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The effect of neoadjuvant short-course radiotherapy and delayed surgery versus chemoradiation on postoperative outcomes in locally advanced rectal cancer patients – A propensity score matched nationwide audit-based study

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ABSTRACT

Objective: To investigate differences in postoperative outcomes between short-course radiotherapy and delayed surgery (SCRT-delay) and chemoradiation (CRT) in patients with locally advanced rectal cancer (LARC).

Background: Previous trials suggest that SCRT-delay could serve as an adequate neoadjuvant treatment for LARC. Therefore, in frail LARC patients SCRT-delay is recommended as an alternative to CRT. However, data on postoperative outcomes after SCRT-delay in comparison to CRT is scarce.

Methods: This was an observational study with data from the Dutch ColoRectal Audit (DCRA). LARC patients who underwent surgery (2014–2017) after an interval of ≥6 weeks were included. Missing values were replaced by multiple imputation. Propensity score matching (PSM), using age, Charlson Comorbidity Index, cT-stage and surgical procedure, was applied to create comparable groups. Differences in postoperative outcomes were analyzed using Chi-square test for categorical variables, independent sample *t*-test for continuous variables and Mann-Whitney *U* test for non-parametric data.

Results: 2926 patients were included. In total, 288 patients received SCRT-delay and 2638 patients underwent CRT. Patients in the SCRT-delay group were older and had more comorbidities. Also, ICU-admissions and permanent colostomies were more common, as well as pulmonic, cardiologic, infectious and neurologic complications. After PSM, both groups comprised 246 patients with equivalent age, comorbidities and tumor stage. There were no differences in postoperative complications.

Conclusion: Postoperative complications were not increased in LARC patients undergoing SCRT-delay as neoadjuvant treatment. Regarding treatment-related complications, SCRT-delay is a safe alternative neoadjuvant treatment option for frail LARC patients.

Introduction

In compliance with European guidelines, neoadjuvant treatment for locally advanced rectal cancer (LARC) in the Netherlands comprises neoadjuvant chemoradiation (CRT), followed by surgery according to total mesorectal excision (TME) principles. Short-course radiotherapy followed by surgery after a prolonged interval (SCRT-delay) is recommended as an alternative to chemoradiation in older patients with comorbidities or frail patients with a poor performance status, because of their higher risk of treatment related complications [1].

Postoperative morbidity and mortality are often increased in

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frail or elderly patients as a result of concomitant comorbidities [2]. Data on surgical management of rectal cancer in these patients is scarce and reported postoperative morbidity and mortality vary widely in the population >65 years old [2–4]. This patient group might benefit from altered treatment, especially when they are more susceptible to treatment-related complications [5]. Moreover, inadequate treatment is associated with poor survival [2]. Unfortunately, the heterogeneity of this group and the lack of data impede an evidence-based choice of neoadjuvant treatment in this patient group [6]. With the aging population, there is need for evidence to justify the choice of the most optimal neoadjuvant treatment in frail patients with LARC.

Previous trials suggest that SCRT-delay could serve as an adequate neoadjuvant treatment for intermediate to high risk rectal cancer [7–9]. Although previous trials showed that an interval <10 days between SCRT and surgery is associated with anastomotic leakage and postoperative mortality [10,11], the rate of postoperative complications in the Stockholm III trial was lower when surgery was delayed for 4–12 weeks after SCRT [12], suggesting that it is better to prolong the interval between SCRT and surgery. Before adding this regimen to current guidelines, more data is needed on postoperative outcomes of SCRT-delay in comparison to CRT. The aim of this study was to investigate the effect of SCRT-delay on postoperative outcomes in comparison with CRT, in both the general and the frail population.

Methods

Study design

This was an observational study with data from the Dutch ColoRectal Audit (DCRA), a nationwide audit which registers clinical outcomes of all patients undergoing primary colorectal surgery in the Netherlands. The DCRA is based on evidence-based guidelines and is validated on a yearly basis with data from the Netherlands Cancer Registry (NCR) [13]. Because data could not be traced back to individual patients, neither informed consent nor ethical approval was required for this study.

Patient selection

All patients with ≥cT2 rectal cancer who underwent surgery between May 2014 (after implementation of a new Dutch colorectal cancer guideline) and December 2017, were selected from the DCRA database. Based on Dutch guidelines, LARC was defined as cT4, cT_{any} with mesorectal fascia (MRF) involvement, or $cT_{any}N2$. All patients with LARC were included in the study. Clinical tumor stage was based on imaging. Patients were excluded in case of metastatic disease, tumors located outside the rectum, emergency or urgent surgery. Also, patients who did not receive neoadjuvant treatment, with a missing start date of neoadjuvant therapy, or patients who underwent surgery after an interval of less than 6 weeks after the end of radiotherapy were excluded. Furthermore, patients who underwent surgery after an initial watch and wait strategy were excluded from the dataset, since the prolonged interval in this group could be associated with higher morbidity and a more difficult surgical resection [14]. Finally, patients who received intraoperative Hyperthermic Intraperitoneal Chemotherapy (HIPEC) or Intraoperative Radiation Therapy (IORT) were excluded.

Neoadjuvant therapy

Neoadjuvant treatment entailed either SCRT (25 Gy in fractions of 5 Gy in 5 days) or CRT (45–50 Gy in fractions of 1.8–2 Gy in 5 weeks and concurrent oral Capecetabine 825–1000 mg/m2 twice daily 5–7 days a week). Interval to surgery was calculated from the end of neoadjuvant treatment. The interval between the end of SCRT and surgery was calculated by subtracting 4 days from the interval when treatment started on Monday or by subtracting 6 days from the interval when treatment started on another day, accounting for discontinuation of therapy in the weekend. The same syntax was used for CRT patients, subtracting 32 or 34 days, respectively.

Data collection

Patient characteristics included gender, age at surgery, BMI (kg/m^2), number and type of comorbidities, and ASA score. Charlson Comorbidity Index was calculated according to the weighted index of comorbidity [15]. Tumor characteristics included clinical TNM-stage, MRF involvement and tumor distance from the anus (measured at colonoscopy). Treatment characteristics included type of neoadjuvant treatment (SCRT or CRT), date of surgery, surgical procedure and approach, intraoperative complications, conversion, and ostomy creation. The subgroup 'Minimally invasive approaches' included transanal endoscopic microsurgery (TEM), local excision and transanal minimally invasive local excision (TAMIS). Hartmann procedure was incorporated in the subgroup '(Low) Anterior Resection'. Subtotal colectomy, proctocolectomy and sigmoid resection were combined in the subgroup 'other surgical procedures' because of low prevalence. Intraoperative complications comprised injury of intra-abdominal structures, complications requiring blood transfusion or other non-specified complications.

Outcome measures

Follow-up time was 30 days after surgery. The primary outcome measure was the occurrence of postoperative complications. Complications were defined according to standards of the DCRA [13]. Postoperative complications comprised both surgical and non-surgical complications and were defined as hospital stay of ≥14 days and/or a complication, re-intervention due to a complication, and/or death during hospital stay or within 30 days after surgery. Postoperative surgical complications included anastomotic failure, abscess, bleeding, ileus, dehiscent fascia, iatrogenic bowel injury, ureter/urethra injury, or other non-specified complications. Postoperative non-surgical complications included pulmonary, cardiac, thrombotic, infectious, neurologic or other non-specified complications.

Postoperative outcome measures included re-intervention, prolonged hospital stay, intensive care unit (ICU) stay and re-admission. Re-intervention involved any laparotomy-, laparoscopic- or radiology-assisted treatment for a complication. Admission to the ICU and length of hospital stay were dichotomized based on the median length of admission. ICU stay was defined as admission to the ICU for at least 1 day. Prolonged hospital stay was defined as admission to the surgical ward for more than 7 days. Pathological outcomes included pathological tumor and nodal stage, pathological complete response rate (ypT0N0) and resection margin.

Missing data

On average, there was 2.3% missing data. Missing values were classified as random and replaced by multiple imputation. All observed data, including the outcome, that were applied to the dataset after imputation were used as predictors [16,17]. The number of imputations depended on the average percentage rate of missingness [18,19]. The imputed data were checked with

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convergence plots. Imputation was successful if the streams intermingled and were free of any trend [17]. Finally, 5 imputed datasets were produced with 5 iterations.

Propensity score matching

Since frail patients are more likely to receive SCRT-delay or to experience postoperative complications, and the type of surgery is a determinant of postoperative complications, the likelihood of confounding by indication needed to be accounted for. To enable a comparison in equivalent groups, propensity score matching was performed [20]. The propensity score was calculated for each patient using logistic regression with the variables age, Charlson Comorbidity Index, cT-stage, and surgical procedure. These covariates were chosen based on their clinical relevance. Propensity score matching was performed using 'nearest-neighbor matching' without replacement and a 1:1 ratio. The average within-pair difference in propensity scores was minimized by setting a caliper of 0.25 multiplied by the standard deviation of the logit of the propensity score [21]. The balance in the matched dataset was expressed in 'standardized mean difference' (SMD), with an SMD < 0.10 indicating a well-balanced set [22–24].

Statistical analyses

Differences in baseline characteristics and treatment outcomes were analyzed using Chi-square test for categorical variables and independent sample *t*-test for continuous variables. Mann-Whitney *U* test was used for non-parametric data. The Bonferroni correction was applied to account for multiple testing. The level of significance was set at $p < 0.05$.

All analyses were performed in IBM SPSS Statistics (version 23 - © 2015 IBM Corporation) and RStudio (Version 1.0.143 – © 2009–2016 RStudio, Inc.,'mice', 'tableone', 'MatchIt' and 'optmatch' packages).

Results

Patient selection

Between May 2014 and December 2017, 8318 patients with ≥cT2 rectal cancer were registered in the DCRA database. Patients without locally advanced tumors (n = 3541), with metastatic disease (n = 986), with tumors located outside the rectum (n = 257), who underwent urgent or emergency surgery (n = 15), who did not receive neoadjuvant treatment or if the start date of neoadjuvant therapy was missing (n = 31), who received chemotherapy only or chemotherapy combined with short-course radiotherapy (n = 102), who underwent surgery after an interval of less than 6 weeks after the end of radiotherapy (n = 298) or after an initial watch and wait strategy (n = 34) and who underwent HIPEC or IORT (n = 128) (Supplementary Fig. 1) were excluded. Finally, 2926 patients were included in the analysis. Non-imputed data are provided in Supplementary Tables 1 and 2

Pre-matching results

Patients in the SCRT-delay group had a higher mean age, had more comorbidities and a higher ASA score (Table 1). Mean BMI was higher in the CRT group. The MRF was less often involved in the SCRT-delay group and clinical N-stage was higher. There was no difference in the distance from the anus at colonoscopy. With an equal interval between neoadjuvant treatment and surgery, patients in the SCRT-delay group more often underwent abdominoperineal resection (APR) and more often received a permanent colostomy. In the SCRT-delay group, 63 patients (21.9%) received a primary anastomosis, compared to 1253 patients (47.5%) in the CRT group. Pulmonic, cardiologic, infectious and neurologic complications were significantly more common in the SCRT-delay group (Table 2). When stratified for procedure, there were significant more complications after APR in the SCRT-delay group; however, pulmonic, cardiologic, infectious and neurologic complications in the SCRT-delay group occurred independent of type of surgical procedure (Supplementary Table 3). There was no difference in the number of re-interventions. In patients that received a primary anastomosis, the frequency of re-interventions for anastomotic leakage was not different after SCRT-delay or CRT (6.3% vs 7.6%, respectively). Patients in the SCRT-delay group were more often admitted to the ICU and hospital stay was more often prolonged. Furthermore, SCRT-delay less often resulted in a pathological complete response compared to CRT (8.0% vs. 16.1%, Table 1). There were no differences in surgical radicality after SCRT-delay or CRT (92.7% vs. 95.2% R0 resections, respectively).

Post-matching results

Baseline characteristics that entered the propensity score model are presented in Supplementary Table 4. After matching, both groups comprised 246 patients and characteristics were well-balanced. Differences in patient, treatment and pathological characteristics between SCRT-delay and CRT in the post-matching cohort are presented in Table 3. After matching, BMI was higher in the CRT group. 57 patients in the SCRT-delay group (23.2%) received a primary anastomosis, compared to 73 patients (29.7%) in the CRT group. Permanent colostomies were more frequent in the SCRT-delay group, but this difference was not significant in the post-matching cohort. There were no differences in pathological outcomes. Overall, there were no differences in postoperative (surgical) complications (Table 4). The number of re-interventions for anastomotic leakage in patients that received a primary anastomosis was not significantly different between groups (5.3% vs. 2.7% after SCRT-delay vs. CRT, respectively). There were no differences in ICU admission and hospital stay.

Discussion

In this nationwide, propensity score matched study we found no difference in the occurrence of surgical complications between patients who underwent SCRT-delay or CRT as neoadjuvant therapy for LARC. However, more pulmonic, cardiologic, infectious and neurologic complications in the pre-matching cohort in the SCRT-delay group. These differences diminished when patients were matched on age, gender, comorbidities, tumor characteristics and distance from the anus.

The pre-matching cohort represents daily clinical practice in the Netherlands. With the addition of SCRT-delay as regimen for LARC to the Dutch guidelines in 2014, more elderly patients are offered neoadjuvant treatment [25]. In our dataset, 642 of 2926 (21.9%) patients who underwent surgery were aged ≥75 years. The percentage of old and frail patients was higher in the SCRT-delay group, but these patients were also represented in the CRT group, which underlines the heterogeneity of the elderly population and the differences in treatment choice due to lack of evidence-based data. Previous studies showed various results in incidence of postoperative morbidity and mortality in the elderly [2–5,26–28]. Taking into account that mortality increases when postoperative complications occur [5,27] and anastomotic leakage results in significantly more anorectal and urinary symptoms and higher Low Anterior Resection Syndrome (LARS) scores [29,30], the lower prevalence of primary anastomosis in the SCRT-delay group in the unmatched cohort might be a result of a defensive attitude towards

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Table 1
Patient, tumor and pathological characteristics in the pre-matching cohort. Data are presented as number (percentage) unless stated otherwise.

	SCRT-delay n = 288	CRT n = 2638	p-value
Patient characteristics			
Gender			0.021 *
Male	161 (55.9)	1663 (63.0)	
Female	127 (44.1)	975 (37.0)	
Age (mean years (sd))	77.89 (8.76)	64.59 (10.25)	<0.001 *
BMI (mean kg/m^2 (sd))	25.54 (3.94)	26.27 (4.35)	0.006 *
Comorbidities	249 (86.5)	1765 (66.9)	<0.001 *
Charlson Comorbidity Index			<0.001 *
0	103 (35.8)	1645 (62.4)	
1	85 (29.5)	554 (21.0)	
2	48 (16.7)	277 (10.5)	
3	31 (10.8)	111 (4.2)	
≥ 4	21 (7.3)	51 (1.9)	
ASA score			<0.001 *
1	20 (6.9)	575 (21.8)	
2	157 (54.5)	1686 (63.9)	
3	103 (35.8)	363 (13.8)	
4	8 (2.8)	14 (0.5)	
Tumor characteristics			
Distance from anus at colonoscopy (mean cm (sd))	6.69 (4.69)	6.36 (4.42)	0.224
cT			0.425
2	8 (2.8)	95 (3.6)	
3	225 (78.1)	1971 (74.7)	
4	55 (19.1)	572 (21.7)	
Distance to MRF > 1 mm	58 (20.1)	721 (27.3)	0.003 *
cN			<0.001 *
0	77 (26.7)	346 (13.1)	
1	80 (27.8)	648 (24.6)	
2	129 (44.8)	1637 (62.1)	
x	2 (0.7)	7 (0.3)	
Treatment characteristics			
Interval between end of neoadjuvant treatment and surgery (median weeks [IQR])	11.00 [9.00, 15.00]	11.00 [10.00, 13.00]	0.472
Surgical approach			<0.001 *
Transabdominal open	58 (20.1)	561 (21.3)	
Transabdominal scopic	204 (70.8)	1933 (73.3)	
TaTME or TAMIS TME	18 (6.2)	134 (5.1)	
Minimally invasive	8 (2.8)	10 (0.4)	
Surgical procedure			<0.001 *
Local excision	8 (2.8)	6 (0.2)	
(Low) Anterior Resection	155 (53.8)	1607 (60.9)	
Abdominoperineal Resection	124 (43.1)	996 (37.8)	
Other	1 (0.3)	29 (1.1)	
Conversion	39 (13.5)	341 (12.9)	0.839
Reason conversion			0.658
Extensive tumor growth	8 (2.8)	6 (0.2)	
Accessibility	28 (9.7)	216 (8.2)	
Intraoperative complication	3 (1.0)	47 (1.8)	
Intraoperative complication			0.954
No	275 (95.5)	2506 (95.0)	
Bleeding	1 (0.3)	17 (0.6)	
Spleen injury	0 (0.0)	1 (0.0)	
Bowel injury	3 (1.0)	19 (0.7)	
Ureter/urethra injury	4 (1.4)	26 (1.0)	
Bladder injury	1 (0.3)	17 (0.6)	
Vagina injury	1 (0.3)	12 (0.5)	
Other	3 (1.0)	40 (1.5)	
Primary anastomosis	64 (22.2)	1257 (47.6)	<0.001 *
Ostomy			<0.001 *
No	57 (19.8)	521 (19.7)	
Diverting ileostomy	27 (9.4)	773 (29.3)	
Permanent ileostomy	1 (0.3)	29 (1.1)	
Diverting colostomy	7 (2.4)	125 (4.7)	
Permanent colostomy	195 (67.7)	1186 (45.0)	
Stoma, unknown type	1 (0.3)	4 (0.2)	
Pathological characteristics			
pT			0.001 *
0	27 (9.4)	512 (19.4)	
1	15 (5.2)	157 (6.0)	
2	75 (26.0)	623 (23.6)	
3	152 (52.8)	1202 (45.6)	
4	19 (6.6)	125 (4.7)	

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Table 1 (*continued*)

	SCRT-delay n = 288	CRT n = 2638	p-value
x	0 (0.0)	13 (0.5)	
Unknown	0 (0.0)	6 (0.2)	
pN			0.831
0	185 (64.2)	1776 (67.3)	
1	67 (23.3)	571 (21.6)	
2	35 (12.2)	282 (10.7)	
x	1 (0.3)	7 (0.3)	
Unknown	0 (0.0)	2 (0.1)	
Pathological complete response, ypT0N0	23 (8.0)	425 (16.1)	<0.001 *
Radicality (R0 resection)	267 (92.7)	2512 (95.2)	0.087

Abbreviations: sd = standard deviation, IQR = interquartile range, BMI = Body Mass Index (kg/m2), ASA = American Society of Anesthesiologists, TaTME = Transanal Total Mesorectal Excision, TAMIS TME = TransAnal Minimal Invasive Surgery - Total Mesorectal Excision, pT = pathological tumor stage, pN = pathological nodal stage.

Table 2
Postoperative outcomes in the pre-matching cohort. Data are presented as number percentage) unless stated otherwise.

	SCRT-delay n = 288	CRT n = 2638	p-value
Any p**ostoperative complication < 30 days after surgery**	124 (43.1)	987 (37.4)	0.070
Non-surgical complications < 30 days after surgery			
Pulmonic	25 (8.7)	102 (3.9)	<0.001 *
Cardiologic	18 (6.2)	71 (2.7)	0.002 *
Infectious	32 (11.1)	136 (5.2)	<0.001 *
Thrombotic	1 (0.3)	14 (0.5)	1.000
Neurological	12 (4.2)	38 (1.4)	0.002 *
Other	48 (16.7)	360 (13.6)	0.188
Surgical complications < 30 days after surgery	66 (22.9)	653 (24.8)	0.538
Re-intervention	31 (10.8)	317 (12.0)	0.598
Type of re-intervention			0.334
Radiologic	2 (0.7)	35 (1.3)	
Surgery, laparoscopic	3 (1.0)	69 (2.6)	
Surgery, open	19 (6.6)	138 (5.2)	
Other	7 (2.4)	76 (2.9)	
Reason re-intervention			0.572
Anastomotic failure [a]	4 of 64 (6.3)	96 of 1257 (7.6)	
Abscess	9 (3.1)	74 (2.8)	
Bleeding	1 (0.3)	11 (0.4)	
Ileus	2 (0.7)	40 (1.5)	
Fascial dehiscence	2 (0.7)	17 (0.6)	
Iatrogenic bowel injury	0 (0.0)	5 (0.2)	
Ureter/urethra injury	2 (0.7)	5 (0.2)	
Other	9 (3.1)	62 (2.4)	
≥ 1 day on ICU	98 (34.0)	712 (27.0)	0.014 *
Hospital stay ≥ 7 days	145 (50.3)	1076 (40.8)	0.002 *
Readmission < 30 days after surgery	36 (12.5)	384 (14.6)	0.539
Death during or ≤ 30 days after surgery	4 (1.4)	23 (0.9)	0.268

Abbreviations: ICU = intensive care unit.
[a] Data shown for patients that received a primary anastomosis.

primary anastomoses in frail and older patients. More postoperative complications were seen in this cohort after APR in the SCRT-delay group. However, the low prevalence indicates that conclusions should be drawn cautiously. Also, the rate of pulmonic, cardiologic, infectious and neurologic complications was higher in this group. However, this was not related to surgical procedure and can therefore most likely be explained by the frailty of the SCRT-delay population. The lack of differences in surgical complications can partly be explained by improved quality of care and better selection of patients [6,31]. Moreover, frail patients that did not undergo surgical resection were not included in this study.

In the pre-matching cohort we found a significant lower pCR rate in the SCRT-delay group (8.0% vs. 16.1%) after a median interval to surgery of 11 weeks. This is comparable with pCR rates of 4.4%–25% in literature, with intervals to surgery varying from 4 to 19 weeks [9,32–40]. However, there were some differences in tumor characteristics between the groups in our dataset. Furthermore, we cannot relate these outcomes to local recurrence rates or survival. Three-year OS of 73–78% vs. 65–82.4% and DFS of 53–59% vs. 52–75.1% have been previously described for SCRT-delay and CRT, respectively [9,32]. However, these studies included younger, WHO 0–1 patients. Differences in survival are partly determined by differences in patient selection for surgical treatment and choices in management of older patients with colorectal cancer might greatly affect population-based survival [41]. Also, the majority of these patients received adjuvant chemotherapy. This is not a part of routine care in the Netherlands.

The post-matching cohort represents a comparison of SCRT-delay and CRT in two groups with equivalent age and comorbidities. Here we did not find a difference in postoperative complications nor in pathological outcomes between SCRT-delay and CRT. These results are in line with 2 randomized trials comparing SCRT-delay ± chemotherapy and CRT [9,32]. Also, in the Stockholm III trial the frequency of postoperative complications decreased by delaying surgery with 4–8 weeks after SCRT [8,12]. This indicates that, considering surgery-related complications and pathological outcomes, SCRT-delay could be a good alternative neoadjuvant treatment option for LARC patients who are unable to undergo CRT. However, information on treatment compliance is lacking from this study. In the Stockholm III trial, 7% of patients were hospitalized for radiation

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Table 3
Differences in patient, treatment and pathological characteristics between SCRT-delay and CRT in the matched cohort. Data are presented as numbers (percentage), unless stated otherwise.

	SCRT-delay	CRT	p-value
	n = 246	n = 246	
Patient characteristics			
Gender			0.078
Male	142 (57.7)	162 (65.9)	
Female	104 (42.3)	84 (34.1)	
Age (mean years (sd))	76.72 (8.86)	75.90 (8.39)	0.294
BMI (mean kg/m^2 (sd))	25.51 (3.96)	26.30 (3.91)	0.027 *
Comorbidities	208 (84.6)	223 (90.7)	0.091
ASA score			0.148
1	20 (8.1)	18 (7.3)	
2	132 (53.7)	152 (61.8)	
3	87 (35.4)	74 (30.1)	
4	7 (2.8)	2 (0.8)	
Tumor characteristics			
Distance from anus at colonoscopy (mean cm (sd))	5.91 (4.17)	6.62 (4.54)	0.071
cT			0.681
2	7 (2.8)	9 (3.7)	
3	190 (77.2)	182 (74)	
4	49 (19.9)	55 (22.4)	
Distance to MRF > 1 mm	52 (21.1)	61 (24.8)	0.123
cN			0.047 *
0	61 (24.8)	37 (15)	
1	68 (27.6)	69 (28)	
2	115 (46.7)	138 (56.1)	
x	2 (0.8)	2 (0.8)	
Treatment characteristics			
Interval between end of neoadjuvant treatment and surgery (median weeks [IQR])	11.00 [9.00, 15.00]	11.00 [10.00, 13.00]	0.361
Surgical approach			0.660
Transabdominal open	48 (19.5)	54 (22)	
Transabdominal scopic	179 (72.8)	175 (71.1)	
TaTME or TAMIS TME	17 (6.9)	13 (5.3)	
Minimally invasive	2 (0.8)	4 (1.6)	
Surgical procedure			0.849
Local excision	2 (0.8)	4 (1.6)	
(Low) Anterior Resection	133 (54.1)	128 (52)	
Abdominoperineal Resection	110 (44.7)	113 (45.9)	
Other	1 (0.4)	1 (0.4)	
Conversion	33 (13.4)	33 (13.4)	1.000
Reason conversion			0.469
Extensive tumor growth	5 (2.0)	10 (4.1)	
Accessibility	24 (9.8)	21 (8.5)	
Intraoperative complication	4 (1.6)	2 (0.8)	
Intraoperative complication			0.967
Bleeding	1 (0.4)	1 (0.4)	
Spleen injury	0	1 (0.4)	
Bowel injury	1 (0.4)	2 (0.8)	
Ureter/urethra injury	3 (1.2)	2 (0.8)	
Bladder injury	1 (0.4)	1 (0.4)	
Vagina injury	1 (0.4)	1 (0.4)	
Other	2 (0.8)	1 (0.4)	
Primary anastomosis	57 (23.2)	73 (29.7)	0.125
Ostomy			0.054
No	50 (20.3)	34 (13.8)	
Diverting ileostomy	25 (10.2)	42 (17.1)	
Permanent ileostomy	1 (0.4)	4 (1.6)	
Diverting colostomy	7 (2.8)	8 (3.3)	
Permanent colostomy	163 (66.3)	158 (64.2)	
Pathological characteristics			
pT			0.293
0	23 (9.3)	38 (15.4)	
1	12 (4.9)	14 (5.7)	
2	64 (26)	62 (25.2)	
3	131 (53.3)	115 (46.7)	
4	16 (6.5)	17 (6.9)	
pN			0.478
0	154 (62.6)	168 (68.3)	
1	59 (24)	48 (19.5)	
2	32 (13)	27 (11)	
x	0	1 (0.4)	

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Table 3 (*continued*)

	SCRT-delay	CRT	p-value
	n = 246	n = 246	
Pathological complete response, ypT0N0	19 (7.7)	31 (12.6)	0.101
Radicality (R0 resection)	226 (91.9)	219 (89)	0.357

Abbreviations: sd = standard deviation, IQR = interquartile range, BMI = Body Mass Index (kg/m2), ASA = American Society of Anesthesiologists, cT = clinical tumor stage, cN = clinical nodal stage, MRF = mesorectal fascia, TaTME = Transanal Total Mesorectal Excision, TAMIS TME = TransAnal Minimal Invasive Surgery - Total Mesorectal Excision, pT = pathological tumor stage, pN = pathological nodal stage.

Table 4
Differences in postoperative outcomes between SCRT-delay and CRT in the matched cohort. Data are presented as numbers (percentage), unless stated otherwise.

	SCRT-delay	CRT	p-value
	n = 246	n = 246	
Any p**ostoperative complication <30 days after surgery**	102 (41.5)	93 (37.8)	0.461
Non-surgical complications < 30 days after surgery			
Pulmonic	18 (7.3)	10 (4.1)	0.173
Cardiologic	14 (5.7)	11 (4.5)	0.681
Infectious	25 (10.2)	16 (6.5)	0.192
Thrombotic	0	1 (0.4)	1.000
Neurological	0	0	1.000
Other	38 (15.4)	38 (15.4)	1.000
Surgical complications < 30 days after surgery	54 (22)	46 (18.7)	0.433
Re-intervention	22 (8.9)	25 (10.2)	0.759
Type of re-intervention			0.769
Radiologic	0	1 (0.4)	
Surgery, laparoscopic	3 (1.2)	2 (0.8)	
Surgery, open	13 (5.3)	13 (5.3)	
Other	6 (2.4)	9 (3.7)	
Reason re-intervention			0.504
Anastomotic failure [a]	3 of 57 (5.3)	2 of 73 (2.7)	
Abscess	7 (2.8)	8 (3.3)	
Bleeding	0	0	
Ileus	1 (0.4)	5 (2)	
Fascial dehiscence	2 (0.8)	1 (0.4)	
Iatrogenic bowel injury	0	2 (0.8)	
Ureter/urethra injury	1 (0.4)	0	
Other	7 (2.8)	6 (2.4)	
≥ 1 day on ICU	72 (29.3)	76 (30.9)	0.768
Hospital stay > 7 days	125 (50.8)	106 (43.1)	0.104
Readmission < 30 days after surgery	28 (11.4)	31 (12.6)	0.781
Death during or ≤ 30 days after surgery	2 (0.8)	4 (1.6)	0.434

Abbreviations: ICU = intensive care unit.
[a] Data shown for patients that received a primary anastomosis.

toxicity. Previous studies suggest that compliance and immediate toxicity are in favor of SCRT (compared to CRT) [1], but more data is needed. Furthermore, long-term outcomes on local recurrence and survival is needed.

This is the first observational study that compares complications after SCRT-delay and CRT in a large population. Since observational studies cannot determine treatment effects as accurately as randomized trials [22], this propensity score matched study may provide a useful estimation of the differences between SCRT-delay and CRT. Nonetheless, the results of this study should be interpreted carefully. Confounding bias is frequently seen in observational studies [42,43]. Patient and disease characteristics may have influenced the selection of patients for neoadjuvant and surgical treatment. Most likely, only well-conditioned patients are included in this database. The biggest pitfall of this study, however, is confounding by indication, since the selection of neoadjuvant treatment is confounded by patient factors, which are also related to the outcome [44,45]. Adjusting for confounding by indication using propensity score analysis is reliable when data on all factors associated with the intervention and the outcome is precise and can be accounted for [23,44]. However, unadjusted confounding may still exist if unmeasured factors influenced treatment selection. This may lead to biased results [22,23,46].

The aging population, the rising incidence and the improved prognosis of rectal cancer will increase the need for surgery in the elderly population in the future [4,26]. Successful treatment of elderly patients depends on whether it is done safely, allowing them to preserve good quality of life, and a life-expectancy that is not reduced by the treatment [2]. Regarding surgery-related complications, SCRT-delay is a good alternative neoadjuvant treatment option for frail LARC patients. However, information on treatment compliance and quality of life is needed. Secondly, before the indication for SCRT-delay can be expanded to intermediate risk rectal cancer or high risk rectal cancer in the general population, more data on long-term outcomes, such as local recurrence and survival, is needed.

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S. Hoendervangers: Conceptualization, Methodology, Formal

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Appendix A. Supplementary data

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