Prehabilitation for older patients with colorectal cancer: patient selection, targets and effectiveness

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Part III

The effect of prehabilitation

7

Can physical prehabilitation prevent complications after colorectal cancer surgery in frail older patients?

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ABSTRACT

Introduction

Frail patients with colorectal cancer (CRC) are at increased risk of complications after surgery. Prehabilitation seems promising to improve this outcome and therefore we evaluated the effect of physical prehabilitation on postoperative complications in a retrospective cohort of frail CRC patients.

Methods

The study consisted of all consecutive non-metastatic CRC patients ≥70 years who had elective surgery from 2014-2019 in a teaching hospital in the Netherlands, where a physical prehabilitation program was implemented from 2014 on. We performed both an intention-to-treat and per protocol analysis to evaluate postoperative complications in the physical prehabilitation (PhP) and non-prehabilitation (NP) group.

Results

Eventually, 334 elective patients were included. The 124 (37.1%) patients in the PhP-group presented with higher age, higher comorbidity scores and walking-aid use compared to the NP-group. Medical complications occurred in 26.6% of the PhP-group and in 20.5% of the NP-group (p=0.20) and surgical complications in 19.4% and 14.3% (p=0.22) respectively. In all frailty subgroups, the medical complications were lower in the PhP-group compared to the NP-group (35.9% vs. 45.5% for patients with ≥2 comorbidities, 36.2% vs. 39.1% for ASA score ≥III, 29.2% vs. 45.8% for walking-aid use). Differences were not significant.

Conclusions

In this study, patients selected for physical prehabilitation had a worse frailty profile and therefore a higher a priori risk of postoperative complications. However, the postoperative complication rate was not increased compared to patients who were less frail at baseline and without prehabilitation. Hence, physical prehabilitation may prevent postoperative complications in frail CRC patients ≥70 years.

INTRODUCTION

Half of the patients diagnosed with colorectal cancer (CRC) in the Netherlands is 70 years or older [1]. Approximately 42% (range 6%–86%) [2] of this older population is considered 'frail' and therefore at higher risk of adverse outcomes after CRC surgery compared to fit patients. 'Frailty' can be defined as a decreased physiological state based on a multisystem interaction [3] that becomes clinically relevant in case of a stressor. Older CRC patients with a poor frailty profile [4, 5], high comorbidity [6-9], low physical performance [10-15], poor nutritional state [16] or cognitive impairment [17] are at increased risk for adverse outcome after surgery. Due to this preoperative vulnerability, patients may not have sufficient capacity to withstand the impact of surgery and any postoperative complication may cause a downward spiral resulting in readmissions, reduced health related quality of life and even in an increased 30-days and one-year mortality [4, 18-27]. Especially medical complications, such as cardiopulmonary complications, are associated with readmissions, higher mortality rates and higher health care costs [28-30].

Prehabilitation – enhancing preoperative capacity to withstand the impact of surgery – has the potential to reduce adverse outcomes after CRC surgery. Multimodal and physical prehabilitation was found to increase pre- and postoperative physical performance [10]. However, the effect of prehabilitation on length of stay and on postoperative complication rates is still debated in the literature [16, 31-40].

Prehabilitation seems most promising to improve the outcome in frail CRC patients. Unfit patients are more likely to improve from prehabilitation than fit patients [41, 42] and only two randomized controlled trials (RCT) found a significant reduction in postoperative complications after prehabilitation in high-risk' CRC patients. These studies looked respectively at patients with ASA score III-IV and/or age >70 [35] and patients with oxygen uptake at the ventilatory anaerobic threshold <11 mL/kg/min [40]. As low preoperative functional capacity is associated with postoperative complications [10-12, 15], conversely prehabilitation may lower the risk of complications [10, 31, 32]. Patients after prehabilitation may be more resilient to hospitalization [43, 44] and therefore are less likely to experience medical complications, like cardiac events, pulmonary complications or delirium [45-47]. In addition, physical activity has beneficial effects on the immune system [48, 49] that may lower the impact of surgical stress (hormonal and metabolic disturbances [50]) which may have a profound effect on anastomotic [51] and (skin) wound healing [52].

Therefore, we aimed to evaluate the effect of physical prehabilitation on postoperative complications, in a retrospective cohort of non-metastatic CRC patients ≥70 years, using both intention-to-treat and per protocol analyses.

MATERIAL AND METHODS

Population and design

This observational cohort study included all CRC patients ≥70 years who received elective surgery in a teaching hospital in the Western part of the Netherlands from January 2014 until December 2019. Patients were excluded if they were not eligible for the physical prehabilitation program; in case of non-elective surgery, metastatic disease, local excision as surgical procedure, clinical admission prior to surgery, partial obstructive tumor symptoms, and/or not able to exercise or refusal of participation.

We retrospectively registered information about participation in the physical prehabilitation program. The physical prehabilitation program was part of a multidisciplinary care program that was initiated in 2014 and offered to CRC patients ≥ 75 years and from 2019 offered to CRC patients ≥70 years. Care professionals referred patients on indication to the clinical geriatrician for a comprehensive geriatric assessment (CGA) and/or to the dietician for nutritional support and/or to the physiotherapist for the physical prehabilitation program. The CGA was performed according to the national guidelines [53]. The decision to let patients participate in the physical prehabilitation program was based on clinical impression (i.e. physical and daily activities, social and living status). When the patients were considered too fit to require additional preoperative exercising, patients were not selected.

Several physical tests were done – including a six-minute walk test (6MWT) and cycle ergo meter test (Steep Ramp Test) – by a clinical physiotherapist to assess baseline endurance, strength and coordination. Patients underwent a supervised exercise program with a local physiotherapist for 30-45 minutes twice a week for at least four weeks. They were also instructed to perform home-exercises. All patients had elective surgery.

Prehabilitation group

We divided the patients in two groups: the physical prehabilitation (PhP) group and the non-prehabilitation (NP) group. Patients in the NP-group did not initiate the program, because of two reasons: 1. The program was not offered to these patients, as they were <75 years and received surgery between 2014 – 2018 and 2. The program was not offered to these patients because they were considered too fit for prehabilitation based on the clinical impression of the care professional.

The PhP-group that was based on an intention-to-treat (ITT) population consisted of all patients who initiated the program, independently of complying the whole program. The PhP-group that was based on the per protocol (PP) population consisted of patients who complied at least four weeks of the physical prehabilitation. [39, 54, 55]. Patients who participated in the physical prehabilitation program for less than four weeks were excluded from the PP analyses

Data collection

Data about patients demographics and tumor characteristics were prospectively registered according to nationwide obligatory data collection of the Dutch ColoRectal Audit (DCRA) registry: age, gender, body mass index (BMI), ASA score, the presence of comorbidities, tumor localization, tumor (T), lymph node (N) and metastatic (M) stage according to the TNM classification of Malignant Tumours (6th edition), type of surgery, surgical approach, surgical procedure, neo-adjuvant therapy and adjuvant therapy. In case the M stage was unknown, it was considered to be M0. The following information was retrospectively obtained from the hospital medical records: G8-score (frailty screening tool), use of a walking-aid (none, walking stick or walker), preoperative living status (alone or together), preoperative outpatient consultation by a clinical geriatrician and/or the dietician.

Outcomes

The primary outcome of this study was the rate of postoperative complications; categorized in medical and surgical complications. The rate of medical complications was defined as the proportion of patients who experienced one or more medical complications (pulmonary, cardiac, neurologic or thrombotic events, infections (other than wound infection) or other complications relating to hospital admission (i.e. persistent vomiting or nausea and urinary retention). Surgical complications included anastomotic leakage, bleeding, abscess, ileus, fascia dehiscence, bowel perforation, leakage ureter/bladder or wound infection). The rate of readmissions in the first 90 days after surgery and one-year mortality were secondary outcomes.

Statistical analysis

We performed descriptive analysis, expressing the continuous variables (non-normal distributed) as median with interquartile range (IQR) and frequencies as numbers and percentages. To test for differences in baseline characteristics and outcomes between the PhP and NP-group, as well as in frail patients, Mann-Whitney tests for the continuous variables and Chi-square tests for frequencies were used. We did not test for differences in one-year mortality in frail patients due to the low number of events. The analyses were performed in the ITT population, followed by analyses in the PP population. All statistical tests were two-sided and a p-value ≤0.05 was considered statistically significant (SPSS version 25.0, Inc., Chicago, IL).

RESULTS

Study population

In total, 458 CRC patients ≥70 years underwent CRC surgery in our hospital between January 2014 – December 2019. One-hundred-twenty-four patients were excluded; 79 patients had received non-elective surgery, local excision and/or had metastatic disease and 45 patients were clinically admitted prior to surgery, had obstructive tumor symptoms, were unable to

exercise or refused participation. Eventually a total of 334 patients were included in the ITT population of whom 124 (37.1%) in the PhP-group and 210 (62.9%) in the NP-group. For the PP population, 38 patients (30.6%) were excluded, because these patients participated for less than four weeks. As a result, eventually 296 patients were included in the PP population of whom 86 (29.1%) in the PhP-group and 210 (70.9%) in the NP-group (Figure 1). Non-compliance was mainly due to a shortened surgical waiting time. It seems these patients were considered fit to receive surgery earlier and not because they were physically unable to comply the program.

Baseline characteristics

In Table 1, the baseline characteristics of the ITT population are described. The median age at diagnosis was 75 years (IQR 73.0-81.0), 230 (68.9%) patients presented with colon carcinoma and 284 (85.0%) underwent laparoscopic surgery. Ninety-three (27.8%) had an ASA score ≥III, 72 (21.6%) had ≥2 comorbidities, 72 (21.6%) were using a walking-aid, 95 (28.4%) had a positive G8 frailty score – however, 42.5% of the G8 data were missing as this screening was not part of standard practice during the study period – and 129 (38.6%) lived alone. Preoperatively, 155 (46.4%) patients had visited the dietician and 111 (33.2%) a clinical geriatrician.

Patients in the PhP-group presented with a higher age at diagnosis (80.0 vs. 74.0 years, $p<0.001$), higher ASA scores (ASA≥III: 37.9 vs. 21.9%, $p=0.002$), more comorbidities (≥2 comorbidities: 31.5 vs. 15.7%, $p=0.001$), more frequent use of a walking-aid (38.7 vs. 11.4%, $p<0.001$) and higher rates of 'living alone' (46.8 vs. 32.8%, $p=0.023$). Patients in the PhP-group were more often referred to a clinical geriatrician preoperatively (54.8% vs 20.5%, $p< 0.001$), suggesting patients in this group were more frail than patients in the NP-group.

In appendix Table A.1, the baseline characteristics of het PP population are presented. The percentages of the baseline characteristics were comparable and the differences between the PhP-group and the NP-group remained in age, ASA score, number of comorbidities, walking-aid use and living status.

Figure 1. Flow diagram of the intention-to-treat (ITT) and per protocol (PP) population

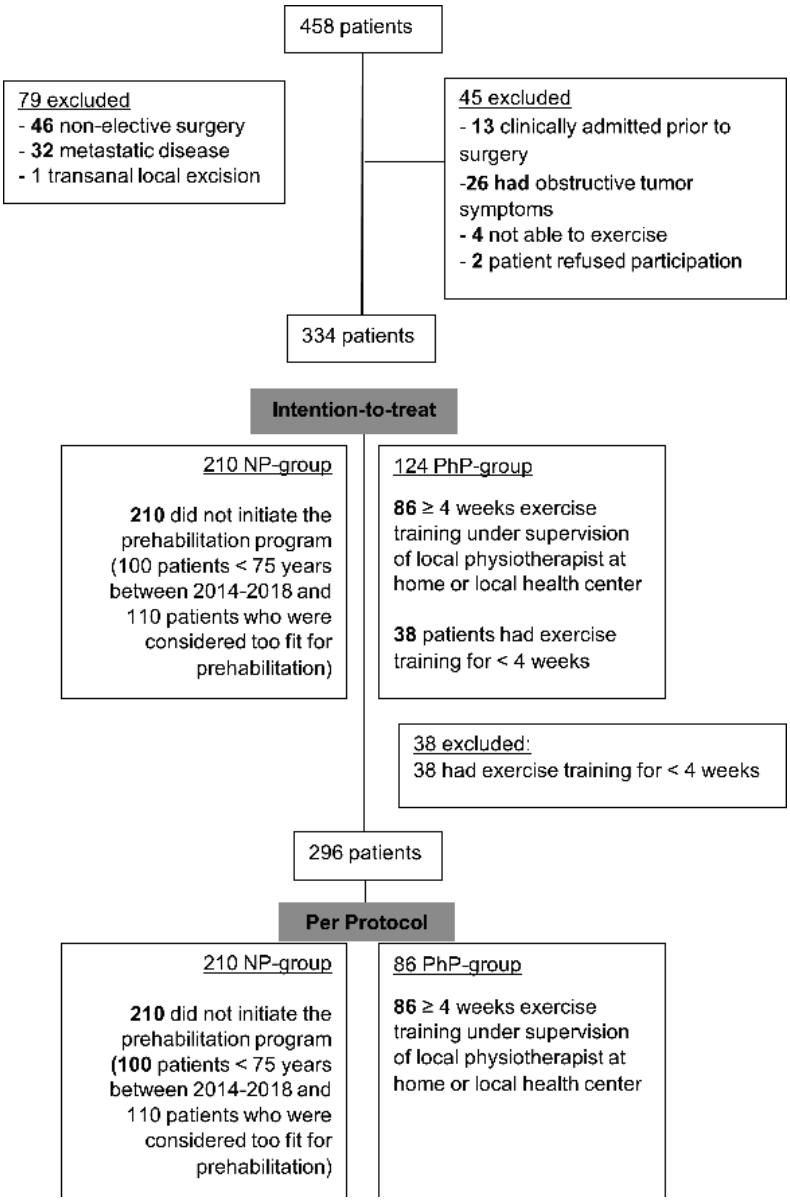


Table 1. Baseline characteristics of the ITT population; stratified by PhP and NP-group

	Total N =334 (% of total)	PhP-group N =124 (%)	NP-group N = 210 (%)	P-value
Patient- and tumour characteristics				
Median Age (IQR)	75.0 (73.0-81.0)	80.0 (76.0-83.8)	74.0 (72.0-78.0)	**<0.001**
Gender				0.341
Male	189 (56.6)	66 (53.2)	123 (58.6)	
Female	145 (43.4)	58 (46.8)	87 (41.4)	
Median BMI (IQR)	26.3 (23.6-29.0)	26.6 (23.6-29.4)	26.0 (23.6-28.7)	0.193
ASA score				**0.002**
ASA I/II	241 (72.2)	77 (62.1)	164 (78.1)	
ASA III/IV	93 (27.8)	47 (37.9)	46 (21.9)	
Number of comorbidities				**0.001**
0-1	262 (78.4)	85 (68.5)	177 (84.3)	
≥2	72 (21.6)	39 (31.5)	33 (15.7)	
Tumour localization				0.924
Colon	230 (68.9)	85 (68.5)	145 (69.0)	
Rectum	104 (31.1)	39 (31.5)	65 (31.0)	
Surgical approach				0.264
Laparoscopic	284 (85.0)	110 (88.7)	174 (82.9)	
Laparotomy	20 (9.5)	6 (4.8)	26 (7.8)	
Laparoscopic robot assisted	24 (7.2)	16 (7.6)	8 (6.5)	
Type of surgery				0.462
Right hemicolectomy	141 (42.2)	50 (40.3)	91 (43.3)	
Left hemicolectomy	15 (4.5)	5 (4.0)	10 (4.8)	
TME or PME	71 (21.3)	23 (18.5)	48 (22.9)	
Sigmoid resection	29 (8.7)	10 (8.1)	19 (9.0)	
LAR	56 (16.8)	28 (22.6)	28 (13.3)	
APR	16 (4.8)	5 (4.0)	11 (5.2)	
Other	6 (1.8)	3 (2.4)	3 (1.4)	
Tumour stage				0.515
T0	12 (3.6)	6 (4.8)	6 (2.9)	
T1-T2	125 (37.4)	43 (34.7)	82 (39.0)	
T3-T4	797 (59.0)	75 (60.5)	122 (58.1)	
Lymph nodes stage				0.332
N0	238 (71.3)	83 (66.9)	155 (73.8)	
N1	71 (21.3)	29 (23.4)	42 (20.0)	
N2	25 (7.5)	12 (9.7)	13 (6.2)	

Table 1. Baseline characteristics of the ITT population; stratified by PhP and NP-group (*continued*)

	Total N =334 (% of total)	PhP-group N =124 (%)	NP-group N = 210 (%)	P-value
Geriatric characteristics				
G8 score				**<0.001***
≤ 14 points	95 (28.4)	43 (34.7)	52 (24.8)	
> 14	97 (29.0)	14 (11.3)	83 (39.5)	
Unknown	142 (42.5)	67 (54.0)	75 (35.7)	
Walking-aid				**<0.001***
Yes	72 (21.6)	48 (38.7)	24 (11.4)	
No	235 (70.4)	66 (53.2)	169 (80.5)	
Unknown	27 (8.1)	10 (8.1)	17 (8.1)	
Living status				**0.023****
Living alone	129 (38.6)	58 (46.8)	71 (32.8)	
Living with partner	200 (59.9)	65 (52.4)	135 (64.3)	
Unknown	5 (1.5)	1 (0.8)	5 (1.5)	
Preoperative consultations				
Dietician				**<0.001**
Yes	155 (46.4)	99 (79.8)	56 (26.7)	
No	179 (53.6)	25 (20.2)	154 (73.3)	
Clinical geriatrician				**<0.001**
Yes	111 (33.2)	68 (54.8)	43 (20.5)	
No	223 (66.8)	56 (45.2)	167 (79.5)	
(neo) adjuvant treatment				
Neo adjuvant therapy				0.309
Chemoradiation	7 (2.1)	2 (1.6)	5 (2.4)	
Radiotherapy alone	47 (14.1)	22 (17.7)	25 (11.9)	
None	280 (83.8)	100 (80.6)	180 (85.7)	
Adjuvant chemotherapy				0.924
Yes	37 (11.1)	14 (11.3)	23 (11.0)	
None	297 (88.9)	110 (88.7)	187(89.0)	

Abbreviations: *PhP* physical prehabilitation, *NP* non prehabilitation, *ASA* American Society of Anesthesiologists, *PME* partial mesorectal excision, *TME* total mesorectal excision, *LAR* low anterior resection, *APR* abdominal perineal resection, *G8* geriatric-8

* No change in p-value when the 'unknown' was used as separate category.

** When "unknown" was used as separate category, the p-value changed from 0.023 to 0.054

Postoperative outcome

Medical and surgical complications

Seventy-six (22.8%) patients experienced one or more medical complications and 54 (16.2%) patients experienced surgical complications. Twenty-three (6.9%) experienced both. The rate of medical complications (26.6 vs. 20.5%, p=0.20) and surgical complications (19.4 vs 14.3% p = 0.22) were not different between the PhP-group and the NP-group. In specific medical and surgical complications, no differences were found between the PhP and the NP-group (table 2).

The results in the PP population were comparable, except for an increase in difference in surgical complications between PhP-group and NP-group (23.3 vs. 14.3%, p=0.06) and the significant higher rates of neurological complications in the PhP-group (7.0 vs. 1.9%, p=0.03).

Secondary outcomes

Thirty-one (9.4%) patients were readmitted and 9 patients (2.7%) died in the first year after surgery. The readmission rates and one-year mortality between the PhP and the NP-group, were not different (respectively 11.6 vs 8.1% (p=0.30) and 4.0 vs 1.9% (p = 0.25)). The PP population showed similar outcomes.

Frailty subgroups

Medical complications

Figure 2A shows that the medical complication rate was lower in the PhP-group compared to the NP-group. Although differences were not significant, the pattern of a lower complication rate were seen in all frail subgroups: (1) ≥2 comorbidities: 35.9 vs. 45.5%, (2) ASA score ≥III: 36.2 vs. 39.1%, (3) walking-aid: 29.2 vs. 45.8%, (4) ≥2 comorbidities and ASA score ≥III: 44.0 vs. 63.2%, (5) ≥2 comorbidities and walking-aid: 35.7 vs. 63.6%, (6) ASA score ≥III and walking-aid: 32.0 vs.55.6%, (7) ≥2 comorbidities, walking-aid and ASA score ≥III: 38.5 vs 63.6%. The PP population had the same repeated pattern of a lower medical complication rate in frail patients in the PhP-group (Figure 2D).

Surgical complications

Figure 2B shows that the surgical complication rate in frail patients was mostly higher in the PhP-group compared to the NP-group: (1) ≥2 comorbidities: 17.9 vs. 21.3%, (2) ASA score ≥III: 19.1 vs. 17.4%, (3) walking-aid: 18.8 vs. 16.7%, (4) ≥2 comorbidities and ASA score ≥III: 20.0 vs. 21.1%, (5) ≥2 comorbidities and walking-aid: 14.3% vs. 9.1%, (6) ASA score ≥III and walking-aid: 16.0 vs. 11.1%, (7) ≥2 comorbidities, walking-aid and ASA score ≥III: 15.4 vs 9.1%. Differences were not significant. The PP population showed a similar pattern with a slight increase in rate of surgical complications in frail patients in the PhP-group (Figure 2E).

Readmission

Figure 2C shows that the readmission rate in frail patients was lower in the PhP-group compared to the NP-group, except for subgroup 5 (≥2 comorbidities and walking-aid) and 7 (≥2 comorbidities, walking-aid and ASA score ≥III): (1) 12.8 vs. 18.2%, (2) 12.8 vs. 17.4%, (3) 10.4 vs. 16.7%, (4) 20.0 vs. 21.1%, (5) 21.1 vs 18.2% (6) 12.0 vs. 22.2%, (7) 23.1 vs. 18.2%. The PP population showed a more distinctive pattern where the readmission rate was lower in the PhP-group compared to the NP-group. Again, differences were not significant (Figure 2F).

Table 2. Postoperative outcome in all patients, in the PhP and NP-group.

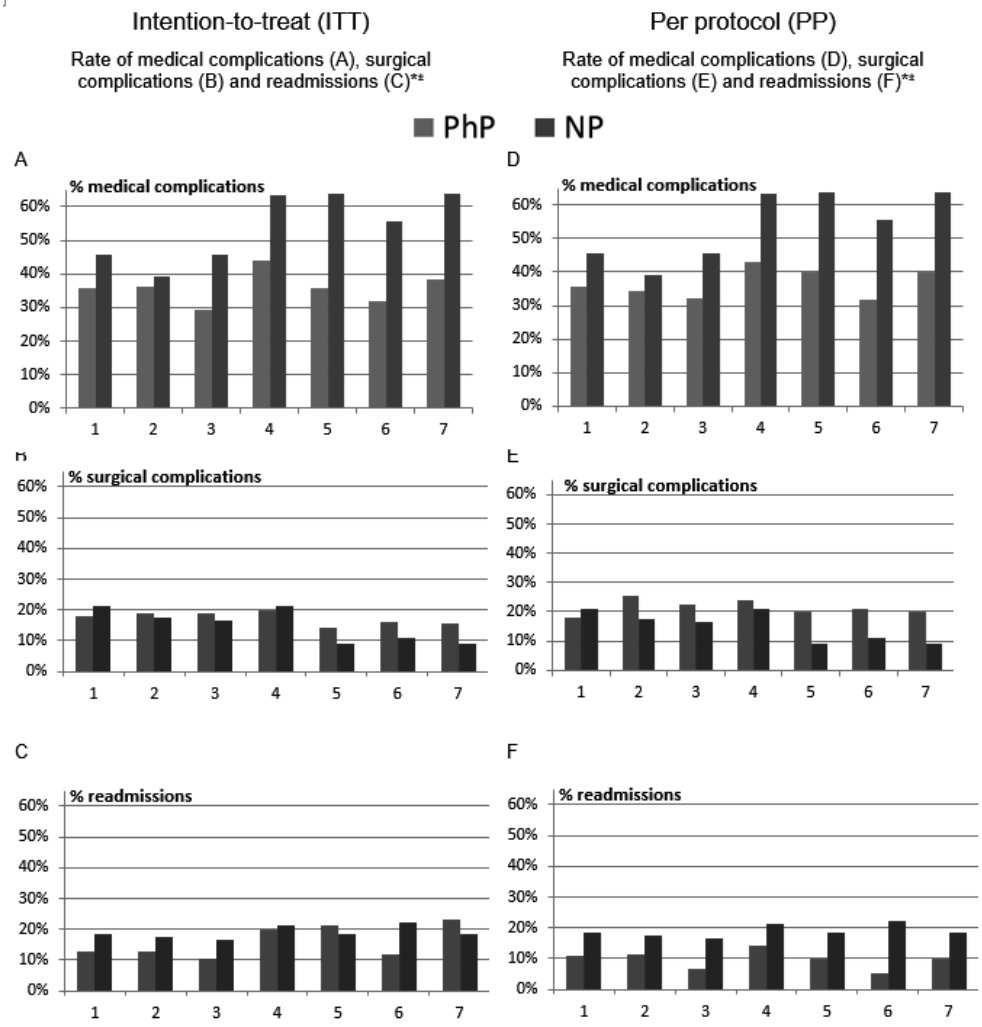
	ITT				**PP**			
	Total N =334	**PhP** N =124	**NP** N = 210	p-value	**Total** N =296	**PhP** N =86	**NP** N = 210	p-value
Medical complications	76 (22.8)	33 (26.6)	43 (20.5)	0.20	66 (22.3)	23 (26.7)	43 (20.5)	0.24
Pulmonary	16 (4.8)	8 (6.5)	8 (3.8)	0.28	14 (4.7)	6 (7.0)	8 (3.8)	0.24
Cardiac	14 (4.2)	6 (4.8)	8 (3.8)	0.65	13 (4.4)	5 (5.8)	8 (3.8)	0.45
Trombo-embolic	2 (0.6)	1 (0.8)	1 (0.5)	0.71	1 (0.3)	0	1 (0.5)	
Neurologic	10 (3.0)	6 (4.8)	4 (1.9)	0.13	10 (3.4)	6 (7.0)	4 (1.9)	0.03
Infections	22 (6.6)	11 (8.9)	11 (5.2)	0.20	18 (6.1)	7 (8.1)	11 (5.2)	0.34
Other*	28 (8.4)	10 (8.1)	18 (8.6)	0.87	25 (8.4)	7 (8.1)	18 (8.6)	0.90
Surgical complications	54 (16.2)	24 (19.4)	30 (14.3)	0.22	50 (16.9)	20 (23.3)	30 (14.3)	0.06
Anastomotic leakage	13 (3.9)	6 (4.8)	7 (3.3)	0.49	13 (4.4)	6 (7.0)	7 (3.3)	0.17
Bleeding	4 (1.2)	2 (1.6)	2 (1.0)	0.59	3 (1.0)	1 (1.2)	2 (1.0)	0.87
Abscess	10 (3.0)	4 (3.2)	6 (2.9)	0.85	10 (3.0)	4 (4.7)	6 (2.9)	0.44
Ileus	17 (5.1)	8 (6.5)	9 (4.3)	0.38	15 (5.1)	6 (7.0)	9 (4.3)	0.34
Fascia dehiscence	2 (0.6)	1 (0.8)	1 (0.5)	0.71	2 (0.7)	1 (1.2)	1 (0.5)	0.51
Bowel perforation	1 (0.3)	1 (0.8)	0		1 (0.3)	1 (1.2)	0	
Leakage ureter/bladder	3 (0.9)	1 (0.8)	2 (1.0)	0.89	3 (1.0)	1 (1.2)	2 (1.0)	0.87
Wound infection	9 (2.7)	4 (3.2)	5 (2.4)	0.65	8 (2.7)	3 (3.5)	5 (2.4)	0.59
Readmissions	31 (9.3)	14 (11.3)	17 (8.1)	0.33	28 (9.5)	11 (12.8)	17 (8.1)	0.21
1-year mortality±	9 (2.7)	5 (4.0)	4 (1.9)	0.25	7 (2.4)	3 (3.5)	4 (1.9)	0.42

Abbreviations: *ITT* intention-to-treat, *PP* per protocol, *PhP* physical prehabilitation, *NP* non prehabilitation

* Persisted vomiting and nausea (gastroparesis), urinary retention

± calculated with chi-square test, because of low number of index events

Figure 2. Rate of postoperative complications in frail patients in the PhP and NP-group.



Description subgroups:
1: ≥2 comorbidities 2: ASA score ≥III 3: walking-aid 4: ≥2 comorbidities and ASA score ≥III 5: ≥2 comorbidities and walking-aid 6: ASA score ≥III and walking-aid 7: ≥2 comorbidities, walking-aid and ASA score
**For all subgroups: differences were not significant ($p > 0.05$)
± In appendix table B1-6, the specific numbers and percentages are described.

DISCUSSION

In this study, patients who were eligible for the physical prehabilitation program (ITT population) and patients who completed the physical prehabilitation program (PP population) had a worse frailty profile based on significantly higher age, higher number of comorbidities, higher ASA scores, more frequent walking-aid use and living alone status and more referrals to a geriatrician based on G8-scores and/or clinical judgement of the surgeon. This was to be expected, as frailty is associated with increased risk of adverse postoperative outcome [4-27] and was therefore an important driver for care professionals to include patients in the physical prehabilitation program. However, in this high-risk group, we found no increase of medical complications, surgical complications and readmissions. This suggests that physical prehabilitation may prevent postoperative complications in frail older CRC patients.

Furthermore, while focusing on frail patients only, medical complications occurred less frequent in patients who initiated the physical prehabilitation program compared to their non-prehabilitation counterparts. Albeit these differences were not significant – probably due to a low number of events – it is remarkable that in all frail subgroups, the medical complication rate was structurally decreased after physical prehabilitation (Figure 2). Especially, when the overall medical complication rate was slightly higher in the physical prehabilitation group than in the non-prehabilitation group (Table 2). Because this recurring pattern did not appear for surgical complications, this may suggest that medical complications are a better target for prehabilitation than surgical complications. This is consistent with other studies.

Barberan-Garcia et al. also showed a positive effect of prehabilitation on preventing medical complications. In a RCT with somatically frail CRC patients, they showed a reduction of medical complications and no difference in surgical complications after prehabilitation [35]. Other studies found that physical prehabilitation can reduce the rate of postoperative pulmonary complications after abdominal surgery [11, 56] and Souwer *et al* found [34] a reduction in cardiac complications. Furthermore, it can be reasoned that medical complications – especially cardiopulmonary complications – are associated with reduced postoperative physical condition and are therefore a potential target for prehabilitation.

For the general geriatric and community-dwelling population, exercises, nutritional interventions, cognitive behavior interventions or multicomponent strategies are known to delay or reverse frailty [57-62]. However it is unclear, whether prehabilitation can counter several aspects of frailty (i.e. low physical performance, high comorbidity, poor nutritional state, cognitive impairment or low psychosocial status) in a population with an underlying malignant disease and in the limited time between diagnosis and surgery [3]. Our findings suggest a positive effect of physical prehabilitation in patients with walking-aid use and higher comorbidity scores. The first is consistent with studies that found that physical prehabilitation improves physical performance [10, 31, 32], especially in patients with the lowest baseline

physical performance [41, 42]. Whether prehabilitation is advantageous for patients with comorbidity is unclear; prehabilitation cannot actually reduce the number of comorbidities, but might reduce the impact of comorbidity in case of stressors. We had no sufficient information available about other frailty domains, like nutritional, cognitive and psychosocial status. Evidence for nutritional prehabilitation alone is inconsistent [28, 32] and should be combined with physical prehabilitation [59, 63]. No studies have investigated the effect of prehabilitation in cognitive frail patients. Only one study investigated the effect of social frailty in older patients receiving CRC surgery and found an association with lower overall survival [64]. To define social frailty, only 'living status' is insufficient. [65]. As a decreased frailty domain tends to overlap with other domains [3], the intervention corresponding to the frailty domain (muscle strength training for low physical performance) may also affect other domains (e.g. increase cognitive or psychosocial resilience). Due to this overlap, multimodal prehabilitation will probably be more effective than physical prehabilitation alone.

For further implementation and research of prehabilitation, it could be interesting to focus on the prevention of medical complications and to identify frailty characteristics that can be reversed through physical (or multimodal) prehabilitation. Implementing a prehabilitation program is challenging due to the demand for short surgical waiting times and a patient's commitment to an intensive program [66, 67]. Therefore, it is important to know whether implementing a program will have a positive effect knowing that not every patient is going to comply to the (whole) program (intention-to-treat basis) and to know the absolute effect of such a program for patients who do comply (per protocol basis).

In our study, 38 of the 124 patients (30.6%) did not comply the physical prehabilitation program, which is comparable to other studies [39, 54]. Despite a non-compliance rate of 30%, [67] we found comparable results between the ITT and PP analysis. Only one difference was notable: in the PP analysis, the difference in surgical complications between the PhP and NP-group was increased in comparison to the ITT population. This might be attributable to a relatively less frail preoperative status of the 38 patients who were excluded from the PP population.

This study has several limitations. Unfortunately, results of the physical assessments and information about improvement of fitness were missing. Moreover, the main limitation is that the numbers are too small for strong conclusions. Assessing the interaction between frailty and prehabilitation for surgical and medical complications with multivariable analysis was considered not reliable and needs to be tested in a larger sample size. Therefore, we have initiated a regional prospective study to further assess the effect of multimodal prehabilitation. Because participation in the physical prehabilitation program was based on frailty characteristics, confounding by indication was apparent [68]. However, this selection bias also constitutes the strength of this study. The fact that the patient group with more co-morbidity

and a higher ASA scores (a high-risk group) does not have higher complication rates after physical prehabilitation is a clinically relevant finding.

Despite the retrospective nature, the strength of our study is that we have evaluated a physical prehabilitation program in a representative real life population. As prehabilitation is of growing interest and several physical and multimodal prehabilitation protocols have been published [69-71], evidence for the effect on postoperative outcome is still scare. Therefore, our results may contribute to tailoring and implementing prehabilitation in clinical practice. Furthermore, our study is one of the few studies that differentiate between surgical and medical complications to evaluate the effect of potential quality improvements.

CONCLUSIONS

In this study, patients ≥70 years with elective colorectal cancer, who initiated or completed a physical prehabilitation program had a worse frailty profile and therefore a higher a priori risk for postoperative complications. However, with physical prehabilitation, rates of medical complications, surgical complications and readmissions were not different compared to patients without prehabilitation. This suggests that physical prehabilitation for frail CRC patients ≥70 years may prevent postoperative complications.

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APPENDIX

Appendix Table A.1. Baseline characteristics of PP population; stratified by PhP and NP-group

	Total N =296 (% of total)	PhP-group N =86 (%)	NP-group N = 210 (%)	P-value
Patient- and tumour characteristics				
Median Age (IQR)	75.0 (73.0-80.0)	80.0 (75,8-83.3)	74.0 (72.0-78.0)	**<0.001**
Gender				0.663
Male	171 (57.8)	48 (55.8)	123 (58.6)	
Female	125 (42.2)	38 (44.2)	87 (41.4)	
Median BMI (IQR)	26.2 (23.6-29.0)	26.6 (23.6-29.7)	26.0 (23.6-28.7)	0.328
ASA score				**0.001**
ASA I/II	215 (72.6)	51 (59.3)	164 (78.1)	
ASA III/IV	81 (27.4)	35 (40.7)	46 (21.9)	
Number of comorbidities				**0.001**
0-1	235 (79.4)	58 (67.4)	177 (84.3)	
≥2	61 (20.6)	28 (32.6)	33 (15.7)	
Tumour localization				0.298
Colon	199 (67.2)	54 (62.8)	145 (69.0)	
Rectum	97 (32.8)	32 (37.2)	65 (31.0)	
Surgical approach				0.212
Laparoscopic	250 (84.5)	76 (88.4)	174 (82.9)	
Laparotomy	23 (7.8)	3 (3.5)	20 (9.5)	
Laparoscopic robot assisted	23 (7.8)	7 (8.1)	16 (7.6)	
Type of surgery				0.119
Right hemicolectomy	121 (40.9)	30 (34.9)	91 (43.3)	
Left hemicolectomy	15 (5.1)	5 (5.8)	10 (4.8)	
TME or PME	67 (22.6)	19 (22.1)	48 (22.9)	
Sigmoid resection	23 (7.8)	4 (4.7)	19 (9.0)	
LAR	49 (16.6)	21 (24.4)	28 (13.3)	
APR	15 (5.1)	4 (4.7)	11 (5.2)	
Other	3 (2.0)	3 (3.5)	3 (1.4)	
Tumour stage				0.264
T0	12 (4.1)	6 (7.0)	6 (2.9)	
T1-T2	114 (38.5)	32 (37.2)	82 (39.0)	
T3-T4	170 (57.4)	48 (55.8)	122 (58.1)	
Lymph nodes stage				0.416
N0	214 (72.3)	59 (68.6)	155 (73.8)	
N1	60 (20.3)	18 (20.9)	42 (20.0)	
N2	22 (7.4)	9 (10.5)	13 (6.2)	

Appendix Table A.1. Baseline characteristics of PP population; stratified by PhP and NP-group (*continued*)

	Total N =296 (% of total)	PhP-group N =86 (%)	NP-group N = 210 (%)	P-value
Geriatric characteristics				
G8-score				**<0.001**
≤ 14 points	77 (26.0)	25 (29.1)	52 (24.8)	
> 14	91 (30.7)	8 (9.3)	83 (39.5)	
Unknown	128 (43.2)	53 (61.6)	75 (35.7)	
Walking-aid				**<0.001**
Yes	55 (18.6)	31 (36.0)	24 (11.4)	
No	217 (73.3)	48 (55.8)	169 (80.5)	
Unknown	24 (8.1)	7 (8.1)	17 (8.1)	
Living status				**0.044****
Living alone	111 (37.5)	40 (46.5)	71 (33.8)	
Living with partner	180 (60.8)	45 (52.3)	135 (64.3)	
Unknown	5 (1.7)	1 (1.2)	4 (1.9)	
Preoperative consultations				
Dietician				**<0.001**
Yes	125 (42.2)	69 (80.2)	56 (26.7)	
No	171 (57.8)	17 (19.8)	154 (73.3)	
Clinical geriatrician				**<0.001**
Yes	91 (30.7)	48 (55.8)	43 (20.5)	
No	205 (69.3)	38 (44.2)	167 (79.5)	
(neo) adjuvant treatment				
Neo adjuvant therapy				**0.047**
Chemoradiation	7 (2.4)	2 (2.3)	5 (2.4)	
Radiotherapy alone	45 (15.2)	20 (23.3)	25 (11.9)	
None	244 (82.4)	64 (74.4)	180 (85.7)	
Adjuvant chemotherapy				0.296
Yes	29 (9.8)	80 (93.0)	187 (89.0)	
None	267 (90.2)	6 (7.0)	23 (11.0)	

Abbreviations: *PhP* physical prehabilitation, *NP* non-prehabilitation, *ASA* American Society of Anesthesiologists, *PME* partial mesorectal excision, *TME* total mesorectal excision, *LAR* low anterior resection, *APR* abdominal perineal resection, *G8*:geriatric-8

* No change in p-value when the 'unknown' was used as separate category.

** When "unknown" was used as separate category, the p-value changed from 0.044 to 0.119.

Appendix Table B.1-6. Postoperative outcomes described in number and percentages per frail subgroup in the PhP and NP-group. Tables correspond to figure 2A-F.

ITT population

B.1: Medical complications

Subgroup	PhP		NP		
	N	N of complications (%)	N	N complications (%)	p-value
1	39	14 (35.9)	33	15 (45.5)	0.410
2	47	17 (36.2)	46	18 (39.1)	0.768
3	48	14 (29.2)	24	11 (45.8)	0.161
4	25	11 (44.0)	19	12 (63.2)	0.208
5	14	5 (35.7)	11	7 (63.6)	0.165
6	25	8 (32.0)	18	10 (55.6)	0.122
7	13	5 (38.5)	11	7 (63.6)	0.219

B.2: Surgical complications

Subgroup	PhP		NP		
	N	N of complications (%)	N	N complications (%)	p-value
1	39	7 (17.9)	33	7 (21.3)	0.727
2	47	9 (19.1)	46	8 (17.4)	0.826
3	48	9 (18.8)	24	4 (16.7)	0.828
4	25	5 (20.0)	19	4 (21.1)	0.932
5	14	2 (14.3)	11	1 (9.1)	0.692
6	25	4 (16.0)	18	2 (11.1)	0.648
7	13	2 (15.4)	11	1 (9.1)	0.642

B.3: Readmissions

Subgroup	PhP		NP		
	N	N of complications (%)	N	N complications (%)	p-value
1	39	5 (12.8)	33	6 (18.2)	0.529
2	47	6 (12.8)	46	8 (17.4)	0.533
3	48	5 (10.4)	24	4 (16.7)	0.450
4	25	5 (20.0)	19	4 (21.1)	0.932
5	14	3 (21.4)	11	2 (18.2)	0.840
6	25	3 (12.0)	18	4 (22.2)	0.370
7	13	3 (23.1)	11	2 (18.2)	0.769

PP population

B.4: Medical complications

Subgroup	PhP		NP		
	N	N of complications (%)	N	N complications (%)	p-value
1	28	10 (35.7)	33	15 (45.5)	0.441
2	35	12 (34.3)	46	18 (39.1)	0.655
3	31	10 (32.3)	24	11 (45.8)	0.304
4	21	9 (42.9)	19	12 (63.2)	0.199
5	10	4 (40.0)	11	7 (63.6)	0.279
6	19	6 (31.6)	18	10 (55.6)	0.141
7	10	4 (40.0)	11	7 (63.7)	0.279

B.5: Surgical complications

Subgroup	PhP		NP		
	N	N of complications (%)	N	N complications (%)	p-value
1	28	5 (17.9)	33	7 (21.2)	0.743
2	35	9 (25.7)	46	8 (17.4)	0.362
3	31	7 (22.6)	24	4 (16.7)	0.587
4	21	5 (23.8)	19	4 (21.1)	0.835
5	10	2 (20.0)	11	1 (9.1)	0.476
6	19	4 (21.1)	18	2 (11.1)	0.412
7	10	2 (20.0)	11	1 (9.1)	0.476

B.6: Readmissions

Subgroup	PhP		NP		
	N	N of complications (%)	N	N complications (%)	p-value
1	28	3 (10.7)	33	6 (18.2)	0.412
2	35	4 (11.4)	46	8 (17.4)	0.454
3	31	2 (6.5)	24	4 (16.7)	0.228
4	21	3 (14.3)	19	4 (21.1)	0.574
5	10	1 (10.0)	11	2 (18.2)	0.593
6	19	1 (5.3)	18	4 (22.2)	0.132
7	10	1 (10.0)	11	2 (18.2)	0.593

Abbreviations: *PhP* physical prehabilitation, *NP* non-prehabilitation

Description subgroups: 1: ≥2 comorbidities 2: ASA score ≥III 3: walking-aid 4: ≥2 comorbidities and ASA score ≥III 5: ≥2 comorbidities and walking-aid 6: ASA score ≥III and walking-aid 7: ≥2 comorbidities, walking-aid and ASA score