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ARTICLE

Clinical Studies

Treatment interval in curative treatment of colon cancer, does it impact (cancer free) survival? A non-inferiority analysis

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BACKGROUND: In treatment of colon cancer, strict waiting-time targets are enforced, leaving professionals no room to lengthen treatment intervals when advisable, for instance to optimise a patient's health status by means of prehabilitation. Good quality studies supporting these targets are lacking. With this study we aim to establish whether a prolonged treatment interval is associated with a clinically relevant deterioration in overall and cancer free survival.
METHODS: This retrospective multicenter non-inferiority study includes all consecutive patients who underwent elective oncological resection of a biopsy-proven primary non-metastatic colon carcinoma between 2010 and 2016 in six hospitals in the Southern Netherlands. Treatment interval was defined as time between diagnosis and surgical treatment. Cut-off points for treatment interval were ≤35 days and ≤49 days.
FINDINGS: 3376 patients were included. Cancer recurred in 505 patients (15.0%) For cancer free survival, a treatment interval >35 days and >49 days was non-inferior to a treatment interval ≤35 days. Results for overall survival were inconclusive, but no association was found.
CONCLUSION: For cancer free survival, a prolonged treatment interval, even over 49 days, is non-inferior to the currently set waiting-time target of ≤35 days. Therefore, the waiting-time targets set as fundamental objective in current treatment guidelines should become directional instead of strict targets

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INTRODUCTION

In treatment of colon cancer with curative intent, surgical resection of the tumour remains the mainstay treatment. Treatment guidelines set waiting-time targets in order to encourage timely treatment, as it is widely believed that longer treatment intervals not only aggravate patient's distress, but also negatively affect oncological outcome. However, these recommendations are mainly based on expert opinions, while unambiguous evidence supporting these waiting-time targets is lacking [1, 2]. Recommendations on timing of definite treatment vary widely in current national and international guidelines [1]. Many studies and recently published reviews conclude that time to treatment initiation is not associated with (oncological) outcome [1–7]. The few studies in which an association was found often did not adjust for confounding variables as comorbidities or post-operative complications, or wielded lengthy treatment intervals [5, 8–12].

Besides the variation in length of advised treatment intervals, the national and international guidelines lack uniformity in definition of the treatment interval [1]. The start of the treatment interval is often defined as date of diagnosis, but the definition of this date is not unequivocal. Studies define date of diagnosis as date of biopsy, date of pathological diagnosis, or date of multidisciplinary team meeting. These events are several days apart in the diagnostic work-up, resulting in significant variance in the length of the interval depending on the applied starting point. Considering the finding that endoscopists can recognise a cancerous lesion with approximately 90% accuracy, the date of endoscopy could be a good definition of the start of the treatment interval, as this can also be used as the starting point of a full diagnostic work-up and a prehabilitation programme [13].

Strict waiting-time targets can be a challenge for overloading health systems and may hinder professionals to prolong treatment intervals when this could in fact benefit the patient. Instead of

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passively waiting, this time interval could for instance be used to optimise a patient's health status by means of prehabilitation.

Major surgery is known to reduce physiological and functional capacity up to 40%, even without the occurrence of postoperative complications [14]. Multimodal prehabilitation programmes limit the reduction in physiological and functional capacity and lower the risk of treatment-related complications [15, 16]. These programmes are already implemented in several countries, but for an optimal result, a sufficiently long treatment interval is key [16]. More flexible waiting-time targets in national and international guidelines would enable such programmes. Therefore, it is important to investigate whether treatment intervals can be prolonged safely without reducing survival probabilities.

With this study we aim to determine whether a treatment interval exceeding the waiting time targets of 35 and 49 days, recommended by the Dutch national guideline, is associated with a clinically relevant deterioration in overall and cancer free survival. As general survival analyses can only show us there are no significant differences in survival between patients treated within set waiting time targets compared to those with longer waiting times, we conducted a non-inferiority analysis as this may help us confirm our hypothesis that longer treatment intervals do not lead to poorer survival compared to standard treatment intervals.

METHODS

Patients and data collection

This retrospective study was conducted using prospectively collected data of six hospitals in the Southern region on the Netherlands (VieCuri Medical Centre, Zuyderland Hospital, Catharina Hospital, Maxima Medical Centre, Maastricht University Medical Centre and Laurentius Hospital), covering circa 10% of all resections for CC in the Netherlands. The study population consisted of all consecutive patients who underwent elective oncological resection of a biopsy proven primary, non-metastatic, colon carcinoma between January 2010 up to and including December 2016. None of the hospitals had implemented any form of prehabilitation in this study period. Patients who had received a temporary stoma in an emergency setting prior to elective surgical resection were included. Patients receiving surgical resection in an emergency setting were excluded, as well as non-adenocarcinomas or patients with metastasis preoperatively or within three months after surgery.

Data were subtracted from the Netherlands Cancer Registry (NCR), a national database collecting data on all newly diagnosed cancer patients [17]. This data includes patient and tumour characteristics, and information on diagnosis and treatment. Anatomical site of the tumour was registered according to the International Classification of Disease-Oncology. The pathological tumour-node-metastasis (pTNM) classification was used for stage notification of the primary tumour. Missing data and additional data were retrospectively collected from patients' medical records. This encompassed additional information on comorbidities (classified using the modified Charlson Comorbidity Index (CCI)), diagnosis (reason for colonoscopy, date of multidisciplinary meeting, date of last diagnostics), information on occurrence and severity of postoperative complications within 90 days of surgery (classified according to the Clavien-Dindo classification (CD; minor I-II, major III-V), date of last follow-up and date of cancer recurrence (local recurrence or metastasis). In order to access these medical records, the encrypted NCR-data was decrypted using a key provided by the NCR. After decryption, several medical-ID numbers did not match existing medical-ID numbers. This precluded us from accessing medical records of these patients. As this resulted in complete missing data on follow-up, these patients had to be excluded. Follow-up data were last completed in between October 2020 and July 2021, based on last contact or date of death as registered in patients' medical records.

Endpoints and definitions

Endpoints of this study were overall survival (OS) and cancer free survival (CFS) five years after treatment. OS was defined as time in months from date of diagnosis (defined as date of first diagnostic setting cancer diagnosis, e.g. date of endoscopy or date of CT when prior to endoscopy) until date of death or last follow-up consult. CFS was defined as time in months from date of surgery until date of cancer recurrence (defined as the first date of either radiologic or pathologic diagnosis of metastasis or tumour recurrence) or last follow-up consult. Follow-up was censored at five years. Groups were created based on treatment interval (≤35 days versus >35 days, and versus >49 days), being defined as the time between date of diagnosis until date of elective surgical resection of the tumour. These targets were established in accordance with the maximum waiting-time targets outlined in our national colorectal cancer guideline, which are drafted by the ministry of health based on expert opinion [18].

Statistical analysis

Data was analysed using IBM SPSS Statistics, version 25.0 (IBM Corp, NY, Armonk, USA). Descriptive statistics were used to provide an overview of the study population by groups based on treatment interval. Continuous variables were expressed as means +/− standard deviation or median with interquartile range (IQR) according to distribution of data; categorical variables were shown as counts and percentages. Continuous variables were compared using unpaired t-tests, non-parametric Mann–Whitney's U tests; categorical variables were compared using Chi-square statistics or Fisher's exact test, as appropriate. Multivariable Cox regression analyses were conducted to calculate the prognostic association between treatment interval and survival (CFS and OS), while adjusting for other prognostic variables. A potential confounding relationship between these variables, treatment interval and the analysed endpoint was tested for each variable separately. Variables included in multivariate analysis were chosen based on statistically significant confounding ($p < 0.005$), differences at baseline and clinical judgement. Those included patient demographics (age, sex, BMI, comorbidities identified at admission), tumour characteristics (localisation, stage, differentiation), reason for diagnostics, treatment characteristics (timing of surgery, surgical approach, adjuvant chemotherapy) and postoperative complications.

Non-inferiority margin

The non-inferiority margin (delta, Δ) was chosen based on existing literature using the point-estimate method. A pooled HR of 1.038 (95%CI 0.985–1.091) [5, 10, 11, 19, 20] suggests an increase in risk of death within 5-years after treatment of 3.8% with a longer treatment interval, ranging from -1.5% up to 9%. Taking the difference between the positive and negative effect of a longer treatment interval, a negative effect of 8% remains. The estimated risk of occurrence of a postoperative complication of any severity was estimated at 40% [16, 19, 21–24]. This risk might be reduced by prehabilitation. Incorporating studies reporting on the odds ratio for a postoperative complication after prehabilitation, a pooled OR of 0.65 (95%CI 0.51–0.80) [15, 16, 21, 23, 25] suggests an overall positive effect, with a risk reduction ranging from 20% to 49%. Few studies report on the difference in risk of long-term mortality (ranging from 1 to 5 years) between patients with and without postoperative complications. This risk differs widely between studies, at lowest 1.4 (specifically for colectomy) and 1.6 (for minor complications in general) [26–28]. Taking the risk of occurrence of a postoperative complication, together with the risk of long-term mortality in case of a postoperative complication and the average effect of prehabilitation, the positive effect can be estimated at 10%. Taking the difference between the negative effect of a longer treatment interval and the positive effect expected from prehabilitation as the acceptable risk, the non-inferiority margin could be set at 2%. For CFS a pooled HR of 0.952 (95%CI 0.644–1.261) [19, 20] suggests a decrease in risk of cancer recurrence within 5-years after treatment of 4.8% with a longer treatment interval, ranging from a decrease of 36% to an increase of 26%. Taking the difference between the positive and negative effect of a longer treatment interval, a positive effect of 10% remains. As this effect is positive and 5x higher than the non-inferiority margin, this margin of 2% could also be accepted in the analysis of CFS. A power calculation was conducted to assure sufficient power to perform non-inferiority testing. In order to achieve 90% power to prove a longer treatment interval to be non-inferior at a significance level of 5%, a population of 3552 patients was needed.

RESULTS

A total of 3376 patients were included in this study (Fig. 1). Median age was 72 years (IQR 64–78), and 1782 patients (52.8%) were male. Tumours were located in the right-sided colon in 1716 patients (50.8%; 662 ileocecal, 546 ascending colon, 266 hepatic flexure, 242 transverse colon) and in the left- sided colon in 1660

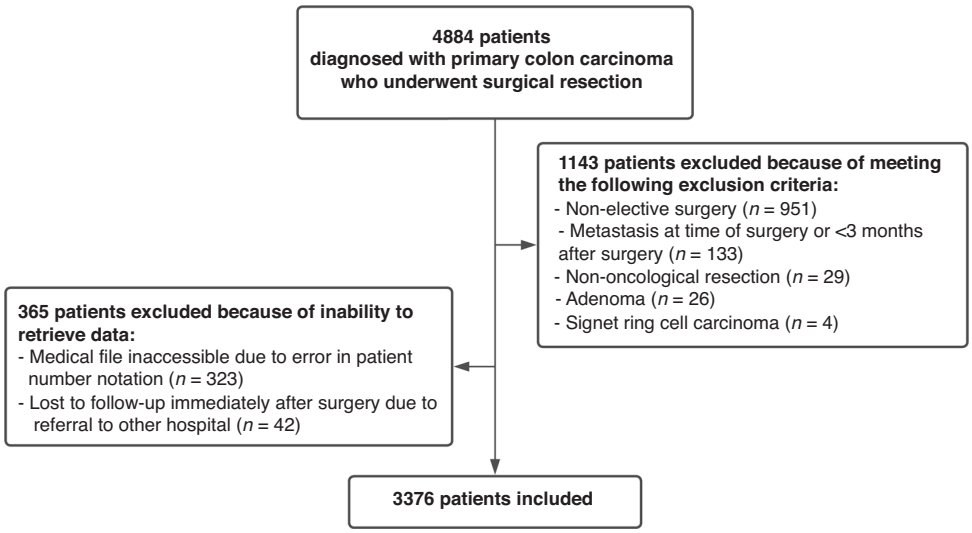

Fig. 1 Flowchart of the study.

patients (49.2%; 124 splenic flexure, 187 descending colon, 1349 sigmoid). Median treatment interval was 31 days (IQR 24–42). Patients with a treatment interval <35 days were treated after a median of 26 days (IQR 21–30), and patients with a treatment interval >35 days after a median of 47 days (IQR 40–57). All-cause mortality occurred in 736 patients (21.8%) during a median follow-up of 60 months (IQR 47–60). Cancer recurred in 505 patients (15.0%) during a median follow-up of 60 months (IQR 37–60). Table 1 displays descriptive data of the included patients. Patients receiving a stoma in an acute setting preceding elective curative surgical treatment were ~1.8x more likely to experience a treatment interval >35 days (64% versus 36%, $p = 0.005$). The group of patients with a treatment interval >35 days contained more patients with comorbidities compared to the reference group (CCI ≥ 3; 16.9% versus 11.0%, $p < 0.001$). As a consequence, more patients with a treatment interval >35 days had an ASA-score of III or IV (17.1% versus 13.5% respectively, $p = 0.005$). Patients with right-sided tumours and tumours with a TNM-stage >I were more often treated within 35 days (Right-sided; 53.2% versus 46.8% ($p < 0.001$), TNM-stage II-III; 77.8% versus 68.8% ($p < 0.001$)). There were more patients with a pT-stage I-II and pN-stage 0 in the groups with a longer treatment interval. Surgical approach did not differ between groups. The group of patients with a treatment interval >35 days contained more patients who developed postoperative complications (36.9% versus 32.0% ($p = 0.004$)). The percentage of patients with major complications was almost equal in both groups (13–14%). Less patients in the groups with longer treatment intervals received adjuvant chemotherapy ($p < 0.001$).

Survival

In total, 342 out of 2128 patients (10.9%) with a treatment interval ≤35 days experienced cancer recurrence, compared to 91 out of 1248 patients (7.3%) with a treatment interval >35 days ($p = 0.001$). All-cause mortality occurred in 427 out of 2128 patients (20.1%) with a treatment interval ≤35 days, versus 309 out of 1248 patients (24.8%) with a treatment delay >35 days ($p = 0.001$). A treatment interval >35 days was not associated with CFS and OS in multivariable cox-proportional-hazards regression analysis (Tables 2 and 3). These results were similar in case of a treatment interval >49 days (Tables 2 and 3).

Applying the predetermined non-inferiority margins on the observed event rates in the group of patients with a normal treatment interval led to a HR of 1.124 for CFS, and 1.100 for OS (Table 4).

For CFS, a treatment interval >35 days (HR = 0.857 (95%CI; 0.691–1.063)) was found to be non-inferior to treatment within 35 days, independent of multiple major confounders (Table 2). Even a treatment interval >49 days (HR = 0.716 (95%CI; 0.507–1.011)) was non-inferior to treatment within 35 days, independent of multiple major confounders (Table 2). Figure 2 shows forest plots of the HRs of these groups compared to the HR of 1 (standard treatment) and the HR corresponding with the non-inferiority margin.

For OS, no association between a treatment interval >35 days and >49 days, and OS was found. However, non-inferiority analysis was inconclusive. The 95%CI (0.872–1.219) accompanying the HR of 1.031, found for a treatment interval >35 days, exceeded the non-inferiority margin of 1.100. This margin was also exceeded by the 95%CI (0.834–1.326) accompanying the HR of 1.051 for a treatment interval >49 days (Table 3). Figure 2 shows forest plots of the HRs of these groups compared to the HR of 1 (standard treatment) and the HR corresponding with the non-inferiority margin.

DISCUSSION

The aim of this study was to determine whether a treatment interval >35 days and >49 days is associated with a clinically relevant deterioration in OS and CFS. For CFS a treatment interval of >35 days between diagnosis of colon cancer and elective oncological resection proved to be non-inferior to treatment within 35 days after diagnosis, independent of multiple major confounders. According to the results in this current study, definite surgical treatment may even be postponed beyond 49 days, as a treatment interval >49 days proved to be non-inferior to treatment within 49 days after diagnosis with regard to CFS. There was no association between a longer treatment interval (>35 days and >49 days) and OS, but non-inferiority could not be concluded.

Only three previous studies assessed the prognostic impact of a longer treatment interval on oncological outcome in colon cancer instead of only OS. Wanis et al. [20], Justesen et al. [29] and Strous et al. [19] (the latter based on a portion of the data used in this study) did not show any association between a longer treatment interval and oncological outcome. These results are in line with the results found in this study. For OS, previous studies showed less clear-cut results. Several studies showed that a longer treatment interval was not associated with poorer OS [3–7]. However, in some, an association between a longer treatment interval and poorer OS was found [5, 8, 10, 12, 30]. Several of these studies were large database studies which did not correct for

Table 1. Baseline characteristics of the study population according to treatment interval.

	Treatment interval ≤ 35 days $n = 2128$	Treatment interval > 35 days $n = 1248$	*p*-value	Treatment interval > 49 days $n = 501$	*p*-value
Age[a]	71 [63–78]	73 [65–79]	<0.001	73 [65–79]	0.006
Sex, *n* (%)			0.734		0.964
Male	1128 (53.0)	654 (52.4)		265 (52.9)	
Female	1000 (47.0)	594 (47.6)		236 (47.1)	
CCI, *n* (%)			<0.001		<0.001
0	1010 (47.5)	516 (41.3)		187 (37.3)	
1	562 (26.4)	328 (26.3)		130 (25.9)	
2	322 (15.1)	194 (15.5)		78 (15.6)	
≥3	234 (11.0)	210 (16.9)		106 (21.2)	
ASA, *n* (%)			0.005		<0.001
I-II	1840 (86.5)	1035 (82.9)		397 (79.2)	
III-IV	288 (13.5)	213 (17.1)		104 (20.8)	
BMI, *n* (%)			0.442		0.472
Healthy (20–30 kg/m^2)	1448 (68.0)	851 (68.2)		346 (69.1)	
Unhealthy (<20 kg/m^2 or >30 kg/m^2)	478 (22.5)	292 (23.4)		121 (24.2)	
Missing	202 (9.5)	105 (8.4)		34 (6.8)	
Reason for diagnosis, *n* (%)			0.722		0.929
National bowel screening programme	311 (14.6)	188 (15.1)		74 (14.8)	
Other	1817 (85.4)	1060 (84.9)		427 (85.2)	
Timing of surgery, *n* (%)			0.005		0.003
Elective	2119 (99.6)	1232 (98.7)		492 (98.2)	
Elective after acute creation of a stoma	9 (0.4)	16 (1.3)		9 (1.8)	
Surgical approach, *n* (%)			0.229		0.180
Laparoscopic	1268 (59.6)	722 (57.8)		278 (55.5)	
Laparoscopic with conversion	194 (9.1)	102 (8.2)		45 (9.0)	
Open	666 (31.3)	424 (34.0)		178 (35.5)	
Subside, *n* (%)			<0.001		0.018
Right-sided colon	1132 (53.2)	584 (46.8)		237 (47.3)	
Left-sided colon	996 (46.8)	664 (53.2)		264 (52.7)	
pT stage, *n* (%)			<0.001		<0.001
I	141 (6.6)	212 (17.0)		116 (23.2)	
II	449 (21.1)	261 (20.9)		112 (22.4)	
III	1301 (61.1)	640 (51.3)		226 (45.1)	
IV	237 (11.1)	135 (10.8)		47 (9.4)	
pN stage, *n* (%)			0.022		0.006
0	1361 (64.0)	855 (68.5)		356 (71.1)	
I	526 (24.7)	277 (22.2)		107 (21.4)	
II	241 (11.3)	116 (9.3)		38 (7.6)	
pTNM stage, *n* (%)			<0.001		<0.001
I	472 (22.2)	390 (31.3)		184 (36.7)	
II	889 (41.8)	465 (37.3)		172 (34.3)	
III	767 (36.0)	393 (31.5)		145 (29.0)	
Differentiation grade, *n* (%)			0.523		0.231
Well/Moderate	1734 (81.5)	1007 (80.6)		406 (81.0)	
Poor/Undifferentiated	293 (13.8)	159 (12.8)		57 (11.4)	
Missing	101 (4.7)	82 (6.6)		38 (7.6)	
Postoperative complication, *n* (%)			0.004		0.004
No	1447 (68.0)	788 (63.1)		307 (61.3)	
Yes	681 (32.0)	460 (36.9)		194 (38.7)	
Postoperative complication grade (CD), *n* (%)			0.008		0.011
None	1447 (68.0)	788 (63.2)		307 (61.3)	
Minor (CD I-II)	401 (18.8)	287 (23.0)		121 (24.2)	
Major (CD III-V)	280 (13.2)	173 (13.8)		73 (14.6)	
Adjuvant chemotherapy, *n* (%)			<0.001		<0.001
No	1484 (69.8)	963 (77.2)		402 (80.2)	
Yes	641 (30.2)	284 (22.8)		99 (19.8)	

ASA American Association of Anesthesiologists, *BMI* body mass index, *CCI* Charlson Comorbidity Index, *CD* Clavien-Dindo classification, *pT-stage* pathological tumour stage, *pN-stage* pathological (lymph) node stage, *pTNM* pathological tumour-node-metastasis stage.
[a]Baseline characteristics are presented as median with interquartile range or counts with percentages.

Table 2. Associations of treatment interval and other covariates with cancer free survival.

	Cancer free survival					
	Univariate		Multivariate[a]		Multivariate[a]	
	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Treatment interval						
≤35 days	*Reference*		*Reference*			
>35 days	0.821 (0.681–0.989)	0.038	0.857 (0.691–1.063)	0.160		
Treatment interval						
≤35 days	*Reference*				*Reference*	
>49 days	0.698 (0.525–0.927)	0.013			0.716 (0.507–1.011)	0.057
Age	1.003 (0.994- 1.012)	0.501	1.004 (0.994–1.015)	0.415	1.006 (0.994–1.018)	0.352
Sex						
Male	*Reference*		*Reference*		*Reference*	
Female	0.903 (0.758 – 1.077)	0.256	0.883 (0.722–1.081)	0.228	0.836 (0.664–1.053)	0.129
CCI						
0	*Reference*		*Reference*		*Reference*	
1	1.072 (0.867–1.326)	0.520	1.136 (0.894–1.443)	0.297	1.176 (0.896–1.544)	0.244
2	1.126 (0.874–1.451)	0.358	1.217 (0.902–1.644)	0.199	1.164 (0.821–1.650)	0.393
≥3	1.060 (0.797–1.408)	0.689	1.149 (0.819–1.611)	0.422	1.352 (0.925–1.976)	0.119
ASA						
I-II	*Reference*	0.761	*NI*		*NI*	
III-IV	1.040 (0.808 – 1.339)					
BMI						
Healthy (20–30 kg/m^2)	*Reference*	0.976	*NI*		*NI*	
Unhealthy (<20 kg/m^2 or >30 kg/m^2)	0.997 (0.811–1.225)					
Reason for diagnostics						
National bowel screening programme	*Reference*		*Reference*		*Reference*	
Other	1.412 (1.074–1.856)	0.014	0.895 (0.614–1.303)	0.562	0.789 (0.519–1.199)	0.268
Timing of surgery						
Elective	*Reference*		*Reference*		*Reference*	
Elective after initial stoma creation	1.477 (0.612–3.565)	0.385	1.232 (0.503–3.020)	0.648	1.497 (0.544–4.120)	0.435
Surgical approach						
Laparoscopic	*Reference*		*Reference*		*Reference*	
Laparoscopic with conversion	1.409 (1.052–1.887)	0.021	1.153 (0.822–1.617)	0.409	1.217 (0.836–1.771)	0.305
Open	1.277 (1.057–1.543)	0.011	1.267 (1.011–1.587)	0.040	1.221 (0.940–1.585)	0.135
Tumour location						
Right-sided colon	*Reference*		*Reference*		*Reference*	
Left-sided colon	1.001 (0.841–1.192)	0.989	1.047 (0.854–1.284)	0.660	0.995 (0.788–1.256)	0.967
pT stage						
I	*Reference*		*Reference*		*Reference*	
II	2.672 (1.476–4.836)	0.001	2.892 (1.421–5.887)	0.003	2.696 (1.207–6.022)	0.016
III	4.548 (2.610–7.923)	<0.001	3.598 (1.816–7.130)	<0.001	3.071 (1.410 – 6.690)	0.005
IV	11.828 (6.673–20.965)	<0.001	8.270 (4.057–16.855)	<0.001	7.516 (3.342–16.902)	<0.001
pN stage						
0	*Reference*		*Reference*		*Reference*	
I	2.164 (1.760–2.661)	<0.001	2.058 (1.558–2.718)	<0.001	1.872 (1.357–2.584)	<0.001
II	5.155 (4.155–6.395)	<0.001	5.369 (3.942–7.311)	<0.001	5.283 (3.716–7.510)	<0.001
pTNM stage						
I	*Reference*		*NI*		*NI*	
II	2.019 (1.481–2.753)	<0.001				
III	4.782 (3.568–6.409)	<0.001				

Table 2. continued

	Cancer free survival					
	Univariate		Multivariate[a]		Multivariate[a]	
	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Differentiation grade						
Well/Moderate	*Reference*		*Reference*		*Reference*	
Poor/Undifferentiated	1.614 (1.227–2.124)	0.001	1.076 (0.822–1.407)	0.595	1.096 (0.806–1.491)	0.559
Postoperative complication						
No	*Reference*		*NI*		*NI*	
Yes	1.032 (0.856–1.244)	0.742				
Postoperative complication grade (CD)						
None	*Reference*		*Reference*		*Reference*	
Minor (CD I-II)	0.845 (0.668–1.069)	0.161	0.809 (0.620–1.056)	0.119	0.838 (0.617–1.137)	0.256
Major (CD III-V)	1.387 (1.080–1.781)	0.010	1.528 (1.160–2.013)	0.003	1.558 (1.144–2.122)	0.005
Adjuvant chemotherapy						
No	*Reference*		*Reference*		*Reference*	
Yes	2.041 (1.712 – 2.434)	<0.001	0.744 (0.559 – 0.989)	0.042	0.796 (0.573–1.106)	0.174

ASA American Association of Anesthesiologists, *BMI* body mass index, *CCI* Charlson Comorbidity Index, *CD* Clavien-Dindo classification, *CI* confidence interval, *HR* Hazard ratio, *pT-stage* pathological tumour stage, *pN-stage* pathological (lymph) node stage, *pTNM* pathological tumour-node-metastasis stage.
[a]Including age, sex, CCI, reason for diagnostics, timing of surgery, surgical approach, tumour location, pT-stage, pN-stage, differentiation grade, postoperative postoperative complications according to CD-classification and treatment with adjuvant chemotherapy, and corrected for time-bias by year of diagnosis.

confounders, or considered colon- and rectal cancer as the same entity despite the differences in preoperative work-up, course of treatment and prognosis. Bagaria et al. [9] published a well conducted study on the treatment interval in colon cancer, concluding that a longer treatment interval was associated with poorer OS. The treatment interval analysed (>84 days) was much longer compared to the treatment interval analysed in our study. Minding current literature on prehabilitation, the treatment interval analysed by Bagaria et al. [9] is longer than required for prehabiliation, as prehabilitation can effectively reduce the incidence of postoperative complications in 3–6 weeks [15, 31]. The negative prognostic association found in these studies was not supported by the results of the current study, as no association between a treatment >35 days or >49 days and 5-year OS was found. In a systematic review by Hangaard et al. [7] it was suggested that a treatment interval up to 8–9 weeks is 'safe' concerning OS in colon cancer. However, with the results of the current study we can only state that this timeframe is 'safe' concerning CFS. For OS we can only state that a treatment interval ≤35 days is not inferior to a treatment interval >35 days or >49 days, but not non-inferior. It is interesting that there non-inferiority for a longer treatment interval could be concluded regarding CFS, but not OS. This suggests patients die from other causes, which may or may not be associated with the treatment interval. During 5-year of follow-up it is plausible that competing risks obscure the association between treatment interval and OS. As the study population in the current study is already of advanced age at time of diagnosis (median 72 years) we believe aging, and factors related with aging as development of comorbidities and deterioration in physical fitness, during the years of follow-up influence OS in a greater degree than the treatment interval experienced before a surgery years before death. This impact might be larger in the group of patients with a longer treatment interval as these patients tend to be older at time of diagnosis, possess more comorbidities at time of diagnosis and experience more (and more severe) postoperative complications. Simultaneously with the current study, Rydbeck et al. conducted a non-inferiority study analysing OS, concluding that a longer treatment interval up to 56 days is non-inferior to treatment within 28 days in regard of OS [32]. The study population consisted of 20836 patients, but did not account for as many additional prognostic factors as the current study.

Both postoperative complications and treatment with adjuvant chemotherapy were included in multivariate analysis as potential mediators. Postoperative complications occurred more often in patients with a longer treatment interval, while there was no difference in surgical approach (laparoscopic (with conversion) or open). Tumour-stage (both pTNM- and pT-stage) also differed between groups based on treatment interval, being more often less advanced in patients with a longer treatment interval. This suggests the increased number of postoperative complications in these patients does not result from larger tumours needing more advanced resections. Patients in the group with a longer treatment interval tended to be older and possessed more comorbidities, possibly contributing to the higher number of postoperative complications. The shift towards lower pT- and pTNM-stage in the groups with a longer treatment interval may be due to prioritising surgery in patients with more advanced tumours, or attempts to remove pT1 tumours endoscopically.

As mentioned before, a strength of this study is using a non-inferiority analysis. The power of the study was sufficient for the non-inferiority design, and allowed us to adjust for multiple major confounders. The endpoint of this study was cancer free survival next to overall survival, which is more specific than overall survival alone. Another strength of this study is the completeness of the variables in the dataset, which enabled the adjustment for a multiplicity of important confounders. There was no selection bias to participating hospitals, and we corrected for time-bias in multivariate analysis (by year of diagnosis). In this study a clear definition of the start and end of the treatment interval was given, namely first diagnostic (endoscopy or CT-scan) setting cancer diagnosis (i.e. the starting point of a full diagnostic work-up and potential starting point of prehabilitation). Colon cancer was analysed as a separate entity, as it differs in epidemiology, pathology and course of treatment from rectal cancer, and should therefore not be considered as the same entity as rectal cancer

Table 3. Associations of treatment interval and other covariates with overall survival.

	Overall survival					
	Univariate		Multivariate[a]		Multivariate[a]	
	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Treatment interval						
≤35 days	*Reference*		*Reference*			
>35 days	1.267 (1.095–1.467)	0.002	1.031 (0.872–1.219)	0.717		
Treatment interval						
≤35 days	*Reference*				*Reference*	
>49 days	1.384 (1.140–1.682)	0.001			1.051 (0.834–1.326)	0.672
Age	1.060 (1.051–1.069)	<0.001	1.043 (1.032–1.053)	<0.001	1.044 (1.032–1.056)	<0.001
Sex						
Male	*Reference*		*Reference*		*Reference*	
Female	0.931 (0.805–1.076)	0.334	0.926 (0.786–1.092)	0.362	0.936 (0.773–1.132)	0.496
CCI						
0	*Reference*		*Reference*		*Reference*	
1	1.577 (1.304–1.906)	<0.001	1.354 (1.100–1.669)	0.004	1.477 (1.163–1.875)	0.001
2	1.935 (1.567–2.391)	<0.001	1.538 (1.213–1.950)	<0.001	1.510 (1.145–1.992)	0.001
≥3	3.059 (2.508–3.733)	<0.001	1.978 (1.568–2.495)	<0.001	2.177 (1.663–2.850)	<0.001
ASA						
I-II	*Reference*	0.761	*NI*		*NI*	
III-IV	1.040 (0.808 – 1.339)					
BMI						
Healthy (20–30 kg/m^2)	*Reference*	0.463	*NI*		*NI*	
Unhealthy (<20 kg/m^2 or >30 kg/m^2)	0.936 (0.783–1.118)					
Reason for diagnostics						
National bowel screening programme	*Reference*		*Reference*		*Reference*	
Other	2.326 (1.759–3.076)	<0.001	1.402 (0.969–2.028)	0.073	1.387 (0.905–2.125)	0.133
Timing of surgery						
Elective	*Reference*		*Reference*		*Reference*	
Elective after initial stoma creation	1.401 (0.665–2.949)	0.375	1.294 (0.572–2.929)	0.536	1.552 (0.568–4.240)	0.392
Surgical approach						
Laparoscopic	*Reference*		*Reference*		*Reference*	
Laparoscopic with conversion	1.536 (1.202–1.962)	0.001	1.348 (1.032–1.760)	0.029	1.359 (1.009–1.831)	0.044
Open	1.636 (1.403–1.907)	<0.001	1.252 (1.044–1.503)	0.015	1.124 (0.908–1.392)	0.284
Tumour location						
Right-sided colon	*Reference*		*Reference*		*Reference*	
Left-sided colon	0.776 (0.671–0.898)	0.001	1.002 (0.846–1.186)	0.983	1.002 (0.824–1.217)	0.987
pT stage						
I	*Reference*		*Reference*		*Reference*	
II	1.267 (0.910–1.764)	0.161	1.073 (0.732–1.572)	0.718	0.968 (0.623–1.506)	0.886
III	1.591 (1.183–2.139)	0.002	1.053 (0.737–1.505)	0.776	0.971 (0.641–1.471)	0.889
IV	3.450 (2.496–4.767)	<0.001	1.905 (1.283–2.829)	0.001	1.799 (1.138–2.844)	0.012
pN stage						
0	*Reference*		*Reference*		*Reference*	
I	1.460 (1.231–1.731)	<0.001	2.016 (1.632–2.489)	<0.001	2.307 (1.811–2.939)	<0.001
II	2.667 (2.199–3.235)	<0.001	3.829 (2.975–4.928)	<0.001	4.301 (3.217–5.750)	<0.001
pTNM stage						
I	*Reference*		*NI*		*NI*	
II	1.482 (1.197–1.835)	<0.001				
III	2.319 (1.885–2.855)	<0.001				

Table 3. continued

	Overall survival					
	Univariate		Multivariate[a]		Multivariate[a]	
	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Differentiation grade						
Well/Moderate	*Reference*		*Reference*		*Reference*	
Poor/Undifferentiated	1.901 (1.586–2.279)	<0.001	1.394 (1.129–1.721)	0.002	1.482 (1.161–1.891)	0.002
Postoperative complication						
No	*Reference*		*NI*		*NI*	
Yes	1.945 (1.683–2.248)	<0.001				
Postoperative complication grade (CD)						
None	*Reference*		*Reference*		*Reference*	
Minor (CD I-II)	1.524 (1.275–1.821)	<0.001	1.124 (0.919–1.375)	0.255	1.074 (0.847–1.362)	0.555
Major (CD III-V)	2.714 (2.267–3.248)	<0.001	2.365 (1.934–2.891)	<0.001	2.436 (1.941–3.058)	<0.001
Adjuvant chemotherapy						
No	*Reference*		*Reference*		*Reference*	
Yes	0.813 (0.687–0.962)	0.016	0.584 (0.458–0.743)	<0.001	0.543 (0.411–0.717)	<0.001

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[a]Including age, sex, CCI, reason for diagnostics, timing of surgery, surgical approach, tumour location, pT-stage, pN-stage, differentiation grade, postoperative postoperative complications according to CD-classification and treatment with adjuvant chemotherapy, and corrected for time-bias by year of diagnosis.

Table 4. Non-inferiority margins with observed event rates and the impact on the Hazard Ratio.

Endpoint	Non-inferiority margin	Observed event rate on standard treatment	Corresponding Hazard Ratio with observed event rate and predefined non-inferiority margin	
Cancer free survival	2%	16.1%	1.124	(16.1% + 2%)/16.1%
Overall survival	2%	20.1%	1.100	(20.1% + 2%)/20.1%

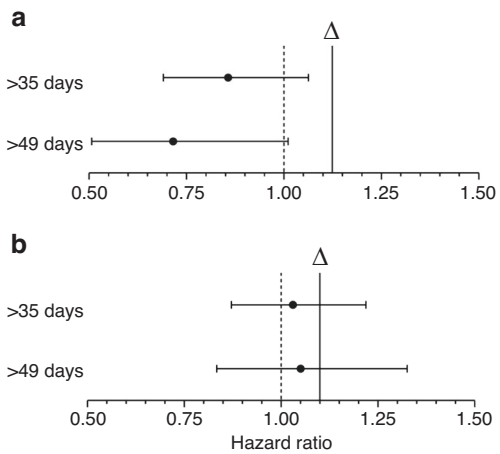

Fig. 2 Forest plots showing multivariate Hazard Ratio and error bars representing the 95% confidence interval for a longer treatment interval tested to a standard Hazard Ratio of 1 and the Non-Inferiority Margin. a CFS for treatment interval >35 days and >49 days. **b** OS for treatment interval >35 days and >49 days. • Hazard Ratio. Δ Non-Inferiority Margin.

which was done in multiple previous studies regarding the impact of a longer treatment interval on CFS and OS. Exclusion of metastatic disease and non-elective surgery provides a realistic group of patients to undergo fast-track diagnostics and is qualified for curative therapy. This provides us with results which are applicable to the actual population in which prehabilitation could be considered. However, there are also a few limitations to this study. Due to the retrospective character, there remains a risk of residual confounding even though we were able to correct for multiple possible confounders. However, residual confounding by patient related factors resulting in a longer treatment interval could not be fully ruled out. Due to an error in notation of key-records, some patients had to be excluded as their medical records could not be re-assessed by the authors to complete missing data. This only concerned a small number of patients. As those were a random sample of the full study population, we believe this did not lead to selection bias. The retrospective observational study design was unavoidable, as prospectively assigning patients to a longer treatment interval without utilising this time for other purposes would be unethical.

In conclusion, for CFS, a treatment interval of >35 days and of >49 days is non-inferior to current set waiting time targets in the elective curative treatment of colon cancer. It is safe to release the somewhat strictly imposed timeframe in elective oncological resection for colon cancer when indicated, for example to achieve maximal results of prehabilitation.

DATA AVAILABILITY

Data and material cannot be shared publicly because of ethical concerns. Patients were included on a no objection base to conduct retrospective data studies and publish findings, but were not asked for permission to publish full encrypted data. Data are available from the VieCuri Institutional Data Access (contact via wetenschapsbureau@viecuri.nl) for researchers who meet the criteria for access to confidential data.

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AUTHOR CONTRIBUTIONS

Guarantor of the integrity of the study: MS. Conceptualisation: MS, RF, CM, MJ, and FV. Literature research: MS, RF, and CM. Methodology: MS, FO, MJ, and FV. Formal analysis: MS and FO. Investigation: MS, RF, and CM. Recourses: EB, JB, GS, JM, JH, and FV. Data curation, analysis and interpretation: MS and FO. Manuscript preparation: MS, RF, and CM. Manuscript editing and review: FO, EB, JB, GS, JM, JH, AB, MJ, and FV. Visualisation: MS and RF. Project administration: MS. Funding acquisition: MS, AB, MJ, and FV.

COMPETING INTERESTS

The authors declare no competing interest.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study was approved by the research committee and the Board of Directors of all six participating hospitals. Data were obtained under the Dutch law 'scientific research and statistics in the interest of public health, where asking for permission is not possible or inappropriate for several reasons', unless patients had objected to the general use of their personal medical record for scientific research. Data were encrypted with an encryption key provided by the NCR. Encryption was shortly lifted to access the patients' number for accessing his/her medical record. A waiver of informed consent was given by the METC Zuyderland under the reference number METCZ20200069.

ADDITIONAL INFORMATION

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