0 cancer on MRI • Rectal cancer 12 cm above the dentate line • Contraindications to MRI • Patients previously treated for pelvic organ cancer • Medical or psychiatric conditions that compromise the patient's ability to give informed consent

CT scan Computed tomography

MRI Magnetic resonance imaging

TME Total mesorectal excision

Neoadjuvant treatment

Patients in both study groups (SGs) were treated with 5-fluorouracil (FU) and radiotherapy for 5–6 weeks. Continuous-infusion 5-FU of 225 mg/m²/day was used during weeks one and five of the RT. No induction or consolidation chemotherapy was commenced. Radiotherapy was delivered using 3D-conformal technique. The mesorectum and regional lymphatic drainage were included in the clinical target volume. No radiotherapy boost was administered. Radiotherapy was given once a day at 2 Gy/day, 5 days per week, for a total of 50 Gy to the primary tumor and pelvic lymph nodes. The same oncologist treated all patients. Eight weeks after completing the nCRT treatment, all patients underwent CEA, pelvic MRI, digital examination, and sigmoidoscopy. The radiologist interpreting the images before the treatment assessed MRI (LZ).

Randomization

At this stage, patients were randomized to either an 8-week or 12-week group with a 1:1 allocation using a computer-generated randomization schedule stratified by neoadjuvant treatment using random permuted blocks of four and six (ES). The randomization sequence was created using a free online tool (<https://www.sealedenvelope.com/>). Random allocations were sequentially numbered in sealed opaque envelopes opened just after finishing the radiotherapy. Although randomization was performed 8 weeks after completion of nCRT, logistical and clinical factors resulted in actual median surgical intervals of 10.3 weeks and 13.3 weeks. Therefore, the effective comparison was between approximately 10-week versus 13-week intervals. The 12-week target was selected based on available evidence at the time of protocol design, suggesting peak tumor regression between 10 and 14 weeks. Due to the nature of the intervention, patients and operating surgeons could not be

blinded. Radiologists assessing MRI, pathologists evaluating specimens, and statisticians performing data analysis were blinded to group allocation.

Surgery

All patients underwent standard LAR with TME and sphincter preservation or APE by three trained colorectal surgeons with an experience of at least 200 cases of rectal cancer resection and a caseload of 50 annually. When the tumor was < 12 cm from the anal verge, all the patients underwent LAR with TME and sphincter preservation, and if the cancer was < 5–6 cm from the anal verge, the patient had faecal incontinence before the treatment or was old and frail, APE was proposed. The participation did not influence the type of resection in the specific study group. The resections were performed in an open or laparoscopic approach at the surgeon's choice. Diverting ileostomy was formed in all the patients. Resected specimens were evaluated macroscopically by a surgeon and pathologist and graded as complete, near complete, or incomplete [14].

The degree of surgical difficulty was assessed using arbitrary scales ranging from 1 to 10, where 1 means the lowest and 10 the highest surgical difficulty. The operating surgeon evaluated it. The duration of surgery and hospital stay were estimated as well. The pCR was assessed using the Dworak tumor regression grade [15]. The final pathology was defined according to the American Joint Committee on Cancer (AJCC) guidelines [15]. Pathological exams included assessment of tumor grade (a low and high-grade adenocarcinoma), tumor budding, lymphovascular invasion before the treatment, and the same parameters following the treatment. Additionally, distal and circumferential margins, number of resected lymph nodes, perineural engagement, and length of resected specimen were assessed. A single pathologist, to exclude bias, performed the pathology review (RS). Postoperative complications were evaluated using the

Clavien-Dindo grading system [16]. Adjuvant chemotherapy was recommended based on multidisciplinary team discussion, primarily for patients with ypStage III disease, high-risk ypStage II features (poor differentiation, lymphovascular invasion, CRM positivity), or incomplete tumor regression. Standard regimens included CAPOX or FOLFOX according to patient fitness and comorbidities.

Anastomotic leak (AL) was defined as a defect of the intestinal wall integrity at the anastomotic site, confirmed clinically, endoscopically by rectoscopy, or radiologically using contrast-enhanced CT or contrast enema. *Postoperative hospital stay* was defined as the number of days from surgery to discharge.

Oncological endpoints were defined as follows:

Disease-free survival (DFS) was defined as the interval between the date of surgery and the first documented disease-related event, including local recurrence, distant metastasis, or death from any cause. Patients without an event were censored at the date of their last follow-up assessment.

Local recurrence (LR) was defined as any radiological, endoscopic, or histopathological evidence of tumor reappearance within the pelvis, including the anastomotic site, presacral area, or pelvic lymph nodes.

Overall survival (OS) was defined as the time from surgery to death from any cause. Patients alive at the last follow-up were censored as of that date.

Distant metastasis-free survival (DMFS) was defined as the interval between surgery and the diagnosis of distant metastatic disease—such as liver, lung, peritoneal, or non-regional lymph node metastases—or death from any cause. Patients without distant recurrence were censored at their last follow-up.

Sample size

The sample size calculation was performed with *G*Power 3.1.9.4* software using the increase of complete pathological response as the primary outcome. Based on the assumption that the pCR is around 10% in our center (unpublished material), prolonging the time to surgery would increase it to 30%. A group of 62 patients is needed to achieve 80% power in detecting this difference at a two-sided level of significance of 5%. Under the assumption of a drop-out rate of up to 10%, a total of 140 patients (70 per group) needs to be enrolled in the study.

Follow-up

We assessed the patients every 3 months for 2 years, then every 6 months for two years, and then once a year. On follow-up visits, patients underwent digital exams, CEA, and CT scans every 6–12 months.

Statistical analysis

Statistical Package for the Social Sciences software version 26.0 (SPSS 26.0; IBM Corp. Released 2019; Armonk, NY: IBM Corp.) was used for data assessment and statistical analysis. Categorical variables were analyzed using χ^2 or Fisher's exact test when appropriate. Continuous variables were analyzed using Student's t-test or Mann–Whitney U test. Survival outcomes were estimated using Kaplan–Meier curves and compared using the log-rank test. Multivariable Cox regression was performed, including T stage, nodal status, CRM status, and administration of adjuvant chemotherapy. Sensitivity analyses were performed for ypT0 outcomes.

Results

Between October 17, 2017, and February 14, 2022, a total of 138 participants were included in the study. Fourteen patients did not receive the expected nCRT and/or subsequent surgical treatment and were excluded from the study (Fig. 1). Consequently, the analysis included 124 participants, 61 in the 8-week group and 63 in the 12-week group. The mean age of included patients was 62 ± 10 in the 8-week group and 66 ± 10 in the 12-week group. Patient and disease characteristics for the study groups are presented in Table 2. The baseline characteristics were well balanced between the study groups.

Surgery

After undergoing nCRT, patients in the 8-week group received surgery with a median delay of 72 days (Q1: 64; Q3: 89), while those in the 12-week group underwent surgery after a median delay of 93 days (Q1: 87; Q3: 105). The distribution of patients undergoing LAR with TME and sphincter preservation and APR was comparable between the two groups. Notably, only one patient (1.6%) from the 12-week group did not undergo radical surgery due to the presence of a locally advanced and unresectable tumor (Table 3). The surgical difficulty assessed by the surgeon did not differ between the groups.

Postoperative complications developed in 25 patients (41%) from the 8-week group and 29 patients (46%) from the 12-week group. The types and severity of complications did not exhibit significant differences, except for a notable inclination toward an increased risk of anastomotic leakage in the 12-week group (RR: 3.22; 95% CI: 0.93–11.16) (see Table 3).

Pathological outcomes

Pathological complete response (Dworak grade 4) was achieved in 14.8% of patients in the 8-week group and 14.5% of cases in the 12-week group ($p = 0.904$). The extended time to surgery did not result in an increased rate of pCR

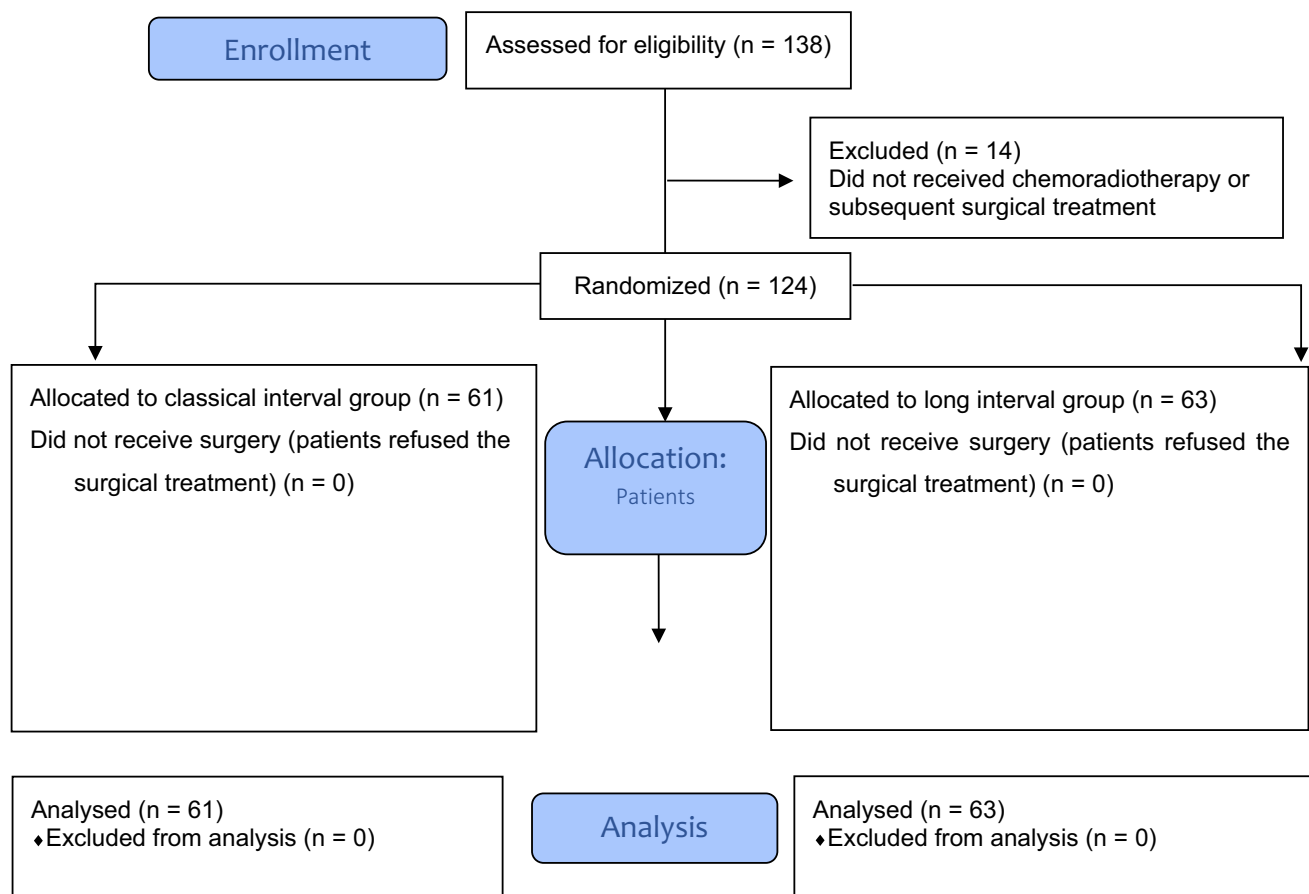


Fig. 1 CONSORT flow chart diagram of the study. Classical interval, 8 weeks; long interval, 12 weeks. TME, total mesorectal excision; APE, abdominoperineal excision

by Dworak grade 4 (RR: 0.98; 95% CI: 0.41–2.31). The sensitivity analysis confirmed such findings, showing no increased rates of ypT0 (RR: 0.87; 95% CI: 0.36–2.11). Pathological CR by Dworak grade 4 was not associated with tumor location in 12.7% of cases with pCR in the lower third part of the rectum and 16.9% of cases with pCR in the middle third part ($p=0.508$). Furthermore, time to surgery demonstrated no significant influence on pathological tumor and nodal stage, positive CRM rate, quality and completeness of the mesorectum, the number of retrieved lymph nodes, length of specimen, and distal margin, as detailed in Table 4.

Adjuvant treatment and long-term outcomes

The median follow-up time for the study cohort was 38 (28; 54) months. Adjuvant chemotherapy was administered for a significantly higher proportion of patients in the 8-week group ($n=37$ (61.7%) vs. $n=25$ (39.7%), $p=0.015$). Univariate Kaplan–Meier analysis showed similar 3-year OS (76.3% vs 80.0%; $p=0.657$) and DFS (62.9% vs 62.2%, $p=0.838$) between patients in the 8-week and 12-week groups (Fig. 2).

The risk of local recurrence (RR: 0.77; 95%CI: 0.21–2.74), liver metastases (RR: 0.64; 95%CI: 0.19–2.17), lung metastases (RR: 0.84; 95%CI: 0.32–2.19), peritoneal metastases (RR: 1.45; 95%CI: 0.25–8.39), and other site metastases (RR: 0.82; 95%CI: 0.29–2.32) in the 12-week group was similar to the 8-week group (Table 5, Figs. 3, 4 and 5).

Discussion

In this trial, we aimed to determine whether the delay of surgery (to 12 weeks) following nCRT for rectal cancer, more than the traditional 8 weeks, helps to achieve a higher pCR rate. We found no statistically significant difference between the groups in the rates of pCR, complications, and oncological outcomes.

The timing between nCRT and LAR or APE is still debatable and can vary from 4 to 12 weeks or more, while the standard time interval is from 6 to 8 weeks. In recent years, many studies supported a longer interval as it may be more beneficial. A meta-analysis by Petrelli et al. in 2016 showed

Table 2 Baseline characteristics

		8-week group (<i>n</i> =61)	12-week group (<i>n</i> =63)	<i>P</i> value
Age (years), mean (SD)		62 (10)	66 (10)	0.096
Sex ratio (M:F)		38:23	40:23	0.890
BMI		29 (6)	28.3 (5)	0.892
Time from the end of neoadjuvant therapy and surgery (weeks)		10.3	13.3	
Comorbidities	Cardiovascular	28 (45.9%)	29 (46.0%)	0.999
	Pulmonary	2 (3.3%)	2 (3.2%)	0.999
	Renal	3 (4.9%)	1 (1.6%)	0.361
	Diabetes	5 (8.2%)	4 (6.3%)	0.741
cT	cT1	0 (0%)	0 (0%)	0.791
	cT2	3 (4.9%)	5 (7.9%)	
	cT3	49 (80.3%)	49 (77.8%)	
	cT4	9 (14.8%)	9 (14.3%)	
cN	cN0	6 (9.8%)	5 (7.9%)	0.917
	cN1	19 (31.1%)	21 (33.3%)	
	cN2	36 (59.0%)	37 (58.7%)	
Tumor location	Middle third	26 (43.3%)	33 (52.4%)	0.315
	Lower third	34 (56.7%)	30 (47.6%)	
MRF+		34 (55.7%)	31 (49.2%)	0.467
CEA (ng/mL) level at baseline, mean (IQR)		3.6 (1.8–10.7)	4.2 (1.7–8.2)	0.553
CEA (ng/mL) level after neoadjuvant treatment, mean (SD)		1.5 (1.2–2.9)	1.5 (1–2.7)	0.899
CEA > 5 ng/mL at baseline		18/45 (40%)	19/40 (47.5%)	0.492
CEA > 5 ng/mL post-nCRT		4/42 (9.5%)	1/37 (2.7%)	0.374

Values are *n* (%) unless otherwise indicated

SD Standard deviation

BMI Body mass index

CEA Carcinoembryonic antigen

MRF Mesorectal fascia

that a more extended waiting period after nCRT before surgery than the classical 6–8 weeks increases the rate of pCR by up to 6% in LARC patients [11]. Rombouts et al. in 2016 compared patient groups according to treatment interval: from 5–6 weeks to 13–14 weeks in 2-week intervals. The authors found that pCR rates were statistically significantly higher in the 9–10 weeks and 11–12 week groups than in the 7–8 week group [12]. However, we found that extending time-to-surgery did not result in an increased rate of a pCR (RR: 0.98; 95% CI: 0.41–2.31). A retrospective study by Kammar et al. in 2020 showed similar results. The authors found that delaying surgery more than 12 weeks after nCRT did not improve tumor regression grade and had no impact on survival [17]. Cambray et al. described opposite results, showing that surgery should not be delayed more than 8 weeks following nCRT unless patients demonstrate a good response to nCRT [18].

Studies by Kalady et al., Kim et al., and Garcia-Aguilar et al. revealed certain tendencies. Although the longer nCRT-to-surgery interval was associated with better clinical outcomes in all of these studies, it could only be observed

until a specific week in each [19–21]. Kalady et al. retrospectively studied 242 patients with stage II–III rectal cancer who underwent nCRT before surgical resection between 1997 and 2007. The prolongation of the interval between completion of nCRT and surgery to more than 8 weeks ($p=0.03$) has been determined to be the only important prognostic factor responsible for higher pCR rates, correlated with decreased local recurrence rate and improved overall survival. The authors indicated that the time interval between 8 and 10 weeks was associated with the most significant number of pCR, and no more gain over 14 weeks was observed. Although Kim et al. found that the pCR rate was the highest in 9–11 weeks intervals, there were no statistically significant differences between the patient groups [20]. Garcia-Aguilar et al. found statistically significant differences above 2 study groups (SG1 underwent surgery 6 weeks following nCRT, and SG2 underwent surgery 11 weeks post nCRT) in pCR rates. The authors found that the patient group who underwent surgery 11 weeks after nCRT had higher pCR rates ($p=0.0217$) [21]. Akgun et al. also compared pCR rates obtained in classical (CI) and in long

Table 3 Treatment characteristics

		8-week group (<i>n</i> = 61)	12-week group (<i>n</i> = 63)	<i>P</i> value
Type of surgery	Rectal resection	41 (67.2%)	42 (66.7%)	0.613
	Abdominoperineal resection	20 (32.8%)	20 (31.7%)	
	Other	0 (0%)	1 (1.6%)	
Length of surgery (minutes), mean (SD)		126 (32)	129 (34)	0.576
Difficulty of surgery (score), mean (SD)		4.8 (1.9%)	5.3 (1.8%)	0.125
Postoperative complications		25 (41%)	29 (46%)	0.570
Clavien-Dindo score	1	11 (18.0%)	9 (14.3%)	0.464
	2	4 (6.6%)	8 (12.7%)	
	3a	4 (6.6%)	4 (6.3%)	
	3b	4 (6.6%)	5 (7.9%)	
	4a	0 (0%)	2 (3.2%)	
	4b	2 (3.3%)	0 (0%)	
	5	0 (0%)	1 (1.6%)	
Severe complications	Clavien-Dindo ≥ 3	10/61 (16.4%)	12/63 (19%)	0.815
Type of complications	Anastomotic leakage	3 (4.9%)	10 (15.9%)	0.076
	Intraabdominal abscess	2 (3.3%)	0 (0%)	0.240
	Wound infection	3 (4.9%)	5 (7.9%)	0.718
	Ileus	9 (14.8%)	7 (11.1%)	0.545
Postoperative hospitalization (days), mean (SD)		10 (5)	12 (7)	0.151

Values are *n* (%) unless otherwise indicated

Table 4 Pathological outcomes

		8-week group (<i>n</i> = 61)	12-week group (<i>n</i> = 63)	<i>P</i> value
Tumor regression grade by Dworak	1	24 (39.3%)	21 (33.9%)	0.904
	2	22 (36.1%)	24 (38.7%)	
	3	6 (9.8%)	8 (12.9%)	
	4	9 (14.8%)	9 (14.5%)	
ypT	0	9 (14.8%)	8 (12.9%)	0.967
	1	2 (3.3%)	3 (4.8%)	
	2	14 (23.0%)	16 (25.8%)	
	3	32 (52.5%)	30 (48.4)	
	4	4 (6.6%)	5 (8.1%)	0.779
ypN	0	40 (65.6%)	43 (69.4%)	
	1	15 (24.6%)	15 (24.2%)	
	2	6 (9.8%)	4 (6.5%)	
ypM	1	2 (3.3%)	0 (0%)	0.244
Pathologic CRM	Positive	8 (13.1%)	4 (6.5%)	0.240
Completeness of mesorectum	Mesorectal plane	43 (84.3%)	44 (78.6)	0.749
	Intramesorectal plane	6 (11.8%)	9 (16.1%)	
	Muscularis propria plane	2 (3.9%)	3 (5.4%)	
Retrieved lymph nodes (number), mean (SD)		25 (16)	23 (14)	0.574
Specimen length (cm), mean (SD)		24 (7)	25 (8)	0.779
Distal resection margin (cm), mean (SD)		2.5 (1.6)	2.3 (1.4)	0.556

Values are *n* (%) unless otherwise indicated

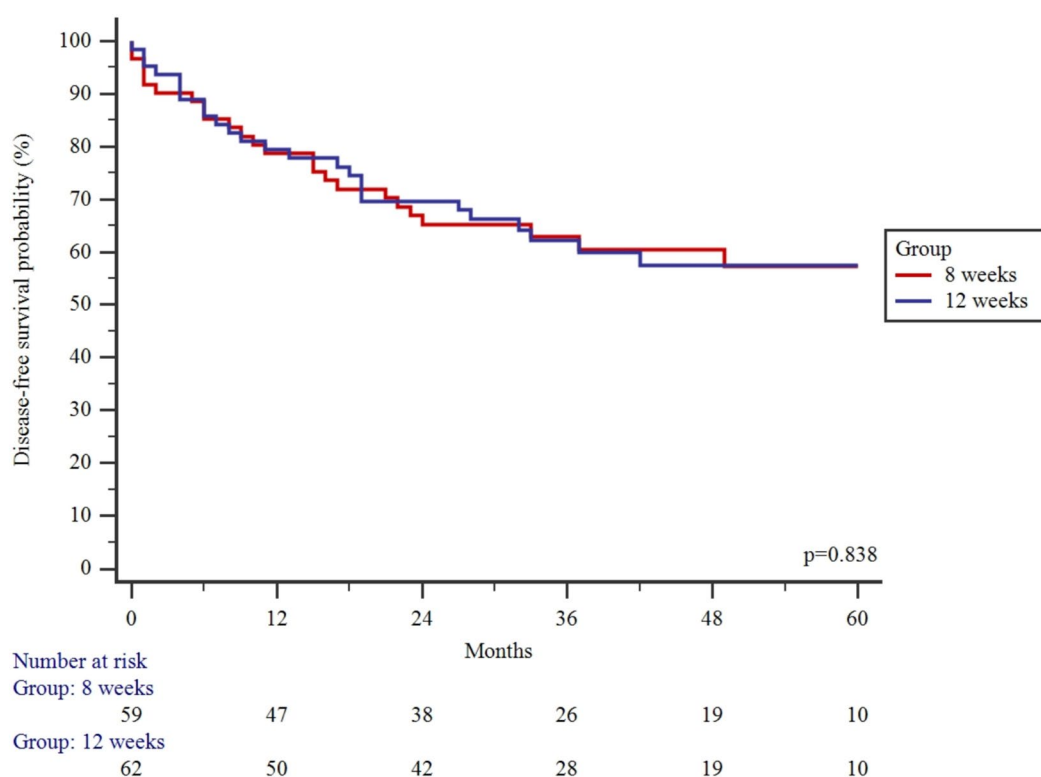


Fig. 2 Disease-free survival probability

Table 5 Recurrence patterns

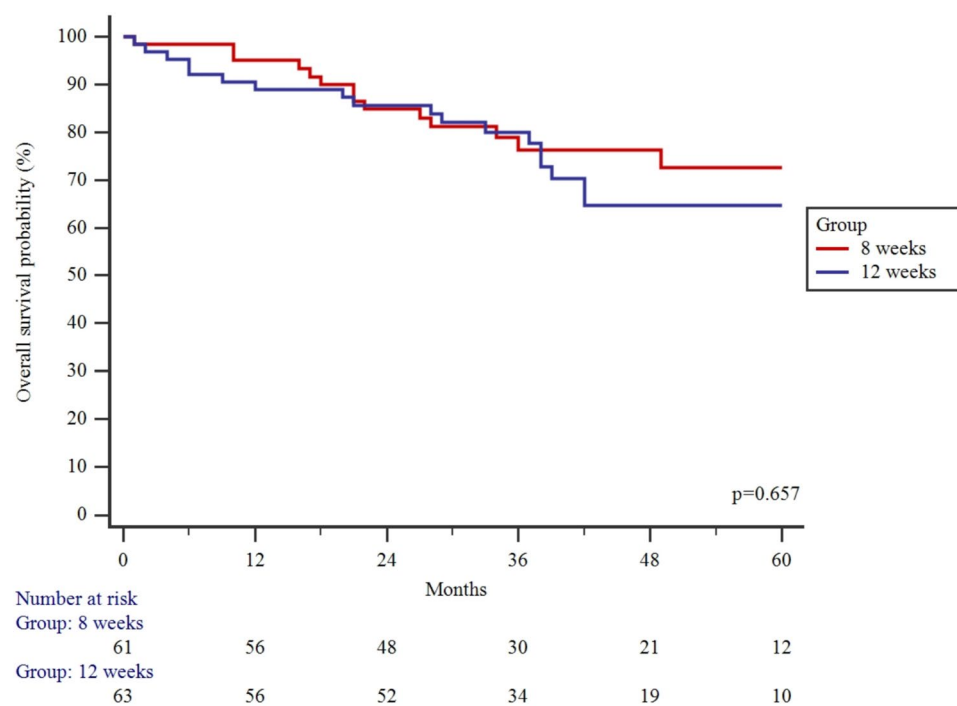
Recurrence type	8-week group (n = 61)	12-week group (n = 63)	P-value
Local recurrence	5/61 (8.2%)	4/63 (6.3%)	0.741
Any distant metastasis	15/61 (24.6%)	16/63 (25.4%)	1.000
Liver metastases	6/61 (9.8%)	4/63 (6.3%)	0.526
Lung metastases	8/61 (13.1%)	7/63 (11.1%)	0.788
Peritoneal metastases	2/61 (3.3%)	3/63 (4.8%)	1.000
Other site metastases	7/61 (11.5%)	6/63 (9.5%)	0.776

Note: Some patients had metastases at multiple sites

(LI) interval groups (surgery performed within 8 weeks or after 8 weeks of nCRT) [22]. The authors found that among 327 patients with LARC, the pCR rate (18.6% vs. 10.0%; $p = 0.027$) and disease regression rates were higher in the LI group than in the CI group. The highest pCR rate was achieved with an interval of 10–11 weeks and 9–10 weeks as well as in the Korean study published by Kim et al. [20, 22]. LARC patients who achieved a pCR have better long-term outcomes, including lower rates of metastases and disease-free survival [23]. However, there is still no reliable prognostic factor for determining a pCR. Several studies investigated the time interval between nCRT and surgery as a predictor factor for tumor response. Kalady et al. described a time interval between nCRT and surgery ≥ 8 weeks as the only significant factor associated with the attainment of a

pCR ($p = 0.02$, OR:2.63) [19]. Macchia et al. published a study that showed that lengthening the interval between nCRT and surgery > 13 weeks improves the pCR and pPR (pathological partial response) [7]. Moreover, the authors described that radiotherapy dosage > 5040 cGy and two-drug (not monotherapy) chemotherapy correlated with pPR [7]. Patients' age, gender, serum CEA levels, distance from the anal verge, and preoperative clinical stage were not associated with pCR [19]. The same results were described in our study. However, the time interval between nCRT and TME was also not statistically significantly associated with pCR in our study.

An unexpectedly high proportion of patients were classified as cN2 on baseline MRI. This likely reflects, at least in part, the known limitations of MRI nodal staging, where

Fig. 3 Overall survival probability

specificity is modest and reactive or inflammatory lymph nodes may meet morphological ‘suspicious’ criteria, leading to clinical overstaging—particularly when multiple small nodes are interpreted as malignant. In addition, our eligibility criteria restricted enrollment to stage II–III disease, enriching the cohort for node-positive and higher-risk features compared with unselected rectal cancer populations. The observed discrepancy between clinical and pathological nodal status (with substantially lower ypN2 rates after resection) is consistent with baseline overstaging and/or effective nodal downstaging following nCRT. Importantly, cN2 proportions were comparable between randomized groups, making differential nodal staging an unlikely explanation for between-group outcome differences.

Surgical quality (rates of tumor-positive margins, TME quality, anastomotic leakage, and intraoperative perforation) was similar between the groups in the study made by Akgun et al. [22]. The extended interval group had a slightly increased rate of perirectal fibrosis, which did not complicate surgery significantly, as it was also observed in the 11-week interval group (vs. 6-week) in the trial published by Garcia-Aguilar et al. in 2011 [21]. In our study, lengthening the time interval between completion of nCRT and surgical resection did not increase the rate of postoperative complications, with the highest number of anastomotic leakages ($n=10$ (15.9%), $p=0.076$). This might lead to better postoperative recovery in the shorter-interval group, leading to higher compliance with adjuvant chemotherapy. The numerically higher leakage rate in the longer-interval group might be related to progressive

radiation-induced fibrosis and impaired tissue healing with prolonged intervals, rather than surgical technique or diversion strategy alone. Timudom et al., in the retrospective study, specifically investigated if extending the waiting time of low-rectal cancer surgery after nCRT increases the rate of perioperative complications. All 60 patients with LARC who underwent nCRT were divided into group A (the mean interval after nCRT was 6.4 weeks) and group B (the mean interval after completion of nCRT was 11.7 weeks). The results obtained in this study support our observations. Researchers concluded that extending the waiting period to more than 8 weeks from nCRT to surgery does not increase perioperative complications, although a slightly higher rate of complications was observed in group B ($p=0.19$), with the most frequent complication being ileus as it was observed in our study within SG1 ($n=9$ (14.8%), $p=0.545$) [24]. Similar results were found by Meliske et al. in 2019. Authors found no significant association between time interval after nCRT and surgical complications, including surgical site complications ($p=0.33$), postoperative ileus ($p=0.54$), except wound infection rate, which was higher if surgery was delayed more than 8 weeks following nCRT ($p=0.05$) [25]. Therefore, extending the waiting period does not significantly increase the risk of complications.

Many studies agree that patients with a pCR are associated with decreased local disease recurrence rates and improved overall survival. The same results were described by Kalady et al. within the >8-week group [19]. Rombouts et al. described similar results as the LARC patients with

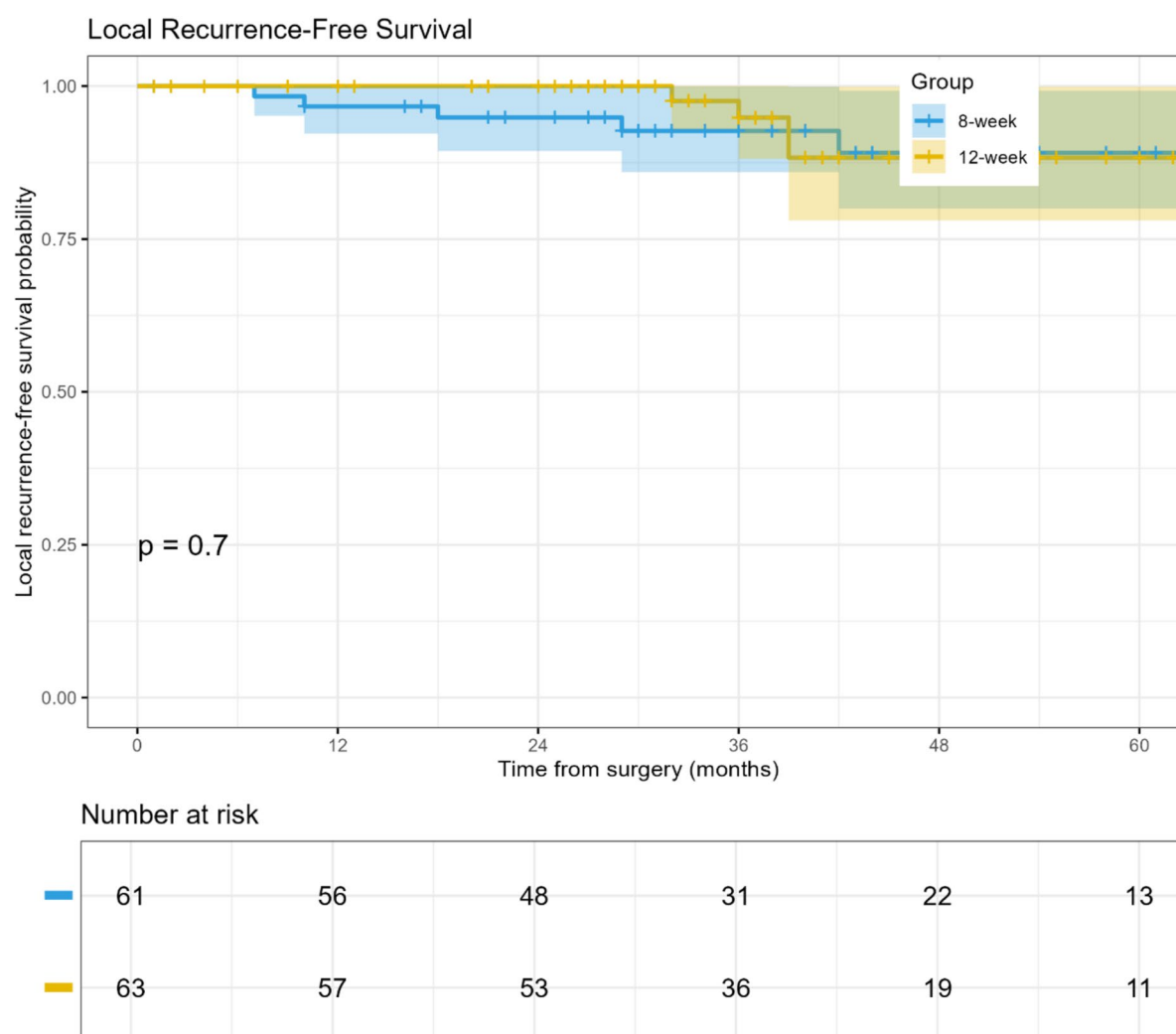


Fig. 4 Local recurrence-free survival

a pCRT had better overall survival than patients without a pCR: 88.9% (95% CI 86.3–91.5) of patients with pCR after 5-year follow-up vs. 71.0% (95% CI 69.3–72.7) of patients without pCR [12]. While in our study the local recurrence rate was similar in both SGs, Zeng et al. described that the 3-year local disease recurrence rate was higher in a short-interval group than in the long-interval group: 12.9% vs. 4.8% respectively ($p = 0.025$) [26].

Our study has several limitations. First, it was conducted as a single-center trial. Second, the number of patients in the 8-week group was below the initially calculated sample size. Third, the effective difference between groups was approximately three weeks. Fourth, TNT was not incorporated because it was not standard at the time of study design. Finally, we did not record the number of eligible patients who declined participation, which may introduce selection

bias. Our trial was designed before the widespread adoption of Total Neoadjuvant Therapy (TNT), which has since become standard for high-risk LARC, showing that a longer waiting period. Although TNT was not part of this protocol, the findings remain relevant for centers that continue to use conventional long-course CRT and provide important historical comparator data. Furthermore, while the 2025 ESMO guideline endorses TNT and tailored treatment intensification or de-intensification, results from traditional CRT with delayed surgery remain informative in settings where TNT is not yet widely implemented. Moreover, despite showing no increase in pCR rate, comparable long-term oncological outcomes support the safety of a prolonged time period before surgery, which is in line with TNT trials, allowing a second assessment for W&W after a near-clinical complete response in the first assessment.

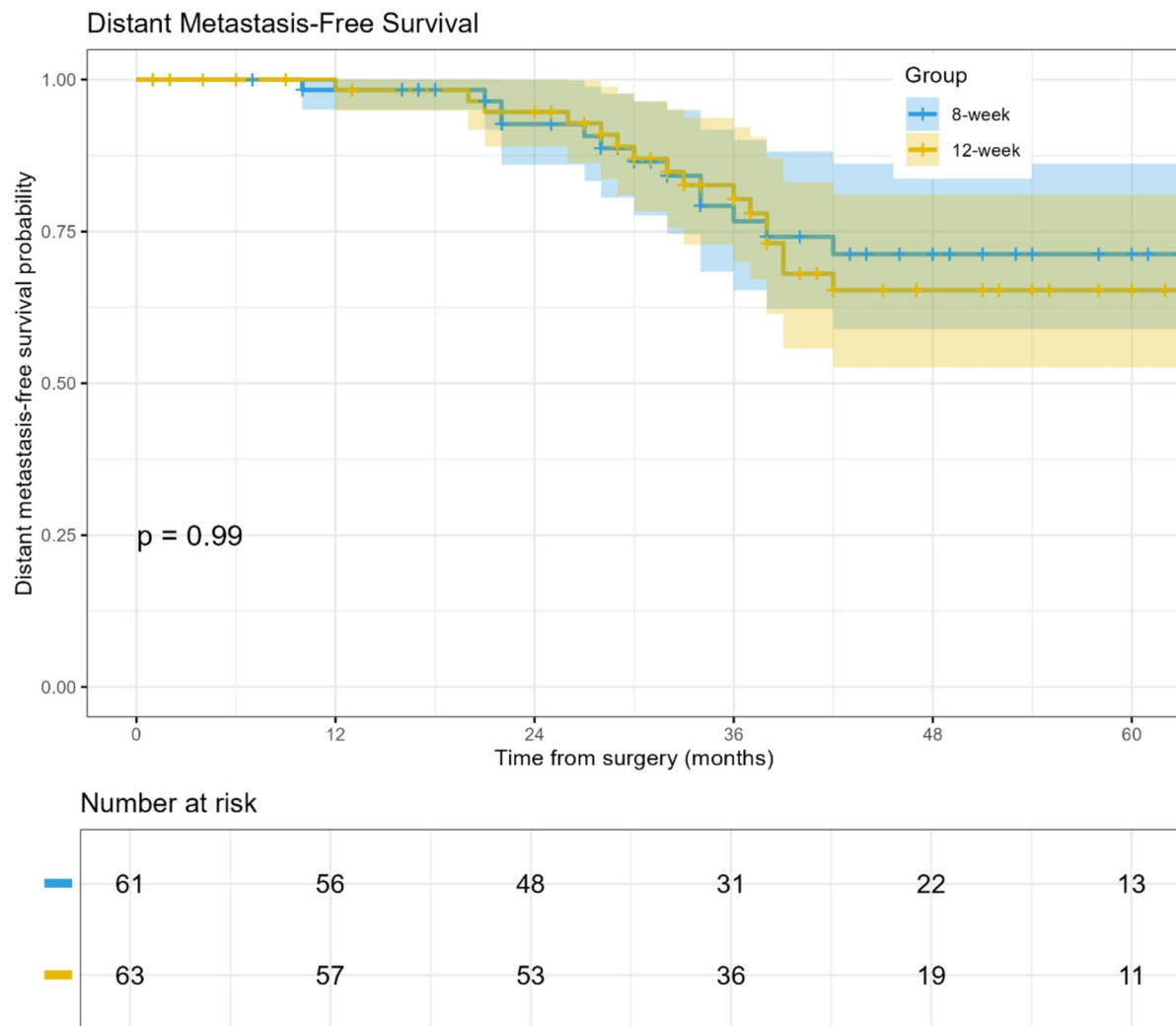


Fig. 5 Distant metastasis-free survival

Conclusion

Extending the interval from nCRT to surgery from approximately 10 to 13 weeks did not improve pathological response or long-term oncological outcomes. These findings should be interpreted cautiously, given the evolving role of TNT and organ preservation strategies.

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Data availability Data is available from the corresponding author upon reasonable request.

Declarations

Competing interests The authors declare no competing interests.

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