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

Hulst, H.C. van der

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

van der Hulst HC, van der Bol JM, Bastiaannet E, Portielje JEA, Dekker JWT

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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

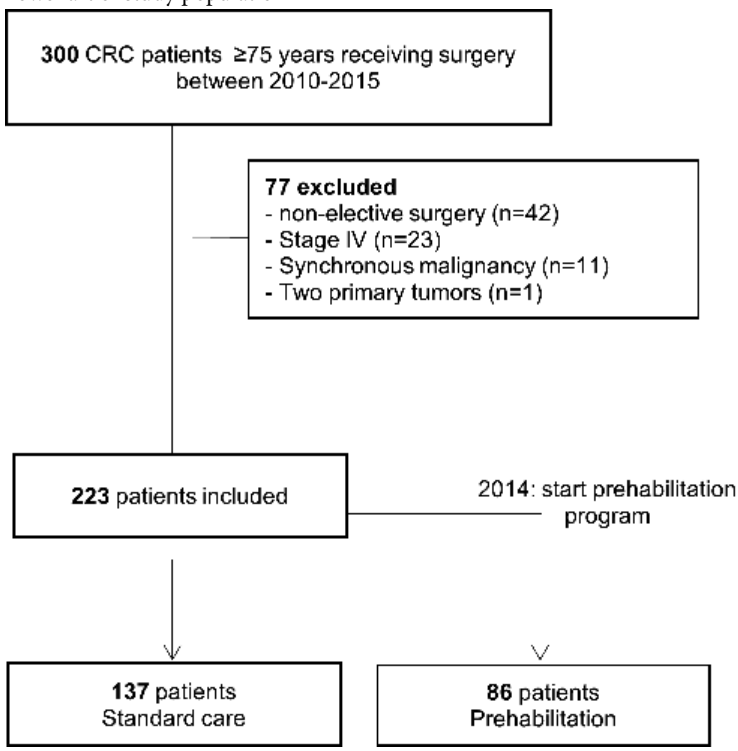
The included patient population was divided in two cohorts: before implementation of the prehabilitation program (2010-2013; standard care group) and after implementation (2014-2015; prehabilitation group). The follow-up time for all outcomes was six years. Survival was analyzed using the Kaplan-Meier 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-

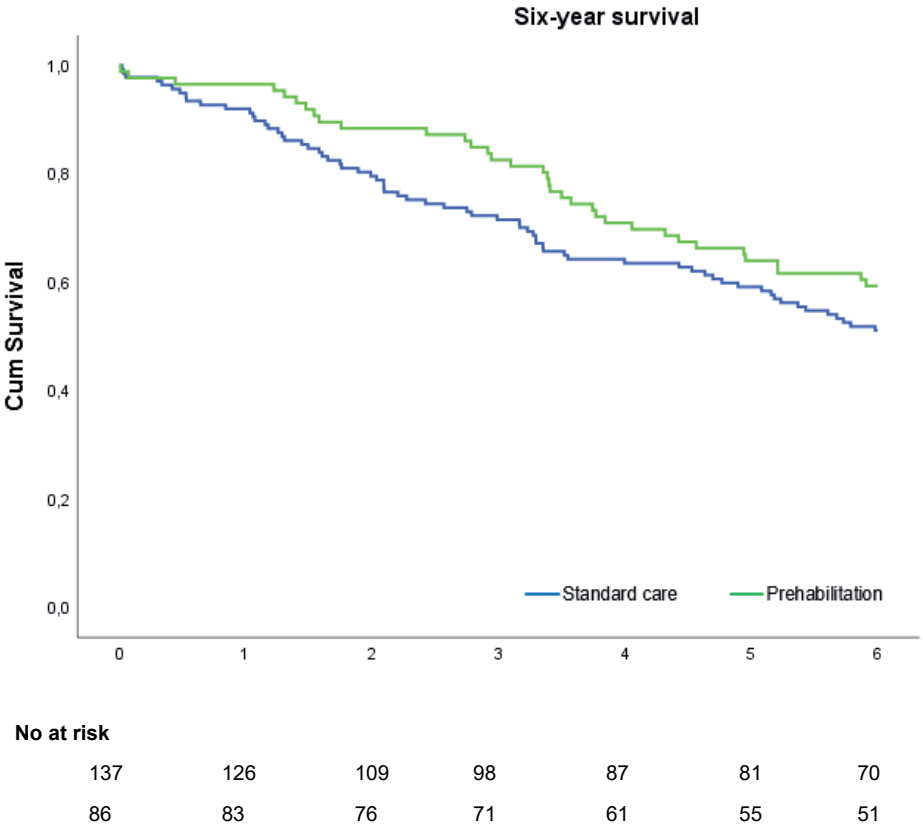
dard care group were still alive compared to 59.3% in the prehabilitation group (p=0.167). The multivariate cox regression analysis showed a hazard ratio (HR) of 0.77 (95% CI 0.51-1.17, p=0.219) for the prehabilitation group compared to standard care (Table 2).

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

	Standard care n=137	Prehabilitation n=86	P-value[ii]
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

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 wnere 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 (%)

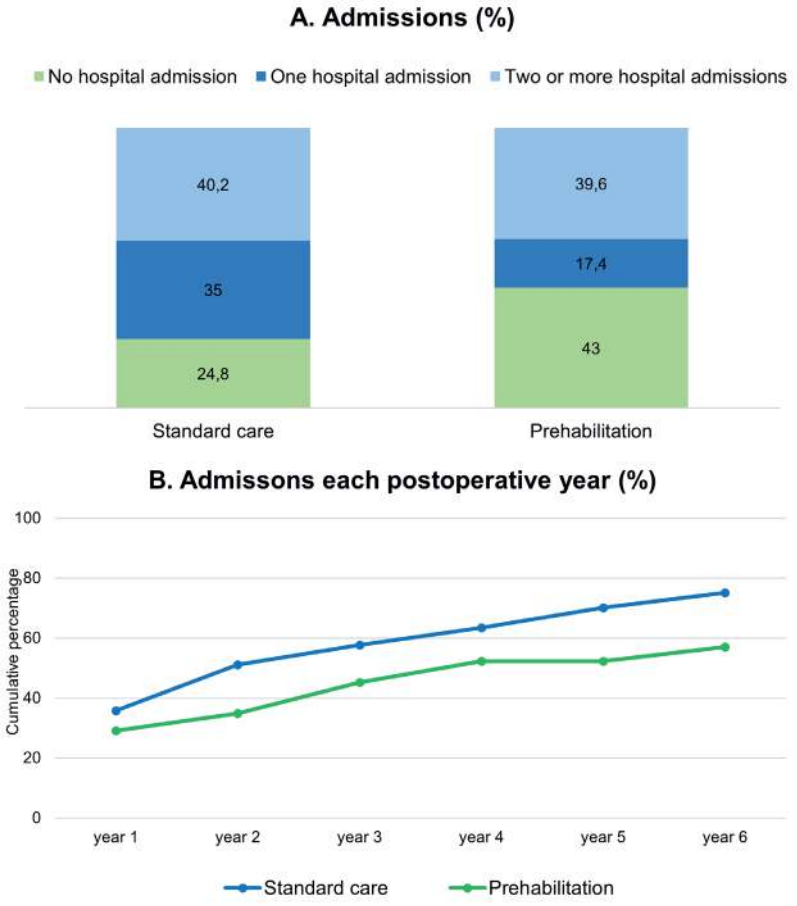
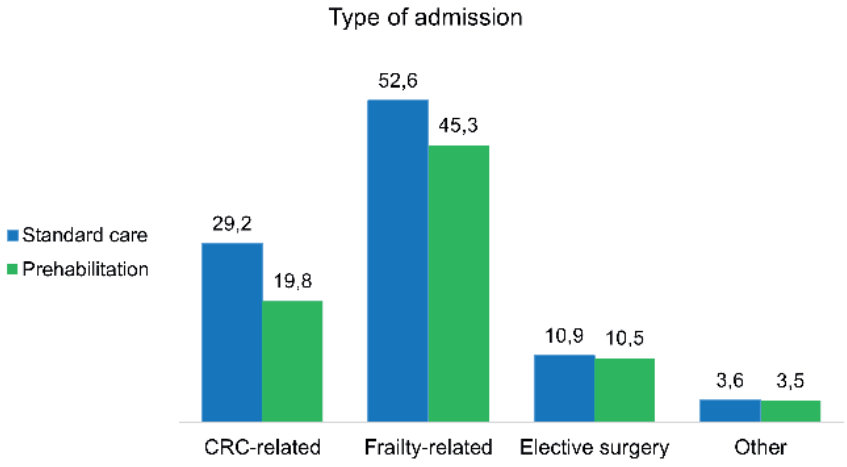


Figure 4. Proportion of hospital admissions per cohort for each admission type



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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