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Randomized controlled trial of 8 weeks' *vs* 12 weeks' interval between neoadjuvant chemoradiotherapy and surgery for locally advanced rectal cancer

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Abstract

Aim The aim was to compare the pathological complete response (pCR) rate at 8 compared to 12 weeks' interval between completion of neoadjuvant chemoradiotherapy (CRT) and surgery in patients with locally advanced rectal cancer.

Method This was a randomized trial which included a total of 330 patients from two institutions. Patients with locally advanced (T3-4N0M0, TxN+M0) rectal cancer were randomized into 8- and 12-week interval groups. All the patients received long-course CRT (45 Gy in 1.8 Gy fractions and concomitant oral capecitabine or 5-fluorouracil infusion). Surgery was performed at either 8 or 12 weeks after CRT. The primary end-point was pCR. Secondary end-points were sphincter preservation, postoperative morbidity and mortality.

Results Two-hundred and fifty-two patients ($n = 125$ in the 8-week group, $n = 127$ in the 12-week group) were included. Demographic and clinical characteristics were similar between groups. The overall pCR rate was 17.9% ($n = 45$): 12% ($n = 15$) in the 8-week group and 23.6% ($n = 30$) in the 12-week group ($P = 0.021$). Sphincter-preserving surgery was performed in 107 (85.6%) patients which was significantly higher than the 94 (74%) patients in the 12-week group ($P = 0.016$). Postoperative mortality was seen in three (1.2%) patients overall and was not different between groups (1.6% in 8 weeks *vs* 0.8% in 12 weeks, $P = 0.494$). Groups were similar in anastomotic leak (10.8% in 8 weeks *vs* 4.5% in 12 weeks, $P = 0.088$) and morbidity (30.4% in 8 weeks and 20.1% in 12 weeks, $P = 0.083$).

Conclusion Extending the interval between CRT and surgery from 8 to 12 weeks resulted in a 2-fold increase in pCR rate without any difference in mortality and morbidity.

Keywords Rectal cancer, neoadjuvant chemoradiotherapy, interval, complete response

What does this paper add to the literature?
Extending the interval between neoadjuvant treatment and surgery has been suggested to increase the pathological complete response rate which is an independent prognostic factor for survival in locally advanced rectal cancer. This study showed that a 12-week interval provides significantly higher pathological complete response rate than the 8-week interval with similar mortality and morbidity.

Introduction

Over 70% of patients with rectal cancer have locally advanced disease at presentation [1]. Neoadjuvant chemoradiotherapy (CRT) is an essential part of the management in these patients, with superior outcomes in terms of surgical margins, sphincter preservation and long-term recurrence-free survival [2]. The best timing of surgery after completion of long-course CRT in rectal cancer is unclear, however. Consensus-based guidelines have conflicting recommendations: the European Society of Medical Oncology suggests 6–8 weeks and

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the National Comprehensive Cancer Network suggests 5–12 weeks. A majority of surgeons prefer to carry out surgery at approximately 6 weeks after completion of CRT [3,4]. Recently, there has been an increasing tendency to extend the interval after completion of neoadjuvant CRT on the basis that this might increase tumour response and pathological complete response (pCR) rate. Longer waiting time is considered to enhance the killing effect of CRT on tumour cells. It was shown that tumour cell elimination was increased with longer intervals after radiotherapy [5].

An important manifestation of the biological aggressiveness of rectal cancers is the response to neoadjuvant CRT. There is clear evidence that the prognosis is much better in patients with a pCR [6]. In a recent study, the response to CRT was found to be an independent prognostic factor on prognosis in Stage III rectal cancer [7]. Thus, the efforts in rectal cancer management have been centred upon increasing pCR rates. Further, pCR may lend itself to an expectant watch and wait policy if this group can be identified before surgery [8].

The aim of the present study was to compare an 8-week to a 12-week interval between completion of CRT and surgery on the pCR rate. The primary end-point was pCR rate. Secondary end-points included the rate of sphincter preservation, operative mortality and morbidity.

Method

This study is a two-centred randomized controlled trial which included 183 patients from Dokuz Eylul University and 69 patients from Uludag University Hospital. Study procedures were in accordance with the Declaration of Helsinki and the approval of Dokuz Eylul University Ethics Committee was received (7 June 2012, No. 2012/21-07). The study protocol was registered to the institutional review board (available at http://hdl.handle.net/20.500.12397/12908) and the National Council of Higher Education Database (available at https://tez.yok.gov.tr/UlusalTezMerkezi/tezSorguSonucYeni.jsp). After oral and written explanations about the aims of the study, the patients gave their written informed consent to participate.

Patients

Inclusion criteria were patients older than 18 years, rectal cancer patients who had a biopsy-proven adenocarcinoma located within 15 cm from the anal verge, and patients who received long-course CRT and underwent partial (for upper rectum cancer only) or total (for middle and distal rectum cancer) mesorectal excision with curative intent. Clinical staging was performed by pelvic MRI and thoracoabdominal and pelvic CT scan. The indication for neoadjuvant CRT was clinical Stage II and III (cT3-T4N0M0, cTxN+M0) patients. Exclusion criteria were clinical Stage I and IV (T1N0 or T2N0 and M1) patients and patients who did not complete the long-course CRT. Any deviations of more than $\pm$ 2 weeks from the planned interval (< 6 and > 10 weeks for the 8-week interval group, < 10 and > 14 weeks for the 12-week interval group) were also excluded.

The rectum was defined as the portion of large bowel located between 0 and 15 cm from the anal verge and was measured by rigid rectosigmoidoscopy [9]. Tumour localization was subsequently subdivided into lower rectum (0–5 cm from the anal verge), mid-rectum (5.1–10 cm) and upper rectum (10.1–15 cm). The preoperative work-up included general clinical examination, digital rectal examination, a complete blood test, biochemistry profile, carcinoembryonic antigen assessment, rigid proctosigmoidoscopy, colonoscopy, tumour biopsy, and computed CT of the abdomen, pelvis and chest. Pelvic MRI and CT of the thorax were used routinely for better preoperative staging.

The need or otherwise for neoadjuvant treatment was decided by a dedicated colorectal multidisciplinary meeting at which all clinical information was available [10]. Patients were staged according to American Joint Committee on Cancer (AJCC) criteria (7th version) [11].

Staging

A high-resolution MRI 1.5 T system with a four-element pelvic phased-array surface coil (Philips Gyroscan Intera Release 8, Eindhoven, The Netherlands) was used. Patients were given antispasmodic drugs. Intravenous contrast, rectal air insufflation or bowel enema were not used. Sagittal fast spin-echo T2-weighted images (TR/TE 3500–4000/70–85, section thickness 3 mm, intersection gap 0.8 mm, matrix 256 × 512, number of signals acquired 6, field of view 22 cm) were captured and used to construct para-axial images perpendicular to the long axis of the tumour by an 18-cm field of view. Fast spin-echo T2-weighted para-coronal images parallel to the long axis were obtained as the last sequence with field of 22-cm view. Easy Vision by Philips Medical System was used to review the images.

Staging was performed according to the European Society of Gastrointestinal and Abdominal Radiology guidelines [12]. A 5-mm maximum short axis diameter was the threshold between benign and involved lymph

nodes. The shortest distance between the outer edge of the tumour or the extramural deposit or involved lymph node, if present, and the mesorectal fascia was measured on the axial images as the circumferential margin (CRM). Involvement of the CRM was defined as this distance ≤ 1 mm.

Neoadjuvant chemoradiotherapy

A four-field box technic with 6–18 MV photons was used for radiotherapy. Oral and intravenous contrasts were administered. Patients were placed supine. A 3-cm margin covering all the tumour and perirectal, presacral and internal iliac lymph nodes was assumed for targeting. The borders were sacral promontory superiorly, 5 cm below the tumour inferiorly, 1 cm behind the sacrum posteriorly, 3 cm anterior to the sacral promontory anteriorly and 1 cm laterally to the most outer part of the bony pelvis. Margins were configured to spare anal canal in proximal and mid-rectal tumours and small bowels and bladder in all patients. A single fraction dose of 1.8 Gy in 25 fractions (45 Gy in total) was given. The boost irradiation was administered for 3 days at 5.4 Gy to the primary tumour directly.

Concomitant chemotherapy included oral capecitabine 825 mg/m^2 twice a day for 5 days a week [13] or 5-fluorouracil 225 mg/m^2 daily infusion [14] during radiotherapy. Weekly monitoring of routine blood tests and clinical findings was performed to observe side effects.

Surgery

It was not possible, for logistical reasons, to perform surgery at the exact 8- and 12-week intervals. Therefore, a 2-week variation was considered acceptable. Any greater variation resulted in exclusion from the study. All procedures were performed based on total mesorectal excision principles [15]. All the surgical procedures were performed by a single senior surgeon in each institution (CT and EO). Total mesorectal excision was performed for mid- and low rectal tumours and partial mesorectal excision comprising a minimum 5-cm distal margin was performed in proximal rectal tumours. Splenic flexure mobilization and high ligation of vascular structures in the medial-to-lateral approach were performed routinely in both the open and laparoscopic procedures. When the distal margin was too low to perform a stapler transection, the rectum was totally mobilized, and resection was completed transanally with a hand sewn single-layer anastomosis. All patients with sphincter-preserving surgery had a diverting loop ileostomy. The intent for sphincter preservation was decided according to post-CRT MRI (performed within 1 week before the surgery). Abdominoperineal excision (APR) was performed if a 1-cm distal margin was not possible or the external sphincter was involved in the tumour. The distal margin was confirmed by frozen section when involvement was suspected.

Pathology

Mesorectum integrity was documented as described by Quirke and colleagues [16]: complete, nearly complete and incomplete. Tumour type, grade, lymph node involvement, lymphovascular and perineural invasion were examined microscopically according to the Collage of American Pathologists' (CAP) guideline. Response to neoadjuvant CRT was assessed by the modified Ryan tumour regression grading that is recommended by the CAP [17]: Grade 0, no viable cancer cells (complete response); Grade 1, single cells or small groups of cancer cells (moderate response); Grade 2, residual cancer outgrown by fibrosis (minimal response); and Grade 3, minimal or no tumour kill, extensive residual cancer (poor response). An involved CRM was considered if the tumour was closer than 1 mm to the radial margin. A clear distal margin was defined as an at least 1-cm tumour-free distal border.

Postoperative follow-up

All postoperative complications were recorded. Postoperative mortality was defined as death occurring within 30 postoperative days or during the first hospitalization. Postoperative complications were defined as the occurrence of any medical or surgical complications within 90 postoperative days or during the first hospitalization. Intention to treat analysis of the primary end-point was performed after a minimum of 3 months of follow-up.

Outcome measures

The primary end-point was the prevalence of pCR rates comparing the two groups. 'No viable tumour cells' at pathological examination (CAP classification: Grade 0) was classified as pCR. Secondary end-points were sphincter preservation, postoperative morbidity and mortality. Patients who did not undergo APR were placed in the sphincter-preserving surgery group. Postoperative morbidity was recorded according to the Clavien–Dindo classification.

Statistics

The pCR rate in the 8-week group was considered to be similar to a 13% pCR rate reported in the literature

for a 6–8-week interval [18]. With the hypothesis that extending the waiting interval to 12 weeks would result in a 2-fold increase in pCR rate to 26%, the minimum sample size for $\alpha = 0.05$ and 85% power was 330 patients. Patients were randomly assigned to the study groups (block randomization, ratio 1:1) before starting CRT by a computer random number generator. The surgeons enrolled and assigned the participants into groups and were aware of the randomization. The pathologist (MU) was blinded to the randomization.

Statistical analysis was performed using SPSS STATISTICS 22 (IBM Inc., Chicago, Illinois, USA). Continuous variables were expressed as mean and range, and categorical variables as frequency and percentage. The differences between groups in categorical variables were determined with the chi-squared and Fisher's exact tests and in continuous variables Student's *t* test. Statistical significance was defined as $P < 0.05$.

Results

Of 554 patients registered with rectal cancer, 330 were randomized into neoadjuvant CRT groups. Stage I ($n = 224$) and Stage IV ($n = 86$) patients were excluded, and four patients refused to participate in the study. Seventy-eight patients were excluded after the randomization due to protocol violation: 30 patients did not complete CRT, 22 patients were recorded as loss of follow-up as they did not appear for surgery after completing CRT, one patient had distant metastasis and was administered further chemotherapy and one patient died. Ten patients (four in the 8-week group and six in the 12-week group) had a clinical complete response confirmed by sigmoidoscopy, biopsy and MRI findings and they were considered for local excision. Twelve patients (nine in the 8-week group and three in the 12-week group) who were candidates for APR for persisting sphincter invasion refused to have any further treatment and were excluded from the study. Thus, there were 125 patients in the 8-week group and 127 patients in the 12-week group available for analysis (Fig. 1).

The mean age was 59.2 ± 11.4 years and 160 (63.5%) patients were men. The tumour was located in the proximal rectum in 87 (34.5%) patients, mid-rectum in 79 (31.3%) patients and distal rectum in 86 (34.1%) patients. Preoperative MRI staging revealed that 29 (11.5%) had Stage II and 223 (88.5%) Stage III rectal cancer; 88.5% had node-positive disease and 32.5% had

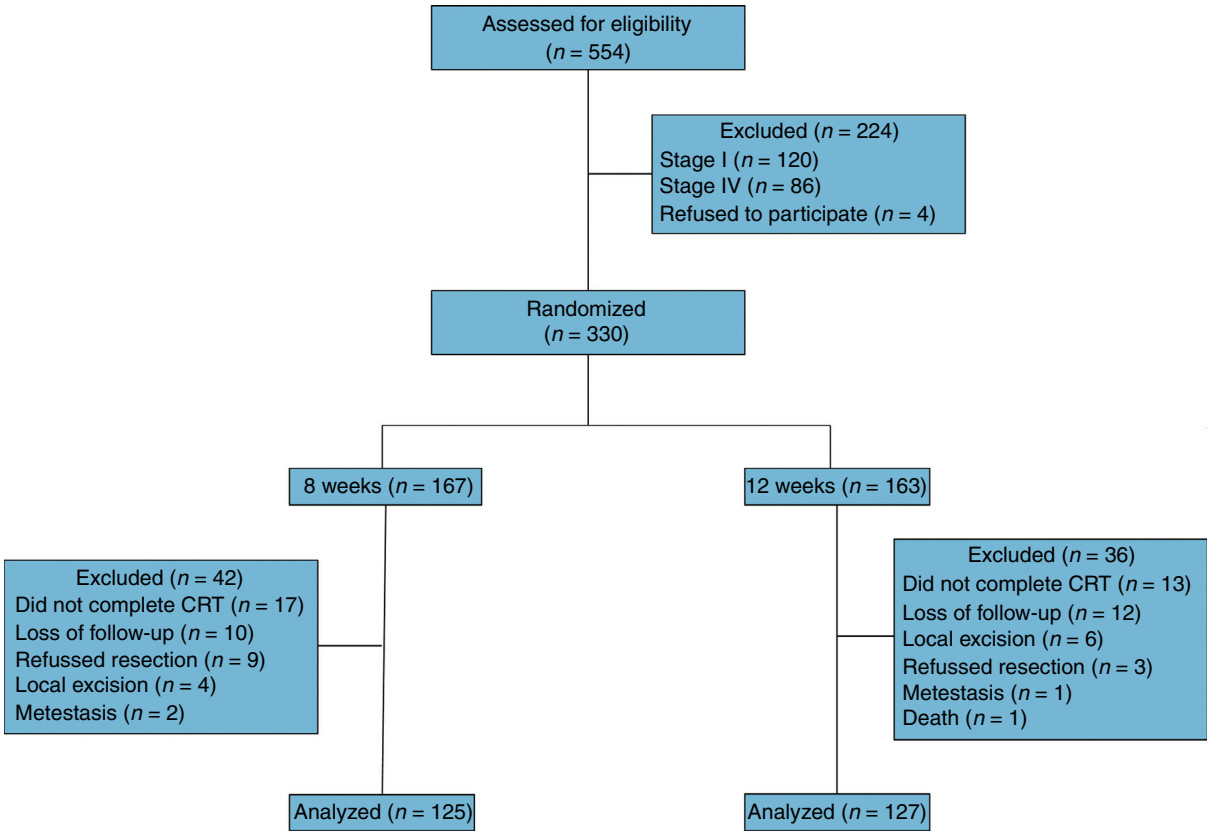

Figure 1 Flow diagram of the study.

involved CRM. Sphincter-preserving surgery was performed in 201 (79.8%) patients with 179 (93.7%) having diverting ileostomy. The procedure was laparoscopic in 94 (37.3%) patients. APR was performed in 33 (26%) patients in the 12-week group and 18 (14.4%) in the 8-week group ($P = 0.016$). Except for the sphincter preservation rate, demographic, clinical and surgical characteristics were no different between groups (Table 1). The median interval between radiotherapy and surgery was 11 (6–14) weeks, 8 (6–10) weeks in the 8-week group and 13 (11–14) weeks in the 12-week group.

A pCR was achieved in 45 (17.9%) patients, 15 (12%) in the 8-week group and 30 (23.6%) in the 12-week group ($P = 0.021$). Pathological T and N downstaging rates were 53.5% and 73.2% in the 12-week group and higher compared with 39.2% T downstaging ($P = 0.015$) and 60% N downstaging ($P = 0.018$) in the 8-week group. Overall, 183 (72.6%) patients had TNM downstaging with no statistical difference between groups ($P = 0.178$). The CRM was involved in seven (2.8%) patients, six (4.8%) in the 8-week group and one (0.8%) in the 12-week group ($P = 0.042$). Mesorectum integrity was complete in 95.2% of the patients in the 12-week group which is significantly superior to the 80.6% rate in the 8-week group ($P = 0.001$). Other histopathological characteristics were similar between groups (Table 2).

During neoadjuvant treatment, 17 patients in the 8-week group and 13 patients in the 12-week group could not complete the protocol due to side effects of chemotherapy (Fig. 1). These patients were not included in the analysis. Postoperative complications occurred in 64 (25.4%) patients with mortality of three (1.2%) patients. The most common causes of morbidity were anastomotic leak ($n = 15$, 7.9%), surgical site infection ($n = 15$, 6%) and urinary tract infection ($n = 15$, 6%). There were no differences between groups in terms of hospital stay ($P = 0.292$), severity and variety of the complications (Table 3).

Patient and clinical characteristics were similar between the two institutions. There was no significant

Table 1 Demographic, clinical and surgical characteristics of the patients.

	Overall	8 weeks ($n = 125$)	12 weeks ($n = 127$)	P
Age (years, mean ± SD)	59.2 ± 11.4	59.9 ± 11.9	58.4 ± 10.8	0.262
Sex				
Male	160 (63.5%)	80 (64%)	80 (63%)	0.486
Female	92 (36.5%)	45 (36%)	47 (37%)	
Tumour location				
Proximal rectum	87 (34.5%)	38 (30.4%)	49 (38.6%)	0.300
Mid-rectum	79 (31.1%)	44 (35.2%)	35 (27.6%)	
Distal rectum	86 (34.1%)	43 (34.4%)	43 (33.9%)	
Pre-CRT MRI staging				
cT1	7 (2.8%)	2 (1.6%)	5 (3.9%)	0.263
cT2	96 (38.1%)	42 (33.6%)	54 (42.5%)	
cT3	122 (48.4%)	67 (53.6%)	55 (43.3%)	
cT4	27 (10.7%)	14 (11.2%)	13 (10.2%)	
cN0	29 (11.5%)	19 (15.2%)	10 (7.9%)	0.078
cN (+)	223 (88.5%)	106 (84.4%)	117 (92.1%)	
cCRM (+)	82 (32.5%)	44 (35.2%)	38 (29.9%)	0.224
Pre-CRT TNM stage				
II	29 (11.5%)	19 (15.2%)	10 (7.9%)	0.078
III	223 (88.5%)	106 (84.8%)	117 (92.1%)	
Surgery				
Sphincter preserving	201 (79.8%)	107 (85.6%)	94 (74%)	**0.016**
APR	51 (20.2%)	18 (14.4%)	33 (26%)	
Procedure				
Open	158 (62.7%)	83 (66.4%)	75 (59.1%)	0.141
Laparoscopic	94 (37.3%)	42 (33.6%)	52 (40.9%)	
Diverting ileostomy (+)	179 (93.7%)	97 (95.1%)	82 (892.1%)	0.293

Bold values are statistically significant.

APR, abdominoperineal excision; CRM, circumferential resection margin; CRT, chemoradiotherapy.

Table 2 Pathological and oncological outcome of the two groups.

	Overall	8 weeks (n = 125)	12 weeks (n = 127)	P
Histopathology				
Adenocarcinoma	235 (93.3%)	116	119	0.486
Mucinous	17 (6.7%)	9	8	
Pathological T stage				
pT0	46 (18.3%)	16 (12.8%)	30 (23.6%)	**0.003**
pTis	3 (1.2%)	1 (0.8%)	2 (1.6%)	
pT1	23 (9.1%)	5 (4%)	18 (14.2%)	
pT2	81 (32.1%)	44 (35.2%)	37 (29.1%)	
pT3	90 (35.7%)	55 (44%)	35 (27.6%)	
pT4	9 (3.6%)	4 (3.2%)	5 (3.9%)	
Harvested lymph nodes (mean ± SD)	11.5 ± 7.6	11.7 ± 6.8	11.2 ± 8.2	0.549
Involved lymph nodes (mean ± SD)	0.4 ± 1.3	0.5 ± 1.3	0.4 ± 1.2	0.654
Pathological N stage				
pN0	194 (77%)	91 (72.8%)	103 (81.1%)	0.072
pN1c	14 (5.6%)	11 (8.8%)	3 (2.4%)	
pN1	36 (14.3%)	17 (13.6%)	19 (15%)	
pN2	8 (3.2%)	6 (4.8%)	2 (1.6%)	
Pathological TNM stage				
0	45 (17.9%)	15 (12%)	30 (22.8%)	0.059
I	62 (24.6%)	34 (27.2%)	28 (22%)	
II	89 (35.3%)	43 (34.4%)	46 (36.2%)	
III	56 (22.6%)	33 (26.4%)	23 (18.1%)	
Lymphatic invasion (+)	37 (14.7%)	13 (10.4%)	11 (8.7%)	0.342
Venous invasion (+)	24 (9.5%)	10 (8%)	14 (11%)	0.274
Perineural invasion (+)	20 (7.9%)	12 (9.6%)	8 (6.3%)	0.231
Distal margin (cm, mean ± SD)	3.1 ± 1.8	2.9 ± 1.5	3.4 ± 1.9	0.063
CRM (+)	7 (2.8%)	6 (4.8%)	1 (0.8%)	**0.042**
Mesorectum integrity				
Complete	221 (88%)	100 (80.6%)	121 (95.2%)	**0.001**
Near complete	20 (8%)	17 (13.7%)	3 (2.4%)	
Incomplete	10 (4%)	7 (5.6%)	3 (2.4%)	
Tumour regression grade				
0	45 (17.9%)	15 (12%)	30 (22)	0.089
1	62 (24.6%)	35 (28%)	27 (21.3%)	
2	119 (46.8%)	64 (50.4%)	55 (43.3%)	
3	26 (10.3%)	11 (8.8%)	15 (11.8%)	
T downstaging (+)	117 (46.4%)	49 (39.2%)	68 (53.5%)	**0.015**
N downstaging (+)	168 (66.7%)	75 (60%)	93 (73.2%)	**0.018**
TNM downstaging (+)	183 (72.6%)	87 (69.6%)	96 (75.6%)	0.178
Pathological complete response (+)	45 (17.9%)	15 (12%)	30 (23.6%)	**0.021**

Bold values are statistically significant.
CRM, circumferential resection margin.

difference between groups regarding mesorectum integrity, CRM, distal margin and harvested lymph nodes (Table 4).

Discussion

Our results suggest that extending the 8-week interval to 12 weeks provides a 2-fold increase in pCR, favourable pathological downstaging in T and N stages and better surgical quality regarding CRM and mesorectum integrity without any increase in postoperative mortality and morbidity. The 12-week interval was inferior to 8 weeks only with respect to sphincter preservation; 26% of the patients underwent APR in the 12-week group *vs* 14.4% in the 8-week group (P = 0.016). Our results also suggest a higher incidence of non-restorative surgery rate in the 12-week group despite similar tumour characteristics and better specimen quality in

Table 3 Postoperative complications regarding waiting interval after chemoradiotherapy.

	Overall	8 weeks (n = 125)	12 weeks (n = 127)	P
Hospital stay (days, mean ± SD)	10.5 ± 10.3	9.8 ± 11.3	11.5 ± 8.5	0.292
Overall complications	64 (25.4%)	38 (30.4%)	26 (20.1%)	0.083
Clavien–Dindo				
I	3	2	1	0.449
II	30	16	14	
III	23	14	9	
IV	5	4	1	
Mortality	3 (1.2%)	2 (1.6%)	1 (0.8%)	0.494
Surgical site infection	15 (6%)	7 (5.6%)	8 (6.3%)	0.513
Ileus	5 (1.9%)	3 (2.4%)	2 (1.5%)	0.269
Urinary tract infection	15 (6%)	10 (8%)	5 (3.9%)	0.136
Pulmonary infection	14 (5.6%)	7 (5.6%)	7 (5.5%)	0.596
Anastomotic leak	15 (7.9%)	11 (10.8%)	4 (4.5%)	0.088
Cardiovascular complications	3 (1.2%)	2 (1.6%)	1 (0.8%)	0.949

Table 4 Comparison of the patient characteristics and operative outcome between the two institutions.

	Institution 1n = 183 (%)	Institution 2n = 69 (%)	P
Age (years, mean ± SD)	59.6 ± 11.2	57.8 ± 11.8	0.253
Sex			
Male	118 (64.5)	42 (60.9)	0.349
Female	65 (35.5)	27 (39.1)	
Tumour location			
Proximal rectum	60 (32.8)	27 (39.1)	0.484
Mid-rectum	61 (33.3)	18 (26.1)	
Distal rectum	62 (33.9)	24 (34.8)	
Pre-CRT TNM stage			
II	22 (12)	7 (10.1)	0.433
III	161 (88)	62 (89.9)	
Groups			
8 weeks	88 (48.1)	37 (53.6)	0.260
12 weeks	95 (51.9)	32 (46.4)	
Surgery			
Sphincter preserving	144 (78.7)	57 (82.6)	0.308
APR	39 (21.3)	21 (17.4)	
Harvested lymph nodes (mean ± SD)	12.2 ± 6.3	10.4 ± 4.8	0.098
Distal margin (cm, mean ± SD)	3.1 ± 1.9	3.2 ± 1.4	0.805
CRM (+)	6 (3.3)	1 (1.4)	
Mesorectum integrity			
Complete	158 (86.8)	63 (91.3)	0.425
Near complete	15 (8.2)	5 (7.2)	
Incomplete	9 (4.9)	1 (1.4)	

APR, abdominoperineal excision; CRM, circumferential resection margin; CRT, chemoradiotherapy.

the 12-week group. We are unable to explain this unexpected result.

A meta-analysis of 13 studies and 19 652 patients published in 2017 revealed similar sphincter preservation rates between shorter and longer interval groups (relative risk 0.99, P = 0.743) [19]. Similarly, in a Dutch study, sphincter preservation rate did not significantly differ in longer interval groups ranging between 5 and 14 weeks (P = 0.393) [20]. Briefly, the recently published data show no beneficial effect of longer intervals on sphincter preservation [21].

In recent years, there has been increasing evidence that extending the interval between adjuvant therapy and surgery would be associated with increased rates of pCR. Dhadda *et al.* [22] assessed the process of tumour regression in 106 patients with cT3/4 rectal cancer who received preoperative radiotherapy or CRT. They compared the tumour volume on CT and the residual pathological volume and found that a tumour size of 54 cm^3 would require 20 weeks after the start of the neoadjuvant treatment to surgery to regress to < 0.1 cm^3 (10 volume-halving times: 140 days). This finding infers a benefit of delaying surgery beyond 6 weeks. According to this study a 20-week interval between the start of neoadjuvant treatment and surgery may be ideal but to extend the interval beyond 8–12 weeks may increase surgical morbidity [22]. Traditionally, surgeons have concerns on delaying surgery beyond 8 weeks due to potentially increased radiation-induced pelvic fibrosis and related surgical complications. But it has been shown that the anastomotic leak and perineal wound complication rates decreased with longer intervals to surgery [19,23]. A recent retrospective Dutch study reported that pCR rates, complications and oncological outcomes were no different between greater or less than 14-week intervals [21]. Our results confirm no differences in surgical and medical complications between 8- and 12-week intervals. Overall complications (30.4% in the 8-week interval *vs* 20.1% in the 12-week interval, $P = 0.083$) and anastomotic leak (10.8% in the 8-week interval *vs* 5.4% in the 12-week interval, $P = 0.088$) were comparable between the groups.

The first randomized controlled trial on this subject was the Lyon study showing that patients who underwent surgery at 6–8 weeks had significantly better rates of pCR compared with patients who underwent surgery at 2 weeks after completion of radiotherapy (respectively 26% *vs* 10%, $P = 0.05$) [24]. This study showed that tumour response was improved with the longer interval and the complications, sphincter preservation rate and short-term oncological outcome were similar. Recently, the results of long-term follow-up of this study have been published [25]. With 17 years of follow-up, the local recurrence rates (14% in the 6–8-week group and 12% in the 2-week group) and overall survival (42% *vs* 40%) at 15 years were similar in the two groups. The results of the Lyon study also confirmed the results of other retrospective studies which have demonstrated that tumour regression may take more than 6–8 weeks [26,27]. In a retrospective study, Kalady *et al.* [26] found that a time interval of longer than 8 weeks was the only independent prognostic factor related to a higher rate of pCR (30% *vs* 16%). Probst *et al.* [27] analysed the National Cancer Database and showed that an interval longer than 8 weeks had increased pCR rates compared with an interval of 6–8 weeks. Similarly, a systematic review showed that overall four of seven studies had higher pCR rates with an extended time interval [28]. Moreover, there was no significant difference in rates of surgical complications or long-term recurrence and survival. In a meta-analysis of 13 studies, patients were divided into two groups: an interval of shorter than 6–8 weeks and an interval of longer than 6–8 weeks. The longer interval was found to be associated with significantly increased pCR rate (19.5 *vs* 13.7%) [29]. In contrast, in 2016, we had the opportunity to read two National Cancer Database analyses. Sun *et al.* [30] found that maximal pCR can be seen with an interval of 8 weeks. Beyond 8 weeks, pathological downstaging plateaued. In the other National Cancer Database analysis, Huntington *et al.* showed that pCR rates were similar between an interval of less than 60 days and more than 60 days [31]. Interestingly, the longer interval was associated with a 26% increased risk of death.

Despite these conflicting results, it is now generally accepted that an extended interval of at least 8 weeks is associated with increased pCR [4]. However, the data on > 8-week intervals are limited. There are a few retrospective cohorts and only two randomized studies published comparing shorter intervals with > 8-week intervals. A population-based study analysed 1073 locally advanced rectal cancer cases in the Netherlands Cancer Registry between 2006 and 2011 [20]. Compared with a treatment interval of 7–8 weeks, pCR rates in locally advanced patients were higher after 9–10 weeks (18.4%) and 11–12 weeks of treatment interval (20.8 %). Treatment interval did not influence overall survival. The authors concluded that treatment intervals of 9–12 weeks between CRT and surgery seem to improve the chances of pCR, without an effect on overall survival. This result supports the conviction that pCR is not directly associated with better oncological results, but just a marker of good tumour biology.

In our study we did not perform a survival analysis due to short median follow-up.

Recently a randomized controlled trial GRECCAR was published [32]. A total of 265 patients with locally advanced rectal cancer who had received chemoradiation (45–50 Gy with 5-fluorouracil or capecitabine) from 24 centres were randomly assigned to either a 7- or 11-week interval to surgery. There was no significant difference in the pCR rates between the standard group and the delayed group (respectively 15% *vs* 17.3%, $P = 0.598$). They found an increase in medical complications after surgery in the delayed group; however, there was no statistically significant increase in the rate

of anastomotic leaks or mean hospital stay. There was no information on long-term survival outcomes. The study concluded that waiting 11 weeks after surgery did not increase pCR and may be associated with a high risk of complications and more difficult surgery. The integrity of the mesorectum was 78.7% in the 7-week group *vs* 90% in the 11-week group ($P = 0.015$). We have a concern whether these results were enough to represent the surgical difficulty, where the difference in mesorectum integrity was not statistically significant and other parameters including blood loss and operative time were similar between groups [32]. Operative time and blood loss were not analysed in our study; thus, it is difficult to comment on surgical difficulty. In our study, a complete mesorectum was achieved in 95.2% of the patients in the 12-week group *vs* 80.6% in the 8-week group ($P = 0.001$). Moreover, CRM involvement was higher in the 8-week group (4.8% *vs* 0.8%, $P = 0.042$). Considering that the preoperative clinical T staging was no different between groups, our results suggest that extending the interval to 12 weeks resulted in better quality of the specimen. In order to exclude the bias due to different surgeons, we reported a comparison between two institutions. Tumour characteristics and operative outcome were no different in the two institutions, confirming that the favourable mesorectum integrity in the 12-week group was independent of different operating surgeons.

Another randomized trial by Akgun *et al.* [33] reported the results of 327 patients. They compared the results of 8-week and > 8-week intervals. They reached the highest pCR rate (29%) at 10–11 weeks. Overall TNM ($P = 0.004$) and T downstaging ($P = 0.001$) were significantly better in the long-interval group. The quality of TME, postoperative complications and anastomotic leak were similar. In this study, there were 160 patients in the short-interval group with a 4–8-week range and 167 patients in the long-interval group with an 8–12-week range. In line with Akgun *et al.*'s design, our protocol intended definite waiting intervals of 8 and 12 weeks. However, during daily clinical practice the timing of surgery showed deviations and so $\pm$ 2 weeks were accepted as an allowable deviation in our study. Apart from the lack of long-term follow-up and oncological outcomes, this was one of the drawbacks of our study. However, we consider that it is very difficult to perform the surgery at a definite time that was planned before and our results represent the actual clinical management. A significant number of patients have been excluded from the study during neoadjuvant CRT. Of 78 protocol violations, 30 patients had side effects due to CRT. Another 22 patients did not appear for planned surgery after completion of the CRT protocol and could not be reached despite all efforts. Most of these patients had been referred to our institution from distant provinces. Twelve patients who were recommended for APR after post-CRT MRI assessment withdrew from surgery and were excluded. As these results point out, compliance and access to the treatment are still substantial problems in rectal cancer management.

Randomized trials on waiting intervals longer than 8 weeks have reported conflicting results. Some trials have reported improved pCR rates with > 8-week intervals. There is one ongoing study comparing a 6-week interval to a 12-week interval in the Royal Marsden Hospital, UK, but results are not yet available (http://www.clinicaltrials.gov/show/NCT01037049). The published results on > 8-week intervals are overall encouraging. Although there is no clear evidence that an increased pCR rate is associated with better long-term oncological outcome, extending the interval between CRT and surgery may allow accurate evaluation of complete responders. This may impact on the decision to defer surgery and adopt a watch and wait policy. Clearly, this has potentially important implications for the future management of colorectal malignant disease.

Conflicts of interest

The authors declare no conflicts of interest.

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