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The effect of time interval from chemoradiation to surgery on postoperative complications in patients with rectal cancer

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ABSTRACT

Background: A prolonged time interval between chemoradiation and total mesorectal excision (TME) may render more rectal cancer patients eligible for organ-sparing approaches but may also cause more pelvic fibrosis and surgical morbidity. We estimated the effect of time interval on postoperative complications and other surgical outcomes in rectal cancer patients.

Methods: This is a population-based cohort study using data of the Dutch Colorectal Audit. Rectal cancer patients treated with chemoradiation followed by TME after an interval of 3–20 weeks were selected (n = 6,268). Time interval from completion of chemoradiation to TME was categorized into 3–6, 7–8, 9–10, 11–12 and 13–20 weeks. Outcomes included postoperative complication (any, and stratified by medical and surgical complications), reintervention, intraoperative complication, incomplete resection, positive circumferential margin (CRM) and pathological complete response (pCR). The interval of 7–8 weeks was the reference group.

Results: Prolonged time intervals were not associated with a higher risk of a postoperative complication (any, surgical or medical), reintervention, and incomplete resection. Intraoperative complications were however more common after 11–12 weeks than after 7–8 weeks (odds ratio (OR) = 1.79, 95% confidence interval (CI) = 1.20–2.69). The interval of 9–10 weeks was associated with less CRM positive resections, and 9–10 and 13–20 weeks with more pCR (relative to 7–8 weeks, OR = 0.74, 95%CI = 0.56–0.98; OR = 1.28, 95%CI = 1.04–1.58; and OR = 1.33, 95%CI = 1.04–1.71, respectively).

Conclusions: Compared with 7–8 weeks, longer time intervals up to 13–20 weeks between chemoradiation and TME are not associated with more postoperative complications or more positive resection margins. Accordingly, prolonging the interval aiming for organ-sparing treatment is safe.

Introduction

Treatment for locally advanced rectal cancer (LARC) involves neoadjuvant chemoradiation (CRT) followed by total mesorectal excision (TME) [1,2]. A time interval between CRT and TME allows downsizing of the tumor in order to facilitate radical surgical resection. The advised time interval varies widely among guidelines and lies between 4 and 12 weeks [3]. However, there is a trend towards longer intervals to increase the probability of a complete tumor response after CRT and, accordingly, the eligibility for organ-sparing treatment [4,5].

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Between 15–31% of the LARC patients treated with CRT achieve a pathological complete response (pCR) [5–7]. Several studies have shown that a longer interval to TME increases the chance of pCR [5,7–11]. Extending the time interval may therefore increase chances for organ-sparing approaches in patients with a preoperatively identified complete tumor response [12–14]. Nonetheless, prolongation of the interval may as well increase the risk of radiation-induced pelvic fibrosis, which could increase surgical complexity [4,15,16]. The GRECCAR-6 trial, in which rectal cancer patients were randomized between TME after 7 weeks versus 11 weeks following CRT, showed significantly more non-surgical complications and worse quality of the mesorectal resections after 11 weeks [15]. Moreover, pelvic fibrosis and difficulties in pelvic dissection were described in the longer interval group.

Knowledge on the impact of a prolonged interval on complication risk is crucial, since the majority of patients do not achieve a complete response and undergo surgery. In this study, we determined the association between time interval from completion of CRT to TME and the risk of postoperative complications in rectal cancer patients. In addition, we assessed the risk of intraoperative complication, reintervention, incomplete resection, positive circumferential margin (CRM) and probability of pCR.

Materials and methods

This is a population cohort study with data from the Dutch ColoRectal Audit (DCRA) [17]. The DCRA is a national audit that registers clinical outcomes <30 days after primary colorectal cancer surgery of patients in the Netherlands. The DCRA dataset is cross-checked on a yearly basis with data from the Netherlands Cancer Registry.

Rectal cancer patients treated with neoadjuvant CRT and surgery between April 2007 and April 2017 were selected (N = 7,029). Exclusion criteria were surgery other than standard TME (i.e. local excision (N = 13, 0.2%), transanal (minimally invasive surgery) TME (N = 89, 1.3%), and partial mesorectal excision (N = 15, 0.2%)), surgical resection or radiofrequency ablation of liver metastases prior to TME (N = 155, 2.2%), intraoperative radiotherapy/chemotherapy (N = 212, 3.0%), and a time interval <3 weeks (N = 76, 1.1%) or >20 weeks (N = 191, 2.7%).

According to the Dutch guidelines [18,19], CRT is indicated in LARC patients (cT4, cT3 ≤1 mm to the mesorectal fascia (MRF), cN2 and/or extramesorectal lymph node involvement), but may also be used for patients with lower stage rectal cancer aiming for organ-sparing treatment. CRT involves 45–50Gy in fractions of 1.8–2Gy in 5 weeks with concurrent capecitabine 825–1000mg/m2 bid. TME included low anterior resection (LAR) with/without deviating stoma, abdominoperineal resection (APR) or, less frequently, a Hartmann's procedure.

Time interval was defined as the number of weeks between completion of CRT and TME. As only the start date of radiotherapy was registered, time interval was calculated by subtracting the start date of radiotherapy from date of surgery minus five weeks (total duration of CRT). Time interval was categorized in groups of 3–6, 7–8, 9–10, 11–12 and 13–20 weeks. These groups were chosen based on previous literature and the ability to identify a trend in risks.

The primary outcome was postoperative complications stratified by any, surgical, and medical (non-surgical) postoperative complications. Postoperative complications were defined by the DCRA as hospital stay >14 days in combination with a complication, reintervention due to a surgical complication, and/or death during hospital stay or within 30 days after surgery. Surgical complications included anastomotic leakage, abscess, bleeding, ileus, dehiscent fascia, iatrogenic injury to bowel and ureter/urethra, and other non-specified complications. Medical complications included pulmonary, cardiac, thrombotic, infectious, neurologic and other non-specified complications. Secondary outcomes were intraoperative complication, reintervention, positive CRM (tumor directly at the CRM or a minimal distance between the tumor and the CRM of ≤1 mm), R1 or R2 resection (microscopic or macroscopic positive resection margin respectively), and pCR (ypT0N0). Patient, disease and treatment variables of interest included year of surgery, age at time of surgery, sex, comorbidities, American Society of Anesthesiologists (ASA) score, body mass index (BMI, kg/m2), disease stage, tumor distance, preoperative complications, surgery before primary tumor resection (for deviating stoma, stenting or other non-specified complications), surgical approach, surgical procedure, stoma presence, extended resections for tumor (T4) and local metastases.

Missing data

Of the 6,591 patients who met the inclusion criteria, time interval could not be calculated in 10.9% due to missing values in start date of radiotherapy and 4,865 (73.8%) patients had at least one missing variable. Missing values were evaluated, classified as random and replaced by multiple imputation using 10 datasets. Time interval was imputed on the continuous scale using the original distribution (up to 639 weeks). The imputation model comprised all patient, disease and treatment covariates including the primary and secondary outcomes. The overall rate of postoperative complications (0.5% missing values) was not imputed but used as predictor in the model. Multiple imputation was performed with use of SPSS software version 23 (IBM SPSS Statistics for Windows, Armonk, NY: IBM Corp.).

Statistical analyses

Baseline characteristics were presented in summary statistics for the original and imputed dataset. To estimate the independent effect of time interval on the primary and secondary outcomes, multivariable logistic regression analyses were performed using the imputed dataset and the 7–8 weeks group as reference category, adjusted for all patient, disease and treatment factors that were associated with time interval and the outcomes based on literature and clinical relevance. Multicollinearity of the covariates was checked with the variance inflation factor ($VIF = 1/(1-R^2)$), estimating how much the variance of a coefficient is increased due to linear dependence with other coefficients [20]. In case of VIF>3.0, variables were combined or removed from the model. A subgroup analysis on complication risks was performed in patients whom underwent surgery after 2014, as the current guidelines were implemented that year. A sensitivity analysis was performed using the original non-imputed dataset. Crude and adjusted odds ratios (ORs) with 95% confidence intervals (CI) and p-values were presented. The level of significance was set at $p < 0.05$. Statistical analyses were performed with SPSS software version 23.

Results

Of the 7,029 rectal cancer patients, 5,688 (80.9%) met the inclusion criteria and underwent TME 3–20 weeks after the completion of CRT (original dataset). After replacing missing values for time interval and selecting those patients with an interval of 3–20 weeks, the pooled imputed dataset yielded 6,268 (89.2% of total) patients.

Based on the original dataset, median time interval to surgery was 10 weeks. Postoperative complications were reported in 2,078 (36.5%) patients, surgical complications in 1,178 (20.7%) patients

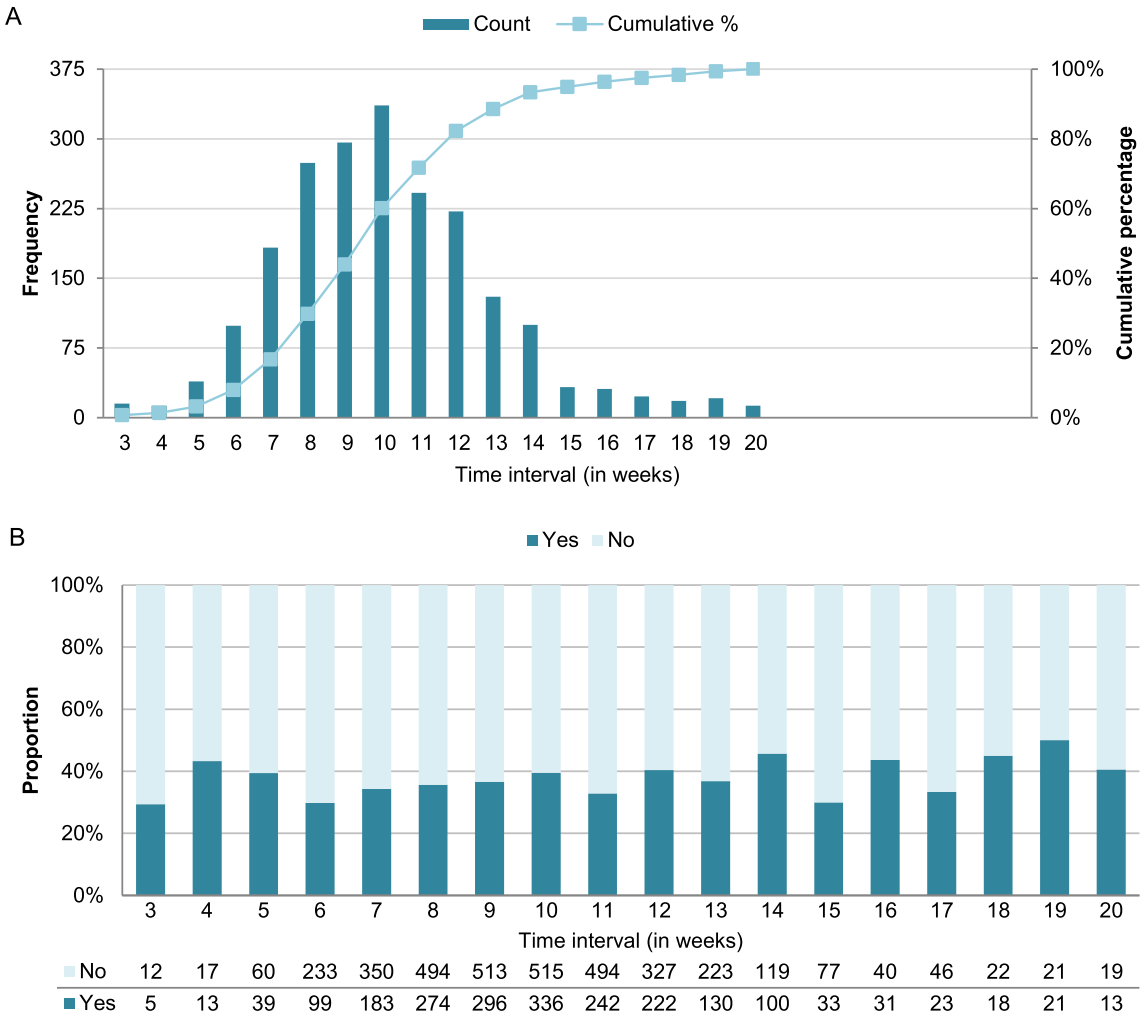

Fig. 1. Frequency, cumulative percentage (A) and proportion (B) of rectal cancer patients developing a postoperative complication (yes or no) in relation to time interval per week between completion of chemoradiation and total mesorectal excision.

and medical complications in 1,001 (17.6%) patients. Fig. 1 shows the frequency, cumulative percentage and proportion of patients developing postoperative complications per week interval.

Four hundred seventy nine (8.4%) patients received surgery after 3–6 weeks, 1,309 (23.0%) after 7–8 weeks, 1,668 (29.3%) after 9–10 weeks, 1,287 (22.6%) after 11–12 weeks and 945 (16.6%) after 13–20 weeks (Table 1). Longer time intervals were more often applied in the more recent years. The groups were comparable in age, sex, BMI, and tumor location. In the longest interval group, more patients had ≥3 comorbid conditions, ASA III, had undergone previous abdominal surgery, and were diagnosed with a higher disease stage (cT4, MRF involvement and cM1) compared with the shortest interval. Also, the longest interval group more often developed preoperative complications, underwent more frequently surgery before the primary tumor resection, a permanent stoma procedure, and extended resections than the other interval groups. Among the groups, the shortest interval group underwent most often open surgery.

Supplement Table 1s presents the summary statistics of the imputed dataset. Postoperative complications were observed in 32.6%, 34.9%, 37.9%, 36.0% and 38.0% from shortest to longest interval group (Table 2). Compared with the 7–8 weeks group, multivariable analyses showed no significantly increased risk of any postoperative, surgical and medical complications and reintervention. The risk of intraoperative complications was higher in the 11–12 weeks group (adjusted OR = 1.79, 95%CI = 1.20–2.69).

No higher risk of anastomotic leakage, abscess, ileus, and other/non-specified surgical complications, nor a higher risk of pulmonary, cardiac, and infectious medical complications was observed in groups with intervals longer than 7–8 weeks (Fig. 2 and Supplement Table 2). The risk of other/non-specified medical complications was significantly higher after 9–10 weeks than after 7–8 weeks (adjusted OR = 1.39, 95%CI = 1.08–1.79).

The interval group of 9–10 weeks was associated with a significantly lower risk of CRM positivity compared with 7–8 weeks (adjusted OR = 0.74, 95%CI = 0.56–0.98) (Table 3). Time interval was not associated with a R1-2 resection. The probability of a pCR was significantly higher after 9–10 and 13–20 weeks than after 7–8 weeks (OR = 1.28, 95%CI = 1.04–1.58 and OR = 1.33, 95% CI = 1.04–1.71, respectively).

In the analyses of patients treated after the implementation of the new guideline in 2014 (N = 2,715), comparable results were observed (Supplement Table 3). Also, the analyses in the original non-imputed dataset showed comparable outcomes (Supplement Table 4). However, unlike the imputed dataset, the original dataset showed a significantly lower risk of reintervention after 3–6 weeks, and a lower risk of a resection with a positive CRM after 3–6 weeks and 11–12 weeks (relative to 7–8 weeks, adjusted OR = 0.37,

Table 1
Patient, disease and treatment characteristics of rectal cancer patients stratified by groups of time interval between neoadjuvant chemoradiation and surgery based on the original dataset.

	Original dataset				
	3–6 weeks n = 479 (%)	7–8 weeks n = 1309 (%)	9–10 weeks n = 1668 (%)	11–12 weeks n = 1287 (%)	13–20 weeks n = 945 (%)
Time interval (weeks), mean; SD	5.6; 0.8	7.6; 0.5	9.5; 0.5	11.4; 0.5	14.7; 2.0
Year of surgery, mean; SD	2011.4; 1.9	2012.3; 2.0	2013.2; 2.0	2013.9; 2.0	2014.2; 1.9
Age at surgery (years), mean; SD	64.4; 9.7	63.5; 10.2	64.1; 10.3	64.3; 10.1	64.4; 10.3
Missing		1 (0.0)	1 (0.0)	1 (0.0)	1 (0.0)
Male sex	297 (62.0)	861 (65.8)	1021 (61.2)	811 (63.0)	601 (63.6)
Missing	1 (0.2)				1 (0.1)
Body mass index, mean; SD	25.8; 4.1	26.1; 4.1	26.1; 4.4	26.3; 4.3	26.0; 4.5
Missing	53 (11.1)	65 (5.0)	42 (2.5)	24 (1.9)	17 (1.8)
Comorbidities					
None	202 (42.2)	496 (37.9)	589 (35.3)	455 (35.4)	299 (31.6)
1 condition	142 (29.6)	411 (31.4)	470 (28.2)	370 (28.7)	311 (32.9)
2 conditions	86 (18.0)	239 (18.3)	343 (20.6)	271 (21.1)	177 (18.7)
≥3 conditions	49 (10.2)	159 (12.1)	264 (15.8)	189 (14.7)	158 (16.7)
Missing		4 (0.3)	2 (0.1)	2 (0.2)	
Previous abdominal surgery	110 (23.0)	336 (25.7)	467 (28.0)	358 (27.8)	283 (29.9)
Missing	7 (1.5)	8 (0.6)	5 (0.3)	3 (0.2)	
ASA classification					
I	137 (28.6)	401 (30.6)	450 (27.0)	315 (24.5)	204 (21.6)
II	285 (59.5)	772 (59.0)	1021 (61.2)	828 (64.3)	591 (62.5)
≥III	49 (10.2)	131 (10.0)	193 (11.6)	144 (11.2)	149 (15.8)
Missing	13 (1.7)	5 (0.4)	4 (0.2)		1 (0.1)
Clinical tumor stage					
T1-2	35 (7.3)	99 (7.6)	135 (8.1)	97 (7.6)	71 (7.6)
T3	352 (73.5)	981 (74.9)	1202 (72.1)	917 (71.3)	631 (66.8)
T4	52 (10.9)	180 (13.8)	275 (16.5)	257 (20.0)	229 (24.2)
Missing	40 (8.4)	49 (3.7)	56 (3.4)	16 (1.2)	
Mesorectal fascia involvement	123 (25.7)	467 (35.7)	768 (46.0)	659 (51.2)	509 (53.9)
Missing	228 (47.6)	485 (37.1)	405 (24.3)	223 (17.3)	166 (17.6)
Clinical nodal stage					
N0	85 (17.7)	237 (18.1)	238 (14.3)	194 (15.1)	155 (16.4)
N1-2	340 (71.0)	990 (75.6)	1343 (80.5)	1042 (81.0)	747 (79.0)
Missing	51 (11.3)	82 (6.3)	87 (5.2)	51 (4.0)	43 (4.6)
Synchronous metastases	9 (1.9)	32 (2.4)	71 (4.3)	49 (3.8)	55 (5.7)
Missing	62 (12.9)	123 (9.4)	71 (4.3)	80 (6.2)	77 (8.1)
Tumor distance					
Low (<6 cm)	235 (49.1)	572 (43.7)	760 (45.6)	663 (51.5)	477 (50.5)
Mid-high (6–20 cm)	220 (45.9)	693 (52.9)	857 (51.4)	586 (45.5)	434 (45.9)
Missing	24 (5.0)	44 (3.4)	51 (3.1)	38 (3.0)	34 (3.6)
Surgery before tumor resection	64 (13.4)	224 (17.1)	258 (15.5)	212 (16.5)	196 (20.7)
Missing	7 (1.5)	20 (1.5)	13 (0.8)	6 (0.5)	2 (0.2)
Preoperative complication[a]	89 (18.6)	291 (22.2)	375 (18.3)	235 (18.3)	235 (24.9)
Missing	8 (1.7)	8 (0.6)			2 (0.2)
Surgical approach					
Open	220 (45.9)	543 (41.5)	631 (37.8)	398 (30.9)	387 (41.0)
Laparoscopy	259 (54.1)	764 (58.4)	1035 (62.1)	885 (68.8)	555 (58.7)
Missing		2 (0.2)	2 (0.1)	4 (0.3)	3 (0.3)
Surgical procedure					
Low anterior resection	58 (12.1)	150 (11.5)	165 (9.9)	142 (11.0)	93 (9.8)
Low anterior resection + dev. stoma	152 (31.7)	481 (36.7)	600 (36.0)	437 (34.0)	276 (29.2)
Hartmann resection	56 (11.7)	156 (11.9)	229 (13.7)	162 (12.6)	134 (14.2)
Abdominoperineal resection	208 (43.4)	515 (39.3)	667 (40.0)	545 (42.3)	440 (46.6)
Missing	5 (1.0)	7 (0.5)	7 (0.4)	1 (0.1)	2 (0.2)
Extended tumor resection	49 (10.2)	100 (7.6)	180 (10.8)	163 (12.7)	173 (18.3)
Missing	8 (1.7)	23 (1.8)	73 (4.4)	25 (1.9)	16 (1.7)
Extended metastatic resection	7 (1.5)	19 (1.5)	51 (3.1)	41 (3.2)	59 (6.2)
Missing		4 (0.3)	3 (0.2)	1 (0.1)	

ASA = American Society of Anesthesiologists. SD = standard deviation. [a] Includes perforation, abscess, obstruction (ileus), blood loss with significant decrease in red blood count, and other non-specified complications.

95%CI = 0.17–0.77; adjusted OR = 0.47, 95%CI = 0.23–0.98; and adjusted OR = 0.57, 95%CI = 0.32–0.72, respectively). Furthermore, no significant probability for pCR in the 9–10 weeks was observed in contrast to the imputed dataset.

Discussion

In current rectal cancer guidelines, an uniform time interval is advised for any patient treated with CRT. However, in patients with a preference for organ-sparing treatment, a prolonged interval can maximize the downsizing effect of the tumor by CRT and increase the chance of a complete response. A prolonged interval also allows extended neoadjuvant therapy, such as a radiation boost or consolidation chemotherapy, which may further increase this chance [21]. On the other hand, in patients with a preference for radical surgery, a short time interval could be applied to reduce the total treatment duration. Moreover, patients who do not respond to CRT may benefit from early surgery. Our findings suggest that a shorter or longer interval than the most frequently applied 7–8 weeks between CRT and TME is safe in terms of postoperative

Table 2
The effect of time interval between chemoradiation and total mesorectal excision on any postoperative complication, surgical complication, medical complication, reintervention and intraoperative complications in rectal cancer patients using the imputed dataset.

Yes versus No	N of events (%)	Crude OR (95%CI)	Adjusted OR (95%CI)[a]	p-value
Any postoperative complication				
3–6 weeks	195 of 598 (32.6)	0.90 (0.73–1.11)	0.91 (0.74–1.13)	0.394
7–8 weeks	481 of 1377 (34.9)	1.00 (Ref)	1.00 (Ref)	
9–10 weeks	656 of 1732 (37.9)	1.14 (0.98–1.32)	1.12 (0.96–1.31)	0.138
11–12 weeks	489 of 1360 (36.0)	1.05 (0.89–1.23)	1.02 (0.86–1.21)	0.844
13–20 weeks	444 of 1169 (38.0)	1.14 (0.96–1.35)	1.06 (0.88–1.26)	0.584
Surgical complication				
3–6 weeks	100 of 600 (16.7)	0.78 (0.58–1.07)	0.84 (0.63–1.13)	0.248
7–8 weeks	281 of 1386 (20.3)	1.00 (Ref)	1.00 (Ref)	
9–10 weeks	398 of 1741 (22.9)	1.16 (0.96–1.41)	1.09 (0.90–1.32)	0.399
11–12 weeks	316 of 1362 (23.2)	1.18 (0.97–1.46)	1.05 (0.85–1.29)	0.654
13–20 weeks	291 of 1180 (24.7)	1.29 (1.05–1.57)	1.10 (0.89–1.36)	0.372
Medical complication				
3–6 weeks	121 of 600 (20.2)	1.07 (0.83–1.39)	1.12 (0.85–1.47)	0.441
7–8 weeks	264 of 1386 (19.0)	1.00 (Ref)	1.00 (Ref)	
9–10 weeks	392 of 1741 (22.5)	1.24 (1.01–1.51)	1.18 (0.98–1.43)	0.079
11–12 weeks	277 of 1362 (20.3)	1.09 (0.82–1.43)	1.01 (0.81–1.27)	0.905
13–20 weeks	264 of 1180 (22.4)	1.23 (0.99–1.53)	1.05 (0.84–1.32)	0.665
Reintervention				
3–6 weeks	59 of 600 (9.8)	0.77 (0.51–1.17)	0.77 (0.53–1.13)	0.179
7–8 weeks	170 of 1386 (12.3)	1.00 (Ref)	1.00 (Ref)	
9–10 weeks	220 of 1741 (12.6)	1.04 (0.82–1.32)	1.05 (0.82–1.34)	0.704
11–12 weeks	171 of 1362 (12.6)	1.03 (0.80–1.33)	1.05 (0.81–1.36)	0.721
13–20 weeks	145 of 1180 (12.3)	1.01 (0.78–1.30)	1.00 (0.77–1.30)	0.999
Intraoperative complication[b]				
3–6 weeks	29 of 600 (4.8)	1.24 (0.57–2.69)	1.24 (0.58–2.68)	0.567
7–8 weeks	53 of 1386 (3.8)	1.00 (Ref)	1.00 (Ref)	
9–10 weeks	91 of 1741 (5.2)	1.40 (0.96–2.04)	1.37 (0.94–2.01)	0.102
11–12 weeks	90 of 1362 (6.6)	1.78 (1.21–2.62)	1.79 (1.20–2.69)	0.005
13–20 weeks	72 of 1180 (6.1)	1.64 (1.07–2.50)	1.45 (0.93–2.26)	0.104

CI = confidence interval. OR = odds ratio. Ref = reference group.[a] Odds ratios adjusted for year of surgery, age, sex, number of comorbid conditions (0, 1, 2, or ≥3), previous abdominal surgery, BMI, ASA score (1, 2, ≥3), cT4-stage, MRF involvement, cN-stage (cN0 versus cN+), cM-stage, distal tumor location (<6 cm), preoperative complications, surgery before primary tumor resection, surgical approach, surgical procedure (LAR without stoma, LAR with temporary stoma, Hartmann or APR), extended tumor resection, and extended resection for pelvic metastases. The variance inflation factor for all covariates was lower than 3 (none were combined or removed from the model).[b] Includes lesion of upper gastro-intestinal organs, colon, or urogenital structures, perforations, complications requiring blood transfusion or splenectomy, or others non-specified complications.

complications.

Several studies observed the effect of time interval on postoperative complications [7,9,15,22,23]. A meta-analysis of five studies concluded no higher risk of postoperative complications in LARC patients with intervals of ≥8 weeks versus <8 weeks [9]. However, four of these studies were nonrandomized and did not perform multivariable analyses, making the results prone to confounding bias [4,7,24,25]. A non-randomized trial investigated the effect of consolidation chemotherapy between CRT and TME on pCR, and applied four different intervals according to the number of chemotherapy cycles (median weeks of 8.5, 11.1, 15.4, and 19.3) [22]. Although pelvic fibrosis was more reported after 11 weeks, surgical difficulty and Clavien-Dindo grade 3–4 complications were comparable between the interval groups. Recently, an observational study evaluated surgical outcomes after an interval of ≥12 weeks versus shorter [23]. Perioperative and postoperative outcomes were comparable between the two groups, similar to our findings. Nevertheless, this study was limited by a small sample size (n = 124) and did not account for the long inclusion period (2007–2016) that could have affected postoperative care. The Stockholm III trial investigated oncological and surgical outcomes following three neoadjuvant schedules (long-course radiotherapy, short-course radiotherapy (SCRT) with immediate surgery and SCRT with delayed surgery) and showed in a pooled analysis of the two SCRT regimens that the postoperative complications risk was significantly lower after SCRT with delayed surgery than after SCRT with immediate surgery (53% versus 41%) suggesting that a very short interval may be a risk factor for complications [26].

In contrast to our findings, the GRECCAR-6 trial reported significantly more overall morbidity after 11 weeks than after 7 weeks (45% versus 32% respectively) [15]. In addition, more conversions, pelvic fibrosis and surgical difficulties, and a longer operative time were reported in the 11 weeks group, although these differences were all non-significant. The authors suggested that these findings could be related to a more fragile mesorectum after a longer interval. Overall morbidity was primarily due to more Clavien-Dindo grade 2 complications and more medical, mainly urinary, complications. In the present study, we observed a significantly higher rate of intraoperative complications after 11–12 weeks which was related to slightly more lesions to urogenital structures and non-specified intraoperative complications (data not shown). An explanation for this might indeed be fibrosis-related. However, no increased risk was observed in the other two long interval groups. Furthermore, the absolute risks were relatively low (range of 5–7%) and no higher risk of postoperative complications was associated with a time interval of 11–12 weeks suggesting that the impact of more intraoperative complications is not substantial. Like in the GRECCAR-6 trial, the interval groups were comparable in reintervention rate and surgical complications.

We observed a significant lower risk of CRM positive resections in the 9–10 interval group and a lower but non-significant risk in the 11–12 weeks group. This is possibly related to more downsizing of the tumor due to a longer interval. However, longer intervals were applied in the more recent years of the registry and improved surgical techniques and better awareness of surgeons may therefore also have played a role, despite adjustment for year of surgery in the analysis. In the GRECCAR-6 trial, distance to the CRM was comparable between the interval groups [15]. In other literature, no

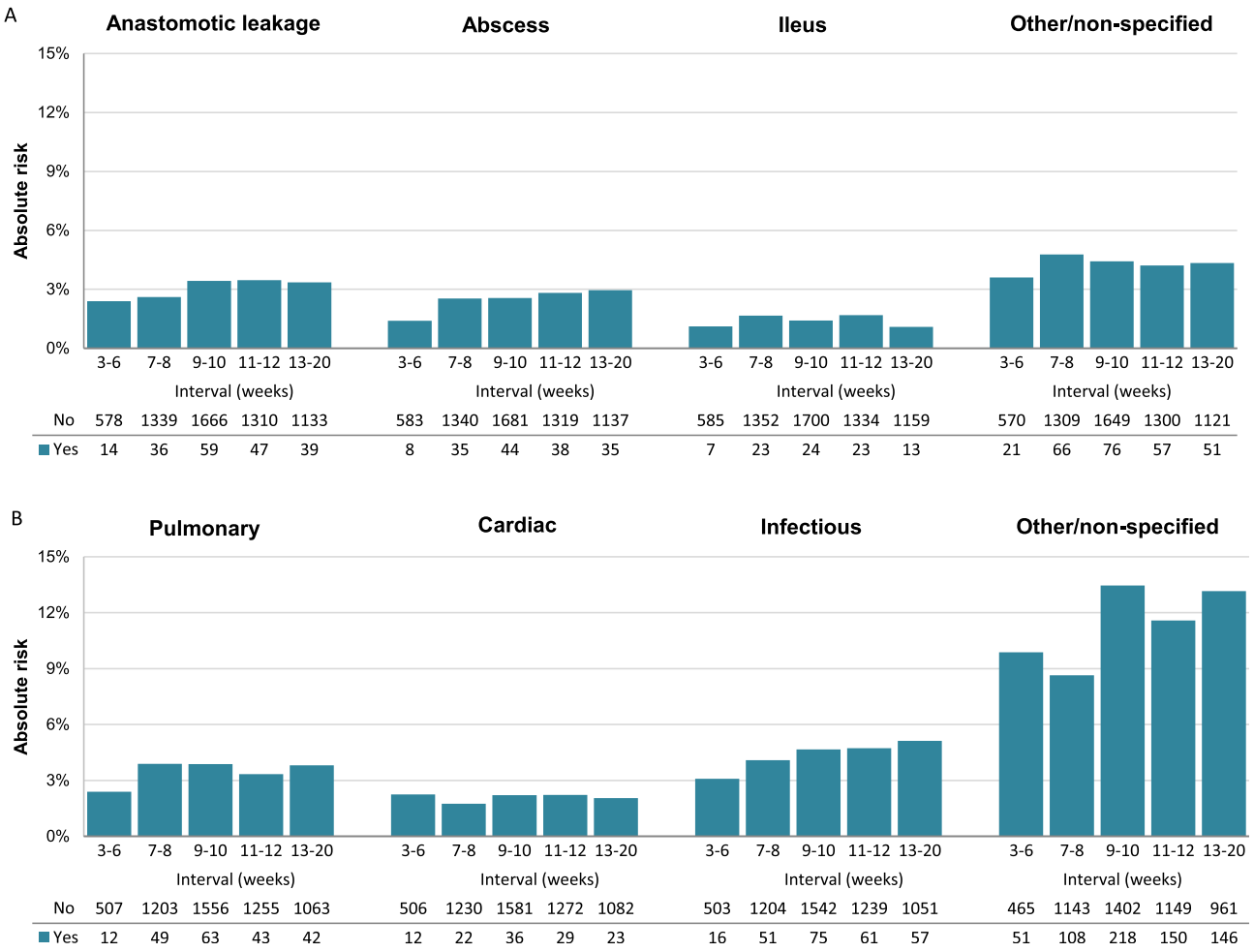

Fig. 2. Absolute proportion of anastomotic leakage, abscess, ileus and other/non-specified surgical complications that required a reintervention (A) and pulmonary, cardiac, infectious and other/non-specified medical complications (B) per time interval group between chemoradiation and total mesorectal excision in rectal cancer patients based on the imputed dataset.

Table 3
The effect of time interval between chemoradiation and total mesorectal excision on positive circumferential margin (CRM), incomplete resection (R1-2), and pathological complete response (pCR) in rectal cancer patients using the imputed dataset.

Yes versus No	N of events (%)	Crude OR (95%CI)	Adjusted OR (95%CI)[a]	p-value
Positive CRM				
3–6 weeks	52 of 585 (8.9)	0.96 (0.65–1.42)	0.85 (0.58–1.23)	0.379
7–8 weeks	127 of 1385 (9.2)	1.00 (ref)	1.00 (ref)	
9–10 weeks	118 of 1746 (6.8)	0.72 (0.55–0.94)	0.74 (0.56–0.98)	0.034
11–12 weeks	90 of 1396 (6.4)	0.68 (0.50–0.93)	0.76 (0.55–1.04)	0.082
13–20 weeks	105 of 1155 (9.1)	0.99 (0.73–1.35)	1.01 (0.75–1.37)	0.974
R1-2 resection				
3–6 weeks	26 of 600 (4.3)	0.98 (0.55–1.76)	0.92 (0.52–1.64)	0.779
7–8 weeks	60 of 1385 (4.3)	1.00 (ref)	1.00 (ref)	
9–10 weeks	66 of 1741 (3.8)	0.88 (0.60–1.28)	0.80 (0.54–1.19)	0.270
11–12 weeks	60 of 1362 (4.4)	1.02 (0.69–1.50)	0.96 (0.65–1.43)	0.846
13–20 weeks	68 of 1180 (5.8)	1.37 (0.95–1.96)	1.13 (0.76–1.69)	0.552
pCR				
3–6 weeks	94 of 600 (15.7)	1.14 (0.86–1.52)	1.20 (0.90–1.60)	0.226
7–8 weeks	193 of 1385 (13.9)	1.00 (ref)	1.00 (ref)	
9–10 weeks	295 of 1741 (16.9)	1.26 (1.03–1.55)	1.28 (1.04–1.58)	0.022
11–12 weeks	213 of 1362 (15.6)	1.14 (0.92–1.42)	1.15 (0.92–1.44)	0.225
13–20 weeks	198 of 1180 (16.8)	1.25 (0.98–1.58)	1.33 (1.04–1.71)	0.022

CI = confidence interval. CRM = circumferential margin. OR = odds ratio. pCR = pathological complete response. Ref = reference group. [a] Odds ratios for positive CRM and R1-2 resection adjusted for year of surgery, cT4-stage, cN-stage (cN0 versus cN+), cM-stage, MRF involvement, surgical procedure, surgical approach and extended resection for tumor and local metastases. Odds ratios for pCR adjusted for year of surgery, cT4-stage, cN + -stage, cM-stage, MRF involvement, and extended resection for tumor and local metastases. The variance inflation factor for all covariates was lower than 3 (none were combined or removed from the model).

subsequent lower risk of local recurrence after longer time intervals has been shown [8,9]. Nevertheless, the variety in time interval categories among studies makes it hard to compare findings. In the GRECCAR-6 trial, more often an incomplete or almost complete mesorectum was observed after 11 weeks (79% versus 90% after 7 weeks) [15]. Unfortunately, we were not able to compare findings on quality of the mesorectum as this item was not registered in the DCRA database until 2016.

In accordance with most literature, a higher probability of pCR in two of the three prolonged intervals was observed [4,5]. The relatively low pCR proportions in the longer interval groups in our study as compared with other studies (such as 31% after ≥13 weeks by Macchia et al.) could be related to patient selection [5]. Differences in neoadjuvant treatment schedules and pathology protocols could also play a role in the variance between pCR-rates among studies. Moreover, all these studies report solely pCR, excluding patients with a good/complete clinical response treated with organ-sparing approaches (who might have had a pCR when they would have receive TME). Future research on tumor response should therefore, besides pCR, also incorporate clinical complete response.

A non-significant increasing trend for infectious (non-surgical) complications from short to long interval and a significant higher rate of medical other/non-specified complications was observed after 9–10 weeks. These observations are possibly related to patient selection and subsequent residual confounding. In contrast to the imputed dataset, the original dataset showed a lower risk of reintervention and CRM positivity after 3–6 weeks. The high amount of missing values resulting in exclusion of 40% of the cases in multivariable analysis might explain this finding. As the proportion of missing values was highest in the 3–6 weeks group, this interval was most prone to biased estimates in the sensitivity analysis.

This study bears several limitations. Patient and disease characteristics may have likely played a role in selecting the interval for patients. Despite adjustment for numerous covariates, residual confounding may still be present in this observational study. Furthermore, we imputed missing values on time interval resulting in higher number of patients in the imputed dataset than in the original dataset, making these results harder to compare. Nevertheless, literature has shown the benefit of multiple imputation of values missing at random, including more precise estimates and less bias [27]. Leaving time interval out of the imputation model resulted in substantial fewer eligible patients. Furthermore, we assumed that all patients were treated with CRT as prescribed in the national guidelines regarding dose and duration as no details of neoadjuvant treatment are registered in the DCRA. However, some patients may have deviated from this. Likewise, variability among centers and surgeons may have influenced patient selection and outcome for which we could not adjust. Lastly, clinical staging has changed over the years such as the definition of positive lymph nodes on MRI, and the definition of cN2 including extramesorectal lymph nodes. This may have resulted in misclassification of some clinical variables and could have affected the outcomes adjusted for disease stage. However, the sub analysis of patients treated after implementation of the current guideline in 2014 showed comparable results.

Conclusions

In this population-based study including Dutch rectal cancer patients, longer time intervals up to 13–20 weeks between completion of CRT and TME did not increase the risk of overall postoperative complications, surgical complications, medical complications, reintervention and incomplete resection when compared with 7–8 weeks. Accordingly, prolonging the time interval aiming for organ-sparing treatment seems safe in terms of complication risk. Further research should focus on markers and tools to better predict which patients will achieve a complete tumor response following CRT and thus who may benefit from a longer interval.

Disclosures

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejso.2019.04.016.

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