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Impact of therapeutic delay in colorectal cancer on overall survival and cancer recurrence – is there a safe timeframe for prehabilitation?

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ABSTRACT

Introduction: Interest in adoption of a prehabilitation programme in management of colorectal cancer is increasing, but current waiting time targets leave no opening for intervention. Prompt treatment following diagnosis is demanded but defending evidence is lacking. We aimed to investigate the impact of prolonged therapeutic delay on overall and cancer-free survival in patients with primary colorectal cancer.

Methods: Retrospective analysis was performed in a detailed dataset of patients with primary colorectal cancer who underwent curative surgical treatment between January 2010 and December 2016. Groups were made according to therapeutic delay ≤35 days or >35 days. Endpoints were overall and cancer-free survival, assessed with Kaplan-Meier survival curves, log-rank tests and Cox proportional hazard analyses.

Results: A total of 790 patients were included of whom 559 had a colonic tumour and 231 a rectal tumour. Median therapeutic delay was 32 days (IQR 26-43 days). Multivariate analysis showed therapeutic delay >35 days was not associated with poorer overall survival (HR = 1.202, p = 0.249) or earlier cancer recurrence (HR = 1.256, p = 0.212). Similar results were found when stratifying analyses for colonic and rectal cancer, and when defining prolonged delay as >49 days.

Conclusion: Prolonged treatment delay does not lead to poorer overall or cancer-free survival in patients with primary colorectal cancer who underwent curative surgical treatment. This allows professionals to push current national waiting time targets in order to adopt a prehabilitation programme without jeopardizing outcomes.

Introduction

Despite diagnostic and therapeutic improvements, colorectal cancer remains the fourth most common cause of death worldwide [1]. In 2014 the Netherlands adopted a population-based screening programme to shorten the delay in diagnosing colorectal cancer and thereby improve survival rates. The impact of the delay from diagnosis to treatment on survival remains uncertain. Multiple studies regarding this therapeutic delay show different results. A number of studies demonstrated that delayed treatment is not significantly associated with survival or oncologic outcome [2–4]. Others showed a negative association between time to treatment and survival in case of rectal cancer but not for colonic cancer [5–7]. The national guidelines of the Netherlands set waiting time targets with a maximum of 35 days as time from diagnosis to treatment. To meet these targets at least 80% of patients should be treated within these 35 days. Remaining patients should be treated within the nationally defined limit of 49 days [8,9].

Another prognostic factor for survival is the occurrence of postoperative complications. A recent study shows that the occurrence of postoperative complications within 30 days after abdominal surgery is a more important factor than intra-operative factors (such as operative time, blood transfusion, wound classification and the current procedural terminology code of the performed operation) and pre-operative risk determined on the basis of patient demographics, comorbidities, laboratory values and lifestyle variables [10]. Emerging evidence suggests that

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prehabilitation (optimising patients' health before surgery) can decrease the incidence of postoperative complications and improve postoperative physical functioning and recovery [11–13]. Logically frail patients, who have impaired overall health and physical fitness, will gain the most from prehabilitation. Of all patients diagnosed with colorectal cancer in 2016, 75% is older than 65 and more than one third had reduced physical functioning [14]. One third of all patients undergoing surgery is classified as 3 or 4 according to the ASA-classification [14] and therefore seems to be a population particularly qualified for prehabilitation.

However, adopting a prehabilitation programme into the current diagnosis-to-therapy work-up for patients diagnosed with colorectal cancer without exceeding current waiting time targets can be challenging. Therefore, the aim of this study is to investigate the influence of a prolonged therapeutic delay on overall and cancer-free survival in surgically treated patients with primary colorectal cancer.

Methods

Patients

The study population consists of patients with biopsy proven primary colorectal cancer who underwent elective surgical treatment between January 2010 and December 2016 in VieCuri Medical Centre (n = 861). All patients were cared for by a multi-disciplinary team. None of the included patients underwent a prehabilitation programme. A frailty screening, consisting of a G8 score and a 4 min walking test, was only standardized in our hospital in 2016, at the end of our study period. For 17 patients biopsy did not prove carcinoma but was highly suspect. These patients had exact the same work-up from diagnosis until surgery as pathologically proven carcinomas and were therefore included in this study. All non-elective surgeries were excluded (n = 96). Patients with carcinoma in situ (n = 7) or metastatic disease at time of surgery (n = 59) were excluded. Metastasis found within 3 months after surgery were considered present at time of surgery and therefore excluded (n = 19). Three neuroendocrine tumours were excluded because of different tumour characteristics and prognosis.

Therapeutic delay was defined as the time from date of diagnosis (defined as date of biopsy that confirmed diagnosis) until date of start treatment (neo-adjuvant treatment or surgery). Therapeutic delay >35 days was defined as prolonged, as this exceeds the national recommendation. Demographic and clinical data on the patients were obtained from the medical records of the patients and combined with data from the Netherlands Comprehensive Cancer Registry (NCR) that collects data on all newly diagnosed cancer patients in the Netherlands. Follow-up data were last completed in October 2018 based on last contact or day of death registered by the NCR and in patients' medical records. Three patients operated in 2010 were lost to follow up, two after one year and one after three years. They were censored at time of the last contact registered in their medical record.

Outcomes

The primary endpoint of this study was overall survival from date of diagnosis. Cancer-free survival for colorectal cancer was determined as secondary endpoint. This 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 metastases or tumour recurrence). Patients dying without cancer recurrence were censored on day of death. The same analysis was performed for colonic cancer and rectal cancer separately, and for delay groups with delay ≤49 days compared to delay >49 days.

Models were adjusted for the variables gender, age, body-mass-index, existence of comorbidities, ASA-classification, occurrence of post-operative complications and severity according to the Clavien-Dindo classification and tumour characteristics as location, differentiation grade and tumour stage according to TNM-classification.

Statistical analyses

Data was analysed using IBM SPSS Statistics, version 25.0 (IBM Corp, NY, Armonk, USA). Analyses included independent T-test, chi-square, fisher's exact and odds ratios to test differences between groups. Time-to-event data was presented as Kaplan-Meier curves and compared using the log-rank test. Multivariate Cox regression analysis was conducted to calculate the prognostic association between treatment delay and survival adjusted for other prognostic variables. Variables included for adjustment were chosen based on clinical judgment and differences between groups at baseline. Those included patient demographics (age, sex, comorbidities identified at admission), tumour characteristics (localisation, stage, differentiation) and the occurrence of post-operative complications, varying based on the analysed endpoint. A potential confounding relationship with delay and the analysed endpoint was tested for each variable separately.

Results

A total of 790 patients were included in this study. Of all tumours 559 were colonic (123 ileocecal, 108 right hemi colon, 34 transverse colon, 40 left hemi colon, 254 sigmoid) and 231 rectal. Median time from diagnosis to treatment was 32 days with an interquartile range (=IQR) of 26–43 days. Patients with a therapeutic delay of 35 days or less were treated after a median of 28 days (interquartile range 23–31) for treatment, whereas patients with prolonged therapeutic delay had a median waiting time of 47 days (interquartile range 40–57). All 790 colorectal cancer patients at risk of dying or recurrence were followed over a median period of 50 months (IQR 32-75 months). Over the total period of follow-up, 179 patients (22.7%) died and 136 patients (17.2%) had recurrence of colorectal cancer. Table 1 shows descriptive data of the included patients.

Longer treatment delay was associated with male gender, OR = 1.390 (95% CI; 1.042–1.853), and localisation in the rectum, OR = 2.160 (95% CI; 1.581–2.950). Tumour stage also showed to be significantly associated with delay ($p < 0.001$). Both an early and advanced tumour stage seemed to be associated with a prolonged therapeutic delay.

Survival

There were no significant differences between groups in overall survival (Fig. 1, p = 0.127), or cancer-free survival (Fig. 2, p = 0.217). In unadjusted analysis a prolonged therapeutic delay was not significantly associated with worse overall survival (HR = 1.227, p = 0.173), or earlier cancer recurrence (HR = 1.284, p = 0.147). Also after adjustment for confounders, the association between delay and survival remained not significant (HR = 1.202, p = 0.249 and HR = 1.256, p = 0.212 for overall and cancer-free survival, respectively) (Tables 2 and 3). Tumour stage was identified as confounder for both overall and cancer-free survival. In the analysis for cancer-free survival localisation of the tumour was also identified as a confounder, more powerful than tumour stage.

Stratified analyses for colonic and rectal cancer showed similar results (Tables 2 and 3). Among colon cancer patients prolonged delay was not significantly associated with overall survival (HR = 1.291, p = 0.171) or cancer-free survival (HR = 1.214,

Table 1
Descriptive data of patients diagnosed with and who underwent elective surgery for colorectal cancer between January 2010 and December 2016 in VieCuri medical centre.

	Total group (n = 790)	Delay 0-35 (n = 474)	Delay >35 (n = 316)	p
Mean age (SD)	70 (10)	69 (11)	70 (10)	0.309
Age (years), n (%)				0.225
<65	231 (29.2)	149 (31.4)	82 (25.9)	
65-75	292 (37.0)	167 (35.2)	125 (39.6)	
>75	267 (33.8)	158 (33.3)	109 (34.5)	
Gender, n (%)				0.025
Male	429 (54.3)	242 (51.1)	187 (59.2)	
Female	361 (45.7)	232 (48.9)	129 (40.8)	
Mean BMI (SD)	26.6 (4.4)	26.7 (4.6)	26.5 (4.2)	0.584
Comorbidities, n (%)	529 (67.0)	315 (66.5)	214 (67.7)	0.711
ASA, n (%)				0.955
ASA-1	188 (24.1)	114 (24.5)	74 (23.6)	
ASA-2	505 (64.8)	300 (64.5)	205 (65.3)	
ASA-3/4	86 (11.0)	51 (11.0)	35 (11.1)	
Localisation tumour, n (%)				<0.001
Colon	559 (70.8)	366 (77.2)	193 (61.1)	
Rectum	231 (29.2)	108 (22.8)	123 (38.9)	
Tumour stage, n (%)				<0.001
I	224 (28.4)	118 (24.9)	106 (33.5)	
II	314 (39.7)	215 (45.4)	99 (31.3)	
III	252 (31.9)	141 (29.7)	111 (35.1)	
Differentiation grade, n (%)				0.773
Well/moderately	627 (84.6)	383 (84.9)	244 (84.1)	
Poorly	114 (15.4)	68 (15.1)	46 (15.9)	
Post-operative complication, n (%)	373 (47.2)	214 (45.1)	159 (50.3)	0.154
Clavien-Dindo classification, n (%)				0.695
I	87 (23.3)	48 (22.4)	39 (24.5)	
II	140 (37.5)	87 (40.7)	53 (33.3)	
III	74 (19.8)	41 (19.2)	33 (20.8)	
IV	59 (15.8)	31 (14.5)	28 (17.6)	
V	13 (3.5)	7 (3.3)	6 (3.8)	

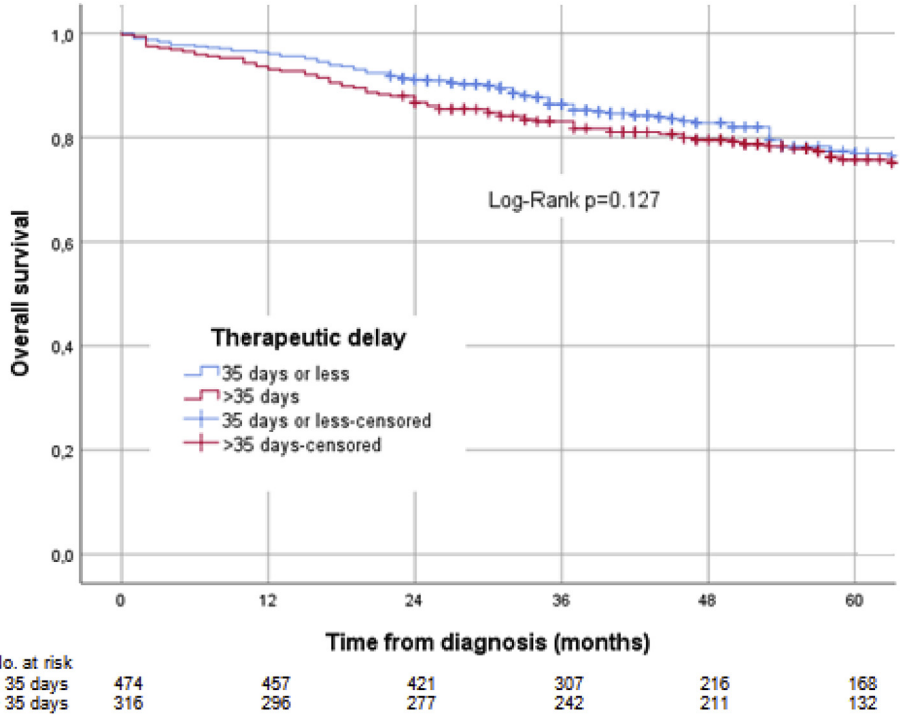

Fig. 1. Kaplan-Meier curves for overall survival after surgery for colorectal cancer, according to therapeutic delay.

p = 0.396). This also applies to rectal cancer (HR = 0.856, p = 0.628 and HR = 1.212, p = 0.541 for overall and cancer-free survival, respectively). In colonic cancer, age over 75 years, advanced tumour stage and the occurrence of a post-operative complication were significantly associated with poorer overall survival. Common post-operative complications in this cohort were wound infections (10.1%), paralytic ileus (10.5%) and pneumonia (7.0%), and less often anastomotic leakage (5.6%) or bleeding (2.3%). In 1.6% of the

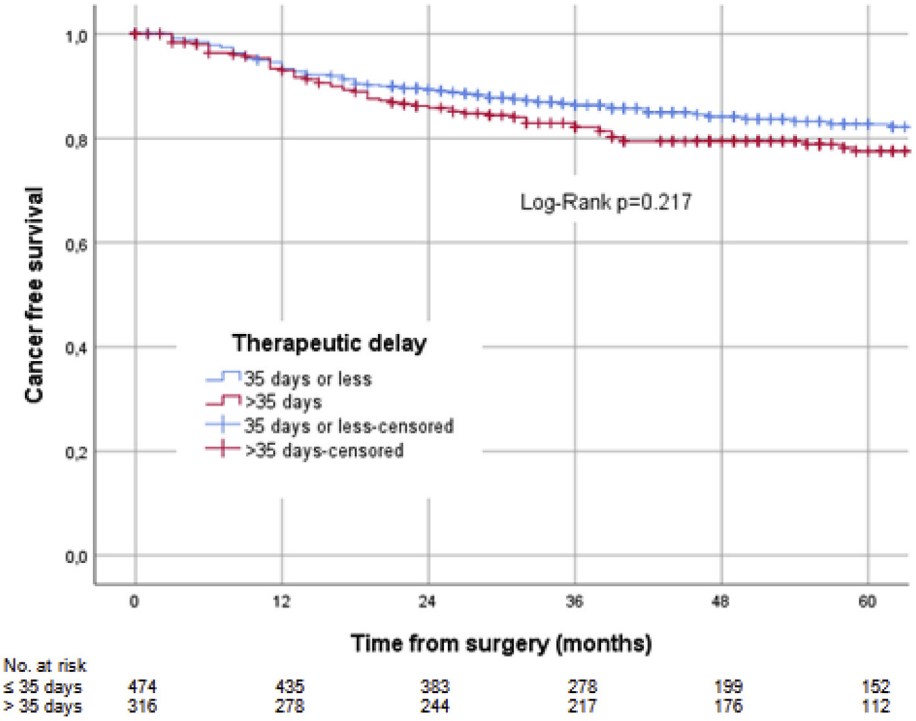

Fig. 2. Kaplan-Meier curves for cancer free survival after surgery for colorectal cancer, according to therapeutic delay.

Table 2
Multivariate analysis of factors associated with overall survival after elective surgical treatment for colorectal cancer.

	Total group (n = 790)		Colon (n = 559)		Rectum (n = 231)	
	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p
Delay						
<=35 days	1		1		1	
>35 days	1.202 (0.880 - 1.642)	0.249	1.291 (0.896–1.860)	0.171	0.856 (0.457–1.605)	0.628
Gender						
Male	1		1		1	
Female	1.001 (0.726–1.380)	0.996	1.121 (0.772–1.629)	0.549	0.942 (0.485–1.830)	0.860
Age (years)						
<65	1		1		1	
65–75	1.462 (0.875–2.441)	0.147	1.791 (0.948–3.382)	0.073	1.005 (0.400–2.522)	0.992
>75	3.394 (2.093–5.504)	<0.001	3.358 (1.826–6.177)	<0.001	3.543 (1.604–7.828)	0.002
Comorbidities						
No	1		1		1	
Yes	1.798 (1.161–2.787)	0.009	1.583 (0.957–2.618)	0.074	2.896 (1.169–7.170)	0.022
Localisation						
Colon	1					
Rectum	1.177 (0.815–1.699)	0.385				
Tumour stage						
I	1		1		1	
II	1.586 (1.014–2.482)	0.044	1.953 (1.085–3.514)	0.026	1.134 (0.512–2.513)	0.757
III	2.177 (1.395–3.399)	0.001	2.825 (1.552–5.142)	0.001	1.402 (0.685–2.870)	0.355
Differentiation						
Well/moderate	1		1		1	
Poor	1.058 (0.707–1.583)	0.784	0.810 (0.504–1.302)	0.384	3.095 (1.392–6.881)	0.006[a]
Post-operative complication						
No	1		1		1	
Yes	1.383 (1.010–1.893)	0.043	1.652 (1.148–2.378)	0.007	0.683 (0.359–1.301)	0.247

[a] Interpretation should be with caution because of impaired statistic power due to small groups.

patients a post-operative complication led to relaparotomy. In rectal cancer, age over 75 years and having one or more comorbidities were significantly associated with poorer overall survival. Advanced tumour stage was associated with impaired cancer-free survival in both colonic and rectal cancer patients.

Impact of delay with a cut-off point of 49 days was tested with multivariate Cox regression analysis. A delay of >49 days did not result in a significant difference in overall survival (HR = 1.155 (95% CI; 0.776–1.720), p = 0.478) or cancer-free survival (HR = 0.932 (95% CI; 0.574–1.513), p = 0.776) compared to a delay ≤ 49 days.

When only analysing patients aged 70 years and older results remained unaltered. No significant association between prolonged

Table 3
Multivariate analysis of factors associated with cancer free survival after elective surgical treatment for colorectal cancer.

	Total group (n = 790)		Colon (n = 559)		Rectum (n = 231)	
	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p
Delay						
<= 35 days	1		1		1	
>35 days	1.256 (0.878–1.799)	0.212	1.214 (0.775–1.902)	0.396	1.212 (0.654–2.246)	0.541
Gender						
Male	1		1		1	
Female	1.147 (0.804–1.636)	0.450	1.149 (0.743–1.775)	0.532	1.199 (0.650–2.209)	0.561
Localisation						
Colon	1					
Rectum	1.866 (1.273–2.737)	0.001				
Tumour stage						
I	1		1		1	
II	2.177 (1.259–3.767)	0.005	2.314 (1.067–5.019)	0.034	2.368 (1.067–5.256)	0.034
III	3.229 (1.899–5.491)	<0.001	3.928 (1.831–8.427)	<0.001	2.550 (1.193–5.453)	0.016
Differentiation						
Well/moderate	1		1		1	
Poor	1.505 (0.973–2.327)	0.066	1.225 (0.730–2.056)	0.442	2.836 (1.279–6.288)	0.010[a]

[a] Interpretation should be with caution because of impaired statistic power due to small groups.

delay and overall survival (HR = 1.016, p = 0.932) or cancer-free survival (HR = 0.953, p = 0.852) was found. Again tumour stage was identified as confounder for both overall- and cancer-free survival (Table 4).

Discussion

In this observational cohort-study of 790 patients with primary colorectal cancer, waiting time from diagnosis to treatment exceeding 35 days did not show significantly worse overall and cancer-free survival compared to patients treated within 35 days. The same results were found when using a cut-off point of 49 days. There was no association between treatment delay and overall or cancer-free survival, even after adjusting for other prognostic factors. Variables that impacted overall survival were age, comorbidities and tumour stage. Patients aged over 75 years had worse overall survival, as well as patients with a comorbidity compared to those without. Advanced tumour stage was associated with worse overall and cancer-free survival. Cancer-free survival was also influenced by the location of the tumour, where rectal tumours were associated with a higher risk of cancer recurrence.

Table 4
Multivariate analysis of factors associated with overall- and cancer free survival after surgical treatment for colorectal cancer for patients >70 years old.

	Overall survival		Cancer free survival	
	HR	p	HR	p
Delay				
<=35 days	1		1	
>35 days	1.016 (0.697–1.482)	0.932	0.953 (0.572–1.587)	0.852
Gender				
Male	1		1	
Female	1.231 (0.838–1.810)	0.290	1.288 (0.773–2.148)	0.331
Comorbidities				
No	1			
Yes	1.709 (0.967–3.020)	0.065		
Localisation				
Colon	1		1	
Rectum	1.093 (0.694–1.722)	0.702	1.608 (0.906–2.855)	0.105
Tumour stage				
I	1		1	
II	1.670 (0.982–2.840)	0.058	1.854 (0.883–3.896)	0.103
III	2.240 (1.323–3.794)	0.003	3.054 (1.509–6.177)	0.002
Differentiation grade				
Well/moderate	1		1	
Poor	0.767 (0.454–1.297)	0.323	0.850 (0.423–1.708)	0.648
Post-operative complication				
No	1			
Yes	1.426 (0.973–2.091)	0.069		

In 2006 VieCuri Medical Centre started a fast and well-structured diagnostic pathway for patients with colorectal cancer. When malignancy is proven by biopsy, patients are directly referred for pre-operative work-up where all diagnostic tests and assessments are planned during a single pre-operative assessment day. These tests and assessments include chest X-ray or CT-scan, abdominal CT-scan, pelvic MRI in case of rectal cancer, ECG, blood samples, anaesthesiology assessment, geriatric screening, dietary assessment if necessary and consultation of colon care nurse, but until 2016 no standardized frailty screening. All this is followed by consultation of an oncologist this same day to discuss the results. After this day patients are discussed in a multidisciplinary team. Afterwards a second outpatient clinic visit is planned with the colorectal surgeon to discuss the definitive plan of surgery [15]. Importance of such a fast and well-structured diagnostic process has been shown in several studies stating that a longer therapeutic delay causes more psychological distress in oncology patients [15–18]. This psychological stress seems to emanate from the time to definite diagnosis and consultation with an oncologist [16–18]. Any prolongation of therapeutic delay that would be caused by adopting a prehabilitation programme occurs in the time after consultation of an oncologist and after the requisite treatment is determined. Therefore, it should not aggravate patients' psychological stress.

Results of previous studies regarding this subject are difficult to compare due to methodological heterogeneity in the definition of therapeutic delay. A consensus on the impact of treatment delay on survival outcomes has not been reached, and the maximum acceptable treatment delay in patients with colorectal cancer remains unclear [14]. Multiple studies, defining therapeutic delay as time from onset of symptoms to time of treatment, did not show an association between prolonged delay and overall survival [2,3,7,19,20]. Others found prolonged delay to be associated with better survival [5]. This effect was probably the result of inclusion of non-electively treated cases, which have both short delay and worse prognosis. Another factor of influence is probably confounding. Only three studies corrected for known confounders. After adjustment for other prognostic factors, no association between prolonged therapeutic delay and impaired overall survival was found [5,21–23]. A plausible explanation for these results is that time from diagnosis to treatment is too short to derive

clinically significant progression, since a colorectal adenocarcinoma may take 10 or more years to develop [14,24,25]. However, most malignancies grow exponentially what theoretically means that treatment delay occurs during a phase with fast tumour grow and increasing risk of metastasis [24].

Several studies considered and analysed colonic and rectal tumours separately, as they differ in epidemiology, pathology and treatment [25–27]. Longer delay in rectal cancer was shown to be associated with impaired survival [5–7]. Only one of these studies showed significant results after adjustment for confounders. In the latter study of 819 curatively operated patients with rectal cancer Gort et al. [6] concluded that a delay >49 results in impaired overall and disease-free survival compared to a delay of 49 days or less. The insignificance of the impact of delay >49 days on overall and cancer-free survival found in our study does not covenant with these findings while using similar in- and exclusion criteria, the same cut-off point and adjustment for the same confounders. However, hazard ratios found in our study lie within the confidence interval of the hazard ratios found by Gort et al. [6], meaning that results of both studies point in the same direction. Taking all results into account, the hazard ratio for survival tends to be lower in patients with a delay ≤49 days compared to those with a delay >49 days. To determine the significance of this difference more research in larger cohorts is needed.

Advanced tumour stage, higher age and suffering from comorbidity was found to be associated with poorer overall survival. These are all non-changeable variables, but the reduced physical fitness and functioning that generally results out of higher age and having one or more comorbidities can be optimised by the means of prehabilitation [11–14]. Prehabilitation programmes differ in composition and duration. Current evidence of prehabilitation in colorectal cancer surgery suggests that a multimodal prehabilitation programme containing physical, psychological and nutritional support will improve postoperative functional recovery [28]. Physical prehabilitation resulted in better postoperative outcomes in patients who improved their physical fitness during a programme of 4–6 weeks [13]. A review about smoking cessation found that an intervention of 4–8 weeks results in fewer postoperative complications [29]. Also nutritional status is of influence. Obesity is shown to be associated with higher mortality [30]. All these interventions take time. Length of prehabilitation is an important determinant of outcome in these programmes. Ideally programmes should take place in the 4–6 weeks before surgery in order to have enough time to take effect [31].

Our study was subject to a number of limitations. Due to its retrospective character, selection bias and confounding may have occurred. The observational study design is unavoidable as assigning patients to a prolonged delay would be unethical [14]. Selection bias could not be fully excluded due to lacking information concerning the reason for delaying therapy. We attempted to correct for all possible confounders with Cox regression analysis. In this dataset five year follow-up was not yet completed by every patient at time of analysis resulting in declining numbers at risk during the years of follow-up. Longer follow-up and population-level databases will be needed to have the power to set an upper limit for acceptable treatment delay. We were not able to determine cancer-specific survival due to missing information about cause of death in a large number of patients. To determine cancer-free survival, patients dying without cancer recurrence were censored at time of death, presuming prognosis without this event would be comparable to the main of the group. This study also has some important strengths. One is the entirety of variables in this dataset. The extent of data enabled a detailed analysis adjusting for a multiplicity of important confounders. The number of patients included was adequate to analyse the influence of delay on overall and cancer-free survival for colonic and rectal cancer separately. Lead-time bias due to neo-adjuvant treatment in rectal cancer patients was prevented by defining therapeutic delay as time until start of therapy instead of surgery. Exclusion of metastatic disease and non-elective surgery provides a realistic group of patients to undergo fast-track diagnostics and qualified for curative therapy.

In summary, time from diagnosis to surgical treatment or neo-adjuvant (chemo)radiotherapy did not impact overall or cancer-free survival in patients with primary colorectal cancer. Results of this study suggest that prolonging treatment delay is safe. Of course our study is not a plea for prolonged waiting time, but our findings allow adopting a prehabilitation programme for both colonic and rectal cancer in a safe way. The upper limit for acceptable treatment delay remains unclear. Comparable studies with larger cohorts and longer follow-up should be conducted to confirm these findings before making major modifications to national guidelines.

Conclusion

Prolonged treatment delay longer than current guidelines seems not to impact overall or cancer-free survival in patients with primary colorectal cancer who underwent curative surgical treatment. This allows professionals to push current national waiting time targets in order to adopt a prehabilitation programme without jeopardizing outcomes.

Declarations of interest

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Ethical approval

Not required due to retrospective character of the study.

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