

Prehabilitation for older patients with colorectal cancer

Patient selection, targets and effectiveness



Heleen van der Hulst

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Patient selection, targets and effectiveness

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1

General introduction



GENERAL INTRODUCTION

In general, there is no doubt about the necessity of a strict training program, adequate nutrition, and social support to succeed in running a marathon [1]. Therefore, it feels reasonable that the similar pillars - physical training, nutritional supplements, and mental support - will help to resist the impact of surgery. This concept is also known as 'prehabilitation'.

Prehabilitation is a multidisciplinary approach that aims to enhance physical capacity prior to surgery and subsequently to improve postoperative outcome. Multimodal prehabilitation includes exercise, nutritional advice, psychosocial support, smoking cessation, and additional medical optimization. Prehabilitation has been studied for various types of surgery, such as spinal, cardiac, aortic, and cancer surgery.

In recent years, prehabilitation is increasingly executed in clinical practice, especially in the field of colorectal cancer (CRC). In the Netherlands, colon and rectal cancer have a serious health impact with 12.000-13.000 new cases per year. Surgery is still the primary treatment option. Because more than half (approximately 55%) of the newly diagnosed patients are 70 years and older [2], surgeons are frequently performing cancer resections in this older population.

Surgery is considered a major stressor and therefore it is not remarkable that older patients with CRC have an increased risk of mortality, complications and increased length of stay after surgery compared to younger patients [3-5]. However, age itself is not the sole determinant of these unfavorable outcomes. Other patients' characteristics are responsible for the increased risk of adverse postoperative outcomes. Identifying these risk factors is challenging, especially in a population that consists of individuals with extremely different health and functional life courses. Frailty - a decreased physiological state based on somatic, functional, cognitive, and psychosocial aspects - is therefore an interesting and relevant patient characteristic. Several studies have demonstrated that frailty is not only associated with mortality and morbidity after CRC surgery, but also with functional decline and lower quality of life [6-8]. The golden standard for identifying frailty includes a geriatric screening followed by a geriatric assessment (GA), that describes somatic, functional, cognitive, and psychosocial impairments.

The complication rate and the risk of functional decline in older patients is still high after CRC surgery despite several care developments in the past decade (such as minimally invasive surgery and enhanced recovery programs (ERAS)) [9]. Prehabilitation is therefore an interesting care improvement as it may reverse frailty characteristics with the aim of lowering the risk of adverse postoperative outcome.

Current evidence shows that prehabilitation in CRC surgery improves pre-and postoperative physical capacity. However, the effect on other postoperative adverse outcomes, for instance postoperative complications, is still not clear [10-14]. One randomized controlled trial (RCT) found a significant reduction of overall postoperative complications after prehabilitation [15] and another RCT found a reduction of severe and medical complications [16]. Other RCT's found no effect on postoperative complications [17-20]. Several challenges must be addressed before the effect of prehabilitation is accurately determined and an effective prehabilitation program is successfully implemented in clinical practice. It is essential to identify the patients with the highest risk of adverse postoperative outcomes, who are most likely to benefit from prehabilitation, and to determine the adverse postoperative outcomes which are most relevant to these patients.

THE AIM OF THIS THESIS

The aim of this thesis is to shape and concretize the concept of prehabilitation towards clinical practice for older patients with colorectal cancer undergoing elective surgery by

1. Identifying preoperative frailty
2. Identifying relevant postoperative outcomes
3. Investigating the effect of prehabilitation

THESIS OUTLINE

In **Part I** of the thesis, several frailty modalities and their potential to identify patients at risk of adverse outcome after CRC surgery were investigated. In **Chapter 2** we analyzed the interaction between comorbidity and age (the old, older and oldest patients) on postoperative complications in a cohort of 38.638 patients ≥ 70 years in the Netherlands between 2011-2019. In **Chapter 3**, we performed an external validation of the American College of Surgeons National Surgical Quality Improvement Program (ACS NSQIP) surgical risk calculator in patients ≥ 70 years undergoing elective non-metastatic CRC surgery in the Netherlands. In **Chapter 4**, we assessed the predictive value of selected geriatric parameters for postoperative outcomes in older patients with rectal cancer.

In **Part II**, relevant postoperative outcomes for older patients with CRC were identified. Time-trends and age-specific differences of surgical and non-surgical complications after CRC surgery were studied in older patients in the Netherlands between 2011-2019 (**Chapter 5**). The postoperative course of physical functioning and quality of life of patients with and without frailty is discussed in **Chapter 6**.

Part III shows the results of two retrospective cohort studies including older CRC patients who participated in a prehabilitation program in Reinier de Graaf Hospital in Delft. In **Chapter 7**, the cohort was stratified by prehabilitation and differences in surgical and non-surgical complications were assessed. In **Chapter 8**, the long-term survival and hospital admissions were studied between patients participating in the prehabilitation program and patients who received standard care.

In the last chapter (**Chapter 9**), the findings in this thesis will be discussed and future perspectives will be provided.

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Part I

Identifying preoperative frailty

2

Age-specific impact of comorbidity on postoperative outcomes in older patients with colorectal cancer

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ABSTRACT

Background

Age and comorbidity are considered the strongest predictors for adverse events after colorectal cancer (CRC) surgery. We aim to study the interaction of age and comorbidity and to gain better insight in options to improve care for the growing group of older patients.

Materials and Methods

We included all patients ≥ 70 years undergoing elective surgery for non-metastatic CRC between 2011-2019 in the Netherlands. Baseline characteristics, surgical and non-surgical complications, readmission and short-term mortality were collected from the Dutch Colorectal Audit (DCRA). The cohort was stratified by 70-79, 80-89 and ≥ 90 years. Comorbidity prevalence and postoperative outcomes were determined per age group. We analyzed the interaction (age-group*comorbidity) with all outcomes using multivariate logistic regression analysis. Age-stratified analysis was indicated if the interaction was significant.

Results

We included 25727 patients of 70-79 years, 12198 patients of 80-89 years, and 713 of ≥ 90 years. Non-surgical complications and mortality increased with older age, while surgical complications significantly decreased. However, the association of a Charlson Comorbidity Index (CCI) score ≥ 3 , cardiovascular and cardiopulmonary disease with adverse postoperative outcome decreased with older age. For example, the odds ratio (OR) of a CCI score ≥ 3 for non-surgical complications was 1.79 (Confidence Interval (CI) 95% 1.66-1.94), 1.50 (CI 95% 1.36-1.65) and 1.21 (CI 95% 0.80-1.81) for respectively 70-79, 80-89 and ≥ 90 years.

Conclusion

The rate of non-surgical complications after CRC surgery increases with older age, although older age itself become less associated with comorbidity. Maybe, risk assessment in the oldest patient should shift towards other predictors, such as frailty.

INTRODUCTION

Colorectal cancer (CRC) is a major health issue in the Netherlands. Surgical resection is the primary treatment option for patients with non-metastatic CRC. As the incidence of CRC is increasing with age and the life expectancy rises, the focus of treatment for CRC patients is shifting towards the older population. At this moment, CRC is diagnosed at an average age of 71 years [1]. Older patients are at increased risk for adverse outcome after surgery, such as postoperative complications, readmissions or mortality [2-6]. Several studies report comorbidity as the strongest predictor for postoperative morbidity and mortality [7, 8]. Although overall comorbidity increases with increasing age [9, 10], the prevalence of several comorbid conditions has different patterns across the older age spectrum. For example, the prevalence of dementia or cardiac disease increases progressively with age, the presence of 'other malignancies' increases more gradually, while diabetes peaks around the age of 80 years and declines in later life [10, 11]. As comorbidity prevalence varies at different ages, the predictive value of comorbidity for postoperative outcome may be different per age group as well. The oldest age group longevity may be associated with milder and less comorbid diseases. Other preoperative factors – such as disability, nutritional status or institutionalization (which are all elements of the geriatric assessment) – may therefore prevail in predicting in postoperative outcome. Thus, investigating the age-specific impact of comorbidity could initiate a more targeted counseling and treatment for the 'old, older and oldest' CRC patients. Therefore, we aimed to determine the prevalence of several comorbid diseases in older patients undergoing CRC surgery and to assess the effect of comorbid diseases on adverse postoperative outcomes in the old, older and oldest age groups.

METHODS

Study population and design

The included patients were selected from the Dutch Colorectal Audit (DCRA). The DCRA is a national obligatory audit (and therefore approved by the institutional review boards of the participating hospitals) that prospectively collects patients' demographics, tumor and treatment characteristics in combination with postoperative outcomes of all patients who received CRC surgery in the Netherlands. More detailed information about the DCRA has been extensively described elsewhere [12]. For the current study we included all patients aged 70 years and older who underwent elective surgery for non-metastatic CRC between 2011-2019. Patients who required stenting or decompressing stoma prior to primary resection or patients who underwent local excision were excluded. The same cohort was used in an earlier study [2].

Baseline variables

Age, sex, American Society Anesthesiology (ASA) score, tumor stage (TNM classification), surgical approach and neo-adjuvant therapy were all obtained through the DCRA. The DCRA registers the preoperative presence of fourteen comorbid diseases that are included in the Charlson comorbidity index (CCI) [13]; myocardial infarction, congestive heart failure (CHF), peripheral vascular disease, cerebrovascular accident (CVA) or transient ischemic attack (TIA), dementia, chronic pulmonary disease, connective tissue disease, peptic ulcer disease, liver disease (mild or moderate to severe), diabetes mellitus (DM) (uncomplicated or with end-organ damage), hemiplegia or paraplegia, moderate to severe chronic kidney disease (CKD), other (localized or metastatic) malignancy, including leukemia and lymphoma, and acquired immunodeficiency syndrome (AIDS) or human immunodeficiency virus (HIV). We calculated the CCI score without adjusting for age. We distinguished two extra comorbid conditions; cardiovascular disease and cardiopulmonary disease. In clinical practice, patients with these conditions are considered at high risk of adverse outcome during and after surgical treatment. Furthermore, cardiovascular and cardiopulmonary disease place an enormous burden on the health care system [14-16]. ‘Cardiovascular disease’ included myocardial infarction, CVA, TIA or peripheral vascular disease and ‘cardiopulmonary disease’ included chronic pulmonary disease, myocardial infarction or CHF.

Outcome measurements

The primary outcome was the occurrence of at least one postoperative complication, stratified by surgical and non-surgical complications. Surgical complications consisted of anastomotic leakage, abscess, bleeding, ileus, fascia dehiscence, bowel perforation, leakage from bladder or ureter, or surgical wound infection. Non-surgical complications were defined as pulmonary, cardiac, thromboembolic and neurologic events, infection (other than pulmonary or wound infection), or other. The secondary outcomes were readmission and mortality. The DCRA registers several postoperative outcomes including postoperative complications, length of stay, readmission, and mortality within 30-days (2011-2017) and 90-days (2018-2019) after surgery.

Statistical analysis

The study cohort was divided in three age groups; 70-79 years, 80-89 years and ≥ 90 years. Baseline characteristics (including patient-, tumor and treatment features) were compared between these three age groups. The prevalence of a CCI score ≥ 3 , cardiovascular disease, cardiopulmonary disease and the fourteen separate comorbid conditions were described. To assess whether the prevalence of several comorbid conditions varies across the older population, we used a five-year interval (70-74, 75-79, 80-84, 85-89, and ≥ 90 years) to graphically illustrate any prevalence changes. To evaluate adverse postoperative outcome, the rate of non-surgical complications, surgical complications, readmissions, and mortality were determined in the three (10-year interval) age groups. To assess any interaction between comorbidity and the (10-years interval) age groups for postoperative outcome, we performed logistic regres-

sion analyses. The comorbid condition and age group were included as independent variables and the postoperative outcome as dependent variable. If the comorbid condition was not associated in univariate analysis, no multivariate analysis – in which we adjusted for clinically relevant variables (age, sex, tumor stage, tumor localization, neo-adjuvant radiotherapy, and surgical approach) – was performed. Then, the interaction term “comorbid disease*age group” was added as independent variable. If the interaction term was significant ($p < 0.05$) in the multivariate analysis, it signified that the effect of the comorbid condition on the postoperative outcome was different between the age groups. Subsequently, age-stratified logistic regression was indicated. The age-stratified logistic regression analysis was univariate and only performed for surgical and non-surgical complications, due to the low number of events in the age group ≥ 90 year and low numbers of readmission and mortality. Based on the age-stratified logistic regression models, we were able to calculate a patient’s individual risk of having a postoperative complication. The risk is scored on a scale from 0 to 1 (0 indicates the impossibility and 1 indicates the certainty of having a complication) and was graphically visualized. We only visualized CCI ≥ 3 , cardiovascular and cardiopulmonary disease, as those were considered the most clinically relevant. Missing data was excluded from analysis when the missing percentage was extremely small ($< 0.1\%$). P-values below 0.05 will be considered as statistically significant and all statistical analysis will be performed with SPSS 25.0.

RESULTS

Study population

As described earlier [2], 39788 patients ≥ 70 years had elective surgery between 2011-2019 in the Netherlands for non-metastatic CRC. We excluded 1150 patients, as 862 patients received a local excision, 278 patients had stenting or a temporary decompressing stoma prior to elective CRC resection, and for ten patients the age was unknown. The current study eventually consisted of 38638 patients; 25727 patients were 70-79 years, 12198 patients were 80-89 years and 713 patients were ≥ 90 years.

Baseline characteristics

Figure 1 shows the differences in patient demographics, tumor and treatment characteristics between the three age groups. All differences were statistically significant. With increasing age, the proportion of female patients increased, as well as the proportion of patients with ASA score III+ and higher CCI score. Rectal carcinoma was less common with older age. The proportion of patients presenting with a higher tumor stage increased with age. Regarding treatment, the proportion of patients receiving open surgery increased in the older age groups. Neo-adjuvant therapy was less frequently initiated in the older patients diagnosed with rectal cancer. Although a significant part of information about neo-adjuvant chemotherapy was missing, chemotherapy was less common in the oldest patients.

Comorbidity prevalence

The prevalence of several comorbid conditions are shown in appendix Table 1; 6480 (16.8%) patients had a CCI score ≥ 3 , 9512 (24.6%) had cardiovascular disease, and 9001 (23.3%) patients had cardiopulmonary disease. Myocardial infarction had occurred in 3311 patients (8.6%). The prevalence of other clinical relevant comorbidities was: 7569 (19.6%) patients had diabetes mellitus and 1854 (4.8%) patient had chronic kidney disease.

Figure 1 shows the prevalence of frequently occurring comorbid diseases over the five-year interval age-spectrum. The prevalence of other malignancy, CHF, and chronic kidney disease continuously increased (respectively 15.5 to 19.1%, 3.2 to 9.0% and 3.1 to 8.8% for patients aged 70-75 years compared to ≥ 90 years). Diabetes peaked in the age group 80-84 years (21.4%) and then sharply declined to 12.8% in patients ≥ 90 years. The prevalence of cardiovascular disease (30%), cardiopulmonary disease (28.1%), CCI ≥ 3 (20.6%), CVA/TIA (16.1%), and myocardial infarction (10.5%) reached its highest point in patients of 85-89 years.

Table 1. Baseline characteristics stratified by age group

	Total n=38638	70-79 years n=25727	80-89 years n= 12198	≥ 90 years n= 713
Median Age (IQR)	76 (73-81)	74 (72-76)	83 (81-85)	91 (90-92)
Sex				
Male	20895 (54.1)	14680 (57.1)	5912 (48.5)	303 (42.5)
Female	17740 (45.9)	11045 (42.9)	6285 (51.5)	410 (57.5)
Median Body Mass Index (IQR)	25.8 (23.4-28.7)	26.1 (23.7-29.1)	25.3 (23.0-28.0)	24.4 (22.2-26.7)
ASA score				
ASA I/II	25852 (66.9)	18691 (72.7)	6805 (55.8)	356 (50.0)
ASA III+	12764 (33.1)	7022 (27.3)	5386 (44.2)	356 (50.0)
Charlson comorbidity index (CCI)				
0	15184 (39.3)	10913 (42.4)	4026 (33.0)	245 (34.4)
1	9801 (25.4)	6404 (24.9)	3191 (26.2)	206 (28.9)
2	7173 (18.6)	4512 (17.5)	2536 (20.8)	125 (17.5)
≥ 3	6480 (16.8)	3898 (15.2)	2445 (20.0)	137 (19.2)
Tumor localization				
Colon	28577 (74.0)	18521 (72.0)	9430 (77.3)	626 (87.8)
Rectum	10053 (26.0)	7200 (28.0)	2766 (22.7)	87 (12.2)
TNM stage				
Stage I	11412 (29.5)	8306 (32.3)	2977 (24.4)	129 (18.1)
Stage II	14503 (37.5)	8881 (34.5)	5257 (43.1)	365 (51.2)
Stage III	12077 (31.3)	8081 (31.4)	3790 (31.1)	206 (28.9)
Unknown	646 (1.7)	459 (1.8)	174 (1.4)	13 (1.8)

Table 1. Baseline characteristics stratified by age group (continued)

	Total n=38638	70-79 years n=25727	80-89 years n= 12198	≥90 years n= 713
Surgical approach				
Open	9276 (24.0)	5625 (21.9)	3388 (27.8)	263 (36.9)
Laparoscopic	27917 (72.3)	19088 (74.2)	8396 (68.8)	433 (60.7)
Robot assisted	688 (1.8)	480 (1.9)	201 (1.6)	7 (1.0)
Other*	361 (0.9)	270 (1.0)	89 (0.7)	2 (0.3)
Unknown	396 (1.0)	264 (1.0)	124 (1.0)	8 (1.1)
Neoadjuvant radiotherapy^a				
None	3902 (38.8)	2682 (37.3)	1163 (42.0)	57 (65.5)
Not specified	5023 (50.0)	3695 (51.3)	1306 (47.2)	22 (25.3)
5x5 Gy	564 (5.6)	368 (5.1)	188 (6.8)	8 (9.2)
Chemoradiation	555 (5.5)	448 (6.2)	107 (3.9)	0
Neoadjuvant chemotherapy^a				
None	5859 (58.3)	4122 (57.3)	1690 (61.1)	47 (54.0)
Yes	1254 (12.5)	1073 (14.9)	181 (6.5)	0
Unknown	2940 (29.2)	2005 (27.8)	895 (32.4)	40 (46.0)

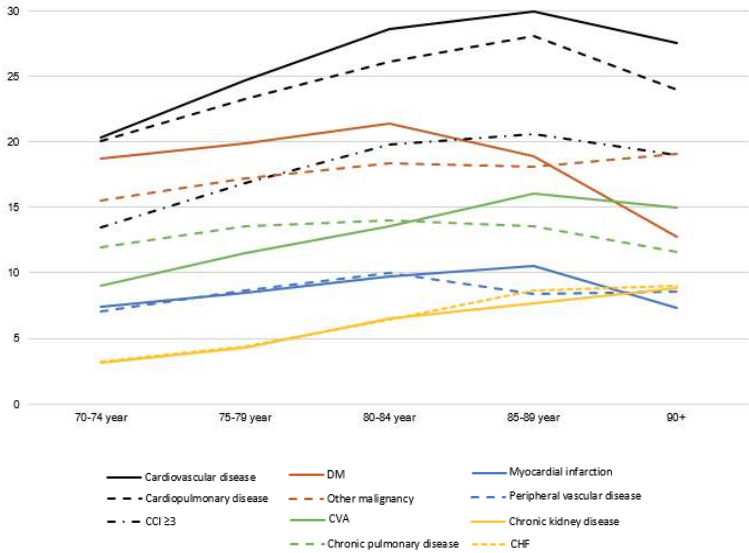
Abbreviations: *IQR* interquartile range, *ASA* American Society of Anesthesiology, *TNM* TNM Classification of Malignant Tumors

Additional missing data: sex (3 patients), *ASA* score (22 patients), localization (8 patients), , radiotherapy (9)

* other: Transanal and transabdominal endoscopic TME (TaTME of TAMIS TME)

^a Exclusively the patients with rectal cancer (n=10053)

Figure 1. Prevalence of several comorbid diseases within the older age spectrum



Abbreviations: *CCI* Charlson Comorbidity Index, *DM* Diabetes Mellitus, *CVA* cerebrovascular accident, *CHF* congestive heart failure

Table 2. Postoperative outcome per age group

	Total n=38638 (%)	70-79 years n=25727	80-89 years n= 12198	≥90 years n= 713
Non-surgical complications	8141 (21.1)	4904 (19.1)	3036 (24.9)	201 (28.2)*
Surgical complications	7164 (18.5)	4705 (18.3)	2360 (19.3)	99 (13.9)
Readmissions	3099 (8.0)	2099 (8.2)	964 (7.9)	36 (5.0)
Short-term mortality	1132 (2.9)	505 (2.0)	577 (4.7)	50 (7.0)

*All differences were significant

Interaction between comorbidity and age

All comorbidities – except for peptic ulcer disease, connective tissue disease and dementia – were significantly associated with surgical complications, non-surgical complications, readmissions, and short-term mortality in multivariate analysis (Appendix Table 2 and 3).

We found a significant interaction between the age group and CCI score ≥ 3 , cardiovascular disease, cardiopulmonary disease, CVA/TIA, and myocardial infarction for non-surgical and surgical complications. Peripheral vascular disease had a significant interaction with age for surgical complications as well. Only cardiovascular disease interacted with age for the risk of readmission. Cardiovascular disease, diabetes mellitus, CVA/TIA, myocardial infarction, peripheral vascular disease, and CHF had a significant interaction with age for the risk of mortality (appendix Table 2 and 3).

Based on the results of the age-stratified analysis (appendix Table 4), the individual risk for postoperative complications with or without comorbidity per age group is visualized in Figure 3 (non-surgical complications) and 4 (surgical complications).

Figure 3 shows that in age group 70-79 years, non-surgical complications were more likely to occur in patients with a CCI score ≥ 3 , cardiovascular disease, or cardiopulmonary disease compared to their counterparts without these comorbidities. With increasing age, the risk difference between patients with and without comorbidity, gradually decreases. In the oldest age group, patients with comorbidity had similar risk of non-surgical complications compared to patients without comorbidity. For CCI score ≥ 3 , this corresponds to an OR of 1.79 (CI 95% 1.66-1.94) for patients 70-79 years, 1.50 (CI 95% 1.36-1.65) for patients 80-89 years and 1.21 (CI 95% 0.81-1.81) for patients ≥ 90 years. For cardiovascular disease and cardiopulmonary disease, a decreasing OR with older age was found as well; respectively an OR of 1.57 (CI 95% 1.47-1.69) for patients 70-79 years, 1.36 (CI 95% 1.24-1.48) for patients 80-89 years, and 0.88 (CI 95% 0.61-1.28) for patients ≥ 90 years and an OR of 1.60 (CI 95% 1.49-1.72) for patients 70-79 years, 1.44 (CI 95% 1.32-1.58) for patients 80-89 years, and 0.92 (CI 95% 0.63-1.28) for patients ≥ 90 years.

Figure 4 shows the individual risk of surgical complications. In age group 70-79 years, surgical complications were more likely to occur in patients with CCI ≥ 3 , cardiovascular disease, and cardiopulmonary disease. Again, with increasing age, the risk difference between patients with and without comorbidity disappears. For CCI score ≥ 3 , this corresponds to OR of 1.50 (CI 95% 1.38-1.62) for patients 70-79 years, 1.22 (CI 95% 1.10-1.36) for patients 80-89 years, and 1.08 (CI 95% 0.63-1.82) for patients ≥ 90 years. The OR of surgical complications for cardiovascular disease and cardiopulmonary disease was respectively 1.42 (CI 95% 1.32-1.52) for patients 70-79 years, 1.08 (CI 95% 0.98-1.19) for patients 80-89 years, and 1.10 (CI 95% 0.69-1.76) for patients ≥ 90 years and an OR of 1.44 (CI 95% 1.38-1.55) for patients 70-79 years, 1.17 (CI 95% 1.06-1.29) for patients 80-89 years, and 1.08 (CI 95% 0.66-1.77) for patients ≥ 90 years.

Figure 3. Risk of non-surgical complication per age group

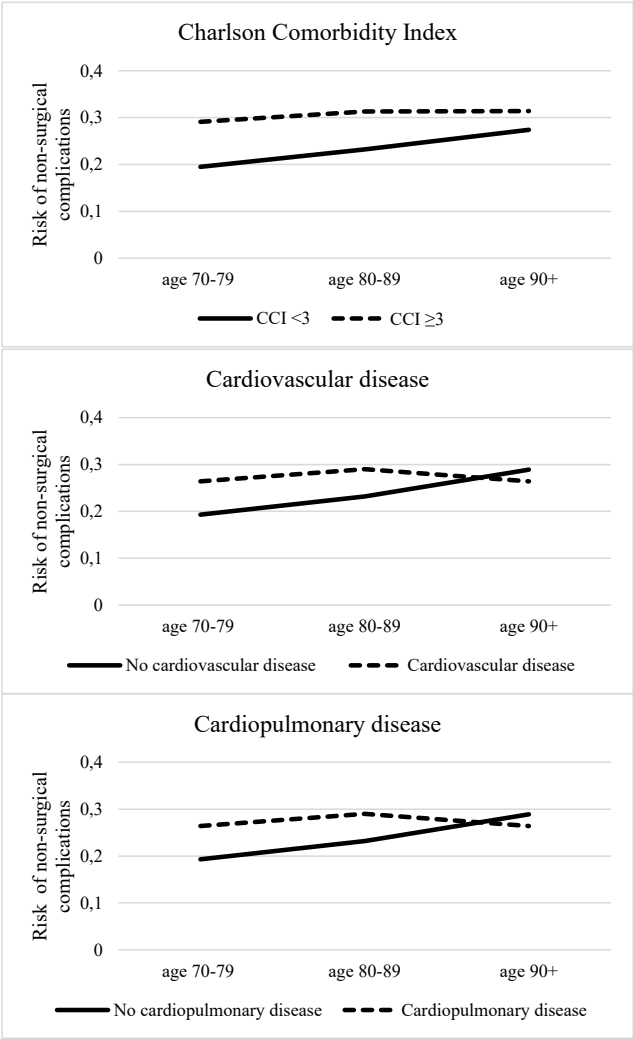
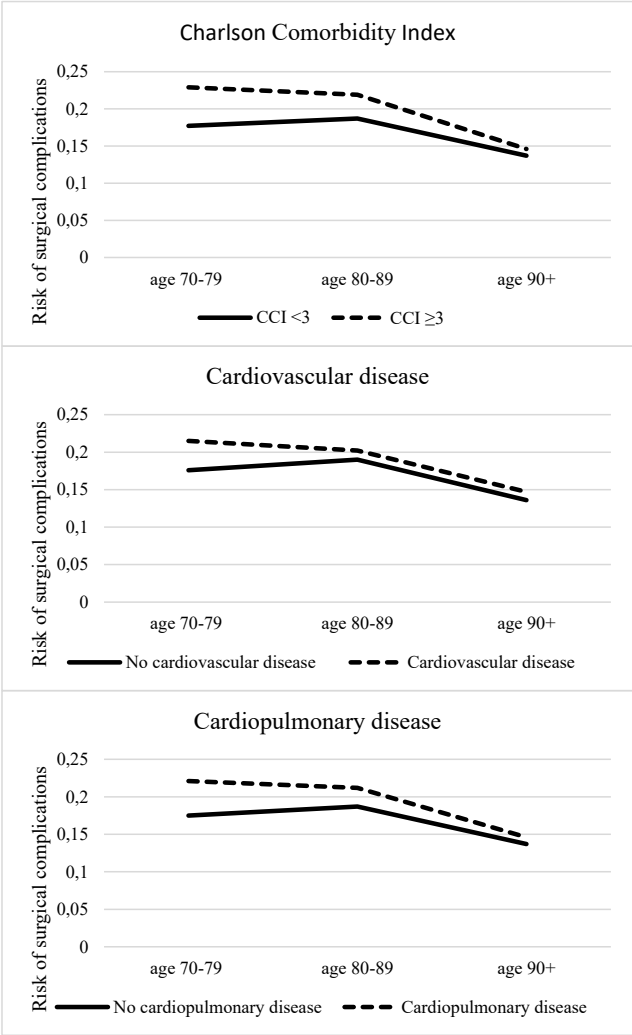


Figure 4. Risk of surgical complication per age group



DISCUSSION

This nationwide population-based study showed that patient-, tumor- and treatment characteristics are different between the old, older, and oldest patients who had elective surgery for non-metastatic CRC. Mortality and the total number of non-surgical complications increased with older age, while the rate of surgical complications and readmission decreased. The prevalence of several comorbid conditions varied within the older population. Although most common comorbid diseases were associated with adverse postoperative outcomes, the strength of the association of CCI score ≥ 3 , cardiovascular disease, and cardiopulmonary disease with surgical and non-surgical complications reduced with increasing age.

The current study is the first in describing the prevalence trend of comorbid diseases in older CRC patients who were selected for elective surgery. Studies performed in a somewhat different populations showed comparable results. Leersum et al [11] included patients diagnosed with CRC at adult age with or without surgical treatment between 1995-2010 and showed a similar change in other malignancy, diabetes, peripheral vascular disease, CVA and pulmonary disease across the older age spectrum. Piccirillo et al [10] included patients diagnosed with cancer (10% CRC) between 1998-2003 at adult age and demonstrated the same pattern in other malignancy and diabetes.

Several studies found an association of comorbid diseases and adverse outcomes after CRC surgery [7]. However, none of these studies tested for an age-specific impact of comorbidity. Two studies – respectively in patients with SARS-CoV-2 [17] and patients selected for radical prostatectomy [18] – supported the age-specific impact of comorbidity by demonstrating a reduced association of comorbidity with adverse outcomes in the oldest patients.

The attenuated association of comorbidity with increasing age might be explained by a relatively fitter health status of the oldest patients. The longevity of these patients may be the result of milder comorbid conditions [10], they may have lived a healthier lifestyle or have more favorable genetics that protects against health problems [19]. On the other hand, we need to be aware that selection bias occurred in this patient population. The study cohort consisted of patients who were elected for surgical treatment. As the proportion of patients receiving non-surgical treatment increases with age [20], a ‘healthier’ selection is more likely to occur in the oldest age category [20, 21]. Furthermore, advanced age may serve as confounder for the increased proportion of female patients (Table 1) [22]. Female patients with CRC present less frequently with comorbidities and female patients with comorbidities are more likely to receive non-surgical treatment than male patients with the same comorbid diseases [23].

Despite the attenuated association of comorbidity with older age on postoperative outcome, still, the total number of non-surgical complications increased, while the rate of surgical complications decreased (Table 2). Surgical complications, such as anastomotic leakage and surgical side infections, are associated with male sex, rectal carcinoma, obesity (high BMI), and comorbid diseases [24-26]. All of these characteristics occurred less frequently in the older age categories (Table 1 and 2). On the contrary, the number of non-surgical complications and mortality increased. This indicates that – despite the reduced association of comorbidity – the oldest age group is still at higher risk of mortality and non-surgical complications than their younger counterparts. Another important factor associated with complications in older patients after CRC surgery, that has not been addressed yet, is frailty [8, 27, 28]. Frailty is a reduced physiological state based on several domains, e.g. the somatic, functional, cognitive and psychosocial state [29] that increases with older age [30]. As frailty is thought to

particularly affect non-surgical complications [31], it is possible that frailty is stronger related to adverse postoperative outcome than comorbidity in the oldest age groups.

In clinical practice, identifying older patients at risk of complications is challenging due to the populations' heterogeneity. Our findings support individualized preoperative care for older patients, aiming to improve postoperative outcomes. First, this study emphasized that several comorbid conditions are associated with adverse postoperative outcomes. Counseling patients about the risks and recovery process and consultation of organ specific medical specialists (e.g. cardiologist, pulmonologist etc.) is therefore already part of standard care. Second, our findings show that some specific comorbid diseases (e.g. CCI ≥ 3 , cardiopulmonary disease and cardiovascular disease) have a less predictive value in risk assessment for the oldest patients (≥ 90 years). This suggests that preoperative optimization in the oldest CRC patients should not focus on comorbidity particularly. As stated before, maybe other predictors – such as frailty – are of more value in risk assessment in the oldest patients. To improve non-surgical complications, prehabilitation – enhancing preoperative functional capacity – could be advantageous as prehabilitation may especially affect patients with frailty and several studies have described that prehabilitation particularly lowers non-surgical complications [31, 32].

The main limitation of this study is the potential selection bias of patients fit for surgery, as already addressed in the discussion. Furthermore, the three (10-year interval) age groups consisted of an unequal number of patients. However, the oldest patient group still included more than 700 patients. It would have been helpful to have information on frailty to define the age-specific impact of frailty as well. Including frailty characteristics in national audits could be considered. Furthermore, other long-term outcomes – such as remaining mobility and remaining cognitive function – could be more relevant than postoperative complications, readmission, and mortality. Nevertheless, the current study is the first to describe an age-specific impact of comorbidity in patients ≥ 70 that undergo elective CRC resection. We used 'true' data; a large and complete nationwide population-based study cohort that described the results of eight years of elective surgery in the Netherlands. Additionally, the DCRA is a validated audit and over the 95% of the collected data is complete [12].

CONCLUSIONS

This nationwide population-based study showed that non-surgical complications and mortality increase with increasing age while surgical complications decrease. Baseline characteristics and comorbidity prevalence are different between the old, older, and oldest patients receiving elective surgery for non-metastatic. In the oldest age group, the strength of the association of CCI ≥ 3 , cardiopulmonary, and cardiovascular disease with surgical and non-surgical complications decreased. Our findings confirm that individualized preoperative care in the older population receiving elective CRC surgery is needed and preoperative risk assessment should shift towards frailty.

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APPENDIX

Appendix table 1. Prevalence per comorbid disease

	Total n=38638 (%)
Type of comorbidity	
CCI ≥3	6480 (16.8)
Cardiovascular disease	9512 (24.6)
Cardiopulmonary disease	9001 (23.3)
Diabetes mellitus*	7569 (19.6)
Other malignancy ^a	6564 (17.0)
Chronic pulmonary disease	5056 (13.1)
Cerebrovascular accident	4482 (11.6)
Myocardial infarction	3311 (8.6)
Peripheral vascular disease	3254 (8.4)
Congestive heart failure	1909 (4.9)
Chronic kidney disease	1854 (4.8)
Peptic ulcer disease	1301 (3.4)
Connective tissue disease	1311 (3.4)
Liver disease ^b	917 (2.4)
Dementia	693 (1.8)
Hemi or paraplegia	66 (0.2)
HIV	14 (0.0)

*with and without chronic complications

^a localized or metastatic

^b mild, moderate or severe

Appendix Table 2. Multivariate regression analysis and interaction between comorbidity and non-surgical and surgical complications

Comorbidity type	Non-surgical complications			Surgical complications		
	n events within comorbid- ity (%)	OR (95% CI)	Interaction* age group	n within comorbidity events (%)	OR (95% CI)	Interaction* age group
CCI ≥ 3	1884 (29.1)	1.61 (1.51-1.71)	0.004	1486 (22.9)	1.35 (1.27-1.45)	0.009
Diabetes mellitus	1847 (24.4)	1.26 (1.18-1.34)	0.312	1554 (20.5)	1.16 (1.09-1.24)	0.814
Other malignancy	1555 (23.7)	1.14 (1.07-1.22)	0.285	1352 (20.6)	1.15 (1.08-1.23)	0.511
Chronic pulmonary disease	1461 (28.9)	1.63 (1.52-1.74)	0.123	1172 (23.2)	1.38 (1.29-1.49)	0.115
Cerebrovascular accident	1203 (26.8)	1.39 (1.29-1.49)	0.020	938 (20.9)	1.18 (1.09-1.28)	0.048
Myocardial infarction	875 (26.4)	1.27 (1.17-1.39)	0.029	734 (22.2)	1.19 (1.09-1.30)	0.004
Peripheral vascular disease	914 (28.1)	1.44 (1.32-1.56)	0.109	716 (22.0)	1.21 (1.10-1.32)	0.033
Congestive heart failure	528 (27.7)	1.44 (1.29-1.60)	0.135	400 (21.0)	1.20 (1.07-1.35)	0.616
Chronic kidney disease	568 (30.6)	1.60 (1.45-1.77)	0.185	411 (22.2)	1.24 (1.10-1.40)	0.647
Liver disease	276 (30.1)	1.63 (1.41-1.89)	1.000	217 (23.7)	1.43 (1.22-1.67)	0.895
Cardiopulmonary disease	2431 (27.0)	1.50 (1.42-1.59)	0.005	1986 (22.1)	1.31 (1.24-1.39)	0.003
Cardiovascular disease	2515 (26.4)	1.41 (1.33-1.49)	0.001	2046 (21.5)	1.23 (1.61-1.31)	<0.001

Appendix Table 3. Multivariate regression analysis and interaction between comorbidity and readmission and short-term mortality

Comorbidity type	Readmissions			Short-term mortality		
	n events within comorbidity (%)	OR (95% CI)	Interaction* age group	n events within comorbidity (%)	OR (95% CI)	Interaction* age group
CCI ≥3	648 (10.0)	1.38 (1.26-1.52)	0.966	364 (5.6)	2.18 (1.91-2.49)	0.069
Diabetes mellitus	679 (9.0)	1.18 (1.08-1.29)	0.418	298 (3.9)	1.45 (1.27-1.67)	0.044
Other malignancy	580 (8.8)	1.15 (1.04-1.27)	0.895	243 (3.7)	1.24 (1.07-1.44)	0.807
Chronic pulmonary disease	451 (8.9)	1.17 (1.06-1.31)	0.090	236 (4.7)	1.71 (1.48-1.99)	0.621
Cerebrovascular accident	423 (9.4)	1.26 (1.12-1.40)	0.083	215 (4.8)	1.66 (1.42-1.94)	0.001
Myocardial infarction	310 (9.4)	1.16 (1.02-1.32)	0.055	186 (5.6)	1.89 (1.60-2.23)	0.009
Peripheral vascular disease	302 (9.3)	1.19 (1.04-1.35)	0.437	176 (5.4)	1.88 (1.59-2.23)	0.029
Congestive heart failure	186 (9.7)	1.30 (1.10-1.53)	0.923	129 (6.8)	2.28 (1.87-2.77)	0.041
Chronic kidney disease	200 (10.8)	1.44 (1.23-1.69)	0.777	118 (6.4)	2.03 (1.66-2.49)	0.141
Liver disease	91 (9.9)	1.37 (1.10-1.72)	0.857	46 (5.0)	1.68 (1.22-2.30)	0.304
Cardiopulmonary disease	825 (9.2)	1.24 (1.14-1.35)	0.105	443 (4.9)	1.96 (1.73-2.23)	0.116
Cardiovascular disease	905 (9.5)	1.29 (1.19-1.40)	0.028	458 (4.8)	1.92 (1.69-2.17)	<0.001

Appendix Table 4. Age-stratified regression analysis and interaction between comorbidity and non-surgical and surgical complications

Comorbidity type	70-79 years		80-89 years		90 -100 years	
	n events (%)	OR (95% CI)	n events (%)	OR (95% CI)	n events (%)	OR (95% CI)
Non-surgical complications						
CCI ≥ 3	1075 (27.6)	1.79 (1.66-1.94)	765 (31.3)	1.50 (1.36-1.65)	43 (31.4)	1.21 (0.81-1.81)
Cerebrovascular accident	661 (25.3)	1.50 (1.37-1.65)	514 (29.2)	1.30 (1.16-1.45)	28 (26.2)	0.89 (0.56-1.41)
Myocardial infarction	516 (25.3)	1.49 (1.34-1.65)	345 (28.3)	1.22 (1.07-1.39)	14 (26.9)	0.93 (0.50-1.76)
Cardiopulmonary disease	1403 (25.2)	1.60 (1.49-1.72)	980 (30.1)	1.44 (1.32-1.58)	46 (26.9)	0.92 (0.63-1.35)
Cardiovascular disease	1435 (24.9)	1.57 (1.47-1.69)	1028 (29.0)	1.36 (1.24-1.48)	52 (26.4)	0.88 (0.61-1.28)
Surgical complications						
CCI ≥ 3	929 (23.8)	1.50 (1.38-1.62)	536 (21.9)	1.22 (1.10-1.36)	20 (14.6)	1.08 (0.63-1.82)
Cerebrovascular accident	575 (22.0)	1.29 (1.17-1.43)	347 (19.7)	1.03 (0.91-1.17)	16 (15.0)	1.11 (0.62-1.98)
Myocardial infarction	483 (23.7)	1.43 (1.28-1.59)	244 (20.0)	1.05 (0.91-1.22)	7 (13.5)	0.96 (0.42-2.20)
Peripheral vascular disease	465 (22.9)	1.36 (1.22-1.52)	240 (20.7)	1.10 (0.94-1.27)	11 (18.0)	1.41 (0.71-2.81)
Cardiopulmonary disease	1271 (22.8)	1.44 (1.38-1.55)	689 (21.2)	1.17 (1.06-1.29)	25 (14.9)	1.08 (0.66-1.77)
Cardiovascular disease	1303 (22.6)	1.42 (1.32-1.52)	714 (20.2)	1.08 (0.98-1.19)	29 (14.7)	1.10 (0.69-1.76)
Readmissions						
Cardiovascular disease	598 (10.4)	1.42 (1.29-1.57)	295 (8.3)	1.09 (0.94-1.25)	12 (6.1)	1.33 (0.65-2.71)
Mortality						
Diabetes mellitus	151 (3.0)	1.81 (1.49-2.19)	139 (5.5)	1.24 (1.02-1.50)	8 (8.8)	1.33 (0.60-2.93)
Cerebrovascular accident	101 (3.9)	2.26 (1.81-2.82)	111 (6.3)	1.44 (1.17-1.79)	3 (2.8)	0.34 (0.11-1.12)
Myocardial infarction	95 (4.7)	2.77 (2.21-3.48)	87 (7.1)	1.65 (1.30-2.09)	4 (7.7)	1.11 (0.39-3.23)
Peripheral vascular disease	85 (4.2)	2.42 (1.91-3.07)	90 (7.7)	1.82 (1.44-2.30)	1 (1.6)	0.21 (0.03-1.51)
Congestive heart failure	52 (5.3)	3.00 (2.24-4.03)	69 (8.0)	1.85 (1.42-2.40)	8 (12.5)	2.07 (0.92-4.61)
Cardiovascular disease	218 (3.8)	2.69 (2.25-3.21)	232 (6.6)	1.69 (1.42-2.00)	8 (4.1)	0.48 (0.22-1.04)

3

Validation of the ACS NSQIP surgical risk calculator in older patients with colorectal cancer undergoing elective surgery

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ABSTRACT

Background

For clinical decision making it is important to identify patients at risk for adverse outcomes after colorectal cancer (CRC) surgery, especially in the older population. Because the American College of Surgeons National Surgical Quality Improvement Program (ACS NSQIP) surgical risk calculator is potentially useful in clinical practice, we performed an external validation in a Dutch multicenter cohort of patients ≥ 70 years undergoing elective non-metastatic CRC surgery.

Methods

We compared the ACS NSQIP calculator mean predicted risk to the overall observed rate of anastomotic leakage, return to operation room, pneumonia, discharge not to home, and readmission in our cohort using a one-sample Z-test. Calibration plots and receiver operating characteristic (ROC) curves were used to determine the calculator's performance.

Results

Six hundred eighty-two patients were included. Median age was 76.2 years. The ACS NSQIP calculator accurately predicted the overall readmission rate (predicted: 8.6% vs. observed: 7.8%, $p=0.456$), overestimated the rate of discharge not to home (predicted: 11.2% vs. observed: 7.0% $p=0.005$) and underestimated the observed rate of all other outcomes. The calibration plots showed poor calibration for all outcomes. The ROC-curve showed an area under the curve (AUC) of 0.75 (95% confidence interval [CI] 0.67-0.83) for pneumonia and 0.70 (0.62-0.78) for discharge not to home. The AUC for all other outcomes was poor.

Conclusions

The ACS NSQIP surgical risk calculator had a poor individual risk prediction (calibration) for all outcomes and only a fair discriminative ability (discrimination) to predict pneumonia and discharge not to home. The calculator might be considered to identify patients at high risk of pneumonia and discharge not to home to initiate additional preoperative interventions.

INTRODUCTION

Primary treatment for patients with non-metastatic colorectal cancer (CRC) is surgical resection [1]. Surgery is a major stressor, especially for the older population. Populations of older patients are often highly heterogeneous and consist of a large proportion of patients with frailty (a clinical syndrome characterized by a decreased physiological capacity contributing to an increased risk of adverse health outcomes). The older population is at increased risk of mortality [2-4], postoperative complications [5-8] and readmissions after CRC surgery [9, 10]. As a consequence, older patients may experience a persistent functional decline up to one year after surgery that can lead to loss of independence [11, 12]. Therefore, it is important to identify patients who are at the highest risk of adverse outcomes, enabling better shared decision making and to consider additional preoperative care, like prehabilitation [13-15].

Easy-to-use models to predict outcome after surgery in the older CRC population are scarce and the majority of these prediction models have moderate to high bias or lack external validation [16]. However, the American College of Surgeons National Surgical Quality Improvement Program (ACS NSQIP) surgical risk calculator (<http://riskcalculator.facs.org>) may potentially be used in daily practice [16], as this online surgical risk calculator originated from a large ACS NSQIP dataset that consisted of 1,414,006 patients (mean age 61.8 years) who received surgery (of all surgical specialties) between 2009-2012 in 393 hospitals in the United States of America (USA) [17] [18]. It predicts the risk for fifteen different surgical outcomes based on 21 variables: 20 preoperative variables and the surgical procedure. The ACS NSQIP surgical risk calculator has not been validated yet in older patients receiving elective CRC surgery.

Therefore, we externally validated the ACS NSQIP surgical risk calculator in a cohort of older patients (≥ 70 years) who underwent elective CRC surgery in the Netherlands.

METHODS

Study population and design

The study population consisted of all consecutive patients ≥ 70 years who received CRC surgery between January 2014 and December 2017 in three Dutch hospitals; Diaconessenhuis in Utrecht, Reinier de Graaf Hospital in Delft and Westfriesgasthuis in Hoorn. Patients were identified through a nationwide obligatory prospective data collection: the Dutch Colorectal Audit (DCRA) [19]. The DCRA contains patients' demographics, tumor and treatment characteristics, and postoperative outcomes of all consecutive CRC patients who underwent surgery in the Netherlands. Each participating hospital is required to provide prospectively collected data. Patients were excluded in cases of metastatic disease, non-elective surgery

or local excision as surgical procedure. The study was approved by the institutional review boards of the participating hospitals.

ACS NSQIP variables

The ACS NSQIP surgical risk calculator consists of 21 variables. The variables age, sex, emergency case, American Society of Anesthesiologists (ASA) class, disseminated cancer, diabetes, history of severe chronic obstructive pulmonary disease (COPD), dialysis, height and weight (for body mass index [BMI] calculation), and type of surgical procedure were collected from the DCRA. The variables functional status, steroid use for chronic condition, ascites within 30 days prior to surgery, hypertension requiring medication, congestive heart failure within 30 days prior to surgery, dyspnea, current smoker within one year, and acute renal failure were collected from the medical records. We did not collect information about systemic sepsis within 48 hours prior to surgery and ventilator dependency, as these symptoms do not occur in case of elective surgery. Discharge not to home (discharge to nursing home or geriatric rehabilitation center) was collected from the medical record.

The risk factors were entered for each patient in the ACS NSQIP online Surgical Risk Calculator (<http://riskcalculator.facs.org>), by two researchers (ES and RdJ). The surgical procedures were remodeled into a Current Procedural Terminology (CPT) code used in the calculator (Appendix Table 1). In the ACS NSQIP Surgical Risk Calculator, age is a categorical variable, divided into ‘under 65 years’, ‘65-74 years’, ‘75-84 years’, and ‘85 years and older’. Our cohort consisted of patients ≥ 70 years, so patients aged 70-74 were categorized as ‘65-74 years’ in the online calculator. In the ACS NSQIP Surgical Risk Calculator functional status was classified as ‘independent’, ‘partially dependent’, and ‘totally dependent’. The definition of each category was provided, but without specific cutoff points for objective evaluation. To determine functional status in our cohort, we used the Katz Activities of Daily Living (ADL) scale [20]. We used five items to evaluate the daily activities; bathing, dressing, toileting, transferring, and feeding. When a patient needed supervision or personal assistance during the activity, one point was given. In case of a Katz-ADL score of 0, patients were categorized as ‘independent’, a Katz-ADL of 1-3, patients were categorized as ‘partially dependent’, and a Katz-ADL of 4-5, as ‘totally dependent’. We did not use the item ‘incontinence’ of the Katz-ADL scale (modified Katz-1 [21]) as ‘incontinence’ may inaccurately define patients as ‘dependent’. Incontinence has a high prevalence in the older population, and many older patients who experience incontinence are still able to take care of themselves. The modified Katz-1 is a validated tool [21-24] and had more agreement with the given definition of functional dependency of the ACS NSQIP calculator than the original Katz-ADL. When the Katz ADL was not scored and no deficits were registered in the medical record, functional status was entered in the calculator as ‘independent’. All other variables in our dataset fulfilled the provided definitions in the ACS NSQIP Surgical Risk Calculator. Information about race/ethnicity was not collected as this information was not required for the ACS NSQIP calculator. We did not use the Surgeon Adjustment of Risks. The preoperative data was not entered by the surgeon, meaning that we

were not able to determine whether the surgeon decided that the risk should be higher than the estimated risk.

Outcomes

The ACS NSQIP Surgical Risk Calculator calculates the risk for fifteen outcomes in the first 30 days after surgery: serious complication, any complication, pneumonia, cardiac complication, surgical site infection, urinary tract infection, venous thromboembolism, renal failure, colectomy ileus, colectomy anastomotic leak, readmission, return to operation room (OR), death, discharge to nursing or rehab facility, and sepsis. The following outcomes in the first 30 days after surgery were available in DCRA database: any complications, pneumonia, anastomotic leakage, readmission, return to the OR, and 30-day mortality. We were unable to validate for 30-day mortality, because of the low rate of deaths in the first 30 days after surgery in our cohort (eight events) and for 'any complications' because of the non-agreement of the definition of any complication in the DCRA and the more extensive definition of any complication in the ACS NSQIP Surgical Risk Calculator. Due to the fact that the risk for anastomotic leakage was not predicted by the ACS NSQIP calculator in case of a proctectomy (no anastomosis is created), we needed to exclude the patients undergoing a proctectomy for the validation of anastomotic leakage. To validate for discharge not to home, patients from Reinier de Graaf Hospital were excluded, because this hospital initiated a program in 2014 that enabled all patients to recover in a rehabilitation center after discharge. In addition, we excluded patients who already lived in a nursing home prior to surgery. Finally, we externally validated the ACS NSQIP online surgical risk calculator for anastomotic leakage, return to OR, pneumonia, discharge not to home, and readmission.

Statistical analysis

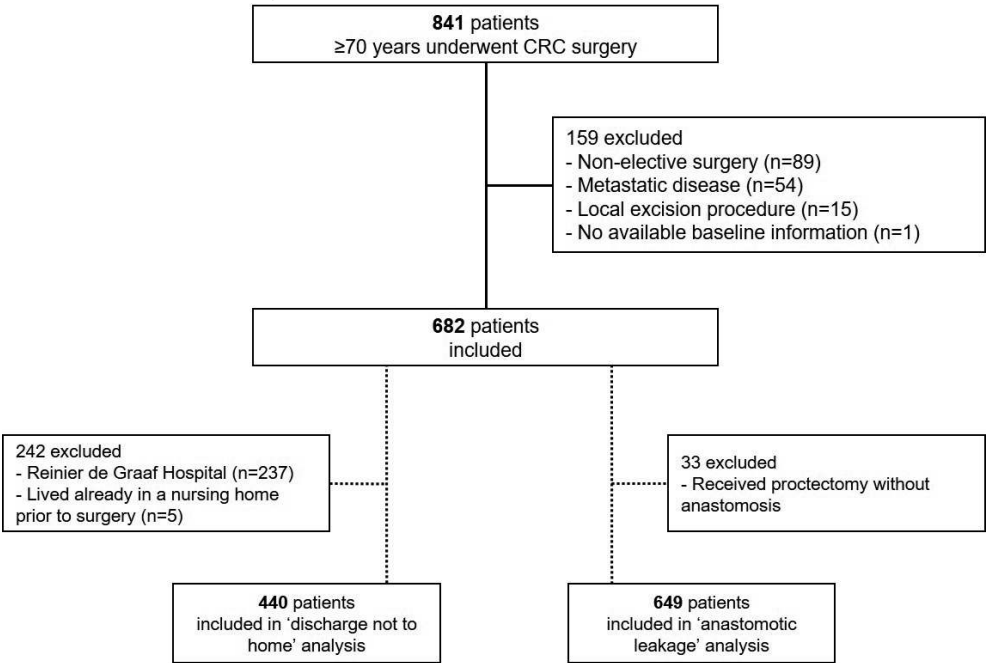
We expressed continuous baseline variables as mean (normally distributed) with standard deviation (SD) and median (non-normally distributed) with interquartile range (IQR). Categorical variables are shown as numbers with percentages. First, for each outcome, we calculated the mean predicted risk - based on the ACS NSQIP calculator - in the study cohort and compared this to the observed rate in the study cohort by using a one-sample Z-test. The mean predicted risk was used as fixed value. Second, for each outcome, we divided the study cohort in six groups based on the predicted risk, resulting in approximately 100 patients per group. The first group consisted of the lowest predicted risk sextile and the sixth group of the highest predicted risk sextile. Then, to assess calibration, we graphically plotted the observed outcome in the six predicted risk groups against the line $y=x$ that expresses the ideal relation between the predicted and observed outcome. Third, to assess discrimination, we used receiver-operator characteristics (ROC) curves and the corresponding area under the curve (AUC) per outcome. The AUC can be interpreted as: $0.5 \leq \text{AUC} < 0.7$ is poor, $0.7 \leq \text{AUC} < 0.8$ is good, $0.8 \leq \text{AUC} < 0.9$ is excellent and $\text{AUC} \geq 0.9$ is outstanding. A p-value ≤ 0.05 was considered statistically significant and we used SPSS version 25.0, Inc., Chicago, IL.

RESULTS

Study population

In total, 841 patients ≥ 70 years underwent CRC surgery between January 2014 and December 2017. We excluded 159 patients due to non-elective surgery (n=89), metastatic disease (n=54), local excision as surgical procedure (n=15) and no available baseline information (n=1). Ultimately, 682 patients were included (Figure 1). For the anastomotic leakage and discharge not to home analysis, we included 649 (33 patients excluded due to receiving a proctectomy) and 440 patients (237 patients from Reinier de Graaf Hospital and five patients who already lived in a nursing home prior to surgery were excluded), respectively.

Figure 1. Flow chart of study population



Baseline characteristics

In Table 1, the ACS NSQIP surgical risk calculator variables and additional baseline characteristics of the study cohort are described. Median age at diagnosis was 76.2 years (IQR 73.4-81.3), 386 patients were male (56.6%) and 504 (73.9%) were diagnosed with colon carcinoma. The majority of the patients (n=578, 84.8%) received laparoscopic surgery, 612 (89.7%) patients were functionally independent, and the majority (393 patients; 57.6%) had an ASA score of II. One hundred-seven (15.7%) patients used oral medication for diabetes and 310 (45.5%) used medication for hypertension.

Mean predicted outcome versus observed outcome in all patients

Table 2 shows the mean predicted and observed risk of each outcome in all patients. The ACS NSQIP surgical risk calculator accurately predicted the readmission rate in our cohort (predicted rate of 8.6% vs. observed rate of 7.8%, $p=0.456$), underestimated the observed rate of anastomotic leakage (2.0% vs. 3.7%, $p=0.002$), return to OR (3.5% vs. 8.4%, $p<0.001$) and pneumonia (1.8% vs. 4.4%, $p<0.001$), and overestimated the observed rate of discharge not to home (11.2% vs. 7.0%, $p=0.005$).

Table 1. Baseline characteristics and ACS NSQIP Surgical Risk Calculator variables of all patients

	Total n=682 (%)
Additional baseline characteristics of the study cohort	
Age (median, IQR)	76.2 (73.4-81.3)
Hospital	
Diakonessenhuis Utrecht	243 (35.6)
Reinier de Graaf Hospital Delft	237 (34.8)
Westfriesgasthuis Hoorn	202 (29.6)
Tumor localization	
Colon	504 (73.9)
Rectum	178 (26.1)
AJCC stage	
Stage 1	208 (30.5)
Stage 2	267 (39.1)
Stage 3	207 (30.4)
ACS NSQIP Surgical Risk Calculator variables ^{a b}	
Age category	
70 - 74 years	247 (36.2)
75 - 84 years	371 (54.4)
≥85 years	64 (9.4)
Gender	
Male	386 (56.6)
Female	296 (43.4)
Functional status	
Independent	612 (89.7)
Partial dependent	54 (7.9)
Totally dependent	8 (1.2)
Unknown	8 (1.2)
ASA class	
I	49 (7.2)
II	393 (57.6)
III	226 (33.1)
IV	14 (2.1)

Table 1. Baseline characteristics and ACS NSQIP Surgical Risk Calculator variables of all patients (*continued*)

	Total n=682 (%)
Diabetes	
No	555 (81.4)
Oral	107 (15.7)
Insulin	18 (2.6)
Organ failure	2 (0.3)
Hypertension requiring medication	310 (45.5)
Congestive Heart Failure in 30-day prior to surgery	25 (3.7)
Dyspnea	25 (3.7)
Current smoker	60 (8.8)
(severe) COPD in history	68 (10.0)
BMI (mean, IQR)	26.2 (23.6-28.4)
Surgical procedures	
Laparoscopic	578 (84.8)
Open	104 (15.2)

Abbreviations: *ACS NSQIP* American College of Surgeons National Surgical Quality Improvement Program, *AJCC* American Joint Committee on Cancer, *ASA* American Society of Anesthesiologists, *BMI* body mass index, *COPD* chronic obstructive pulmonary disease, *IQR* Interquartile range

^aThe variables 'urgency' and 'disseminated cancer' are omitted, as all patients (100%) had elective surgery and non-metastatic disease as a consequence of the inclusion criteria.

^bThe variables 'ascites', 'steroid use', 'dialysis' and 'acute renal failure' are left out in Table 1 (prevalence <1%)

Table 2. Mean predicted and observed risk per outcome

All patients (n=682)				
	Predicted risk in % (mean)	n of events	Observed risk in % (95% CI)	p-value
Anastomotic leakage*	2.0	24	3.7 (2.2-5.2)	0.002
Return to OR	3.5	57	8.4 (6.3-10.5)	<0.001
Pneumonia	1.8	30	4.4 (2.9-5.9)	<0.001
Readmission	8.6	53	7.8 (5.8-9.8)	0.456
Discharge not to home**	11.2	31	7.0 (4.6-9.4)	0.005

Abbreviations; *CI* confidence interval, *OR* operation room

*Patients receiving proctectomy (n=33) were excluded

**Patients from Reinier de Graaf Hospital (n=237) and patients who already lived in a nursing home prior to surgery (n=5) were excluded.

Calibration

In Figure 2 (A-E) the calibration plots per outcome are shown. The calibration plot of anastomotic leakage (A), return to OR (B), pneumonia (C), discharge not to home (D), and readmission (E) show that the observed and predicted outcomes are graphically different from the line that indicates the ideal relation between observed and predicted outcome (line $y=x$). For anastomotic leakage, return to OR and pneumonia, the ACS NSQIP surgical risk calculator underestimated the risk in our cohort. For discharge not to home, the calculator graphically overestimated the risk in the highest predicted risk group (Figure 2D). The calibration plot for readmission showed an alternating under- and overestimation of the observed readmission risk (Figure 2E).

Discrimination

In Figure 3 (A-E), the ROC-curves per outcome are shown. The AUC for anastomotic leakage (A), return to OR (B), and readmission (E) were poor, corresponding to an AUC of 0.57 (95% CI 0.47-0.67), 0.55 (95% CI 0.47-0.64), and 0.59 (95% CI 0.50-0.68), respectively. The discriminative ability of the ACS NSQIP calculator for pneumonia (C) and discharge not to home (D) were fair, with an AUC of 0.75 (95% CI 0.67-0.83) and 0.70 (95% CI 0.62-0.78), respectively.

Figure 2. Calibration plots of observed versus predicted rate of anastomotic leakage (A), return to OR (B), pneumonia (C), discharge not to home (D) and readmission (E) in %.

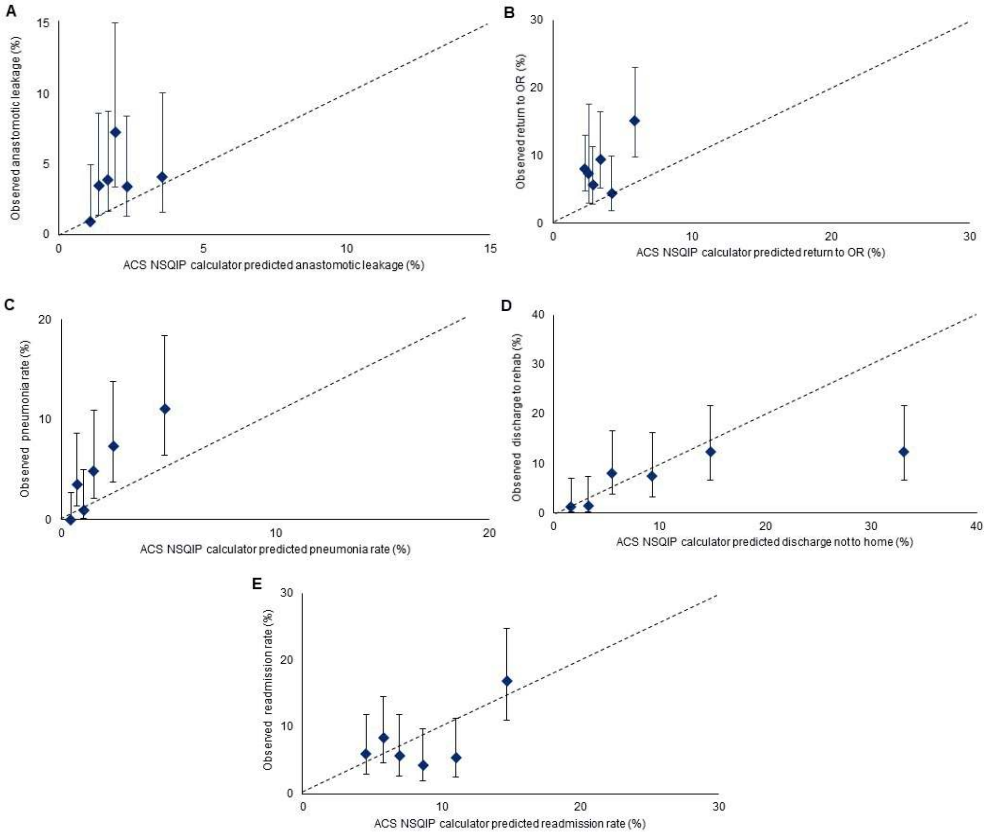
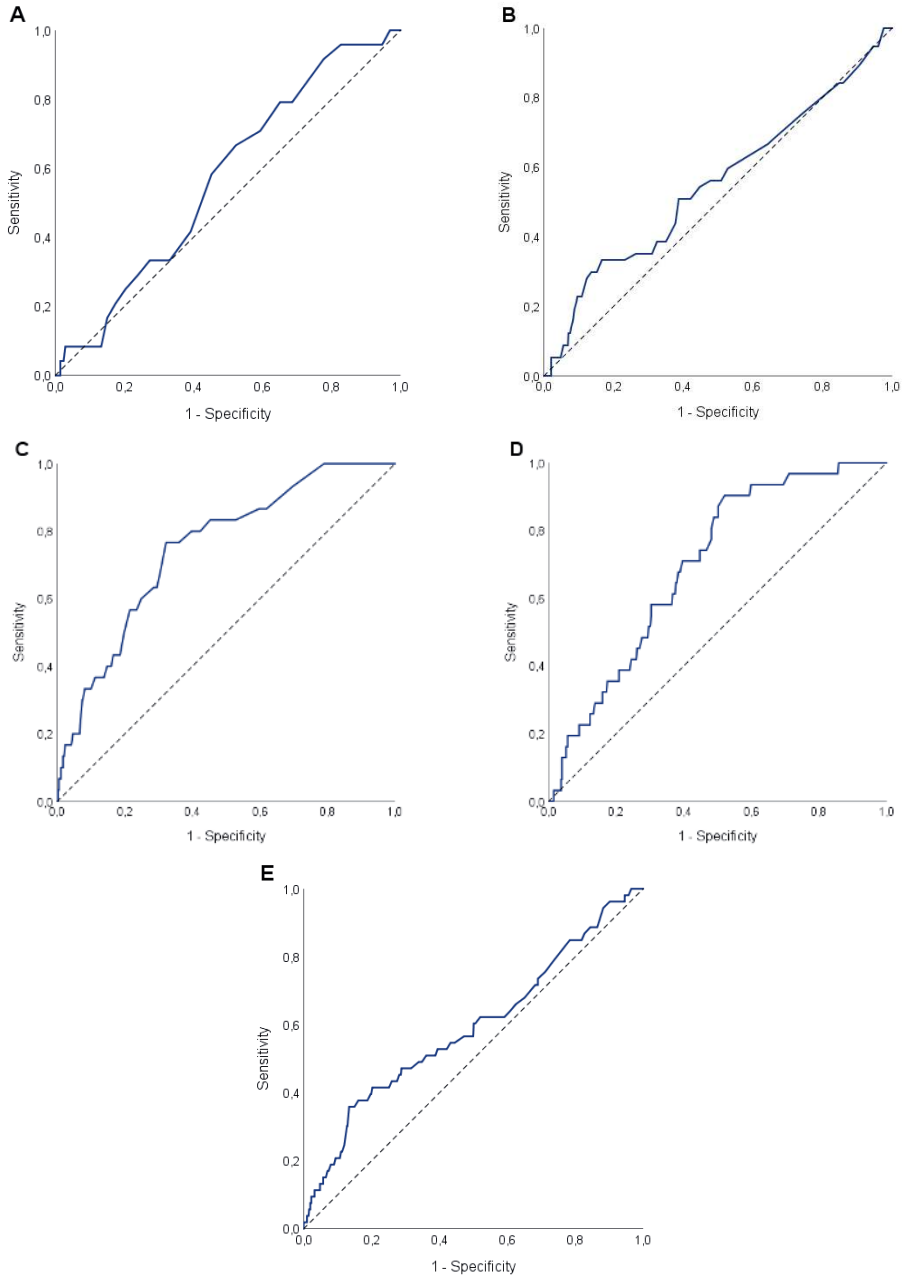


Figure 3. Receiver operating characteristic (ROC) curves of anastomotic leakage (A), return to OR (B), pneumonia (C), discharge not to home (D) and readmission (E) and the corresponding area under the curve (AUC)



A: Anastomotic leakage AUC: 0.57 (95% CI 0.47-0.67), **B: Return to OR** AUC: 0.55 (95% CI 0.47-0.6), **C: Pneumonia** AUC: 0.75 (95% CI 0.67-0.83), **D: Discharge not to home** AUC: 0.70 (95% CI 0.62-0.78), **E: Readmission** AUC: 0.59 (95% CI 0.50-0.68)

DISCUSSION

Our findings show that the ACS NSQIP surgical risk calculator has a poor calibration for all outcomes, a poor discriminative ability to predict anastomotic leakage, return to OR, and readmission, and a fair discriminative ability for pneumonia and discharge not to home in a cohort of CRC patients ≥ 70 years undergoing elective surgery in the Netherlands.

This study emphasizes that calibration and discrimination are both required to determine the validity of a prediction model (a good calibration does not guarantee a good discrimination, and vice versa) and to consider a model's use in clinical practice. A good calibration is important for informing patients about their individual prognosis after surgery (e.g., patients could be informed that 8 out of 100 patients will be readmitted after surgery) and a good discrimination separates the high- from the low-risk patients and will help the care professional to select patients for additional preoperative interventions.

The ACS NSQIP calculator has already been validated in different population cohorts. Some studies found a good overall performance [25, 26], others a poor performance [27-30]. For patients undergoing colorectal procedures, the ACS NSQIP calculator accurately predicted postoperative outcomes (e.g. postoperative complications, return to OR, or discharge to rehabilitation center) [31-34]. However, these study cohorts are not completely comparable to our study population, as we focused specifically on the older population (≥ 70 years) and colorectal cancer as indication for surgery.

The ACS NSQIP calculator particularly underestimated the observed outcome in our cohort and is therefore not useful for individual risk prediction in the older CRC population in the Netherlands. Differences in study population were the main reason for this underestimation. The mean age of patients in our cohort was higher compared to the ACS NSQIP dataset (78 vs. 62 years). Considering that frailty is more common in an older population [35], patients in our cohort had a higher a priori risk of postoperative morbidity than the patients in the ACS NSQIP dataset [4, 5, 36, 37]. As showed in Table 1, the proportion of frail patients in our cohort was low (only 9.1% of patients were partially or totally dependent and only 35.2% had an ASA score of $\geq$ III). However, the ACS NSQIP frailty predictors alone do not completely define 'frailty' [38]. Therefore, adding other frailty markers (e.g. physical performance or nutritional status [36, 37]) could improve the individual risk prediction of the ACS NSQIP surgical risk calculator in our cohort [39, 40]. From 2019 onwards, additional frailty predictors have been included in the online calculator (if age ≥ 65 years) to predict four specific geriatric outcomes (postoperative delirium, functional decline, new mobility aid use, and new/worsening pressure ulcer), but were not used to predict surgical and admission-related outcomes [16, 39, 41].

Furthermore, our study cohort consists of patients diagnosed with colon or rectal cancer, which is in contrast to the ACS NSQIP dataset that included patients with non-malignant diseases as well. Although the calculator adjusts for surgical procedure, the underlying malignant colorectal disease may have resulted in a poorer preoperative condition of our cohort (e.g. anemia, weight loss, or malnutrition [42-44]) and contributed to the underestimation of the observed outcomes.

The calculator's fair discriminative ability for pneumonia and discharge not to home indicates an additional value to tailor preoperative interventions, like prehabilitation. Pneumonia and discharge not to home are common adverse outcomes in the older CRC population. Medical complications – including pulmonary – may occur in 40.5% of the patients [6] and are associated with decreased quality of life, readmissions, and mortality [45-48]. Souwer et al. described a postoperative discharge not to home rate of 18% in 707 CRC patients ≥ 70 years in the Netherlands [40]. Prehabilitation improves pre- and postoperative functional capacity [49], which is associated with home discharge [50, 51] and reduces postoperative complications, including pulmonary complications [14, 15, 49, 52].

In addition to a model's performance, its clinical applicability is important when considering the utility of a prediction model in daily practice. Risk models that use fewer predictors showed similar performance compared to a 21-item model such as the ACS NSQIP calculator, which is time-consuming [53]. Because there is still a lack of an easy-to-use model to predict adverse postoperative outcomes, specifically for the older CRC population, future studies should develop a population-specific prediction model and need to focus on the clinical applicability as well to improve the use in daily practice.

This study had some limitations, mostly due to the retrospective design of this study. We were unable to determine the validity of the ACS NSQIP on other relevant outcomes, e.g., 'any complications', 'serious complications' and 'cardiac complications', because the definitions of these complications in the ACS NSQIP dataset did not match the definitions in the DCRA dataset or on geriatric outcomes (e.g., functional decline), as we were unable to collect these outcomes from the medical record. Furthermore, the ACS NSQIP updated the online risk calculator in December 2020. We have checked the results after the updated calculator for a random sample of patients, and differences in results before and after the update were small, which is consistent with the statement made on the calculator's website (<http://riskcalculator.facs.org>).

The major strength of this study is the validation of the ACS NSQIP surgical risk calculator in a multicenter cohort of patients ≥ 70 years undergoing elective CRC surgery with a respectable sample size and completeness of data. Also, outcome and calculator information were handled separately, reducing bias.

CONCLUSIONS

The ACS NSQIP surgical risk calculator had a poor individual risk prediction (calibration) for all outcomes and only a fair discriminative ability (discrimination) to predict pneumonia and discharge not to home in patients ≥ 70 years undergoing elective CRC surgery in the Netherlands. The calculator might be considered to identify patients at high risk of pneumonia and discharge not to home to initiate additional preoperative interventions, such as prehabilitation. For the older CRC population, an easy-to-use and population-specific prediction model is necessary.

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APPENDIX

Appendix Table 1. The Current Procedural Terminology used in the ACS NSQIP surgical risk calculator

ACS NSQIP procedures	n=682
44204 - Laparoscopic colectomy partial with anastomosis	466
44206 - Laparoscopic colectomy partial with end colostomy (Hartmann procedure)	67
44140 - Colectomy partial with anastomosis	69
44143 - (Hartmann procedure) Colectomy partial with end colostomy and closure of the distal segment	11
44144 - Colectomy partial with resection, with colostomy or ileostomy and creation of mucofistula	15
44210 - Laparoscopy, surgical; colectomy, total, abdominal, without proctectomy, with ileostomy or ileoproctostomy	19
44147 - Colectomy partial abdominal and transanal approach	1
44205 - Laparoscopy, surgical; colectomy, partial with removal of terminal ileum with ileocolostomy	1
45110 - Proctectomy; complete combined abdominoperineal with colostomy	8
45395 - Laparoscopy, surgical; proctectomy, complete, combined abdominoperineal, with colostomy	25

4

Predictive value of selected geriatric parameters for postoperative outcomes in older patients with rectal cancer

- A multicenter cohort study

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ABSTRACT

Introduction

Older patients have a higher risk for complications after rectal cancer surgery. Although screening for geriatric impairments may improve risk prediction in this group, it has not been studied previously.

Methods

We retrospectively investigated patients ≥ 70 years with elective surgery for non-metastatic rectal cancer between 2014-2018 in nine Dutch hospitals. The predictive value of six geriatric parameters in combination with standard preoperative predictors was studied for postoperative complications, delirium, and length of stay (LOS) using logistic regression analyses. The geriatric parameters included the four VMS-questionnaire items pertaining to functional impairment, fall risk, delirium risk, and malnutrition, as well as mobility problems and polypharmacy. Standard predictors included age, sex, body mass index, American Society of Anesthesiologists (ASA)-classification, comorbidities, tumor stage and neoadjuvant therapy. Changes in model performance were evaluated by comparing Area Under the Curve (AUC) of the regression models with and without geriatric parameters.

Results

We included 575 patients (median age 75 years; 32% female). None of the geriatric parameters improved risk prediction for complications or LOS. The addition of delirium risk to the standard preoperative prediction model improved model performance for predicting postoperative delirium (AUC 0.75 vs 0.65, $p=0.03$).

Conclusions

Geriatric parameters did not improve risk prediction for postoperative complications or LOS in older patients with rectal cancer. Delirium risk screening using the VMS-questionnaire improved risk prediction for delirium. Older patients undergoing rectal cancer surgery are a pre-selected group with few impairments. Geriatric screening may have additional value earlier in the care pathway before treatment decisions are made.

INTRODUCTION

Colorectal cancer (CRC) is the 3rd most common malignancy in the West with rectal cancer accounting for 30% of the cases. The median age at diagnosis for rectal cancer patients is 63 years and a substantial proportion is above 70 years of age [1]. Surgery remains the cornerstone of treatment. Older patients are at an increased risk of postoperative complications and mortality [2], and the occurrence of any complication is associated with a decreased postoperative quality of life in older patients with rectal cancer[3]. However, older patients are also a heterogeneous group with regard to comorbidities, physical capabilities and the presence of geriatric impairments such as decreased mobility, malnutrition, polypharmacy and cognitive problems. Several studies have found an association between these geriatric impairments and adverse postoperative outcomes in older patients with CRC [4-7]. Adequate risk stratification in older patients is required to support informed decision-making and to adjust perioperative strategies such as the implementation of prehabilitation (preoperative physical optimization) programs.

One method to screen for possible geriatric impairments is the Dutch Patients Safety program ('VeiligheidsManagementSysteem', VMS) [8]. The VMS-questionnaire encompasses four geriatric domains: fall risk, malnutrition risk, delirium risk and physical impairments [8], and is meant to be administered to all older patients (>70 years) admitted to the hospital. Patients diagnosed with impairments can receive additional care according to their needs (e.g., supplements in case of malnutrition, delirium prevention or fall prevention measures). For hospitalized older patients, higher scores on the frailty screening using the VMS-questionnaire are associated with adverse outcomes and 6-month mortality [9, 10]. A recent study by Souwer *et al.* in 550 older patients with CRC showed that an increasing number of geriatric impairments as measured with the VMS was associated with postoperative complications and lower overall survival [6]. In their subsequent study, Souwer *et al.* developed a prediction model for severe postoperative complications in older patients with CRC. After adding the geriatric domains of the VMS, polypharmacy and the use of mobility aid to standard preoperative variables, the model's predictive value marginally improved [11]. Geriatric impairments have been incorporated in few other prediction models for older patients with CRC [11-14]. Although, compared to colon cancer, the treatment of rectal cancer is more often multimodal and rectal surgery is associated with higher morbidity rates [15], the predictive value of geriatric parameters has not been previously assessed specifically in patients undergoing surgery for rectal cancer [16].

Therefore, the aim of this study was to determine whether the addition of geriatric risk factors (physical impairment, fall risk, malnutrition risk, delirium risk, polypharmacy and use of mobility aid) to standard preoperative prognostic variables improves the predictive value for adverse postoperative outcomes in older patients with rectal cancer.

METHODS

Study design and patient inclusion

In this retrospective multicenter study in nine hospitals in The Netherlands (Alrijne Hospital in Leiderdorp, Diaconessenhuis in Utrecht, Haga Hospital in the Hague, Martini Hospital in Groningen, Reinier de Graaf Hospital in Delft, Dijklander Hospital in Hoorn, Gelre Hospital in Apeldoorn, Meander Medical Center in Amersfoort, Bernhoven Hospital in Uden), patients aged 70 years and older who underwent elective surgery for non-metastatic rectal cancer were eligible for inclusion. Patients who underwent transanal endoscopic microsurgery or who received palliative treatment for other forms of cancer were excluded. All participating hospitals provided perioperative care according to the Enhanced Recovery After Surgery (ERAS) protocol [17]. In most hospitals in The Netherlands, all electively admitted patients 70 years and older are subjected to the VMS questionnaire. The inclusion periods ranged between the hospitals depending on when VMS-questionnaires were administered (Supplementary Table S1). The study complies with the Declaration of Helsinki and was approved by the institutional review boards of the participating hospitals.

Data collection

Patients' demographics, tumor characteristics and postoperative outcomes within 30 days after surgery were prospectively registered according to nationwide data collection for the Dutch ColoRectal Audit (DCRA): age, sex, American Society of Anesthesiologists (ASA)-score [18], comorbidities (Charlson Comorbidity Index (CCI) [19]), tumor stage according to the American Joint Committee on Cancer (AJCC) [20], surgical approach (laparoscopic or open), surgical procedure (low anterior resection (LAR) or abdominal perineal resection (APR)/ Hartmann's procedure), construction of a stoma, (neo)adjuvant therapy, and postoperative outcomes. The dataset was retrospectively manually completed in a cloud-based database (Castor EDC) [21] by a resident physician or a medical student with information from the Electronic Medical Records (EMR): body mass index (BMI), geriatric parameters, postoperative delirium and discharge destination.

Geriatric parameters

The VMS-questionnaire consists of four geriatric parameters: fall risk, delirium risk, malnutrition risk, and functional impairment. The questionnaire was administered preoperatively by nursing staff and entered into the EMR. Fall risk was present if the patient had experienced a fall in the previous six months. Delirium risk was present if at least one out of the three questions (presence of cognitive problems, needing help with self-care in the past 24 hours or a history of delirium) was answered with "yes". Malnutrition risk was assessed using the Short Nutritional Assessment Questionnaire [22]) or the Malnutrition Universal Screening Tool [23]. Patients with a score of ≥ 2 were considered at risk. Functional impairment was defined as a KATZ activities of daily living (ADL) score ≥ 2 based on six items (one point if assistance was needed): bathing, dressing, toileting, eating, transferring from bed to chair

and the use of any incontinence material [24]. In Martini hospital, the item ‘need help with eating’ was replaced with ‘use of a walking aid’, and only the total score (≥ 2 vs < 2) was available. Information on polypharmacy (use of five or more medications) and the use of mobility aid (with the exception of Martini hospital) were also collected from the EMR.

Outcomes

The primary outcome was the occurrence of any complications within 30 days after surgery. The secondary outcomes were severe complications (Clavien-Dindo classification[25] ≥ 3), requiring reintervention, unplanned intensive care unit (ICU) admission or leading to death, postoperative delirium, 30-day mortality, discharge to another institution and length of stay (LOS). Prolonged LOS was defined as > 14 days, based on the DCRA definition of a complicated postoperative course. Postoperative delirium was present if the diagnosis delirium was registered by the treating physician or a geriatrician, haloperidol was prescribed or a Delirium Observation Screening Scale ≥ 3 was registered in the medical record. Discharge to another institution was defined as a (temporary) discharge to a rehabilitation center or nursing home if the patient was living at home prior to surgery. Patients who died during hospital admission were excluded from the analyses for this outcome.

Statistical analysis

Continuous variables were presented as mean and standard deviation (SD) or as median and interquartile range (IQR). Frequencies were presented as number and percentage. We aimed to assess whether geriatric parameters can improve risk prediction compared to only standard preoperative predictors regarding the primary and secondary study outcomes. First, we built a logistic regression model for each outcome using only standard preoperative parameters (standard model). The parameters that were considered included age, sex (male vs female), ASA-score (III-IV vs I-II), CCI (score ≥ 2 vs < 2), tumor stage (III vs 0-II), neoadjuvant therapy (present vs absent) and obesity (BMI ≥ 30 vs < 30). Univariable logistic regression analyses were performed to determine associations between each variable and outcome and reported as odds ratios (OR) with 95% confidence intervals (CI). The standard model was then built using manual forward selection where predictor variables were added one by one starting with the variable that had the strongest association with the outcome (smallest p-value). At each step, changes in model performance were evaluated by comparing the Area Under the Curves (AUC) and 95% CIs using the Hanley & McNeil method²⁶. Each new variable was retained in the standard model if it significantly improved the model performance (significant difference between AUCs ($p < 0.05$)).

Second, we evaluated whether geriatric parameters (functional impairment, delirium risk, fall malnutrition risk, fall risk, mobility aid or polypharmacy) could be used to improve the predictive ability of the standard model. For each outcome, the model performance between the standard model and the model including each geriatric parameter was again compared by measuring differences in the AUCs using the Hanley & McNeil method [26]. To avoid

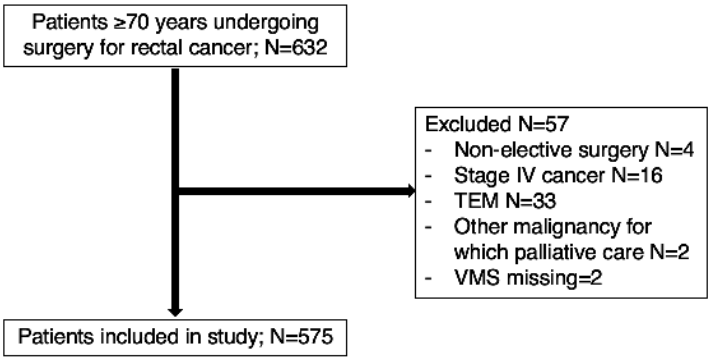
overfitting, a maximum of one variable per ten outcome events was allowed in each model [27]. Comparisons between AUCs were performed using MedCalc (MedCalc Software Ltd, Ostend, Belgium). All other analyses were performed using SPSS version 25.0. A two-tailed p-value <0.05 was considered statistically significant for all analyses.

RESULTS

Patient inclusion

Flow chart of study inclusion is depicted in Figure 1. A total of 632 patients underwent resection for rectal cancer during the inclusion periods. Of these, 57 patients were excluded due to the prespecified exclusion criteria, leaving 575 patients for the analyses.

Figure 1. Flow chart of patient inclusion



Baseline and treatment characteristics of included patients

The baseline characteristics of included patients are summarized in Table 1. The median age was 75 years (IQR 73–80) and 185 (32.2%) patients were female. ASA-score was III-IV in 145 (25.2%) patients and 140 (24.3%) patients had CCI score of 2 or higher. The tumor stage was I in 213 (37.0%) patients, II in 171 (29.7%) patients and III in 162 (28.2%) patients. For two patients (0.3%), the T-stage was not known (these patients had AJCC stage I-II).

A total of 468 (81.4%) patients underwent a LAR (226 (48.3%) without a stoma, 242 (51.7%) with stoma. Sixty (10.4%) patients underwent APR or Hartmann's procedure. For 47 (8.2%) patients the type of resection was not known but all received a stoma without anastomosis. Laparoscopic or open surgery was performed in 467 (81.2%) and 108 (18.8%) patients, respectively. A total of 287 (49.9%) patients underwent neoadjuvant therapy (radiotherapy (N=180, 31.3%) or chemoradiation (N=107, 18.6%). Twenty-four (4.2%) patients received adjuvant chemotherapy.

Table 1. Patient, tumor and treatment characteristics

	Total N = 575 (%)
Age, median (IQR)	75.5 (72.9–80.4)
Sex	
Male	390 (67.8)
Female	185 (32.2)
BMI, median (IQR) (missing: 22)	26.0 (23.8–28.1)
ASA-score	
I/II	430 (74.8)
III/IV	145 (25.2)
Charlson comorbidity index	
0-1	435 (75.7)
≥2	140 (24.3)
AJCC stage*	
Stage 0	27 (4.7)
Stage I	213 (37.0)
Stage II	171 (29.7)
Stage III	162 (28.2)
Surgical approach	
Laparoscopic	467 (81.2)
Open	108 (18.8)
Type of surgery	
LAR without stoma	226 (39.3)
LAR with stoma	242 (42.1)
Abdominoperineal resection / Hartmann surgery	60 (10.4)
Not specified	47 (8.2)
Neoadjuvant therapy	
None	288 (50.1)
Short course radiotherapy	180 (31.3)
Chemoradiation	107 (18.6)
adjuvant chemotherapy^a	
No	548 (95.3)
Yes	24 (4.2)
Missing	3 (0.5)

Abbreviations: *AJCC* American Joint Committee on Cancer; *ASA* American Society of Anesthesiologists; *APR* abdominoperineal resection; *BMI* body mass index; *IQR* interquartile range; *LAR* low anterior resection

*For two patients, the T-stage was missing, but the N-stage was 0 (AJCC stage I-II).

Table 2. Geriatric parameters

	Total N = 575 (%)
VMS: Risk of delirium	
No (score 0)	474 (82.4)
Yes (score 1–3)	82 (14.3)
Missing	19 (3.3)
VMS: Risk of falls	
No	493 (85.7)
Yes	43 (7.5)
Missing	39 (6.8)
VMS: Risk of malnutrition	
No (SNAQ 0–1)	461 (80.2)
Yes (SNAQ 2–6)	84 (14.6)
Missing	30 (5.2)
VMS: Functional impairment (KATZ-ADL)	
Not impaired (score 0–1)	537 (93.4)
Impaired (score 2–6)	25 (4.3)
Missing	13 (2.3)
Polypharmacy (≥5 medications)	
No	327 (56.9)
Yes	241 (41.9)
Missing	7 (1.2)
Use of mobility aid	
No	405 (70.4)
Yes	42 (7.3)
Missing	128 (22.2)

Abbreviations: *ADL* Activities of Daily Living; *SNAQ* Short Nutritional Assessment Questionnaire; *VMS* ‘VeiligheidsManagementsSysteem’ Safety Management System

Table 3. Comparison of baseline and treatment characteristics between patients without any geriatric risk factors and patients with at least one geriatric risk factor

	No risk factors (n=154)	At least one risk fac- tor (n=329)	p-value
Age, median (IQR)	74.8 (72.4–78.6)	76.2 (73.3–81.3)	<0.001
Sex			0.02
Male	116 (75.3)	213 (64.7)	
Female	38 (24.7)	116 (35.3)	
BMI, median (IQR)	25.8 (23.6–28.0)	26.3 (24.0–28.4)	0.17
ASA-score			<0.001
I-II	137 (89.0)	209 (63.5)	
III-IV	17 (11.0)	120 (36.5)	
Charlson comorbidity index			<0.001
0-1	138 (89.6)	221 (67.2)	
≥2	16 (10.4)	108 (32.8)	
Tumor stage			0.62
0-II	108 (70.1)	238 (72.3)	
III	46 (29.9)	91 (27.7)	
Neoadjuvant therapy	79 (52.3)	167 (51.4)	0.85
Surgical approach			<0.001
Open	7 (4.5)	65 (19.8)	
Laparoscopic	147 (95.5)	174 (52.9)	
Type of surgery			<0.001
LAR without stoma	81 (52.6)	104 (31.6)	
LAR with stoma	56 (36.4)	151 (45.9)	
APR / Hartmann surgery	5 (3.2)	42 (12.8)	
Not specified (no anastomosis)	12 (7.8)	32 (9.7)	

Abbreviations: *ASA* American Society of Anesthesiologists, *APR* abdominoperineal resection, *BMI* body mass index, *IQR* interquartile range, *LAR* low anterior resection, *VMS* 'VeiligheidsManagement-Systeem' Safety Management System

Geriatric parameters

Data on geriatric parameters are shown in Table 2. A total of 329 (57.2%) had at least one geriatric risk factor. The most often reported geriatric parameters were polypharmacy (N=241 (41.9%)), malnutrition risk (N=84 (14.6%)) and delirium risk (N=82 (14.3%)). Most patients were at risk for delirium due to reporting having cognitive problems (N=42 (51.2%)). Fall risk and functional impairment were reported for 43 (7.5%) and 25 (4.3%) patients, respectively. Forty-two (7.3%) patients used a mobility aid.

Baseline and treatment characteristics between patients with at least one geriatric risk factor and patients without geriatric risk factors

Table 3 shows the baseline characteristics between patients with at least one geriatric risk factor (N=329) and patients without any risk factors (N=155). For 91 (15.8%) patients, data on at least one geriatric parameter was missing and they were not included in the analyses. Patients with at least one risk factor were older ($p<0.001$), more often female ($p=0.02$), had higher ASA-scores ($p<0.001$) and more comorbidities ($p<0.001$). They more often underwent open surgery ($p<0.001$) and APR or Hartmann's procedure ($p<0.001$).

Outcomes

Results of the univariable logistic regression analyses are shown in Table 4.

Overall complications

Overall complications occurred in 253 (44.0%) patients. Of the standard preoperative predictors, ASA-score and CCI were associated with overall complications in univariable analysis. The final prediction model only included ASA score (AUC 0.57, 95% CI 0.52–0.62) as CCI did not significantly improve model performance. Although functional impairment, delirium risk and mobility aid were associated with overall complications in univariable analyses, the addition of any of these geriatric parameters to the standard model did not improve model performance.

Severe complications

Seventy-one (12.3%) patients had severe complications. None of the standard preoperative variables were associated with severe complications in univariable analyses. Regarding the geriatric parameters, only mobility aid was associated with the outcome. However, use of mobility aid did not discriminate between patients with and without severe complications (AUC 0.56, 95% CI 0.47–0.64).

Postoperative delirium

Forty-five (8.0%) patients had postoperative delirium. Age, ASA-score and CCI were associated with this outcome in univariable analysis. Only ASA-score remained in the final model with standard preoperative variables (AUC 0.65, 95% CI 0.56–0.74).

When delirium risk was added to the standard model, the discriminative ability of the model improved significantly (AUC 0.75, 95% CI 0.71–0.78, $p=0.03$). Other geriatric parameters did not improve the model performance.

Length of stay

The median LOS was 6 days (IQR 5–10); 73 (12.7%) patients were admitted for >14 days (prolonged LOS). The final prediction model of standard preoperative variables only included age (AUC 0.60, 95% CI 0.54–0.67). None of the geriatric parameters improved the model performance for prolonged LOS.

Discharge to another care facility

Forty-five (8.0%) patients were discharged to another institution. The standard variables associated with this outcome included age and female sex. Only age remained in the final prediction model (AUC 0.71, 95% CI 0.63–0.80). Regarding the geriatric parameters, adding functional impairment (KATZ-ADL score ≥ 2) to the model resulted in a modest increase in the model performance (AUC 0.73, 95% CI 0.69–0.76, $p=0.049$). Other geriatric parameters did not increase the predictive ability of the model.

30-day mortality

Fifteen (2.6%) patients died within 30 days of surgery. Of the standard preoperative variables, age and CCI were associated with mortality in univariable analysis. No prediction model was developed due to the low numbers of events.

Table 4. Results from univariable analyses for overall complications, severe complications, postoperative delirium, prolonged LOS, discharge to another care facility and 30-day mortality

	Overall complications (n=253)			Severe complications (n=71)		Postoperative delirium (n=45)		Prolonged LOS (n=73)		Discharge to another care facility (n=45)		30-day mortality (n=15)	
	Missing (n)	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value
Standard preoperative risk predictors													
Age	0	1.0 (1.0–1.1)	0.13	0.2 (1.0–1.1)	0.23	1.1 (1.0–1.2)	0.003	1.1 (1.0–1.1)	0.02	1.2 (1.1–1.2)	***	1.1 (1.0–1.3)	0.005
Male sex	0	1.4 (1.0–1.9)	0.09	1.3 (0.8–2.4)	0.30	1.7 (0.8–3.6)	0.14	1.4 (0.8–2.5)	0.23	0.5 (0.3–0.9)	0.02	1.3 (0.4–4.2)	0.65
ASA III–IV	0	2.1 (1.4–3.0)	***	1.4 (0.8–2.4)	0.23	3.9 (2.1–7.2)	***	1.4 (0.8–2.5)	0.19	1.3 (0.7–2.5)	0.49	2.7 (1.0–7.5)	0.06
CCI 2 or higher	0	1.9 (1.3–2.8)	***	1.6 (0.9–2.7)	0.09	3.3 (1.8–6.2)	***	1.3 (0.8–2.3)	0.35	1.7 (0.9–3.3)	0.11	3.7 (1.3–10.4)	0.01
BMI≥30	22	1.1 (0.7–1.8)	0.68	1.3 (0.6–2.5)	0.53	0.3 (0.1–1.3)	0.10	1.0 (0.5–2.0)	0.98	0.4 (0.1–1.3)	0.14	1.6 (0.4–5.8)	0.49
Neoadjuvant therapy	8	1.0 (0.7–1.4)	0.96	1.0 (0.6–1.7)	0.89	0.9 (0.5–1.7)	0.81	0.9 (0.6–1.5)	0.72	1.0 (0.5–1.7)	0.86	0.7 (0.2–2.1)	0.56
AJCC stage III	0	1.1 (0.8–1.6)	0.68	1.3 (0.8–2.3)	0.28	0.9 (0.5–1.8)	0.82	1.4 (0.8–2.3)	0.24	0.8 (0.4–1.7)	0.57	1.7 (0.6–4.9)	0.31
Geriatric risk predictors													
VMS: functional impairment	13	3.4 (1.4–8.4)	0.007	1.8 (0.6–4.9)	0.27	2.3 (0.8–7.0)	0.14	2.2 (0.9–5.7)	0.11	2.5 (0.8–7.6)	0.12	3.5 (0.7–16.0)	0.12
VMS: delirium risk	19	2.4 (1.5–4.0)	***	1.7 (0.9–3.2)	0.09	5.7 (2.9–10.9)	***	2.3 (1.2–4.1)	0.008	4.2 (2.2–8.1)	***	1.5 (0.4–5.2)	0.57
VMS: fall risk	39	0.7 (0.4–1.4)	0.74	1.7 (0.7–3.8)	0.22	0.6 (0.1–2.5)	0.47	0.7 (0.2–2.0)	0.68	0.6 (0.1–2.5)	0.46	3.0 (0.8–11.)	0.10

Table 4. Results from univariable analyses for overall complications, severe complications, postoperative delirium, prolonged LOS, discharge to another care facility and 30-day mortality (*continued*)

		Overall complications (n=253)	Severe complications (n=71)	Postoperative delirium (n=45)	Prolonged LOS (n=73)	Discharge to another care facility (n=45)	30-day mortality (n=15)
VMS: malnutrition risk	30	1.3 (0.8–2.2)	1.1 (0.5–2.1)	2.2 (1.1–4.5) 0.03	1.6 (0.9–3.1)	2.5 (1.2–5.1)	2.9 (1.0–8.7) 0.06
Mobility aid	128	2.4 (1.2–4.5) 0.009	2.7 (1.2–5.9) 0.01	1.2 (0.3–4.0) 0.81	1.6 (0.7–3.6)	4.0 (1.9–8.8) ***	1.0 (0.1–7.7) 0.97
Polypharmacy (≥5 medications)	7	1.4 (1.0–2.0)	1.2 (0.7–2.0)	2.4 (1.3–4.5) 0.006	1.2 (0.8–2.0)	1.7 (0.9–3.0)	2.8 (0.9–8.2) 0.07

Abbreviations: *ADL* Activities of Daily Living, *AJCC* American Joint Committee on Cancer, *ASA* American Society of Anesthesiologists, *BMI* body mass index, *CCI* Charlson Comorbidity Index, *CI* confidence interval, *OR* odds ratio, *VMS* (VeiligheidsManagementSysteem “Safety Management System”)
*** <0.001. Significant associations between risk factors and postoperative outcomes are shown in boldface.

DISCUSSION

In our cohort of 575 older patients undergoing surgery for rectal cancer, adding geriatric parameters to standard preoperative risk factors did not improve risk prediction for postoperative complications. The VMS-items delirium risk and functional impairment were of added value in predicting postoperative delirium and post-discharge institutionalization, respectively. To our knowledge, this is the first study exploring the value of assessing geriatric parameters to improve risk prediction for short-term outcomes in older patients undergoing surgery for rectal cancer.

Our findings are not in line with previous studies that have focused on older patients undergoing CRC surgery. Whereas geriatric parameters did not predict severe complications in our study, Souwer *et al* [6]. found a marginally improved prediction of severe complications after adding geriatric impairments (previous delirium, self-reported cognitive impairment, need for ADL assistance, use of mobility aid and polypharmacy) to standard variables. In the studies by Kiran *et al.*, Murray *et al.*, and Cohen *et al.*, functional dependency predicted 30-day mortality[13, 14] and 30-day morbidity [12]. This is in contrast to our finding that functional dependency (or functional impairment) only improved the prediction for discharge to another care facility and not for other outcomes. However, as our cohort consisted exclusively of patients with rectal cancer, a direct comparison of our results and the results of the aforementioned studies is not feasible.

The fact that our findings do not support frailty screening using the current geriatric risk factors to predict overall or severe complications in rectal cancer surgery can be due to several reasons. First, we included older patients who had already been selected for surgery. The prevalence of geriatric risk factors was relatively low, also when compared to the previous cohort of Souwer *et al* [6]. that also included patients with colon cancer. The treatment of rectal cancer is multidisciplinary and many different treatment options exist, ranging from chemoradiation followed by watch-and-wait [28] or transanal microsurgery[29] to direct surgical resection. It is highly likely that frailer patients with more impairments more often received non-surgical treatment [30]. The modest discriminative value of the standard predictor variables (e.g., age or ASA-score) also supports this hypothesis. Second, although we assessed the risk for several geriatric impairments, there are other preoperative risk factors that may have more predictive value in older surgical patients. Physical decline contributes to the development of geriatric impairments such as falling and needing help with ADL, and measuring markers of physical decline may improve risk prediction in the older patient population. For example, low muscle mass and poor aerobic capacity have been shown to be strongly associated with adverse outcomes in colorectal surgery [31, 32]. Third, rectal surgery is complex and postoperative outcomes (such as anastomotic leak) are strongly influenced by surgical factors (extent of resection, invasiveness of surgery, height of anastomosis, deviating ostomy)[15]. In our cohort, patients with at least one geriatric risk factor had open surgery

and received a stoma more often. Preoperative prediction models cannot rely on intraoperative surgical variables which were thus not included in the logistic regression analyses. However, patient characteristics that were associated with having at least one geriatric risk factor in our cohort (advanced age, higher ASA-scores and a higher comorbidity burden) likely had influence on perioperative decision-making, for example regarding stoma construction. More vulnerable patients thus received different surgical treatment.

Interestingly, we noted the relatively low percentage of patients receiving APR in our cohort (10%). In other recent Dutch cohorts in which patients of all ages were included, the percentages of patients undergoing APR were higher (27-46%) [33-35]. We also observed that most patients underwent surgery for stage I/II cancer which may in part explain the lower percentage of APR. Older patients with very distal cancers who would have to undergo APR as well as patients with more advanced disease may have instead opted for non-surgical treatment and were thus not included in our study.

Postoperative delirium is associated with an increased risk for cognitive decline and mortality [36]. Identifying at-risk patients can be used to implement delirium prevention measures. Previous studies in other cohorts of older surgical patients have shown that a history of delirium and cognitive problems are associated with a higher risk of postoperative delirium [37-39]. Both items are a part of the delirium risk screening incorporated in the VMS-questionnaire. In the present cohort, we showed that delirium risk screening together with ASA-score resulted in a fair discriminative ability for postoperative delirium of the prediction model (AUC 0.75), implying that delirium risk screening with the VMS-questionnaire is a useful addition to the preoperative risk assessment in patients with rectal cancer.

Preoperative frailty screening serves two main purposes: first, it aids in risk stratification and helps to guide the decision-making process regarding the surgical trajectory, and second, it provides opportunities to address modifiable risk factors [40, 41]. Frailty screening may therefore have the most value for older patients with rectal cancer when it is implemented directly after diagnosis and before decisions on treatment trajectory are made. Ideally, an initial frailty screening is quick and has adequate discriminatory power to determine which patients require further work-up, for example in the form of a Comprehensive Geriatric Assessment [42]. Future studies should determine whether frailty screening with the geriatric parameters addressed here would have additional prognostic value in an earlier phase in the treatment pathway for rectal cancer. It should be noted that measuring modifiable risk factors would be especially advantageous as it helps targeting preoperative interventions such as prehabilitation for selected patients [43].

The major strength of this study was the large sample size and the inclusion of only older patients with rectal cancer. We were able to collect data in multiple hospitals which increases the generalizability of the results. The limitations of the study include the already mentioned

selection bias for the fittest older patients which probably limited the number of patients with more geriatric impairments as these patients did not undergo surgery. Furthermore, frailty screening with VMS was an implemented practice in the participating hospitals and patients at risk most likely received a geriatric consultation and/or additional care, for example consultation by a physiotherapist or a dietician, nutritional supplements, delirium prevention measures (such as counseling, early signaling, single room or rooming in) or fall prevention measures. Some of these interventions may have weakened the association between the geriatric parameters and outcomes. Lastly, we measured a set of parameters that were readily available from the medical records. The VMS-questionnaire is a short screening tool, and even though we augmented the screening instrument with two additional geriatric parameters (polypharmacy and mobility issues), the method has its shortcomings. There are other parameters that may have stronger prognostic value in the older surgical population (such as cognition, muscle mass, aerobic capacity), and prospective data collection focusing especially on modifiable risk factors would be needed to determine which set of variables would have optimal prognostic value.

CONCLUSIONS

In this multicenter study in 575 older patients with rectal cancer, preoperative screening for geriatric parameters did not improve risk prediction for postoperative overall or severe complications. However, delirium risk screening with the VMS-questionnaire significantly improved risk prediction for postoperative delirium. Geriatric risk screening may have additional value when performed early after diagnosis and before treatment decisions are made. Future studies should determine which risk factors should be considered when making treatment decisions for older patients with rectal cancer in a prospective setting. Focus on modifiable risk factors is especially warranted in order to find targets for preoperative optimization and to further improve postoperative outcomes.

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APPENDIX

Supplementary Table S1. Inclusion periods per hospital

Hospital	Inclusion period
Alrije Hospital, Leiderdorp	January 2014 – December 2017
Diakonessenhuis, Utrecht	January 2014 – December 2017
Haga Hospital, The Hague	January 2014 – December 2017
Martini Hospital, Groningen	January 2014 – December 2017
Reinier de Graaf Hospital, Delft	January 2014 – December 2017
Dijklander Hospital, Hoorn	January 2014 – December 2017
Gelre Hospital, Apeldoorn	March 2015 – September 2018
Meander Medical Center, Amersfoort	January 2014 – December 2015 & January 2018 – March 2018
Bernhoven Hospital, Uden	January 2017 – December 2018

PART II

Identifying relevant postoperative outcomes

5

Surgical and non-surgical complications after colorectal cancer surgery in older patients; time-trends and age-specific differences

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ABSTRACT

Background

Trends of surgical and non-surgical complications among the old, older and oldest patients after colorectal cancer (CRC) surgery could help to identify the best target outcome to further improve postoperative outcome.

Materials and Methods

All consecutive patients ≥ 70 years receiving curative elective CRC resection between 2011-2019 in The Netherlands were included. Baseline variables and postoperative complications were prospectively collected by the Dutch ColoRectal audit (DCRA). We assessed surgical and non-surgical complications over time and within age categories (70-74, 75-79 and ≥ 80 years) and determined the impact of age on the risk of both types of complications by using multivariate logistic regression analyses.

Results

Overall, 38648 patients with a median age of 76 years were included. Between 2011-2019 the proportion of ASA score ≥ 3 and laparoscopic surgery increased. Non-surgical complications significantly improved between 2011 (21.8%) and 2019 (17.1%) and surgical complications remained constant (from 17.6% to 16.8%). Surgical complications were stable over time for each age group. Non-surgical complications improved in the oldest two age groups. Increasing age was only associated with non-surgical complications (75-79 years; OR 1.17 (95% CI 1.10-1.25), ≥ 80 years; OR 1.46 (95% CI 1.37-1.55) compared to 70-74 years), not with surgical complications.

Conclusion

The reduction of postoperative complications in the older CRC population was predominantly driven by a decrease in non-surgical complications. Moreover, increasing age was only associated with non-surgical complications and not with surgical complications. Future care developments should focus on non-surgical complications, especially in patients ≥ 75 years.

INTRODUCTION

Postoperative complications after colorectal cancer (CRC) surgery are common [1] and are accountable for short-term consequences (prolonged length of stay, readmission and mortality) and long-term outcomes (lower five-years survival [2] and quality of life [3]). To improve postoperative complications after CRC surgery, special attention should be paid to the older population. In this group of older patients, postoperative complications occur more often [4-7] and result in higher morbidity than in younger patients [8].

The impact of postoperative complications is not only age-specific (young vs old), but it also depends on the type of complication as well. Warps *et al* [9] showed that non-surgical complications (like cardiopulmonary events) had a stronger impact on long-term survival for CRC patients than surgical complications (like anastomotic leakage or bleeding). Furthermore, our research group found that prehabilitation in older CRC patients predominantly affects non-surgical complications [10]. These results suggest that surgical and non-surgical complications should be evaluated separately, especially in the older population.

Considering several care developments that have been (partly) implemented in clinical practice, such as minimally invasive surgery, enhanced recovery after surgery (ERAS), geriatric co-management and prehabilitation programs, it would be interesting to have information about recent trends of both postoperative surgical and non-surgical complications in older (≥ 70 years) CRC patients. As these developments have already been shown to gradually close the gap in postoperative mortality between younger and older CRC patients [11, 12], it is unknown whether there is still a gap in postoperative complications between the old, older and oldest patients

The studies that have investigated the risk for postoperative complications in several age-groups within the older CRC population (≥ 70 years) showed inconsistent results. Some found an increased risk of overall postoperative complications with increasing age [6, 13-15], others found no difference [16] or only an increased risk of infectious complications [17]. However, these studies did not differentiate clearly between surgical and non-surgical complications.

This study aims to describe both types of postoperative complications, i.e. surgical and non-surgical, with respect to both time-trends as well as age-specific (70-74 years, 75-79 years and ≥ 80 years) results in older patients with colorectal cancer on a population level.

MATERIAL AND METHODS

Study population and design

For this nationwide population-based cohort study, patients were identified through the Dutch Colorectal Audit (DCRA). The DCRA is an obligatory audit, which registered all newly diagnosed colorectal malignancies in the Netherlands to monitor, evaluate and improve Dutch colorectal cancer care [18]. The DCRA prospectively collects patients' demographics, tumor- and treatment characteristics and postoperative outcome parameters. As the DCRA is an obligatory audit and all DCRA data is de-identified, medical ethics committee approval or informed consent was not required [22]. This observational cohort study included all consecutive patients of 70 years and older who received elective surgery for stage I-III colon or rectal cancer between 2011 and 2019 in the Netherlands. Patients were excluded in case of local excision or elective surgery after stenting or after an ileostomy procedure.

Data collection and outcome parameters

The following baseline information was extracted from the DCRA: age at diagnosis, sex, American Society Anesthesiology (ASA) score, Charlson Comorbidity Index (CCI) [19], clinical and pathologic tumor (T) and nodal (N) stage, neo-adjuvant therapy and surgical approach (open, laparoscopic, robot-assisted and other). Open surgery did not include converted laparoscopic surgeries. The ASA score was subdivided in ASA I/II and $\geq$ III and the CCI in 0, 1, 2 and $\geq$ 3 (according to an earlier DCRA study [1]). The DCRA registered several outcome measurements including postoperative mortality, postoperative surgical and non-surgical complications, length of stay and readmission. The primary outcome is the proportion of surgical and non-surgical complications. A surgical complication is defined as the occurrence of at least one surgical complication (anastomotic leakage, abscess, bleeding, ileus, fascia dehiscence, bowel perforation, leakage from bladder or ureter or surgical wound infection) and a non-surgical complication is defined as the occurrence of at least one non-surgical complication (pulmonary, cardiac, thromboembolic or neurologic event, infection (other than pulmonary or wound infection) or other). Between 2011 and 2017, the DCRA registered all outcome measurements till 30 days after surgery and from 2018 till 90 days after surgery. Due to this change in registration, we need to keep in mind that the postoperative complication rate for 2018 and 2019 will be a slight overestimation in comparison to the complication rate in 2011-2017.

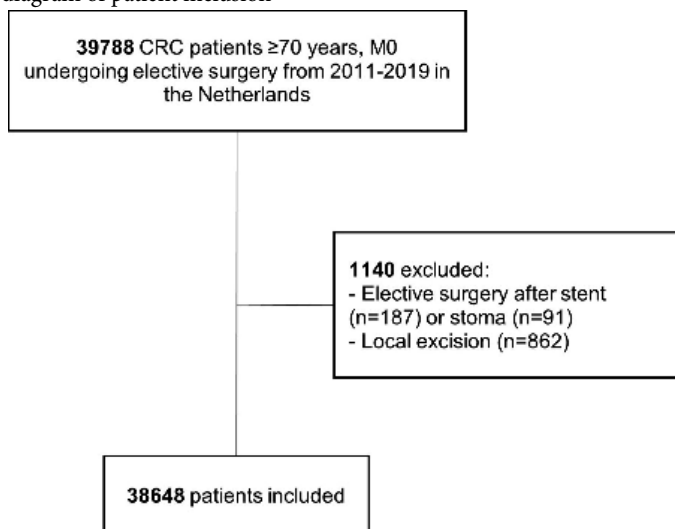
Statistical analysis

Continuous baseline variables were expressed as mean (normally distributed) with standard deviation (SD) and median (non-normally distributed) with interquartile range (IQR) and categorical variables as frequencies with percentages. To give a understandable overview of the trend in baseline characteristics, we compared the complete nine years by cohorts of three years; 2011-2013, 2014-2016 and 2017-2019. The postoperative complication rates (any, surgical and non-surgical) were depicted for each year separately. We performed multivariate logistic regression analysis to assess whether postoperative complications remained similar ($p > 0.05$), decreased ($OR < 1.0$ and $p < 0.05$) or increased ($OR > 1.0$ and $p < 0.05$) over the complete time period (2011-2019). Year of surgery was included as continuous variable. For multivariate analysis we considered age, sex, ASA-class, tumor localization, tumor stage and neo-adjuvant radiotherapy as clinically relevant. Only for tumor stage, the 'unknown' (missing and not judgeable) cases were categorized. The missing values of all other independent variables were excluded from the logistic regression analysis, as they hardly occurred ($< 0.002\%$) and were considered at random. As we assumed collinearity (based on epidemiological grounds) between 1. 'year of surgery' and 'surgical approach' and 2. 'CCI score' and 'ASA score' combined with a significant interaction ($p < 0.05$), both 'surgical approach' and 'CCI score' were excluded from the multivariate model. Subsequently we have stratified our cohort by three age categories: 70-74 years, 75-79 years and ≥ 80 years (as these groups had comparable number of patients) and performed the same analyses. Finally, we determined the impact of age on surgical or non-surgical complications during the complete study period using a multivariate logistic regression analysis including age as categorical variable. P-values below 0.05 were considered as statistically significant and all statistical analysis were performed with SPSS 25.0.

RESULTS

Study population

Overall, 39788 patients ≥ 70 years underwent stage I-III CRC resection between 2011-2019 in the Netherlands. Of these, 1140 patients were excluded as 862 received a local excision and 278 patients had elective surgery after stenting or after a temporary decompressing stoma. Eventually, the study included 38648 patients (Figure 1).

Figure 1. Flow diagram of patient inclusion

Baseline characteristics

Table 1 shows the patient-, tumor- and treatment characteristics of the years 2011-2013, 2014-2016 and 2017-2019. The median age was comparable between the three year cohorts and ranged between 76 and 77 years. The proportion of patients undergoing CRC resection with an ASA score $\geq$ III increased from 30.2% (2011-2013) and 30.4% (2014-2016) to 38.4% in 2017-2019. We found a clear decrease in open CRC resections (45.1% in 2011-2013 to 10.4% in 2014-2016) and increase in laparoscopic surgery (54.8% in 2011-2013 to 78.8% in 2014-2016) and robot-assisted surgery (0% in 2014-2016 to 5.3% in 2017-2019). Regarding patients with rectal cancer, neo-adjuvant radiotherapy played an increasingly minor role in standard care. Between 2011-2013, 19.8% of the older patients were not treated with neo-adjuvant radiotherapy, in contrary to 43.6% in 2014-2016 and 52.8% in 2017-2019.

Table 1. Baseline characteristics of the study cohort in proportions (%)

	2011-2013 N=11678	2014-2016 N=13911	2017-2019 N=13059
Median Age (IQR)	77 (73-82)	76 (73-81)	76 (73-81)
Sex			
Male	6220 (53.3)	7684 (55.2)	6994 (53.6)
Female	5458 (46.7)	6223 (44.7)	6063 (46.4)
ASA score			
ASA I/II	8126 (69.6)	9685 (69.6)	8047 (61.6)
ASA III+	3532 (30.2)	4224 (30.4)	5012 (38.4)

Table 1. Baseline characteristics of the study cohort in proportions (%) (*continued*)

	2011-2013 N=11678	2014-2016 N=13911	2017-2019 N=13059
Charlson comorbidity index			
0	4709 (40.3)	5376 (38.6)	5105 (39.1)
1	3044 (26.1)	3446 (24.8)	3312 (25.4)
2	2129 (18.2)	2702 (19.4)	2344 (17.9)
≥3	1796 (15.4)	2387 (17.2)	2298 (17.6)
Tumor localization			
Colon	8505 (72.8)	10316 (74.2)	9761 (74.7)
Rectum	3168 (27.1)	3593 (25.8)	3297 (25.2)
TNM stage			
Stage 0	193 (1.7)	205 (1.5)	208 (1.6)
Stage 1	3024 (25.9)	4051 (29.1)	3734 (28.6)
Stage 2	4523 (38.7)	5228 (37.6)	4754 (36.4)
Stage 3	3671 (31.4)	4344 (31.2)	4066 (31.1)
Unknown*	267 (2.3)	83 (0.6)	297 (2.3)
Surgical approach			
Open	5264 (45.1)	2832 (10.4)	1182 (9.1)
Laparoscopic	6403 (54.8)	10952 (78.7)	10569 (80.9)
Robot assisted	0	0	688 (5.3)
Other**	0	84 (0.6)	277 (2.1)
Unknown	11 (0.1)	43 (0.3)	343 (2.6)
Neo adjuvant radiotherapy^a			
None	599 (18.9)	1566 (43.6)	1740 (52.8)
Not specified	2569 (81.1)	1946 (54.2)	510 (15.5)
5x5 Gy	0	30 (0.8)	534 (16.2)
Chemoradiation	0	51 (1.4)	504 (15.3)
Neo adjuvant chemotherapy^a			
None	1916 (60.5)	1742 (48.5)	2203 (66.8)
Yes	356 (11.2)	366 (10.2)	532 (16.1)
Unknown	896 (28.3)	1485 (41.3)	562 (17.0)

Abbreviations: ASA American Society of Anesthesiologists

Additional missing data: sex (6 patients), ASA score (22 patients), localization (8 patients)

* missing or not judgeable

** other: Transanal and transabdominal endoscopic TME (TaTME of TAMIS TME)

^a Exclusively the patients with rectal cancer

[±] missing cases were excluded in chi-square test

Time-trends of postoperative complications

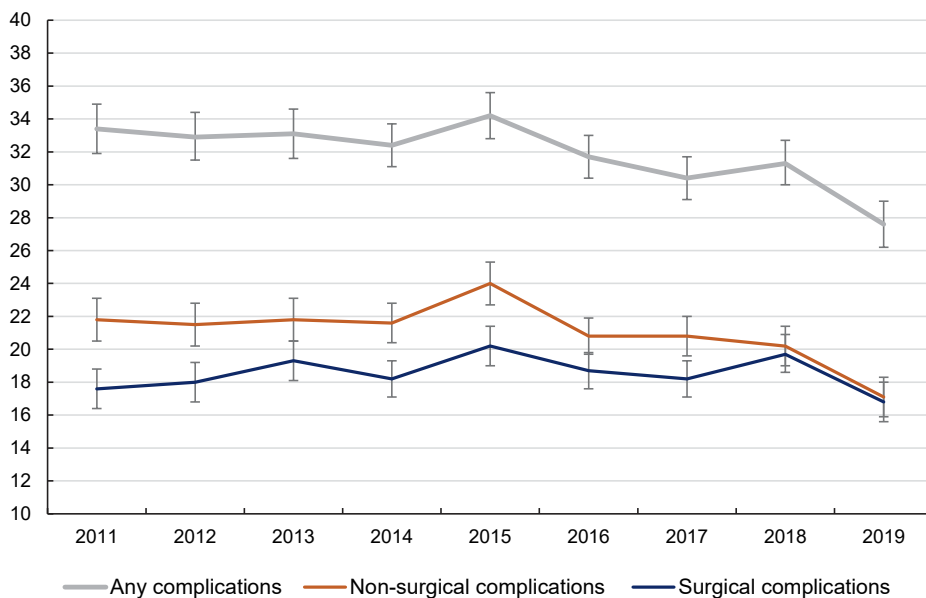
In the complete study cohort (n=38648), 12324 (31.9%) patients experienced any complications, 7166 (18.5%) experienced one or more surgical complications, 8143 (21.1%) experienced one or more non-surgical complications and 3220 (8.3%) experienced both. Figure 2 shows the trend of any complications, surgical and non-surgical complications. In 2011, 33.4% of the patients experienced any complications, 17.6% surgical complications and 21.8% non-surgical complications compared to respectively 27.6%, 16.8% and 17.1% in 2019. Both any, surgical and non-surgical complications peaked in 2015 to respectively 34.2%, 20.2% and 24.0%. The multivariate time-trend analyses showed a significant reduction in any (OR 0.97 (95% CI 0.96-0.98, $p<0.001$) and non-surgical complications (OR 0.97 (95% CI 0.96-0.98, $p<0.001$). The rate of surgical complications (OR 1.00 (95% CI 0.99-1.01, $p=0.524$) was constant over time.

Age-specific time-trends in postoperative complications

Overall, surgical complications occurred in 18.3% of the patients aged 70-74 years, in 18.3% of the patients aged 75-79 years and in 19.0% of the patients aged ≥ 80 years. Increasing age was not associated with surgical complications; the OR for patients aged 75-79 year was 1.00 (95% CI 0.94-1.06) and 1.03 (95% CI 0.97-1.10) for patients aged ≥ 80 compared to patients aged 70-74 years. Non-surgical complications occurred in 17.8%, 20.4% and 25.1% in patients aged 70-74 years, 75-79 years and ≥ 80 years respectively. Increasing age significantly increased the risk for non-surgical complications, as the OR for age 75-79 years was 1.17 (95% CI 1.10-1.25) and for ≥ 80 years 1.46 (95% CI 1.37-1.55) compared to patients aged 70-74 years.

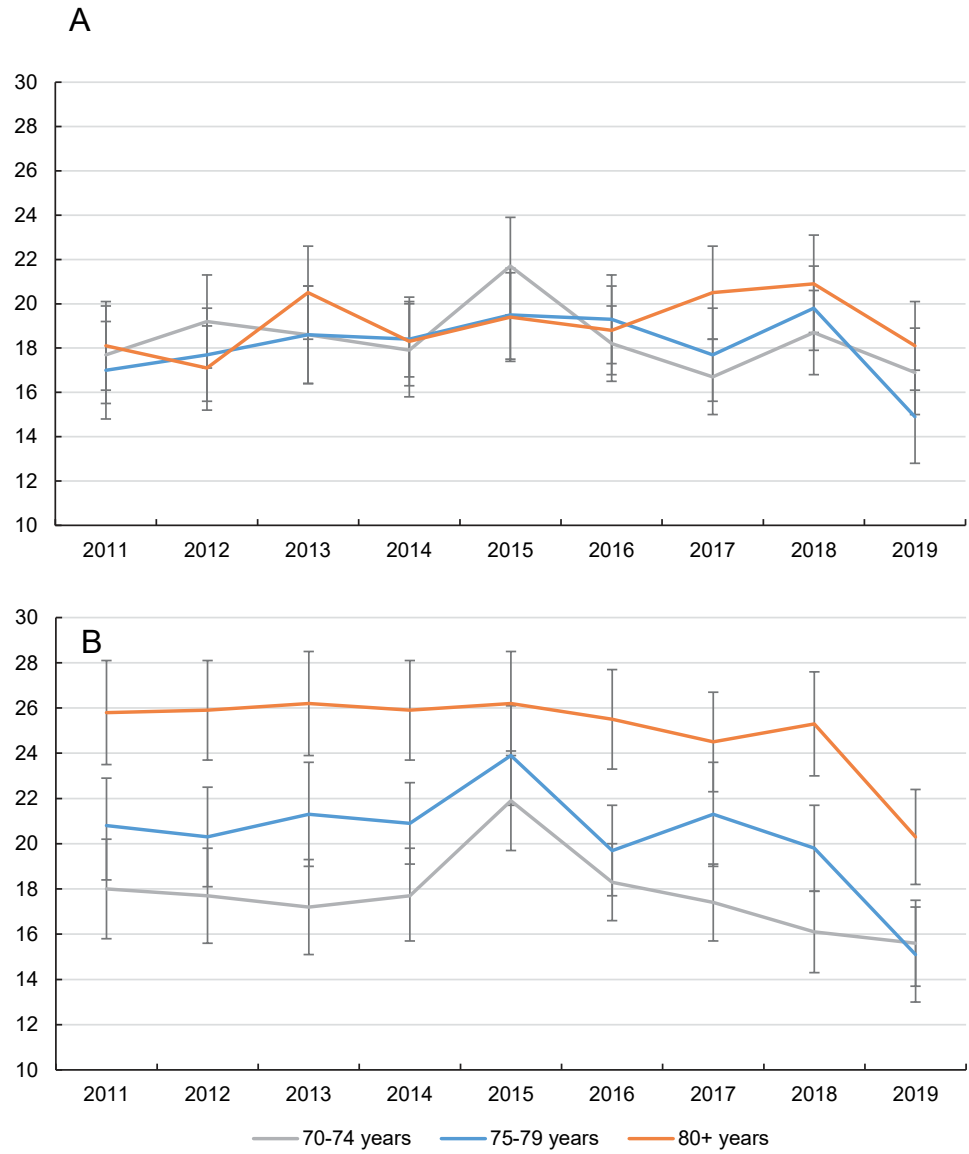
The trends of surgical (A) and non-surgical (B) complications per age group are shown in Figure 3. Within the age groups 70-74 years, 75-79 years and ≥ 80 years, 17.7%, 17.0% and 18.1% experienced surgical complications in 2011 compared to 16.9%, 14.9% and 18.1% in 2019. None of these improvements were significant ($p>0.05$). The rate of non-surgical complications was 18.0%, 20.8% and 25.8% in 2011 compared to 15.6%, 15.1% and 20.3% in 2019. The improvement was only significant for patients aged 75-79 years and ≥ 80 years. (70-74 years: $p=0.061$, 75-79 years; $p=0.009$, ≥ 80 years; $p<0.001$).

Figure 2. The time-trend (in proportions) of postoperative complications between 2011 and 2019 in the Netherlands



NB. “Any complication” does not represent the sum of surgical and non-surgical complications, as one patient may experience both a surgical and a non-surgical complication

Figure 3. The time-trend (in proportions) of surgical (A) and non-surgical (B) complications between 2011 and 2019 in the Netherlands



DISCUSSION

This study provides insight in the time-trends and age-specific risk differences of postoperative complications in patients of 70 years and older receiving elective non-metastatic CRC surgery by differentiating between surgical and non-surgical complications. Between 2011 and 2019, the rate of complications declined. This improvement must be completely attributed to the reduction of non-surgical complications, since the surgical complication rate did not significantly improve. The same trends were observed after stratifying by age category. Increasing age was only associated with non-surgical complications and not with surgical complications.

To our knowledge, this is the only study describing such recent and nationwide time-trends of postoperative complications in older CRC patients. Our findings are in line with the study from de Neree tot Babberich et al., that consisted of patients receiving elective CRC surgery of all ages in the Netherlands from 2009-2016. They described a slight increase in surgical and non-surgical complications in 2015/2016 (in line with Figure 2) and suggested that complications may have been registered and identified more thoroughly [1]. Furthermore, changes in baseline characteristics (Table 1) could positively or negatively affect the a priori risk of postoperative complications, such as the increased proportion of comorbidity (ASA and CCI score $\geq$ III), a higher percentage of early CRC cancer (the Dutch colorectal cancer screening program was initiated in 2014) or a less frequent use of neo-adjuvant radiotherapy [20].

Since we corrected for these baseline characteristics, our findings suggest that several care developments (such as minimally invasive surgery, enhanced recovery after surgery (ERAS), comprehensive geriatric assessments (CGA) and prehabilitation programs) have a larger effect on non-surgical complications than on surgical complications. Minimally invasive surgery, the ERAS protocol and geriatric screening followed by a CGA have been increasingly implemented throughout the Netherlands over the last decade [21]. Prehabilitation has been taken up by several hospitals in the context of research or quality-improvement programs, but is not widely implemented yet [22-25]. Earlier studies showed that minimally invasive surgery and the ERAS protocol mainly improve postoperative medical morbidity [26-30]. Evidence for geriatric-specific care pathways – such as preoperative comprehensive geriatric assessment (CGA) and in-hospital geriatric co-management – to reduce (non)-surgical complications, is still inconsistent. Although Ommundsen et al described a significant decrease in Grade I-V complications after CGA [31], Hempenius et al [32] found no effect on postoperative delirium or overall complications. Geriatric co-management improves 90-days mortality [33] and reduces delirium and other geriatric syndromes (e.g. falls, pressure ulcers) [34]. However, a positive effect on postoperative complications was only found in (two out of seven) studies which are not performed in older CRC patients [35]. Furthermore, a recent study from our group suggested that prehabilitation in older patients has more value for reducing non-surgical complications than surgical complications [10]. Two randomized trials

demonstrated that prehabilitation reduces the overall postoperative complication rate [24, 36] Interestingly, in the Barbaran-Garcia-study this reduction was also driven by a decrease in non-surgical complications and no reduction was observed for surgical complications [36].

The present study demonstrated that the risk for non-surgical complications increased with increasing age and the risk for surgical complications was similar among the old, older and oldest CRC patients. Several studies support the fact that – within the older population – increasing age is associated with any complication [6, 13, 14, 17]. However, none of these studies initially differentiate between surgical and non-surgical complication. Some studies indicate a potential higher impact of age on non-surgical complications than surgical complications. For example, Kvasnovsky et al, in a retrospective cohort of elderly patients receiving laparoscopic CRC surgery, described an increase of infectious complications (especially chest infections), from 14.8% (in patients < 65 years) to 22.7% (in patients 65-80 years) and to 44.4% in patients > 80 years ($P = 0.01$) [17]. Barina et al, including a retrospective cohort of 47704 older patients (≥ 65 years) undergoing laparoscopic CRC surgery, showed an increase in overall postoperative complications with increasing age, however there was no association among patients aged 65-74 years, 75-84 years and $\geq 85+$ years regarding anastomotic leakage or surgical site infections [14].

Approximately 40% of the older CRC population is frail [37], characterized by an high vulnerability state that increased the risk for adverse health outcomes [38] like postoperative complications [4, 6, 7, 39-42]. It is suggested that non-surgical complications, such as cardiopulmonary complications, are related to a poor preoperative condition or reduced postoperative activity during hospital admission [43]. Frailty may have a limited interaction with surgical complications, as perioperative factors (e.g., surgical approach, surgeon expertise) and tumor characteristics (tumor size, lymph node invasion) may outweigh frailty. The increasing prevalence of frailty with increasing age [44] might explain why the age-specific differences are predominantly found in non-surgical complications and not in surgical complications.

The decrease in non-surgical complications was only seen in the oldest two age groups (figure 3) and suggests that the oldest patients may be more prone to improvement of the non-surgical complications or that clinical practice already has shifted attention in pre- and perioperative care towards the oldest patients. This supports the hypothesis that future care developments – like prehabilitation – should target non-surgical complications in the geriatric population.

Our study has a few limitations. Our cohort only included patients that were considered fit enough for surgical treatment. This selection may have influenced complications rates. The lower complication rates in recent years may have been due to an improved selection prior

to surgery. Furthermore, this pre-selection could have been more dominant in the oldest age groups as older patients are less likely to undergo surgery, especially for rectal cancer [45, 46]

Although colon and rectal cancer are usually combined in the literature, both diseases have different patient characteristics and postoperative outcome [47]. We have checked whether results were different for colon and rectal cancer in our study. The stratified analysis showed comparable results. However, for rectal cancer surgery results were less straightforward for two reasons. First, surgical complications increased in 2018-2019. This could have been because from 2018 the registration-period in DCRA changed from 30- to 90-days post-surgery and because of a significantly lower number of defunctioning stomas over recent years. Second, in recent years the differences in non-surgical complication rates between the old, older, and oldest patients were smaller. As rectal cancer patients tend to be somewhat younger than colon cancer patients, the results for older rectal cancer patients could be slightly skewed. Especially because in rectal cancer there are more alternatives to surgical treatment (chemotherapy, radiotherapy, watch and wait), surgery is offered less frequent to older patients [45]. This could explain the smaller gap between the old, older and oldest patients, as in the oldest group only the most fit would undergo surgery.

we had no data on the severity of complications, and we were unable to rank complications using the Clavien-Dindo Classification. Likewise, we had no information about the potential long-term impact of complications. Furthermore, we had no detailed information about frailty characteristics that could have been helpful to further interpret our findings. However, the main strength of this study is its large sample size representing 'real life' data on a national level. The completeness of the DCRA data has been reported to be over 95% [18].

CONCLUSIONS

Over the years, the overall improvement in postoperative complications after CRC resection in the older population was predominantly driven by a decrease in non-surgical complications. Moreover, increasing age was only associated with non-surgical complications and not with surgical complications. Therefore, future care developments should preferably focus on non-surgical complications, especially in the oldest patients (≥ 75 years).

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6

Daily functioning and quality of life after colorectal cancer surgery for patients with frailty; data from the multicenter prospective TENT study

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Submitted



ABSTRACT

Background and purpose

We aimed to describe the course of physical functioning and quality of life (QoL) after CRC surgery for older patients with and without frailty and patients with and without complications and to assess the interaction between frailty and postoperative complications on these outcomes.

Methods

Patients ≥ 70 years, receiving stage I-III CRC surgery, and participating in the TENT study were included. Geriatric assessment, physical functioning (Katz-ADL, Lawton iADL), QoL (EQ-5D-3L, EQ-VAS) and complications were collected. Follow-up for functioning and QoL was at six and twelve months after surgery. Frailty was defined as $\geq 2/4$ impaired geriatric domains. Multivariate linear mixed models were used to determine the change in functioning and QoL and logistic regression analysis to determine interaction between frailty and complications.

Results

We included 138 patients; median age was 79 years, 51.4% was male and 79.7% had colon cancer. Seventy-five (54.3%) patients were frail and 56 (40.6%) patients experienced complications. Frail and non-frail patients experienced comparable complication rate (37.3% vs 44.4%, $p=0.396$). Postoperative changes in functioning and QoL were similar for frail and non-frail patients. Patients with complications experienced a temporary drop in ADL (-0.40 (95% CI -0.72- -0.08)) and EQ-5D-3L (0.12 (0.05-0.19)) at six months, which restored after one year. No interaction between frailty and complications on functional and QoL decline was found.

Conclusions

CRC surgery equally affects frail and non-frail patients and patients with or without complications after one year. However, lower baseline of functioning and QoL puts frail patients at risk of losing independence.

INTRODUCTION

More than half of all patients diagnosed with colorectal cancer (CRC) is 70 years or older[1]. Due to increasing incidence of CRC with age and the increasing life expectancy, the proportion of older patients with CRC will continue to grow. The older population is very heterogeneous, and these patients present with a broad variety of health status and medical histories. Therefore, it is necessary to assess an older patients' individual surgical risk prior to surgical treatment; the primary treatment for curative CRC [2]. Geriatric screening followed by a geriatric assessment (GA) is considered standard care and determines frailty on somatic, functional, cognitive, and psychosocial domains [2]. The patients identified as frail have an increased risk of postoperative adverse events like complications, readmission, and mortality [3-9].

Patient-centered outcome measures, such as physical functioning and QoL, play an important role in risk assessment for the older population [10, 11]. Several studies showed that CRC surgery is associated with functional decline [12-14] and other studies found that surgery temporarily improves the QoL for older patients with colorectal cancer [15-22].

However, there are only a few studies investigating the impact of frailty on patient-centered outcomes after CRC surgery, despite the high prevalence (40%) of frailty in the older population [23] and its higher risk of adverse outcome after CRC surgery. Two studies showed that patients with frailty, compared to patients without frailty, had lower physical functioning and QoL at baseline and in the follow-up period after surgery [15, 16]. One study found an association of frailty with a reduction in QoL [24], as two other studies found no association between frailty and the decline in physical functioning and QoL [14, 21]. A decline in postoperative functioning and QoL is usually linked to the occurrence of any postoperative complication [25-27]. As frailty is a relevant concept for clinical practice and only a few studies investigated the impact of frailty on daily functioning and QoL, more insight is needed to improve preoperative counselling and expectation management and to optimize pre-, peri-, and postoperative care. Therefore, first we aimed to describe the course of physical functioning and QoL for older patients with and without frailty and for patients with and without complications one year after CRC surgery. Second, we aimed to assess the interaction between frailty and postoperative complications on these outcomes.

METHODS

Triage Elderly Needing Treatment (TENT) study

This study was executed in the context of the TENT study, which is an ongoing prospective cohort study that was initiated in 2016 to investigate *'the associations between geriatric characteristics and outcomes of treatments that are relevant to older patients'*[28]. Patients aged 70

years and older who need intensive treatment and have a consultation in oncology outpatient clinics are eligible. A pathway was implemented to perform a geriatric screening and GA at baseline and to assess follow-up by telephone at six and 12 months after the primary treatment. In case of an abnormal geriatric screening, patients were referred to the geriatrician for a GA. In case of a normal geriatric screening, patients received a short GA by telephone. Informed consent was required to participate. The study was approved by the Medical Ethics Committee (ID number NL53575.058.15) at the LUMC. Details on the design and data collection are described in the published study protocol [28].

Study population

The current study consists of all patients who were diagnosed with CRC needing surgical treatment of the primary tumor and enrolled in the TENT study between May 2016 and February 2021 at Leiden University Medical Center (LUMC) in Leiden (academic hospital), Haga Hospital in The Hague, and Reinier de Graaf Hospital in Delft (teaching hospitals). Patients were excluded in case of metastatic disease or surgery with a palliative intent.

Data collection

Patients demographics, tumor and treatment characteristics, and postoperative complications were prospectively collected through the medical record. Race or ethnicity data was not available in the medical record and therefore not included in the TENT study. The tumor stage was based on the TNM Classification of Malignant Tumors 8th edition. Next to the surgical treatment, patients could receive neo- and/or adjuvant therapy (neoadjuvant radiotherapy, chemoradiation or (neo)adjuvant chemotherapy). Neoadjuvant radiotherapy and chemoradiation were only indicated in patients with rectal cancer. Postoperative complications were defined as any postoperative complication during admission; such as infections, delirium, ileus, and re-operation [28].

Geriatric screening and assessment

The geriatric-8 (G8) score [29] and Six-Item Cognitive Impairment Test (6CIT) [30] were used for geriatric screening. The G8 (range 0-17 points) was impaired when ≤ 14 and the 6CIT (range 0-28 points) when > 7 . The GA consisted of four domains: somatic, functional, psychological and social domain. If two or more domains were impaired, patients were defined as 'frail'. A domain was impaired if one of the components was abnormal. The somatic domain consisted of polypharmacy (≥ 4 medications), malnutrition (≤ 11 points on the Mini Nutritional Assessment Short Form (MNA-SF[31]), and comorbidity (Charlson comorbidity index (CCI) score ≥ 1). The functional domain included fall incidents in the last six months, institutionalization, and functional dependency based on the Katz Activities of Daily Living (ADL) questionnaire and the Lawton Instrumental Activities of Daily Living (iADL). The ADL questionnaire ranges from 0 to 6 with higher scores meaning higher dependency and was impaired if ≥ 2 [32]. The iADL questionnaire ranges from 0 to 5 for men (impaired when ≤ 4) and from 0 to 8 for women (impaired when ≤ 7) with higher scores meaning lower

dependency [33]. The psychological domain consisted of history of delirium, history of dementia, and cognitive impairment based on 6CIT > 7. The social domain contained the living status and was defined abnormal when a patient lived alone.

Next to the GA, the EQ-5D-3L and EQ-VAS questionnaires were collected to express a patients' current QoL. The EQ-5D-3L is a validated five items questionnaire [34]. Each item – 'mobility', 'self-care', 'activity', 'pain', and 'anxiety' – is categorized in three levels (1. no problems, 2. some problems, 3. severe problems). The overall result is expressed in a combination of five numbers (for example 22123 meaning; some problems in mobility, some problems in self-care, no problems in activity, some problems in pain, and severe problems in anxiety). The EQ-5D-3L five number combination can be converted to a country-specific validated index value that ranges from 0-1. We modified the EQ-5D-3L according to official guidance using the Dutch value sets [35, 36]. The EQ-VAS [34] is a description of a patient's overall health status on a visual analogue scale ranging from 0-100 that corresponds to the patient's indication for their health status that day. In the TENT study, the question was described by the researcher and the verbal answer of the patient was registered.

Outcomes

The primary outcomes were the course in ADL, iADL (physical functioning), EQ-5D-3L, and EQ-VAS (QoL) and were collected by telephone at six and twelve months after surgery. To assess any change over time, the mean ADL, iADL, EQ-5D-3L index value, and EQ-VAS were used.

Statistical analysis

Normally distributed continuous baseline variables were compared by the T-test and non-normally distributed by the Mann-Whitney U test. Categorical variables were compared by the Chi-square test. The iADL scores for male and female were analyzed separately. For the first analysis – to assess the course of physical functioning and QoL from baseline to one year after CRC surgery – we used a multivariate linear mixed model (LMM). The LMM was performed with a first-order autoregressive structure with heterogeneous variances (AR1 heterogeneous) as covariance type, a maximum likelihood AS and 100,10 iterations. The key model included time (T0, T6, T12) and potential confounders (age, sex, tumor location (colon/rectum) and tumor stage) as independent variables to determine whether ADL, iADL, EQ-5D-3L, and EQ-VAS change over time. To assess any difference in one-year postoperative course for patients with and without frailty, we included 'frailty status' (frail or not frail) to the key model (model 1). The interaction term frailty*time was added separately to the model to test whether the change in time was different for frail and non-frail patients. To assess a difference in one-year postoperative course for patients with and without complications, we included 'complications' (any or no complications) as independent variable instead of frailty status to the key model (model 2). Again, the interaction term complications*time was added

separately. If the interaction was significant ($p < 0.05$), stratified analysis was indicated. Model 1 and 2 were both visualized in a line graphic.

For the second analysis, logistic regression analysis was used to further investigate the effect of frailty and complications on a decline in functioning or QoL. The dependent variable was defined as a clinical relevant decline in ADL, iADL, EQ-5D-3L and EQ-VAS at six and at twelve months. In accordance to other TENT studies [37], a clinical relevant decline in ADL and iADL was defined as a decline of ≥ 1 point [38] and a decline in EQ-5D-3L and EQ-VAS was based on the minimal clinically important difference and respectively defined as ≥ 0.06 and ≥ 7 points [39]. The independent variables included frailty or complications, and the baseline values as a continuous variable (baseline levels of physical functioning and QoL for patients with frailty are lower than for patient without frailty). The interaction term frailty*complications was added to determine any interaction between frailty and complications. Unfortunately, we were not able to adjust for other potential confounders due to low number of events.

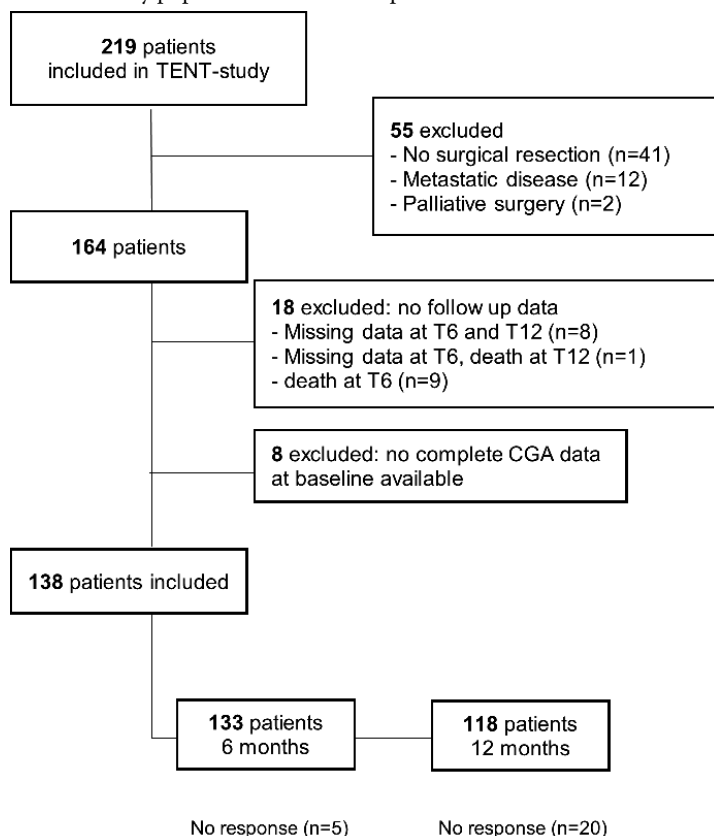
We ran the analyses on complete data, meaning that missing data were excluded. P-values below 0.05 will be considered as statistically significant and all statistical analysis will be performed with SPSS 25.0.

RESULTS

Study population

In total, 219 patients aged ≥ 70 years were diagnosed with CRC and participated in the TENT study between May 2016 and February 2021. Fifty-five patients were excluded because they did not fit the inclusion criteria. Of the 18 patients without follow-up data, nine patients had died prior to six months, one patient did not respond at six months and died prior to 12 months and eight patients did not respond at all. Patients who died had higher percentage of CCI ≥ 2 (80% vs 30.5%, $p = 0.001$) and any complications (80% vs 39.6%, $p = 0.012$) compared to patients with follow-up data ($n = 146$). In addition, for eight patients frailty could not be assessed due to incomplete GA data. Eventually, the study cohort consisted of 138 patients (Figure 1). Between six and twelve months, we observed no additional deaths.

Figure 1. Flow chart of study population and follow-up



Baseline characteristics

Table 1 shows the baseline characteristics of the study population. Median age was 79 years (IQR 74-82), 51.4% was male and the majority of patients was diagnosed with colon carcinoma (79.7%). Seventy-five patients (54.3%) were considered frail and 63 patients (45.7%) were considered not frail. Age, sex, body mass index (BMI), tumor location, and tumor stage did not differ between both groups. Two patients (1.4%) were ADL dependent and 12 (17.1%) men and 16 (24.2%) women were iADL dependent. Compared to patients without frailty, patients with frailty had lower QoL at baseline: EQ-5D-3L (0.88 vs 0.80, $p=0.032$) and EQ-VAS (75.80 vs 68.75, $p=0.006$).

One-year postoperative course of physical functioning and QoL in older patients with CRC

In the entire study cohort, ADL decreased at six months (ADL estimate difference -0.19 (95% CI -0.34- -0.04; $p=0.015$)) and restored at twelve months after surgery. IADL decreased at six (men 0.25 (95% CI 0.05-0.45 $p=0.015$); women 0.66 (95% CI 0.34-0.99; $p<0.001$) and twelve months (men 0.34 (95% CI 0.11-0.40, $p=0.004$); women 0.60 (95% CI 0.32-0.89; $p<0.001$)).

The EQ-5D-3L score decreased at six months (0.04 (95% CI 0.0-0.08; $p=0.036$) and restored at twelve months. The EQ-VAS scores did not change over time.

One-year postoperative course of physical functioning and QoL for patients with and without frailty

The one-year postoperative course of ADL, iADL, and EQ-5D-3L for patients with frailty and without frailty was similar (Figure 2), reflected by the non-significant interaction between time and frailty (ADL $p=0.855$, iADL men $p=0.130$, women $p=0.345$ and EQ-5D-3L $p=0.935$). However, frail patients showed a constant lower level of ADL (0.15 (95% CI -0.31- -0.01), $p=0.048$), iADL (men: 0.61 (95% CI 0.31-0.90), $p < 0.001$), women: 0.52 (95% CI 0.04-0.99), $p=0.033$) and EQ-5D-3L (0.07 (95% CI 0.01-0.13), $p=0.032$) compared to non-frail patients. The postoperative course of EQ-VAS for frail and not frail patients was slightly different, reflected by the significant interaction between time and frailty for EQ-VAS ($p=0.020$). In the first six months, the EQ-VAS significantly improved for frail patients (estimated difference 5.74 (95% CI 1.38 – 10.10), $p=0.011$) and remained constant for non-frail patients (1.88 95% CI -1.53 – 5.29); $p=0.275$).

One-year postoperative course of physical functioning and QoL for patients with and without complications

Fifty-six patients (40.6%) experienced at least one or more complications. Frailty was not associated with any postoperative complication: 37.3% ($n=28$) of the patients with frailty and 44.4% ($n=28$) of the patients without frailty experienced any complication ($p=0.396$).

Figure 3 showed that the one-year postoperative course of ADL and EQ-5D-3L differs for patients with and without complications, reflected by a significant interaction between time and complications (ADL $p=0.023$, EQ-5D-3L $p=0.002$). At six months, ADL decreased for patients with complications (-0.40 (95% CI -0.72 - -0.08) $p=0.015$) in contrary to patients without complications (-0.05 (95% CI -0.18-0.09) $p=0.499$). Similarly, EQ-5D-3L decreased after six months for patients with complications (0.12 (95% CI 0.05-0.19) $p=0.001$), however no change was observed (-0.01 (95% CI -0.05-0.04) $p=0.686$) for patients without complications. At twelve months, ADL and EQ-5D-3L levels returned to the baseline level. The one-year postoperative course of iADL and EQ-VAS for patients with and without complications were similar, reflected by the non-significant interaction (iADL $p=0.087$ (men) $p=0.173$ (women), EQ-VAS $p=0.208$).

Table 1. Baseline characteristics including patient demographics, tumor- and treatment characteristics, and geriatric screening

	Total n=138 (%)	Frail n=75 (%)	Not frail n=63 (%)	P-value ^a
Patient and tumor characteristics				
Median age (IQR)	79.0 (74.0-82.0)	80.0 (75.0-83.0)	77.0 (74.0-81.0)	0.069
Sex				0.587
Male	71 (51.4)	37 (49.3)	34 (54.0)	
Female	67 (48.6)	38 (50.7)	29 (46.0)	
Mean BMI (SD)	25.8 (23.7-29.2)	25.7 (22.6-29.4)	25.8 (24.1-28.9)	0.974
Tumor location				0.449
Colon	110 (79.7)	58 (77.3)	52 (82.5)	
Rectum	28 (20.3)	17 (22.7)	11 (17.5)	
Tumor stage (TNM)				0.120
Stage I	36 (26.1)	20 (26.7)	16 (25.4)	
Stage II	47 (34.1)	29 (38.7)	18 (28.6)	
Stage III	51 (37.0)	29 (34.7)	25 (39.7)	
Missing	4 (2.9)	0 (0.0)	4 (6.3)	
Neo- and adjuvant therapy *				0.875
Neoadjuvant radiotherapy **	6 (21.1)	5 (29.4)	1 (9.1)	
Neoadjuvant chemotherapy	3 (2.2)	2 (2.7)	1 (1.6)	
Chemoradiation **	2 (7.1)	1 (5.9)	1 (9.1)	
Adjuvant chemotherapy	14 (10.1)	3 (4.0)	11 (17.5)	
Charlson comorbidity index				NA
0-1	95 (68.8)	43 (57.3)	52 (82.5)	
≥2	43 (31.2)	32 (42.7)	11 (17.5)	
Geriatric-8				NA
Abnormal	85 (61.6)	53 (70.7)	32 (50.8)	
Missing	10 (7.2)	3 (4.0)	7 (11.1)	
6-CIT				NA
Abnormal	13 (9.4)	13 (17.3)	0 (0.0)	
Missing	5 (3.6)	4 (5.3)	1 (1.6)	
Polypharmacy (≥4 medications)	52 (37.7)	30 (40.0)	22 (34.9)	NA
Malnutrition (≤ 11 points)	70 (50.7)	45 (60.0)	25 (39.7)	NA
Fall incidents	23 (16.7)	22 (29.3)	1 (1.6)	NA
Institutionalization	3 (2.2)	3 (4.0)	0 (0.0)	NA
ADL ^a				NA
Dependent	2 (1.4)	2 (2.7)	0 (0.0)	
iADL ^b				NA
Men - Dependent	12 (17.1)	12 (33.3)	0 (0.0)	
Women - Dependent	16 (24.2)	15 (40.5)	1 (3.4)	
History of delirium	14 (10.2)	14 (18.9)	0 (0.0)	NA

Table 1. Baseline characteristics including patient demographics, tumor- and treatment characteristics, and geriatric screening (*continued*)

	Total n=138 (%)	Frail n=75 (%)	Not frail n=63 (%)	P-value^u
Dementia	1 (0.7)	1(1.3)	0 (0.0)	NA
Living alone	51 (37.0)	42 (56.0)	9 (14.3)	NA
Quality of Life				
EQ-5D-3L index value (mean, SD)	0.84 (0.20)	0.80 (0.23)	0.88 (0.15)	0.032
EQ-VAS (mean, SD)	71.95 (14.67)	68.75 (16.62)	75.80 (10.85)	0.06

*for the majority of the patients information about additional treatment was missing (for chemotherapy n=121, for radiotherapy n=132)

**Neoadjuvant radiotherapy and chemoradiation was only indicated in patients with rectal cancer

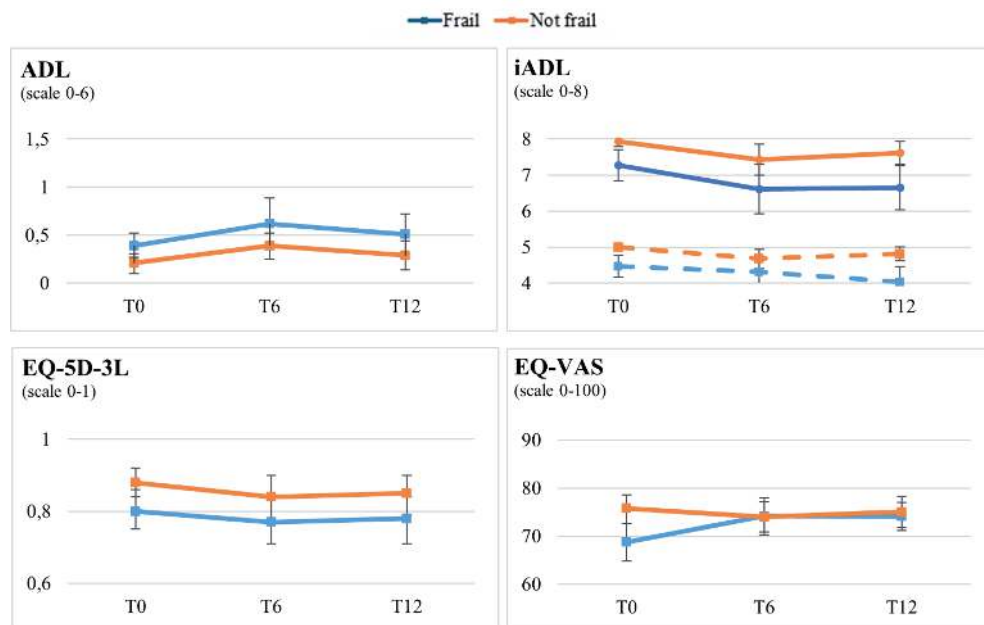
μ NA: not applicable. Variables were used in the frailty definition.

for 16 patients EQ-5D-3L score was unknown (8 frailty group, 8 non-frail group)

for 8 patients EQ-VAS score was unknown (4 frailty group, 4 not-frail group).

Abbreviations: *IQR* interquartile range, *SD* standard deviation, *TNM* TNM Classification of Malignant Tumors 8th edition

Figure 2. Observed means of ADL, iADL, EQ-5D-3L index value and EQ-VAS at baseline (T0), six months (T6), and twelve months after surgery (T12) for patients with and without frailty. Number of patients are shown in the table below.



ADL	T0	T6	T12
Not frail (n)	74	62	52
Frail (n)	74	71	65

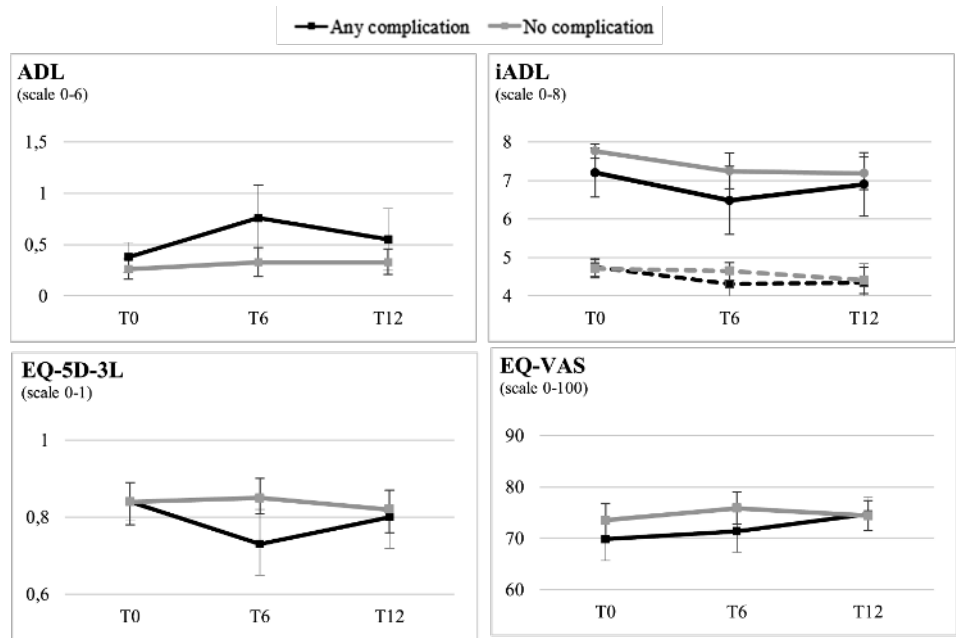
EQ-5D-3L	T0	T6	T12
Not frail (n)	55	62	52
Frail (n)	67	68	65

iADL*	T0	T6	T12
Not frail (n)	29 34 28	34 26 27	
Frail (n)	37 36 36	35 32 33	

EQ-VAS	T0	T6	T12
Not frail (n)	59	61	53
Frail (n)	71	66	62

* first column: women, second column; men.

Figure 3. Observed mean of ADL, iADL, EQ-5D-3L index value, and EQ-VAS at baseline (T0), six months (T6), and twelve months after surgery (T12) for patients with any and no complications. Numbers of patients are shown in the table below.



ADL	T0	T6	T12
No compl (n)	85	81	79
Any compl (n)	60	59	45

EQ-5D-3L	T0	T6	T12
No compl (n)	85	81	79
Any compl (n)	60	59	45

iADL*	T0	T6	T12
No compl (n)	29	34	28
Any compl (n)	37	36	36

EQ-VAS	T0	T6	T12
No compl (n)	85	81	79
Any compl(n)	60	59	45

* first column: women, second column; men.

Interaction between frailty and complications

At six and twelve months after CRC surgery, respectively 28 (21.1%) and 22 (18.8%) patients experienced a clinical relevant decline in ADL, 38 (28.6%) and 35 (29.7%) patients in iADL, 39 (30%) and 34 (29.1%) patients in EQ-5D-3L and 32 (27.4%) and 26 (22.6%) patients in EQ-VAS.

As shown in Table 2, frailty and complications were only associated with a decline in EQ-5D-3L at six months, respectively corresponding to an OR of 2.44 (95% CI 1.08-5.54, p=0.033) and OR 2.31 (95% CI 1.05-5.08, p=0.037). Frailty or complications were not associated with a clinical decline in ADL, IADL, or EQ-VAS. There was no significant interaction between

frailty and complications on a clinical relevant decline in physical functioning or QoL at six and twelve months.

Table 2. Logistic regression of frailty and complications for a clinical relevant decline in ADL, iADL, EQ-5D-3L, and EQ-VAS after six and twelve months after surgery.

	Frailty			Complications			Frailty* complications
	N	OR (CI)	p-value	n	OR (CI)	P-value	P-value
Six months							
ADL decline (n=28)	15	1.18 (0.50-2.77)	0.710	14	1.66 (0.71-3.91)	0.243	0.424
iADL decline male (n=16)	10	2.00 (0.59-6.79)	0.268	10	2.29 (0.72-7.25)	0.160	0.260
iADL decline Female (n=22)	15	1.44 (0.44-4.73)	0.544	11	1.97 (0.64-6.21)	0.238	0.918
EQ-5D-3L decline (n=39)	26	2.44 (1.08-5.54)	0.033	22	2.31 (1.05-5.08)	0.037	0.311
EQ-VAS decline (n=32)	17	1.36 (0.58-3.21)	0.477	15	1.57 (0.66-3.73)	0.305	0.540
Twelve months							
ADL decline (n=22)	14	1.70 (0.64-4.49)	0.293	9	1.35 (0.52-3.53)	0.541	0.731
iADL decline male (n=15)	11	2.51 (0.64-9.84)	0.188	6	1.09 (0.32-3.69)	0.894	0.102
iADL decline female (n=20)	14	2.23 (0.64-7.75)	0.208	6	0.55 (0.16-1.92)	0.349	0.533
EQ-5D-3L decline (n=34)	20	1.50 (0.63-3.53)	0.358	14	1.19 (0.51-2.80)	0.684	0.933
EQ-VAS decline (n=26)	15	1.77 (0.63-4.94)	0.276	10	1.51 (0.52-4.36)	0.446	0.903

DISCUSSION

This prospective cohort of older patients undergoing CRC surgery shows that frail patients experience lower physical functioning (ADL, iADL) and lower QoL (EQ-5D-3L) before, at six, and at twelve months after surgery compared to non-frail patients. Nevertheless, the post-operative changes in physical functioning and QoL were similar. Furthermore, patients with complications had comparable physical functioning and QoL scores after one year compared to patients without complications. However, the patients with complications experienced a temporary drop in ADL and EQ-5D-3L scores at six months, which was not observed in patients without experiencing any complications. Lastly, frailty and complications did not interacted on the postoperative course of physical functioning and QoL. Our findings suggest that CRC surgery equally affects frail and non-frail patients and patients with or without complications after one year. As particularly patients with frailty have lower levels of physical functioning and QoL – and apparently do not benefit from surgery with functional or QOL recovery – these patients are at high risk of further deterioration and losing independence.

The course of physical functioning after surgery in older patients with CRC in our study is in line with earlier studies. The majority of the studies found the largest functional decline in the first three months after CRC surgery, followed by an partial improvement of physical function after six to twelve months [12, 14-16]. The postoperative course of QoL after CRC

in the present study was consistent with studies that showed a constant QoL after surgery [22,41,42], although several other studies described an improvement of QoL after CRC surgery in older patients [15, 16, 22, 24, 40-42]. As our study had no information about QoL at three months after surgery, we were not able to observe a change in QoL in the first three months.

Insight in postoperative physical functioning and QoL, particularly in patients with frailty, is limited to a few studies. In agreement with our study; Ronning et al found persistent lower scores in physical functioning and QoL over the first postoperative 16-24 months for patients with frailty compared to patients without frailty [15] and Souwer et al showed that the levels of physical functioning and QoL in the one-year follow-up period were persistently lower in disadvantage of the functional dependent patients [16]. However, Van der Vlies et al [21] and Ronning et al [14] found no association of frailty indicators on functional decline or a reduced QoL, respectively at three or at 16-28 months after surgery. The GOSAFE study, found the opposite. This study aimed to “*prospectively collect a baseline multidimensional evaluation before major elective surgery in patients (≥ 70 years) from 26 international units. Short-/mid-/long-term surgical outcomes were recorded with QoL and Functional recovery (FR) data*” [43]. Montroni et al (multicenter study with 646 patients) found that preoperative frailty (Flemish Triage Risk Screening Tool ≥ 2 and Eastern Collaborative Oncology Group performance status ≥ 2) was associated with a decline in QoL and with the failure of functional recovery three and six months after specifically CRC surgery [24]. Our results only found a significant association of frailty with a decline in EQ-5D-3L, but not with ADL, iADL and EQ-VAS.

The observed numbers of any complications of 41.1% is in line with earlier studies [44]. The reduction in physical functioning and QoL after experiencing a complication followed by the return to baseline level after one year [26, 27, 45] has been described before. Other studies described a permanent reduction in QoL in case of complications after CRC surgery [13, 25, 46].

Interestingly, in our study, frail patients were not at higher risk of any complications compared to non-frail patients. The majority of the studies describe otherwise [9]. Although the GA is the golden standard to identify frailty in oncology, using a cut-off value may lead to loss of information [47, 48]. It is possible that the risk of complications is different for – for example – a patient with an impaired social domain than for a patient with an impaired functional domain. Also, we were not able to differentiate between surgical and non-surgical complications. As a general agreement exists that GA particularly predict medical complications, this may have contributed to a similar complication rate in the frail and non-frail group. More research is needed to investigate the potential interaction between frailty, complications and postoperative physical functioning, and QoL. In a larger sample size, it could be possible to analyze each frailty domain separately and investigate its interaction with complications, physical functioning and QoL.

As our findings show that patients with frailty have lower levels of physical functioning and QoL prior and after surgery, these patients are still at risk to further deteriorate and lose self-sustainability. The preoperative GA is therefore extremely important to keep identifying these patients at risk. Pre-, peri- and postoperative care optimization could be considered to prevent further decline. Prehabilitation (enhancing functional capacity prior to surgery) in combination with revalidation (enhancing functional capacity after surgery) may bridge the gap between patients with and without frailty. Especially when increasing physical activity is associated with improved physical functioning and QoL [49, 50]. Prehabilitation and rehabilitation projects should therefore include patient-reported outcomes to evaluate the effect of the interventions.

This study faces some limitations. First, we had to exclude nine patients from the study population as these patients died in the follow-up period and therefore had no follow up data. As the incidence of complications was higher in the deceased patients, selection bias may have occurred. Furthermore, at twelve months we had twenty missing cases due to no response (not due to death), which means that the observed data at twelve months is harder to interpret. We chose not to impute the missing data as >10% was missing (20/138) and linear mixed models allows to include patients with one missing follow-up moment without the need for imputations. The study population consisted of patients receiving surgical treatment, which means that the similar impact of CRC surgery in frail and non-frail patients could have been a consequence of the selection that has already been made by surgeons. The main strengths of the study are its real-life population and its contribution to the few studies that have investigated patient-centered outcome in the older and frail population undergoing CRC surgery.

CONCLUSIONS

This prospective study cohort of older patients with colorectal cancer in the Netherlands showed that frail patients had lower physical functioning and QoL prior and at six and twelve months after surgery compared to non-frail patients. However, as the postoperative course was similar in both groups, it suggests that CRC surgery equally affects frail and non-frail patients. Nevertheless, we need to be aware that frail patients – with lower physical functioning and QoL prior and after surgery – are still at high risk of further deterioration and losing independence.

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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 $\geq III$, 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 ergometer 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 $\geq$ III, 72 (21.6%) had $\geq$ 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 $\geq$ III: 37.9 vs. 21.9%, $p=0.002$), more comorbidities ($\geq$ 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 the 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

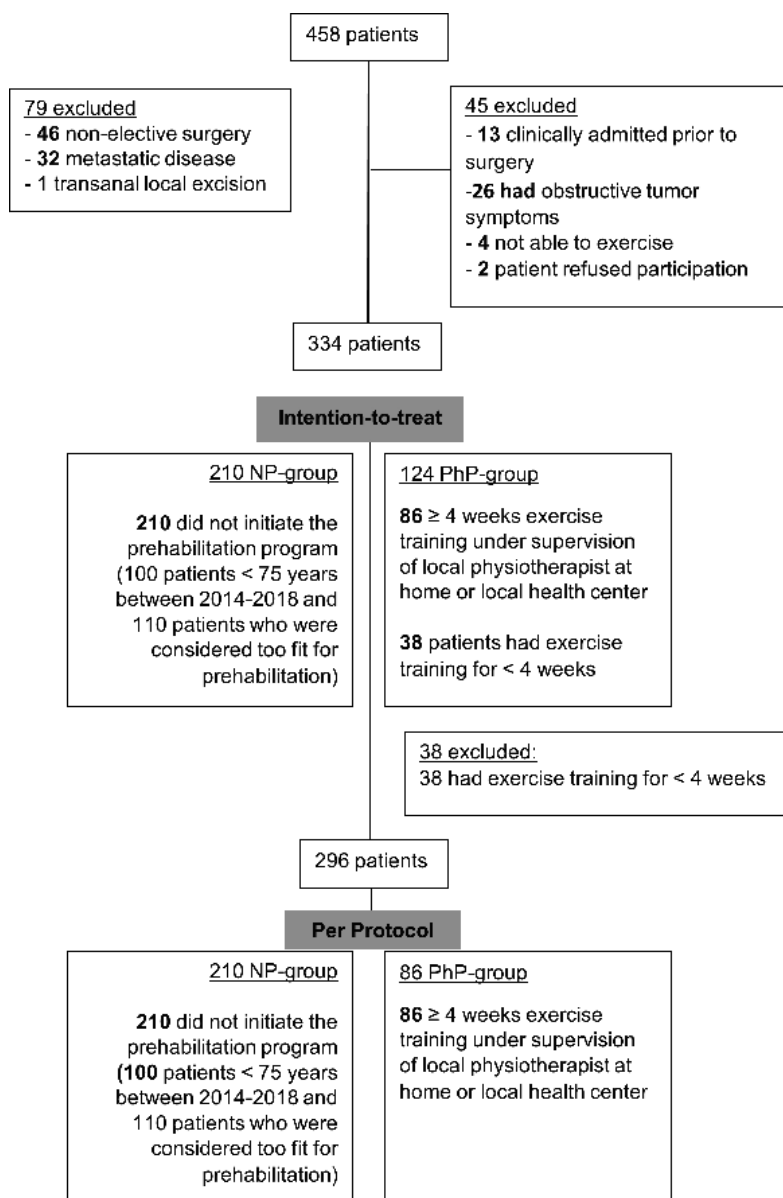


Table 1. Baseline characteristics of the ITT population; stratified by PhP and NP-group

	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 $\geq$ III: 36.2 vs. 39.1%, (3) walking-aid: 29.2 vs. 45.8%, (4) ≥ 2 comorbidities and ASA score $\geq$ III: 44.0 vs. 63.2%, (5) ≥ 2 comorbidities and walking-aid: 35.7 vs. 63.6%, (6) ASA score $\geq$ III and walking-aid: 32.0 vs.55.6%, (7) ≥ 2 comorbidities, walking-aid and ASA score $\geq$ 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 $\geq$ III: 19.1 vs. 17.4%, (3) walking-aid: 18.8 vs. 16.7%, (4) ≥ 2 comorbidities and ASA score $\geq$ III: 20.0 vs. 21.1%, (5) ≥ 2 comorbidities and walking-aid: 14.3% vs. 9.1%, (6) ASA score $\geq$ III and walking-aid: 16.0 vs. 11.1%, (7) ≥ 2 comorbidities, walking-aid and ASA score $\geq$ 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 $\geq III$): (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.

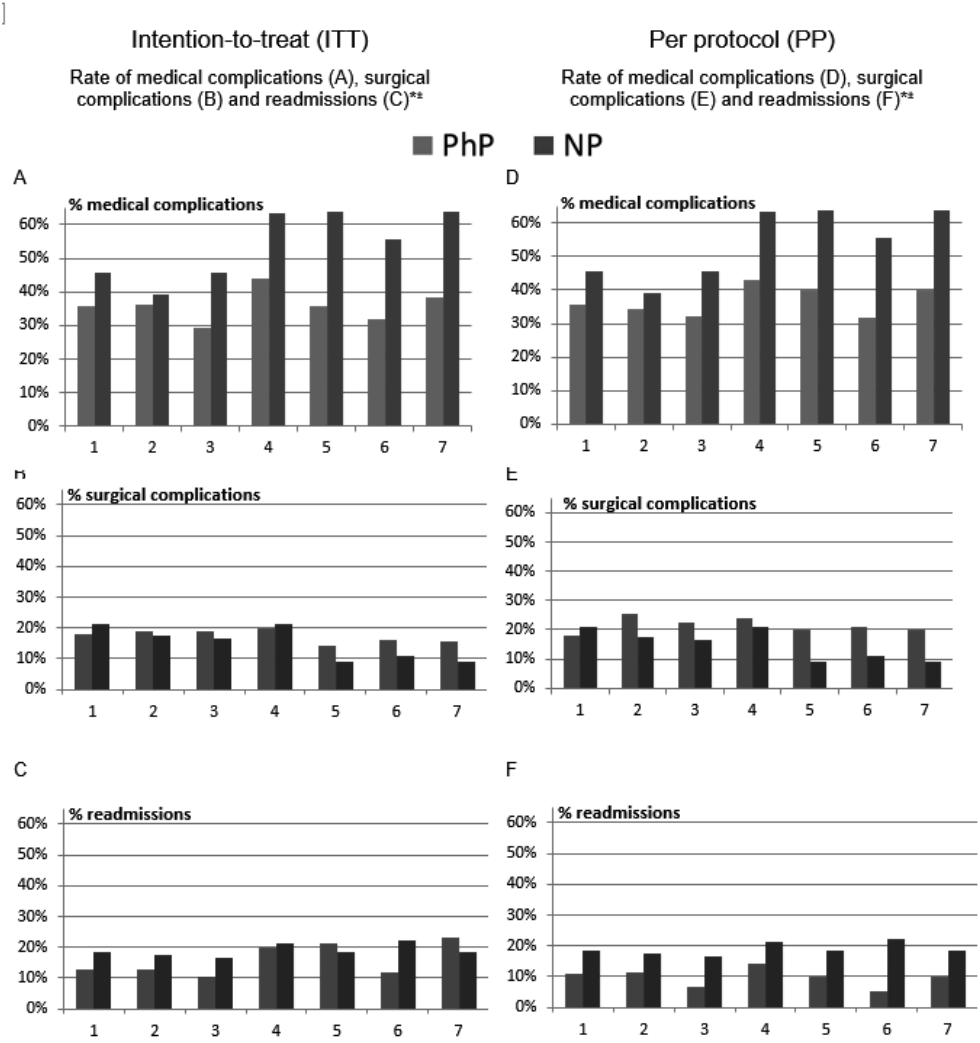
	ITT				PP			
	Total N = 334	PhP N = 124	NP N = 210	p- value	Total N = 296	PhP N = 86	NP N = 210	p- value
Medical complications	76 (22.8)	33 (26.6)	43 (20.5)	0.20	66 (22.3)	23 (26.7)	43 (20.5)	0.24
Pulmonary	16 (4.8)	8 (6.5)	8 (3.8)	0.28	14 (4.7)	6 (7.0)	8 (3.8)	0.24
Cardiac	14 (4.2)	6 (4.8)	8 (3.8)	0.65	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$\pm$	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

$\pm$ 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 $\geq$ III 3: walking-aid 4: ≥ 2 comorbidities and ASA score $\geq$ III 5: ≥ 2 comorbidities and walking-aid 6: ASA score $\geq$ 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 scarce. 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		p-value
	N	N of complications (%)	N	N complications (%)	
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		p-value
	N	N of complications (%)	N	N complications (%)	
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		p-value
	N	N of complications (%)	N	N complications (%)	
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		p-value
	N	N of complications (%)	N	N complications (%)	
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		p-value
	N	N of complications (%)	N	N complications (%)	
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		p-value
	N	N of complications (%)	N	N complications (%)	
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 $\geq$ III 3: walking-aid 4: ≥ 2 comorbidities and ASA score $\geq$ III 5: ≥ 2 comorbidities and walking-aid 6: ASA score $\geq$ III and walking-aid 7: ≥ 2 comorbidities, walking-aid and ASA score

8

The effect of prehabilitation on long-term survival and hospital admissions in older patients undergoing elective colorectal cancer surgery

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ABSTRACT

Introduction

There is a growing body of evidence for a beneficial effect of prehabilitation on short-term outcomes after colorectal cancer (CRC) surgery in older patients. However, long-term effects on survival or hospital admissions have not been investigated. This study reports these long-term outcomes from a previously published observational cohort study.

Methods

We compared patients ≥ 75 years who received elective CRC surgery in Reinier de Graaf Hospital before (2010-2013: standard care) and after implementation of a multimodal prehabilitation program (2014-2015; prehabilitation). With a six-year follow-up period, we analyzed survival using the Kaplan-Meier method and the occurrence of one or more hospital admissions using logistic regression analyses.

Results

Overall, 137 patients were included in the standard care group and 86 patients in the prehabilitation group. There were no differences in patients, tumor and treatment characteristics. After six years, 51.1% in the standard care group and 59.3% in the prehabilitation group ($p=0.167$) were still alive. When corrected for confounders in the prehabilitation group, less patients had one or more hospital admissions during follow-up (odds ratio (OR) 0.43 (95% CI 0.24-0.77)).

Conclusions

Unfortunately these limited historical cohorts did not allow for strong conclusions concerning long-time survival. However, after prehabilitation less patients had hospital admissions during follow up. Hopefully, this first study into the long-term effects of multimodal prehabilitation will trigger more future research.

INTRODUCTION

Prehabilitation is a promising care development that enhances functional performance to withstand the impact of surgery and is increasingly implemented in the field of colorectal cancer (CRC) surgery. For colon and rectal cancer, surgery is the primary curative treatment option. Multimodal prehabilitation identifies the preoperative vulnerabilities and increases the pre- and postoperative physiological capacity [1]. This could be especially effective for frail geriatric patients, as they have an increased risk of postoperative complications [2].

A general agreement exists about the potential of prehabilitation in clinical practice. However, the exact effect of multimodal prehabilitation on short-term outcomes (e.g. postoperative complications, length of stay or readmissions) is still debatable due to small sample sizes, differences in prehabilitation programs and study populations [3-9]. So far two randomized studies (Barbarian-Garcia *et al* and van Berkel *et al*) in patients with colorectal cancer found a positive effect of prehabilitation on postoperative complications [6, 9].

It can be debated whether randomized trials are best suited to study the effects of prehabilitation, especially in the heterogenic groups of geriatric patients [10]. Therefore, other types of studies are useful in this field. Our research group previously studied the impact of prehabilitation on one-year mortality in older CRC patients [10]. The study compared all patients ≥ 75 years receiving elective CRC surgery before (2010-2011), during development (2012-2013) and after (2014-2015) implementation of a multimodal prehabilitation program. It showed that the one-year mortality improved (from 11 to 3%, $p=0.08$) after implementation of the multimodal prehabilitation program.

While it has been shown that the survival difference between young and older CRC patients entirely depends on mortality in the first year after surgery [11], for the case of prehabilitation, it is crucial to know how patients fare in the long run.

To the best of our knowledge only one study was published about the long-term outcomes of prehabilitation [12] and showed no improvement of five-year survival after prehabilitation. However, based on the reported effects of multimodal prehabilitation especially on non-surgical complications [6, 9, 13, 14] and their consequences for survival [15], a beneficial long-term effect of prehabilitation could be expected. Furthermore, in our own clinical experience with prehabilitation for older CRC patients, we frequently see them take up a more active and healthy lifestyle after surgery. This may prevent future health problems. With growing life expectancy, health care utilization is extremely relevant in this time of overburdened healthcare systems. Therefore, in this study we investigated long-term survival for the patients from our earlier published study, as well as the number and type of hospital admissions for the first six years after surgery.

METHODS

Population and design

This observational cohort study included all consecutive patients aged 75 years and older who underwent CRC surgery between January 2010 and December 2015 in Reinier de Graaf Hospital in Delft. Since Reinier de Graaf Hospital initiated a comprehensive multidisciplinary care program in 2014 for the patients ≥ 75 years undergoing elective CRC surgery, we compared patients receiving CRC surgery between January 2014 and December 2015 to patients receiving surgery between January 2010 and December 2013. We excluded patients who underwent non-elective surgery, had stage IV CRC, had a synchronous malignancy or were diagnosed twice with a primary CRC over the inclusion time.

Comprehensive multidisciplinary care program

Detailed information about the comprehensive multidisciplinary care program (prehabilitation program) or the participants has been described earlier [10]. In brief, the prehabilitation program was offered to all patients ≥ 75 years undergoing elective CRC surgical resection from 2014 onwards. The care program was not indicated for patients with an increased risk for subacute surgery (due to obstructive tumors), patients who were considered too fit for preoperative optimization (based on clinical impression, physical and daily activities and social and living status) or patients who refused participation. All potential candidates received a geriatric screening and could be referred to a medical specialist for further optimization prior to surgery. If indicated, patients were referred to the clinical geriatrician for a comprehensive geriatric assessment (CGA), to a physiotherapist to initiate supervised physical training or a dietician for nutritional support. If patients were not able to maintain oneself at home because of physical, nutritional, cognitive or emotional problems on the sixth admission day after surgery, patients were discharged to a rehabilitation center.

Data collection

Patient demographics, tumor and treatment characteristics were collected from the nationwide obligatory data collection of the Dutch ColoRectal Audit (DCRA) registry. Only for patients in the prehabilitation group, geriatric baseline variables were available and collected from the medical record.

We assessed survival and the number and type of hospital admissions within the six years after CRC surgery. Information about life status, date of death and admission history (including the admission indication) was extracted at once from the electronic patient files by qualified data managers of Reinier de Graaf Hospital. The follow-up ended on 1 January 2022.

A hospital admission was defined as a clinical admission for at least 24 hours. We categorized admissions by four groups: colorectal cancer disease-related and/or colorectal cancer surgery-related admissions (1), comorbidity-related admissions (2), admissions related to

elective surgery (3) and other (4). We hypothesized that prehabilitation may affect these four categories differently considering a beneficial long-term health care utilization due to possible life-style change. Admissions related to CRC disease and/or colorectal cancer surgery consisted of metastatic disease-related complications (such as malaise, persistent vomiting, obstipation, intake problems or ascites) or chemotherapy-related complications (such as diarrhea) and anastomotic leak, bleeding, abscess, wound infection, fascial dehiscence, rectal prolapse or ostomy-related complication. The comorbidity-related admissions were caused by the following medical conditions: cardiac disease (atrial fibrillation, decompensation cordis, myocardial infarction), traumatic complications (all types of fractures or contusions due to a fall), peripheral arterial disease, venous thrombosis, neurologic disease (cerebral vascular accident, epilepsy), pulmonary embolism, respiratory disease (pneumonia, COPD), urologic disease (urinary retention, urinary tract infections, urosepsis) and other (fever of unknown origin, malaise not related to metastases). Admissions related to an elective surgery included orthopedic surgery (knee or hip replacement surgery or cuff tear arthropathy), gynecologic surgery (posterior repair for vaginal prolapse), curative oncological surgery (breast, prostate) or hernia repair surgery. The fourth category 'other' consisted of admissions that did not fit any of the other three categories. Two medical specialists assigned the admissions to one of the four categories independently (JWD and JVDB).

Statistical analysis

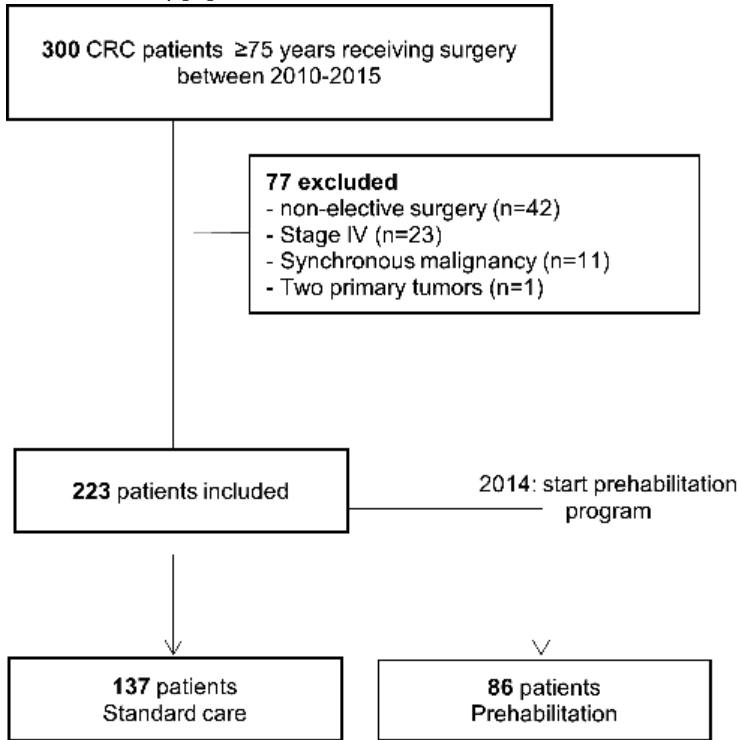
The included patient population was divided in two cohorts: before implementation of the prehabilitation program (2010-2013; standard care group) and after implementation (2014-2015; prehabilitation group). The follow-up time for all outcomes was six years. Survival was analyzed using the Kaplan-Meier method and multivariate cox regression analysis to adjust for clinically relevant variables (age, gender, ASA-score and tumor stage). The total number of admissions in the follow up period were categorized in three groups: 'no admissions', 'one admission' and 'two or more admissions'. To perform a multivariate logistic regression analysis, only 'no admission' and 'one or more admissions' were used. In addition, we described the occurrence of at least one admission for each follow-up year. The total number of the four admission types were categorized in 'no admissions' and 'one or more admissions'. We investigated the number and type of hospital admittances with the aim to have more insight in healthcare expenditure. For that reason, we choose to include patients who died in the follow-up period in the total number of patients. Then we were able to describe a more real healthcare expenditure (patients who die do not influence healthcare costs). All statistical tests were two-sided and a p-value smaller than 0.05 was considered statistically significant. The statistical analyses were performed with SPSS 25.0.

Results

In Reinier de Graaf Hospital, 300 patients ≥ 75 years received CRC surgery between 2010 and 2015. Seventy-seven patient were excluded; 42 received non-elective surgery, 23 had stage IV CRC and 11 had a synchronous malignancy. One patient was diagnosed twice with a primary

colorectal tumor over the inclusion period (Figure 1). Eventually, 223 patients were included; 137 (61.4%) patients in the standard care group and 86 (38.6%) patients in the prehabilitation group. In the prehabilitation group, 73 out of 86 (85%) received prehabilitation. For more details, we refer the our earlier study [10].

Figure 1. Flowchart of study population



Baseline characteristics

Table 1 shows the baseline characteristics stratified by the standard care and prehabilitation group. No differences in patients, tumor or treatment characteristics were found. In the prehabilitation group, 54 (62.8%) patients had physical training with a physiotherapist, 74 (86.0%) patients received dietician consultation, 34 (39.5%) patients were referred to the geriatrician for a comprehensive geriatric assessment and 32.5% of the patients in the prehabilitation group received transfusion in case of anemia compared to 12.4% in the standard care group

Long-term survival

The Kaplan-Meier curve (Figure 2) showed that patients in the prehabilitation group had a better survival than patients in the standard care group over the entire follow-up period. However, the difference was not significant. After six years, 51.1% of the patients in the stan-

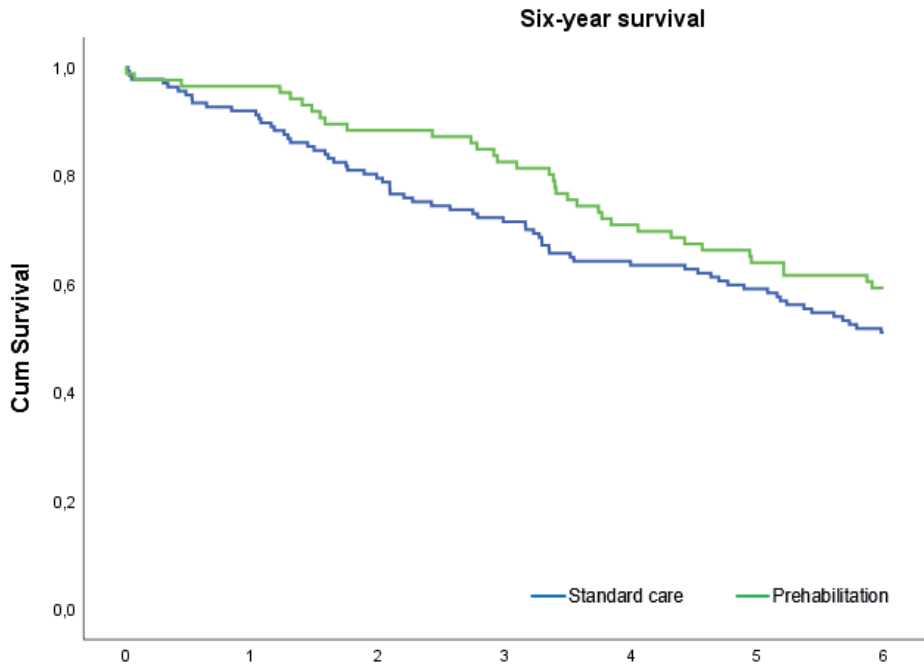
standard care group were still alive compared to 59.3% in the prehabilitation group ($p=0.167$). The multivariate cox regression analysis showed a hazard ratio (HR) of 0.77 (95% CI 0.51-1.17, $p=0.219$) for the prehabilitation group compared to standard care (Table 2).

Table 1. Baseline characteristics of the standard care group and prehabilitation group

	Standard care n=137	Prehabilitation n=86	P-value ^a
Patient and tumor characteristics			
Median age (IQR)	80.4 (77.3-83.4)	81.0 (77.1-83.2)	0.682
Gender			0.748
Male	70 (51.1)	42 (48.8)	
Female	67 (48.9)	44 (51.2)	
Mean BMI (SD)	26.3 (4.2)	26.0 (3.8)	0.622
ASA score			
I-II	82 (59.9)	52 (60.5)	
III-IV	55 (40.1)	34 (39.5)	
Preoperative comorbidity			
Pulmonary comorbidity	33 (24.1)	17 (19.8)	0.451
Cardiac comorbidity	56 (55.3)	34 (34.7)	0.843
Vascular comorbidity	63 (46.0)	35 (39.5)	0.344
Charlson comorbidity index ≥ 2	61 (44.5)	33 (38.3)	0.181
Tumor location			0.445
Colon	102 (74.5)	60 (69.8)	
Rectum	35 (25.5)	26 (30.2)	
Tumor stage (TNM)			0.185
I	37 (27.0)	32 (37.2)	
II	46 (33.6)	29 (33.7)	
III	54 (39.4)	25 (29.1)	
Treatment characteristics			
Neo-adjuvant therapy			
Radiotherapy	20 (14.6)	13 (15.1)	0.916
Chemoradiation	6 (4.4)	2 (2.3)	0.422
Surgical approach			0.352
Open	32 (22.6)	15 (17.4)	
Laparoscopic	106 (77.4)	71 (82.6)	
Adjuvant chemotherapy	5 (3.6)	3 (3.4)	0.949
Physiotherapy	-	54 (62.8)	
Dietician consultation	-	74 (86.0)	
Preoperative CGA	-	34 (39.5)	
Preoperative transfusion (in case of anemia)	17 (12.4)	28 (32.5)	<0.001

Abbreviations: *IQR* interquartile range, *SD* standard deviation, *BMI* body mass index, *ASA* American Society of Anesthesiology, *TNM* TNM Classification of Malignant Tumors, *CGA* comprehensive geriatric assessment

Figure 2. Kaplan-Meier curves for the standard care group and prehabilitation group



No at risk						
137	126	109	98	87	81	70
86	83	76	71	61	55	51

No at risk						
137	126	109	98	87	81	70
86	83	76	71	61	55	51

Table 2. Adjusted hazard ratio (survival) and odds ratio (≥ 1 admission) of the standard care group (reference) compared to the prehabilitation group

Six years of follow up						
	Survival			≥ 1 admission		
	%	HR* (95% CI)	p-value	N (%)	OR* (95% CI)	p-value
Standard care	51.1	1 (ref)		103 (75.2)	1 (ref)	
Prehabilitation	59.3	0.77 (0.51-1.17)	0.219	49 (57.0)	0.43 (0.24-0.77)	0.005

*Adjusted for: age, gender, ASA-score and tumor stage

Hospital admissions

In the first six postoperative years, 63 (28.3%) patients needed one hospital admission and 89 (39.9%) patients needed two or more hospital admissions.

Figure 3A shows that 24.8% (n=34) of the patients in the standard care group compared to 43.0% (n=37) of the patients in the prehabilitation group did not require an admission ($p=0.005$), 35.0% (n=48) compared to 17.4% (n=15) were admitted once ($p=0.005$) and 40.2% (n= 55) compared to 39.6% (n=34) were admitted twice or more ($p=0.928$) respectively. The multivariate logistic regression analysis showed an OR of 0.43 (95% CI 0.24-0.77, $p=0.005$) for 2014-2015 (2010-2013 as reference) and emphasized a protective effect of the prehabilitation group on hospital admission (Table 2).

Figure 3B showed that for each follow-up year, the proportion of patients who needed one hospital admission or more were higher in the standard care group than in the prehabilitation group. For year 2 ($p=0.018$), year 5 ($p=0.007$) and year 6 ($p=0.005$), the differences were significant.

Type of admission

Figure 4 describes the six year rate of the four admission categories. In the standard care group – of the patients who were admitted – 29.2% of the patients required hospital admission related to CRC disease/surgery compared to 19.8% in the prehabilitation group. Comorbidity-related admissions occurred in 52.6% and in 45.3% of respectively the patients in the standard care and prehabilitation group. The proportion of patients who were admitted due to elective surgery was 10.9% in standard care and 10.5% in prehabilitation group. Other admissions occurred in 3.6% and 3.5% respectively. None of these differences were significant.

Figure 3. Percentage of hospital admissions in the first six years after standard care and prehabilitation
(A). Percentage of hospital admissions each postoperative year (%)

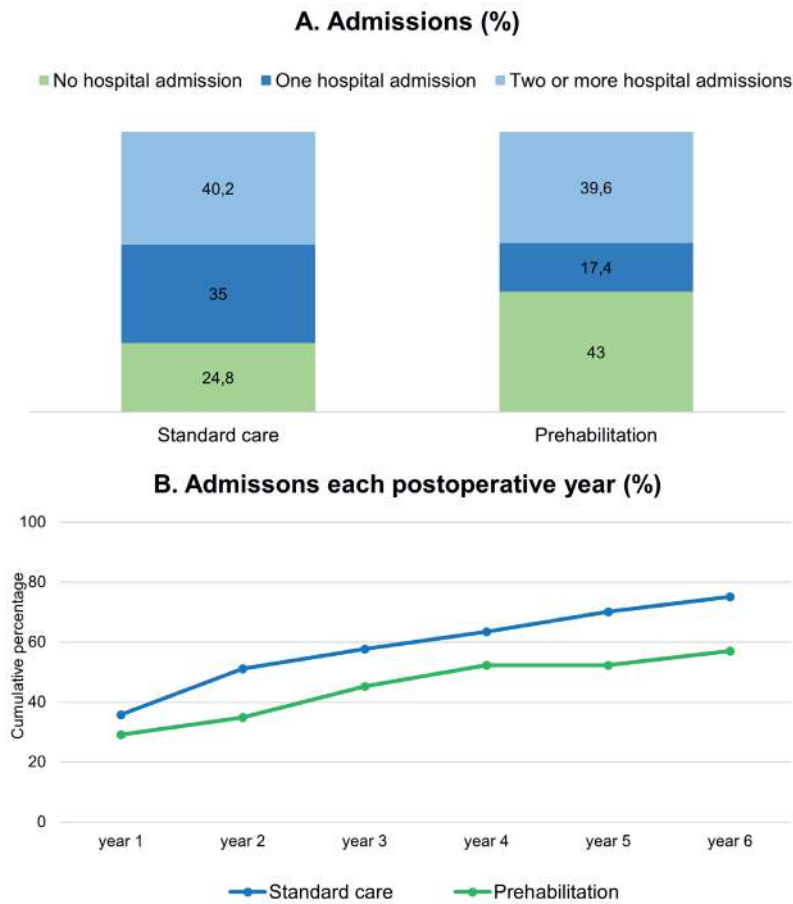
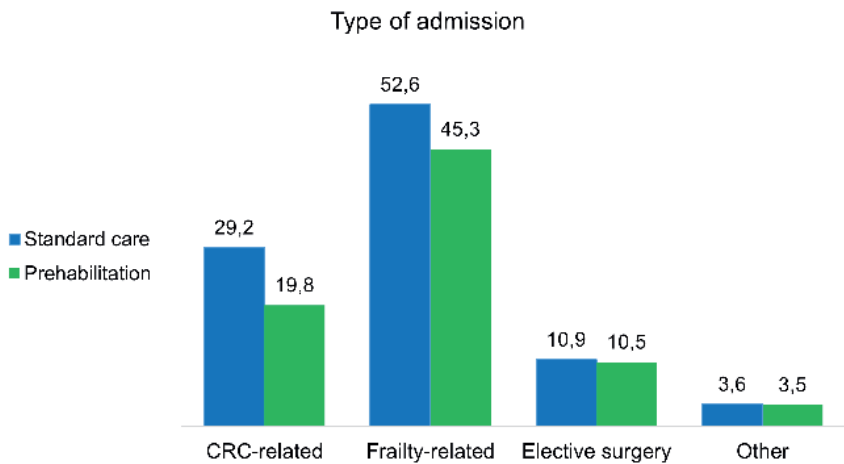


Figure 4. Proportion of hospital admissions per cohort for each admission type



DISCUSSION

To our knowledge, our study is the first to describe long-term survival and hospital admissions of multimodal prehabilitation in a representative older patient population undergoing elective non-metastatic CRC surgery. Over the entire six year follow-up period, the survival numbers in the cohort after implementation of the multimodal prehabilitation program was higher than the cohort prior to the implementation. However, differences were not significant. After six years, 59.3% of the patients who participated in a multimodal prehabilitation program were still alive compared to 51.1% of the patients who did not participate. In addition, patients who participated in the prehabilitation program were less frequently admitted in the first six postoperative years. Although more research is needed to support our findings, we think that our results may increase the interest in the long-term effects of multimodal prehabilitation.

Only one previous study described long-term survival after prehabilitation in patients undergoing elective CRC surgery. The study of Trépanier et al [12] consisted of a pooled study population of 202 adult patients (including two RCT's and one prospective cohort) and found no differences in overall five-year survival between patients participating in a trimodal prehabilitation program compared to the control group. However, Trépanier et al described a much higher five-year survival of 91.7% (prehabilitation) and 96.4% (controls) compared to our study. The patient inclusion in Trépanier et al was not limited to elderly, resulting in a median age of 68.5 years compared to 80.5 years in our study. Besides, patients selected for RCT's do not tend to represent the general population [16], which is emphasized by the relative high five-year survival rates [17]. In their study they also looked at five-year disease-free survival (DFS). They found a significantly better five-year DFS in patients diagnosed with stage III CRC after prehabilitation (73.4%) compared to the control group (50.9%, $p=0.044$). This positive association of prehabilitation with DFS in patients with stage III CRC remained after adjusting for confounders (HR 0.45 (95% CI 0.21-0.93)). They argued that exercise reduced the risk of disease recurrence by several physiological and biochemical processes [18-21]. Interestingly, these results are in line with our finding that the number of CRC-related admissions was lower in the prehabilitation group than in the standard care group. Although we need to keep in mind that the lower proportion of CRC-related admission in the prehabilitation group, could be the result of the lower tumor stage (Table 1).

Although differences were not significant, a potential positive long-term survival after prehabilitation could be a result of a protective role against non-surgical postoperative complications [6, 9, 13]. The study of Warps et al – including 43.908 colon and 16.955 rectal cancer patients – found that non-surgical complications have an higher impact on five-year survival than surgical complications [15]. This could be an explanation for the persistent higher long-term survival rate in the prehabilitation group, supported by the fact that in our earlier study,

the rate of cardiac complications (e.g. non-surgical complications) in cohort 2014-2015 was significantly lower compared to cohort 2010-2013 [10].

Improving long-term outcome in older patients undergoing CRC surgery should not focus on survival only. When older patients experience loss in physical and/or mental health during their gained years, it will negatively affect their quality of life and increase the need for health care services. This may specifically apply to the frail population. Frailty is common in the older patients [22] and is associated with higher needs for hospital services [23-26]. In our clinical experience with training older patients, we frequently see them engaging in more active and healthier lifestyle after their operation. Participation in a prehabilitation program may create awareness and initiate behavior change towards an healthier lifestyle [27, 28] and subsequently increase functional capacity [1, 3, 4, 8, 13, 29]. This is consistent with the finding that there were less comorbidity-related admissions after prehabilitation.

Therefore, long-term outcome after prehabilitation should also be considered in the context of cost-effectiveness (i.e. healthcare expenditure). Unfortunately, we were not able to perform a cost-effectiveness analysis due to lack of information about pre- and postoperative costs. For that reason we used the number and type of hospital admissions as a proxy for health care utilization. The reduced need for hospital services after prehabilitation found in this study is partly consistent with the study of Barberan-Garcia [30]. That study reported a significant lower rate of 30-days hospital admissions after prehabilitation compared to usual care (3% vs 18%, $p=0.009$) and described an increased value for money, which was mainly due to the reduced number of hospital admissions. However, no differences in hospital admissions were found after six and 12 months. Cost-effectiveness or care utilization in prehabilitation for older CRC patients has not been investigated any further. However, the interest in cost-effectiveness of prehabilitation programs is growing [31], especially when implementation in clinical practice is limited by the lack of economic evaluation [32].

Our study has several limitations inherent to the limitations of the earlier study [10]. Due to the retrospective design, the use of historic cohorts and a relatively small sample size, bias could have occurred. This does not allow for strong conclusions, but still suggests a potential long-term benefit of multimodal prehabilitation. Considering the difficulty of survival studies in older patients, the follow-up period of six years gives a valuable insight. Furthermore, it is difficult to determine a long-term effect of prehabilitation on healthcare expenditure. Even if it could prevent serious illnesses through better overall fitness, longevity (albeit in good health) may increase costs simply because different mild and moderate physical and/or mental health issues will arise over time. Cost-effectiveness analysis is very difficult and would have to take into account an impossibly extensive dataset. That is why we chose to use number and type of hospital admittances as surrogate markers for healthcare expenditure. Clearly this can be debated and is by no means adequate to cover all relevant issues.

Unfortunately, we had no information about hospitalization outside our centre, but in our region patients are costumed to visit and be referred to the same hospital. In our opinion the number and type of hospital admittances as shown do provide some interesting insights in the possible long-term impact multimodal prehabilitation can have on healthcare expenditure. At last, future studies in prehabilitation should not only focus on long-term effects on survival and hospital admissions, but also measure physical functioning, cognitive functioning and quality of life in older patients with frailty.

The main strength of our study is that it is the first to investigate the long-term effects of multimodal prehabilitation in older patients who had elective surgery for non-metastatic CRC. The study is strengthened by the long follow-up time, its representative sample of the general population and complete medical file examination.

CONCLUSIONS

This study is the first to describe long-term survival and hospital admissions after multimodal prehabilitation in older patients undergoing elective non-metastatic CRC surgery. Unfortunately, these limited historical cohorts did not allow for strong conclusions concerning long-time survival. However, after prehabilitation less patients had hospital admissions during follow up. Hopefully, this study will trigger future research into the long-term effects of multimodal prehabilitation.

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9

General discussion



GENERAL DISCUSSION

This thesis may help to build an optimal prehabilitation program for older patients with non-metastatic CRC who are eligible for elective surgery. We aimed to identify patients who are most likely to benefit from prehabilitation, to identify the relevant outcomes, and to determine the effect of prehabilitation in clinical practice. In the following discussion, we have outlined the main findings of this thesis, further discussed the results, and presented our future perspective.

9.1 FINDINGS OF THIS THESIS

Part I – Identifying preoperative frailty

The nationwide population-based study in **Chapter 2** included 38.638 older patients with non-metastatic CRC receiving elective surgery. The results showed that older age and several comorbid diseases were both associated with non-surgical complications. However, the strength of the association of comorbid disease with non-surgical complications decreased with older age. This means that the impact of – for example – cardiopulmonary disease on non-surgical complications is higher in patients aged 70-79 years than patients aged ≥ 90 years. These findings emphasize the need for individualized preoperative risk assessment in the older population, which should not focus on comorbidity alone. In **Chapter 3**, we found that the ACS NSQIP surgical risk calculator – a potentially relevant risk assessment tool – had a poor individual risk prediction (calibration) for all postoperative outcomes and only a fair discriminative ability (discrimination) to predict pneumonia and discharge not to home in older patients undergoing elective CRC surgery in the Netherlands. The calculator can thus only be considered to identify patients at high risk of pneumonia and discharge not to home. An easy-to-use and population-specific prediction model is still not available for the older population. In **Chapter 4** we investigated the additional value of geriatric characteristics for risk assessment in a retrospective multicenter study of 575 older patients with rectal cancer receiving surgery. We found that preoperative screening for geriatric parameters did not improve risk prediction for postoperative overall and severe complications. Only delirium risk screening significantly improved the risk prediction for postoperative delirium.

Part II – Identifying relevant postoperative outcome

In **Chapter 5**, our population-based study of 38.648 older patients described the time-trends and age-specific differences of surgical and non-surgical complications after CRC surgery between 2011-2019 in the Netherlands. It shows that the reduction in postoperative complications after CRC resection over the years was predominantly driven by an improvement in non-surgical complications. However, the rate of non-surgical complications consistently increases with older age. This means that future care developments should preferably focus on non-surgical complications, especially in the oldest patients. The study in **Chapter 6** sug-

gested that CRC surgery in the Netherlands equally affects physical functioning and quality of life in frail and non-frail patients. Although frail patients had lower levels of functioning and quality of life prior and one year after surgery compared to non-frail patients, the postoperative change was similar between both groups. Caution should be taken that frail patients are still at risk of further deterioration and loss of independence due to the lower baseline physical functioning and quality of life.

Part III – The effect of prehabilitation

In **Chapter 7**, we found that patients of ≥ 70 years with CRC who followed a physical prehabilitation program had a worse frailty profile and therefore a higher a priori risk of postoperative complications. However, after physical prehabilitation, rates of surgical complications, non-surgical complications, and readmissions were not different from patients without prehabilitation. These findings suggest that physical prehabilitation may prevent postoperative complications in frail patients. In **Chapter 8**, we were the first to describe long-term survival and hospital admissions after multimodal prehabilitation in older patients with non-metastatic CRC. Although the use of historical cohorts did not allow for strong conclusions concerning survival, the study showed that the number of patients needing hospital admissions in the first six years after surgery was lower after prehabilitation.

9.2 IDENTIFYING PREOPERATIVE FRAILITY

Healthcare innovations – such as prehabilitation – aim to improve the quality, accessibility, and affordability of care and need to agree with “*appropriate care; the current approach to care delivery in the Netherlands*”[1]. Therefore, it is essential to identify patients who will benefit most from prehabilitation.

We were interested in the use of frailty to select patients for prehabilitation. The Dutch guideline for CRC recommends a two-step preoperative assessment for identifying frailty; the Geriatric-8 screening tool followed by a geriatric assessment (GA) that includes somatic, functional, cognitive, and psychosocial impairments [2]. Frailty is an increased state of vulnerability and several studies found that frailty increases the risk of adverse postoperative outcome, such as mortality, postoperative complications, and readmissions [3]. As surgery is still the primary treatment option for CRC, the majority of the older patients will receive surgery. Alternative treatment options – especially for colon cancer – are limited and non-surgical treatment has very poor survival rates [4, 5]. This means that care professionals are dealing with a high number of frail patients who undergo surgery for colon or rectal cancer.

It has proven to be very difficult to include frailty in one tool or model with the aim to identify patients for prehabilitation. One of the reasons is the high heterogeneity of the frailty definition. This heterogeneity is reflected in the broad spectrum of frailty definitions that are

used in current literature. A recent systematic review and meta-analysis “*Effect of frailty on postoperative complications, mortality, and survival in older patients with non-metastatic colon cancer*” of Moreno-Carmona *et al* (JGO, 2024) [3] highlights this. The study included 14 studies and 43.683 patients with non-metastatic colon cancer of 65 years and older and found that frailty was associated with a higher rate of postoperative complications and mortality in the first 30 days, at 3-6 months, and at one year. These results are consistent with earlier reviews [6, 7]. The 14 studies used almost 14 different frailty definitions: the clinical frailty scale, the Rockwood frailty index, the Vulnerable Elders Survery (VES-13), the modified frailty index, the Dutch National Patient Safety Program (VMS), Groningen frailty Indicator ≥ 4 or ≥ 5 , fried frailty phenotype criteria, comprehensive geriatric assessment (CGA), Identification of seniors at risk-hospitalized patients (ISAR-HP), multidimensional prognostic index, modified version of the Balducci criteria, and some specific geriatric parameters. Although all tools had similar components, such as comorbidity, functional status, physical performance, or nutrition, heterogeneity was high and not one definition stood out. As a result, it is impossible to compare these studies and come up with one definition of frailty.

Not only the heterogeneity of frailty, also the loss of information by using one tool makes it hard to fully capture the concept of frailty. If we simply add up the impaired domains and define a cut-off score to identify patients as frail or not frail, each geriatric domain is seen as a separate entity. However, the interaction between the different domains is relevant and improves the predictive value [8, 9]. For example, Oud *et al* showed that “*looking at the interaction between the various domains instead of looking at the individual risk domain, increased predictive performance*”[9]. The interaction between the different frailty domains brings us back to the complexity of geriatric syndromes. Therefore, summarizing frailty in one definition is impossible, indicating that the interpretation of the GA by a clinical geriatrician is necessary [10]. This is supported by the opinion of several healthcare professionals, as the geriatric assessment is seen as an additional tool. Care professionals prefer a strong collaboration between different specialists in preoperative risk assessment [11].

In conclusion, frailty parameters contribute to the preoperative risk assessment of older patients with CRC, but a dichotomous concept of frailty is insufficient to determine whether patients could benefit from prehabilitation.

9.3 IDENTIFYING RELEVANT POSTOPERATIVE OUTCOMES

Target outcomes (for prehabilitation) are outcomes that have a substantial impact on the individual patient or the healthcare in general. One relevant outcome in CRC surgery is physical capacity. Major colorectal surgery may reduce physical capacity up to 20-40% [12], can cause permanent reduction of physical and role functioning [13], and the majority of the patients

may not return to their preoperative level of physical capacity after CRC surgery [14]. For the older patients, physical capacity is considered even more important than for their younger counterparts, as low physical capacity can lead to loss of independence and self-reliance [15]. **Chapter 6** emphasized the postoperative functional decline in older patients. Furthermore, low physical capacity is a major risk factor for postoperative complications [16-20] and patients with reduced physical capacity are thought to be less resilient to complications than those with normal or high physical capacity [21].

Postoperative complications occur commonly and are associated with higher readmission rates, lower quality of life, increased short- and long-term mortality, further reduction of physical functioning, and increased healthcare costs [22-31]. **Chapter 5** showed that 27.6% of the older patients undergoing elective CRC surgery in 2019 in the Netherlands experienced a postoperative complication, 16.8% experienced surgical, and 17.1% non-surgical complications. These numbers are consistent with other studies [23, 32-35]. Postoperative complications are therefore a crucial target for healthcare innovation.

Although from the perspective of the individual (older) patient, survival and quality of life are arguably the most important outcomes to consider [36], but may be less useful as target outcomes in prehabilitation research. Current postoperative mortality rates following CRC surgery in older patients are relatively low [37-39] and quality of life generally remains stable or improves after surgery [40-42]. This means that studies using these endpoints would require exceptionally large sample sizes to achieve sufficient statistical power to investigate the effect of prehabilitation. Furthermore, the causal link between prehabilitation and either mortality or quality of life is likely to result indirectly from improvements in physical capacity or postoperative complications, which are more easily studied.

An important yet underexplored aspect of prehabilitation is its cost-effectiveness. This outcome is particularly relevant, as the implementation of prehabilitation into clinical practice is restricted by the absence of economic evaluation [43]. While the interest in assessing the cost-effectiveness of prehabilitation programs is increasing [44], current data on this topic remains limited.

In conclusion, we propose that the target outcomes for prehabilitation are particularly pre- and postoperative physical capacity, postoperative complications and cost-effectiveness. We will further elaborate the effect of prehabilitation on these outcomes in Chapter 9.4.

9.4 THE EFFECT OF PREHABILITATION

Particularly due to their retrospective design, our studies in **Chapter 7** (prehabilitation may prevent postoperative non-surgical complications in frail patients) and **Chapter 8** (prehabili-

tation reduces the number of long-term hospital admissions) were at risk of bias. In order to interpret our findings, we need to compare our results with the current status of evidence regarding the effect of prehabilitation in (older) patients undergoing elective CRC surgery, especially on physical capacity, postoperative complications and cost-effectiveness.

The interest in prehabilitation has accelerated in the last two decades and several meta-analyses, systematic reviews, RCT's, and observational studies have been published. Current evidence describes an improvement of pre- and postoperative physical capacity after prehabilitation [32, 45-48]. The effect of prehabilitation on reducing postoperative complications in patients scheduled for CRC surgery is still inconsistent. Some RCT's found a significant reduction of overall postoperative complications [49] or a reduction of severe and medical complications [50], while others found no effect [51-55]. Eventually, the meta-analyses and systematic reviews [32, 45-48] concluded no significant reduction in postoperative complications compared to usual care. We need to be aware that each meta-analysis and systematic review described a relatively high risk of bias of the included articles, which indicates that the level of evidence is low.

Despite this inconsistency, there is still a general agreement on the potential of prehabilitation to improve postoperative complications. We believe that the potential particularly applies for non-surgical complications instead of surgical complications. Both types of complications originate from a different pathophysiology. Surgical complications, such as anastomotic leakage and wound infections, are mainly attributed to surgical stress, which triggers an immune response involving hormonal and metabolic disturbances [56-58]. Non-surgical complications, such as cardiopulmonary complications, are considered more closely associated with a patient's preoperative condition and reduced postoperative activity during hospitalization [17]. Given that prehabilitation enhances pre- and postoperative physical capacity and therefore improving resilience to hospitalization, we hypothesized that prehabilitation is more suitable for reducing non-surgical complications [59, 60].

Although the risk of surgical complications may also decrease by an increased physical activity and increased fitness is important to overcome the sequelae of a surgical complication [61, 62], current literature supports a more favorable link between prehabilitation and non-surgical complications. Two RCT's (prehabilitation vs usual care prior to CRC surgery) differentiated between non-surgical and surgical complications; Molenaar *et al* found fewer non-surgical complications after prehabilitation [50] and Berkel *et al* found no difference in complication type [49]. Another RCT, performed in patients receiving major abdominal surgery (approximately 56% CRC surgery) only found a reduction in non-surgical complications, not in surgical complications [63]. Several observational studies described a positive association of prehabilitation with non-surgical complications as well; two studies reported fewer postoperative pulmonary complications following abdominal surgery after physical prehabilitation [17, 64], Souwer *et al* [65] identified a reduction in cardiac complications

after prehabilitation, and **Chapter 7** showed that prehabilitation is more likely to prevent non-surgical complications than surgical complications.

The current overburdened healthcare system needs innovations that reduces healthcare capacity and costs. Whether prehabilitation helps reducing costs, is still unclear, but we know that postoperative complications after CRC surgery is associated with high costs [66]. A recent systematic review including 45 studies describing “*cost-effectiveness of prehabilitation for patients awaiting elective surgery compared with usual preoperative care*” supports the potential cost-effectiveness after prehabilitation [67]. However, only Barberan-Garcia *et al* [68] included patients with CRC and found lower short-term care utilization, but no significant reduction in hospital costs. One recent observational study of Sabajo *et al* [69] including 196 patients who participated in a prehabilitation program prior to elective CRC surgery in the Netherlands, found almost a 20% reduction of in-hospital costs after prehabilitation compared to standard care. In **Chapter 8**, we used the number (and type) of hospital admissions in the first six years after surgery as proxy for long-term healthcare utilization or healthcare costs. As patients who participated in the prehabilitation program were less frequent admitted in first six years after surgery, our findings suggests that both short- and long-term costs need to be considered for cost-effectiveness analysis.

It could be debated whether the (in)effectiveness of prehabilitation on postoperative complications (or other outcomes) is ‘true’ or masked by other (methodologically) explanations, i.e. the severe heterogeneity of the prehabilitation program, the underestimation of the effect difference by using RCT’s and logistical and financial issues.

Prehabilitation programs are extremely heterogeneous. Programs differ in patient population, in composition (physical, nutritional, mental, lifestyle, and/or medical domain), duration, and outcome. Due to the heterogeneity it is very difficult to compare multiple prehabilitation programs [70]. Earlier studies therefore suggested standardization of prehabilitation programs to reduce heterogeneity. Standardized programs reduce heterogeneity and improve reproducibility, but it may overlook important individual characteristics. A personalized program based on individual impairments and needs, can strengthen the ‘true’ therapeutic effect of prehabilitation. This particularly applies to the older population that is characterized by patients with a wide range of comorbid diseases, functional, cognitive and social impairments. The optimal approach probably integrates both elements. In this context, the Dutch Association of Surgery (Nederlandse Vereniging voor Heelkunde; NVvH) published a position paper on prehabilitation “*Standpunt prehabilitatie*” [71]. The paper includes general criteria and recommendations to guide Dutch hospitals in implementing prehabilitation programs with the aim to reduce heterogeneity. Standardization is encouraged, although the criteria allow sufficient room for personalization and local applicability.

Prehabilitation studies have reported treatment periods that ranged from two to six weeks. Evidence shows that a three to four week prehabilitation program is sufficient to improve physical capacity [72, 73]. It can be debated whether this relatively short time allows for clinical benefits that outweigh adverse postoperative outcomes. However, extending the optimization period in clinical practice is challenging. First, both healthcare professionals and patients fear the potential tumor progression during a delay, although no association between delayed surgery and disease-free survival was found [74]. Second, hospitals must adhere to quality standards of the “*Multidisciplinaire normering oncologische zorg in Nederland*” (SONCOS) [75] that set a maximum interval of six weeks between the first outpatient visit and the start of the treatment. However, the criteria are questionable as the interval of six weeks is rather consensus-based than evidence-based. Besides, if we consider prehabilitation as a form of non-oncological neo-adjuvant therapy (improving physical capacity and potentially postoperative complications) it allows for extending the preoperative period for optimization purpose.

Furthermore, it can be questioned whether a RCT is the optimal study design for investigating prehabilitation. Although several RCT's have been performed, meta-analyses and systematic reviews found a relatively high risk of bias. It is impossible to blind patients and care professionals, resulting in an increased awareness of enhancing preoperative capacity in the control group (being more active, making more healthy lifestyle choices) and thus resulting in an underestimation of the effect difference. Furthermore, patients included in RCT's are less likely to represent the real-life population [76], which is supported by Franssen *et al* [48]. This review about prehabilitation prior to CRC surgery, analyzed the pooled results of RCT's for postoperative complications and separately analyzed the pooled results of observational studies. Interestingly, only the pooled results of the observational studies found a positive effect of prehabilitation on the reduction of postoperative complications. As the observational studies included more high-risk patients than the RCT's, the RCT's may have underestimated the effect due to decreased real-life representation. We need to keep in mind that the control groups in observational studies are usually historical cohorts, which means that any outcome difference between the control and prehabilitation group could be a result of other care innovations such as the ERAS program and the use of minimally invasive surgery.

At last, the logistic challenges associated with implementing a prehabilitation program, such as integrating a new care pathway within an existing framework, limited expert staff, time, resources, and financial support, contribute to the heterogeneity of a program and increase the risk of patient dropout and incomplete data collection [77, 78].

9.5 FUTURE PERSPECTIVE

Based on the findings of this thesis in combination with the current status of evidence regarding prehabilitation prior to CRC surgery, we can conclude that prehabilitation – when tailored in an optimal format – has great potential as a new care innovation. As we need more supporting evidence, future research needs to address the challenges of prehabilitation. The challenges in prehabilitation lie in the heterogeneity of the patient population (Ch 9.2), the broad variety in outcomes (Ch 9.3), heterogeneity of a prehabilitation program itself and methodological and financial issues in prehabilitation research (Ch 9.4).

To prevent unnecessary heterogeneity, studies need to be performed in populations of a specific disease or surgery. The included population should not be limited to frail patients (especially when frailty is based on a dichotomous definition). Given the current evidence that prehabilitation significantly improves pre- and postoperative capacity, we believe that prehabilitation programs should focus on patients with (the) low(est) physical capacity as they have most to gain and should particularly consist of physical interventions. This approach will decrease program heterogeneity, enhance interpretability of the results and simplify the implementation in clinical practice as well. Furthermore, simply adding up each domain could lead to information loss and may underestimate the effects. Each modality needs to be investigated separately and the most relevant outcomes for these domains need to be addressed first (for example weight or sarcopenia for nutritional interventions and depressive symptoms or anxiety for psychological interventions). Then, the combined effects of different prehabilitation modalities can be assessed more accurately and it would be easier to interpret the interaction between two or more domains.

Future prehabilitation research should reconsider its methodological framework. While RCT's remain the golden standard, alternative designs with observational data, such as a stepped wedge design or a target emulation trial (suggested by Franssen *et al* [48]), may offer more real-life insights.

Finally, we recommend the use of pre- and postoperative physical capacity, non-surgical complications and cost-effectiveness as primary outcomes in prehabilitation research. Cost-effectiveness is critical to sustain future prehabilitation programs. Initial costs for adequate care pathways and expert staff are currently not funded by The Dutch Healthcare Authority (NZa) due to the lack of positive evidence [79]. However, if we want to continuously improve healthcare, institutes need to consider subsidizing the initial costs for potential care improvements. Only then we can ensure that future care is able to shift to 'appropriate' care [1].

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Part IV

Appendices

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SUMMARY

Prehabilitation is a potential healthcare innovation that enhances physical capacity prior to surgery with the aim to improve postoperative outcome. Multimodal prehabilitation consists of physical exercise, nutritional advice, psychosocial support, lifestyle adjustments (such as smoking cessation), and additional medical optimization.

The last decade, prehabilitation has been increasingly initiated in the field of colorectal cancer (CRC). Surgery is still the primary treatment option for patients with non-metastatic colon or rectal cancer. Unfortunately, postoperative complication rate and functional decline after surgery is still common, particularly in the older patients. A significant part of this older population is frail. Frailty – an impaired physiological state based on several physiological domains (somatic, functional, cognitive, and psychosocial)– is associated with higher morbidity, higher mortality rates and lower functional capacity and quality of life after CRC surgery. Because of the increased risk for adverse postoperative outcome, frail patients may benefit the most from prehabilitation.

Current evidence shows a positive impact of prehabilitation on pre- and postoperative physical capacity. However, the effect on postoperative complications or other adverse postoperative outcomes is still uncertain. An adequate tailored prehabilitation program is necessary to overcome several challenges in prehabilitation research and to improve the interpretation of future study results. Therefore we aim to shape and concretize the optimal prehabilitation program by identifying frailty (Part I), identifying relevant outcomes (Part II) and investigating the effect of prehabilitation (Part III).

In **Chapter 2 (Part I)**, a nationwide population-based study of 38.638 older (≥ 70 years) patients with non-metastatic CRC undergoing surgery, we found that older age and comorbidity increased the risk of non-surgical complications. However, the strength of the association of specific comorbid disease (e.g. cardiopulmonary disease) with non-surgical complications was lower in the older age groups, which means that the effect of e.g. cardiopulmonary disease on non-surgical complications was lower in patients aged ≥ 90 years than patients aged 70-79 years. In **Chapter 3**, we externally validated the ACS NSQIP surgical risk calculator in a Dutch cohort of patients ≥ 70 years undergoing elective CRC surgery. Although the risk assessment tool included a broad variety of risk factors, including several frailty parameters, the surgical risk calculator had a poor individual risk prediction and only a fair discrimination for pneumonia and discharge not to home. The tool has therefore a limited use to identify Dutch CRC patients at risk. In **Chapter 4**, a multicenter cohort study of 575 older (≥ 70 years) patients with rectal cancer who underwent surgery, we found no improvement of risk prediction for severe and overall complications by adding frailty characteristics to the standard prediction model. Only the risk prediction of postoperative delirium improved by using a preoperative delirium risk screening.

The findings show that frailty characteristics contribute to the preoperative risk assessment of older patients with CRC. However, we believe that the use of a dichotomous concept of frailty (frail/non-frail) is not sufficient to identify patients with an increased risk of postoperative adverse outcome. Various studies that investigated the impact of frailty, use a broad spectrum of frailty definitions and results are therefore difficult to compare. Furthermore, using a dichotomous form of frailty by simply adding up the impaired domains of the geriatric assessment (considered the golden standard for frailty), may result in information loss and does not reflect the complexity of the geriatric syndromes. This means that clinical geriatricians are necessary for interpretation of the geriatric assessment.

In **Part II**, we assessed relevant outcomes for prehabilitation. We presented the rate of surgical and non-surgical complications of patients ≥ 70 years between 2011-2019 in the Netherlands in **Chapter 5**. Over the years, postoperative complications decreased, mainly driven by the reduction of non-surgical complications. Interestingly, the rate of non-surgical complications still increased in the older age groups, indicating that non-surgical complications are the main outcome that – particularly in the older patients – needs improvement. In **Chapter 6** we described functional capacity and quality of life in older patients with CRC receiving surgery. Patients were stratified by frailty and non-frailty. Frail patients had lower functional capacity and quality of life before and after surgery. The surgery itself equally affected patients with and without frailty.

Target outcomes have (high) impact on the individual patient and healthcare in general. We propose that prehabilitation programs should at least focus on pre- and postoperative physical capacity, postoperative complications, and cost-effectiveness. Physical decline after surgery occurs frequently, increases the risk of further deterioration and is associated with several other adverse outcomes, such as postoperative complications, readmission, morbidity and mortality. Especially postoperative complications are common in the older population (**Chapter 5**) and are responsible for higher readmission rates, lower quality of life, increased short- and long-term mortality, further reduction of physical functioning, and increased healthcare costs. Although a few studies have evaluated the cost-effectiveness of prehabilitation, this outcome is essential. Especially when the implementation of prehabilitation (research) into clinical practice is limited by the lack of economic evidence.

In **Part III**, we investigated the effect of prehabilitation in older patients receiving CRC surgery in Reinier the Graaf Hospital in Delft using two observational cohorts. In **Chapter 7**, we compared patients who participated in a prehabilitation program with patients who received standard care. Although patients in the prehabilitation group had a higher a priori risk (due to a worse frailty profile), they had similar rates of surgical complications, non-surgical complications, and readmissions compared to the patients in the standard care group. This suggests that prehabilitation lowers the risk of postoperative complications after CRC surgery in frail patients. In **Chapter 8**, we described the long-term impact of prehabilitation using

six-year mortality and hospital admissions after surgery. We found no difference in long-term mortality. The patients who participated in the prehabilitation program experienced less hospital admissions in the six years after surgery than the patients with standard care.

Our findings are in line with other studies. However, prehabilitation is not evidence based (yet). Emphasized by the most recent meta-analysis (including fourteen randomized controlled trials (RCT)), prehabilitation significantly improves physical capacity, but the impact on postoperative complications (and other adverse outcome) is still uncertain.

The lack of evidence for prehabilitation might be related to the challenges that prehabilitation (research) is facing: heterogeneity of the included patient population, the heterogeneity of the prehabilitation program, the variety in postoperative outcomes, and methodological and financial difficulties. We have proposed directions for future research to overcome these challenges.

We believe that prehabilitation should particularly consist of a physical intervention and should focus on patients with low physical capacity. This approach will lower the heterogeneity of the population and the program and will improve the interpretation of results. The other domains need to be investigated separately to identify the target outcomes (for example sarcopenia for nutritional interventions and depressive symptoms for psychological interventions). Furthermore, alternative designs for RCT's should be considered. As a RCT includes patients who do not represent the real-life population and blinding for a prehabilitation program is impossible (patients in the standard care group will be more aware of their health status), the effect of prehabilitation is underestimated. At last, healthcare institutes should financially support the initial set up of promising care innovation projects. Potential care innovations are by definition not evidence-based. Only then, prehabilitation may shift from a potential care innovation to a definitive care innovation.

NEDERLANDSE SAMENVATTING

Prehabilitatie is een zorginnovatie die de conditie van de patiënt vóór een operatie verhoogt met als doel om de kans op complicaties na operatie te verkleinen. Met prehabilitatie wordt vaak multimodale prehabilitatie bedoeld en dit bestaat uit meerdere pijlers: fysieke training, voedingsadviezen, psychische ondersteuning, leefstijl veranderingen en medische optimalisatie (o.a. ijzersuppletie bij bloedarmoede).

De afgelopen jaren wordt prehabilitatie steeds vaker in de (Nederlandse) praktijk geïmplementeerd, met name voor patiënten met colon of rectum carcinoom (CRC). Jaarlijks worden ca 12.500 mensen met CRC gediagnosticeerd, van wie 50% ouder is dan 70 jaar. Omdat een operatie de primaire behandeling is voor patiënten met stadium 1-3 CRC, worden er in de praktijk veel oudere patiënten geopereerd. De oudere populatie wordt gekenmerkt door een grote variatie in gezondheid. Hierin is het concept van 'kwetsbaarheid' of 'frailty' van toepassing. 'Frailty' is een verminderde fysiologische toestand gebaseerd op beperkingen op het somatische, functionele, cognitieve en/of psychosociale domein. Patiënten die frail of kwetsbaar zijn, hebben een hogere mortaliteit, hogere morbiditeit en een lagere functionele capaciteit en kwaliteit van leven na CRC-chirurgie. Vanwege het verhoogde risico op ongunstige postoperatieve uitkomsten, zouden juist deze kwetsbare patiënten het meeste baat kunnen hebben bij prehabilitatie.

Wetenschappelijk onderzoek laat zien dat prehabilitatie de conditie van de patiënt voor en na een CRC operatie kan verbeteren. Het effect op andere postoperatieve uitkomsten, zoals postoperatieve complicaties is nog onzeker. Prehabilitatie onderzoek is echter uitdagend en een goed afgestemd prehabilitatie programma is essentieel om de onderzoeksresultaten te kunnen interpreteren. Met dit proefschrift beschrijven wij daarom een zo optimaal mogelijk prehabilitatie programma door kwetsbaarheid te identificeren (Deel I), relevante uitkomsten voor prehabilitatie onderzoek te bepalen (Deel II) en het effect van prehabilitatie te onderzoeken (Deel III)

Hoofdstuk 2 (Deel I) beschrijft een landelijk cohort van 38.638 patiënten ≥ 70 jaar met niet-gemetastaseerd CRC die een operatie ondergingen. Hieruit blijkt dat een hogere leeftijd en comorbiditeit beide het risico op niet-chirurgische complicaties verhogen. De associatie tussen specifieke comorbiditeit (o.a. cardiopulmonale aandoeningen) en niet-chirurgische complicaties is echter minder sterk in de oudste leeftijdsgroepen. Dit betekent dat het risico van o.a. cardiopulmonale aandoeningen op niet-chirurgische complicaties lager was bij patiënten van ≥ 90 jaar dan bij patiënten van 70–79 jaar. In **Hoofdstuk 3** valideren we de 'ACS NSQIP surgical risk calculator' in een Nederlands cohort van patiënten ≥ 70 jaar met niet-gemetastaseerd CRC. Hoewel deze Amerikaanse risicocalculator bestaat uit een breed scala aan risicofactoren en kwetsbaarheidsparameters, bleek de individuele voorspelling voor alle uitkomsten ("calibratie") beperkt. Het onderscheid tussen wel/geen event ("discriminatie") was beperkt tot een matige

discriminatie voor pneumonie en ontslag naar een zorginstelling. De tool is daardoor beperkt bruikbaar in de Nederlandse praktijk. In **Hoofdstuk 4** – een cohort studie van 575 oudere patiënten met rectum carcinoom die geopereerd zijn – vonden we geen verbetering van de risicovoorspelling voor ernstige en het totaal aantal complicaties door kwetsbaarheidskenmerken aan het standaardmodel toe te voegen. Alleen de risicovoorspelling voor postoperatief delier verbeterde door gebruik te maken van een preoperatieve delierscreening.

Deze bevindingen tonen aan dat kwetsbaarheidskenmerken bijdragen aan de preoperatieve risico-inschatting bij oudere patiënten met CRC. Het gebruik van een tweedelig kwetsbaarheidsconcept (kwetsbaar/niet-kwetsbaar) is echter onvoldoende om patiënten met een verhoogd risico op ongunstige postoperatieve uitkomsten te identificeren. In de literatuur worden veel verschillende definities van kwetsbaarheid gebruikt, waardoor onderzoeksresultaten moeilijk met elkaar te vergelijken zijn. Bovendien kan het simpel optellen van de aangedane domeinen van het geriatrisch assessment (dat wordt beschouwd als de gouden standaard voor het vaststellen van kwetsbaarheid) leiden tot informatieverlies en doet daarmee onvoldoende recht aan de complexiteit van geriatrische syndromen. Interpretatie van het geriatrisch assessment door een klinisch geriater blijft daarom noodzakelijk.

In **Deel II** beoordeelden we relevante uitkomstmaten voor prehabilitatie. In **Hoofdstuk 5** beschrijven we chirurgische en niet-chirurgische complicaties bij oudere patiënten na CRC chirurgie tussen 2011-2019 in Nederland. Postoperatieve complicaties zijn de afgelopen jaren afgenomen, met name door de daling van niet-chirurgische complicaties. Opvallend was dat het percentage niet-chirurgische complicaties bleef toenemen in de oudste leeftijdsgroepen, wat erop wijst dat juist dit type complicatie een belangrijk aangrijpingspunt vormt voor verbetering bij oudere patiënten. In **Hoofdstuk 6** beschrijven we de functionele capaciteit en kwaliteit van leven van oudere CRC-patiënten rondom de operatie, gestratificeerd naar kwetsbare en niet-kwetsbare patiënten. Kwetsbare patiënten hadden zowel vóór als na de operatie een lagere functionele capaciteit en kwaliteit van leven. De chirurgische ingreep zelf had een vergelijkbaar effect op patiënten met en zonder kwetsbaarheid. Vanwege de blijvende lagere functionele capaciteit en kwaliteit van leven, blijven de kwetsbaren wel een groter risico houden op verlies van zelfstandigheid.

Het verbeteren van uitkomsten is zinvol als deze een aanzienlijke impact hebben op zowel de individuele patiënt als de gezondheidszorg in het algemeen. Prehabilitatie moet zich daarom ten minste richten op fysieke capaciteit, postoperatieve complicaties en kosteneffectiviteit. Functionele achteruitgang na chirurgie komt frequent voor, verhoogt het risico op verdere achteruitgang en is geassocieerd met diverse andere ongunstige uitkomsten, zoals postoperatieve complicaties, heropnames en mortaliteit. Met name postoperatieve complicaties komen veel voor bij oudere patiënten (Hoofdstuk 5) en zijn verantwoordelijk voor hogere heropnamecijfers, een lagere kwaliteit van leven, verhoogde korte- en lange termijn mortaliteit, verdere afname van fysieke capaciteit en hogere zorgkosten. Hoewel maar enkele studies de

kosteneffectiviteit van prehabilitatie hebben geëvalueerd, is deze uitkomst essentieel. Op dit moment wordt de implementatie van prehabilitatie in de klinische praktijk onder andere beperkt door het ontbreken van economische onderbouwing.

In **Deel III** onderzochten we aan de hand van twee observationele studies het effect van prehabilitatie bij oudere patiënten met CRC die geopereerd zijn in het Reinier de Graaf Gasthuis in Delft. In **Hoofdstuk 7** vergeleken we patiënten die deelnamen aan een prehabilitatie programma met patiënten die standaardzorg ontvingen. Patiënten die aan het prehabilitatie programma hadden meegedaan bleken preoperatief kwetsbaarder dan de niet-prehabilitatie groep. Ondanks het verhoogde risico op nadelige uitkomsten, was het percentage chirurgische complicaties, niet-chirurgische complicaties en heropnames gelijk. Deze uitkomsten suggereren dat prehabilitatie het risico op postoperatieve complicaties zou kunnen verminderen. In **Hoofdstuk 8** beschrijven we als eerste studie de lange termijn uitkomsten na prehabilitatie. We zagen geen verschil in de zes-jaarsmortaliteit tussen patiënten die wel en niet hadden deelgenomen aan het prehabilitatie programma. Wel was het aantal ziekenhuis opnames in de eerste zes jaar na operatie, significant lager in de prehabilitatie groep. Onze bevindingen zijn in overeenstemming met andere studies. Desondanks is prehabilitatie (nog) niet evidence-based. In de meest recente meta-analyse, waarin veertien gerandomiseerde gecontroleerde studies (RCT's) zijn geïnccludeerd, verbetert prehabilitatie significant de fysieke capaciteit, maar blijft het effect op postoperatieve complicaties en andere ongunstige uitkomsten onzeker.

Het gebrek aan overtuigend bewijs hangt samen met de uitdagingen waarmee (onderzoek naar) prehabilitatie wordt geconfronteerd, zoals de heterogeniteit van de geïnccludeerde patiëntenpopulatie, de variatie in prehabilitatie programma's, de diversiteit aan postoperatieve uitkomstmaten en methodologische en financiële beperkingen. We doen enkele voorstellen om in de toekomst met deze uitdagingen om te gaan.

Prehabilitatie zou met name moeten bestaan uit een fysieke interventie en zou zich moeten richten op patiënten met een lage fysieke capaciteit. Deze benadering zal de heterogeniteit van zowel de populatie als het prehabilitatie programma verminderen en de interpretatie van onderzoeksresultaten verbeteren. De andere domeinen dienen afzonderlijk te worden onderzocht om relevante uitkomsten te identificeren (bijvoorbeeld sarcopenie voor voedingsinterventies en depressieve symptomen voor psychologische interventies). Daarnaast dienen alternatieve onderzoeksopzetten voor RCT's overwogen worden. Aangezien RCT's vaak patiënten includeren die niet representatief zijn voor de dagelijkse praktijk en blinding bij een prehabilitatie programma onmogelijk is (patiënten in de standaardzorggroep worden zich meer bewust van hun gezondheidstoestand), wordt het effect van prehabilitatie onderschat. Tot slot moet het makkelijker worden om innovatieprojecten, zoals prehabilitatie, financieel te ondersteunen. Potentiële zorginnovaties zijn namelijk per definitie niet evidence-based. Alleen op deze manier kan prehabilitatie de transitie maken van een potentiële naar een definitieve zorginnovatie.

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ABOUT THE AUTHOR

Heleen van der Hulst was born on 8th May 1994 in Leidschendam, the Netherlands. After graduating grammar school at St-Maartenscollege in Voorburg, she started the study Medicine at Leiden University Medical Centre in 2012. She obtained her medical degree with honours in 2019. Already interested in scientific research, she was able to start a PhD-trajectory at the Surgical Department of Reinier de Graaf Hospital in Delft under the supervision of prof. dr. J.E.A. Portielje, dr. J.W.T. Dekker and dr. J.M. van der Bol in 2019 that focused on prehabilitation for older patients with colon or rectal carcinoma. During her PhD-trajectory, she helped initiating a multicenter cohort study (Better Be on Top “BEBOP”) in the South-West region of the Netherlands, performed several retrospective studies and presented her studies on national and international congresses. In 2021, Heleen started as resident not in training at the Surgery Department in Reinier de Graaf Hospital and continued the Phd-trajectory next to the clinical activities. Over the years, the interest in General Practitioner (GP) increased and Heleen eventually applied for the GP training program. After expanding her clinical experience during her work at the emergency department of Elisabeth-TweeSteden Hospital in Tilburg, she started the residency in general practice in September 2024. Her Phd-trajectory was successfully completed in 2026. Heleen lives together with Marc and their daughter Saar (Born March 2025) in Ulvenhout.

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Het proefschrift is klaar! Graag wil ik degene bedanken die hebben geholpen om dit proefschrift tot stand te laten komen.

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Na de fulltime onderzoeksperiode verliep het promotietraject parallel aan het werk in de kliniek. Mijn eerste baan als klinische dokter kon ik starten bij de geriatrie in het Reinier de Graaf, een leerzame omgeving met prettige collega's. Daarna heb ik anderhalf jaar bij de chirurgie doorgebracht; alle mede-assistenten en chirurgen wil ik graag bedanken voor de leerzame, gezellige en bedrijvige sfeer; een tijd die ik voor geen goud had willen missen. De dagen gaven uiteindelijk genoeg energie om weer een alinea voor het proefschrift te schrijven.

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