Timing of surgery after short course radiotherapy for rectal cancer: real-world evidence

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LAYMEN SUMMARY (495/500 words excluding figures)

Doel onderzoek

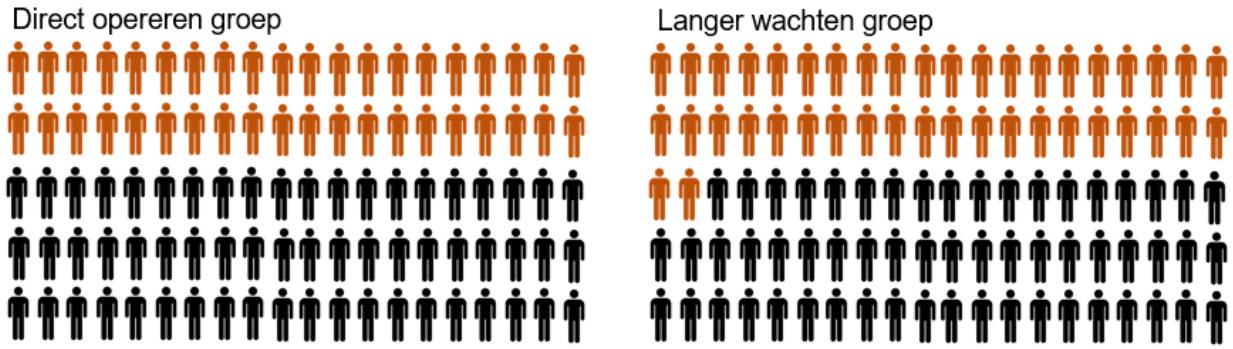
Middelhoog risico endeldarmkanker wordt behandeld met vijf bestralingen gevolgd door een operatie waarbij de endeldarm wordt verwijderd. Vroeger werd de endeldarmoperatie binnen een week gepland na de laatste bestralingsdag. Een paar jaar terug toonde een lotingsonderzoek dat vier tot acht weken wachten met opereren het risico op complicaties na de operatie kleiner maakt ten opzichte van (t.o.v.) opereren binnen een week. En dat langer wachten de kans groter maakt dat er geen levende tumorcellen meer zijn na de bestraling (een 'volledige tumorrespons'). Langer wachten ging wel gepaard met meer ernstige bijwerkingen van de bestraling. Sinds deze resultaten bekend zijn, adviseert de Nederlandse behandelrichtlijn om de voor- en nadelen van langer wachten t.o.v. direct opereren te bespreken met patiënten. Dit onderzoek had als doel om de conclusies van het lotingsonderzoek te bevestigen met gegevens uit de Nederlandse praktijk.

Methode en resultaten

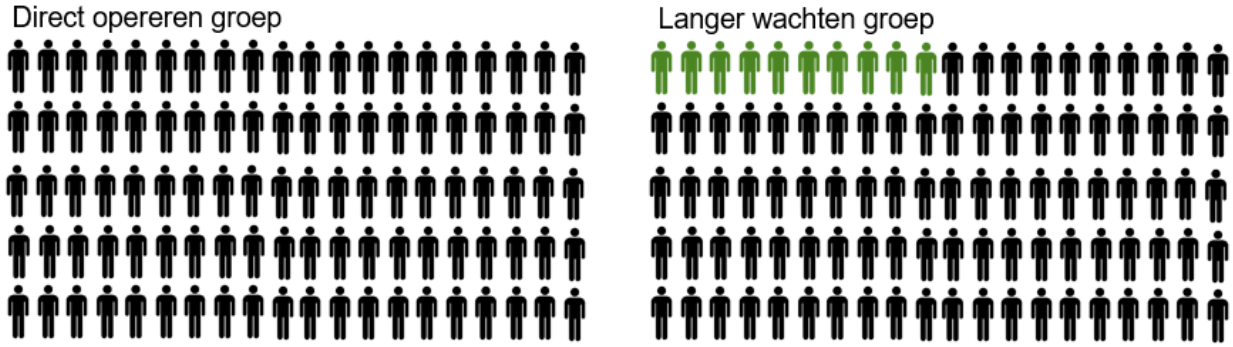
Voor dit onderzoek maakten we gebruik van de registratie die gegevens bevat over alle operaties voor darmkanker in Nederland. We selecteerden patiënten met middelhoog risico endeldarmkanker die behandeld waren met vijf bestralingen en een endeldarmoperatie binnen een week ('direct opereren' groep) of na vier tot twaalf weken ('langer wachten' groep) in 2018 tot en met 2021. Na selectie telde de direct opereren groep 664 patiënten en de langer wachten groep 238 patiënten. De patiënten in de direct opereren groep waren wat jonger, hadden een lager operatierisico en ondergingen minder vaak een operatie waarbij een stoma werd aangelegd dan patiënten in de langer wachten groep. Voor deze verschillen corrigeerden we met een statische methode. Complicaties binnen drie maanden na de operatie kwamen net zo vaak voor in de direct opereren als in de langer wachten groep (40 op de 100 t.o.v. 42 op de 100, Figuur 1).

De kans op een complete respons was hoger in de langer wachten dan in de direct opereren groep (10 op de 100 vs. 0 op de 100, Figuur 2).

Figuur 1: aantal patiënten met complicaties na de operatie (oranje) t.o.v. geen complicaties (zwart) in de direct opereren en langer wachten groep



Figuur 2: aantal patiënten met een volledige tumorrespons (groen) t.o.v. geen volledige tumorrespons (zwart) in de direct opereren en langer wachten groep



Conclusie

In dit onderzoek was het risico op complicaties na de operaties net zo groot bij direct opereren als bij langer wachten na bestraling voor endeldarmkanker. Onze resultaten zijn anders dan de resultaten van het lotingsonderzoek. Het lotingsonderzoek liep van 1998 tot en met 2013 en maakte gebruik van een ouderwetse manier van bestralen. De huidige manier van bestralen is

preciezer en geeft waarschijnlijk minder risico op complicaties na de operatie. We denken dat we om die reden geen effect konden aantonen van de wachttijd op het risico op complicaties na de operatie.

Wel konden we bevestigen dat langer wachten een grotere kans geeft op een volledige tumorrespons. Wanneer er sprake is van een volledige tumorrespons na de bestraling, is in principe geen endeldarmoperatie nodig. Wij adviseren dus om langer te wachten bij patiënten die graag zonder operatie behandeld willen worden. Om te beoordelen of er sprake is van een volledige tumorrespons, moet enkele weken na de bestraling een MRI-scan en kijkonderzoek worden verricht. Wanneer patiënten liever geopereerd worden, is direct opereren nog steeds een goede behandeling.

ABSTRACT (241/250 words)

Background: A prolonged interval between short course radiotherapy (SCRT, 25 Gy in 5 fractions) and surgery for rectal cancer (4-8 weeks, SCRT-delay) has been associated with a lower postoperative complication rate and higher pathological complete response (pCR) rate than SCRT and surgery within a week (SCRT-direct surgery). The current study sought to confirm these associations in nationwide real-world data of Dutch rectal cancer patients.

Method: Patients with intermediate risk rectal cancer (T3(MRF-)N0M0 and T1-3(MRF-)N1M0) treated with either SCRT-delay (4-12 weeks) or SCRT-direct surgery in 2018-2021 were selected from a nationwide Dutch cohort. Confounders were eliminated using inverse probability of treatment weighting (IPTW). The 90-day postoperative complication rate and pathological complete response (pCR) rate were compared using log-binomial and Poisson regression.

Results: 664 patients were included in the SCRT-direct surgery and 238 in the SCRT-delay group. After IPTW, the 90-day postoperative complication rate was comparable between SCRT-direct surgery and SCRT-delay (40% vs. 42%, RR = 1.1 [95%confidence interval (CI): 0.9; 1.3], p=0.6). pCR occurred more often following SCRT-delay than following SCRT-direct surgery (10% vs. 0.3%, RR = 39 [95%CI: 11, 139], p < 0.001).

Conclusion: Real-world evidence could not confirm an advantage in postoperative complications following SCRT-delay compared to SCRT-direct surgery, but did confirm the increased pCR rate following SCRT-delay. SCRT-delay followed by a response assessment should be offered to patients who are interested in watch & wait strategy. SCRT-direct surgery still is a valid option for patients who prefer surgical management.

BACKGROUND

Total mesorectal excision (TME) preceded by short course radiotherapy (SCRT, 25 Gy in 5 fractions) has been the recommended treatment strategy for intermediate risk rectal cancer (T1-3(MRF-)N1M0 and T3cd(MRF-)N0-1M0) in the Netherlands for over twenty years [1]. Addition of neoadjuvant SCRT to surgery was proven to reduce local recurrence rates in the randomized Swedish rectal cancer and Dutch TME trials [2,3]. Rather arbitrarily, these trials used an interval of maximum one week between completion of SCRT and surgery (SCRT-direct surgery). This short interval remained the standard, backed up by negative results of a slightly longer interval: a retrospective study demonstrated an increased risk of postoperative complications when the time between *start* of SCRT and TME exceeded 13 days [4]. Also, a subgroup analysis of the Dutch TME trial showed an increased risk of 1-year overall mortality in older patients operated upon within 4-7 days of completion of SCRT compared to 1-3 days [5].

Later, short course radiotherapy with a prolonged interval to surgery (4-8 weeks, SCRT-delay) came into picture as a better tolerable neoadjuvant strategy than chemoradiation (50 Gy in 25 fractions combined with a chemosensitizer) for frail locally advanced rectal cancer patients [6,7]. The optimal timing of surgery after SCRT was again up for debate. Prospective studies followed, showing acceptable toxicity and improved tumour downstaging after SCRT-delay [8–10]. Randomized evidence in favour of SCRT-delay came from the Stockholm III trial, which showed a lower postoperative complication rate (41% vs. 53%, p=0.001) and a higher pathological complete response rate (pCR, 10% vs. 0.3%, p<0.001) than after SCRT-direct surgery, at the expense of more acute radiation-induced toxicity grade 3-4 (7% vs. 0.3%, p<0.001) [11,12].

Since publication of the Stockholm III trial, the Dutch treatment guideline advises to discuss both SCRT-direct surgery and SCRT-delay with intermediate risk rectal cancer patients (shared decision making) [1]. In our experience, there is practice variation regarding this advice. The current study therefore sought to confirm the results of the Stockholm III trial using Dutch nationwide real-

world data of intermediate risk rectal cancer patients. The postoperative complication rate and the pCR rate are compared between SCRT-direct surgery and SCRT-delay in an inverse probability of treatment weighted (IPTW) analysis.

MATERIALS & METHODS

Patients

Patients who were treated for intermediate risk rectal cancer (lower border of the tumour below the sigmoid take-off and cT3(MRF-)N0M0 or cT1-3(MRF-)N1M0 staging) with SCRT and surgery during 2018-2021 in the Netherlands were eligible [1,13]. Exclusion criteria were recurrent rectal cancer, neoadjuvant chemotherapy, other type of resection than partial mesorectal excision (PME) or TME (e.g. local excision, sigmoid resection, coloproctectomy) or TME preceded by local excision. Patients were selected for the SCRT-direct surgery and the SCRT-delay group if the interval between completion of radiotherapy and surgery was maximum one week (0-7 days) or 4-12 weeks (28-84 days), respectively. This study used a broader interval for SCRT-delay than the Stockholm III trial because some centres in the Netherlands perform response evaluation and surgery at 10-12 weeks after completion of SCRT, in line with the STAR-TREC study [14].

Data were extracted from the Dutch Colorectal Audit (DCRA). The DCRA is a mandatory registration that collects patient-, tumour-, treatment- and surgical and pathological outcome data of all patients who are surgically treated for colorectal cancer in the Netherlands [15]. The clinical audit board of the DCRA approved the research proposal of the current study. No further ethical review was required under Dutch law.

Outcomes

The primary outcome was the 90-day postoperative complication rate, defined as the occurrence of any complication within 90 days postoperatively or during the primary hospitalization. Secondary outcomes were 90-day complications requiring reintervention (Clavien-Dindo III), organ failure requiring admittance to the intensive care unit (ICU, Clavien-Dindo IV), death of a patient (Clavien-Dindo V), anastomotic leakage, surgical site infection, abscess not at the anastomosis, length of hospital stay (number of days between surgery and hospital discharge), unplanned hospital readmittance within 90 days of initial hospital discharge and pCR. Anastomotic leakage was defined as intra-abdominal fluid or abscess at the anastomosis requiring treatment. This outcome was only evaluated in patients in whom an anastomosis was created.

Statistical analysis

Missing values in the variables clinical nodal stage (n=3, 0.3%), clinical metastatic stage (n=32, 3.5%), involvement of the mesorectal fascia (n=67, 7.4%), and neoadjuvant chemotherapy (n=5, 0.6%) were assumed to be zero and patients were included accordingly (Supplementary File B). Missing values in other baseline patient-, tumour- and treatment characteristics were assumed to be missing at random and were imputed using single imputation [16]. Both baseline and outcome variables were used as input for the imputation model (Supplementary File C) [17]. Predictive mean matching was used for imputation of numeric variables, logistic regression for dichotomous, polytomous regression for categorical and a proportional odds model for ordered variables [18]. Missing values in extramural invasion and extralevator vs. conventional APR could not be imputed due to multicollinearity with clinical tumour stage and type of resection, respectively. Instead, missing values in extramural invasion were handled by the missing indicator method and missing values in type of APR (n=4) were assumed to be conventional APRs. The imputation model ran 10 iterations. Convergence was checked by plotting the mean and standard deviation of the

imputed values. Validity of the imputed values was checked by comparison to the observed values (Supplementary File C).

IPTW was applied to eliminate confounding [19]. First, the propensity score (PS) was calculated using a binomial logistic regression with SCRT-direct surgery vs. SCRT-delay as the outcome and the potential confounders as predictors (Supplementary File C) [20]. Then, each case was assigned a weight, which was calculated as the inverse of the probability to receive the treatment that was actually received (using the PS model). For stabilization, the weights were multiplied by the prevalence of the treatment that was actually received [20]. The mean of the weights was 0.999 and their range was 0.37 to 3.6, giving no indication of misspecification of the PS model. Balance was checked by inspecting the baseline characteristics after IPTW. Differences between groups were expressed as the standardized mean difference (SMD), calculated as the mean difference between groups divided by the pooled standard deviation [21]. An SMD of ≤ 0.10 was considered well balanced [21].

Outcomes were described before and after IPTW and were compared between groups using binomial regression for dichotomous outcomes and Poisson regression for count outcomes, both with log link and a robust standard error [20,22]. A p-value < 0.05 was considered significant. Analyses were repeated with the SCRT-delay group restricted to an interval of 4-8 weeks (28-56 days), in order to make our results directly comparable with those of the Stockholm III trial. Furthermore, analysis were repeated in the complete case population to explore the impact of missing data.

The minimal detectable difference was calculated to see if our sample size was sufficient to confirm the difference in postoperative complication rate (12% absolute difference) that was demonstrated by the Stockholm III trial. Given our sample size, a postoperative complication rate of 41%, an alpha of 5%, a power of 80% and a two-sided alternative hypothesis, this study could detect a difference of 11% or more.

Analyses were done using R-language version 4.2.0 and packages mice, ipw, survey, sandwich and EnvStats [23–25].

RESULTS

Of 7391 patients in the Netherlands who had surgery for cT1-3 primary rectal cancer during the study period, 664 were included in the SCRT-direct surgery group and 238 in the SCRT-delay group (Supplementary File A).

Before imputation and IPTW, patients in the SCRT-direct surgery group were slightly younger (67 (median, interquartile range (IQR): 58-74) versus (vs.) 68 (median, IQR: 60-77), SMD = 0.18), had a lower ASA classification (ASA 1-2: 81% vs. 72%, SMD = 0.26) and were more often treated with a (L)AR without ostomy (41% vs. 28, SMD = 0.29) and less often with an APR (17% vs. 21%), (L)AR with permanent ostomy (16% vs. 22%) or (L)AR with deviating ostomy (26%, vs 29%, SMD = 0.29) than patients in the SCRT-delay group (Table 1). After imputation and IPTW, baseline characteristics were well balanced.

Before IPTW, 90-day postoperative complications occurred in 265 patients (40%) of the SCRT-direct surgery group and 101 (42%) in the SCRT-delay group (risk ratio (RR) = 1.1 [95% confidence interval (CI): 0.9; 1.3], p = 0.5, Table 2). Anastomotic leakage occurred in 71 patients (16%) and 24 patients (18%), respectively (RR = 1.1 [95%CI: 0.7; 1.7], p = 0.6). Similarly, other postoperative complications and length of hospital stay were comparable between groups. pCR occurred in 2 patients (0.3%) in the SCRT-direct surgery group and in 26 (11%) in the SCRT-delay group (RR = 36 [95%CI: 8.7; 152], p < 0.001).

After IPTW, 90-day postoperative complications occurred in 266 patients (40%) of the SCRT-direct surgery group and 101 (42%) in the SCRT-delay group (RR = 1.1 [95%CI: 0.9; 1.3], p = 0.6). Anastomotic leakage occurred in 69 patients (16%) and 28 patients (18%), respectively (RR = 1.1 [95%CI: 0.7; 1.9], p = 0.7). Again, the other postoperative outcomes were similar between groups. pCR occurred in 1.7 patients (0.3%) in the SCRT-direct surgery group and in 24 (10%) in the SCRT-delay group (RR = 39 [95%CI: 11; 139], p < 0.001).

Sensitivity analyses with SCRT-delay restricted to an interval of 4-8 weeks and complete case analysis gave similar results (Supplementary File E-I).

DISCUSSION

This study using Dutch nationwide real-world data found a similar 90-day postoperative complication rate after SCRT-direct surgery as after SCRT-delay (40% vs. 42%, p=0.6). The pCR rate was significantly higher in the SCRT-delay than in the SCRT-direct surgery group (10% vs 0.3%, p<0.001).

This study could not confirm the 12% decrease in the postoperative complication rate following SCRT-delay compared to SCRT-direct surgery that was demonstrated by the Stockholm III trial, despite a sufficient sample size. This conclusion was consistent in sensitivity analysis, where SCRT-delay was restricted to a 4-8 weeks interval. The difference between our results and those of the Stockholm III trial might be explained by the improvements in radiotherapy technique since the start of the Stockholm III trial. The Stockholm III trial recruited patients between 1998 and 2013 [11]. During the largest part of the study, radiotherapy was administered with a three-beam or four-beam box technique [26]. Nowadays, intensity modulated radiotherapy (IMRT) is the standard, which has better precision and results in less dose to the healthy tissues than the three- or four-

beam box technique [27–29]. We believe that contemporary radiotherapy technique increases the risk of postoperative complications to a lesser extent than the technique used in the Stockholm III trial, diminishing the effect of the interval between SCRT and TME on the postoperative complication rate.

The increased probability of pCR following a prolonged interval between SCRT and TME has consistently been reported in literature [30,31]. Similarly, a prolonged interval between chemoradiation (50 Gy in 25 fractions combined with a chemosensitizer) and TME for rectal cancer is associated with an improved pCR rate [32]. Patients who showed a pCR could in theory have been management by watch & wait strategy instead of TME [33]. This strategy averts the morbidity of surgery and has been associated with improved quality of life and less bowel, urinary and sexual dysfunction [34–36]. In order to evaluate eligibility for watch & wait, we recommend to perform a response evaluation in patients treated with SCRT-delay. The appropriate timing, sensitivity/specificity of the response evaluation and the oncological safety of the watch & wait strategy after SCRT are a focus of future research. SCRT-delay and a response evaluation should be offered to patients who are interested in watch & wait.

A substantial proportion of rectal cancer patients is not interested in watch & wait strategy [37,38]. Based on our data, prolonging the interval to surgery does not confer any advantages in terms of postoperative complications on this group. In the Stockholm III trial, 7% of patients in the SCRT-delay group were admitted to the hospital due to acute radiation-induced toxicity [11]. Again, we believe this number overestimates the toxicity rate of current clinical practice due to the older radiotherapy techniques used in the Stockholm III trial. A recent prospective cohort study on SCRT-delay showed no unplanned hospital admissions, but one in three patients suffered from temporary Grade III (i.e. severe and disabling but not life-threatening) acute radiation-induced toxicity during the interval [39]. SCRT-direct surgery still seems a good option for patients who prefer surgical management.

There are several explanations for the relation between timing of surgery and the risk of postoperative complications. First, inflammation of the irradiated tissues might impair surgery. Radiation-induced toxicity peaks at week 1 and 2 after completion of SCRT and gradually recovers thereafter [39]. This peak may reflect the least favourable timeframe to perform surgery, which is in line with the older studies that showed increased morbidity when SCRT-direct surgery was slightly delayed [4,5]. Also, radiotherapy is known to trigger the immune system on a systemic level [40]. Some studies have suggested that preoperative radiotherapy impairs the immune response to surgery, which would be measurable by a decreased postoperative leukocyte count or a decreased pre-to-postoperative leukocyte ratio [41–43]. The SCRT-delay group of the Stockholm III trial had a significantly higher pre-to-postoperative leukocyte ratio than the SCRT-direct surgery group, implying that the immune response had recovered at 4-8 weeks after SCRT [43]. Another theory is that a prolonged interval increases the risk of pelvic fibrosis. In a non-randomized non-blinded trial, surgeons scored a higher level of fibrosis in the group that had an eleven week compared to a six week interval between CRT and TME. However, this difference did not translate into an increased postoperative complication rate [44]. Lastly, a prolonged interval offers the opportunity to improve patient fitness and nutritional status before surgery. Such prehabilitation programs have been proven to shorten the hospital length of stay and might improve the postoperative complication rate [45]. SCRT-delay combined with a prehabilitation program seems a good strategy for frail patients.

This study comes with limitations. In some centres in the Netherlands, it already is standard of care to schedule a response evaluation after SCRT-delay and offer watch & wait strategy in case of a clinical complete response. Patients on watch & wait strategy were not yet registered in the DCRA during the study period. The pCR rate in this study will therefore be an underestimation of the real organ preserving potential of SCRT-delay.

There always is the risk of residual confounding in non-randomized studies. Since traditionally SCRT-delay was offered to frail patients, residual confounding in our study will probably disfavour the postoperative complication rate in the SCRT-delay group.

This study had sufficient sample size to detect a difference of 11% in the 90-day postoperative complication rate between groups. We found no indication of a difference (RR = 1.1 [95%CI: 0.9; 1.3], p=0.6). Nonetheless, it still is possible that the interval between SCRT and TME has a modest effect on the postoperative complication rate that we did not detect.

This study used single imputation for handling missing data, where multiple imputation is the preferred method [16]. Single imputation does not account for the uncertainty of missing values and may provide too narrow confidence intervals. The only variable with a high proportion of missing values (24%) was the Charlson comorbidity index. Valid imputation of missing values in this variable seemed plausible using predictors such as age, ASA classification, BMI, type of resection and postoperative complications. Otherwise, the proportion of missing data was low. We believe that the use of single instead of multiple imputation will not have a clinically relevant impact on our results.

In conclusion, the postoperative complication rate following SCRT-direct surgery and SCRT-delay was similar in contemporary real-world data. SCRT-delay was associated with a significantly higher probability of a complete response. We recommend SCRT-delay with scheduling of a response evaluation for patients who are interested in watch & wait strategy. SCRT-direct surgery still seems a good option for patients who prefer surgical management.

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TABLES AND FIGURES

Table 1. Patient-, tumour- and treatment characteristics of intermediate risk rectal cancer patients treated with short course radiotherapy (SCRT)-direct surgery and SCRT-delay, before and after single imputation (SI) and inverse probability of treatment weighting (IPTW).

	Before SI and IPTW				After SI and IPTW		
	SCRT-direct surgery (n=664)	**SCRT-delay (n=238)**	**SMD**	**Missing**	**SCRT-direct surgery (n=664)**	**SCRT-delay (n=238)**	**SMD**
Gender = female	234 (35)	85 (36)	0.01	0	234 (35)	84 (35)	0.02
Age in years (median [IQR])	67 [58, 74]	68 [60, 77]	**0.18**	3 (0.3)	68 [59, 75]	66 [59, 75]	<0.01
BMI class			**0.13**	18 (2.0)			0.03
Underweight (< 18.5)	10 (1.5)	4 (1.7)			11 (1.6)	3.9 (1.6)	
Normal weight (18.5-24.9)	237 (37)	100 (43)			255 (38)	91 (38)	
Overweight (25.0-29.9)	279 (43)	92 (39)			278 (42)	97 (41)	
Obese (≥ 30.0)	123 (19)	39 (17)			121 (18)	46 (19)	
History of bowel resection	11 (1.7)	1 (0.4)	**0.12**	0	8.9 (1.3)	3.4 (1.4)	0.01
Ostomy before start of treatment	11 (1.7)	6 (2.5)	0.06	5 (0.6)	12 (1.8)	3.4 (1.5)	0.03
Preoperative anaemia	41 (6.2)	16 (6.7)	0.02	0	43 (6.5)	16 (6.8)	0.01
Preoperative bowel obstruction	9 (1.4)	3 (1.3)	0.01	11 (1.2)	11 (1.7)	3.6 (1.5)	0.01
ASA classification			**0.26**	0			0.04
1	120 (18)	27 (11)			108 (16)	36 (15)	
2	417 (63)	146 (61)			416 (63)	153 (64)	
3	123 (19)	61 (26)			135 (20)	47 (20)	
4	4 (0.6)	4 (1.7)			5.7 (0.9)	2.1 (0.9)	
CCI			**0.13**	219 (24)			0.02
0	277 (59)	124 (59)			391 (59)	141 (59)	
1	107 (23)	40 (19)			136 (21)	49 (21)	
2	55 (12)	32 (15)			84 (13)	30 (13)	
3	24 (5.1)	10 (4.7)			38 (5.7)	13 (5.4)	
4-7	9 (1.9)	5 (2.4)			15 (2.3)	4.8 (2.0)	
Clinical tumour stage			**0.22**	0			0.02
cT1	14 (2.1)	1 (0.4)			11 (1.7)	3.6 (1.5)	
cT2	135 (20)	40 (17)			129 (20)	47 (20)	
cT3ab	209 (31)	94 (40)			223 (34)	78 (33)	
cT3x	148 (22)	48 (20)			144 (22)	53 (22)	
cT3cd	158 (24)	55 (23)			156 (24)	56 (24)	
Clinical nodal stage = cN1	538 (81)	195 (82)	0.03	3 (0.3)	543 (82)	195 (82)	0.01
Tumour location[+]			0.07	69 (7.6)			0.07

Distal (0-3cm)	155 (25)	62 (28)		167 (25)	59 (25)	
Midrectal (3-6cm)	208 (34)	69 (31)		234 (35)	76 (32)	
Proximal (≥ 6cm)	247 (41)	92 (41)		264 (40)	102 (43)	
Surgical approach			**0.12**	26 (2.9)		0.04
Laparotomy	15 (2.3)	2 (0.9)		13 (1.9)	4.1 (1.7)	
Laparoscopy	390 (60)	137 (61)		401 (60)	147 (62)	
TaTME	73 (11)	25 (11)		72 (11)	23 (9.6)	
Robot-assisted laparoscopy	172 (27)	62 (27)		179 (27)	64 (27)	
Type of resection			**0.29**	4 (0.4)		0.03
Extralevator APR	32 (4.8)	12 (5.0)		32 (4.8)	11 (4.8)	
Conventional APR	80 (12)	39 (16)		91 (14)	32 (13)	
(L)AR with permanent ostomy	108 (16)	53 (22)		118 (18)	42 (18)	
(L)AR with deviating ostomy	172 (26)	68 (29)		178 (27)	67 (28)	
(L)AR without ostomy	268 (41)	66 (28)		245 (37)	86 (36)	

Variables are displayed as number (proportion) unless indicated otherwise. Differences between groups are expressed as the standardized mean difference (SMD), calculated as the difference of the group means divided by the pooled standard deviation. IQR: interquartile range. BMI = body mass index. Anaemia: Haemoglobin of < 7 mmol/l in males or < 6,5mmol/l in females. Bowel obstruction: hospital admission or endoscopic intervention for obstructive symptoms. ASA = American Society of Anaesthesiologists. CCI = Charlson comorbidity index. [+]Measured as the distance between the lower border of the tumour and the anorectal junction on sagittal MRI. TaTME = transanal total mesorectal excision. APR = abdominoperineal resection. (L)AR = (low) anterior resection.

Table 2. 90-day postoperative complications and pathological complete response rate after short course radiotherapy and surgery within a week (SCRT-direct surgery) versus a prolonged interval (4-12 weeks) to surgery (SCRT-delay) before and after inverse probability of treatment weighting (IPTW)

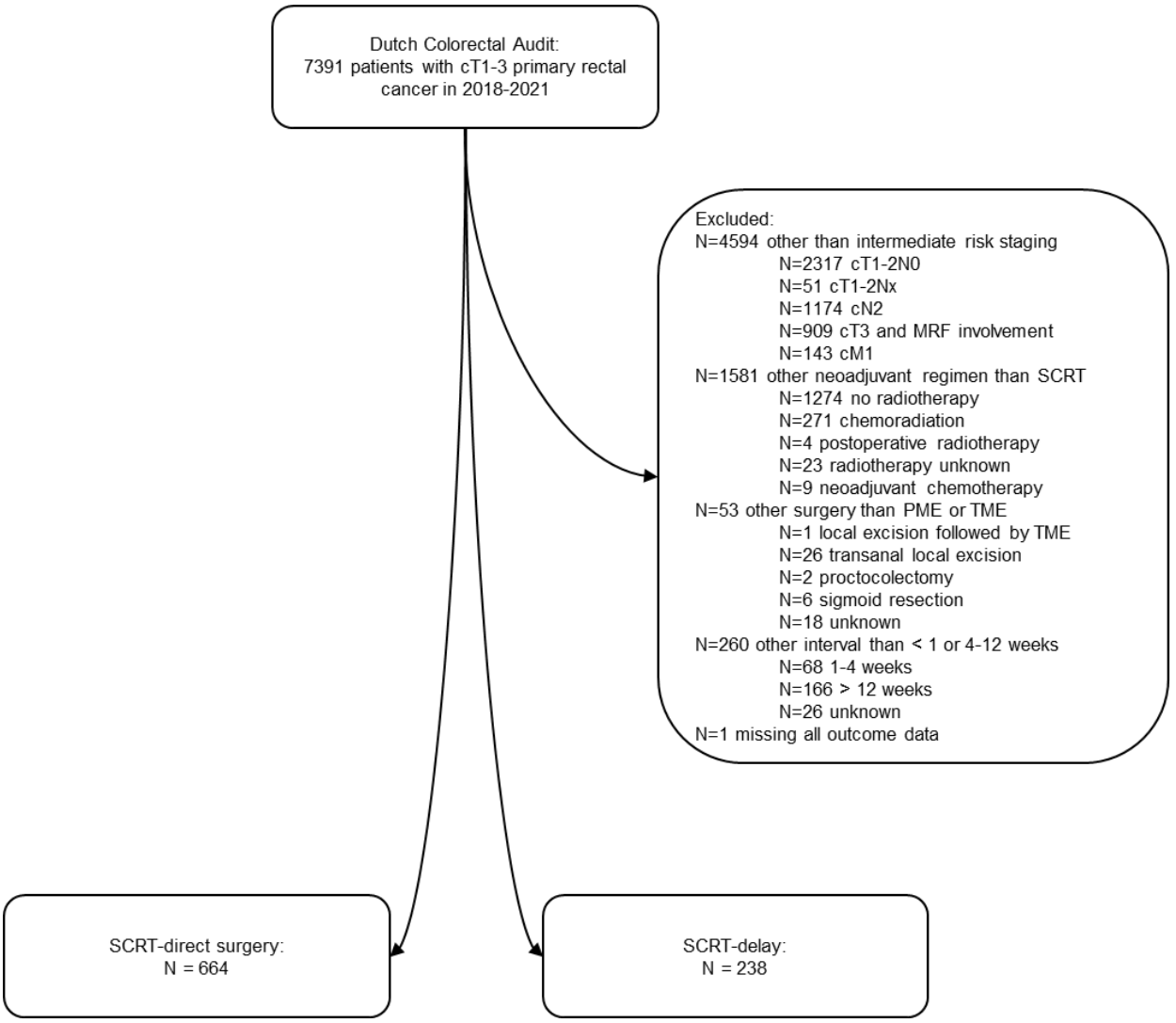
	Before IPTW					After IPTW					
	SCRT-direct surgery (n=664)	SCRT-delay (n=238)	RR	95%CI	p-value	SCRT-direct surgery (n=664)	SCRT-delay (n=237)	RR	95%CI	p-value	Missing
Complication (any)	265 (40)	101 (42)	1.1	[0.9; 1.3]	0.5	266 (40)	101 (42)	1.1	[0.9; 1.3]	0.6	0
Anastomotic leakage*	71 (16)	24 (18)	1.1	[0.7; 1.7]	0.6	69 (16)	28 (18)	1.1	[0.7; 1.9]	0.7	0
Abscess	46 (6.9)	21 (8.8)	1.3	[0.8; 2.1]	0.3	46 (7.0)	21 (9.0)	1.3	[0.7; 2.4]	0.4	0
Surgical site infection	23 (3.5)	11 (4.6)	1.3	[0.7; 2.7]	0.4	23 (3.5)	11 (4.5)	1.3	[0.6; 2.7]	0.5	0
Reintervention	119 (18)	47 (20)	1.1	[0.8; 1.5]	0.5	119 (18)	51 (21)	1.2	[0.8; 1.7]	0.3	0
ICU admittance	54 (8.5)	14 (6.2)	0.7	[0.4; 1.3]	0.3	56 (8.8)	12 (5.4)	0.6	[0.4; 1.1]	0.1	44 (4.9)
Mortality	4 (0.6)	4 (1.7)	2.8	[0.7; 11]	0.1	4.0 (0.6)	3.1 (1.3)	2.2	[0.6; 7.9]	0.2	12 (1.3)
Length of hospital stay (median [IQR])	5 [4, 9]	5 [4, 8]	1.0	[0.8; 1.1]	0.6	5 [4, 9]	5 [4, 8]	1.0	[0.1, 7.1]	<1.0	4 (0.4)
Hospital readmittance	137 (21)	41 (18)	0.8	[0.6, 1.2]	0.3	138 (21)	42 (18)	0.9	[0.6; 1.2]	0.4	16 (1.8)
pCR	2 (0.3)	26 (11)	36	[8.7; 152]	**<0.001**	1.7 (0.3)	24 (10)	39	[11, 139]	**<0.001**	5 (0.6)

Variables are displayed as number (proportion) unless indicated otherwise. RR = risk ratio. 95%CI = 95% confidence interval. Length of hospital stay was calculated as the number of days between surgery and the day of discharge. *Anastomotic leakage was only evaluated among 440 patients in the SCRT-direct surgery and n=134 in the SCRT-delay group in the unweighted population (corresponding to 423 and 153 patients in the weighted population, respectively) in whom an anastomosis was created

SUPPLEMENTARY FILES

A. **Flowchart of patient inclusion**
B. **Distribution of missing values assumed to be zero between treatment groups**
C. **List of variables used in imputation and IPTW**
D. **Observed vs. imputed baseline characteristics**
E. **Baseline characteristics before and after IPTW with SCRT-delay restricted to a 4-8 weeks interval**
F. **Outcome analyses with SCRT-delay restricted to a 4-8 weeks interval**
G. **Baseline characteristics before and after IPTW in complete cases**
H. **Outcome analyses restricted to complete cases**
I. **Treatment group, ICU admittance and number of complete cases per year of treatment**

Supplementary File A. Flowchart of patient inclusion



cT = clinical tumour stage. cN = clinical nodal stage. MRF = mesorectal fascia. cM = clinical metastatic stage. SCRT = short course radiotherapy. PME = partial mesorectal excision. TME = total mesorectal excision.

Supplementary File B. Distribution of missing values between treatment groups that were assumed to be zero during patient selection

	SCRT-direct surgery (n=664)	SCRT-delay (n=238)
MRF involvement	52 (7.8)	15 (6.3)
cN stage	2 (0.3)	1 (0.3)
cM stage	22 (3.3)	10 (4.2)
Neoadjuvant chemotherapy	3 (0.5)	2 (0.8)

SCRT: short course radiotherapy. MRF: mesorectal fascia. cN stage: clinical nodal stage. cM stage: clinical metastatic stage.

Supplementary File C. Specification of variables used in single imputation (SI) and inverse probability of treatment weighting (IPTW). For SI, both baseline and outcome data were used as input for the imputation model but only imputed baseline values were used during analysis. For IPTW, baseline variables were regressed on treatment group.

Variable	Type of variable	Imputation method
Baseline variables		
Treatment group	Dichotomous	-
Gender	Dichotomous	-
Age	Continuous	Predictive mean matching
BMI class	Factor	Polytomous regression
History of bowel resection	Dichotomous	-
Ostomy before start of treatment	Dichotomous	Logistic regression
Preoperative anaemia	Dichotomous	-
Preoperative bowel obstruction	Dichotomous	Logistic regression
ASA classification	Ordered factor	-
CCI	Ordered factor	Polytomous regression
Clinical tumour stage*	Ordered factor	-
Clinical nodal stage	Dichotomous	Logistic regression
Tumour location^{+}	Continuous	Predictive mean matching
Surgical approach	Factor	Polytomous regression
Type of resection	Factor	-
Outcome variables		
Complication (any)	Dichotomous	-
Reintervention	Dichotomous	-
ICU admittance	Dichotomous	Logistic regression
Mortality	Dichotomous	Logistic regression
Length of hospital stay	Continuous	Predictive mean matching
Hospital readmittance	Dichotomous	Logistic regression
Anastomotic leakage	Dichotomous	-
Abscess	Dichotomous	-
Surgical site infection	Dichotomous	-
Pathological tumour stage	Ordered factor	Polytomous regression
Pathological nodal stage	Ordered factor	Polytomous regression

BMI: body mass index. ASA: American Society of Anaesthesiologists. CCI: Carlson's Comorbidity Index. *A clinical tumour stage of cT3x was placed in order between cT3ab and cT3cd. $^{+}$ Distance of the lower border of the tumour to the anorectal junction on sagittal MRI in mm.

Supplementary File D. Observed versus imputed values for variables with more than 5% missing

	Observed	Imputed
CCI		
0	401 (59)	129 (59)
1	147 (22)	39 (18)
2	87 (13)	27 (12)
3	34 (5.0)	17 (7.8)
4-7	14 (2.0)	7 (3.2)
Tumour location[+]		
Distal (0-3cm)	217 (26)	12 (17)
Midrectal (3-6cm)	277 (33)	31 (45)
Proximal (≥ 6cm)	339 (41)	26 (38)

CCI: Charlson comorbidity index. [+]Measured as the distance between the lower border of the tumour and the anorectal junction on sagittal MRI

Supplementary File E. Patient-, tumour- and treatment characteristics of intermediate risk (rectal cancer patients treated with short course radiotherapy (SCRT)-direct surgery and SCRT-delay, before and after inverse probability of treatment weighting (IPTW) with SCRT-delay restricted to a 4-8 weeks interval

	Before SI and IPTW				After SI and IPTW		
	SCRT-direct surgery (n=664)	SCRT-delay (n=123)	SMD	Missing	SCRT-direct surgery (n=664)	SCRT-delay (n=122)	SMD
Gender = female	234 (35)	45 (37)	0.03	0	235 (35)	43 (35)	<0.01
Age in years (median [IQR])	67 [58, 74]	67 [59, 74]	0.01	3 (0.4)	67 [58, 74]	67 [59, 75]	0.01
BMI class			0.09	15 (1.9)			0.10
Underweight (< 18.5)	10 (1.5)	2 (1.6)			10 (1.5)	1.6 (1.3)	
Normal weight (18.5-24.9)	237 (37)	50 (41)			251 (38)	48 (39)	
Overweight (25.0-29.9)	279 (43)	48 (39)			278 (42)	46 (38)	
Obese (≥ 30.0)	123 (19)	23 (19)			125 (19)	26 (22)	
History of bowel resection	11 (1.7)	1 (0.8)	0.08	0	10 (1.5)	1.2 (1.0)	0.05
Ostomy before start of treatment	11 (1.7)	1 (0.8)	0.08	3 (0.4)	10 (1.5)	0.8 (0.7)	0.08
Preoperative anaemia	41 (6.2)	5 (4.1)	0.10	0	39 (5.9)	7.8 (6.4)	0.02
Preoperative bowel obstruction	9 (1.4)	1 (0.8)	0.05	8 (1.0)	10 (1.5)	1.3 (1.1)	0.04
ASA classification			0.27	0			0.08
1	120 (18)	16 (13)			115 (17)	25 (20)	
2	417 (63)	70 (57)			410 (62)	72 (59)	
3	123 (19)	36 (29)			135 (20)	25 (20)	
4	4 (0.6)	1 (0.8)			4.2 (0.6)	0.6 (0.5)	
CCI			0.18	205 (26)			0.10
0	277 (59)	66 (60)			394 (59)	78 (64)	
1	107 (23)	19 (17)			136 (20)	22 (18)	
2	55 (12)	18 (16)			83 (13)	15 (12)	
3	24 (5.1)	5 (4.5)			38 (5.7)	5.8 (4.8)	
4-7	9 (1.9)	2 (1.8)			14 (2.0)	2.0 (1.6)	
Clinical tumour stage			0.24	0			**0.15**
cT1	14 (2.1)	1 (0.8)			13 (1.9)	3.0 (2.4)	
cT2	135 (20)	24 (20)			133 (20)	20 (17)	
cT3ab	209 (32)	50 (41)			219 (33)	42 (34)	
cT3x	148 (22)	20 (16)			143 (21)	32 (26)	
cT3cd	158 (24)	28 (23)			157 (24)	25 (21)	
Clinical nodal stage = cN1	538 (81)	108 (89)	0.20	3 (0.4)	548 (82)	99 (81)	0.03
Tumour location[+]			0.05	57 (7.2)			**0.12**
Distal (0-3cm)	155 (25)	33 (28)			168 (25)	30 (25)	
Midrectal (3-6cm)	208 (34)	39 (33)			234 (35)	37 (31)	

Proximal (≥ 6cm)	247 (41)	48 (40)			263 (40)	55 (45)	
Surgical approach			0.20	19 (2.4)			0.02
Laparotomy	15 (2.3)	2 (1.7)			14 (2.2)	2.6 (2.1)	
Laparoscopy	390 (60)	61 (52)			391 (59)	73 (60)	
TaTME	73 (11)	13 (11)			73 (11)	13 (11)	
Robot-assisted laparoscopy	172 (27)	42 (36)			186 (28)	33 (27)	
Type of resection			0.35	4 (0.5)			0.03
Extralevator APR	32 (4.8)	8 (6.5)			34 (5.1)	5.8 (4.7)	
Conventional APR	80 (12)	18 (15)			85 (13)	15 (12)	
(L)AR with permanent ostomy	108 (16)	25 (20)			113 (17)	22 (18)	
(L)AR with deviating ostomy	172 (26)	42 (34)			181 (27)	34 (28)	
(L)AR without ostomy	268 (41)	30 (24)			251 (38)	46 (38)	

Variables are displayed as number (proportion) unless indicated otherwise. Differences between groups are expressed as the standardized mean difference (SMD), calculated as the difference of the group means divided by the pooled standard deviation. As a rule of thumb, an SMD ≤ 0.10 is considered well balanced. IQR: interquartile range. BMI = body mass index. Anaemia: Haemoglobin of < 7 mmol/l in males or < 6,5mmol/l in females. Bowel obstruction: hospital admission or endoscopic intervention for obstructive symptoms. ASA = American Society of Anaesthesiologists. CCI = Charlson comorbidity index. [+]Measured as the distance between the lower border of the tumour and the anorectal junction on sagittal MRI. TaTME = transanal total mesorectal excision. APR = abdominoperineal resection. (L)AR = (low) anterior resection.

Supplementary File F. 90-day postoperative complications and pathological complete response rate after short course radiotherapy and surgery within a week (SCRT-direct surgery) versus prolonged interval (4-8 weeks) to surgery (SCRT-delay) before and after inverse probability of treatment weighting (IPTW)

	Before IPTW					After IPTW					
	SCRT-direct surgery (n=664)	SCRT-delay (n=123)	RR	95%CI	p-value	SCRT-direct surgery (n=664)	SCRT-delay (n=122)	RR	95%CI	p-value	Missing
Complication (any)	265 (40)	50 (41)	1.0	[0.8; 1.3]	0.9	267 (40)	47 (39)	1.0	[0.7; 1.4]	0.8	0
Anastomotic leakage*	71 (16)	11 (15)	0.9	[0.5; 1.7]	0.9	71 (16)	14 (17)	1.1	[0.4; 2.8]	0.9	0
Abscess	46 (6.9)	11 (8.9)	1.3	[0.7; 2.4]	0.4	46 (6.9)	8.3 (6.8)	1.0	[0.5; 1.8]	<1.0	0
Surgical site infection	23 (3.5)	6 (4.9)	1.4	[0.6; 3.4]	0.4	23 (3.5)	5.1 (4.2)	1.2	[0.5; 3.0]	0.7	0
Reintervention	119 (18)	27 (22)	1.2	[0.8; 1.8]	0.3	119 (18)	27 (22)	1.2	[0.7; 2.1]	0.4	0
ICU admittance	54 (8.5)	4 (3.3)	0.4	[0.1; 1.1]	0.07	55 (8.6)	3.3 (2.8)	0.3	[0.1; 1.0]	0.05	33 (4.2)
Mortality	4 (0.6)	3 (2.5)	4.1	[0.9; 18]	0.06	4.0 (0.6)	2.2 (1.9)	3.1	[0.8; 12]	0.1	9 (1.1)
Length of hospital stay (median [IQR])	5 [4, 9]	5 [4, 8]	1.0	[0.8; 1.2]	0.8	5 [4, 9]	5 [4, 8]	0.9	[0.1; 15]	<1.0	3 (0.4)
Hospital readmittance	137 (21)	20 (17)	0.8	[0.5; 1.2]	0.3	138 (21)	21 (17)	0.8	[0.4; 1.6]	0.5	12 (1.5)
pCR	2 (0.3)	14 (12)	38	[8.8; 166]	**<0.001**	1.9 (0.3)	14 (12)	39	[8.5; 182]	**<0.001**	5 (0.6)

Variables are displayed as number (proportion) unless indicated otherwise. RR = risk ratio. 95%CI = 95% confidence interval. Length of hospital stay was calculated as the number of days between surgery and the day of discharge. *Anastomotic leakage was only evaluated among 440 patients in the SCRT-direct surgery and 72 in the SCRT-delay group in the unweighted population (corresponding to 432 and 80 patients in the weighted population, respectively) in whom an anastomosis was created. pCR = pathological complete response.

Supplementary File G. Patient-, tumour- and treatment characteristics of intermediate risk rectal cancer patients treated with short course radiotherapy (SCRT)-direct surgery and SCRT-delay, before and after inverse probability of treatment weighting (IPTW) in the complete case population

	Before IPTW			After IPTW		
	SCRT-direct surgery (n=405)	SCRT-delay (n=176)	SMD	SCRT-direct surgery (n=405)	SCRT-delay (n=176)	SMD
Gender = female	147 (36)	59 (34)	0.06	144 (36)	63 (36)	<0.01
Age in years (median [IQR])	68 [59, 74]	67 [60, 75]	0.03	68 [59, 75]	67 [60, 75]	0.01
BMI class			**0.14**			0.05
Underweight (< 18.5)	7 (1.7)	1 (0.6)		5.6 (1.4)	2.0 (1.1)	
Normal weight (18.5-24.9)	138 (34)	68 (39)		145 (36)	65 (37)	
Overweight (25.0-29.9)	182 (45)	75 (43)		178 (44)	74 (42)	
Obese (≥ 30.0)	78 (19)	32 (18)		78 (19)	36 (20)	
History of bowel resection	9 (2.2)	1 (0.6)	**0.14**	7.0 (1.7)	2.3 (1.3)	0.03
Ostomy before start of treatment	7 (1.7)	3 (1.7)	<0.01	6.6 (1.6)	2.1 (1.2)	0.04
Preoperative anaemia	25 (6.2)	7 (4.0)	0.10	23 (5.7)	9.5 (5.4)	0.01
Preoperative bowel obstruction	6 (1.5)	2 (1.1)	0.03	5.4 (1.3)	1.5 (0.9)	0.04
ASA classification			0.20			0.01
1	56 (14)	21 (12)		53 (13)	24 (14)	
2	270 (67)	105 (60)		261 (65)	113 (64)	
3	76 (19)	47 (27)		86 (21)	37 (21)	
4	3 (0.7)	3 (1.7)		4.4 (1.1)	1.9 (1.1)	
CCI			**0.13**			0.03
0	238 (59)	101 (57)		237 (58)	105 (60)	
1	94 (23)	36 (21)		90 (22)	39 (22)	
2	47 (12)	27 (15)		52 (13)	22 (13)	
3	18 (4.4)	7 (4.0)		17 (4.3)	6.9 (3.9)	
4-7	8 (2.0)	5 (2.8)		9.1 (2.2)	3.5 (2.0)	
Clinical tumour stage			**0.23**			0.05
cT1	9 (2.2)	1 (0.6)		7.0 (1.7)	4.2 (2.4)	
cT2	86 (21)	35 (20)		85 (21)	36 (20)	
cT3ab	138 (34)	75 (43)		150 (37)	65 (37)	
cT3x	71 (18)	23 (13)		66 (16)	28 (16)	
cT3cd	101 (25)	42 (24)		99 (24)	43 (24)	
Clinical nodal stage = cN1	330 (82)	153 (87)	**0.15**	338 (83)	147 (84)	0.01
Tumour location[+]			0.08			0.10
Distal (0-3cm)	103 (25)	48 (27)		105 (26)	48 (27)	

Midrectal (3-6cm)	141 (35)	55 (31)		141 (35)	53 (30)	
Proximal (≥ 6cm)	161 (40)	73 (42)		160 (39)	75 (43)	
Surgical approach			**0.12**			0.05
Laparotomy	6 (1.5)	1 (0.6)		5.0 (1.2)	2.6 (1.5)	
Laparoscopy	238 (59)	100 (57)		235 (58)	105 (60)	
TaTME	45 (11)	18 (10)		43 (11)	17 (9.6)	
Robot-assisted laparoscopy	116 (29)	57 (32)		122 (30)	51 (29)	
Type of resection			**0.30**			0.04
Extralevator APR	23 (5.7)	9 (5.1)		21 (5.3)	8.0 (4.6)	
Conventional APR	54 (13)	31 (18)		59 (15)	25 (14)	
(L)AR with permanent ostomy	66 (16)	36 (21)		73 (18)	31 (18)	
(L)AR with deviating ostomy	105 (26)	55 (31)		113 (28)	51 (29)	
(L)AR without ostomy	157 (39)	45 (26)		140 (35)	61 (35)	

Variables are displayed as number (proportion) unless indicated otherwise. Differences between groups are expressed as the standardized mean difference (SMD), calculated as the difference of the group means divided by the pooled standard deviation. As a rule of thumb, an SMD ≤ 0.10 is considered well balanced. IQR: interquartile range. BMI = body mass index. Anaemia: Haemoglobin of < 7 mmol/l in males or < 6,5mmol/l in females. Bowel obstruction: hospital admission or endoscopic intervention for obstructive symptoms. ASA = American Society of Anaesthesiologists. CCI = Charlson comorbidity index. [+]Measured as the distance between the lower border of the tumour and the anorectal junction on sagittal MRI. TaTME = transanal total mesorectal excision. APR = abdominoperineal resection. (L)AR = (low) anterior resection.

Supplementary File H. 90-day postoperative complications and pathological complete response rate after short course radiotherapy and surgery within a week (SCRT-direct surgery) versus prolonged interval (4-12 weeks) to surgery (SCRT-delay before and after inverse probability of treatment weighting (IPTW) in the complete case population

	Before IPTW					After IPTW				
	SCRT-direct surgery (n=405)	**SCRT-delay (n=176)**	**RR**	**95%CI**	**p-value**	**SCRT-direct surgery (n=405)**	**SCRT-delay (n=176)**	**RR**	**95%CI**	**p-value**
Complication (any)	174 (43)	76 (43)	1.0	[0.8; 1.2]	<1.0	174 (43)	74 (42)	1.0	[0.8; 1.3]	0.9
Anastomotic leakage*	47 (18)	16 (16)	0.9	[0.5; 1.5]	0.7	46 (18)	18 (16)	0.9	[0.4; 1.7]	0.7
Abscess	31 (7.7)	17 (9.7)	1.3	[0.7; 2.2]	0.4	31 (7.7)	17 (9.5)	1.2	[0.6; 2.5]	0.6
Surgical site infection	15 (3.7)	10 (5.7)	1.5	[0.7; 3.3]	0.3	15 (3.6)	12 (6.5)	1.8	[0.7; 4.5]	0.2
Reintervention	81 (20)	36 (21)	1.0	[0.7; 1.5]	0.9	80 (20)	38 (21)	1.1	[0.7; 1.7]	0.7
ICU admittance	37 (9.1)	7 (4.0)	0.4	[0.2; 1.0]	**0.04**	38 (9.5)	5.7 (3.3)	0.3	[0.2; 0.7]	**0.006**
Mortality	2 (0.5)	2 (1.1)	2.3	[0.3; 16]	0.4	2.1 (0.5)	1.8 (1.0)	2.0	[0.2; 17]	0.5
Length of hospital stay (median [IQR])	5 [4, 9]	5 [4, 8]	0.9	[0.8; 1.1]	0.5	5 [4, 9]	5 [4, 8]	1.0	[0.1; 15]	<1.0
Hospital readmittance	90 (22)	31 (18)	0.8	[0.5; 1.1]	0.2	90 (22)	32 (18)	0.8	[0.5; 1.3]	0.4
pCR	2 (0.5)	20 (11)	23	[5.4; 97]	**<0.001**	1.8 (0.4)	19 (11)	25	[6.8; 95]	**<0.001**

Variables are displayed as number (proportion) unless indicated otherwise. RR = risk ratio. 95%CI = 95% confidence interval. Length of hospital stay was calculated as the number of days between surgery and the day of discharge. *Anastomotic leakage was only evaluated among 262 patients in the SCRT-direct surgery and 100 in the SCRT-delay group in the unweighted population (corresponding to 253 and 112 patients in the weighted population, respectively) in whom an anastomosis was created.

Supplementary File I. Treatment group, risk of admittance to the intensive care unit (ICU) and number of complete cases per year of treatment

	2018 (n=301)	2019 (n=217)	2020 (n=187)	2021 (n=197)
SCRT-delay	48 (16)	46 (21)	61 (33)	83 (42)
ICU admittance	23 (8.2)	25 (12)	6 (3.3)	14 (7.4)
Complete case	79 (26)	182 (84)	159 (85)	161 (82)

SCRT: short course radiotherapy.

Complete case analysis induced an inverse association between SCRT-delay and ICU admittance. On further exploration, this association seemed confounded by year of treatment. The majority of incomplete cases originated from 2018, while the probability of receiving SCRT-delay increased throughout the years and the risk of ICU admittance was notably low in 2020, presumably due to the covid pandemic. In complete case analysis, patients treated in 2020 gained a strong influence on the risk estimate of ICU admittance following SCRT-delay.