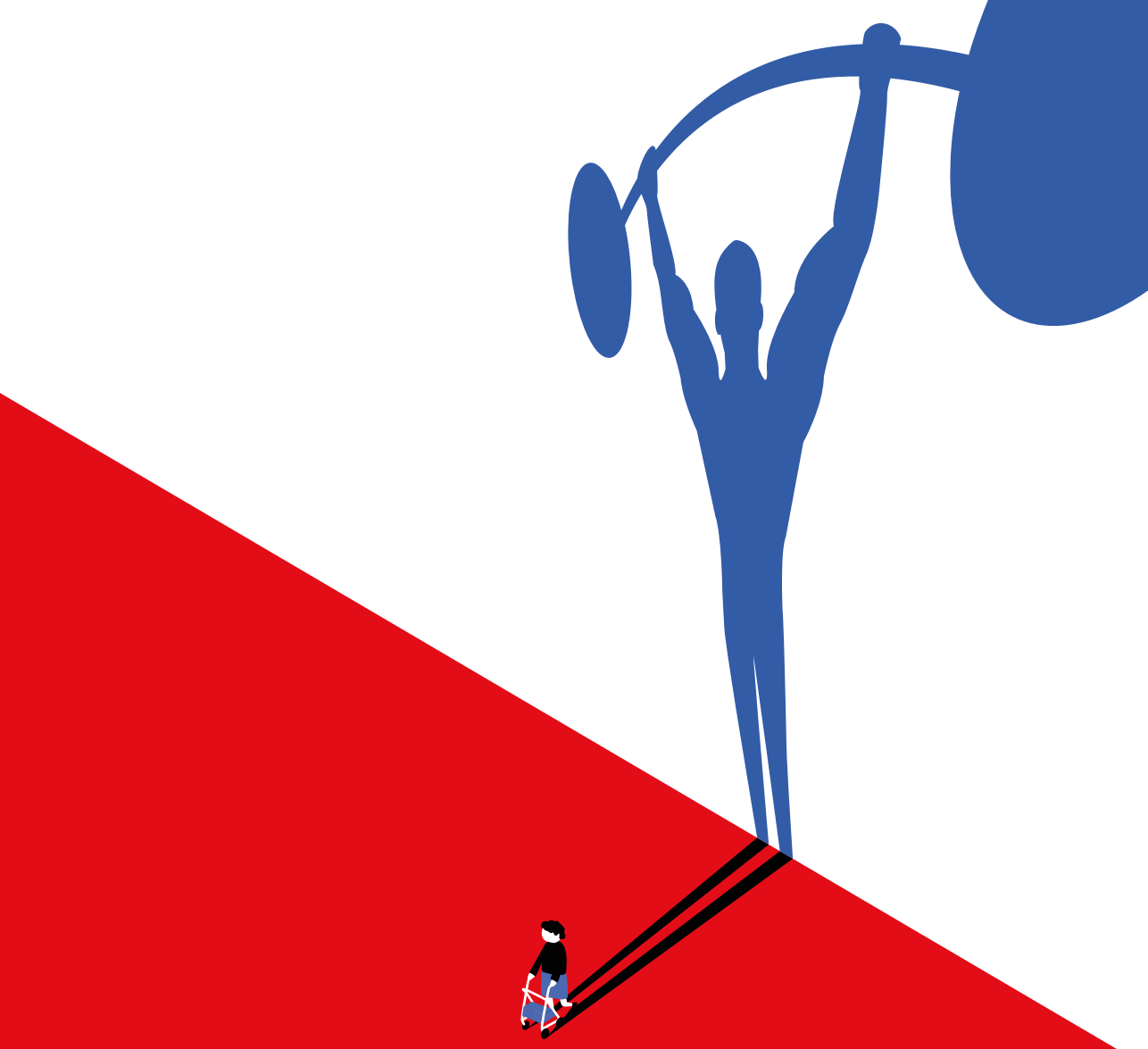

TOWARDS RESILIENCE

Prehabilitation for the elderly with colorectal cancer

EMMA R.J. BRUNS

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prehabilitation for the elderly with colorectal cancer

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Towards resilience – Prehabilitation for the elderly with colorectal cancer
PhD Thesis, University of Amsterdam, Amsterdam, The Netherlands

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TOWARDS RESILIENCE

prehabilitation for the elderly with colorectal cancer

ACADEMISCH PROEFSCHRIFT

ter verkrijging van de graad van doctor

aan de Universiteit van Amsterdam

op gezag van de Rector Magnificus

prof. dr. ir. K.I.J. Maex

ten overstaan van een door het College door Promoties ingestelde commissie,

in het openbaar te verdedigen in de Aula der Universiteit

op woensdag 27 november, te 13.00 uur

door

Emma Rosemarie Jeanne Bruns

geboren te Antwerpen - Wilrijk

Voor wie nooit oud was

Voor wie nooit oud is

Voor wie nooit oud zal zijn

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Faculteit der Geneeskunde

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General introduction and outline of the thesis

Background

The aging population

Prosperity and the increased quality of health care have introduced a new challenge in health care this century. The baby boom generation born in the fifties is gradually becoming a granny room. By 2020, over 50% of all patients attending the hospital in the Western world will be 65 years or over.[1] As can be easily observed, old age is merely but a number. The elderly phenotype is characterized by a loss of quality and decline of function of several organ systems.

Grey hair, wrinkles, poor posture and slow pace are some of the features that come to mind about elderly people when we are asked to describe them. Although we often do not die solemnly of old age, the effects of the wear and tear of life make bodies more at risk to experience adverse health outcomes when faced with a stressor. This age-related decline has also been defined as frailty.[2]

Over the past years, research has had its focus both on the pathophysiologic origins of frailty and its clinical implementation by means of risk prediction models. At one end of the spectrum, fundamental scientists such as de Grey published pioneering work in the field of gerontology in order to grasp the underlying concepts of aging and how to revert them.[3,4] At the other end, geriatricians, such as Fried and Rockwood introduced clinical instruments to assess clinical manifestations of frailty.[2,5]

More specifically, regarding the context of surgery, the growing number of old patients and especially the frail older patient pose a challenge to do temporary harm in order to obtain a better result.[6,7] The pragmatic clinical practice demands a sensitive and specific tool that would allow surgeons to quickly screen older patients; first to assess whether a surgical intervention will be a favorable choice, and second to identify any modifiable risk factors for an unfavorable outcome, such as a poor physical condition, malnutrition or polypharmacy. Even more so, the time prior to surgery is often limited and does not allow for all frailty-inducing factors (e.g. social isolation, cognitive impairment) to be tackled.

The current research concerning the understanding, definition and implementation of the concept of frailty is mainly an area of geriatricians. Their sense of nuance

and thorough, holistic approach has led to very detailed, mainly descriptive frailty models. By combining these efforts with the surgical approach, it might be possible to shift the paradigm from the identification of a frail patient to identifying the opportunity to become resilient.

Most old patients do not like to be defined as frail. Especially in the period prior to surgery, a sense of strength or at least the opportunity to change the odds, is quite important.[8] A frail patient can also be seen as a patient that has the opportunity to become resilient. Naturally, this is a possibility of change within a certain bandwidth caused by irreversible factors of frailty such as old age and existing comorbidity. However, by identifying modifiable factors[9] (e.g. decreased physical condition, poor diet), the inherent drive of many patients to maintain their autonomy (stay at own home, playing tennis, etc.) can help to revert this condition.[8]

Resilience can be generally defined as the physical and mental capacity to positively adapt when faced with a stressful or adverse situation.[10] It might be best stated by in Man's search for meaning written by Victor Frankl, a Jewish psychiatrist who survived Auschwitz: "Everything can be taken from a man but one thing: to choose one's attitude in any given set of circumstances, to choose one's own way."

The fact that an elderly patient is diagnosed with cancer requiring a surgical intervention, can generally not be changed. However, similar to any challenge in life (e.g. passing an exam, playing an important football game, losing a family member), one can physically and mentally prepare. This is no different in a clinical setting.

Colorectal cancer

As we have successfully succeeded in declining the rate of people dying from infectious diseases and cardiovascular events, our cells get to divide longer than ever. Chances are that in this process errors occur, resulting in premalignant growth and eventually cancerous tumors.

Since the introduction of nationwide screening in combination with the abovementioned fact of the ageing population, Dutch hospitals are faced with almost 15 000 new patients diagnosed with colorectal cancer each year, of which more than 60 per cent is over 65 years old.[11]

Up until today, the cornerstone of treatment of colorectal cancer is surgery. A curative resection can be performed in the majority of the cases while the risks of bowel perforation due to a mechanical obstruction and the secondary effects of cancer (cachexia, anaemia, etc.) are eliminated. However, operating on elderly patients also poses significant risks. Frailty, defined above as an increased vulnerability towards stressors such as a surgical intervention, is more common in elderly patients, in particular in those diagnosed with cancer.[12]

Over the past decades, great efforts have been made to improve the outcomes of colorectal surgery. During the peroperative phase, minimally invasive techniques and safety checklists have been introduced. In the peri- and postoperative phase, enhanced recovery after surgery-programs are widely implemented across the field. However, the preoperative period remains to be a potential window of opportunity.[13]

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Aim of the thesis

Frailty and Resilience

On average, frail patients have a fourfold higher risk of adverse outcomes such as postoperative complications and delayed recovery compared to their non-frail counterparts. Frailty can present itself in a wide array of phenotypes in which it can manifest itself (e.g. ADL-dependent, depression, malnutrition, social isolation, etc.). The aim of this thesis is to bifold. First, to define what frailty means in a surgical context. Second, to shift the idea of frailty towards an opportunity to revert this condition or at least make older patients more resilient to withstand a stressor such as a surgical intervention.

Preoperative optimization

Prehabilitation, defined as a multimodal approach to enhance a patient's condition prior to surgery has been gaining interest over the past years. The intervention is so intuitive that a layman might wonder why prehabiliation programs are only scarcely present in daily practice. An answer can lie in the fact that there is a lack of evidence for such behavioral interventions that require various disciplines (dietary specialists, physiotherapists, surgeons, geriatricians) to collaborate. As only 7% of all randomized controlled trials worldwide specifically focus on the elderly, the evidence is in this specific group is even more limited. The aim of this thesis is to assess the feasibility of prehabilitation in frail elderly patients, to focus on those who have the most to gain.

Outline of the thesis

Part I – The concept of frailty

In an era of data and the desire for transparency of society, the administrative load of health care jobs is increasing. In **Chapter 1**, we aim to investigate the value of the first clinical impression of health care professionals in comparison to a validated screening tool to predict the patient's outcome. Both tools aim to identify elderly patients at risk for a functional decline or mortality after 90 days. In the field of tools to assess frailty and its physical dimension in particular, doctors prefer to use a minimally invasive and quick tool. In **Chapter 2**, three commonly used physical frailty measurement methods: hand grip strength, muscle mass and clinical frailty, were assessed in elderly attending the hospital. It was the aim to evaluate their overlap and the look at 1-year mortality after measurement.

We focused on the concept of frailty in elderly patients diagnosed with colorectal cancer. In **Chapter 3**, we assessed the relationship between low muscle mass (psoas major at the level of lumbar three) and postoperative complications in elderly patients who received surgery for colorectal cancer. In **Chapter 4**, we performed a Snapshot study of all patients operated for rectal cancer in 71 Dutch hospitals to assess anaemia as a potentially associated factor with postoperative outcome. Lastly, in **Chapter 5,** we evaluated a nationwide implemented value instrument for frailty, the VMS (Veiligheids Management Systeem), in its performance regarding its value in preoperative risk screening in elderly patients receiving surgery for colorectal cancer.

Part II – Prehabilitation in colorectal surgery

Following the identification of modifiable targets of frailty, we investigated current initiatives regarding preoperative optimization of patients undergoing colorectal surgery. In **Chapter 6**, we performed a systematic review to create an overview of the current studies investigating preoperative physical training in older patients receiving surgery for colorectal cancer. In **Chapter 7**, a comparable systematic review was performed to provide an overview of the current studies investigating preoperative oral nutritional support in patients receiving surgery for colorectal cancer. In **Chapter 8**, the value of intravenous iron supplementation in colorectal cancer patients with anaemia was assessed by means of a retrospective cohort study.

Part III – The Fit4Surgery approach

Based on the results of the inventory we made of the current initiatives regarding prehabilitation worldwide, we developed the Fit4Surgery approach. Nationwide, the foundation Fit4Surgery was founded in order to gather knowledge, bring experts together and facilitate collaboration through standardization and implementation. In **Chapter 9**, we describe the current state of the concept of prehabilitation and a model to create a framework for implementation. Lastly, in **Chapter 10**, we describe the results of our own pilot "Fit4SurgeryTV" in which we aimed to assess the feasibility of an at-home prehabilitation in the frail elderly receiving surgery for colorectal cancer.

Part I

The concept of frailty

1

Clinical impression as an instrument to predict adverse medical outcomes in elderly patients attending the emergency department

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Abstract

Introduction

Emergency departments (ED) are hectic environments making it challenging to identify older patients who are at increased risk for adverse outcomes. The evidence of the superior value of screening tools over clinical impression by medical personnel is limited. The aim of this study was to assess whether the first clinical impression by medical personnel of the elderly patient is at least as good as a validated screening tool in predicting 90-day mortality or functional decline.

Methods

In this prospective cohort study, we recruited patients ≥70 years who presented at the ED of Gelre Hospital, Apeldoorn, The Netherlands, from May-August 2017. Within 30 minutes upon arrival of the patient, medical personnel were asked to estimate the patient's risk on loss of function (Daily Living Activities), based on the first clinical impression. APOP (Acute Presenting Older Patient)-screening was performed subsequently. The main outcome was composite decline, defined as mortality or functional decline within 90-days. The area under the ROC curve (AUC) was assessed for clinical impression and the APOP screener.

Results

A total of 238 patients with a median age of 81 years (IQR 76-87) were included in this study. A total of 440 clinical observations were made by 82 individual observers. During 90-day follow up, 101 (42%) patients experienced the composite decline, of which 36 (15%) patients died and 65 (27%) experienced functional decline. The AUC of clinical impression was higher than the APOP for composite outcome (0.75 (95% CI: 0.69 - 0.82) vs 0.61 (95% CI: 0.54 - 0.69) $p<0.05$).

Discussion

This study shows that clinical impression is at least as good as a validated screening tool. Although the development of predictive screening tools is promising, clinical impression should maintain a role in the risk assessment of the patient.

Introduction

The population of older patients attending the emergency department (ED) is ever-increasing, representing between 12 to 24 percent of the total number of presentations at the ED[1–3]. Older patients attending the ED frequently suffer from complex medical issues in multiple domains[4,5]. Consequently, they are at higher risk for negative medical outcomes such as hospital (re)admissions, treatment complications and death[6].

Although age is an overall risk factor for adverse outcomes, the aged population is highly heterogeneous varying from 'young-old's' with an active lifestyle and healthy diet to 'old-old's' with serious comorbidity or frailty[7]. The importance of detecting those who are at higher risk is threefold. First, physicians, patients and their peers might be able to make better informed decisions about active treatment options such as an operation. Second, adequate risk stratification is important in order to optimize medical outcomes, quality of life, care and healthcare costs[8]. Third, identification of patients at increased risk provides an opportunity to revert a feeble condition[1].

Since the ED is inherently a hectic environment requiring rapid decisions, subtle vulnerabilities in older patients can easily be overlooked. Elaborate risk assessment tools are not suited for the ED, as they are time-consuming and often impossible to administer in this surrounding. Therefore, to achieve early detection of older patients who are at higher risk, several relatively quick screening methods have been developed[9–11]. For instance, the APOP screener is a validated screening tool detecting older patients attending the ED who are at increased risk for mortality and functional decline. By means of patient characteristics and a short questionnaire, the algorithm calculates the individual's chance of 90-day mortality and functional decline[12].

Before the introduction of such screening instruments, clinicians have long based their treatment decisions on a combination of objective symptoms, but also on their clinical impression of the patient[13,14]. Clinical impression of medical personnel may be an important but often overlooked component of modern medical decision making. If clinical impression is an accurate tool for risk stratification, it could be implemented as a less time-consuming alternative. The aim of this study was to

compare clinical impression at presentation with a validated risk screening tool (APOP-screener) to predict composite decline, defined as mortality or functional decline in older patients attending the ED after 90 days.

Methods

Patient Selection

Between May and August 2017, all patients 70 years or older reporting to the ED between 10 am and 7 pm at Gelre Hospital, Apeldoorn, The Netherlands, who were referred for the specialty's surgery, internal medicine, gastroenterology, orthopedics, ophthalmology, were considered eligible. Patients referred for neurology and cardiology were not eligible due to logistic reasons. Exclusion criteria were: 1; Patient in a possible life-threatening situation (e.g. unstable patient, trauma setting), 2; Severe cognitive impairment with no proxy, 3; Language barrier (inability to communicate in Dutch, German or English and no translator available), 4; Logistic reasons (e.g. patients leaving the ED before inclusion), 5; no permission from medical personnel to approach patient for any other reason. The study was approved by the Institutional Review Board of Academic Medical Centre (AMC) in Amsterdam, The Netherlands and the local Review Board of Gelre Hospital in Apeldoorn, The Netherlands. The study conforms to the ethical guidelines of the Declaration of Helsinki.

Procedure & Data Collection

Upon arrival at the ED, patients were given a leaflet informing them about the study and they were asked if they wished to participate. Permission was obtained by written informed consent. Author HS gathered patient baseline characteristics by means of measurement, questionnaires and information retrieved from electronic medical records. These were age, gender, laboratory measurements taken (yes/no), medical specialty to which the patient had been referred, whether the reason for referral had been a fall, arrival by ambulance, living in an institutional care facility, number of different medications, Katz Index of Activities of Daily Living (KATZ-ADL) -6- questionnaire (assessing physical state two weeks prior to ED attendance)[15], the number of prescribed medications (polypharmacy was described as five or more) the 6-item cognitive impairment test (6-CIT)[16] (cognitive impairment was defined as a score >7) and Short Nutritional Assessment Questionnaire (SNAQ) score[10] (malnutrition was defined as a score ≥2).

Clinical impression

Within 30 minutes upon arrival of the patient, medical (treating physicians) and paramedical (nurses) personnel assessed the patient using their clinical impression of the patient. Each patient was assessed by 1-3 members of the medical personnel. They stated their impression of functional decline within 90 days for each patient between 0% and 100% (0% = no chance of the outcome occurring, 100% = outcome definitely occurring). Baseline characteristics of assessors were also collected. These were age, gender, role (medical/paramedical), years of clinical experience, whether or not it was the first time the observer saw this patient and whether the observer had prior medical knowledge about the patient.

APOP Screener

The APOP is a validated instrument to predict mortality and functional decline after 90 days in older patients attending the ED[12]. It constitutes of an algorithm composed of three tools: 1) Identification of Seniors at Risk (ISAR) screening tool[9], a validated screening tool for older patients attending the hospital who are at risk for functional decline and mortality, consisting of four questions assessing mobility, ADL-dependency, use of a walking device and education level; 2) Six Item Cognitive Impairment Test (6-CIT)[16]; and 3) the KATZ-ADL-6 questionnaire[15]. The formula 1/(1+e(-linear predictor)) was applied with the adjusted regression equation to determine the individual risks of experiencing the outcome. Based on these risks, the area under the ROC curve (AUC) was calculated for mortality and a composite decline (functional decline + mortality). A full description of the development and validation of the APOP-screener is provided in the original article by Gelder et al.[12].

Outcomes

The primary outcome for this study was composite decline, defined as either death or functional decline within 90 days. This composite outcome was chosen to comply with the original APOP-study, in which the authors defined the outcome as either mortality or functional decline, meaning a decrease of one point or more in the KATZ-ADL-6 score (Supplementary Figure 1) or novel admission to a rehabilitation center or novel institutionalization in a nursing home.

Follow-up

After 90 days, the patients were contacted by telephone in order to assess their functional status. Three attempts in three consecutive days were made. Both patient

records and the national registry were checked for survival of all patients prior to telephone contact. In case of no response by telephone and no documentation of death in the state records, the patient was defined as lost to follow up and excluded from the analyses.

Statistical methods

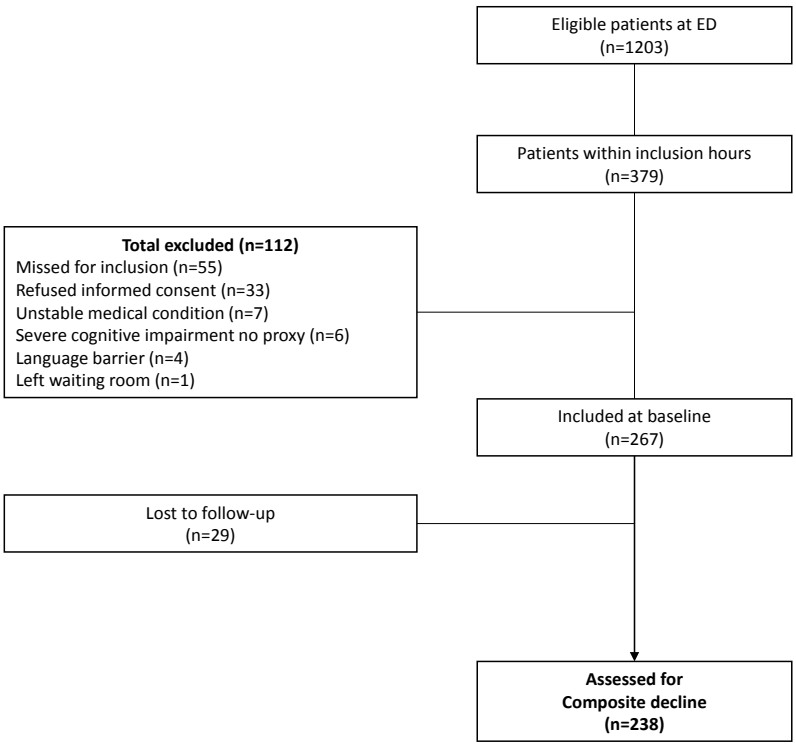
First, we compared age and gender between patients not enrolled in this study with our study population. Study population and medical personnel baseline characteristics were analyzed using descriptive statistics. A Pearson's chi square test was performed for categorical variables, for normally distributed continuous variables, the independent samples t-test was used; for not normally distributed variables we used Mann-Whitney U. For both clinical impression and the APOP-screener AUC's were calculated using ROC curve analysis for the composite outcome. The level of statistical significance was set at $p<0.05$ for all analyses. All statistical analyses were performed with the Statistical Package for Social Sciences (SPSS) version 23.

Results

Study recruitment

During the study period, 1203 older patients attended the ED, of whom 379 were eligible for inclusion. A number of; 112 patients were not enrolled, mostly because they were missed for inclusion (n=55) or because they refused to participate in the study (n=32). During follow-up, 29 (11%) patients could not be reached. Therefore, the study cohort consisted of 238 patients. The patient flow diagram and reasons for exclusion are shown in Figure 1.

Figure 1. Patient flow diagram



Study population

Patient characteristics of eligible but not enrolled patients were compared to the study population for age and gender. The populations differed only with respect to gender (more women in the study group (62%) than in the excluded group (49%, p=0.022).

The patients in the study group had a median age of 81 years (IQR 76-87). After 90 days, 36 (15%) patients had died and 65 (27%) patients had experienced functional decline, resulting in a total composite decline group of 101 (42%) patients.

Patients who experienced composite decline were older at baseline (median: 85 years (IQR 79-89) vs 78 (IQR 74-84), p<0.001). There were no differences in gender (female 61% vs 61%, p=0.98), baseline institutionalization (17% vs 12%, p=0.26) or polypharmacy (53% vs 48%, p=0.42). Patients who experienced composite decline were less often admitted to the general surgery department (35% vs 52%, p=0.008) but more often to the geriatrics department (27% vs 5%, p<0.001). Patients with composite decline were more at risk for malnutrition (51% vs 38%, p=0.04) and more often ADL-dependent (41% vs 27%, p=0.03).

Lastly, patients who experienced composite decline were more often diagnosed with cognitive impairment (based on the 6-CIT score >7) (14% vs 1%, p<0.001), and had arrived at the hospital more often by ambulance (47% vs 40%, p=0.03). There were no significant differences regarding fall-related ED visits (42% vs 37%, p=0.5), indication for laboratory investigation (81% vs 70%, p=0.05) and use of a walking device (48% vs 44%, p=0.55). Baseline characteristics of this study population are summarized in Table 1.

Observer characteristics

The study used assessments made by 82 different observers. Of these observers, 61 (74%) were female, 42 (51%) were nurses, and 40 (49%) were physicians. The observers had a median age of 34 years (IQR 28-48) and a median clinical experience of 8 years (IQR 2-25). Observer characteristics are summarized in Table 2.

Table 1. Patient baseline characteristics

Patient characteristics	**Total**	**Composite Decline^**	**Without decline**	**p-value**
	N (%)	N (%)	N (%)	
Total	238 (100)	101 (42)	137 (58)	
Age (median, IQR)	81 (76–87)	85 (79-89)	78 (74-84)	<0.001
Female	144 (61)	61 (61)	83 (61)	0.98
Institutionalized before admission	33 (14)	17 (17)	16 12)	0.26
Polypharmacy (³5 medications)	119 (50)	53 (53)	66 (48)	0.42
Sent to ED for specialty:				
General surgery	106 (44)	35 (35)	71 (52)	0.008
Internal medicine	65 (27)	30 (30)	35 (25)	0.48
Geriatric medicine	34 (14)	27 (27)	7 (5)	<0.001
Pulmonary medicine	16 (7)	4 (4)	12 (9)	0.14
Gastroenterology	12 (5)	4 (4)	8 (6)	0.51
Orthopedic surgery	4 (2)	1 (1)	3 (2)	0.48
Urology	1 (0.4)	0 (0)	1 (1)	0.39
Functional				
At risk for malnutrition (SNAQ score ≥2)	104 (44)	52 (51)	52 (38)	0.038
Cognitive impairment (6-CIT, score >7)*	48 (24)	20 (26)	28 (23)	0.58
ADL-dependent (KATZ-ADL-6 dependent for 2 or more items)	78 (33)	41 (41)	37 (27)	0.027
Experienced fall past 6 months**	129 (61)	50 (61)	79 (60)	0.92
Fall related ED visit	93 (39)	42 (42)	51 (37)	0.50
Diagnosed with dementia	16 (7)	14 (14)	2 (1)	<0.001
Arrival by ambulance	94 (39)	48 (47)	55 (40)	0.030
Indication for lab	178 (75)	82 (81)	96 (70)	0.051
Use of walking device***	97 (45)	40 (48)	57 (44)	0.55
APOP-screener high risk^				

*N=201 Patients diagnosed with dementia did not do the 6-CIT. **N=213 *** N=215
Notes: SNAQ = Short Nutritional Assessment Questionnaire, 6-CIT= Cognitive Impairment Test, ADL = Activity Daily Living
^Composite Decline = KATZ-ADL loss of 1 point or more, mortality after 90 days or institutionalization in a nursing home or rehabilitation center

Outcomes

Clinical Impression

Medical personnel made a total of 440 first clinical impressions. A clinical impression was made once in 95 (40%) patients, twice in 132 (55%) patients and three times in 11 (5%) patients. All patients were assessed at least once by a nurse, and 202 (85%) patients were also assessed by a physician (the remaining patients were not seen by a physician within the 30-minute time window). The median predicted chance for composite outcome occurring was 40% (IQR 20-70) by nurses and 50% (IQR 20-80) by physicians. These results are summarized in Table 2.

Table 2. Characteristics Observers

Characteristics observers	**N (%)**
Total number of observers	82
Age (median, IQR)	34 (28-48)
Female	61 (74)
Clinical experience, years (median, IQR**)	8 (2-25)
Nurses	42 (51)
Physicians	40 (49)
Total observations	443
First time seeing this patient	390 (88)
No previous knowledge about patient	268 (61)
Number of observations per patient*	95 (35)
1	157 (60)
2	10 (4)
3	1 (1)
4	40% (IQR** 20-70)
Estimated chance of composite decline	50% (IQR** 20-80)
Nurses	
Physicians	

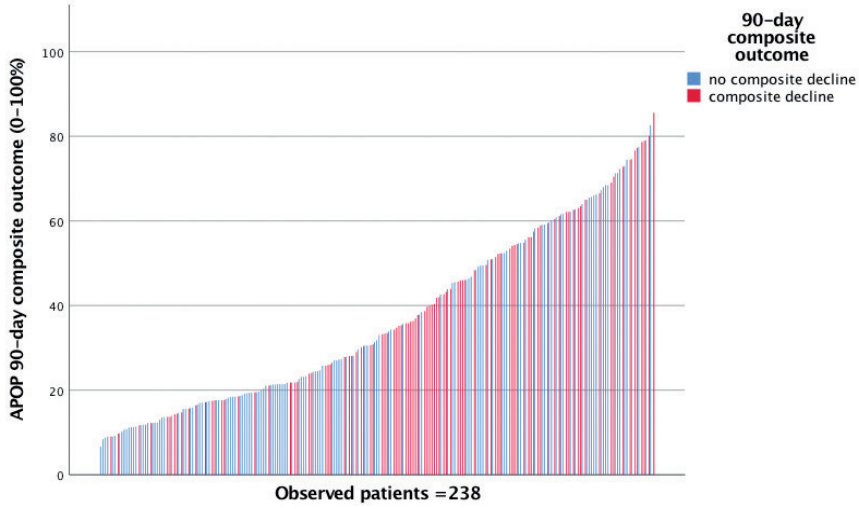
*n= 238, observations made in patients lost to follow-up were excluded ** interquartile range

APOP Screener

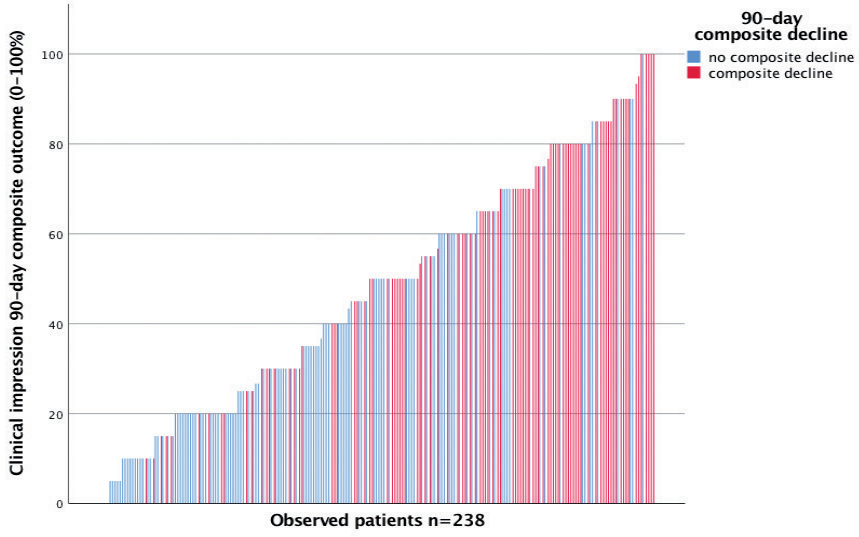
By means of the APOP screener, patients had a median predicted chance of 37% (IQR: 18%-54%) for the outcome. Histograms of distribution are presented in Figure 2.

Figure 2. Histograms of predicted 90-day composite decline

2a. APOP-screener



2b. Clinical Personnel



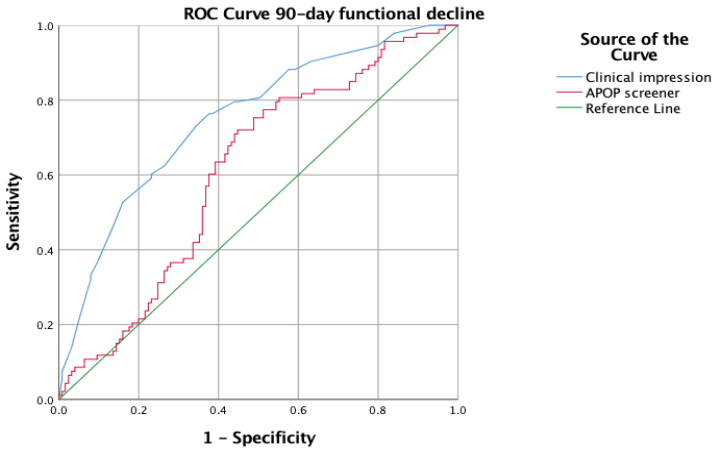
Composite decline

In total, 101 (42%) patients experienced composite decline; 36 (15%) patients had deceased, 52 (22%) experienced decline of the KATZ-ADL of one or more point, 10 (4%) patients were newly institutionalized in a rehabilitation center or a nursing home and 13 (5%) patients had both a decline in KATZ-ADL score and were institutionalized. These results are summarized in Table 3. ROC curves for the outcome showed an AUC of 0.75 (95% CI: 0.69 - 0.82) for clinical impression versus an AUC of 0.61 (95% CI 0.54 - 0.69) for the APOP. These results are visualized in Figure 3.

Table 3. Outcomes

Outcome	N (%)
Total	238
Composite decline	101 (42)
Mortality after 90 days	36 (15)
Functional decline	65 (27)
decline of KATZ-ADL one point or more	52 (22)
novel admission to rehabilitation center/nursery home	10 (4)
decline of KATZ-ADL and novel institutionalization	13 (5)

Figure 3. ROC curve analysis for 90-day composite decline



	Clinical Impression	APOP Screener
AUC	0.75	0.61
95% CI	0.69-0.82	0.54-0.69

Discussion

The aim of this study was to compare the ability of clinical impression of medical personnel with a validated screening tool to predict adverse outcomes in older patients visiting the ED. The APOP screener has previously been validated as a screening tool for adverse medical outcomes[12]. The results of this study suggest that clinical impression predicts 90-day mortality and functional decline at least at a comparable level as the APOP screener. In an era of registration and measurements, the value of the clinical impression of medical personnel should not be neglected.

With an increasing body of clinical data, there is a growing tendency to develop and rely on prediction models[17–19]. Simultaneously, there is increasing awareness of the potential harm that cognitive biases can have on our clinical judgement[20,21]. Furthermore, the media and directory boards of hospital and national registries also tend to prefer objective lists over subjective clinical judgement resulting in an increasing number of screening tools in clinical practice. However, these screening tools are rarely well validated. In 2017, Jørgensen et al. published a systematic review on the use of risk assessment for older patients at the emergency department. Four studies including assessment of Clinical Frailty Scale, Deficit Accumulation Index, ISAR-HP and The Study of Osteoporotic Fracture frailty index were compared[22]. The review concluded that the limited number of studies and their methodological value was not enough to justify replacing clinical assessment for a screening tool.

A difficult underlying question of this study is to define what clinical impression is. The results show a that patients suffering 90-day composite decline were at baseline more often older, at risk for malnutrition and ADL-dependent. Age, malnutrition and ADL-dependency are all individual risk factors for adverse outcomes during hospital stay.[23] Their cumulative phenotype of these elements (e.g. thin patient in a wheelchair entering the ED) results a worrisome clinical impression. The clinical and scientific value of clinical impression will therefore not benefit from a traditional deconstructive approach (univariate analysis) but should be seen as a quick tool of the human mind to evaluate a large number of variables into a first risk assessment.[21]

However, any new screening instrument will only work if it has been successfully implemented. The ED is a crucial place to perform screening but also has limited

time to perform fast and effective risk assessment. Some screening tools, such as the Deficit Accumulation Index, can take over 15 minutes to complete[24]. Quick screening tools, such as the measurement of hand grip strength, the surprise question and the clinical frailty scale, have been shown to adequately predict adverse outcomes[25–27]. Clinical impression can be regarded as an instrument in the same 'quick-scan' category and can possibly serve as a first triage-step to select patients who are in need of a more elaborate assessment such as the Comprehensive Geriatric Assessment[28].

Our study has some limitations that should be taken into account. First, with respect to the internal validity of this study, the use of inclusion time slots created a potential selection bias. Patients who present to the ED at night are often more severely ill and have higher rates of functional decline and mortality. Whether the predictive value of the clinical impression is affected by this bias is unclear.

Second, clinical impression as a tool is subjective and consequently influenced by interobserver variability. It is likely that different clinicians have different ways of looking at a patient (due to years of experience, time of day, specialty). As can be seen in Table 2, some clinicians had prior medical knowledge about the patient which possibly clouds the pure effect of clinical impression at first sight. Furthermore, it would be of interest whether the level of expertise (clinician vs nurse) and years of experience have a specific effect on the precision of the clinical impression, but the limited sample size preluded this sub analysis.

Third, the results should be interpreted taken incorporation bias into account. The clinical decisions for treatment are likely to be based on the clinical impression and thus could have influenced the status of the patient after 90 days. However, this bias also applies to the APOP-screener, in which elements such as polypharmacy or cognitive impairment could possibly create a comparable bias. This limitation therefore did not influence the comparison between the two screening tools.

Lastly, our study showed an AUC of 0.61 for the APOP screener. During the execution of this study, the APOP-screener was further refined and validated in another population. Studies with larger sample sizes showed a better predictive value of the screener and thus our study can be hampered by its limited sample size.[29]

To conclude, although the AUC for clinical impression was higher than that of the APOP screener, it would be rash to conclude that clinical impression has a higher predictive value. In an era of evidence-based medicine, we are sometimes forced to deconstruct every clinical tool we have into data. In this methodology also lies a potential limitation. Even though we cannot yet fully disentangle the way clinicians construct their clinical impression of a patient, it might be a highly valuable asset, especially in a high-pressure clinical setting that requires rapid decisions. Even more so, a hybrid model (such as the in-hospital early warning system (EWS), for example)[30] where the prediction model is combined with clinical impression, could result in a solution that has the best of both worlds.

This study suggests that a quick clinical impression is not inferior to a time-consuming validated screening tool in predicting adverse medical outcomes for older patients attending the ED. One might state that although it is often a matter of gut feeling, it is possible to discern between patients who are at risk for negative outcomes using clinical impression. Even more so, if we don't take our clinical impression into account in a prediction model, it will still affect our clinical decisions. Therefore, even in the modern era of big data and elaborate risk prediction models, clinical impression can be considered a useful tool to assess older patients at the ED.

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2

Physical frailty and mortality after one year in elderly patients attending the hospital: what are we measuring?

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Abstract

Aim

Age-related physical frailty (declined muscle mass and/or muscle function) is a risk factor for falls, infections and mortality. The aim of this study was to assess the relationship between three expressions of physical frailty in an older population attending the hospital and to explore the prognostic relevance of physical frailty on mortality.

Methods

A prospective observational study was performed in patients ≥70 years attending the radiology department for an abdominal CT scan. Decreased muscle strength was measured as grip strength (GS) and defined according to gender-specific cut-offs. Low muscle mass (MM) was defined as the lowest gender-specific 25th percentile of the psoas area at L3-level. Clinical frailty (CF) was defined as a Clinical Frailty Score (CFS) ≥5. Mortality rates were assessed after 1 year.

Results

In total, 174 patients were included. A total of 81 (46%) patients were physically frail based on at least one of the three instruments. Among them, 50 (29%) had decreased GS, 44 (25%) patients had low MM and 12 (7%) patients were CF; only 2% were frail according to all three instruments. The overall mortality rate after 1 year was 12% (n=10) in physically frail patients, whereas this was 19% (n=18) in non-frail patients (p=0.12).

Conclusions

In this study, 46% of older patients attending the hospital were physically frail on one or more validated instruments. Physical frailty was not associated with increased risk for 1-year mortality. There was limited overlap between grip strength, muscle mass and clinically frailty suggesting multifactorial pathophysiologic backgrounds.

Introduction

Risk of age merely resides in the number of lived years itself. Older patients comprise a heterogeneous group with wide variability in physical condition. Old age results in a biological phenotype, characterized by cognitive decline, rigidity and slow pace.[1] Consequently, old age is associated with an increasing prevalence of frailty.[2] The frailty syndrome can be defined as a state of increased vulnerability towards stressors.[3] It can be observed in three dimensions: socially, psychologically and physically.[4–6] When confronted with stressors such as an operation or a fall at home, physically frail patients are more prone to be injured e.g. suffering from postoperative complications or fractures, respectively.[7,8] Physical frailty, often expressed as poor functional performance, and sarcopenia, expressed as declined muscle mass or function, are thought to have shared roots in pathophysiology.[5]

Basically, muscle tissue serves two purposes. Primarily, muscle tissue serves as a reservoir for amino acids and is an actor in glucose regulation, useful to withstand the body during stressful events such as surgery or infection. The amount of muscle tissue can be measured as muscle mass on imaging studies.[9] Secondarily, muscle tissue provides the body with motor function preventing the body from swallowing disorders, falling and social isolation, respectively leading to pneumonias, hip fractures and depression. This function can be measured by testing the strength of different muscle groups. The most often used group is the hand musculature, defined as grip strength. In combination or due to other causes such as other comorbidity (e.g. peripheral arterial diseases, diabetes, copd), overall muscular weakness can lead to a high clinical frailty score.

Daily clinical practice requires screening tools that can easily and accurately identify patients at risk for a poor outcome. Grip strength, muscle mass and clinical frailty scores have all been shown to be moderate at identifying patients at risk for adverse outcomes.[10,11] Because of this moderate prognostic value, there is no clear consensus on which instrument to use and whether they might overlap. The aim of this study was therefore to examine physical frailty in an older population attending the hospital by means of three validated physical frailty instruments (grip strength, muscle mass, clinical frailty score) to assess their overlap and their value in predicting 1-year mortality.

Methods

Patient Selection

This prospective cohort study was assessed by the Institutional Review Board of the Academic Medical Centre (AMC) in Amsterdam, The Netherlands, which decided officially that the study dit not require in depth assessment. Permission was obtained by written informed consent from the patient or his representative (e.g. cognitive disorder) which was added in the medical file. The authors certify that they comply with the ethical guidelines for publishing in the Journal of Cachexia, Sarcopenia and Muscle: update 2017. Between January 2016 and April 2016, all non-hospitalized patients with an age of ≥ 70 years attending the department of Radiology in the Gelre Hospital in Apeldoorn undergoing a CT scan of the abdomen were included. Patients were excluded if the CT scan did not include the m.m. psoas major at the level of the third lumbar vertebral body (L3) (CT abdomen, CT colonography, CT urinary tract, CTA abdomen and CTA follow up stent graft). We also excluded all hospitalized patients and patients who were not able to execute grip strength examination.

Procedure & Data collection

Upon arrival at the clinic, patients were given a leaflet informing them about the study and asked if they wished to participate. Additional tests were performed by one of the authors (PK). Baseline characteristics were retrieved from medical files and consisted of gender, age, intoxications, medication, comorbidity, referring specialty, lab values (hemoglobin, creatinine, glomerular filtration rate, albumin), living situation, a fall within 6 months and indication for the CT-scan. Patients were considered anemic if hemoglobin levels were <13.2 g/dl in men and <12.2 g/dl women.[12]

Cognitive function and physical state were measured by the same investigator. Cognition assessment consisted of a mini mental state exam (MMSE), clock drawing test (CDS) and presence of depression by the geriatric depression scale (GDS).13 Low cognition was considered as a MMSE score below 24 or CDS below 4 points. Patients included in the 'impaired' group of one or both tests were considered to have an impaired cognitive function.14 Patients were considered at risk for depression if the GDS score was above 6.[15]

Activities of daily living were assessed by the KATZ-ADL 6 questionnaire. Patients were considered to be dependent if they scored more than 1.16 The Charlson Comorbidity Index (CCI) was used to assess comorbidity. It provides a weighted score of the patients' comorbidities to predict short and long term outcomes.17 It was obtained using the patients' electronic file and by asking the patient about their comorbidities at the intake with the researcher. Comorbidity was described as a CCI-index ≥3. Polypharmacy was defined by the use of 'five-or-more-different medications'. The national civil statistics were checked for survival one year after inclusion. Lastly, the researcher answered the 'surprise question'. This question asks whether the researcher would be surprised if the patient would die within the next year. This question has been validated in previous research as a predictor for 1-year mortality.[18]

Measurement of handgrip strength

Handgrip strength of the dominant hand was assessed with a JAMAR hydraulic dynamometer using a validated protocol.[19] The participant had to squeeze the dynamometer with maximum strength in sitting position with an adducted and neutrally rotated shoulder, a 90° flexed elbow, and a neutral position of the wrist. To ensure that the patient cooperated accurately, patients were shown the operating procedures of the dynamometer prior to measurements. The highest result of the three grip strength trials was used. Results were expressed in kilograms. Cut-off values for sarcopenia were 30 kilograms for men and 20 kilograms for women, according to the European Working Group on Sarcopenia in Older People (EWGSO).[20]

Measurement of muscle mass

We measured the Total Psoas Index (TPI) on the abdominal CT scans at the level of the third lumbar vertebral body (L3). At this level, the psoas muscle surface area is believed to correlate with muscle mass on full body level.[21] TPI was calculated with the following formula: (left psoas area + right psoas area) / height*height (mm/m^2).[22] Total psoas index was measured with the computer software Sectra PACS, 2014. Researcher PK, performed measurements after instructions of a radiologist. Low muscle mass was defined as TPI in the lowest gender specific quartile (<25th percentile).[20]

Measurement of clinical frailty

Among the various screening tests to recognize frail persons, the Clinical Frailty Scale (CFS) designed by Rockwood is the one based on clinical judgment.[23,24] To ground this clinical assessment the following questions were answered for each participant: frequency and intensity of physical exercise or activity, extent of independency (for example to be able to perform high order ADL tasks) and the researcher's estimation of 1 year survival. Each score has a name (1= 'Very Fit', 2= Well, 3= Managing Well, 4= Vulnerable, 5= Mildly Frail, 6= Moderately Frail, 7= Severely Frail, 8= Very Severely Frail, 9= Terminally ill). In this study, frailty was defined as a CFS of five or more.[25]

Assessment of bias

To assess the risk of selection bias, baseline characteristics and reasons for patients that were missed (logistical reasons, refusal or inability to participate) were recorded. Aiming to suit the sample to a relatively homogeneous older population, only patients with an elective indication for a CT scan were included and the indication for the scan was recorded. One researcher (PK) performed all measurements. After data collection, a radiologist monitored the measurements in a random sample to assess internal validity.

Statistical analysis

Normally distributed continuous data were presented with mean and standard deviation (SD), and skewed data were presented with median and range. To assess between-group differences (high vs. low grip strength), the $\chi 2$ test was used for categorical and dichotomous data and Mann Whitney-U test or t-test was used for continuous data. For all analyses, a p-value of <0.05 was considered significant. After univariate logistic regression, odds ratios (OR) of the predictors with 95% confidence intervals (C.I.) were calculated and presented. SPSS (version 24,0; IBM-SPSS Statistics 24, UK) was used to perform all statistical analyses mentioned above.

Results

Study population

In total, 315 patients ≥70 years underwent an abdominal CT scan during the study period. Of this group, 99 patients could not be included due to logistical reasons, e.g. simultaneous presentation of two patients or limited time. The remaining 216 patients were asked to participate in the study. Of this group, 39 patients refused to participate or had to be excluded because of the inability to complete the measurements. Another three patients were excluded because L3 level was not visualized on the CT scan. A total of 174 patients (55%) remained for analysis (Figure 1). No significant differences were found in age and gender between included and excluded patients.

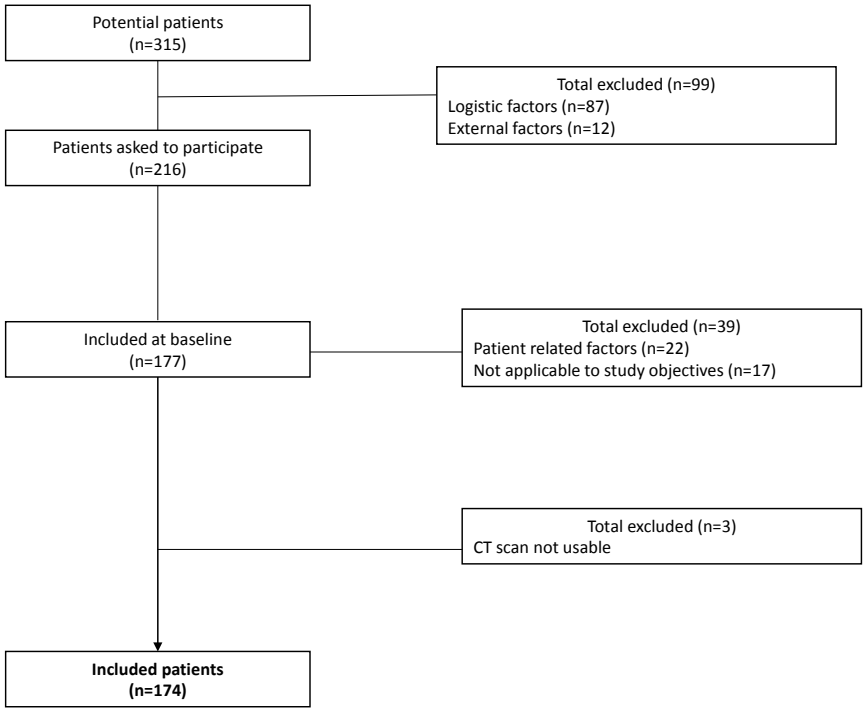
Baseline characteristics

The physically frail patients (F) had a median age of 77 years (70-92) and 39 (48%) were female and had an average BMI of 25.4 kg/m^2 (±1.5). The non-frail group (NF) had a median age of 75 years (70-88), 28 (30%) were female and had an average BMI of 26.6 kg/m^2 (±4.0). Age, gender and BMI differed significantly between the two groups.

With regard to their level of functioning, frail patients were more often institutionalized (F: 6 (7%) vs NF 0 (0%), p=0.008) and if living independently, they were more often alone (F: 28 (25%) vs NF: 15 (16%), p=0.005). A total of 10 (12%) frail patients vs 12 (13%) non-frail patients experienced a fall (p=0.91) and 22 (27%) frail patients were ADL-dependent vs 17 (18%) non-frail (p=0.16). These differences were not significant. Concerning cognitive function, 14 (18%) frail patients were impaired compared to 12 (13%) non-frail patients (p=0.41). A total of 4 (5%) frail patients were at risk for depression compared to 2 (2%) of non-frail patients (p=0.31).

44 (54%) frail patients had severe comorbidity scoring over 3 on the Charlson Comorbidity Index (CCI) compared to 39 (42%) of non-frail patients (p=0.10). Polypharmacy was present in 28 (35%) frail patients compared to 25 (27%) non-frail patients (p=0.27).

Figure 2. Flow diagram of inclusion of participants



A total of 56 (69%) of frail patients compared to 62 (67%) of non-frail patients (p=0.73) underwent a CT-scan due to suspicion or follow-up for cancer. Comorbidity, polypharmacy and a CT indication for cancer did not differ significantly. Lastly, frail patients had significantly lower average Hb level of 13.1 (±1.7) g/dl compared to 14.1 (±11.4) in non-frail patients (p=0.001). These results are summarized in Table 1.

Table 1. Patient characteristics

		Included patients (N=174)	Physically frail¶ (N=81)	Physically non-frail (N=93)	p-value
Physical					
Age in years	Median (range)	76.5 (70-92)	77 (70-92)	75 (70-88)	0.0001
70-74 years	N (%)	67 (38)	22 (27)	45 (48)	
75-79 years	N (%)	63 (36)	27 (33)	36 (39)	
80-84 years	N (%)	29 (17)	21 (26)	8 (9)	
> 85 years	N (%)	15 (9)	11 (14)	4 (4)	
Gender (female)	N (%)	67 (38)	39 (48)	28 (30)	0.011
BMI (kg/m²)	Mean (SD)	26.1 (4.3)	25.4 (4.5)	26.6 (4.0)	0.05
Smoking	N (%)	25 (14)	16 (20)	9 (10)	0.059
Functional					
Living situation					
- Institutionalized	N (%)	6 (3)	6 (7)	0 (0)	0.008
- Alone	N (%)	43 (25)	28 (25)	15 (16)	0.005
ADL-dependent (Katz-ADL ≥ 1)	N (%)	39 (22)	22 (27)	17 (18)	0.16
Falls	N (%)	22 (13)	10 (12)	12 (13)	0.91
Surprise Question	N (%)	172 (99)	79 (97)	93 (100)	0.13
Cognitive					
Depression (GDS > 6)	N (%)	6 (3)	4 (5)	2 (2)	0.31
Impaired cognition (MMSE< 24 or CDS < 4)	N (%)	26 (15)	14 (18)	12 (13)	0.41
Medical					
Comorbidities (CCI)	Median (range)	2 (0-9)	3 (0-9)	2 (0-8)	NS
Comorbidities (CCI≥3)	N (%)	83 (48)	44 (54)	39 (42)	0.10
Polypharmacy	N (%)	53 (30)	28 (35)	25 (27)	0.27
Indication for CT-scan					0.082
Suspected Malignancy	N (%)	24 (14)	9 (11)	15 (16)	
Follow-up Malignancy	N (%)	84 (48)	40 (49)	44 (47)	
Gastroenterology	N (%)	13 (7)	9 (11)	4 (4)	
Urology	N (%)	18 (10)	5 (6)	13 (14)	
Vascular	N (%)	26 (15)	11 (14)	15 (16)	
Gynecology	N (%)	9 (5)	7 (8)	2 (2)	

Table 1. (Continued)

		Included patients (N=174)	Physically frail¶ (N=81)	Physically non-frail (N=93)	p-value
Medical					
Laboratory values					
- Hb (g/dl)	Mean (SD)	13.3 (1)	13.1 (1.7)	14.1 (1.4)	0.001
- Creatinine (umol/l)	Mean (SD)	83.5 (22.0)	80.1 (17.4)	86.5 (25.1)	0.076
- GFR (l/min)	Median (range)	72 (23-90)	71.3 (12.6)	71.3 (14.6)	0.99
- Albumin (g/l)	Mean (SD)	34.2 (4.5)	32.4 (5.3)	35.7 (3.0)	0.007

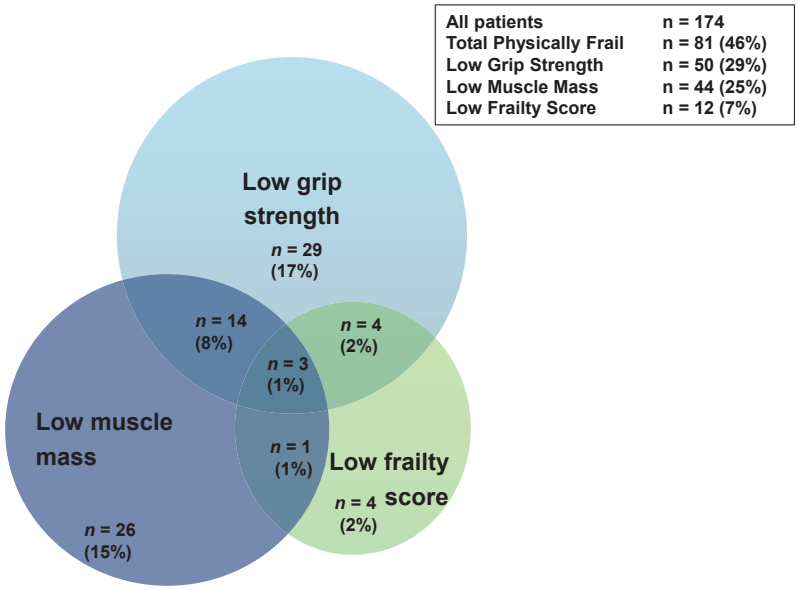
¶ = patients were physically frail if they had low GS and/or low MM and/or were clinically frail
GS = hand grip strength in kilograms, BMI = Body Mass Index (weight/(height²)), Hb = Hemoglobin level, GFR = Glomerular Filtration Rate, ADL = Activity of Daily Living, CFS = Clinical Frailty Scale, CCI = Charlson Comorbidity Index, GDS = Geriatric Depression Scale, MMSE = Mini Mental State Exam, CDS = Clock Drawing Score. N = number, SD = Standard Deviation.
* In case of missing values, the deviating number of participants per group is denoted.
**CT indication for cancer = suspicion on cancer or follow-up after diagnosis

Outcomes

Physical frailty

The median age of the total group was 76 years (70-92) and 67 (38%) were female. Eighty-one (46%) patients were physically frail based on at least one of the three instruments: 50 (29%) patients had low grip strength, 44 (25%) patients had low muscle mass and 12 (7%) patients were considered clinically frail. A total of 19 (13%) patients scored positively on two instruments. Three (2%) patients scored frail on all instruments. Results are summarized in Table 2 and visualized in Figure 2.

Figure 2. Comparison of physical frailty assessment instruments



Mortality after one year

Among physically frail patients (i.e. those with at least one frailty assessment), the 1-year mortality was 12% (n=10) compared to 19% (n=18) among non-frail patients (p=0.22). These results are summarized in Table 2. Also, logistic regression showed no significant association between mortality after one year and low grip strength, low muscle mass, low clinical frailty score, age > 80 years, female gender, overweight state or severe comorbidity. These results are summarized in Table 3.

Table 2. Physical frailty and mortality

		Physically frail* (N=81)	**Non-frail (N=93)**	**p-value**
Grip Strength (kg)				
Male	Mean (SD)	31 (6.9)	40 (5.9)	<0.001
Female	Mean (SD)	19 (4.5)	24 (3.0)	<0.001
Muscle mass (mm^2/m^2)				
Male	Mean (SD)	434 (138)	574 (96)	0.020
Female	Mean (SD)	351 (100)	447 (103)	<0.001
Clinical frailty Score				
Overall	Mean (SD)	3.1 (1.4)	2.5 (1.1)	0.003
Mortality after 1 year				
All physical frail	N (%)	10 (12)	18 (19)	0.22

Physically frail = Low grip strength or low muscle mass or low clinical frailty score

Table 3. Univariable analysis of 1-year mortality

	Univariable analyses	
	OR (95% CI)	p-value
Physical frailty	0.6 (0.2-1.4)	0.21
Low Grip Strength	1.2 (0.5-3.0)	0.66
Low Muscle Mass	1.1 (0.4-2.6)	0.97
Low Clinical Frailty Score	2.2 (0.3-17.7)	0.46
Age > 80 years	1.2 (0.5-3.0)	0.66
Gender (female)	1.4 (0.6-3.3)	0.45
Overweight (BMI >25)	0.7 (0.3-1.6)	0.42
Severe comorbidity (CCI≥3)	0.8 (0.3-1.8)	0.58

Discussion

In this prospective cohort study, 46% of older patients attending the hospital were physically frail assessed by either low grip strength, decreased muscle mass or clinical features of frailty. Mortality after 1 year was 12% in physically frail patients, whereas this was 19% in non-frail patients; this was not a significant difference. The prevalence of clinically frail patients (7%) was much lower compared to the prevalence of frailty according to low grip strength (29%) or decreased muscle mass (25%).

Previous studies have shown that grip strength, muscle mass and clinical frailty are all independently associated with adverse events in a hospitalized population.[26,27] With an increasing burden of disease caused by aging, the demand to develop accurate and easy-to-use frailty instruments is growing. Each of these instruments is associated with the volume, the quality and the functional performance of muscle tissue. However, our study shows that there is only limited overlap between these three dimensions, suggesting that multiple pathophysiologic pathways cause physical frailty.

However, the validity of these measurements to represent true frailty is debatable, because our study shows no significant differences in 1-year mortality between patients defined as frail on one of the three instruments. More importantly, the level of overlap between the three instruments is very limited, and only 2% of the patients were frail base on all three assessments. In addition, although functional performance plays a major role in the development of frailty, psychological and social dimensions might play a compensatory role.[28] The desire to create a golden bullet to assess a patient's vulnerability might therefore appear to be a perilous simplification. Theou et al.[29] described a similar observation reviewing eight different frailty scales and illustrating distinct differences in identification and risk prediction between measurement tools.

The results of our study should be interpreted in the light of several limitations. Frail patients were significantly older and had lower albumin levels. Both aging as itself and a poor nutritional state can influence muscle mass and thus might contribute to bias that must be considered in the interpretation of the results. Also, we included patients aged 70 years or older visiting the outpatient clinic for CT

imaging of the abdomen. However, due to logistical reasons, we were only able to include 55% of the total amount of the total amount of patients, introducing a possibility for selection bias.

This study should be placed in the framework of the recently updated consensus statement of the European Working Group on Sarcopenia in Older People.[30] The field of research on sarcopenia is vastly dynamic and ranges from its biological origins to its use in clinical practice. The revised consensus statement includes an algorithm for case-finding emphasizing the importance of clinical symptoms (falling, difficulty rising from chair, etc.) as a first step in diagnosing sarcopenia. The ongoing debate about the use of minor muscles such as the psoas as a representative for total body strength is also an important aspect of the consensus statement.[31] The results of this study are primarily illustrative for the ongoing search of ways to interpret and further investigate the use of diagnostic instruments for sarcopenia in clinical practice rather than a solid statement to be implemented.

In conclusion, this study illustrates that measuring physical frailty remains a challenging field of research. Although each of the instruments has individually been validated as a risk assessment instrument for older patients in previous studies, our results illustrate that there is a wide variety in phenotypes among frail patients. The aging population will pose a major challenge to our health care system the coming years. The gradual decline of muscle mass and function have resulted in an estimated range of 10-20% community-dwelling older patients being physically frail.[32] Screening for frailty with validated and user-friendly instruments in order to both identify patients at risk and to possibly target these patients to revert their physical frailty, will be of paramount importance. However, further research both regarding the fundamental pathophysiology of frailty and the complete social, psychological and physical components of frailty will be essential.

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3

Lower muscle density is associated with major postoperative complications in older patients after surgery for colorectal cancer

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Abstract

Background

Reduced muscle density is associated with an increased risk of postoperative complications. We examined the prognostic value of muscle density as a predictor of postoperative complications in elderly patients undergoing surgery for colorectal cancer.

Methods

Patients (≥ 70 years) who underwent surgery for colorectal cancer between 2006-2013 were selected from a prospective single center database. The Hounsfield Unit Average (HUA or HU/mm^2) of the psoas muscles at the level of the third lumbar vertebra was calculated on the scan. High and low muscle density groups were identified based on the lowest gender specific HUAC quartile. Major postoperative complications (Clavien-Dindo (CD) ≥3) within 30 days after surgery were retrospectively documented. Logistic regression analysis was used to identify risk factors for postoperative complications.

Results

A total of 373 patients (median age = 78 years) were included in this study. The mean muscle density score was 24.5 ± 4.3 HU/mm^2 for males and 26.3 ± 5.0 HU/mm^2 for females. The cut-off points for the lowest gender specific quartile was ≤ 22.0 HU/mm^2 for males and ≤ 23.5 HU/mm^2 for females. After multivariable regression, there was a statistically significant association between muscle density and CD≥3 (OR =1.84 (95% CI 1.11-3.06), p=0.019). Anastomotic leakage in patients with a primary anastomosis (n=287) occurred more often in patients with low muscle density (11.7% vs 23.3%, p=0.016). The associations remained significant after correction for confounders.

Conclusion

Low muscle density is associated with major postoperative complications in older patients who undergo surgery for colorectal cancer.

Introduction

Colorectal cancer is a common form of cancer in the Western world.[1] On average, 60% of these patients are over 70 years old.[2] Since 1975, the incidence of colorectal cancer has been increasing and it is expected to increase even further with the aging of the general population.[3] Compared to their younger counterparts, older patients with colorectal cancer are at higher risk for complications after surgery.[5] The decision to perform surgery in older patients can be challenging due to poor performance status and the presence of comorbidities.[4] The length of postoperative hospital stay (LOS) and the risk of postoperative morbidity increases with age. Surgery therefore can result in functional decline and even mortality.[6-8]

However, age might not be the best discriminative factor for deciding whether or not to operate. Recently, there has been a rising interest in the association between muscle density and postoperative outcome after surgery.[5] Loss of skeletal muscle density and loss of strength are associated with impaired functional status. An absolute muscle density of more than two standard deviations below the mean muscle density of healthy young adults is associated with inactivity, chronic disease and cancer.[6] Image-analyses software can be used to measure the cross-sectional muscle area accurately, and can be used to identify patients with low muscle density.

Colorectal cancer patients are at risk for physical frailty for two reasons. Firstly, age is a risk factor for low muscle density.[7] Fifty percent of colorectal cancer patients are over 70 years old.[8] Secondly, cancer is a risk factor for low muscle density. Low muscle density is associated with poor physical function and nosocomial infections in patients diagnosed with oesophageal[9],pancreatic[10] and colorectal cancer.[11,12] Previous studies have illustrated that low muscle density is associated with longer hospital stays after colorectal cancer surgery in patients of all ages.[12] The current study hypothesized the presence of an association between lower muscle density and major postoperative complications after surgery for colorectal cancer in elderly patients.

Methods

Patient selection

Patients were identified from a prospectively collected database of patients who underwent surgery for colorectal cancer between 2006 and 2013 in Gelre Hospital in Apeldoorn, The Netherlands. A total of 889 patients were registered in the database. All patients aged 70 years or older who underwent elective and acute surgery for colorectal cancer between 2006 and 2013 were included in this study. Patients were excluded if preoperative CT imaging of the abdomen was not available.

Data collection

Baseline patient characteristics such as: gender, date of birth and date of surgery, were prospectively registered in a database. Medical files were used to retrospectively collect additional information about patient characteristics such as the degree of comorbidity (according to the Charlson Comorbidity Index (CCI) version ICD 10[13]) and the American Society of Anesthiologists (ASA score).[14] Tumor characteristics were described according to the American Joint Committee on Cancer Classification (AJCC) (TNM staging manual[15]). Treatment characteristics included neoadjuvant treatment: urgency of surgery, laparoscopic or open technique, the segment that was resected and whether or not an anastomosis or a stoma was constructed. Postoperative course included: LOS (in days, starting at the day of surgery and ending at the day of discharge), intensive care unit (ICU) admission, readmission within 30 days after discharge, postoperative complications and postoperative mortality within 30 days after surgery. Major postoperative complications were categorized using the Clavien-Dindo score.[16] A Clavien-Dindo score ≥3 was considered as a major complication which resulted in an intervention, ICU admittance or death within 30 days after surgery.

Measurement of muscle density and definition of study groups

Abdominal CT scans are used for tumor staging in the preoperative work-up for colorectal cancer surgery. For the purpose of this study CT scans were used to perform a Hounsfield Unit Average Calculation (HUAC). Hounsfield Units (HU) express the muscle density and reflect the amount of fatty infiltration. The HUAC reflects the average muscle density after correction for surface area. The HU for muscle tissue has an average of 60.17 Low HU is indicative of high amounts

of fatty infiltration in the muscle. HU and the surface area (mm2) of the left and right psoas muscle at the level of the third lumbar vertebra (L3) was measured with the computer software Secta Rix / Pax, 2014. At this level, the surface area of the psoas muscles is representative of muscle density on a full body level.18 In addition, it gives information about the surface area of the following muscles: erector spinae muscles, quadratus lumborum muscles,transversus abdominis muscles, interior- and exterior oblique muscles and the rectus abdominis muscles.19 The following formulas were used in order to calculate the HUAC: 1. Right Hounsfield Unit Calculation = (Right Hounsfield Unit * Right psoas Area) / (Total Psoas Area); 2. Left Hounsfield Unit Calculation = (Left Hounsfield Unit * Left Psoas Area) / (Total Psoas Area); 3. HUAC = (Right Hounsfield Unit Calculation + Left Hounsfield Unit Calculation) / 2.17,20,21 Measurements were performed by researcher CM. The researcher received instructions on how to identify the level of L3 from a professional radiologist. After analysis, the radiologist measured HUAC in a randomly selected sample of 10% of the total patient population to assure correct measurement. As carried out Joglekar (2014) study, low muscle density was defined as HUAC scores in the lowest gender specific quartile (<25th percentile) while high muscle density was defined as HUAC scores in the highest gender specific quartile (>25th percentile).17

Outcome and statistical analysis

The outcome of interest was major postoperative complications. Low muscle density and high muscle density groups were compared using SPSS (version 20,0; SPSS Inc, Chicago, IL)[22]. Continuous data with a normal distribution was compared with the independent T-test and presented with mean and standard deviation (SD). Continuous skewed distributions were presented as median with minimum and maximum and tested for statistical differences with the Mann-Whitney U test. For dichotomous and categorical outcomes, low and high muscle density groups were compared with the χ^2. To analyze specific trends in categorical groups the linear by linear association was used. A p-value of < 0.05 was considered statistically significant.

Logistic regression analysis was used to analyze the association between muscle density and the severity of postoperative complications. Muscle density was categorized as either low density (25^{th} gender specific quartile) or high density ($> 25^{th}$ gender specific quartile). A multivariable model was used to adjust for

confounding factors. Potential confounders were added to the model one by one, according to the forward procedure. The following potential confounders were added to the model: BMI, AJCC, ASA, age, gender, urgency of surgery and CCI. Univariable and multivariable odds ratios (OR) of the primary determinant, potential confounders and multivariable (adjusted) ORs with 95% confidence intervals (C.I.) were calculated and presented.

Results

Patient characteristics

Baseline patient characteristics are listed in Table 1. In total, 417 patients of ≥ 70 years were included. Of these patients, 44 were excluded because no preoperative CT-scan of the abdomen was available. Therefore, 373 patients were included for analyses in this study. The median age of all patients was 78 years (i.q.r. 75-82 years). For male patients, the mean muscle density score was 24.5 ± 4.3 HU/mm^2. For female patients, the mean muscle density score was 26.3 ± 5.0 HU/mm^2. The cut-off points for the lowest gender specific quartile were ≤ 22.0 HU/mm^2 for males and ≤ 23.5 HU/mm^2 for females. Age did not significantly differ between patients with low muscle density and patients with high muscle density. Patients with low muscle density had higher ASA scores ($p<0.001$) and a higher CCI ($p<0.001$) when compared to patients with high muscle density. There were more acute surgeries in patients with low muscle density compared to patients with high muscle density (24% vs 12%, $p = 0.012$). A primary anastomosis was created in an equal number of patients within the low and high muscle density group (79.3% vs 76.1%, $p=0.571$).

Table 1. Baseline characteristics

Characteristic	Total number of patients (N = 373) (n(%))	Low muscle density (N = 92) (n(%))	High muscle density (N = 281) (n(%))	p-value^
Demographics				
Age in years, median (i.q.r.)	78 (75-82)	79 (79-83)	77 (74-82)	0.068#
Male gender	181 (49)	46 (50)	135 (48)	0.744
BMI, kg/m2*				
Median (i.q.r.)	25 (23-28)	26 (23-30)	25 (23-28)	
≥ 25 kg/m2	192 (52)	45 (48)	147 (52)	0.730
≥ 30 kg/m2	56 (15)	21 (23)	35 (12)	0.768
Acute surgery	57 (15)	22 (24)	35 (12)	0.012
Cancer				
Segment of resection				0.490
Rectum	86 (23)	18 (20)	68 (24)	
Sigmoid	7 (2)	1 (1)	6 (2)	
Left sided colon	122 (33)	31 (34)	91 (32)	
Right sided colon	136 (37)	34 (37)	101 (36)	
Transversum	20 (5)	8 (9)	12 (4)	
Total colon	2 (1)	0 (0)	3 (1)	
Resection technique				0.089
Laparoscopic	171 (46)	35 (38)	136 (48)	
Open	194 (52)	55 (60)	139 (49)	
Anastomosis	287 (77)	73 (79)	214 (76)	0.571
Stoma	119 (32)	28 (30)	91 (32)	0.728
Deviating stoma	51 (14)	11 (12)	40 (14)	0.572
Permanent stoma	72 (19)	18 (20)	54 (19)	0.941
Adjuvant treatment1	54 (63)	10 (56)	44 (65)	0.574
Radiotherapy1	37 (43)	8 (44)	29 (43)	
Chemoradiotherapy1	17 (20)	2 (11)	15 (22)	
AJCC$				0.161
1	38 (10)	12 (15)	26 (10)	
2	146 (39)	36 (44)	110 (44)	
3	105 (28)	27 (33)	78 (31)	
4	45 (12)	7 (9)	38 (15)	
ASA†				0.001
ASA 1	22 (7)	5 (6)	17 (6)	
ASA 2	176 (50)	27 (33)	149 (56)	
ASA 3 and 4	152 (43)	50 (61)	102 (38)	

Table 1. (Continued)

Characteristic	Total number of patients (N = 373) (n(%))	Low muscle density (N = 92) (n(%))	High muscle density (N = 281) (n(%))	p-value^
Comorbidity				
Charlson Comorbidity Index#				0.617
3	92	17 (18)	75 (27)	
4	70	16 (17)	54 (19)	
5	66	16 (17)	50 (18)	
6	46	16 (17)	30 (11)	
7	34	9 (10)	25 (9)	
8	17	5 (5)	12 (4)	
9	3	1 (1)	1 (0)	
10	3	0 (0)	3 (1)	

[1] Only of patients with rectum cancer.
^ Chi^2 is used, unless otherwise mentioned.
# Tested with the Mann-Whitney U test.
* BMI = Body Mass Index (≥ 25 kg/m^2 indicates overweight); $ AJCC[17] = American Join Committee on Cancer; † ASA[16] = American Society of Anesthiologists; # Charlson Comorbidity.

Postoperative outcome

Postoperative outcome measures are listed in Table 2. In total, 202 (54%) patients developed postoperative complications, 82 (22% of 373) had minor complications and 120 (32% of 373) patients had major complications (Grade ≥ 3). The severity of complications differed between patients with low muscle density and patients with high muscle density with relatively more major postoperative complications in patients with low muscle density (42% vs 29%, $p<0.05$). The 30-day mortality of patients with high muscle density was not significantly lower compared to patients with low muscle density (11% vs 6%, p= 0.162). Patients with low muscle density had a longer LOS (high: 10 days vs low: 13 days, p = 0.025), were more often admitted to the ICU (high: 19% vs low: 30% p=0.019) and had more readmissions within 30 days after leaving the hospital (p=<0.001) compared to patients with high muscle density. In patient with a primary anastomosis, a significant difference was found for anastomotic leakages with a rate of 11.7% in patients in the high muscle density group compared to 23.3% in the low muscle density group (p=0.016).

Table 2. Postoperative outcome

	All patients (N = 373)(n (%))	**Low muscle mass (N = 92) (n(%))**	**High muscle mass (N = 281) (n (%))**	**p-value^**
Clavien-Dindo*				0.017
Grade 0	171 (46)	33 (36)	138 (49)	
Grade 1 and 2	82 (22)	20 (22)	62 (22)	
Grade ≥ 3	120 (32)	39 (42)	81 (29)	
Mortality within 30 days after surgery	27 (7)	10 (11)	17 (6)	0.162
Length of hospital stay in days, median (min-max)	11 (1-130)	13 (2-126)	10 (1-130)	0.025#
Anastomotic leakage[1]	42 (15)	17 (23)	25 (12)	0.016
ICU admission	80 (21)	28 (30)	52 (19)	0.019
Readmission within 30 days	39 (11)	20 (22)	19 (7)	<0.001

[1] Only of patients with a primary anastomosis; ^ Chi^2 is used, unless otherwise mentioned.
Mann-Whitney U test. * Clavien-Dindo[19]

The association between muscle density and the severity of postoperative complications is summarized in Table 3. Age, urgency of surgery and CCI did not significantly influence this association. ASA and gender appeared to be confounders in the association with major postoperative complications. After adjustment for ASA and gender in the multivariable analyses of major complications, there was a statistically significant association between muscle density (as a continuous variable) and major postoperative complications within 30 days after surgery (OR = 1.84 (95% CI 1.11-3.06), p = 0.019).

Table 3. Uni- and multivariable analysis for major postoperative complications compared to no complications (reference group)

	Univariable analyses		**Multivariable analyses[1]**	
	OR (95% CI)	**p-value**	**OR (95% CI)**	**p-value**
Continuous muscle mass defined by HUAC (continue) *	1.14 (1.06-1.24)	0.001	1.09 (1.04-1.14)	0.001
Low muscle mass defined by HUAC*	1.99 (1.22-3.24)	0.006	1.80 (1.11-2.97)	0.021
ASA[$]				-
ASA 1				
ASA 2	1.00 (0.43-2.68)	0.983	-	-
ASA 3 or 4	1.75 (0.77-3.98)	0.186	-	-
Gender, male	1.59 (1.02-2.48)	0.040	-	-
Age	1.01 (0,94-1.09)	0.848	-	-
Acute surgery	1.05 (0.57-1.95)	0.853	-	-
Charlson Comorbidity Index[#]		0.21		-
1	1.35 (0.75-2.43)	0.32	-	-
2	0.90 (0.48-1.70)	0.74	-	-
3	2.18 (1.03-4.63)	0.04	-	-
4	1.18 (0.45-3.13)	0.74	-	-
5	2.31 (0.72-7.38)	0.16	-	-

[1] Adjusted for ASA and gender.
Major complications = Clavien-Dindo score ≥ 3.* HUAC[20] indicates Hounsfield Unit Average Calculation; [$] ASA[16] = American Society of Anesthiologists; [#] Charlson Comorbidity Index[18]

Discussion

Older patients undergoing surgery for colorectal cancer with low muscle density (defined by HUAC) have more major postoperative complications within 30 days (OR 1.8). Patients with low muscle density (defined as muscle density in <25th gender specific quartile) had significantly higher ASA-scores and were more often operated acutely.

The study represents a large cohort of consecutive elderly patients and contributes to the growing number of evidence that besides age and tumor stage, other patient-related factors influence prognosis.[12,17,23,24] In the light of society's critical voice towards the efficiency of surgery[25], especially in an elderly population[26], the demand for a good prediction models is rising. Muscle tissue as a derivative for functional, physical and nutritional state has proven to be a successful target to assess preoperative risk.[5]

The unfavorable effect of a poor physical state prior to surgery seems common sense. Age has proven to be an independent risk factor for decreased muscle mass, which was one of the main reason to focus specifically on elderly patients in this study.[27] Defining risk assessment instruments that can identify a specific group at risk is essential, both in developing prediction models and targeting anchors for preoperative optimization.[28,29]

Despite the strong clinical presumption, the lack of a more fundamental understanding of the relationship between muscle density and postoperative complications is a limiting factor in this field of research. It is likely that sarcopenia, as also osteoporosis, are symptoms of a greater underlying pathophysiological concept.[30,31] This concept, frailty, a syndrome characterized by loss of biologic reserves resulting in increased vulnerability to minor stressors and risk for adverse outcomes, including disability, hospitalization, and death is a growing field of interest, both fundamentally as clinically.[27,32,33] This suggestion is strengthened by the observation that the overall condition (ASA-score, comorbidity) of the patients with decreased muscle mass was significantly inferior compared to their counterparts. Observations of cohort studies grand a frame work for experimental researchers to gain more insights in the physiological mechanisms.[34]

Regarding the basic setup of this cohort study, a retrospective study always lacks essential information about the baseline characteristics of the included patients.[35] Although the study specifically targeted elderly patients diagnosed with colorectal cancer, data concerning their current levels of activity, diet and other factors influencing the amount of muscle tissue were lacking. This was the main reason for our research group to set up a following prospective cohort study, calibrating frailty (low grip strength, declined mental state) with low muscle density. However, contrary to their prevalence in the hospital, the amount of research performed in elderly populations is limited.[36] In the preparation of a interventional study, cohort studies like these could provide valuable information on which patient could benefit the most.

There are various ways to measure muscle tissue. The recent growth of interest in this area is still in an exploratory phase, resulting in a wide range of instruments.[5,37] Even if authors use the same instrument, a wide variation of cut-off points can be observed. We have based our choice of measuring muscle density based on the methods described by Joglekar et al.[17] The lowest gender specific HUAC quartiles were cut-off at 18.8 HU/mm^2 for males and 20.3 HU/mm^2 for females. In our study, cut-off points were set on 22.0 HU/mm^2 for males and 23.47 HU/mm^2 for females. A lower HUAC suggests a higher amount of fatty infiltration. The overall difference in cut-off points can be explained by the fact that 30% of the patients in the study of Joglekar et al.[17] were morbidly obese compared to 15% in our study. Nevertheless, it is surprising that both Joglekar et al.[17] and our study observed a lower HUAC in man compared to women. In a gender-specific subgroup analysis, body mass indexes did not differ significantly. The preferred centripetal distribution of fat in men might explain this difference.

In conclusion, lower muscle density is associated with serious postoperative complications in elderly undergoing surgery for colorectal cancer. However, in order to use 'sarcopenia' as a predictive and prognostic instrument in a clinical setting, more research is needed. Regarding sarcopenia, future research should target two important areas: firstly, a more fundamental understanding of the protective effect muscle tissue in stressful events (e.g. surgery), secondly, a standardized measure instrument and validated cut-off points to measure sarcopenia. Strengths of different parties have to be combined in order to develop targets to identify patients at risk and enhance their condition preoperatively.

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4

Effects of preoperative anaemia on the post-operative course and oncological outcome in patients undergoing rectal cancer surgery

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Accepted Diseases of the Colon & Rectum

Abstract

Background

There is still controversy about the relationship between preoperative anaemia and outcomes after rectal cancer surgery.

Objective

The aim of this study was to analyze the association between preoperative anaemia and postoperative complications and survival of patients undergoing surgery for rectal cancer in the era of laparoscopic surgery and modern perioperative care.

Methods

This was a cohort study performed in 71 hospitals including all patients who underwent resection for rectal cancer in 2011 of which preoperative haemoglobin level was registered. Short-term outcome parameters were any postoperative complication or mortality within 30 days postoperatively, and pelvic infectious complications defined as anastomotic leakage, and presacral abscess. Long-term outcomes were chronic sinus diagnosed at any time during three-year follow-up, three-year local and distant recurrence rates, and three-year overall survival.

Results

Out of 2095 patients, 1857 had a registered preoperative hemoglobin level, of whom 576 (31%) were anaemic and 1281 (69%) were non-anaemic. Preoperative anaemia was not independently associated with postoperative complications (Hazard Ratio (HR) 1·1, 95% Confidence Interval (CI) 0·9-1·4, p=0·24) or 30-day mortality (HR 1·4, 95% CI 0·7-2·8, p=0·29). Preoperative anaemia was associated with three-year overall survival (HR 2.1, 95% CI 1.7-2.5, p<0.0001), after multivariable analysis: HR 1·4, 95% CI 1·1-1·8, p=0·008) and with local recurrence rate (HR 1.6, 95% CI 1.1-2.4, p=0.026) but not with distant recurrence rate (HR 1.2, 95% CI 1.0-1.5, p=0.054).

Conclusions

Anaemia is associated with overall survival it might be considered as one of the warning signs in identifying high-risk patients. However, preoperative anaemia appears to have only limited association with postoperative and disease specific outcome after rectal cancer surgery in contrast to published meta-analysis of small historical series.

Introduction

Surgery remains the cornerstone of the treatment of rectal cancer with curative intent. Despite improvements in surgical technique and perioperative care, resection of rectal cancer is still associated with a substantial risk of postoperative complications.[1] Assessment and adjustment of modifiable risk factors of patients prior to surgery can serve as a potential window of opportunity to optimize postoperative outcome.[2] An important modifiable risk factor reflecting a patient's condition is the haemoglobin (Hb) level.[3,4] Anaemia has been associated with fatigue, impaired physical performance and increased morbidity and mortality, also in patients with rectal cancer.[5,6] The efficacy of preoperative treatment of anaemia by means of red blood cell transfusion, erythropoiesis-stimulating agents or iron, remains a matter of debate, since the short-term advantages have not yet convincingly been shown to outweigh the potential risks (i.e. oncological) and associated costs.[7,8] Furthermore, many regard anaemia more as a symptom of significant tumor load and overall weak condition of the patient, rather than a causative factor for poor outcome .[5,9]

The current literature on the relation between preoperative anaemia and the long-term postoperative outcome after rectal cancer surgery is restricted to relatively small studies with several methodological shortcomings. First, they use different survival parameters (disease-free, cancer specific, overall). Second, they often base their conclusions on univariate analyses. Finally, they provide limited information on potential confounders for the relation between anaemia and outcome. Most studies were conducted before the era of laparoscopic surgery and before the implementation of programmes on enhanced recovery after surgery. A recent systematic review with meta-analysis included only two studies on the independent association between anaemia and overall survival after rectal cancer surgery.[7,10,11] Van Halteren et al.[10] included 144 patients between 1995 and 1999 among whom 30% was treated with adjuvant radiotherapy, and Lee et al.[11] included 247 patients between 2002 and 2007 who had locally advanced rectal cancer and routine preoperative chemoradiotherapy, illustrating the selected populations with historical changes in treatment approach.

Therefore, the aim of this study was to analyze the association between preoperative anaemia and postoperative complications, local and distant recurrence rates, and overall survival in a large multicenter follow-up study of rectal cancer surgery in The Netherlands.

Methods

Study design and patient population

The Dutch Snapshot Research Group (DSRG) performed a retrospective study in 71 Dutch hospitals, including all patients undergoing surgery for rectal cancer in 2011. The methods of this research project have been described in more detail in the first manuscript of the DSRG.[12] The foundation of the snapshot database was the obligatory national registry of the Dutch Surgical Colorectal Audit (DSCA), which contains baseline characteristics and short-term postoperative outcomes (30 days) following a surgical resection.[13] These data were enhanced with diagnostic and treatment details and three-year surgical and oncological outcomes through a web-based application by collaborators of the DSRG. Data entry was performed by one or two residents or research nurses. In case of questions, supervision of a consultant surgeon was available at each center. Patients with a registered pre-treatment Hb level were eligible for this specific study.

Definitions and outcome parameters

Patients were considered anaemic according to the WHO criteria of anaemia, defined as a Hb level <7.5mmol/l in women and <8.0 mmol/l in men.[14] The Hb level should have been measured within 4 weeks before primary resection or start of neo-adjuvant therapy.

Short-term outcome parameters were any postoperative complication or mortality within 30 days postoperatively, and pelvic infectious complications defined as anastomotic leakage, and presacral abscess. Long-term outcomes were chronic sinus diagnosed at any time during three-year follow-up, three-year local and distant recurrence rates, and three-year overall survival.

Baseline characteristics such as age, gender, Body Mass Index (BMI), ASA-classification according to the American Society of Anesthesiologists[15], comorbidity (overall, cardiac, diabetes, pulmonary), TNM stage according to the American Joint Committee on Cancer (AJCC)[16] and neo-adjuvant and adjuvant therapy were recorded, besides type, approach and urgency of surgery.

Statistical Analysis

All analyses were performed using SPSS (version 20.0; SPSS Inc., Chicago, IL). For

continuous data, normality was assessed visually. Normally distributed variables were described with mean and standard deviations and the independent T-test was used to compare differences between the anaemic and non-anaemic patients. Not-normally distributed continuous variables were described with their median and interquartile range (IQR) and differences were assessed with the Mann-Whitney U test. Dichotomous and categorical outcomes were compared with the Chi-Squared test. Actuarial survival and recurrence rates were assessed using the Kaplan Meier method and differences evaluated using the log-rank test. The independent relation between anaemia and the outcomes was assessed by means of a Cox multiple regression model, including potential confounders for this relation. Confounders were defined according to risk factors previously described in literature: age, gender, BMI, ASA-score, TNM-stage, comorbidity, preoperative treatment, additional resection, surgical approach, surgical procedure. Potential confounders were defined as those variables that were associated with both anaemia and each of the outcomes, expressed with a p value <0·1. For each outcome, this could imply that different potential confounders were included in the model. Throughout the analyses, a p-value of <0·05 was considered statistically significant.

Results

Baseline characteristics

Of the total Snapshot cohort of 2095 patients, 1857 patients were eligible for the present analysis based on known preoperative Hb level. Median completeness of the data at hospital level was 100% (IQR 96·7-100). The mean age was 67 (±11·1) years and 1168 (63%) were male. The mean Hb level in men was 8·4 (±1·1) mmol/l and 7·9 (±0·9) mmol/l in women. Based on the gender-specific cut-off, 575 (31%) patients were anaemic.

The baseline characteristics of the total cohort, as well as the anaemic and non-anaemic groups are displayed in Table 1. Anaemic patients were older (mean age 70 vs. 65 years, p<0·0001), significantly more often ASA III-IV (29% vs 11%, p<0·0001), were less frequently overweight (48% vs 58%, p<0·0001), had more overall comorbidity (78% vs 65%, p<0·0001), had more cardiac comorbidity (44% vs 27%, p<0·0001), and had diabetes more often (25% vs 16%, p<0·0001).

Treatment characteristics

Preoperative therapy differed significantly, with anaemic patients receiving chemoradiotherapy more often (40% vs 35%) and short course radiotherapy less often (44% vs 52%) (p=0·028). The surgical procedure also differed significantly between the two groups. Anaemic patients underwent more often a Hartmann's procedure (25% vs 16%, p<0·0001), and the surgical approach was more often open (58% vs 50%, p=0·004). These results are summarized in Table 1.

Short-term outcome

Short term outcomes for both groups are shown in Table 2. Patients with anaemia experienced significantly more overall complications (43% vs 35%, p=0·004). Pelvic infectious complications consisting of anastomotic leakage, presacral abscess, abscess on top of the rectal stump and chronic sinus formation did not differ significantly (17% vs 15%, p=0·21). Age, gender, ASA-score, comorbidity, additional resection, surgical approach and type of procedure were associated with preoperative anaemia and pelvic septic outcomes. In the multivariable analysis, preoperative anaemia was not independently associated with postoperative complications (HR 1·1 95% CI 0·9-1·4, p=0·24; Table 3).

Table 1. Baseline Characteristics & Surgical Procedure

Variable		Total cohort N = 1857		Anaemic patients (men<8.0 mmol/l, women<7.5 mmol/l) N = 576		Non-anaemic patients (men≥8.0 mmol/l), women≥7.5 mmol/l)) N = 1281		p-value
Age in years			N=1857		N=576		N=1281	<0·0001
overall	Mean (SD)	67 (11·0)		70 (11·0)		65 (10·8)		
≤60	N (%)	495 (27)		103 (18)		392 (30)		
61-70	N (%)	619 (33)		172 (30)		447 (35)		
71-80	N (%)	569 (31)		215 (37)		354 (28)		
>80	N (%)	174 (9)		86 (15)		88 (7)		
Gender			N=1857		N=575		N=1282	
male	N (%)	1168 (63)		370 (64)		798 (62)		0·40
Preoperative Hb (mmol/l)	Mean (SD)	8.2 (1·1)	N=1857	7·0 (0·8)	N=576	8·7 (0·6)	N=1281	<0·0001
BMI (kg/m^2)			N=1786		N=558		N=1228	<0·0001
overweight*	N (%)	985 (55)		267 (48)		718 (58)		
ASA-classification			N=1814		N=564		N=1250	<0·0001
ASA I-II	N (%)	1515 (84)		403 (71)		1112 (89)		
ASA III-IV	N (%)	299 (16)		161 (29)		138 (11)		
Comorbidity			N=1815					
Overall	N (%)	1254 (69)		443 (78)	N=566	811 (65)	N=1249	<0·0001
Cardiac	N (%)	409 (22)		193 (44)	N=443	216 (27)	N=811	<0·0001
Diabetes	N (%)	239 (13)		109 (25)	N=443	130 (16)	N=811	<0·0001
Pulmonary	N (%)	213 (12)		70 (16)	N=443	143 (18)	N=811	0·65
Pathological TNM Stage			N=1762		N=551		N=1211	0·002
Stage I (T1-2N0M0)	N (%)	623 (35)		178 (32)		445 (37)		
Stage II (T3-4N0M0)	N (%)	412 (23)		160 (29)		252 (21)		
Stage III (T1-4N1-2M0)	N (%)	241 (14)		75 (14)		166 (13)		
Stage IV (T1-4N1-2M1)	N (%)	486 (28)		138 (25)		348 (29)		

Table 1. (Continued)

Variable		Total cohort N = 1857		Anaemic patients (men<8.0 mmol/l, women<7.5 mmol/l) N = 576		Non-anaemic patients (men≥8.0 mmol/l), women≥7.5 mmol/l)) N = 1281		p-value
Distance to anorectal junction			N=1467		N=459		N=1009	0·27
≤ 3 cm	N (%)	440 (30)		148 (32)		292 (29)		
3.1-7.0 cm	N (%)	504 (64)		160 (35)		345 (34)		
>7 cm	N (%)	523 (36)		151 (33)		372 (37)		
Preoperative treatment			N=1742		N=547		N=1195	0·028
None	N (%)	191 (11)		62 (11)		129 (11)		
5x5 GY	N (%)	861 (49)		243 (44)		618 (52)		
Chemoradiotherapy	N (%)	632 (36)		219 (40)		413 (35)		
Other radiotherapy schedule	N (%)	58 (4)		23 (4)		35 (3)		
Surgical procedure			N=1857		N = 576		N=1281	<0·0001
Low anterior resection*								
With ileostomy	N (%)	646 (35)		161 (28)		485 (38)		
Without ileostomy	N (%)	260 (14)		66 (11)		194 (15)		
Abdominoperineal resection*	N (%)	574 (31)		190 (33)		384 (30)		
Hartmann's procedure	N (%)	355 (19)		145 (25)		210 (16)		
Proctocolectomy	N (%)	22 (1)		14 (2)		8 (1)		
Surgical approach			N=1824		N=565		N=1259	0·004
Open	N (%)	954 (52)		326 (58)		628 (50)		
Laparoscopic	N (%)	739 (40)		198 (35)		541 (44)		
Converted	N (%)	121 (7)		41 (7)		80 (6)		
Additional resection for local ingrowth	N (%)	127 (7)	N=1823	68 (12)	N=562	59 (5)	N=1261	<0·0001
Surgical timing			N=1814		N=566		N=1248	0·030
Elective	N (%)	1786 (98)		552 (98)		1234 (99)		
Urgent	N (%)	28 (1)		14 (2)		14 (1)		

*BMI³25kg/m², including patient who underwent TEM followed by completion surgery

A higher mortality rate within 30 days was observed in anaemic patients (5% vs 2%, p<0·0001). After correction for age, gender, ASA-score, TNM-stage, comorbidity, pre-operative radiotherapy and surgical procedure, preoperative anaemia was not independently associated with 30-day mortality (HR 1·4, 95% CI 0·7-2·8, p=0·29; Table 4).

Table 2. Surgical and oncological outcomes

Variable		**Anaemic patients (men<8.0 mmol/l, women<7.5 mmol/l) N = 576**		**Non-anaemic patients (men≥8.0 mmol/l), women≥7.5 mmol/l)) N = 1281**		**p-value**
Surgical						
Overall complications <30 days	N (%)	244 (43)	N=563	436 (35)	N=1240	0·004
Surgical septic complications*	N (%)	91 (17)	N=533	181 (15)	N=1230	0·21
Cardiac complications	N (%)	29 (13)	N=230	35 (8)	N=413	0·093
Pulmonic complications	N (%)	47 (20)	N=232	62 (15)	N=413	0·088
Received blood transfusion during stay	N (%)	154 (28)	N=544	110 (9)	N=1189	<0·0001
Mortality within 30 days	N (%)	29 (5)	N=563	21 (2)	N=1239	<0·0001
Radical Resection (R0)	N (%)	534 (96)	N=559	1176 (95)	N=1231	0·99
Oncological**						
3-year local recurrence rate	HR (95%CI)	1.6 (1.1-2.4)	N=567	0.6 (0.4-0.9)	N=1269	0.026
3-year distant recurrence rate	HR (95%CI)	1.2 (1.0-1.5)	N=567	0.8 (0.7-1.0)	N=1269	0·061
3-year overall survival	HR (95%CI)	2.1 (1.7-2.5)	N=568	0.5 (0.4-0.6)	N=1272	<0·0001

* Anastomotic leakage, presacral abscess, abscess rectal stump chronic sinus
** Assessed by Cox Regression

Table 3. Logistic regression overall complications within 30 days

Variable	N = 1857	Univariable analysis			Multivariable analysis		
Factor	**Patients (%)**	**HR**	**CI (95%)**	**p-value**	**HR**	**CI (95%)**	**p-value**
Gender-specific anaemia	575 (31)	1·4	1·1-1·7	0·001	1·1	0·9-1·4	0·24
Age (years)							
<60	495 (27)	1					
61-70	619 (33)	1.1	0·8-1·4	0·49			
71-80	569 (31)	1.2	0·9-1·6	0·13			
>80	174 (9)	1.6	1·1-2·3	0·009	1·3	0·9-2·0	0·15
Gender							
female	690 (37)	0·7	0·6-0·9	0·001	0·7	0·6-0·9	0·001
BMI							
obese	997 (54)	1·1	0·9-1·3	0·29			
ASA-score							
ASA I-II	1516 (82)	1					
ASA III-IV	299 (16)	2·3	1·8-2·9	<0·0001	1·9	1·4-2·5	<0·0001
TNM-Stage							
Stage I	496 (27)	1					
Stage II	368 (20)	1·1	0·9-1·5	0·32			
Stage III	30 (2)	1·0	0·8-1·4	0·79			
Stage IV	639 (34)	1·0	0·8-1·3	0·69			
Overall Comorbidity	1254 (67)	1·4	1·1-1·7	0·003	1·2	0·9-1·5	0·16
Preoperative treatment							
None	191 (10)	1					
5x5 GY	861 (46)	1.1	0·8-1·5	0·41			
CRT*	632 (34)	0·9	0·6-1·9	0·91			
RT*	54 (3)	1·0	0·6-1·3	0·63			
Additional resection for local ingrowth	68 (12)	1·3	0·9-2·0	0·088	1·4	0·9-2·1	0·094
Surgical approach							
Open	440 (24)	1					
Laparoscopic	505 (27)	0·7	0·5-0·8	<0·0001			
Converted	523 (28)	0·9	0·6-1·4	0·81	0·7	0·6-0·9	0·001
Procedure							
Low anterior resection							
With ileostomy	160 (28)	1					
Without ileostomy	66 (11)	1·0	0·7-1·3	0·98			
APR*	190 (33)	0·9	0·7-1·2	0·46			
Hartmann's procedure	145 (25)	1·1	0·8-1·4	0·69			
Proctocolectomy	14 (2)	2·3	1·0-5·8	0·053	1·9	0·8-4·7	0·15

*CRT = chemoradiotherapy, RT = radiotherapy, APR = Abdominoperineal resection

Table 4. Logistic regression postoperative mortality within 30 days

Variable	N = 1857	Univariable analysis			Multivariable analysis		
Factor	**Patients (%)**	**HR**	**CI (95%)**	**p-value**	**HR**	**CI (95%)**	**p-value**
Gender-specific anaemia	575 (31)	3·1	1·8-5·6	<0·0001	1·4	0·7-2·8	0·29
Age (years)							
<60	495 (27)	1					
61-70	619 (33)	3·6	0·8-16·8	0·10			
71-80	569 (31)	12·3	2·9-51·9	0·001	13·2	1·7-101·2	0·013
>80	174 (9)	18·3	4·1-82·9	<0·0001	11·1	1·3-97·9	0·030
Gender							
female	1168 (63)	0·4	0·2-0·8	0·008	0·3	0·1-0·8	0·010
BMI							
obese	997 (54)	0·9	0·5-1·5	0·63			
ASA-score							
ASA I-II	1516 (82)	1					
ASA III-IV	299 (16)	5·4	3·1-9·6	<0·0001	2·2	1·1-4·5	0·029
TNM-Stage							
Stage I	496 (27)	1					
Stage II	368 (20)	1·2	0·6-2·6	0·62			
Stage III	30 (2)	1·9	0·9-4·3	0·098			
Stage IV	639 (34)	0·9	0·4-2·1	0·88	1·5	0·6-3·8	0·37
Overall Comorbidity	1254 (67)	5·3	1·9-14·8	0·001	2·9	0·8-9·9	0·091
Preoperative treatment							
None	191 (10)	1					
5x5 GY	861 (46)	0·5	0·2-1·0	0·07			
CRT*	632 (34)	0·2	0·1-0·6	0·001	0·8	0·3-1·9	0·62
Other R*T	54 (3)	0·3	0·0-2·2	0·22	0·4	0·1-1·4	0·16
Additional resection for local ingrowth	68 (12)	0·9	0·3-2·9	0·85			
Surgical approach							
Open	440 (24)	1					
Laparoscopic	505 (27)	0·7	0·4-1·4	0·35			
Converted	523 (28)	1·1	0·4-3·1	0·89			
Procedure							
Low anterior resection							
With ileostomy	160 (28)	1					
Without ileostomy	66 (11)	2·2	0·9-5·6	0·080			
APR*	190 (33)	1·8	0·8-4·0	0·15			
Hartmann's procedure	145 (25)	2·3	1·0-5·3	0·060	1·0	0·4-2·6	0·97
Proctocolectomy	14 (2)	9·7	2·5-38·2	0·001	6·0	1·2-28·6	0·026

*CRT = chemoradiotherapy, RT = radiotherapy, APR = Abdominoperineal resection

Long term outcomes

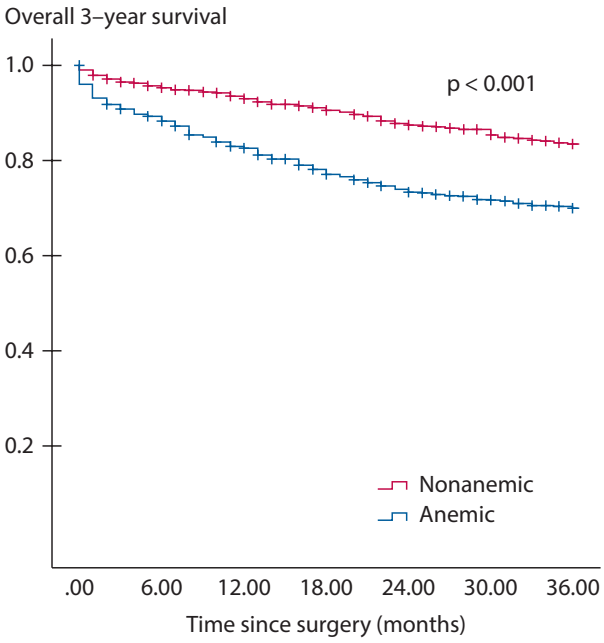
On the long term, anaemic patients had significantly lower overall three-year survival rates (71% vs 84%, p<0·0001; Figure 1). After correction for age, ASA-score, TNM-stage, radical resection, comorbidity, preoperative radiotherapy, blood transfusion during hospital stay, surgical approach and surgical procedure, anaemia was independently associated with three-year overall survival (HR 1·4, 95% CI 1·0-1·8, p=0·008). Preoperative anaemia was associated with 3-year local recurrence rate (HR 1.6, 95% CI 1.1-2.4, p=0.026) but not with distant recurrence rate (HR 1.2, 95% CI 1.0-1.5, p=0.054). Results are visualized in Table 2 and 5.

Table 5. Cox Regression 3-year overall survival

Variable		Univariable analysis			Multivariable analysis		
Factor	**Patients (%)**	**HR**	**CI (95%)**	**p-value**	**HR**	**CI (95%)**	**p-value**
Gender-specific anaemia	575 (31)	2·1	1·7-·.5	<0·0001	1·4	1·1-1·8	0·008
Age (years)							
<60	495 (27)	1·0					
61-70	619 (33)	1·1	0·8-1·5	0·67			
71-80	569 (31)	1·9	1·5-2·6	<0·0001	1·4	1·0-2·0	0·039
>80	174 (9)	3·6	2·5-5·0	<0·0001	2·0	1·3-3·2	0·001
Gender							
female	690 (37)	0·8	0·7-1·1	0·14			
BMI							
obese	997 (54)	0·9	0·7-1·1	0·31			
ASA-score							
ASA I-II	1516 (82)	1·0					
ASA III-IV	299 (16)	2·8	2·3-3·6	<0·0001	2·6	1·9-3·6	<0·0001
TNM-Stage							
Stage I	496 (27)	1·0					
Stage II	368 (20)	2·0	1·4-2·7	<0·0001	1·7	1·2-2·5	0·002
Stage III	30 (2)	2·9	2·0-4·0	<0·0001	2·9	2·0-4·2	<0·0001
Stage IV	639 (34)	2·7	2·0-3·6	<0·0001	2·6	1·9-3·6	<0·0001
Radical Resection							
R0	1710 (96)	1·0					
R 1-2	80 (4)	4·1	3·0-5·6	<0·0001	2·4	1·7-3·5	<0·0001
Comorbidity overall	1254 (67)	1·8	1·4-2·3	<0·0001	1·1	0·8-1·5	0·49
Preoperative treatment							
None	191 (10)	1·0					
5x5 GY	861 (46)	0·5	0·4-0·7	<0·0001			
CRT*	632 (34)	0·9	0·5-1·6	0·84	0·7	0·5-1·1	0·15
other RT	54 (3)	0·6	0·4-0·9	0·003	2·6	1·9-3·6	0·95
Septic complications	69 (12)	1·2	0·9-1·5	0·31			
Blood transfusion during stay	264 (15)	3·1	2·5-4·0	<0·0001	1·7	1·3-2·2	<0·0001
Surgical approach							
Open	505 (27)	1·0					
Laparoscopic	440 (24)	0·7	0·6-0·9	0·004	1·0		
Converted	523 (28)	1·3	0·9-1·9	0·17	0·9	0·7-1·2	0·55
Procedure							
Low anterior resection							
With ileostomy	160 (28)	1·0					
Without ileostomy	66 (11)	1·1	0·7-1·7	0·60			
APR*	190 (33)	2·1	1·6-2·7	<0·0001	1·7	1·3-2·4	0·001
Hartmann's procedure	145 (25)	2·8	2·1-3·8	<0·0001	1·5	1·1-2·1	0·018
Proctocolectomy	14 (2)	5·4	2·9-10·1	<0·0001	2·4	1·1-5·2	0·021

*CRT = chemoradiotherapy, RT = radiotherapy, APR = Abdominoperineal resection

Figure 1. Kaplan Meijer of 3-year overall survival



Numbers at risk

Anemic	567	498	460	417	383	353	318
Nonanemic	1271	1206	1158	1102	1045	1004	909

Discussion

The results of this study illustrate that preoperative anaemia was not independently associated with postoperative complications in patients undergoing surgery for rectal cancer. However, preoperative anaemia still appeared to be independently associated with lower three-year overall survival, although with a hazard ratio of 1·4. The clinical relevance of anaemia as a solitary factor has become limited but could still be considered as one of the warning signs for an overall frail state of rectal cancer patients.

This study investigating preoperative Hb level in patients with rectal cancer clearly supports the existing evidence of anaemia being a perilous sign for poor overall condition.[2,3,7] Patients with preoperative anaemia were older, had higher ASA-scores and had more often comorbidities.

However, at the heart of the scientific debate concerning anaemia lies the question whether it is a confounding symptom reflecting an overall poor physical state and progressed oncological disease, or whether anaemia itself could be a causative factor. In this study, anaemia was independently associated with lower three-year overall survival rate, though a hazard ratio of 1·4 has limited clinical relevance. These results provide three key observations offering an indication for further research: at the level of pathophysiology, medical treatment and holistic approach to clinical practise.

First, from the perspective of pathophysiology, these results are limited in providing more in-depth information about the origin of the anaemia and its treatment. A previous study by Wilson et al.[7] illustrated that anaemia can be caused by intestinal blood loss and iron deficiency. The latter can be subdivided in absolute (decreased nutritional intake) and functional (decreased uptake from duodenum and system inflammation causing storage of iron in enterocytes) iron deficiency.[17] The cause of anaemia determines the optimal treatment but this might be difficult to determine in the individual patient and might even be multifactorial. Furthermore, hemoglobin levels are not static and require follow-up in time. The database that was used only provided a single preoperative hemoglobin value which impedes the possibility to differentiate between patients with acute or chronic anaemia. Similarly, there was no attributive information on the hemoglobin values after neo-adjuvant therapy.

This is hard to retrieve from retrospective studies, because relevant data are often not well registered, indicating the need for better prospective data.

It is possible that a percentage of these patients received iron (oral or intravenous), erythropoiesis stimulants or a blood transfusion preoperatively, which may have influenced the results. Although anaemia is a risk factor in itself, several studies have illustrated that both iron, erythropoiesis stimulants and blood transfusion also have potential harmful effects, both in the short term (wound healing) and on oncologic outcomes (recurrence) in the long term.[18–20]

Secondly, from a medical treatment perspective, it has been concluded that not treating patients with anaemia should be considered to be inferior[21]. However, current evidence is still not conclusive about the real impact of preoperative treatment of anaemia on postoperative and long-term outcome in rectal cancer, as well as on the optimal type of treatment. Further prospective randomized research is needed to investigate the effect of anaemia, in particular of iron supplementation in rectal cancer patients with preoperative iron deficiency anaemia in order to investigate its effects on both postoperative outcomes and survival.[22]

Lastly, concerning a holistic approach to clinical practise, preoperative anaemia should not be regarded as a solitary risk factor. As it is representative for a multifactorial deteriorated physical state, pre-operative anaemia should be considered as a warning sign, indicating a patient group that might benefit of some type of prehabilitation.[2] Especially in the perioperative phase, in which the body is put at significant stress levels, the effects of anaemia pose the patient at increased risk for complications. Hemoglobin plays a key role in transport of oxygen towards tissues.[23] Impaired oxygen supply leads to decreased wound healing, muscle performance and overall fatigue which are detrimental, especially for oncological patients undergoing surgery.[3,24,25] More specifically, iron serves both as a building block for haemoglobin and plays an important role in oxidative metabolism of muscle performance.[23] Consequently, iron supplementation can play a crucial role in a prehabilitation program (consisting of exercise, nutritional support and psychological enhancement)[26–28], since it will potentially affect cardiorespiratory and muscle strength endurance and overall fatigue.[29,30] Furthermore, iron supplementation could potentially be a quick win if compared to the challenges that might be faced when implementing pre-operative interventions such as physical

training and nutritional support (e.g. compliance, logistical issues, costs).[31]

Although this snapshot study was an elegant way to establish a quick overview with a large number of patients, representing the current state of this specific clinical field, it is important to mention several limitations of this study. Because of retrospective data collection, relevant data were missing to some extent. Measuring preoperative Hb levels was also not part of a standardized protocol but measured as part of routine daily practice. This collaborative research was not specifically designed to look at preoperative anaemia, for which reason we are not informed about pre-operative treatment of anaemia and changes in Hb level during the whole treatment period, including neo-adjuvant therapy. Unfortunately, we are not able to retrieve additional data from the participating centres, because the dataset was anonymized after data collection was completed in 2015. Despite these shortcomings, this study adds substantially to the available literature on this topic, because of being the largest cohort until now and the representativeness for current practice related to recently collected data. The design results in a similar follow-up duration for included patients, without historical changes as observed in longitudinal cohort studies. Furthermore, this study has a high external validity due to its multicentre design and unselected patient population.

Conclusion

In conclusion, this multicentre cohort study including 1857 patients undergoing surgery for rectal cancer illustrates lower overall three-year survival in patients with preoperative anaemia after correction for confounding factors. However, the effect of anaemia as a solitary factor seems to be of relatively limited clinical relevance. Assessment and adjustment of preoperative anaemia and its cause could serve both as a warning sign, and as a potential element of a wider prehabilitation program for rectal cancer patients undergoing surgery.

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5

Discriminative value of frailty screening in colorectal cancer patients scheduled for surgery

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Submitted

Abstract

Introduction

Surgical resection is the cornerstone of treatment for colorectal cancer, but surgery carries a risk of complications and functional decline especially in the elderly. The first step in preventing these adverse outcomes is to identify patients at risk. The Dutch Safety Management System (VeiligheidsManagementsSysteem, [VMS]) is used to identify frail elderly patients upon hospital admission. We aimed to assess whether VMS-frailty can predict adverse outcomes in elderly patients undergoing surgery for colorectal cancer.

Methods

Data from patients ^{3}70 years who underwent an elective resection for colorectal cancer between April 2015–December 2017 in Gelre Hospitals, The Netherlands. Patients between 70-79 years old were considered frail if they had a VMS score^{3}3 or if they were ^{3}80 years of age with a score ^{3}1. Frail and non-frail groups were compared with respect to 30-day postoperative mortality, complications, length of stay, post-discharge institutionalization and 3-month readmissions, and predictors of adverse outcomes were assessed in univariable logistic regression analysis.

Results

A total of 231 patients were included among whom 32 (14%) were considered frail. Frail patients were older (median age 83 vs 74 years, p<0.01), had higher American Society of Anesthesiologists (ASA) scores (ASA III-IV: 61% vs 27%, p<0.01), more comorbidities (Charlson Comorbidity Index [CCI]^{3}2: 38% vs 19%, p=0.02). 30-day mortality rate was low (7 patients, 3%) and there was no significant difference between frail (F) and non-frail (NF) patients (F: 9% vs NF: 2%, p=0.06). Frail patients were more likely to be admitted for ^{3}2 weeks (F: 35% vs NF: 11%, p<0.01), and had more post-discharge institutionalization (F: 14% vs NF: 3%, p=0.02). In univariable logistic regression analysis, VMS-frailty, age^{3}80 years and ASA-score III-IV were predictors of 30-day mortality, LOS^{3}2 weeks and post-discharge institutionalization.

Conclusion

VMS-frailty predicts 30-day mortality and functional decline in elderly colorectal cancer patients. However, to what extent VMS can improve surgical risk prediction

compared to ASA-scores, comorbidities or patient age is unclear. A more tailor-made instrument for elderly surgical patients is needed in order to serve both as a tool for risk assessment and identification of modifiable risk factors.

Introduction

As we age, chances are that one will develop an indication for surgery one day. A surgical intervention poses significant stress to the human body and requires substantial resilience to cope with this acute disturbance of homeostasis.[1] Ageing is linked to a gradual decline in resilience, resulting in the 'frail patient' as can be observed by declining muscle mass, osteoporosis and decreased kidney and liver functioning.[2,3] This condition of frailty leads to an increased vulnerability towards stressors such as a surgical intervention.[4,5]

The likelihood of having cancer increases with age. In The Netherlands, each year over 13.000 patients are diagnosed with colorectal cancer of which the majority is over 70 years old.[6,7] As surgery remains to be the cornerstone of treatment for colorectal cancer, a large proportion of older patients undergoing surgery for this indication are likely to be frail. Several studies have demonstrated a strong association between preoperative frailty and adverse outcomes such as postoperative complications and delayed recovery.[8,9]

In order to optimize the quality of care for hospitalized older patients, the majority of hospitals in The Netherlands screen patients with the "Safety Management System" (VeiligheidsManagementsSysteem) or VMS-questionnaire upon admission. This frailty screening instrument assesses physical, nutritional and cognitive risks by means of a 13-item questionnaire.[10] The instrument has been validated for hospitalized elderly patients (^{3}70 years) illustrating that patients with increased scores were significantly more at risk for 30-day mortality.[11]

Although the VMS is since 2015 nationally implemented as a standard screening tool for all elderly patients admitted to the hospital, there is limited evidence regarding its value specifically in the surgical population. Adequate risk stratification in surgical patients is essential to support informed decisions and to develop tailor-made prehabilitation programs.[12,13] It was the aim of this study to assess the predictive value of VMS-screening for postoperative outcomes in elderly patients undergoing surgery for colorectal cancer.

Methods

Patient selection

Patients were identified from a prospectively maintained database of patients who underwent surgery for colorectal cancer between April 2015 and January 2018 in Gelre Hospitals in Apeldoorn and Zutphen, The Netherlands. The inclusion start date was based on the initiation of VMS-screening at the two hospitals. All patients 70 years or older who underwent elective surgery for an adenocarcinoma of colon or rectum were eligible for inclusion. Patients who underwent acute surgery or transanal endoscopic microsurgery were excluded. Patients with incomplete VMS-data were also excluded. Approval for the study was granted by the local Ethics Review Committee of Gelre Hospitals Apeldoorn in December 2017.

Data collection

Answers to the VMS-questionnaire filled in upon admission and before surgery or at the outpatient clinic visit preceding surgery were retrospectively collected from electronic patient files. Baseline patient characteristics including age, gender, body mass index (BMI), living situation, smoking and alcohol use, preoperative laboratory values within three months of surgery (haemoglobin, serum albumin and serum creatinine), polypharmacy (defined as the use of five or more medications), degree of comorbidity (Charlson Comorbidity Index [CCI][14]) and the American Society of Anesthesiologists (ASA) score[15] were extracted from electronic patient files. Tumor stage was extracted from pathology reports and described according to the 7th Edition of American Joint Committee on Cancer Classification (AJCC)[16]. Treatment characteristics included neoadjuvant and adjuvant chemotherapy and radiotherapy, aim of surgery (palliative/curative), type of surgery (laparoscopic/open/conversion), segment of resection, and whether a deviating or permanent stoma was constructed. Postoperative data were collected on hospital length of stay (LOS), unplanned intensive care unit (ICU) admissions, discharge destination (home vs another facility), postoperative complications within 30 days of surgery, 30-day and 3-month unplanned readmissions and 30-day and 3-month mortality. The patient was considered to have postoperative delirium if the attending physician or consultant geriatrician had explicitly made the diagnosis. Postoperative complications were categorized according to the Clavien-Dindo Classification (CDC) (0–5)[17]. Severe complications required an endoscopic, radiological or surgical re-intervention (CDC 3), an ICU admission (CDC 4) or led to

death (CDC 5). The highest grade of complication was scored per patient.

VMS-frailty groups

Frailty was defined as an accumulation of frailty characteristics as measured with the VMS-questionnaire. VMS consists of questions in four different domains regarding risk of delirium (3 questions, positive if ³1 point), risk of malnutrition (4 questions, positive if ³2 points), history of falls (1 point if one or more falls in the previous six months), and presence of physical impairment based on the KATZ-ADL questionnaire18 (6 items, positive if ³2 points). The cut-off values for frailty in this study were based on a study by Heim et al.19 where being 70–79 years old and having 3 or more frailty characteristics or being ³80 years old and having 1 or more frailty characteristics (VMS+age) was found to be the strongest predictor of adverse outcomes after hospital admission.

Statistical analysis

Categorical baseline data were presented as number (percentage) and frail and non-frail groups were compared with the $\chi 2$ test or Fisher's exact test. Continuous data were tested for normality using the Shapiro-Wilk statistic, and presented as mean (standard deviation) or as median (interquartile [IQR] range) and frail and non-frail groups were compared with t-test or Mann-Whitney U test depending on the distribution of the data.

The main outcome of interest was 30-day mortality. Secondary outcomes included overall and serious complications within 30 days of surgery, unplanned ICU admissions, reoperations, LOS, post-discharge institutionalization, and unplanned 30-day and 3-month readmissions. The $\chi 2$ test of Fisher's exact test for categorical outcomes and the Mann-Whitney U test for LOS were used to compare the frail and non-frail groups. The $\chi 2$ test was also used to compare patients with and without risk of delirium (at risk if ³1 point in the VMS-delirium domain) with regard to occurrence of postoperative delirium. Univariable and multivariable logistic regression analyses were carried out for potential predictors of 30-day mortality, LOS³2 weeks and post-discharge institutionalization. Results of the regression analyses were presented as odds ratios (OR) with 95% confidence intervals (CI). For all analyses, a p-value of <0.05 was considered statistically significant. All analyses were performed with SPSS statistics for Windows, version 23.

Results

Cohort

Between April 2015 and January 2018, 233 patients 70 years or older underwent elective colorectal cancer surgery in Gelre Hospitals Apeldoorn and Zutphen. Out of these patients, two (0.9%) did not have complete VMS data and were excluded from analyses. The final cohort consisted of 231 patients.

Frailty

Out of 231 patients, 32 (14%) scored positive on the VMS-frailty instrument. Of the 32 frail patients, 30 (94%) were 80 years or older. Fourteen patients (47%) in the older frail group scored positive in two or more VMS-domains. Compared to the younger cohort, older patients were significantly more likely to score positive on the domains addressing the risk of delirium (old: 27% vs young: 9.3%, $p<0.01$) and physical impairment (old: 10% vs young: 0.6%, $p<0.01$). A previous history of falls and risk of malnutrition did not differ significantly between the two age groups. The results of the frailty screening are shown in Table 1.

Baseline characteristics

Regarding baseline characteristics of the patients, the median age was higher in the frail group (83 [71–93] years vs 74 [70–88] years, $p<0.01$), and the proportion of males was lower in the frail group, although not to a statistically significant degree (F: 47% vs NF: 61%, $p=0.12$). The median BMI was lower in the frail group (F: 24.6 kg/m^2 vs NF: 25.6 kg/m^2, $p<0.05$) with more frail patients being underweight (BMI<20kg/m^2) and more non-frail patients being obese (BMI^{3}30 kg/m^2). Significantly more frail patients lived alone (F: 52% vs NF: 24%, $p<0.01$). Regarding comorbidity burden, median CCI was higher in the frail group, and frail patients were more likely to have a CCI^{3}2 (F: 38% vs NF: 19%, $p=0.02$). Frail patients were also more likely to use more than five daily medications (F: 69% vs 4NF: 2%, $p<0.01$). Frail patients had lower preoperative albumin (F: 33 mmol/l [26–38] vs NF: 35 mmol/l [24–43], $p=0.02$) and haemoglobin levels (F: 6.8 g/dl [5.1–9.4] vs NF: 8.3 g/dl [5.1–10.6], $p<0.01$), and significantly more frail patients had anemia (F: 81% vs NF: 44%, $p<0.01$). The preoperative ASA-classification was also higher in frail patients (ASA III-IV, F: 61% vs NF: 27%, $p<0.01$). The baseline characteristics are shown in Table 2.

Table 1. VMS-screening in younger and older patient groups

	Age 70–79 years (N=161)	**Age ≥80 years (N=70)**	**p-value**
VMS negative	116 (72.0)	40 (57.1)	<0.01
1 domain positive	37 (23.0)	16 (22.9)	
2 domains positive	6 (3.7)	6 (8.6)	
3 domains positive	2 (1.2)	7 (10.0)	
4 domains positive	0 (0.0)	1 (1.4)	
VMS-frail	2 (1.2)	30 (42.9)	<0.01
Delirium: patients with ≥1 point	15 (9.3)	19 (27.1)	<0.01
Memory problems	10 (6.2)	13 (18.6)	<0.01
Help with self-care	3 (1.9)	9 (12.9)	<0.01
Confusion during previous illness/hospitalization	7 (4.3)	5 (7.1)	0.52
Patients with ≥1 fall in the last 6 months	15 (9.3)	11 (15.7)	0.16
Physical impairment: patients with ≥2 points	1 (0.6)	7 (10.0)	<0.01
Help with bathing	1 (0.6)	6 (8.6)	<0.01
Help with dressing	2 (1.2)	6 (8.6)	0.01
Help with toileting	1 (0.6)	3 (4.3)	0.08
Help with transfers	0 (0.0)	2 (2.9)	0.09
Help with feeding	0 (0.0)	0 (0.0)	-
Use of incontinence material	8 (5.0)	12 (17.1)	<0.01
Malnutrition: patients with ≥2 points	24 (14.9)	17 (24.3)	0.09
More than 6kg weight loss	16 (9.9)	10 (14.3)	0.34
More than 3g weight loss	7 (4.3)	4 (5.7)	0.74
Decreased appetite	23 (14.3)	17 (24.3)	0.07
Supplemental drinks/tube feeding	10 (6.2)	9 (12.9)	0.09

Table 2. Baseline characteristics

	Total (N= 231) N (%)	**Frail (N=32)** N (%)	**Non-frail (N=199)** N (%)	**p-value**
Age in years (median, range)	75 (70–93)	83 (71–93)	74 (70–88)	<0.01
Gender, male	137 (59.3)	15 (46.9)	122 (61.3)	0.12
BMI in kg/m^2, median (range)	25.3 (16.4–41.8)	24.6 (17.9–33.1)	25.6 (16.4–41.8)	0.05
BMI<20	11 (4.8)	5 (15.6)	6 (3.0)	0.01
BMI 20-24.9	101 (43.7)	15 (46.9)	86 (43.2)	
BMI 25-29.9	84 (36.4)	9 (28.1)	75 (37.7)	
BMI≥30	35 (15.2)	3 (9.4)	32 (16.1)	
Smoking, N (%) (N=230)	22 (9.6)	2 (6.5)	20 (10.1)	0.75
Alcohol, ≥2 units per day, N (%) (N=229)	55 (24.0)	3 (9.4)	52 (26.4)	0.04
Polypharmacy (≥5 medications)	105 (45.5)	22 (68.8)	83 (41.7)	<0.01
Living situation				<0.01
Alone	62 (27.3)	16 (51.6)	46 (23.5)	
With partner/other	165 (72.7)	15 (48.4)	150 (76.5)	
Preoperative laboratory values				
Hemoglobin, g/dl	8.1 (5.1–10.6)	6.8 (5.1–9.4)	8.3 (5.1–10.6)	<0.01
Anemia (N=230)	114 (49.6)	26 (81.3)	88 (44.4)	<0.01
Creatinine, umol/ l	76 (52–161)	76 (52–146)	76 (52–161)	0.87
Albumin, mmol/l	34 (24–43)	33 (26–38)	35 (24–43)	0.02
Hypoalbuminemia (N=179)	94 (52.5)	17 (70.8)	77 (49.7)	0.05
ASA classification (N=230)				<0.01
I-II	158 (68.7)	12 (38.7)	146 (73.4)	
III-IV	72 (31.3)	19 (61.3)	53 (26.6)	
Comorbidities (CCI), median (range)	1 (0–6)	1 (0–3)	0 (0–6)	<0.01
0	111 (48.1)	9 (28.1)	102 (51.3)	0.05
1	70 (30.3)	11 (34.4)	59 (29.6)	
2	32 (13.9)	8 (25.0)	24 (12.1)	
≥3	18 (7.8)	4 (12.5)	14 (7.0)	

ASA American Society of Anesthesiologists; *BMI* Body Mass Index; *CCI* Charlson Comorbidity Index; *VMS* VeiligheidsManagementsSysteem [Safety Management System]

Tumor and treatment characteristics

Tumor stage did not differ between frail and non-frail patients. However, treatment was more often palliative in the frail patient group (F: 9.4% vs NF: 1.5%, p=0.04). Most resections were performed laparoscopically in both groups, and colon resections were more common in the frail group (F: 91% vs NF: 74%, p=0.04). Compared to frail patients, patients in the non-frail group were more likely to receive adjuvant chemotherapy (F: 18% vs NF: 31%, p=0.03). A summary of these results is presented in Table 3.

Table 3. Tumor and treatment characteristics

	Total (N= 231)	**Frail (N=32)**	**Non-frail (N=199)**	**p-value**
	N (%)	**N (%)**	**N (%)**	
Tumor stage*				0.203
Stage I	82 (35.5)	7 (21.9)	75 (37.7)	
Stage II	61 (26.4)	10 (31.3)	51 (25.6)	
Stage III	78 (33.8)	12 (37.5)	66 (33.2)	
Stage IV	10 (4.3)	3 (9.4)	7 (3.5)	
Aim of treatment				0.04
Curative	225 (97.4)	29 (90.6)	196 (98.5)	
Palliative	6 (2.6)	3 (9.4)	3 (1.5)	
Segment of resection				0.131
Colon ascendens/transversum	93 (40.3)	19 (59.4)	74 (37.2)	
Colon transversum/descendens	18 (7.8)	2 (6.3)	16 (8.0)	
Sigmoid	56 (24.2)	6 (18.8)	50 (25.1)	
Rectum	53 (22.9)	3 (9.4)	50 (25.1)	
Other**	11 (4.8)	2 (6.3)	9 (4.5)	
Resection technique				0.45
Laparoscopic surgery	213 (92.2)	30 (93.8)	183 (92.0)	
Open surgery	8 (3.5)	0 (0)	8 (4.0)	
Conversion	10 (4.3)	2 (6.3)	8 (4.0)	
Anastomosis				0.07
Without deviating stoma	201 (87.0)	28 (87.5)	173 (86.9)	
With deviating stoma	18 (7.8)	0 (0)	18 (9.0)	
No anastomosis	12 (5.2)	4 (12.5)	8 (4.0)	
Additional therapy				
Neoadjuvant chemotherapy	13 (5.6)	0 (0)	13 (6.5)	0.22
Neoadjuvant radiotherapy	16 (6.9)	1 (3.1)	15 (7.5)	0.71
Adjuvant chemotherapy	37 (16.0)	1 (3.1)	36 (18.1)	0.03

* American Joint Commission on Cancer Classification, 7th Edition (in case of two tumors, highest tumor stage considered)

** Including resections of other organs, resections of two colon segments, ileocecal resections and resections of previous anastomosis

Postoperative outcomes

Regarding the primary outcome, only seven patients (3%) experienced 30-day mortality, and there was no significant difference between frail and non-frail patients (F: 3 [9.4%] vs NF: 4 [2.0%], p=0.06). One patient in the frail group died after palliative resection and multiple organ failure, the other two died after resection of curative intent and anastomotic leakage. The four patients in the non-frail group died from complications after resections of curative intent (causes of death were multiple organ failure, two anastomotic leakages and stroke). Five patients (1.5%) died during the 3-month follow-up. In the non-frail group, to deaths were attributable to metastatic colorectal cancer and one patient died from sepsis during chemotherapy. In the frail group, one patient died from sepsis after hip fracture and for one the cause of death was unclear.

Postoperative complications occurred in 95 (41%) patients, and 37 (16%) had severe complications (CDC^{3}3). Twenty-three (10%) patients required a reoperation, and 21 (9.1%) had an unplanned ICU admission. The proportion of frail patients having overall complications, severe complications or reoperations did not significantly differ from non-frail patients. Frail patients tended to have more unplanned ICU-admissions (F: 6 [19%] vs NF: 15 [7.5%], p=0.05). The median LOS was longer in the frail group (6 [IQR 5–15] vs 5 [IQR 4–8] days, p=0.01) and frail patients were more likely to be admitted for longer than two weeks (F: 10 [35%] vs. NF: 22 [11%], p<0.01). 30-day and 3-month readmissions did not differ significantly between the groups. However, post-discharge institutionalization was significantly more common for frail patients (F: 4 [14%] vs. NF: 6 [3.0%], p=0.03). Patients scoring ^{3}1 point in the VMS-domain delirium were more likely to be diagnosed with postoperative delirium (6/34 [18%] vs 11/197 [4.6%], p=0.02). Postoperative outcomes are summarized in Table 4.

Table 4. Postoperative outcomes

	Total (N= 231)	**Frail (N=32)**	**Non-frail (N=199)**	
	N (%)	**N (%)**	**N (%)**	**p-value**
Any complications (CDC>0)	95 (41.1)	17 (53.1)	78 (39.2)	0.14
Severe complications (CDC≥3)	37 (16.0)	7 (21.9)	30 (15.1)	0.33
Reoperations	23 (10.0)	5 (15.6)	18 (9.0)	0.33
Unplanned ICU admissions	21 (9.1)	6 (18.8)	15 (7.5)	0.05
Length of hospital stay (days), median (IQR)**	5 (4–8)	6 (5–15)	5 (4–8)	0.01
<2 weeks	194 (85.8)	19 (65.5)	175 (77.4)	<0.01
³2 weeks	32 (14.2)	10 (34.5)	22 (11.2)	
Post-discharge institutionalization	10 (4.4)	4 (13.8)	6 (3.0)	0.03
Readmissions				
30 days**	26 (11.7)	4 (14.3)	22 (11.3)	0.75
3 months***	13 (5.8)	1 (3.4)	12 (6.2)	1.00
Mortality				
30 days (CDC 5)	7 (3.0)	3 (9.4)	4 (2.0)	0.06
3 months***	5 (2.2)	2 (6.9)	3 (1.5)	0.13
Cause of death within 3 months***				
Colorectal cancer		0 (0)	2 (66.7)	-
Other		2 (100)	1 (33.3)	
	Total (N=231)	VMS-delirium+ (N=34)	VMS-delirium- (N=197)	p-value
Postoperative delirium	17 (7.4)	6 (17.6)	11 (5.6)	0.02

** Excluding in-hospital mortality
*** Excluding 30-day mortality
CDC Clavien-Dindo Classification; *ICU* intensive care unit

Finally, univariable logistic regression analysis was used to assess factors associated with 30-day mortality, post-discharge institutionalization and LOS³2 weeks. VMS-frailty (OR 5.0, 95% CI 1.1–23.7; p=0.04), age³80 years (OR 6.1, 95% CI 1.2–32.3; p=0.03), CCI³2 (OR 5.2, 95% CI 1.1–23.9; p=0.04) and ASA III-IV (OR 14.3, 95% CI 1.7–120.9; p=0.02) were significant predictors of 30-day mortality. VMS-frailty (OR 5.1, 95% CI 1.3–19.3; p=0.02), age³80 years (OR 6.1, 95% CI 1.5–24.2; p=0.02) and ASA III-IV (OR 5.0, 95%CI 1.2–20.5; p=0.03) were significant predictors of post-discharge institutionalization. VMS-frailty (OR 4.2, 95% CI 1.7–10.1; p<0.01), age³80 years (OR 4.4; 95% CI 2.0–9.7; p<0.01), ASA III-IV (OR 2.5, 95% CI 1.2–5.4; p=0.02) and anemia (OR 2.6, 95% CI 1.2–5.8; p=0.02) were significant predictors of LOS³2 weeks. Due to the small number of events in each outcome category, no multivariable regression analyses were performed. Results of the logistic regression analyses are presented in Table 5.

Table 5. Univariable analysis for 30-day mortality and functional decline

	30-day mortality		**Post-discharge institutionalization**		**Length of stay ³2 weeks**	
	OR (95% CI)	**p-value**	**OR (95% CI)**	**p-value**	**OR (95% CI)**	**p-value**
VMS-frailty	5.0 (1.1–23.7)	0.04	5.1 (1.3–19.3)	0.02	4.2 (1.7–10.1)	<0.01
Age (³80)	6.1 (1.2–32.3)	0.03	6.1 (1.5–24.2)	0.01	4.4 (2.0–9.7)	<0.01
Comorbidity (CCI³2)	5.2 (1.1–23.9)	0.04	0.4 (0.5–3.4)	0.42	0.9 (0.3–2.3)	0.81
ASA (III-IV)	14.3 (1.7–120.9)	0.02	5.0 (1.2–20.5)	0.03	2.5 (1.2–5.4)	0.02
Gender (male)	4.3 (0.5–36.0)	0.18	1.1 (0.3–3.8)	0.94	1.4 (0.6–3.1)	0.40
Anemia	6.4 (0.8–53.9)	0.08	2.5 (0.6–10.1)	0.19	2.6 (1.2–5.8)	0.02
Tumor stage (III-IV)	1.2 (0.3–5.5)	0.59	2.5 (0.7–9.1)	0.17	1.7 (0.8–3.7)	0.15
Living alone	1.1 (0.2–5.6)	0.94	4.4 (1.2–16.1)	0.03	1.8 (0.9–4.2)	0.12

CCI Charlson Comorbidity Index; *CI* confidence interval; *OR* odds ratio; *VMS* VeiligheidsManagementsSysteem (Safety Management System)

Discussion

Despite the wide implementation of VMS-screening in the Dutch healthcare system, its value in the prediction of adverse outcomes has only been addressed in a handful of studies. Increasing VMS-frailty predicted 6-month mortality in hospitalized elderly patients[11], and VMS combined with age predicted adverse outcomes after three months for acutely and electively admitted elderly patients[19]. To our knowledge, this study is the first one considering VMS-frailty as a predictor of adverse outcomes specifically in elderly patients undergoing elective colorectal cancer surgery.

In our cohort, 30-day mortality was low which is probably a reflection of careful patient selection for elective surgery as well as of the high quality of health care provided. As a consequence, we were unable to find a significant difference between frail and non-frail patients with respect to this outcome. Furthermore, as overall and serious complications did not differ between frail and non-frail patients, it seems unlikely that VMS can outperform traditional surgical risk assessment with ASA-scores, comorbidities or age. Regarding our surrogate markers for functional decline, VMS-frail patients had significantly longer hospital stays and were more likely to be discharged to a destination other than home. However, older age and living alone are also strongly associated with these outcomes, and a prospective cohort study would be required to evaluate the true predictive power of VMS-frailty for functional decline in this patient group.

The goal of the development of frailty screening instruments in a surgical population is twofold: risk stratification and identification of modifiable risk factors.[1,20] Regarding risk stratification, vulnerable patients can be identified with frailty screening instruments including physical tests (grip strength, gait speed, Timed Up-and-Go)[21,22], questionnaires (Groningen Frailty Indicator[23], Identification of Patients at Risk–Hospitalized Elderly questionnaire[24]), biomarkers (interleukin-6, hemoglobin, CRP)[25] and assessments based on clinical impression (surprise question[26], Clinical Frailty Scale[27]). While many of the screening instruments do identify modifiable risk factors, they cannot account for the full spectrum of the patient's frailty status. The gold standard for frailty remains to be the Comprehensive Geriatric Assessment (CGA). The advantage of CGA is that it provides a more thorough view on the origins of frailty for each individual

patient which can then be used as a basis for pre- and postoperative interventions. However, it is time-consuming and therefore not feasible for every patient.

The VMS attempts to kill two birds with one stone: it is a reasonably quick frailty assessment and it identifies potentially modifiable risk factors (malnutrition, fall risk, delirium risk). Traditional frailty characteristics such as anemia, low BMI, polypharmacy and a higher burden of comorbidities were more prevalent in the VMS-frail group, suggesting that VMS can indeed identify the frail patients. However, to what extent the addition of VMS-screening to the already existing preoperative work-up (ASA-classification, comorbidities) can improve risk prediction is unclear. Furthermore, when it comes to the identification of modifiable risk factors, VMS screens only a limited number of domains and cannot be considered a substitute for the more elaborate assessment such as the CGA. Delirium risk screening with VMS seems to be of additional value as scoring positive on the domain delirium (regardless of overall frailty status) predicted the occurrence of postoperative delirium. It should be noted that the occurrence of delirium might have been underestimated in our study due to retrospective data collection. However, our results are in agreement with a previous prospective cohort study where VMS-delirium predicted in-hospital delirium in elderly patients.[11]

The results of this study should be interpreted with respect to several limitations. Regarding patient selection, the patients in our cohort represent the fittest elderly as the frailest patients would not be considered candidates for surgery. Consequently, VMS-scores in our cohort were probably lower than in patients not undergoing surgery. Furthermore, it was not possible to study the effects of VMS-screening on treatment decisions or patient optimization. Patients with increasing frailty most likely received additional care in the form of nutritional supplements, physiotherapy, medication changes or other interventions designed to optimize their condition before or after surgery. These interventions are likely to have made the VMS-frail population less prone for adverse outcomes, weakening the association. Lastly, we were not able to collect data on functional decline after the operation. However, LOS^{3}2 weeks and post-discharge institutionalization can be considered surrogate markers of functional decline, and these outcomes were more prevalent in the VMS-frail group.

In conclusion, the two goals of frailty screening – risk assessment and targeting

preoperative modifiable risk factors – do not necessarily have to be tackled by one frailty screening instrument such as the VMS. Our study supports traditional risk screening with ASA-classification, comorbidities and age in the prediction of adverse postoperative outcomes. At-risk patients may benefit from additional in-depth analysis of potentially modifiable risk factors such as decreased muscle mass, poor nutritional state, anemia and polypharmacy. Although the VMS addresses some elements that could be targeted pre- and postoperatively, further research is required to optimize preoperative screening of elderly patients undergoing colorectal cancer surgery.

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Part II

Prehabilitation in colorectal surgery

6

The effects of physical prehabilitation in elderly patients undergoing colorectal surgery: a systematic review

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Abstract

Aim

Prehabilitation, defined as the enhancement of the preoperative condition of a patient, is a possible strategy to improve the postoperative outcome. Lack of muscle strength and poor physical condition, increasingly prevalent in older patients, are risk factors for postoperative complications. Eighty five percent of patients with colorectal cancer are aged over 60 years. Since surgery is the cornerstone of their treatment, this review systemically examined the literature on the effect of physical prehabilitation in older patients undergoing colorectal surgery.

Method

Trials and case-controlled studies investigating the effect of physical prehabilitation in patients over 60 years undergoing colorectal surgery were retrieved from PubMed, EMBASE, CINAHL and the Cochrane library. Patient characteristics, type of intervention and outcome measurements were recorded. The risk of bias and heterogeneity was assessed.

Results

Five studies including 353 patients were identified. They were small containing an average of 77 patients and were moderate methodological quality. Compliance rates of the prehabilitation program varied from 16 to 97%. None of the studies could identify a significant reduction of postoperative complications or length of hospital stay. Four studies showed physical improvement (walking distance, respiratory endurance) in the prehabilitation group. Clinical heterogeneity preluded a meta-analysis.

Conclusion

Prehabilitation is a possible means of enhancing the physical condition of the patient preoperatively. The quality of studies in older patients undergoing colorectal surgery is poor, despite the increase in the elderly with colorectal cancer. Defining specific patient groups at risk and standardizing the outcome are essential to improve the results of treatment.

Introduction

Colorectal cancer is one of the leading causes of death worldwide.[1] Age has been defined as a risk factor for cancer [2], illustrated by 85% of patients diagnosed with colorectal cancer being over 60 years old [3]. Age is a risk factor for being frail which has been defined as a state of limited reserve to withstand stress such as a surgical intervention.[4] Limited reserve is the result of poor nutritional, physical or mental state.[5] It is estimated that about 45% of colorectal cancer patients is considered to be frail.[4] In the short term, frail patients have a fourfold greater risk on major postoperative complications.[6] In the long term, frail patients are more likely to experience a poorer functional performance postoperatively resulting in institutionalization and loss of capacity to perform daily life activities.[7]

Surgery is the cornerstone of the treatment of colorectal cancer.[8] The introduction of minimally invasive techniques and fast-track programs have reduced the stress response significantly.[9–11] Optimization of water and electrolyte administration, early enteral nutrition and early removal of the urinary catheter have been proven to shorten the length of hospital stay and reduce readmissions.[11,12] Older patients, especially if frail are more prone to complications and require specific preoperative risk stratification.

To identify frail patients, geriatricians have developed a vast number of assessment tools aimed to identify and quantify the potential 'red flags' associated with perioperative complications.[4,13] Decreased muscle mass[14], low walking speed [6] and poor nutritional state [15] are associated with postoperative complications. The success of fast-track programmes would be increased by identifying and then tackling risk factors preoperatively. The process of enhancing the functional capacity of the individual to enable him or her to withstand a stressful event is also called "prehabilitation".[16] The is showing promising results in orthopedics, cardiothoracic and other abdominal surgery.[17,18]

As the aging population grows [19], the incidence of colorectal cancer will also rise and will become an ever more significant health burden. Obtaining the best possible outcome is therefore in the interest of all but compared with high risk procedures such as cardiothoracic and major abdominal surgery, the window of opportunity for prehabilitation in colorectal surgery might actually be smaller. Older patients

particularly if frail could potentially benefit from prehabilitation. In this systematic review we aim to assess the effects of prehabilitation in patients aged over 60 years undergoing colorectal surgery.

Method

Search strategy

The review was registered before starting on PROSPERO and conducted in accordance with the PRISMA guidelines [20]. The search strategy was designed in collaboration with a clinical librarian. The Cochrane, MEDLINE, EMBASE and CINAHL databases were searched systematically, screening all publications up to January 2016. Complete search terms are shown in Appendix A (original article). The corresponding authors of included trials were contacted to identify additional relevant trials and supplementary information.

Inclusion criteria

Eligible articles were all randomized controlled trials or case-controlled studies evaluating the effect of physical prehabilitation (*per se* or as a part of a multimodal program) on patients aged over 60 years who were to undergo elective colorectal surgery. Physical prehabilitation was defined as the process of enhancing functional capacity of the individual to enable him or her to withstand a stressful event [21], more specifically focusing on enhancing physical state by combining aerobic and strengthening exercises.[22] A full description of the content of the intervention (frequency, intensity, time and type) was required. Measurements both pre- and peri- or postoperatively had to be performed. Outcome measurements had to record postoperative morbidity, physical state (hand grip strength, muscle mass, six-minute walking test) and mental state (EORTC-QLQ 30, SF-36). Studies were also included when physical prehabilitation was part of a multimodal program, for example including nutritional supplements.

Data extraction

Two reviewers (EB and BvdH) independently performed the data extraction in which they were blinded to each other's process. Any point of disagreement on the inclusion of a study was resolved by discussion with a senior author (BCvM). Data were extracted following a standardized data extraction form, which recorded the study characteristics (design, methods), baseline characteristics (age, gender,

diagnosis, neoadjuvant treatment, comorbidity, body composition), characteristics of the intervention (type of exercise, duration and frequency of exercise, intensity of exercise, other interventions) and the outcome (types, timing, adverse events and duration of follow-up). The primary outcome was postoperative complications. Secondary outcomes included physical improvement, length of hospital stay, quality of life and the compliance rate.

Statistical Analysis

Risk of bias

Risk of bias was assessed using by using the Cochrane Collaboration tool [23] and the Newcastle-Ottawa Scale (NOS) [24]. For the former a score below or equal to 3 out of 6 was regarded as "high risk", 4 out of 6 "moderate risk" and 5 or 6 out 6 "low risk". The Newcastle-Ottawa Scale (NOS)[24] can be used for cohort and case control studies. A rating system is used with a maximum of nine stars rewarded for best level quality. A score above 7 out of 9 was considered to be good quality.

Data synthesis and analysis

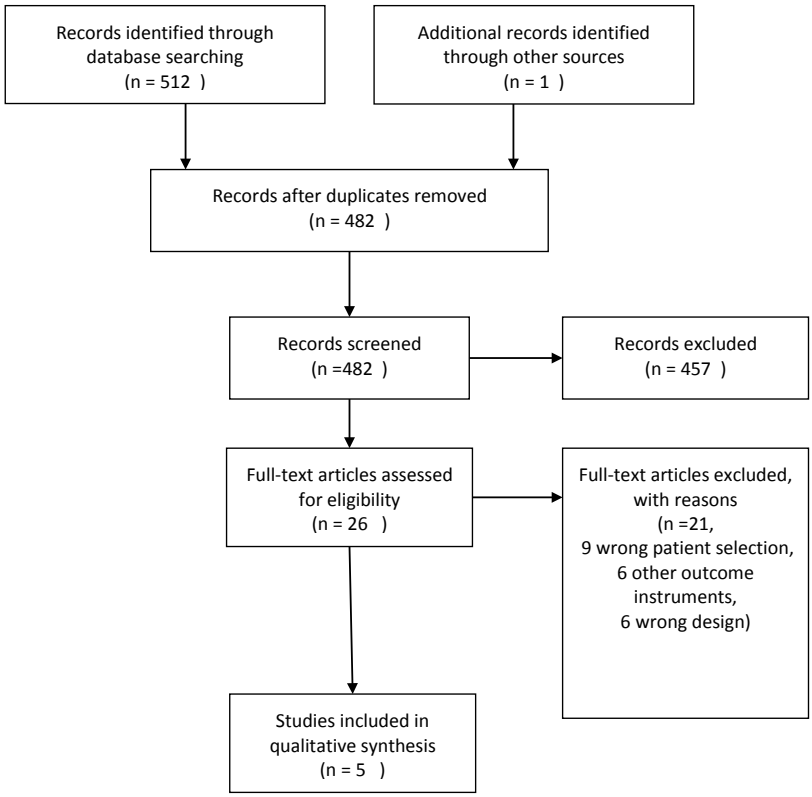
Meta-analysis was considered on two conditions. First, the data should be clinically and statistically (I^2<50%) homogeneous. Secondly the results of the studies should include a systematic report with comparable outcome variables.

Results

Search results

The results of the search are presented in Figure 1. The initial search resulted in 512 articles with one other being added later based on supplementary information. Of these 30 duplicates were removed and 457 publications were excluded based on title and abstract. Leaving 26 for full text review and more detailed evaluation. Of these 21 did not fulfil the inclusion criteria resulting in a final number of five articles.

Figure 1. Prisma flow diagram



Risk of bias

Within-study risk of bias was assessed by two reviewers independently and shown in Table 1a (Cochrane risk of bias tool) and in Table 1b (Newcastle-Ottawa scale for randomized controlled trials and case control studies). Based on the Cochrane risk of bias tool we assessed the randomized controlled trials.[25–27] One study scored 4 out of 6 and was considered as "moderate risk" of bias. [25] Two studies scored 5 out of 6 and were considered as "low risk" of bias.[26,27] With the Newcastle-Ottawa scale, we assessed two case control studies.[28,29] They both scored eight out of nine and were considered of good quality.[28,29]

Table 1a. The Cochrane risk of bias assessment

	Adequate sequence generation	Allocation concealment	Blinding	Incomplete outcome data addressed	Free of selective reporting	Free of other bias	Total score/6
Carli et al [25]	Y	-	N	Y	Y	Y	4
Dronkers et al [26]	Y	Y	N	Y	Y	Y	5
Gillis et al[27]	Y	Y	N	Y	Y	Y	5

Table 1b. Newcastle-Ottawa scale

	Selection	Comparability	Exposure	Total score /9
Li et al [28]	★★★★	★	★★★	8
West et al [29]	★★★★	★	★★★	8

Patient characteristics

Baseline characteristics of the included patients are shown in Table 2. The search resulted in three randomized controlled trials [25–27] and two case controlled studies[28,29]. They were published between 2010 and 2015. Together they included 353 patients, all scheduled for elective colorectal surgery. Of these 87% had colorectal cancer. Use of laparoscopic surgery varied from 3%-76%. Baseline comorbidity defined according to the ASA-classification (American Society of Anesthesiologists) [30] was mentioned in four studies. Patients classified as ASA 1 ranged from 0-50%, ASA 2 from 41-85% and ASA 3 or more from 9-26%. Overall, baseline characteristics between groups did not differ significantly.

Table 2. Patient characteristics

Study		Participants (N =number, M = male)			Diagnosis	Procedure	ASA
Author	**Design**	**N: male (M)/%)**	**Intervention (I): N (age ± SD) Control (C): N (age ± SD)**	**BMI (kg/m²) (± SD)**	**N Colorectal cancer (%)**	**N: open (%)**	**Grade I (I/C) Grade II (I/C) Grade III+(I/C)**
Carli 2010[28]	RCT	112 M/% (65/57)	I: 58 (61 ±16) C: 54 (60 ± 15)	I: 28 (±6) C: 27 (±5)	I: 35 (63%) C: 31 (61%)	I: 44 (76) C: 41 (76)	Grade I I: 3 (5%) C: 4 (7%) Grade II: I: 42 (72%) C: 39 (72%) Grade III+: I: 13 (22%) C: 11 (20%)
Dronkers 2010[25]	RCT	42 M/% (31/74)	I: 22 (71±6.3) C: 20 (69 ± 6.4)	I: 27 (±3.6) C: 26 (±3.1)	I: 22 (100%) C: 20 (100%)	/	/
Gillis 2014[73]	RCT	77 M/% (48/62)	I: 38 (66±13.6) C: 39 (66±13.6)	I: 27 (±4.6) C: 28 (±4.3)	I: 38 (100%) C: 39 (100%)	I: 1 (3) C: 4 (10)	Grade I I: 4 (11%) C: 4 (10%) Grade II: I: 24(63%) C: 26 (67%) Grade III+: I: 10 (26%) C: 9 (23%)
Li 2013[26]	Case-Control	87 M%(41/47)	I: 42 (67 ±11) C: 45 (66 ±12)	I: 27 (±4) C: 27 (±6)	I: 42(100%) C: 45 (100%)	I: 8 (19) C: 3 (7)	Grade I I: 3 (7%) C: 6 (13%) Grade II: I: 31(74%) C: 29 (65%) Grade III+: I: 8 (19%) C: 10 (22%)
West 2015[27]	Case-Control	35 M% (23/66)	I: 22 (64 ±19) C: 13 (72 ±10)	I: 27 (±5.1) C: 25 (±3.9)	I: 23 (100%) C: 12 (100%)	I: 11 (65) C: 8 (73)	Grade I I: 11 (50%) C: 0 (0%) Grade II: I: 9 (41%) C: 11 (85%) Grade III+ I: 2 (9%) C: 2 (15%)

Table 3. Intervention characteristics

	Duration (days)	Aerobic (% peak HR)	Duration (D) (min) Frequency (F) (x/week)	Strength/ Intensity (n repetitions)	Duration (min)	Frequency (x/week)	Other interventions	Control
Carli 2010 25	38	50-80%	D: 20-30 F: 7	Full body (8-12)	15	3	-	Walking/ breathing
Dronkers 2010 26	21	55-75%	D: 20-30 F: 7	Lower limbs (8-15)	15	2	Breathing exercises	Breathing exercises
Gillis 2014 27	24	40%	D: 20 F: 3	Full body (8-12)	20	3	Breathing exercises, Nutritional advise + protein supplement, Anxiety reduction	Postoperative exercise, breathing exercises, nutrition advise + protein supplements, anxiety reduction
Li 2013 28	33	50%	D:30 F: 3	Full body (voluntary)	15	3	Breathing exercises, Nutritional advise + Protein supplement, Anxiety reduction	Nothing
West 2015 29	42	50-80%*	D: 20-40 F: 3	-	-	-	-	Nothing

HR = heart rate, D= duration, F= frequency
*Interval

Intervention characteristics

A summary of the interventions is shown in Table 3. All trials included cardiopulmonary aerobic exercise as a form of prehabilitation. The frequency varied from three times a week with supervision to a required amount of twice a day without supervision. Four studies added resistance training to the prehabilitation program [25–28]. The duration of the prehabilitation program ranged from 21 to 42 days and duration of each session from 20 to 40 minutes, consisting of cardiopulmonary exercises and strength training. Two trials included the administration of nutritional supplements [27,28]. Three studies added respiratory exercises [26–28]. Two trials added anxiety reduction therapy [27,28]. No exact description of the content and execution of the intervention was given in any of the studies. The wide variability of duration, moments of measurement and measurement tools resulted in substantial clinical heterogeneity, making the results unsuitable for meta-analysis.

Complications

Four trials investigated the effect of prehabilitation on postoperative complications [25–28]. In the studies using the Clavien-Dindo scoring system [25,27,28], 59 complications were seen in the prehabilitation group (n=136), of which 20 were categorized as grade I, 17 as grade II and 12 as grade III compared with 55 complications in the control group (n=138), of which 19 were categorized as grade I, 26 grade II and 10 grade III or more (Table 4). There was no significant difference between these rates in the prehabilitation and control groups.

Length of hospital stay

The length of hospital stay was recorded in four trials [25–28]. None of the studies showed a significant difference between the groups (Table 4). The length of stay ranged from 4 to 16.2 days in the prehabilitation group and from 4 to 21.6 days in the control group.

Physical performance

All studies performed a physical test at the time of inclusion of the patient. Three of five studies [25,27,28] used the six minute walking test (6MWT)[31] to measure physical performance. This is a validated instrument to measure recovery after colorectal surgery [32]. Gilles et al [27] measured a significant increase in walked

distance both during the prehabilitation period (prehabilitation MD*[1]+25.2m vs control MD -16.4m p<0.001) and postoperatively (prehabilitation MD +23.4m vs control MD -21.8 p = 0.020). Li et al [28] also showed a significant improvement in the prehabilitation group preoperatively (prehabilitation +42m vs control +0m p <0.01 and postoperatively (prehabilitation +37m vs control -27m p<0.01). Carli et al [25] on the contrary demonstrated a significant decline in physical performance of the bicycle/strengthening group during the process of prehabilitation (prehabilitation MD -10m vs control MD +8m p<0.051) and postoperatively (prehabilitation MD -34m vs control MD -12m p<0.019). The remaining two studies did not use the six-minute walking test. Dronkers et al [26] assessed physical performance in various ways. They executed a Timed-Up-and-Go test [33], chair rise time [34], maximal inspiratory pressure [35] and a respiratory muscle analyzer [36]. Only the respiratory muscle analyzer, testing inspiratory endurance by calculating the total energy (Joules) expended against a load, showed a significant improvement of the prehabilitation group compared with the control group (prehabilitation MD +146 vs control MD -45 p<0.01). West et al[29] assessed physical performance by measurement of the oxygen uptake (ml/kg/min) at lactate threshold during exercise [37]. The intervention group improved significantly after prehabilitation (prehabilitation MD +2.1 vs control -0.7 p<0.001) (Table 4).

Psychological performance

Three studies used the Hospital Anxiety and Depression Scale (HADS)[38,39] to record psychological effects of the prehabilitation program. Anxiety and depression are both scaled from 0 to 21. A score above 8 is considered as a significant risk of anxiety or depression.

In the study on depression performed by Carli et al [25]. both groups also showed reduction after the prehabilitation program (bike/strengthening MD -0.8 vs walking/breathing MD -0.2, p>0.05) and postoperatively (bike/strengthening MD -0.8 vs walking/breathing MD -0.4, p>0.05). The authors state that none of the between-group comparisons was statistically significant. In the study performed by Gillis et al [27] between-group differences both in anxiety as in depression did not differ significantly. The results of within group tests were not mentioned. In the study of Li et al [28], only the HADS score in the prehabilitation group was recorded.

1 * MD = mean difference

Both anxiety (after prehabilitation MD -1, after surgery MD -2) and depression (after prehabilitation MD -1.5, after surgery MD -0.5) did not change significantly over time.

Dronkers et al [26] used the AFQ (Abbreviated Fatigue Questionnaire [40]) and the EORTC-QLQ-C30 quality of life questionnaire [41]. The AFQ-scores vary from 4 (no fatigue) to 28 (extreme fatigue). The EORTC-QLQ-C30 scales from 0 (poor quality) to 100 (perfect quality). Mean differences were reported. None of the questionnaires showed a significant improvement in the prehabilitation group after prehabilitation (AFQ, prehabilitation group –MD 0.5, control group MD -0.7, p=0.91, EORTC QLQ-C30, prehabilitation group health MD +2, functional MD +5, symptom -35, control group health MD -3, functional -2, symptom +25). Results are summarized in Table 4.

Compliance

Four of five studies reported compliance and found a rate between 16% and 97% [25,26,28,29] (Table 5), by asking patients whether they adhered to the program. Four of five studies used a compliance instrument including a diary [26–29]. Two studies provided data from the use of a pedometer in the prehabilitation period [26,29] and four used peer-to-peer motivation such as phone calls [26–29]. Combining the above results, the risk of clinical heterogeneity was high, and a meta-analysis was therefore preluded.

Table 4. Outcome measurements

Study **I = intervention** **C = control**	**CLINICAL** • **Hospital-related complications** • **Length of hospital stay**	**PSYCHOLOGICAL** • **Hospital Anxiety and Depression Score** • **Abbreviated Fatigue Questionnaire** • **Short Health Survey 36** • **EORTC QLQ C30 quality of life**	**PHYSICAL** • **Six Minute Walk Test** • **Timed up and Go** • **Chair Rise Time** • **Maximal Inspiratory Pressure** • **Respiratory Muscle Analyser** • **LASA physical activity questionnaire** • **Physical work capacity**
Carli 2010 [25]	Clavien-Dindo[m] (grade ≥ 1) I: 22 C: 18 (p>0.05) LOS[n] (days) I: 11.9 C: 6.6 (p>0.05)	HADS[f] (mean difference) Anxiety after prehab I: -0.3 C: -0.4 (p>0.05) after surgery I: -1.8 C: -2.0 (p>0.05) Depression after prehab I: -0.8 C: -0.2 (p>0.05) after surgery I: -0.8 C: -0.4 (p>0.05)	**6MWT[a] (mean difference, meters)** **after prehab (meters)** **I: -10 C: +8 (p=0.051)** **4 weeks after surgery** **I: -34 C: -12 (p=0.019)**
Dronkers 2010 [26]	Local registration: I: 9 C: 8 (p = 0.65) LOS (days): I: 16.2 C: 21.6 (p=0.31)	AFQ[l] (mean difference) I: -0.5 C: -0.7 (p=0.91) EORTC QLQ-C30[c] Global Health Status I: 2 C: -3 (p=0.88) Functional Scale I: 5 C: -2 (p=0.72) Symptom Scale I: -35 C: 25 (p=0.20)	TUG[g] (s) I: -0.2 C: 0.2 (p=0.34) CRT[h] (s) I: 0.3 C: -0.3 (p=0.87) MIP[i] (cmH_2O) I: 14 C: 5 (p=0.09) **RMA[k] energy (J)** **I: 146 C: -44 (p<0.01)** LAPAQ[j] energy (kcal/day) I: 198 C: 652 (p=0.15) activities (min/day) I: 39 C: 69 (p=0.18) PWC[b] (O_2mL/kg/min) I: -1.7 C: 1.3 (p=0.16)
Gillis 2014 [27]	Clavien-Dindo[m] (grade ≥ 1) I: 12 C: 17 (p=0.51) LOS (days): I: 4 C: 4 (p=0.45)	HADS[f] (mean difference) Anxiety after surgery I: -2.6 C: -1.7 (p=0.33) Depression after surgery I: -0.6 C: -0.6 (p=0.99) SF-36[d] mental health I: 11.2 C: -0.3 (p=0.09)	**6MWT[a] (mean difference, meters)** **after prehab** **I: +25.2 C: -16.4 (p<0.001)** **8 weeks after surgery** **I: +23.4 C: -21.8 (p=0.020)** SF-36[d] physical functioning I: 1.4 C: -4.5 (p=0.47)

Table 4. (Continued)

Study **I = intervention** **C = control**	**CLINICAL** • **Hospital-related complications** • **Length of hospital stay**	**PSYCHOLOGICAL** • **Hospital Anxiety and Depression Score** • **Abbreviated Fatigue Questionnaire** • **Short Health Survey 36** • **EORTC QLQ C30 quality of life**	**PHYSICAL** • **Six Minute Walk Test** • **Timed up and Go** • **Chair Rise Time** • **Maximal Inspiratory Pressure** • **Respiratory Muscle Analyser** • **LASA physical activity questionnaire** • **Physical work capacity**
Li 2013 [28]	Clavien-Dindo[m] (grade ≥ 1) I: 20 C: 15 (p=0.67) LOS (days): I: 4 C: 4 (p=0.71)	HADS[l] (mean difference) Anxiety after prehab I: -1 4 weeks after surgery I: -2 Depression after prehab I: -1.5 4 weeks After surgery I: -0.5	**6MWT[a] (mean difference, meters)** **after prehab I: +42 C: 0 (p<0.01)** **8 weeks after surgery I: +37 C: -27 (p<0.01)**
West 2015 [29]	/	/	**VO_2 at θ_L mean difference (ml/kg*min)[m]** **after prehab I: 2.1 C: -0.7 ml/kg (p<0.0001)**

Table 5. Measurements of compliance

	Supervision Frequency (1, <5, >5)	**Compliance instrument***	**Material provided**	**Progress visible****	**Peer to peer motivation**	**Consequence if task not performed**	**Compliance recorded**
Carli 2010[25]	>5	No	Yes	No	No	No	16%
Dronkers 2010 [26]	>5	Yes	Yes	Yes	Yes	No	97%
Gillis 2014[27]	1	Yes	Yes	No	Yes	No	No
Li 2013 [28]	1	Yes	Yes	No	Yes	No	45%
West 2015[29]	>5	Yes	Yes	Yes	Yes	No	96%

*Compliance instrument: diary ** Pedometer

Discussion

The present systematic review suggested that physical prehabilitation preoperatively can improve the physical condition of older patients undergoing colorectal surgery, but it demonstrated no significant effect on the reduction of complications, or the length of hospital stay. Owing to clinical heterogenicity, the present review cannot therefore provide support for the potential benefit of reduced complications due to physical prehabilitation in older patients undergoing colorectal surgery.

Only 7% of all randomized controlled trials published worldwide specifically feature older patients [42]. Reduced mobility, comorbidity and lack of funding all form barriers in research in the elderly .[43] as exemplified in the present study in which the search produced five small trials each with a moderate risk on bias. Only two studies [25,44] performed an adequate sample size calculation. The small sample size and the overall small number of trials targeting the older patient preclude high quality evidence.

Patients with ASA grade IV-V have an increased risk of postoperative complications.[55–58]. These patients in particular could benefit from a prehabilitation program, but they were all excluded by the criteria of the study. This may partly be due to the large variance in age whereby a mean age of 60 years with a standard deviation of 19 years will fail to highlight the older patient. Such data do not include frailty, which is a symptom more prevalent in the elderly. This may have an even stronger predictive value for the benefit of this prehabilitation program [50]. There were no identified characteristics to determine the level of frailty in the included studies and thus data are lacking on this question.

The recorded compliance in the five included studies varied from 16-97%. This large range is of great concern. The difference of providing exercise material at home and with one visit to give instructions (Carli et al [25]) with a compliance rate of 16% compared with a fully supervised in hospital program (Dronkers et al[26]) having a compliance rate of 97%, might be because Carli et al[25] did not register physical improvement in the prehabilitation group where Dronkers et al [26] did so.

None of the included studies made a distinction between open and laparoscopic

procedures or standard and enhanced postoperative recovery. Especially in colorectal surgery, the introduction of laparoscopic techniques and other minimal invasive procedures has resulted in a significant reduction of the stress response induced by surgery [51,52]. Prehabilitation so far has proven to be most effective in 'high risk' procedures, such as cardiothoracic and major abdominal surgery [53,54]. Regarding the surgical intervention, the effect of prehabilitation depends on a balance of the risk of the procedure and the risk factors pertaining to the patient. Thus, it might be expected that the effect of complications in this low risk population would be smaller.

In conclusion, the present review suggests that prehabilitation is a possible strategy to enhance physical performance preoperatively in patients undergoing colorectal surgery, although it does not result in a significant reduction of complications or length of hospital stay. It is therefore of paramount importance to improve the quality of knowledge in this field. This review offers four recommendations for future studies. First, available risk stratification models [13,55] should be used to target a patient group at risk. Secondly, the intervention requires understanding of the altered physiology of the older patient [56,57,58]. The integration of prehabilitation in the daily treatment routine of an older patient will be essential to obtain compliance without which possible effects of prehabilitation will not be known [59,60]. This also applies to the multimodal program, which includes nutritional and psychological data parallel to physical training. This hypothesis is strengthened by the study by Chia et al, who recently published the results of a multimodal program, which observed a reduction in the length of hospital stay after multimodal prehabilitation [61,62]. Thirdly, older patients require a tailormade approach regarding the execution of a trial. The interventions of the included studies instructed all patients to follow the same program, without adapting to existing habits. Literature states that older patients preferably eliminate unpredictable factors out of their life, even more so in the case of a life event, such as getting diagnosed with cancer [60]. For example, visiting the patient at home. Fourthly trials should use validated, consistent measurement instruments such as the 6MWT for the assessment of functional capacity, the SF-36 (short form health survey)[47,63] for quality of life and the Clavien-Dindo classification [64] for postoperative complications.

As patients become older their capability to adapt rapidly to maintain homeostasis, deteriorates [65]. There are many challenges for the elderly undergoing surgery and

their treatment must take age-related factors into account. The trend to super specialization has restricted knowledge among individual practitioners and the essence of future trials will be collaboration between doctors in different fields.

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7

Oral nutrition as a form of preoperative enhancement in patients undergoing surgery for colorectal cancer: a systematic review

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Surgical Infections

Abstract

Background

Nutritional status has major impacts on the outcome of surgery, in particular in patients with cancer. The aim of this review was to assess the merit of oral preoperative nutritional support as a part of prehabilitation in patients undergoing surgery for colorectal cancer.

Methods

A systematic literature search and meta-analysis was performed according to the Preferred Reporting of Systematic Reviews and Meta-Analyses (PRISMA) recommendations in order to review all trials investigating the effect of oral preoperative nutritional support in patients undergoing colorectal surgery. Primary outcome was overall complication rate. Secondary outcomes were wound infection rate, anastomotic leakage rate, length of hospital stay.

Results

Five randomized controlled trials and one controlled trial were included. The studies contained a total of 583 patients with an average age of 63 (23-88) years of which 87% were diagnosed with colorectal cancer. Malnourishment rates varied from 8%-68%. All studies provided an oral protein supplement. Overall compliance varied between 72-100%. There was no significant reduction of overall complication rate in the interventional groups (OR [95% CI]: 0.82 [0.52-1.25]).

Discussion

Current studies are too heterogeneous to conclude that preoperative oral nutritional support could be a potential strategy to enhance the condition of patients undergoing colorectal surgery. Patients at risk rather have a relative lean body mass deficit (sarcopenia) than an absolute malnourished status. Compliancy is an important element of prehabilitation. Targeting patients at risk, combining protein supplements with strength training and defining standardized patient related outcomes will be essential to obtain satisfactory results.

Introduction

"Let food be thy medicine and medicine thy food". The words of Hippocrates could not be more true. A good nutritional status plays a crucial role in the successful recovery from a surgical intervention. Currently, surgery remains the cornerstone in the treatment of colorectal cancer.[1] This specific group of patients, of whom more than 50% are over 65 years old[2], has two imminent factors to be nutritionally at risk. First, age itself is an independent risk factor for poor nutritional status.[3] Second, cancer can induce significant weight loss resulting in malnutrition.[4] Recent studies show that two out of three patients diagnosed with colorectal cancer experience weight loss preoperatively, one in five even more than 10%.[5]

Compared to other gastrointestinal malignancies however, colorectal cancer is not a major risk factor for cachexia. Nevertheless, a status of relative protein deficiency is related to declined muscle mass or sarcopenia.[6] Sarcopenia poses a significant risk for postoperative complications to patients undergoing colorectal surgery.[7] Hence, enhancing the nutritional status of patients at risk might be a potential strategy to decrease postoperative morbidity.[8]

The 'enhanced recovery after surgery' (ERAS) programs have greatly contributed to the speed and quality of recovery of colorectal patients.[9] Nutritional support is a substantial part of these programs, but only in the peri- and postoperative periods. The waiting period prior to surgery could serve as a potential window of opportunity to enhance the nutritional status of the patients. This preoperative enhancement has been coined prehabilitation and can consist of any form of patient optimization before surgery.[10]

Nutritional interventions can take many forms during this period. The European Society for Parenteral and Enteral Nutrition (ESPEN) guidelines on nutrition in cancer patients state that nutrition counseling with oral nutritional supplements is the preferred first step in ensuring adequate nutrient intake.[11] As most patients will be cared for in an outpatient setting in the weeks before surgery, oral nutritional support would also be more practical and cost-effective than parenteral nutrition.[12]

The aim of this systematic review and meta-analysis is to assess whether preoperative oral nutritional support can reduce the rate of postoperative surgical

complications and/or improve postoperative recovery rate in terms of hospital stay, quality of life, and functional outcome after colorectal surgery.

Methods

A systematic literature search and meta-analysis was performed according to the Preferred Reporting of Systematic Reviews and Meta-Analyses (PRISMA) recommendations.[13]

Study Selection

The last update of the search was performed on August 30th 2016 (revised for new publications 1st August 2017) involving Medline and Embase databases. The search was constructed together with a clinical librarian and consisted of three search term categories: type of surgery, timing of nutritional intervention, and content of nutritional intervention. The search string can be found in the Appendix. Hand search of references of results was performed. Two authors (EB and TA) independently screened all titles and abstracts and the following full text articles. Disagreement was addressed by discussion and consensus. Following this process, a reference search of all included papers and relevant review articles was performed to identify any missed studies.

Eligibility Criteria

Studies were included if they answered the clinical question as defined by the PICO (population, intervention, control, outcome) format. In order to study cause-effect relationships, only randomized controlled trials (RCTs) and prospective cohort studies were included. The included patients had to be 60 years or older and undergoing colorectal surgery. The intervention consisted of oral nutritional support in the form of macronutrients (proteins, carbohydrates, fats), eventually together with micronutrients (e.g. immunonutrition, vitamin supplements) or dietary advice which is defined as any form of professional consultation involving dietary analysis and consequent advices. Because immediate preoperative nutritional support is also part of the ERAS protocol[14] (e.g. preoperative carbohydrate loading), we chose to only include studies that administered oral nutrition for at least 48 hours preoperatively. The control group was to receive a diet without specific nutritional support. The primary outcome was overall complication rate, preferably using the Clavien-Dindo scale.[15] Secondary outcomes were wound infection rate, anastomotic

leakage rate (definitions used by authors of original studies), length of hospital stay, quality of life and recovery (e.g. functional capacity) after the operation.

In order to study the effects of oral nutrition alone, studies investigating the effect of nutrition as a part of a multimodal prehabilitation program involving e.g. exercise or psychological prehabilitation were excluded. Studies investigating the effect of parenteral nutritional support were also excluded. Review articles, (retrospective) case-controlled studies, case reports, opinion papers, animal studies and studies not in English were also excluded.

Assessment of Methodological Quality

Two authors (EB and TA) independently assessed the methodological quality of the studies. The Cochrane risk of bias tool considering seven items was used to grade the risk of bias.[16] A score below 4 out of 7 was regarded as 'high risk', 4 out 7 as 'moderate risk' and above 4 out of 7 as 'low risk'. Disagreement was solved by discussion and consensus.

Data Extraction

Study characteristics, including study design, sample size, study population and type and duration of nutritional support were obtained from the included studies by two authors (EB and TA). If mentioned, the following data were extracted: overall complication rate, wound infection rate, anastomotic leakage rate, length of hospital stay, quality of life, measures of postoperative recovery and compliancy rate. If data were missing, first authors of the included papers were contacted.

Statistical Analysis

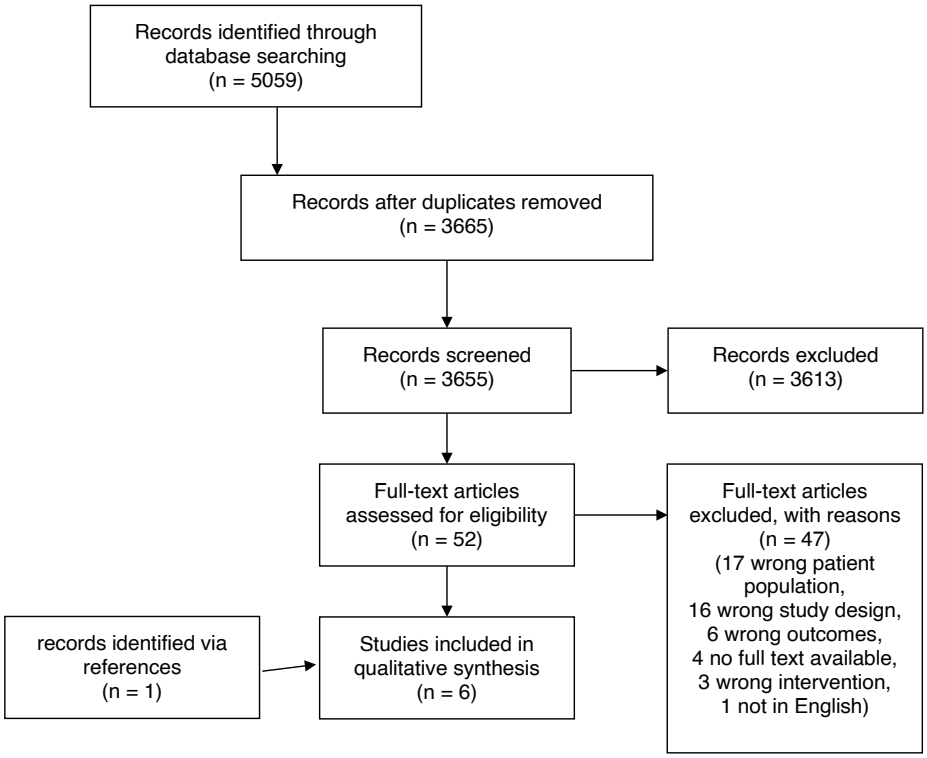
Meta-analysis was used to estimate the pooled odds ratio (OR) for categorical data, or mean difference (MD) for continuous data to compare the postoperative outcomes of patients with and without nutritional support. Review Manager version 5.3 (The Nordic Cochrane Centre, Copenhagen, Denmark) was used to estimate the pooled results, using the Mantel–Haenszel estimator to calculate ORs. After visual inspection for clinical heterogeneity, the Higgins I^2 value was used to assess statistical heterogeneity. A random-effects model was used to pool data. $P<0.05$ was considered statistically significant.

Results

Search Results

A complete flowchart of the search is presented in Figure 1. The initial search in PubMed and Embase resulted in 5059 articles. After removal of duplicates and title and abstract screening, 52 articles remained for full text reading. We excluded 47 articles because the study design, patient population and/or intervention did not meet the inclusion criteria. Five studies satisfied the inclusion criteria, and one additional study was found in a Cochrane review[17]. Five RCTs[18–22] and one prospective controlled study[23] were selected for analysis.

Figure 1. PRISMA flow diagram of study



Risk of Bias

Two reviewers independently assessed the risk of bias, the results are presented in Table 1. The assessment was done with Cochrane risk of bias tool. One study was considered to be at high risk of bias.[23] Three studies were considered at moderate risk[19,20,22], and two studies at low risk of bias.[18,21]

Table 1. Risk of Bias

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Braga 2002 (group 1)	+	+	-	+	?	+	+
Braga 2002 (group 2)	+	+	-	+	?	+	+
Burden 2011	+	+	?	?	?	+	+
Finco 2007	+	+	-	?	?	+	+
Gillis 2016	+	+	+	+	+	+	+
Horie 2006	-	?	-	?	?	+	+
Smedley 2004	+	+	-	-	?	+	+

Baseline Characteristics

The baseline patient and surgery characteristics are summarized in Table 2. All studies were published between the year 2002 and 2016 and included a total of 583 patients undergoing colorectal surgery. The mean age of the participants was 63 years (range 23-88). In four studies, all included patients were diagnosed with colorectal cancer.[18,19,21,23] Smedley *et al.*[22] and Finco *et al.*[20] included 33% and 50% of patients with a benign indication for colorectal surgery, respectively. Regarding the

physical characteristics of the patients, malnourishment rates were mentioned in four studies[18,19,21,22]; percentages varied from 8% to 68%. Burden *et al*.[19] randomized more malnourished patients in the intervention group while Horie *et al.*[23] excluded malnourished patients altogether. The definition of malnourishment differed between studies. Five studies[19–23] reported the average body mass index (BMI) of the participants. Three studies[19,21,22] reported the average handgrip strength (GS) of the participants. GS can be regarded as a functional measurement of sarcopenia. However, as GS cut-off points for sarcopenia are BMI- and gender-specific[6], it was not possible to calculate the percentage of functionally compromised patients. The study by Braga *et al.*[18] contributed two intervention groups and one control group to this review: group 1 (50 patients) received preoperative immunonutrition, group 2 (50 patients) received comparable nutrition but without micronutrients, and the control group (50 patients) received no supplements.

Intervention Characteristics

Table 3 gives an overview on the intervention characteristics. A liquid oral supplement was provided in all of the studies. In the study by Braga *et al*.[18] one group of participants received Oral Impact (Novartis/Nestlé), one group received isoenergetic, isonitrogenous formula, and one group did not receive any supplements. Oral Impact was further provided by two other studies.[20,23] Two studies provided Fortisip (Nutricia)[19,22] and one study provided a whey protein supplement (Immunotec)[21]. Sponsorship of the supplements was not documented by Finco *et al.*[20] and Horie *et al.*[23]

The supplements consisted mainly of carbohydrates (approximately 50% of the total amount). While Gillis *et al*.[21] solely provided protein at an average of 19.8g per day (which amounts to 22% of the daily requirement of a 70-kg person according to the ESPEN guidelines[11]), the amount of protein in the supplements in the other studies ranged from 18g to 67.2g (20% to 74% of the daily requirement[11]). Three studies provided immunonutrition (Oral Impact) which contains the micronutrients arginine, omega-3 fatty acids and ribonucleic acids (RNA).[18,20,23]

Table 2. Baseline characteristics

Reference	Study design	# patients (average age)	Physical characteristics of patients			Definition mal nourishment	CRC^	Laparoscopic surgery	Sponsoring
			Hand grip strength	BMI (kg/m²)	Malnourished				
*Braga et al. 2002(1)**	RCT, single-center study in Italy	100 (61)	Not reported	Not reported	I: 12% vs C: 10%	Patients reporting weight loss ≥10% in the last 6 months.	100%	0%	Novartis Consumer Health, Bern, Switzerland
*Braga et al. 2002(2)***	RCT, single-center study in Italy	100 (62)	Not reported	Not reported	I: 8% vs C: 10%	Patients reporting weight loss ≥10% in the last 6 months.	100%	0%	Novartis Consumer Health, Bern, Switzerland
Burden et al. 2011	RCT, multicenter study in England	116 (65)	I: 26.6 (±10.4 kg) vs C: 27.7 (±9.9 kg)	I: 25.0 (±4.8) vs C: 26.8 (±4.7)	PG-SGA: I: 56% vs C: 37%, *p<0.05*	PG-SGA score B or C. GS <85% of age- and gender-specific reference range.	100%	I: 96% vs C: 97%	Nutricia Ltd, Wilts, UK
Finco et al. 2007	RCT, single-center study in Italy	28 (67)	Not reported	I: 24.8 (±2.9) vs C: 29.0 (±3.5)	Not reported	Malnourishment was not mentioned.	50%	100% (no information on conversion rate)	Not mentioned
Gillis et al. 2016	RCT, single-center study in Canada	43 (68)	I: 30.6 (±10.7 kg) vs C: 30.2 (±8.8 kg)	I: 26.6 (±5.0) vs C: 25.2 (±4.5)	PG-SGA: I: 41% vs C: 33% NRS-2002: I: 15% vs C: 14%	PG-SGA score B or C. NRS-2002 score ≥3.	100%	I: 90% vs C: 75%	Immunotec, Inc.
Horie et al. 2006	CT, single-center study in Japan	67 (66)	Not reported	I: 22.8 (±2.9) vs C: 22.8 (±3.2)	Excluded	Patients reporting weight loss ≥10% in the last 6 months.	100%	0%	Not mentioned
Smedley et al. 2004	RCT, multicenter study in England	179 (60)	I: 74.1 (±23.1 kPa) vs C: 71.5 (20.7 kPa)	I: 26.9 (±4.9) vs C: 27.8 (±5.6)	I: 53% vs C: 68%	BMI stratified according to age (>65 years old, BMI <24kg/m²)	67%	0%	Numico Research, Wageningen, The Netherlands

*immunonutrition group **extra nutrition group without immunonutrition ^CRC = diagnosed with colorectal cancer
BMI body mass index, *C* control group, *CT* controlled trial, *GS* grip strength, *I* intervention group, *kPa* kilopascals, *NRS* nutritional risk screening, *PG-SGA* patient-generated subjective global assessment, *RCT* randomized controlled trial

Most studies asked the patients to consume a standard amount of supplement ranging from 400ml to 1000ml per day. Smedley *et al*.[22] instructed the patients to drink as much as possible between meals while Gillis *et al*.[21] provided the patients with an amount of protein that had been calculated to cover the individual protein deficit. Gillis *et al*.[21] were also the only ones providing the patients with a non-nutritive placebo.

The duration of the complete preoperative program varied between the studies. Three studies provided the supplements for five days in the week preceding surgery.[18,20,23] The intervention in the three other studies spanned the entire preoperative period starting from cancer diagnosis and the decision to operate and ending at hospital admission.[19,21,22] Gillis *et al*.[21] and Finco *et al*.[20] further continued with the supplements postoperatively for a duration of four weeks and three days, respectively.

Table 3. Intervention characteristics

Reference	Type and amount of nutrition	Duration	Extra energy per day (kJ/ kcal)	Protein content (% of energy)	Carbohydrate content (% of energy)	Fat content (% of energy)	Extra	Compliance	Control group
*Braga et al. 2002(1)**	Oral Impact (Novartis) 1000ml per day (4x74g sachets)	5 days	5200 kJ/ 1236 kcal	67.2g (22%)	160.8g (52%)	33.2g (24%)	15.2g arginine, 4g omega-3 fatty acids, 1.8g RNA	Mean intake 905mL/day	No supplements
*Braga et al. 2002(2)***	Formula not commercially available 1000ml per day (4x74g sachets)	5 days	5200 kJ/ 1236 kcal	67.2g (22%)	160.8g (52%)	33.2g (24%)	–	Mean intake 915mL/day	No supplements
Burden et al. 2011	Fortisip (Nutricia) 400ml per day (2x200ml cartons)	Mean 37.6 days (SD 42.8, range 10-252)	2520 kJ/ 600 kcal	24g (16%)	73.6g (49%)	23.2g (35%)	–	Full intervention 72% Half intervention 16%	Dietary advice, no supplements
Finco et al. 2007	Oral Impact (Nestlé) 750ml per day (3x74g sachets)	5 days pre-op, 3 days post-op starting on post-op day 1	3900 kJ/ 927 kcal	50.4g (22%)	120.6g (52%)	24.9g (24%)	11.4g arginine, 3g omega-3 fatty acids, 1.35g RNA	Not mentioned	Low-fiber diet, normal diet starting on post-op day 3
Gillis et al. 2016	Whey protein isolate (Immunocal) Average of 19.8g (SD 7.8g) per day	33.5 days pre-op (range 22.5-48.5), 4 weeks post-op	3313 kJ/ 792 kcal	19.8g (100%)	–	–	–	Whey protein: 93.7% Placebo: 96.6%	Nutrition counseling and non-nutritive placebo.
Horie et al. 2006	Oral Impact Japanese version (Ajinomoto) 750ml per day (3x74g sachets)	5 days	3900 kJ/ 927 kcal	50.4g (22%)	120.6g (52%)	24.9g (24%)	9.6g arginine, 2.49g omega-3 fatty acids, 0.96g RNA	100%	No supplements
Smedley et al. 2004	Fortisip (Nutricia) Average of 360ml (SD 177ml) per day	Mean 15.1 days (range 7-61)	2267 kJ/ 542 kcal	18g (16%)	66.2g (49%)	20.9g (35%)	–	Patients were asked to consume supplement *ad libitum*.	No supplements

*immunonutrition group **extra nutrition group without immunonutrition

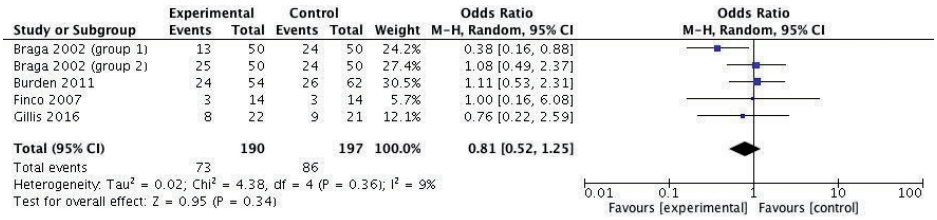
BMI body mass index, *RNA* ribonucleic acid, *SD* standard deviation

Outcomes

Overall Complication Rate

All included studies provided information on overall complications but the outcome was not reported similarly between studies (dichotomous[18–21] vs. count data[22,23]). Dichotomous data were analyzed using risk ratios with Mantel-Haenszel in a random effects method. Comparative meta-analysis of overall complication rates is presented in Figure 2; the rate was not significantly different between the intervention and control groups (OR [95% CI]: 0.82 [0.52-1.25]).

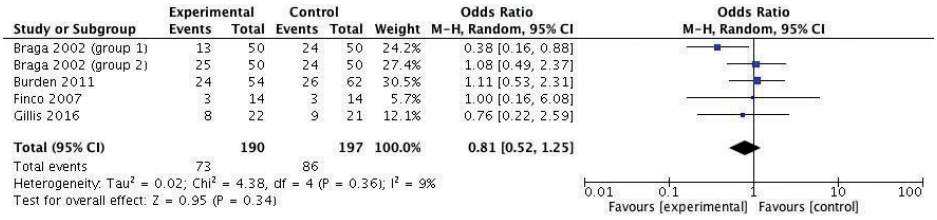
Figure 2. Meta-analysis of overall complications



Wound Infection Rate

Four studies recorded wound infection rates[18–20,23] with Horie *et al.*[23] observing a significant difference in the wound infection rate between the intervention and control groups (0% vs. 14.7%, p<0.05). The data were analyzed using risk ratios with Mantel-Haenszel in a random effects method; the meta-analysis of wound infection rates is visualized in Figure 3. The overall effect showed no advantage for preoperative nutritional support (OR [95% CI]: 0.57 [0.30-1.09]).

Figure 3. Meta-analysis of incision infections



Anastomotic Leakage Rate

Three studies reported anastomotic leakage rates[18,20,23]; due to the small number of studies, no meta-analysis was undertaken for this outcome. The leakage rates varied from 0% to 12% in the nutrition group compared to 0% to 10% in the control group. None of the studies could observe a significant difference between the treatment arms.

Length of Hospital Stay

Four studies reported length of hospital stay.[18,20–22] The mean number of days varied from 7.6 to 12.8 days in the nutrition group compared to 6.8 to 17.8 days in the control group. Due to the large clinical and statistical heterogeneity between the studies, no meta-analysis was undertaken for this outcome.

Other Outcomes

Two studies measured quality of life four weeks after surgery: Gillis *et al.*[21] used the Short Form Health Survey 36 (SF-36)[24] and Smedley *et al.*[22] used the SF-36 and EuroQol[25] instruments. No significant differences were found in the results of these questionnaires. Gillis *et al.*[21] also looked into functional walking distance with the 6-minute walk test (6MWT)[26] and changes in lean body mass four weeks after surgery, but found no differences between intervention and control groups. Smedley *et al.*[22] quantified weight loss after surgery, but again the groups were not significantly different. All outcomes are summarized in Table 4.

Compliance

Compliance to the intervention was recorded in four studies.[18,19,21,23] Rates varied between 72% and 100% (Table 5). Three studies used patient diaries as a compliance instrument[18,19,21], Horie *et al.*[23] did not specify how compliance was recorded. Gillis *et al.*[18] had weekly contact with the participants to identify problems with compliance. No extra measures to increase compliance were taken in any of the studies.

Table 4. Outcomes

Reference	Overall complications rate (% of patients)	Wound infections rate (% of patients)	Anastomotic leakage rate (% of patients)	Length of hospital stay (days±SD)	Other measures of recovery
Braga et al. 2002(1)[a]	I: 13 (26%) vs C: 24 (48%), p<0.05	I: 3 (6%) vs C: 5 (10%), ns	I: 3 (6%) vs C: 5 (10%), ns	I: 9.5±2.9 vs C: 12.2±3.9, p<0.0005	–
Braga et al. 2002(2)[b]	I: 25 (50%) vs C: 24 (48%), ns	I: 4 (8%) vs C: 5 (10%), ns	I: 6 (12%) vs C: 5 (10%), ns	I: 12.0±4.5 vs C: 12.2±3.9, ns	–
Burden et al. 2011	I: 24 (44%) vs C: 26 (42%), ns	I: 8 (15%) vs C: 16 (25%), ns	Not reported	Not reported	–
Finco et al. 2007	I: 3 (21%) vs C: 3 (21%), ns	I: 2 (14%) vs C: 1 (7%), ns	I: 0 (0%) vs C: 0 (0%), ns	I: 7.7±2.3 vs C: 6.8±1.6, ns	–
Gillis et al. 2016	I: 8 (38%) vs C: 9 (42%), ns	Not reported	Not reported	I: 7.6±6.7 (range 3-28),C: 17.8±51.6 (range 3-282), ns	6MWT, QoL or change in LBM not significantly different between groups 4 weeks postoperatively.
Horie et al. 2006	I: 1 case vs C: 9 cases, p<0.05[ϕ]	I: 0 (0%) vs C: 5 (14.7%), p<0.05	I: 0 (0%) vs C: 1 (2.9%), ns	Not reported	–
Smedley et al. 2004	I: 20 cases vs C: 34 cases, ns[ϕ]	Not reported	Not reported	I: 12.8±4.5 vs C: 14.1±6.6, ns	Postoperative weight loss or QoL not significantly different between groups.

[a]immunonutrition group [b]extra nutrition group without immunonutrition,[ϕ]reported as number of complications, significant results are emboldened 6MWT 6-minute walking test, C control group, I intervention group, LBM lean body mass, SD standard deviation, QoL quality of life

Table 5. Compliancy Enhancement

Reference	Supervision frequency (<1, 1-2, >2)ʃ	Compliance instrument*	Recorded Compliance	Material provided	Progress visible**	Peer-to-peer motivation	Consequence if task not performed
Braga et al. 2002(1)[a]	1	Yes	unknown	Yes	No	No	No
Braga et al. 2002(2)[b]	1	Yes	unknown	Yes	No	No	No
Burden et al. 2011	1	Yes	72%	Yes	No	No	No
Finco et al. 2007	1	No	unknown	Yes	No	No	No
Gillis et al. 2016	>2	Yes	94%	Yes	No	No	No
Horie et al. 2006	1	Not described	100%	Yes	No	No	No
Smedley et al. 2004	1	Not described	unknown	Yes	No	No	No

[a]immunonutrition group [b]extra nutrition group without immunonutrition
* Patient diary
** Feedback result visible to patient

Discussion

The current review was unable to record an effect of preoperative oral nutritional supplementation on the rate of postoperative complications in patients undergoing colorectal surgery. Although the preoperative phase might be a window of opportunity to improve the nutritional status of the patients, a clear-cut recipe for preoperative nutritional enhancement in colorectal surgery has not been defined. Nevertheless, based on the limitations of this review and of the included studies, several suggestions can be made to improve the quality of future research in this field.

The number of included studies was restricted, and the overall methodological quality was moderate. A meta-analysis was precluded in some cases due to the restricted amount of data available or due to the clinical and methodological heterogeneity between the included studies. Prehabilitation as an intervention has been gaining momentum only in recent years which limits the amount of available evidence. Furthermore, considering the fact that more than 50% of colorectal cancers are diagnosed in patients older than 65 years[2], the scarcity and the small sample sizes could also be explained by the fact that only 7% of all trials worldwide specifically target older patients.[27]

With regard to inclusion criteria, patients who would most likely benefit from a nutritional intervention were not well represented in the studies. The included patients were relatively young (<65 years) and in a good nutritional status (rates of malnourishment were generally low, and the average BMI was well within the recommended range for older people). Burden *et al.* suggested that patients that have been losing weight preoperatively could profit from preoperative nutritional support.[19] Indeed, malnourishment increases the risk for postoperative morbidity in patients undergoing colorectal surgery.[28] However, traditional measures of malnourishment, such as weight loss and low BMI, do not capture the whole picture. Instead, the deficits might be subtler. Sarcopenia refers to a low skeletal muscle mass that results from age-related impaired protein turnover.[29] It is exacerbated by inadequate protein intake and sedentary lifestyle.[30] The loss in lean body mass can be masked by excess fat tissue on the scale, which is illustrated by the fact that the majority of sarcopenic colorectal cancer patients are overweight or obese.[31] Sarcopenia is accompanied by declining muscle strength and reduced

functional capacity[29] and sarcopenic patients have a higher risk for postoperative complications after colorectal surgery.[7,32–34] Sarcopenia is readily diagnosed by measuring grip strength or by means of a standard preoperative CT-scan.[6,35] Targeting sarcopenic patients and improving their nutritional status with a focus on protein intake might decrease postoperative morbidity, but few studies so far have included measures of sarcopenia in the baseline assessment.

There are certain pitfalls when it comes to the design of the intervention. Most studies provided the patients with a liquid supplement consisting mostly of carbohydrates. However, as patients at risk do not necessarily have an absolute poor caloric intake but rather a relative protein deficiency, enhancing protein intake could be the key to successful recovery. The ESPEN guidelines recommend a daily protein intake of 1.2g/kg/day.[11] In most of the included studies, it was not possible to determine whether these requirements were met as only three of them provided information on the baseline caloric and protein intake of the patients[19,21,22] and most provided an identical amount of supplement to the patients.[18–20,22,23] Only Gillis *et al.* calculated the protein deficit of the patients and provided them with an amount that should cover the deficit.[21] Furthermore, the fact that patients were asked to consume up to a liter a day of an artificial supplement might have decreased compliance. If a nutritional supplement is to become a daily habit, patients have to find it desirable. A tailor-made approach that not only considers the individual dietary requirements of the patients but also successfully integrates the supplements into the daily routine might prove to be essential.

The mere provision of extra dietary calories is overlooking the fact that inadequate nutrition is only a part of the problem. As already mentioned, both sedentary lifestyle and poor protein intake contribute to the development of sarcopenia.[30] A combination of exercise and enhanced protein intake is the most successful strategy to increase muscle mass.[36–38] Therefore, prehabilitation programs combining nutritional supplements with exercise might be able to demonstrate a synergistic effect that translates to improved recovery. Gillis *et al.* and Chia *et al.* have shown that multimodal prehabilitation programs involving protein supplementation and strength training can lead to a better functional recovery.[39,40]

Patients are most likely to benefit from a tailor-made and multifactorial prehabilitation approach.[41,42] However, it will be essential to deconstruct a

prehabilitation program into individual elements to measure their specific attributive value. Therefore, this review focused specifically on the effects of nutritional enhancement as it is a complex intervention in itself.

Lastly, at the outcome level, the choice of a validated and relevant indicator to assess the effect of a preoperative nutritional intervention on recovery remains a challenge. Current studies use traditional measurements of recovery such as rate of complications and length of hospital stay. Especially length of hospital stay is influenced by many factors outside the investigator's control and may not be sensitive enough to detect an effect from a nutritional intervention.[43] Furthermore, studies are often underpowered to detect a statistical difference in the occurrence of a single complication, e.g. anastomotic leakage. From a nutritional point of view, it might be appealing to look at recovery based on a single nutritional element (such as basal rate metabolism or serum albumin). However, small changes in laboratory values have no substantial meaning for the patient. Patients undergo an operation in order to enhance their physical condition, and if recovery is to be described from the patient's perspective, an improvement in postoperative functional capacity (measured with e.g. 6MWT or Short Physical Performance Battery[44]) might be a more relevant outcome.

In conclusion, a beneficial effect of preoperative oral nutritional support on postoperative recovery of patients undergoing colorectal surgery is yet to be demonstrated. Based on the observed challenges, this review offers four recommendations for future studies. First, patients at risk for poor postoperative outcomes need to be identified and targeted: the old, malnourished patients are especially at risk and might benefit the most from nutritional interventions. Second, due to the limited results of nutritional interventions alone, the effects of a combined intervention with nutrition and exercise in the setting of a multimodal prehabilitation program should be further investigated. Third, outcomes should be measured with validated tools from a perspective that matters to the patient and that is relevant to the nutritional intervention. Lastly, as no patient is the same, a tailor-made approach might result in greater yields. So that in the end, food can be our medicine.

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8

Short-term effect of peroperative intravenous iron therapy in colorectal cancer patients with anemia: results of a cohort study

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Accepted Transfusion

Abstract

Background

In the treatment of preoperative anaemia, which is associated with increased postoperative morbidity, iron supplementation can replace blood transfusion and erythropoiesis-stimulating agents. The aim of this study was to assess the efficacy of preoperative intravenous (IV) iron infusion in optimizing haemoglobin (Hb) level in anaemic colorectal cancer patients.

Methods

A retrospective cohort study was performed on patients who underwent surgery for colorectal cancer between 2010-2016 in a single teaching hospital. The primary outcome measure, the change in haemoglobin level, was assessed by comparing anaemic patients receiving usual care (UC; i.e. no iron therapy and no blood transfusion) with anaemic patients receiving IV iron therapy (no blood transfusion).

Results

A total of 758 patients with colorectal cancer were eligible, of which 318 (41.9%) were anaemic. The IV and the UC group included 52 and 153 patients with mean Hb levels at diagnosis of 6.3 and 6.9 mmol/L, respectively. In the IV group, preoperative Hb level was significantly increased as compared to UC group (0.65 mmol/L vs 0.10 mmol/L, $p<0.001$). High increase in Hb level after iron infusion was associated with initial higher transferrin and lower ferritin levels (high versus poor responders: median transferrin 2.9 vs 2.7 g/L, median ferritin 12 vs 27 μg/L).

Conclusion

Implementation of IV iron therapy in anemic colorectal cancer patients leads to a distinct increase of preoperative haemoglobin level. IV iron therapy is most effective in patients presenting with more severe anaemia, and with higher transferrin and lower ferritin levels, markers for an absolute iron deficiency (ID) compared to functional ID.

Introduction

Colorectal cancer is the third most commonly diagnosed cancer in men and second in women worldwide[1], and patients present with anaemia in up to a third of the cases.[2] Anaemia in this respect is emerging as an important health problem. It is not only associated with fatigue[3], impaired physical performance and cognitive function, but most importantly also with increased morbidity and mortality.[4-6]

Iron deficiency (ID) is the most common cause of preoperative anaemia in colorectal cancer patients.[7] Contributing mechanisms to the development of iron deficiency (ID) anaemia include chronic tumor-induced blood loss and also impaired iron homeostasis associated with chronic disease. While chronic blood loss will cause absolute iron deficiency (AID), characterized by depleted iron stores, impaired iron homeostasis will cause functional ID (FID), characterized by reduced iron uptake and iron mobilization from the reticuloendothelial system, both leading to a reduction of biologically available iron for erythropoiesis.[8]

Enhancement of a patient's condition prior to surgery has been gaining attention ever since the beneficial outcomes of such protocols were shown.[9, 10] More specifically, normalization of preoperative haemoglobin (Hb) level by blood management strategy is an important element in this spectrum of preoperative care.[11-13]

The high prevalence of ID anaemia in colorectal cancer patients provides an opportunity to optimize preoperative Hb level by preoperative iron supplementation with the purpose of reducing the use of blood transfusions and erythropoiesis-stimulating agents.[14] Avoiding blood transfusions and erythropoiesis-stimulating agents in oncological patients seems important because of its association with an increased risk of cancer recurrence and increased mortality[15-17]. Oral iron has been shown to correct anaemia but is also known to be slow in terms of absorption rate, to cause constipation, and to be ineffective in patients with FID as oral iron is poorly absorbed in the duodenum in these patients, due to increased production of hepcidin.

Therefore, compared to oral iron, intravenous (IV) iron therapy is likely to be more effective in treating anaemia, as shown in patients undergoing orthopedic[18] or

general abdominal surgery[19]. Based on these advantages, over the course of the last 5 years administration of iV iron has also been introduced in our institution. In this study, we retrospectively compare preoperative IV iron with usual care (UC; i.e. no iron therapy) in colorectal cancer patients with anaemia, with regard to increasing preoperative Hb level, and reducing postoperative complications and blood transfusions. In addition, predictive factors of good response to IV iron therapy will be studied.

Methods

Patient selection

All patients undergoing resection for colorectal cancer between January 1, 2010 and July 1, 2016, at the Department of Surgery, Reinier de Graaf Hospital, The Netherlands, were identified. Patients who had surgery in the emergency setting, and those with missing data with respect to baseline Hb levels and blood transfusions were excluded.

Outcome Measures

Primary outcome was the change in Hb level (i.e. Hb at diagnosis – Hb preoperative) and secondary outcomes included the percentage of patients with a blood transfusion and complication less than 30 days postoperatively.

Defining Patient Groups

Consecutive patients diagnosed with anaemia (men Hb <8.0 mmol/L, 12.9 g/dL; women Hb <7.5 mmol/L, 12.0 g/dL) were eligible for inclusion. Initially, to provide a clear overview, the total cohort with anaemia was divided in two main groups (IV versus UC).

The UC group consisted of patients receiving usual care, defined by no IV iron therapy less than 6 weeks prior to surgery. In general, and after the disadvantages of oral iron supplementation, none of the patients awaiting surgery in our center did receive preoperative oral iron therapy. According to the criteria of the Dutch Blood Transfusion Guideline, during the entire study period, a blood transfusion was given according to the 4-5-6 rule, depending on the severity of the anaemia and the condition of the patient. [20]

The IV group consisted of patients receiving IV iron therapy less than 6 weeks prior to surgery, defined by a dose of 1000 to 2000mg iron(III)carboxymaltose (Ferinject) or iron(III)isomaltoside (Monofer). In our institution, a patient blood management protocol (PBM) was implemented in July 2013. Before implementation of this protocol, treatment of preoperative anaemia was heavily depending on the interest in, and knowledge of, PBM of each physician. As a result, there was heterogeneity in the cohort patients with anaemia treated with IV iron therapy before July 2013. As part of the implemented PBM protocol, iron status was measured in all consecutive patients diagnosed with colorectal cancer and treatment with IV iron therapy was considered for patients with anaemia. However, each physician did have the possibility to deviate from the PBM protocol, depending on their clinical assessment. As a result, there was also heterogeneity in the cohort of anaemic patients treated with intravenous iron therapy after July 2013. Due to this heterogeneity, comparing a before- and after July 2013 cohort would not yield relevant results.

In addition, two subgroups (IV vs UC) were formed, in which all factors possibly directly affecting Hb level (i.e. preoperative blood transfusion and neoadjuvant chemotherapy) were excluded. Patients receiving their first IV iron infusion less than 7 days prior to surgery (IV group), and patients receiving IV iron infusion between 6 and 12 weeks before surgery (UC group) were additionally excluded.

Statistical Analyses

To assess the primary outcome, the difference between Hb level at diagnosis and preoperative Hb level were calculated and analysed in the two subgroups. In addition, predictive factors of good response to IV iron were identified. For comparison, chi-square and Mann-Whitney U tests were performed. To assess the association between IV iron therapy and postoperative blood transfusion and complication, all anaemic (i.e. UC + IV group) patients were included in uni- and multivariable logistic regression analyses. Amongst the variables included in the logistic regression analyses is timeframe surgery (2014-2016 vs. 2010-2013), because in the course of time new surgical techniques or procedures could potentially contribute to a decrease in the postoperative blood transfusion and complication rate. A significance level of 0.05 was considered to be significant.

Data Collection

The use of preoperative IV iron therapy and pre-, peri-, and postoperative blood

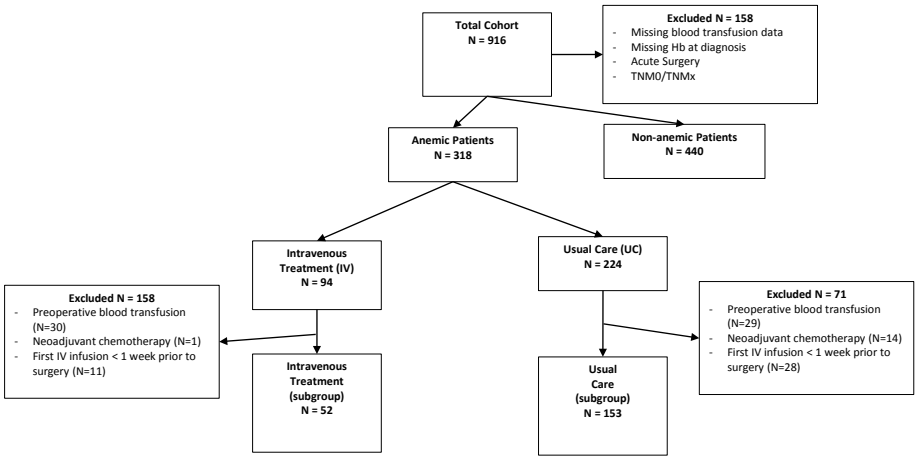
transfusion was retrospectively collected. In this respect, preoperative period was defined as less than 6 weeks before surgery, and postoperative period as less than 30 days after surgery. In addition, Hb values at diagnosis of colorectal cancer, preoperative (i.e. one day before surgery) and postoperative (i.e. one day after surgery) were manually obtained from medical records. Clinical and pathological data, including age, gender, American Society of Anesthesiologists physical status classification (ASA-classification), overall comorbidities (i.e. cardiologic, vascular, diabetes, pulmonic, neurologic, thrombotic, urologic, musculoskeletal, infectious, malignancy, endocrine) tumor type, pathological tumor stage, neoadjuvant treatment, and postoperative overall complications (i.e. pulmonic, cardiologic, thrombotic, infectious, neurologic) were collected by the Dutch Surgical Colorectal Audit, a disease-specific national audit.21 This audit collects information on patient, tumor, treatment, and 30-day and in-hospital outcome characteristics of all patients undergoing a resection for primary colorectal carcinoma in the Netherlands. The data set is based on evidence-based guidelines and is cross-checked on a yearly basis with data from the Netherlands Cancer Registry.

Ethical approval for this study was provided by the Ethical Committee METC Zuidwest Holland (METC-nr 16-012, approved by secretary mw. drs. E. Roep, date of approval 03/02/2016). Our institution, a teaching hospital, is making use of opt-out consent. Each included patient had given consent by not declining to give consent.

Results

In total, 916 patients underwent surgery for colorectal cancer. A total of 158 patients were excluded because of missing data on blood transfusion or Hb level at diagnosis, or surgery in the emergency setting. A total of 318 patients (41.9%) were anaemic at diagnosis, of which 94 patients received intravenous iron treatment and 224 patients received usual care. After excluding all factors possibly directly affecting Hb level, 52 and 153 patients remained in the IV and UC subgroup.

Figure 1. Patient flow diagram



IV versus UC, total anaemic cohort

An overview of the baseline characteristics is presented in table 1. Both groups had a mean age above 70 years (IV=71.8 ±11.1, UC=73.7 ±9.9, p=0.15). In the UC group, the majority was male as compared to the IV group (58.5% vs 44.7%, p=0.02) and there were more patients with comorbidity (87.1% vs 79.8%, p=0.01) and with a rectum tumor (20.5% vs 5.3%, p=0.001). Regarding physical condition, surgical procedure and tumor stage, no significant differences were found. In the IV group, Hb level at diagnosis was significantly lower (6.12 mmol/L vs 6.61 mmol/L, p<0.001) and more patients received a preoperative blood transfusion (31.9% vs

12.9%, p<0.001). Out of 30 IV patients additionally receiving a preoperative blood transfusion, 13 patients (mean Hb level at diagnosis of 5.7 mmol/L) received blood transfusion prior to iron infusion, while in 17 patients (mean Hb level at diagnosis of 5.7 mmol/L) blood infusion was administered after iron transfusion. Mean Hb level at diagnosis was considerably higher in IV patients who did not receive preoperative blood transfusion (6.3 mmol/L).

Table 1. Patient baseline characteristics of all anaemic patients at diagnosis, IV versus UC group

	IV group (n=94)	**UC group (n=224)**	**p-value**
Age (years mean, SD)	71.8 ± 11.1	73.7 ±9.9	0.15
Gender (male) (%)	42 (44.7)	131 (58.5)	0.02
ASA-classification			0.06
I-II	71 (75.5)	145 (64.7)	
III-IV	23 (24.5)	79 (35.3)	
Comorbidity (overall) (%)	75 (79.8)	195 (87.1)	0.01
Tumor localization (%)			0.001
colon	89 (94.7)	178 (79.5)	
rectum	5 (5.3)	46 (20.5)	
TNM stage (%)			0.68
I-II	59 (62.8)	135 (60.3)	
III-IV	35 (37.2)	89 (39.7)	
Surgery			
timeframe			0.06
2010-2013	53 (56.4)	151 (67.4)	
2014-2016	41 (43.6)	73 (32.6)	
laparoscopic (%)	72 (76.6)	153 (68.3)	0.14
Hb (mmol/L)			
at diagnosis (mean, SD)	6.12 ±0.89	6.61 ±0.87	<0.001
Number patients with preop. BT (%) | Hb at diagnosis			<0.001
yes	30 (31.9) | 5.67 mmol/L	29 (12.9) | 5.56 mmol/L	
prior to iron infusion	13 | 5.68 mmol/L	NA	
after iron infusion	17 | 5.67 mmol/L	NA	
no	64 (68.1) | 6.32 mmol/L	195 (87.1) | 6.77 mmol/L	
Number patients with postop. BT (%) | number of units transfused			
yes	10 (10.6) | 28	45 (20.1) | 91	
no	84 (89.4)	179 (79.9)	
Number patients with postop. complication (%)			
yes	24 (25.5)	77 (34.4)	
no	70 (74.5)	147 (65.6)	

Abbreviations: IV = intravenous iron group, UC = usual care group, BT = blood transfusion, preop. = preoperative, postop. = postoperative

IV versus UC, subgroup

An overview of the baseline characteristics is presented in table 2. In total, 105 patients were included (IV=52, UC=153). In the IV group, 32 and 20 patients received a 1000-2000mg dose of iron(III)isomaltoside and iron(III)carboxymaltose, respectively. Both groups had a mean age above 70 years (IV=71.3 ±11.6, UC=74.3 ±9.5, p=0.09). In the UC group, more males were included as compared to the IV group (60.8% vs 44.2%, p=0.04) and there were more patients with a high ASA score (34% versus 19.2%, p=0.04). In the IV group, significantly more patients were operated laparoscopically (82.7% vs 64.7%, p=0.02). Regarding comorbidity, tumor localization and tumor stage, no significant differences were found. In the IV group, Hb level at diagnosis was significantly lower (6.3 mmol/L vs 6.9 mmol/L, p<0.001).

Patients with intravenous iron treatment showed a significant higher increase of Hb level as compared to patients with UC (IV=0.65 mmol/L vs UC=0.10 mmol/L, p<0.001). In identifying characteristics associated with Hb level response after iron infusion, patients receiving one dose of iron infusion (1000mg) were classified into high and poor responders. A cut-off value of 0.6 mmol/L (i.e. median Hb level increase) was used (table 3). In total, 33 patients were included (high responder=17, poor responder=16). No significant differences were found for age, gender, ASA score, comorbidity, tumor localization and tumor stage. Regarding iron status at diagnosis, high responders showed more distinct signs of anaemia and iron deficiency as compared to poor responders (high versus poor responder, median values: Hb 6.0 mmol/L vs 6.8 mmol/L, transferrin saturation (TSAT) 5.3% vs 11%). In addition, increased transferrin (median 2.9 g/L vs 2.7 g/L), and decreased ferritin (median 12 µg/L vs 27 µg/L) levels were found in the high responder group.

Association between intravenous iron therapy and postoperative complications and blood transfusions

All anaemic patients, as presented in table 1, were included in logistic regression analyses. In univariable analysis, preoperative intravenous iron administration (OR=0.47, 95%CI 0.23 to 0.99, p=0.04) was observed to prevent the administration of postoperative blood transfusion. No significant result was found in multivariable analysis (OR=0.54, 95%CI 0.24 to 1.21, p=0.14) (table 4). In both uni- and multivariable analysis, no advantageous effect was found on postoperative

complications (OR=0.66, 95% CI 0.28 to 1.12, p=0.12 and OR=0.91, 95%CI 0.50 to 1.68, p=0.77, respectively) (table 5).

Table 2. Patient baseline characteristics and outcome, IV versus UC subgroup

	IV (n=52)	**UC (n=153)**	**p-value**
Characteristics			
Age (years mean, SD)	71.3 ± 11.6	74.3 ± 9.5	0.09
Gender (male) (%)	23 (44.2)	93 (60.8)	0.04
ASA-classification			0.045
I-II	42 (80.8)	101 (66.0)	
III-IV	10 (19.2)	52 (34.0)	
Comorbidity (overall) (%)	11 (21.2)	21 (13.7)	0.20
Tumor localization (%)			0.08
colon	48 (92.3)	126 (82.4)	
rectum	4 (7.7)	27 (17.6)	
TNM stage (%)			0.36
I-II	34 (65.4)	89 (58.2)	
III-IV	18 (34.6)	64 (41.8)	
Surgery			
timeframe			0.31
2010-2013	31 (59.6)	103 (67.3)	
2014-2016	21 (40.4)	50 (32.7)	
laparoscopic (%)	43 (82.7)	99 (64.7)	0.02
Haemoglobin (mmol/L)			
at diagnosis (mean, SD)	6.3 ± 0.8	6.9 ±0.7	<0.001
Outcome			
Haemoglobin(mmol/L)			
increase diagnosis-preop. (mean, SD)	0.65 ±0.74	0.10 ±0.74	<0.001

Abbreviations: IV = intravenous iron group, UC = usual care group, preop. = preoperative

Table 3. Patient baseline characteristics high responder (=>0.6 mmol/L Hb increase) versus poor responder (<0.6 mmol/L Hb increase), receiving 1 dose iron infusion (1000mg)

	IV high responder (n=17)	**IV poor responder (n=16)**	**p-value**
Age (years mean, SD)	69.3 ±13.1	73.6 ±9.0	0.28
Gender (male) (%)	5 (29.4)	5 (31.2)	0.91
ASA-classification			1.0
I-II	13 (76.5)	13 (81.2)	
III-IV	4 (23.5)	3 (18.8)	
Comorbidity (overall) (%)	14 (82.4)	12 (75.0)	0.69
Tumor localization (%)			0.60
colon	16 (94.1)	14 (87.5)	
rectum	1 (5.9)	2 (12.5)	
TNM stage (%)			0.62
I-II	12 (70.6)	10 (62.5)	
III-IV	5 (29.4)	6 (37.5)	
Iron status at diagnosis (median; IQR - mean ± SD)			
Hb (mmol/L)	6.0; 1.5 – 6.2 ±0.8	6.8; 1.1 – 6.6 ±0.7	
TSAT (%)	5.3; 4.6 – 7.3 ± 4.6	11; 15 – 16.3 ±14.3	
transferrin (g/L)	2.9; 0.4 – 3.1 ±0.5	2.7; 0.2 – 2.7 ±0.4	
ferritin (µg/L)	12; 27 – 36 ±52	27; 67 – 142 ±360	

Abbreviations: IV = intravenous iron group, TSAT = transferrin saturation

Table 4. Regression analysis on relationship between preoperative intravenous iron and postoperative blood transfusion in anaemic patients (n=318)

		univariable			**multivariable**	
	OR	**95% CI**	**p-value**	**OR**	**95% CI**	**p-value**
Age (years)	1.02	0.99 - 1.05	0.23	1.02	0.99 - 1.06	0.26
Gender						
female vs. male	0.69	0.38 - 1.26	0.23	0.52	0.27 1.04	0.06
Comorbidity (overall)	1.27	0.54 - 2.99	0.59	1.04	0.39 2.74	0.94
ASA-classification						
III-IV vs. I-II	1.84	1.01 - 3.33	0.045	1.77	0.89 - 3.53	0.11
TNM stage						
III-IV vs. I-II	0.72	0.39 - 1.33	0.30	0.66	0.34 - 1.28	0.22
Surgery						
laparoscopic versus open	0.51	0.28 - 0.92	0.026	0.55	0.28 - 1.06	0.08
Tumor localization						
rectum vs. colon	1.03	0.47 - 2.26	0.94	1.10	0.98 - 1.24	0.12
Timeframe surgery						
2014-2016 vs 2010-2013	0.69	0.37 - 1.30	0.25	0.65	0.32 - 1.32	0.24
Preoperative Hb (0.1 mmol/L increase)	0.48	0.33 - 0.69	<0.001	0.40	0.26 - 0.60	<0.001
Preoperative intravenous iron	0.47	0.23 - 0.99	0.046	0.54	0.24 - 1.21	0.14

Table 5. Regression analysis on relationship between preoperative intravenous iron and postoperative complications in anaemic patients (n=318)

		univariable			**multivariable**	
	OR	**95% CI**	**p-value**	**OR**	**95% CI**	**p-value**
Age (years)	1.01	0.99 - 1.03	0.51	1.02	0.99 - 1.04	0.30
Gender						
female vs. male	0.43	0.26 - 0.70	0.001	0.36	0.20 - 0.63	<0.001
Comorbidity (overall)	0.67	0.35 - 1.26	0.21	0.48	0.23 - 0.99	0.049
ASA-classification						
III-IV vs. I-II	1.54	0.94 - 2.53	0.09	1.62	0.90 - 2.90	0.11
TNM stage						
III-IV vs. I-II	0.76	0.47 - 1.25	0.28	0.58	0.34 - 1.00	0.050
Surgery						
laparoscopic versus open	0.33	0.20 - 0.55	<0.001	0.32	0.18 - 0.55	<0.001
Tumor localization						
rectum vs. colon	1.09	0.58 - 2.06	0.79	1.03	0.94 - 1.13	0.54
Timeframe surgery						
2014-2016 vs 2010-2013	0.99	0.60 - 1.62	0.96	0.94	0.54 - 1.63	0.81
Preoperative Hb (0.1 mmol/L increase)	1.12	0.85 - 1.47	0.44	1.08	0.79 - 1.48	0.65
Preoperative intravenous iron	0.66	0.38 - 1.12	0.12	0.91	0.50 - 1.68	0.77

Discussion

The present study illustrates the efficacy of IV iron therapy in the optimization of preoperative Hb level in colorectal cancer patients with anaemia, as compared to usual care. We found that IV iron therapy is most effective in patients presenting with more severe anaemia, and with higher transferrin and lower ferritin levels, markers for an AID, as compared to FID. In present study, the distinct Hb increase after iron infusion did not translate into an expected decrease in the percentage of patients with a postoperative blood transfusion. This is most likely due to the confounding effect of preoperative blood transfusions, which could not be adequately corrected for in this retrospective cohort. Our observed perioperative blood transfusion rates are fairly comparable with the perioperative blood transfusion rates presented in other large cohort studies[22, 23], and our results, therefore, could legitimately be generalized.

Our results add to a growing body of evidence in the literature demonstrating the efficacy of preoperative IV iron therapy in colorectal cancer patients and contribute to the ongoing debate whether preoperative IV iron therapy is improving postoperative outcome. Our results are consistent with the results of a prospective randomised trial by Keeler et al., comparing the effect of preoperative oral versus IV iron in anaemic colorectal cancer patients.[24] No overall benefit was seen with IV iron in reducing blood transfusions and postoperative complications, despite the fact that in the study by Keeler et al. oral iron administration represented usual care. However, in addition to the study by Keeler et al., we also identified patient characteristics associated with haemoglobin level response after iron infusion. Evidently, higher transferrin and lower ferritin levels, markers for absolute iron deficiency, were associated with a higher haemoglobin level response after iron infusion. Increased ferritin level, a marker for functional iron deficiency, could be the cause of poor haemoglobin level response after iron infusion. In this respect, increased uptake and retention of the administered intravenous iron within cells of the reticuloendothelial system may lead to a poor availability of administered iron for erythropoiesis.[8] Therefore, these results stress the importance of distinguishing between the two types of iron deficiency and emphasize the efficacy of intravenous iron namely in patients with absolute iron deficiency. It is noteworthy that in present international guidelines on the treatment of anaemia in oncological patients a distinction between type of iron deficiency is already made: IV iron

should be withheld in patients with an active infection and/or if serum ferritin exceeds 1000 μg/L [25, 26]. Despite this, in current clinical practice, no distinction is made between type of iron deficiency. Ongoing and future randomised clinical trials have to establish whether the optimization of preoperative haemoglobin level by preoperative IV iron therapy is resulting in improved postoperative outcome.[11, 13]

Strength and limitations

A key strength of our study is the identification of patient characteristics associated with haemoglobin level response after iron infusion in colorectal cancer patients. To our knowledge, this is the first study identifying the potential clinical relevance of identifying the type of ID in the treatment of preoperative anaemia not only with oral iron but even with IV iron.

The main limitations of our study are three-fold, leading to key recommendations for future research. First, this study represents a retrospective cohort of consecutive patients, involving several limitations. The significant differences between the IV iron and UC group (e.g. baseline Hb levels and timeframe surgery) could, despite correction in the multivariable regression analyses, potentially indicate selection bias and have significant impact on the outcome. Moreover, iron status was not consistently monitored in each patient. The past years, great efforts have been made to optimize the results of colorectal cancer surgery. In addition to surgical techniques and procedures[9, 10, 27] blood transfusion strategy, as part of patient blood management (PBM), has changed in the course of time. In this regard, the optimal transfusion threshold, dosing, and age of red blood cell (RBC) units have been studied. Presently, a restrictive transfusion threshold is recommended for hospitalised adult patients and seems to be safe in the oncological setting.[28, 29] Moreover, standard-issue RBC units rather than fresh RBC units (storage length, <10 days), and, to initiate, 1 rather than 2 RBC units are advised.[29] Although we corrected our results for the year of treatment, the combined efforts to optimize colorectal cancer care (e.g. centralization, protocols, laparoscopy) might have contributed differently to the results. This emphasizes the importance of performing a randomised controlled trial comparing usual care (i.e. no therapy or oral iron) with IV iron supplementation in colorectal cancer patients, in which, importantly, IV iron has to be administered as early as possibly, preferably at least three weeks prior to surgery for its optimal effect[11].

Second, this study focused specifically on preoperative treatment of anaemia. However, investigation and treatment of merely haemoglobin levels appears to be a suboptimal way to indicate overall performance and therefore, presently, various multimodal programs are being introduced. [30, 31] The use of such various modalities could be valuable in preoperative prehabilitation, specifically in elderly patients (>75 years), in which an increased 1-year mortality of up to 25% is observed.[32, 33] In line with the previous limitation, in present study, various multimodal programs may similarly introduce confounding of our results that are not easily corrected for. A randomised trial could correct for both continuing pre- as well as postoperative care optimization.

The third limitation was that only short-term effects of IV iron therapy were studied. In this respect, iron is an important growth factor for rapidly proliferating cells, including bacteria and tumor cells.[8, 34] Several animal experiment studies have shown exposure to iron to be a risk factor for developing colorectal cancer and tumor growth.[35, 36] In this regard, intraluminal colorectal tumors might be more affected by oral iron administration, while IV iron with a higher risk of non-transferrin bound serum iron and reactive oxygen species presence might also influence systemic tumor growth. Randomised trials on the short-term benefits versus the potential long-term hazards of iron therapy in colorectal cancer patients should therefore acknowledge the type of anaemia and the associated choice of iron therapy.

Conclusion

We were able to show that implementation of IV iron therapy leads to optimization of preoperative Hb level. Furthermore, we showed the importance of assessing the type of ID. Iron infusion is most effective in patients with more severe anaemia and with higher transferrin and lower ferritin levels, markers for AID, as compared to FID. Following the optimization of preoperative Hb level, strikingly, no significant decrease in the percentage of patients with a postoperative blood transfusion and postoperative complication were observed. However, from present cohort study, due to its retrospective nature, we cannot entirely conclude that IV iron and the associated Hb increase does decrease the postoperative blood transfusion and complication rate. Future randomised trials are thus required to not only establish the short-term benefits, but also the potential long-term hazards of preoperative IV iron therapy in colorectal cancer patients.

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Part III

The Fit4Surgery approach

9

Improving outcomes in oncological colorectal surgery by prehabilitation

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Abstract

Introduction

The cornerstone in the treatment of colorectal cancer is surgery. A surgical event poses a significant risk of decreased functional decline and impaired health related quality of life. Prehabilitation is defined as the multimodal preoperative enhancement of a patient's condition. It may serve as a strategy to improve postoperative outcomes. Prehabilitation requires a multidisciplinary effort of medical health care professionals and a behavioral change of the patient.

Methods

The goal of prehabilitation is threefold: first, to reduce postoperative complications, second, to enhance and accelerate the recovery of the patient and third, to improve overall quality of life. In this article, we introduce the FIT-model illustrating a possible framework towards the implementation of both evidence-based and tailor-made prehabilitation for patients undergoing surgery for colorectal cancer.

Results

The model is comprised of three pillars: 'Facts' (how to screen patients and evidence on what content to prescribe), 'Integration' (data of own questionnaires assessing motivation of patients and specialists) and finally 'Tools' (which outcome measurements to use).

Discussion

Developing implementable methods and defining standardized outcome instruments will help to establish a solid base for patient centered prehabilitation programs. Any party introducing prehabilitation requiring multidisciplinary teamwork and behavioral change can potentially use this framework.

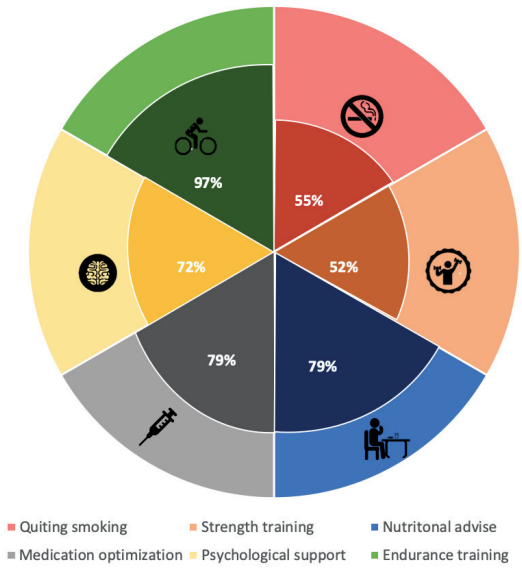
Introduction

Colorectal cancer is the third most common type of cancer in men and the second most common in women, with over 1,3 million new cases diagnosed annually worldwide. Over 80 per cent of these patients are over 60 years old.[1] Currently, surgery remains the cornerstone of treatment. However, the physical stress associated with surgery brings significant morbidity and mortality, especially in patients with diminished physical reserves.[2,3]

The rate of complications is considerably increased (up to 50%) in vulnerable patients.[4] These vary from minor wound infections to more severe adverse events such as prolonged ileus and anastomotic leakage.[5] On the short term, these complications impede early mobilization and discharge his original residency. Moreover, on the long term, they pose a risk to the patient's survival and quality of life on the long term. Recent studies have identified several modifiable risk factors for complications in patients undergoing colorectal surgery (such as malnutrition, poor functional capacity, cigarette smoking, anemia, and anxiety).[6,7,8,9] The preoperative period can serve as a window of opportunity to enhance the condition of high-risk patients and consequently decrease surgery-associated morbidity and mortality.[10,11]

This preoperative enhancement has been coined prehabilitation and can consist of any form of patient optimization before surgery.[12] The research group of Carli et al. has proposed a model illustrated in figure 1, demonstrating the potential benefit of prehabilitation.[13] The enhanced recovery after surgery (ERAS) program has significantly accelerated recovery and made patients less care dependent on high level care after surgery.[14,15] However, ERAS specifically focuses on the postoperative period and only starts 48 hours prior to operation. Prehabilitation can shift the classic 'waiting period' to a time frame in which patients can influence their own treatment outcomes. The waiting period prior to surgery is a salient time for patients to improve their lifestyle choices. The patient's functional capacity may thereby be improved before surgery, leading to a smaller decline of function during the postoperative period and possibly even faster recovery.[13]

Figure 1. Prehabilitation model according to Carli[3]

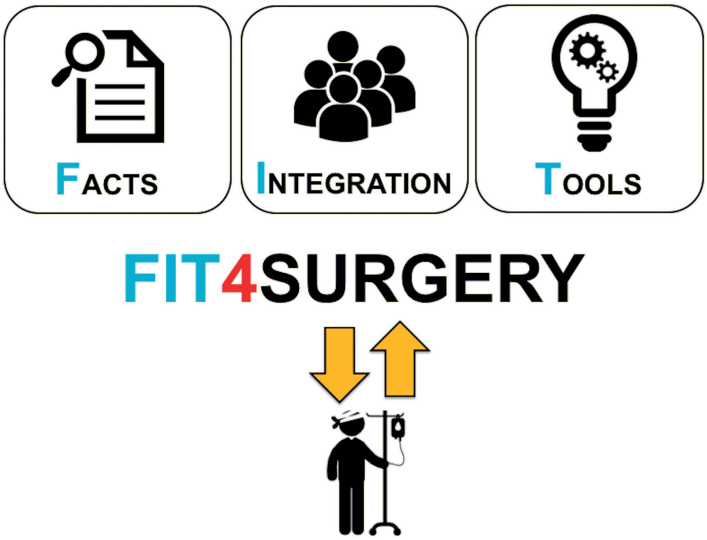


The goal of prehabilitation is threefold: first, to reduce postoperative complications, second, to enhance and speed up recovery and third, to improve overall health related quality of life (HRQoL). To date, research has been performed on single modal programs mostly focusing on nutritional status or exercise training as is also demonstrated in our previous systematic review on physical prehabiliation.[16] However, taking into account the multifactorial origins of a patient's vulnerability, a multimodal approach combining nutritional support, exercise training, psychological support, smoking cessation and anemia correction, might be more effective, as is hinted pilot studies of Chia and Gillis and several larger studies of which protocols have been published.[17–19]

Prehabilitation requires the multidisciplinary collaboration of medical experts and to support behavioral changes of a patient. Optimal implementation will be indispensable to ensure optimal compliance amongst patients. This narrative review introduces the FIT-model (Facts, Integration, Tools) to assess the current screening methods, prehabilitation contents, user assessment and outcome measurement of prehabilitation in patients undergoing surgery for colorectal cancer (figure 2). In *Facts*, we describe the need for triage and the different

components considered essential in a multimodal prehabilitation program. In *Integration,* we present questionnaires which we used to assess the motivation of patients and specialists regarding prehabilitation. In *Tools*, we describe the available outcomes measurements.

Figure 2. The FIT-model



Facts - prehabilitation screening and contents

Based on the prehabilitation hypothesis, patients with poor overall wellbeing may benefit most from a prehabilitation program. In some cases, surgical intervention should be reconsidered, or surgery should be postponed to substantially improve the patients' functional capacity. Currently, five modifiable risk factors have been described in colorectal cancer surgery: poor functional capacity, malnutrition, cigarette smoking, anemia and anxiety. [6,7,8,9] Although there are more modifiable risk factors such as social economic state, support system, we would like to focus on the five key elements mentioned above since they have a great impact within a short timeframe. Furthermore, a synergistic effect is to be expected that will also have a domino effect on other risk factors (e.g. better physical condition will facilitate patient to increase activity radius which can possibly lead to more social interaction).

Physical Condition

Screening

Declined preoperative functional capacity is an independent risk factor for postoperative complications and delayed recovery in patients undergoing colorectal surgery.[20,21] Impaired functional capacity (decreased muscle performance, poor cardiorespiratory state) leads to impaired functional performance. Especially older patients are at an increased risk for adverse outcome due to comorbidities, sarcopenia and functional impairment.[22] Physical performance can be assessed in multiple ways, ranging from questionnaires (e.g. KATZ-ADL), to physical tests (grip strength, cardiopulmonary exercise testing [CPET], 6-minute walk test [6MWT]).

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Preoperative exercise interventions can increase physical performance in colorectal cancer patients.[23,24] Current physical programs vary from a complete training program involving both cardiorespiratory exercises combined with strength training in a sports facility to at-home exercise programs.[25–27] Since physically frail patients are often not used to exercise on a daily basis, researchers should strive to construct a feasible but exerting workout[28]. Even though a research setting often demands a standardized intervention, it should be the aim of investigators to develop methods in which it is possible to adapt the training to the patient's baseline condition.

Nutrition

Screening

About 55% of all patients and 25-40% of surgical patients are undernourished on admission to the hospital[29,30],[31]. Moreover, malnutrition is further intensified during hospitalization especially in patients undergoing major surgery.[32] Malnutrition has been recognized as an independent risk factor for perioperative morbidity and severe postoperative complications.[33,34] Nutritional support is therefore recommended, sometimes even in seemingly well-nourished patients to target relative deficiencies (e.g. protein).[35–37] There are various screening instruments to assess nutritional state of which the Patient-Generated Subjective Global Assessment Short Form (PG-SGA SF) is an example of a screening tool that can be used to identify malnutrition. It is an internationally validated instrument that identifies malnutrition in oncologic patients by assessing weight loss, comorbidity, metabolic stress combined with a physical examination.[38,39] The Short Nutritional

Assessment Questionnaire (SNAQ) is another validated instrument to identify patients at risk for postoperative complications due to a poor nutritional state (also in non-oncological patients).[40] The SNAQ score consists of three questions assessing weight loss, appetite and need for supplemental nutrition such as parental or tube feeding. A recent study showed that a score >3 is specifically associated with postoperative complications in patients undergoing surgery for colorectal cancer.[9]

More specifically in the case of colorectal cancer patients, it should be noted that impaired nutritional status can also refer to a state of relative protein deficiency which manifests itself as sarcopenia or loss in lean body mass.[41] Sarcopenia is defined as a combination of loss of muscle mass and muscle strength.[42] Importantly, it is often not detected with standard malnutrition screening tools that measure low body mass index (BMI) or recent weight loss, as many sarcopenic colorectal cancer patients are overweight or obese.[43] Various methods to screen for sarcopenia have been described by the European Working Group of Sarcopenia in Old People (EWSGO) including measurement of psoas density on CT-scan, hand grip strength measurement etc.[44]

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It is not only challenging to measure the contents of a patient's diet, but also to interfere with it. Diets are notoriously difficult to adhere to and each patient will likely require tailor-made optimization. Regarding protein intake, the European Society of Enteral and Parenteral Nutrition (ESPEN) advices a total of 1.5g/kg/day in cancer patients.[43] Recent studies aim for a total protein intake of 1.5 to 1.8 g/kg/day.[17] The daily estimated habitual protein intake can be estimated and a dietary specialist can provide patients with a tailored dietary advice aiming at a total intake of two portions of 20-40g/protein a day. Since colorectal cancer patients are often able to eat normally, severe cachexia requiring tube or parenteral feeding is not frequently encountered.

At the level of micronutrients, vitamin D is associated with muscle mass and muscle strength.[45] Vitamin D will be supplied daily immediately after cancer diagnosis according to guidelines of the World Health Organization (10µg for men <70 years and for women aged 50-69 years or for women <50 years with coloured skin or little sun exposure, and 20µg for women and men aged 70 years and older). Many

elderly patients may have other micronutrient deficiencies or ingest vitamins and minerals below recommended doses before and after surgery.[46] Therefore, it may be recommended to provide the patients with a multivitamin/mineral supplement.

Smoking

Screening

Cigarette smoking is a well-known risk factor for postoperative complications.[47] Smoking has a transient effect on the tissue microenvironment and a prolonged effect on inflammatory and reparative cell functions leading to delayed healing and complication.[48] Wound contraction and collagen metabolism are also affected by a smoking-induced alteration in vitamin C turnover and by a change in inflammatory cell response.[47] Evidence has shown that preoperative smoking cessation interventions reduce postoperative morbidity. [49]

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A period of 4 to 8 weeks smoking cessation prior to surgery has already been shown to significantly reduce postoperative complications and morbidity.[49] Patients may be referred to institutes that can help them to stop smoking. Successful smoking cessation may be achieved in just a few weeks as long as the patient is offered a combination of intensive counseling and nicotine replacement therapy.[50]

Anemia

Screening

Preoperative iron deficiency anemia is associated with increased morbidity and mortality.[51,52] Furthermore, anemia is associated with overall fatigue and impaired physical performance.[53] As the most common cause of anemia in colorectal cancer patients in case of iron deficiency anemia, low hemoglobin levels (men <8g/dl, women< 7.5g/dl) should be assessed in combination with low ferritin (<10ug/l) and low transferrin saturation (<16%) levels.[54]

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Patients should be preoperatively screened to identify insufficient hemoglobin levels. In case of iron insufficiency, optimization of hemoglobin levels using iron injections is preferable. Oral iron supplementation suffers from low compliancy and has more side effects whereas red blood cell transfusions are associated with higher perioperative morbidity and inferior long-term oncological outcomes.[55,56]

The specific dose is calculated according to the severity of anemia and the weight of the patient.[57][55],[56] By using iron injections, anemia may be corrected in a relatively short timeframe. In order to first achieve sufficient hemoglobin levels, postponing surgery may also be considered. Importantly, an optimal hemoglobin level may enhance patients' fitness levels, thereby also allowing for optimal exercise training.

Anxiety and mood disorders

Screening

Psychological status (mood, motivation, knowledge) may also play an important role in surgical recovery. It is well documented that patients awaiting major surgery experience anxiety concerning their upcoming operation, its outcome, and their course of healing and recovery.[58,59] They may also feel depressed, hold unrealistic expectations (overly optimistic or pessimistic) about their health status, and possess inadequate strategies for coping in the pre- and postoperative periods. Any of these factors may influence pain and interfere with postoperative functioning.[60] Furthermore, high levels of cortisol induced by anxiety might have a negative effect in muscle strengthening.[61] Various instruments have been developed to assess mood and anxiety state. The Generalized Anxiety Disorder (GAD)-7 questionnaire for anxiety, the Patient Health Questionnaire (PHQ)-9 for depression and the Hospital and Depression Scale (HADS) combining both are examples of international validated questionnaires. The GAD-7 is a valid and efficient tool for screening for generalized anxiety disorder and assessing its severity in clinical practice and research.[62] The PHQ-9 including nine questions is half the length of many other depression measures, has comparable sensitivity and specificity, and consists of the actual nine criteria on which the diagnosis of DSM-IV depressive disorders is based.[63] HADS is a 14-question measure with seven items each for depression and anxiety.[64] It generates separate scores for anxiety and depression as well as a combined score of psychological distress and has been shown to have good psychometric properties for factor structure, homogeneity, and internal consistency and has been used in studies of patients with a variety of healthcare problems.[65]

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Patients can experience stress and anxiety prior to and after surgery. Cognitive training in the form of psychological counselling, meditation or yoga can reduce

anxiety and stress perioperatively.[60] Furthermore, providing the patient with detailed information of the upcoming treatment and course of hospitalization and the opportunity to contact former colorectal cancer patients can reduce preoperative anxiety.[66]

A summary of all screening methods and interventions is provided in Table 1.

Table 1. Prehabilitation Content Elements

Content	Measurement	Intervention	Compliance
Exercise Cardiovascular Strength Functional	6MWT*, CPET*, TUG* Muscle Mass, Hand Grip Strength KATZ-ADL*	3x/week HIT* 30 min bicycle Strength 10-15 min arms (flex/ext), trunk (chair rise), legs (knee raising, heel raises), 6-10 reps, 1-2 reps	Activity Tracker (e.g. Actigraph) (Digital) Diary
Nutrition Protein intake Micronutrients	MNA*, SNAQ*, PG-SGA* Diary	2x day snack/supplement containing 40g protein, 1.5-1.8g/kg/protein/day multivitamin supplement	(Digital) Diary Product registration
Psychological Anxiety Depression Knowledge Social	GAD-7*, HADS* PHQ-9*, HADS* Patient interview Anamnesis	Psychological counseling, meditation, yoga Information sessions, Former patient contact	Daily logging of mood
Smoking	Anamnesis	Personalized counseling	(Digital) Diary Intoxication Screening
Anemia	Hemoglobin Transferrin saturation	Diet optimalisation Iron supplementation	Medication accountability tracking

* 6MWT= six minute walking test[72], CPET=cardiopulmonary exercise test[73], TUG=Timed Up and Go[74], KATZ-ADL=questionnaire about daily living dependency[21], HIT=high intensity interval training[75], MNA=Mini Nutritional Assessment[76], SNAQ=Short Nutritional Assessment Questionnaire[43], PG-SGA=Patient-Generated Short Global Assessment[42], GAD-7= Generalized Anxiety Disorder Assessment[67], HADS=Hospital and Depression Scale[70], PHQ-9=Patient Health Questionnaire[68]

Integration: implementation in the field

In order to achieve successful integration and implementation of a prehabilitation program, behavioral change is required in both patients and those providing the care. Therefore, we investigated the attitude of patients and surgeons towards prehabilitation.

Patients

In 2016-2017, a prehabilitation pilot study in patients undergoing colorectal surgery for cancer took place in Maxima Medical Center, Veldhoven/Eindhoven, the Netherlands (NL54547.015.15, submitted data). This pilot study was initiated to test the feasibility and safety of a multimodal prehabilitation program at both patient and organizational level.

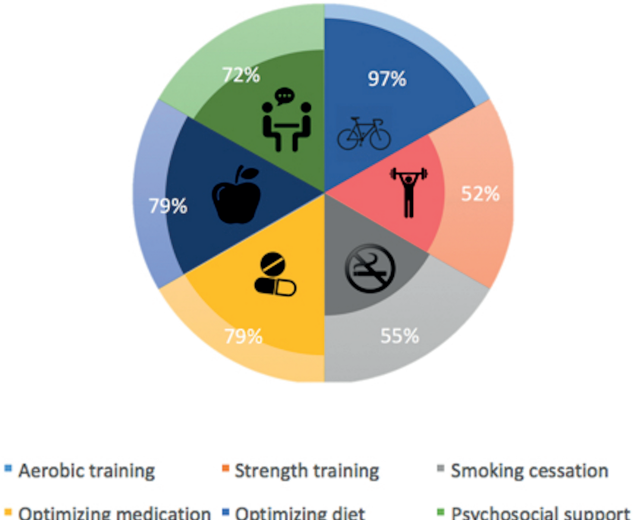
Fifty patients were assigned to intervention (n=20) or control group (n=30). They participated in a multimodal prehabilitation of four weeks in hospital physical training (high intensity endurance and strength training, 3x per week), tailored dietary advice and supplements (total protein intake of 1.5 to 1.8 g/kg/day, 0.4 gram/kg/day after strength training and daily before sleep, 50% of recommended daily allowance for multivitamins, and extra vitamin D), a smoking cessation program (including intensive counselling and any nicotine replacement therapy), and psychological support (one session at the psychologist providing strategies to cope with stress and anxiety). Perioperative care and rehabilitation were given according to the ERAS guidelines.[67] Four weeks after surgery, patients were asked to give feedback on the prehabilitation program.

Evaluation of the program showed high patient appreciation. The attendance rate to the weekly training sessions by the physiotherapist was 88% and patient satisfaction was high (4 on a scale of 1 to 5). Reasons for joining the prehabilitation program were the motivation to optimally prepare for surgery (90%), distraction from the disease in the period before surgery (70%), and to be able to self-manage and change the condition (90%). Overall, these results suggest that prehabilitation could be of additional value to patients undergoing colorectal cancer surgery. A full description of the pilot study is provided in the original article.

Colorectal surgeons

In 2016, a questionnaire was distributed to explore colorectal surgeons' intentions to cooperate in prehabilitation programs. Dutch colorectal surgeons were contacted via email to respond to an online questionnaire (Supplementary Table 1 in original article). A link to the survey was also distributed via the online newsletter of the Dutch Colorectal Cancer Group. The questionnaire contained items related to the surgeons' attitudes concerning the content, the design and the delivery of prehabilitation programs. Descriptive statistics were used to analyze these data. A total of 29 colorectal surgeons responded (27% response rate). Prehabilitation was considered an essential part of optimal care by 93% of the surgeons. Aerobic training (97%), optimization of medication (79%) or improved nutrition (79%) were the most popular forms of prehabilitation. A total of 86% were willing to postpone the operation in order to optimize the patient. Seventy-six percent considered a period of 2-4 weeks sufficient, and 93% agreed that insurance companies should cover the costs of prehabilitation. A prehabilitation program was available in 15 of the 29 responding hospitals (52%) and consisted most often of optimization of medication (80%), smoking cessation (60%) and/or psychosocial support (60%). A total of 90% of the surgeons was willing to participate in research on prehabilitation. Seven hospitals (24%) were already performing research.

Figure 3. Prehabilitation contents according to questionnaire performed among Dutch colorectal surgeons.



Networks

In 2016, the Fit4Surgery project group was founded in The Netherlands with the aim of creating the first online platform bringing together scientific evidence, clinical expertise and evidence/data from all other stakeholders (ranging from personal trainers to supermarkets). The merging of clinical, scientific and personal data will result in the design of an optimal multimodal prehabilitation program for each individual patient facing surgery. The current state of the healthcare system is characterized by divided coordination and the lack of overview for the individual patient. The Fit4Surgery platform aims to be a wisely accessible platform, providing all knowledge and tools required to participate in prehabilitation. The Fit4Surgery platform focuses on patients' interests and the empowerment of caretakers, thereby exceeding organizational, political and financial incentives.

Future prehabilitation may not take place within the hospital. To achieve sustainability in healthcare, it in the interest of all to aim for more cost-effective quality, prevention of disease, and the introduction scalable healthcare solutions. Although the targets seem clear, and do fit the prehabilitation concept completely, there is still a gap towards clinical practice. To facilitate these changes a new collaboration has to be created between the different parties, such as hospitals, patient organizations, health insurance companies, technical developers for patient monitoring devices and business developers to support the financial plans and business modal. In this way, we may achieve a prehabilitation concept which may improve sustainability in treatment for a large number of patients.

Tools: outcome measurement

The goal of prehabilitation is threefold: first, to reduce postoperative complications, second, to enhance and speed up recovery and third, to improve overall quality of life. The chosen instruments to measure outcome should reflect these three dimensions. Furthermore, measuring compliance to the prehabilitation program is vital to ensure its effect. Based on previous literature on prehabilitation, we propose validated and frequently used measurement instruments in each domain.

Compliance

Since prehabilitation is a behavioral intervention, adherence and correct implementation of the intervention might be a challenge. It is therefore recommended that research groups objectify adherence to specific prehabilitation

contents.[68] Compliance can be defined as the percentage of attendance to the prehabilitation program (e.g. attendance to training sessions or exercise modalities, compliance to protein intake). Besides compliance, a sufficient quality of execution or so-called fidelity will be essential in order for the program to be successful.[68] Furthermore, measuring compliance for scientific purposes is important but it should be noted that a prehabilitation program is also largely based on the patient's intrinsic motivation. An overly present paternalistic approach with police-like compliance measurement can be potentially harmful.

Regarding the different components of prehabilitation, both active and passive ways to register compliance and fidelity remain scarce. Physical activity can be easily quantified by wearables with sensors. However, adequate methods to monitor nutritional intake, smoking cessation and adherence to a psychological program without too much interference with the patient's daily life remain to be a field of pioneering research for the years to come.[69,70]

Reduction of postoperative complications

Considering the use of postoperative complications as a measurement tool, it should be noted that the definitions for complications are extremely heterogeneous between studies. For example, one of the most serious complications of colorectal surgery is anastomotic leakage and currently no consensus on the definition exists.[71] Therefore, it might be of more use to implement the Comprehensive Complication Index (CCI) which calculates the sum of morbidity and mortality presented on the Clavien-Dindo scale.[72] Since the CCI assesses the resulting action that was undertaken to treat a complication, interference due to heterogeneity of definitions is diminished.

Enhancement of recovery

At minimum, the goal after surgery is to return the patient to his original level of functioning prior to diagnosis. Cardiopulmonary exercise testing serves as a gold standard in measuring physical performance. It provides an objective assessment of the integrative exercise responses involving the pulmonary, cardiovascular, and skeletal muscle systems, which are not adequately reflected through the measurement of individual organ system function.[73] Overall recovery is currently expressed in standardized tests such as the 6-minute walk test which has been proven to be strongly correlated with postoperative outcomes in colorectal surgery.[74,75]

However, it remains a major challenge to develop a validated outcome instrument that allows patients to track their progress according to their own baseline rather than a population-based mean. Previous literature has introduced the concept of "time to return to normal activities", in which normal activities (e.g. getting dressed, cycling, shopping for groceries) are defined by a comprehensive item bank (Supplementary Table 2 in original article) reflecting physical performance based on information from validated patient reported outcomes measurements.[76,77] Ideally, information regarding functional performance could be registered by activity diaries or passively by using sensors and mobile devices.

Increasing quality of life

Questionnaires remain to be the most frequently used and validated way to assess quality of life in patients. In colorectal surgery, the EORTC-QLQ-CR29/C30, including physical, emotional and social functioning and mobility and overall well-being, is most commonly used.[78] Overall quality of life can be measured by the Short Form Health Survey (SF-36) questionnaire.[79]

Conclusion

The preoperative period maintains a window of opportunity to address modifiable risk factors such as nutrition, functional capacity, anemia, cigarette smoking and mood/anxiety and to optimize a patient's condition prior to surgery. This can be achieved by implementing a prehabilitation program, defined as the multimodal preoperative enhancement of a patient's condition. The goal is to reduce postoperative complications, to enhance recovery and to improve overall quality of life. This review offers an integrative FIT-model (Facts, Integration, Tools) in order to successfully investigate and implement prehabilitation in the coming years. Facts comprises all the evidence that has been gathered in scientific research and by platforms on which patients can track their progress. Integration includes efforts to establish a continuous dialogue between patients and medical experts in order to identify potential bottlenecks and deal with them in an agile way. Furthermore, integration involves the development of online platforms that gather facts and feedback and can offer both an overview of all the available evidence and a tailormade program for every patient.

Lastly, Tools refers to the development of all instruments and methods to create evidence and implement prehabilitation. These can vary from research methods

to measure progress to devices that allow the patient to perform prehabilitation at home. The basis of the current prehabilitation method should focus adjusting modifiable risk factors such as malnutrition, poor physical state, smoking, anemia and poor cognitive state. However, a standard prehabilitation program should only serve as a starting point. A tailored approach focusing on specific individual risk factors of each patient could potentially be more effective. Future research should focus on the value of prehabilitation as optimal preparation for colorectal surgery and other abdominal surgical procedures. Developing implementable methods and defining standardized outcome instruments will help to establish a solid base for patient centered prehabilitation programs.

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10

Fit4SurgeryTV: at-home prehabiliation for frail elderly planned for colorectal cancer surgery

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Abstract

Objective

The preoperative phase is a potential window of opportunity. Although frail elderly patients are known to be more prone to postoperative complications, they are often not considered capable of accomplishing a full prehabilitation program. The aim of this study was to assess the feasibility of Fit4SurgeryTV, an at-home prehabilitation program specifically designed for frail elderly with colorectal cancer (CRC).

Design

The Fit4SurgeryTV program consisted of a daily elderly-adapted computer-supported strength training workout and two protein-rich meals. Frail patients ^{3}70 years with CRC were included. The program was considered feasible if 80% of the patients would be able to complete 70% of the program.

Results

Fourteen patients (median age 79, 5 males) participated. At baseline, 86% patients were physically impaired and 64% were at risk for malnourishment. Median duration of the program was 26 days. The program was feasible as patients followed the exercises for 6/7 (86%) days and prepared the recipes 5/7 (71%) days per week. Patients specifically appreciated at-home exercises.

Conclusion

This study showed that at-home prehabilitation in frail elderly with CRC is feasible. As a result, patients might be fitter for surgery and might recover faster. The perioperative period could serve as a pivotal time point in reverting complications of immobility.

Introduction

Excellent results start with optimal preparation.[1] The ability to endure a surgical operation requires substantial physical and psychological resilience of the human body.[2] Older age is associated with age-dependent frailty which can substantially diminish the patient's perioperative resilience. As more than 50% of colorectal cancer patients are 70 years or older[3], a large number of patients are at an increased risk for adverse outcomes and functional decline after the operation. In the past decades, great efforts have been made to improve outcomes in colorectal cancer patients scheduled for surgery. Regarding the perioperative and postoperative periods, the introduction of minimally invasive techniques and the implementation of fast track programs have increased the quality of care substantially.[4]

In the past years, the preoperative period has been increasingly recognized as a window of opportunity to further improve patient outcomes. Based on the identification of preoperative risk factors, prehabilitation programs that attempt to modify these risk factors have been developed.[5,6] Decreased muscle mass (sarcopenia) has been shown to be an independent risk factor for postoperative complications such as anastomotic leakage, readmission and even mortality.[7] This decreased physical state results from a combination of poor protein intake, physical inactivity and increased metabolic demands caused by the tumor.[8] In order to increase muscle mass, strength training combined with enhanced protein intake has been shown to be effective also in frail older people.[9]

Previous studies have shown that current prehabilitation programs are often not applicable in the older patient leading to low compliance and disappointing results.[10] It was the aim of this study to specifically target three challenges defined in literature. The first aim was to identify and target (pre-) frail patients as they might benefit the most from a prehabilitation program.[7,11] The second aim was to adapt the program to the elderly patient as the content of the available prehabilitation programs is often not tailored for the older patient leading to low compliance.[10] The third aim was to integrate the prehabilitation program into the patient's daily life to further increase participation rates.[12] Based on these targets, an home-based digital Fit4SurgeryTV program was developed. The purpose of this pilot study was to assess the feasibility of the program for frail elderly undergoing surgery for colorectal cancer.

Methods

Study Design

The introduction of a prehabilitation program is a physical intervention aiming to introduce new habits of daily exercise and a protein-enhanced diet as has also been defined by Silver et al. as a process on the continuum of care between cancer diagnosis and acute treatment, providing targeted interventions that improve a patient's health to reduce future impairments.[13] During the research phase, literature reviews were performed, patients were interviewed and experts were consulted about the introduction of new habits into the lives of older patients and how to motivate them.[12] The patient interviews consisted of five single interviews with frail elderly patients that had been operated for gastro-intestinal cancer about their exercise and eating habits. The most important adaptations compared to previous 'one-size-fits-all' prehabilitation programs were: 1) the possibility to execute the program at home (since transport is a major obstacle for frail elderly patients); 2) a feasible and safe exercise program requiring little time and no additional exercise material (since fall prevention is essential in this group and financial resources are limited); 3) an digital device that activates the user rather than waits for the user to switch it on (frail elderly patients often experience a threshold to initiate new things, especially concerning digital devices); 4) a social reward (since elderly patients tend to focus more on the positive events in the future as a motivation rather than the fear for complications during a surgical procedure).

Based on the findings, a pilot study of elderly-adapted prehabilitation program combining physical training with a nutritional intervention was designed. Minimal duration of the program was 18 days, maximum duration was 32 days. This time framed was based upon previously described prehabilitation programs and the logistical planning capacity of the participating hospitals. Study approval was granted by the Medical Ethics Committee of the Academic Medical Center, Amsterdam, the Netherlands, in June 2016. The study was performed in compliance with the Declaration of Helsinki and all patients gave written informed consent. This study conforms to all STROBE guidelines and reports the required information accordingly.

Physical Training

The goal of the physical training component was to create a daily strength-training program that is feasible for the frail elderly patients. An adapted form of the seven-minute-workout focusing on the movements needed to mobilize after the operation was created together with physiotherapists specialized in elderly care. The workout used bodyweight only and did not require any additional material. A description of the workout is shown in Table 1.

Table 1. Contents of the prehabilitation program

Physical Exercises (Senior 7-minute Workout)	**Protein-rich meals (20-30g protein per meal)**
Warming up: - walking/dancing (1 minute)	Example breakfast: - 200g low fat cottage cheese - handful of blueberries - 20g almonds
Leg exercises: - squats (40 seconds + 20 second break) - lunges (40 seconds + 20 second break)	Example snack after workout: - spelt bagel - 2 slices of goat cheese - 10g walnuts (optionally with honey)
Arm exercises: - moving arms in circles (40 seconds + 20 second break) - arm lifting (40 seconds + 20 second break)	
Core exercises: - adapted plank (40 seconds + 20 second break) - crunch (40 seconds + 20 second break)	

Nutritional Aid

The European Society of Parenteral and Enteral Nutrition (ESPEN) recommends a daily protein intake of 1.5–1.8g/kg/day for cancer patients. Five hospitalized elderly patients at the department of gastrointestinal surgery were interviewed about their daily diet and how to introduce new sources of protein-rich nutrition without disturbing the current diet drastically (Interviews in Appendix 1). Together with dietary specialists, a 7-day menu consisting of two small meals per day (breakfast and snack, 20-30g protein in each) was developed. In order to prepare the meals, the ingredients were delivered at home prior to start of the program. An example of the daily menu is provided in Table 1.

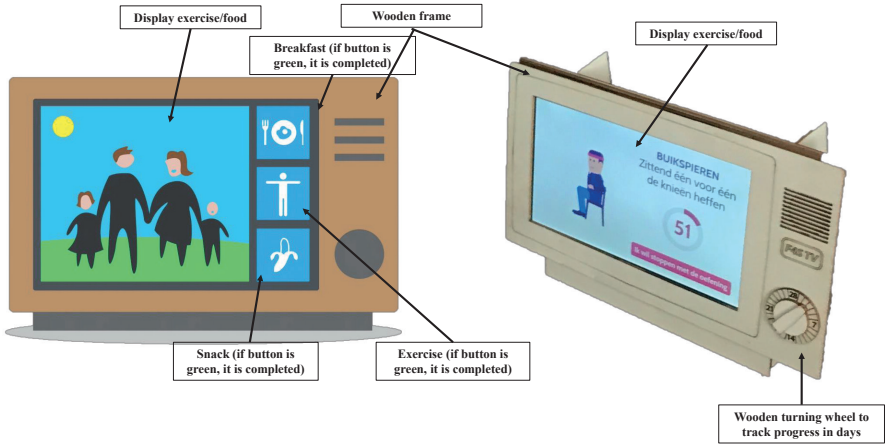
Reward

Earlier research on the motivation of elderly has shown that positive prospects (e.g. attending the wedding of their children, maintaining residence) create a superior motivational trigger compared to the fear of postoperative complications.[12,14] Therefore, a system for collecting rewards was incorporated into the program. On a daily basis, digital awards could be collected according to whether the exercises and recipes had been completed. An additional screen showed day by day progress visualized by golden medals. At the end of the program and after the operation, the awards could be exchanged for a reward consisting of four day passes to the nearby zoo. In this pilot setting, all patients received the same award regardless of the number of medals, but this might be further developed in the future.

Fit4SurgeryTV

The introduction of a new habit requires abandoning existing routines. Psychological research concerning the motivation of elderly has shown that patients generally have strong adversity towards the introduction of new things, especially in emotionally stressful periods such as the preoperative period.[12,14] At the same time, logistical challenges can pose an additional obstacle which can result in low compliance even if the patient would otherwise be motivated to participate. Furthermore, compliance to an at-home program without an activation trigger is low.[10,15] Keeping these challenges in mind, an digital activating companion was developed (Fit4SurgeryTV, Figure 1). On a daily basis, the Fit4SurgeryTV created an activation trigger by alerting the patient to the exercises and the recipes. The patients had some degree of freedom when performing the exercises: at the beginning of the program, they could express their preference for when they would like to be alerted to the daily exercises. In addition, they could postpone or cancel individual exercises or recipes during the program. At the scheduled time, the device would make a sound like an old cuckoo clock followed by a voice indicating what type of activity would follow (exercise, breakfast or snack). The device was a prototype developed solely for the purposes of this study and is not commercially available. Upon onset of the program, the researcher would visit the home of a patient to perform baseline measurements and to deliver the device and the researcher would assess final measurements. The day prior to operation, patients would attend the hospital and return the device. In case of any technical problems or adverse events, the researcher could be reached by telephone.

Figure 1. Fit4SurgeryTV digital device



Patients

From February 2017 until February 2018, all frail elderly patients (≥70 years) scheduled for elective colorectal cancer surgery in Gelre Hospitals, Apeldoorn (February 2017–February 2018), OLVG Hospital, Amsterdam (October 2017–February 2018) or Meander Hospital, Amersfoort (November 2017–February 2018) were eligible for inclusion. Frailty was defined according to the current Dutch guidelines stating either a Veiligheids Management Systeem (Safety Management System, VMS)–score ≥1 or an Identification of Seniors at Risk–Hospitalized Patients (ISAR–HP) score ≥2.[16,17] Exclusion criteria were severe cognitive (e.g. dementia) or physical (e.g. bedridden) inability to join the program or being scheduled for surgery within two weeks of starting the program.

Baseline characteristics and measurements

Baseline demographics including the patient's age, height, weight, comorbidities, alcohol use and cigarette smoking, marital status and place of residence were recorded. Electronic patient files were consulted for preoperative hemoglobin levels, tumor stage, type of operation performed and postoperative outcomes including complications (graded according to severity with the Clavien-Dindo classification), mortality, length of hospital stay and readmissions.

At the start of the program, measurements and questionnaires on physical functioning, frailty, nutritional state, cognitive functioning and quality of life were performed.

Frailty and physical state were assessed with:

- Fried criteria[18] (5 points, ³3 was considered frail)
- Low hand grip strength (dominant hand) (HGS) (gender- and body mass index (BMI)-specific cut-off points were used to determine low HGS)
- Slow 4-meter gait speed (GS) (>6 seconds was considered slow)
- Low level of physical activity (sitting for more than four hours per day, less than one walk per month, and no biking or jogging)
- Self-reported exhaustion
- Weight loss (more than 4,5kg weight loss in the past year)
- Clinical Frailty Scale[19] (9 points, £5 was defined as frail)
- Short Physical Performance Battery (SPPB)[20] (12 points, ³5 was defined as physically impaired)
- KATZ- Independence of Activities of Daily Living (KATZ-ADL-6 questionnaire)[21] (6 points, ³2 was defined as ADL-dependent)
- Nutritional state was assessed with:
- Mini Nutritional Assessment (MNA)[22] (14 points, <12 was indicative of malnourishment)

Cognitive functioning was assessed with:

- Mini Mental State Exam (MMSE)23 (30 points, £24 was considered cognitive impairment)
- Geriatric Depression Scale (GDS-2/15)24 (15 points, >2 was considered an increased risk for depression)
- Quality of life was assessed with:
- European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ C29/30)25
- One day prior to operation, physical state (Fried criteria, Clinical Frailty Scale, HGS, GS, SPPB), and quality of life were assessed again.

Compliance & evaluation

One week after initiation of the program, the patient was contacted by phone to investigate any issues or questions relating to the program. Compliance to the program was assessed during this phone call and at the end of the program by asking the patients on how many days during the previous week they completed the exercises and followed the recipes. At the end of the program, an evaluation questionnaire was performed to assess the user experience concerning the exercise program, the diet and the digital device.

Outcomes

Previous research of adherence to at-home lifestyle interventions in other patients groups have shown a wide range of compliance rates (16-67%) and have defined success if an average of 70% adherence is obtained.[26,27] This pilot study aimed to assess feasibility, defined as 80% of all patients completing at least 70% of the program. Compliance to the exercise program and the diet were assessed separately. Adverse events during the prehabilitation program were registered during the program. The patient was contacted after one week and at the end of the program.

Statistical methods

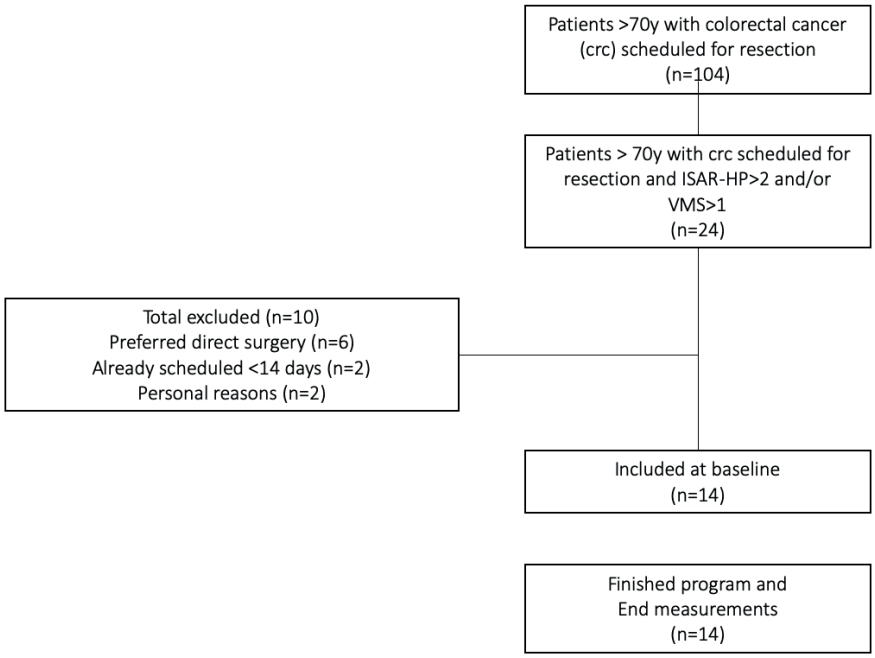
Normally distributed continuous data were presented with mean and standard deviation (SD), and skewed data were presented with median and interquartile range (IQR). The differences between baseline and end measurements were calculated and presented as percentage change. SPSS version 24.0 for Windows (IBM Corp. Armonk, NY) was used to perform all statistical analyses mentioned above.

Results

Patient inclusion

In total, 104 patients ≥70 years underwent a resection for colorectal cancer at Gelre Hospitals, Meander Medical Center and OLVG Hospital during the inclusion periods. Of these, 24 patients were considered to be frail according to the inclusion criteria. Ten patients could not be included: six preferred to be scheduled for operation as soon as possible, two patients were already scheduled for operation within 14 days two patient refused participation for personal reasons. Fourteen patients participated in this pilot study. The flow chart of patient inclusion is presented in Figure 2.

Figure 2. Flow chart of patient inclusion in the pilot study



Baseline characteristics

The median age of the patients was 79 years (IQR 74–86) and five (36%) were male. The patients had a median BMI of 25 kg/m^2 (IQR 21–28). Regarding comorbidities, ten patients (71%) suffered from cardiac diseases, one (7%) had a pulmonary disease and five (36%) were diagnosed with diabetes. Twelve (86%) patients used five or more medications. The median American Society of Anesthesiologists (ASA)–classification was 3 (IQR 2-3). The majority of the patients had stage I (n=6, 43%) or stage II (n=6, 43%) colorectal cancer. Their median preoperative hemoglobin level was 7.1 mmol/l (IQR 6.2–8.1). Four (29%) patients lived alone and none of the patients were institutionalized. Regarding frailty assessment, the patients had a median Fried score of 3 (IQR 2–3) and a median Clinical Frailty Score of 4 (IQR 3–5). A median HGS of 19kg (IQR 16–26) and a median 4–meter GS of 6.5 seconds (IQR 4.7–8.0) were recorded. Nine (64%) patients were at risk for malnourishment. Considering physical impairment measured with the KATZ-ADL-6 questionnaire, 12 (86%) patients were ADL-dependent. One (7%) patient was cognitively impaired and three (21%) patients were at risk for depression. The patients scored a median of 58% (IQR 48–69) for overall quality of life. All baseline characteristics are summarized in Table 2.

Peri- and postoperative characteristics

All patients were initially operated laparoscopically, and one (7%) patient had a conversion to open surgery due to extensive adhesions. Hemicolectomy was performed in eight (57%) patients, low anterior resection in five (36%) patients and one (7%) patient underwent transanal endoscopic microsurgery. Postoperatively, three (21%) patients had a minor complication (Clavien-Dindo grade I-II) and one (7%) patient had a major complication (Clavien-Dindo grade III-IV). The average length of hospital stay was seven days (IQR 4–8). Within 30 days, there was one (7%) readmission and no mortality.

Table 2. Baseline characteristics

	N =14	
Age (years), *median (IQR)*	79	74–86
Male, *n* (%)	5	36
BMI (kg/m^2), *median (IQR)*	25	21–28
ASA-classification, *n* (%)	3	2–3
Comorbidities		
Cardiac, *n* (%)	10	71
Pulmonary, *n* (%)	1	7
Diabetes, *n* (%)	5	36
Polypharmacy (³5), *n* (%)	12	86
Intoxications		
Alcohol (>2 glasses/day), *n* (%)	2	14
Smoking (>10sig/day), *n* (%)	1	7
Cancer stage (AJCC)		
I, *n* (%)	6	43
II, *n* (%)	6	43
III, *n* (%)	2	14
Hemoglobin at diagnosis (mmol/l), *median (IQR)*	7.1	6.2–8.1
Living alone, *n* (%)	4	29
Institutionalized, *n* (%)	0	0
ADL-dependent (KATZ-ADL³2), *n* (%)	12	86
KATZ-ADL, median (IQR)	6.5	3.7-8.0
Cognitive impairment (MMSE<24), *n* (%)	1	7
MMSE, median (IQR)	28	27-29
Depression (GDS>2), *n* (%)	3	21
At risk for malnutrition (MNA<12), *n* (%)	9	64
MNA, median (IQR)	11	10-12
Fried score (/5, ³3 is frail), *median (IQR)*	3	2-3
Clinical Frailty Scale (/9, ³5 is frail), *median, (IQR)*	4	3-5
Hand grip strength (kg), *median (IQR)*	19	16–25
4-meter gait speed (sec, >6s is slow), *median (IQR)*	6.5	4.7–8.0
Short Physical Performance Battery (/12, £5 is frail), *median (IQR)*	6	5–10
Quality of life (EORTC), *median (IQR)*	58	48–69

Notes: BMI= Body Mass Index, ASA= American Society of Anesthesiologists, AJCC = American Joint Committee on Cancer, MMSE = Mini Mental State Exam, GDS = Geriatric Depression Score, MNA = Mini Nutritional Assessment, EORTC = European Organisation of Research and Treatment of Cancer

Outcomes

Feasibility and compliancy

All patients finished the program with a median duration of 26 days (IQR 19–31). On average, patients performed the exercises 6 days (86%) per week. Thirteen patients did skip a training one to three times. If patients did not train, they were either tired (2, 15%), busy with other things (2, 15%) or forgot (3, 23%). Regarding the dietary component of the program, patients prepared the recipes 5 (71%) days per week. If recipes were not prepared, they were too difficult (1, 7%) or not tasty (4, 28%). All patients preferred an at-home program and nine (64%) patients had self-reported physical improvement. Twelve patients (86%) regarded the reward after the operation as an additional motivation. Regarding the Fit4SurgeryTV device, 12 (86%) patients evaluated the device as having a clear user interface. Two (14%) patients stated that it was difficult to use the touch screen and one patient (7%) experienced technical issues. Finally, the patients gave the program an overall grade of 8/10 (IQR 7–8). These results are summarized in Table 3.

Changes in functional performance and quality of life

Out of the five functional performance measurements performed at baseline and at the end of the program, only HGS declined (pre: median 19kg (IQR 16–25), post: median 18kg (IQR 18–24), difference: –1%) and Clinical Frailty Scale remained at the same level (pre: median 4 (IQR 3–5), post: median 4 (IQR 3–4), difference 0%). Fried score (pre: median 3 (IQR 2–3), post: median 2 (IQR 1–4), difference: +20%), GS (pre: median 6.5 seconds (IQR 4.7–8.0), post: median 5.9 (IQR 4.6–7.6), difference +6%) and SPPB (pre: median 6 (IQR 5–10), post: median 9 (IQR 6–10), difference +25%) all increased. Overall quality of life also increased (pre: median 58% (IQR 48–69), post: median 75% (IQR 65-83), difference +17%). These results are summarized in Table 4.

Table 3. Compliancy registration and evaluation

	N=14	
Overall		
Duration program (days), *median (IQR)*	26	19–31
Overall judgement of total program (1=worst, 10=best), *median (IQR)*	8	7–8
Experienced progress, *n (%)*	9	64
Preferred at-home program, *n (%)*	14	100
Having a reward afterward was a strong motivation, *n (%)*	12	86
Physical training		
Number of days exercise completed (average per week), *n (%)*	6	86
Total number of patients that skipped a training (1-3 times)	13	93
Reasons for not completing		
too tired, *n (%)*	2	15
busy with other things, *n (%)*	2	15
forgot, *n (%)*	3	23
Recipe preparation		
Number of days recipes prepared (average per week), *n (%)*	5	71
Total number of patients that skipped a training (1-3 times)	14	100
Reasons for not preparing		
too difficult, *n (%)*	1	7
not tasty, *n (%)*	4	28
Fit4SurgeryTV		
Clear user interface, *n (%)*	12	86
Difficult to use touch screen, *n (%)*	2	14
Experienced technical issues, *n (%)*	1	7
Other comments		
"I would like to keep device after operation to continue the daily exercises."		
"I do not consider occasional sadness as bad quality of life."		
"Hummus is not something our generation is willing to eat."		

Table 4. Functional and quality of life measurements

	Before prehabilitation median (IQR)	**After prehabilitation median (IQR)**	**Difference**
Fried score (/5, ≥3 is frail)	3 (2–3)	2 (1–4)	+20%
Clinical Frailty Scale (/9, ≥5 is frail)	4 (3–5)	4 (3–4)	0%
Hand grip strength (kg)	19 (16–25)	18 (18–24)	–1%
4-meter gait speed (sec, >6 is slow)	6.5 (4.7–8.0)	5.9 (4.6–7.6)	+6%
Short Physical Performance Battery (/12, ≤5 is impaired)	6 (5–10)	9 (6–10)	+25%
Overall quality of life (EORTC)	58 (48–69)	75 (65–83)	+17%

EORTC = European Organisation of Research and Treatment of Cancer

Discussion

The results of this pilot study show that an at-home digital prehabilitation program for frail elderly undergoing surgery for colorectal cancer is feasible and has the potential to improve the patients' physical functioning and quality of life. Although the study was not powered to investigate the effects of the intervention on postoperative complications and recovery, the results suggest that it is possible to diminish the preoperative risk by reverting frailty. This study provides a base for further research in the development of prehabilitation programs, specifically for patients who are at an increased risk for adverse postoperative outcomes and delayed recovery.

In recent years, research into prehabilitation has received considerable attention which has resulted in a wide range of initiatives with mixed results.[28,29] The current dogma states that interventions must be uniform so that their effects can be tested in the setting of a randomized controlled trial. However, this approach might not work when considering prehabilitation programs for the heterogeneous group of elderly patients with their varying needs and demands. For instance, some patients might benefit from strength training whereas others may only require a nutritional intervention. The need for personalized prehabilitation programs was emphasized by Wynter et al. in their statement: "Prehabilitation represents a shift away from the impairment driven, reactive model of care towards a proactive approach that enables patients to become active participants in their care".[1] Offering all patients a one-size-fits-all intervention fails to take individual preferences into account which can lead to low compliance. Fortunately, the first steps towards tailor-made prehabilitation programs have already been taken. For example, Barberan et al. have published promising results of a personalized prehabilitation program that specifically targeted high-risk elderly patients undergoing major abdominal surgery showing both functional improvement and a significant decrease in postoperative complications.[30]

Performing prehabilitation research in elderly patients has additional barriers and obstacles including logistical challenges, technological inabilities and physical disabilities.[15] The aim of this study was to focus on this group in particular and to involve them not only as patients but as a part of the team that developed the Fit4SurgeryTV. In order to obtain compliance with a digital prehabilitation device in this group, the introduction of a shared conversation at the beginning rather than a shared decision at the end was crucial. Therefore, the evaluation of the included

patients of the program and the device can be considered as valuable as the numeric outcomes of their performance. A large number of patients stated that they would like to keep the device even after hospitalization. Prehabilitation offers the possibility to use a surgical intervention to pivot a frail lifestyle. By introduction of daily exercise, a Fit4SurgeryTV can be a promising method to ensure functional performance of elderly in the long term.

This study has some limitations. Clearly, a total of fourteen patients is a limited sample size. Its results serve primarily as a hypothesis forming stepping stone for a larger study. Since the study population consisted mainly of female patients, a more representative sample should also be studied in the future. Unfortunately, not all eligible patients were included creating the risk for selection bias. The fact that an operation may have to be delayed in order to complete a training program poses a mental challenge for many patients as a longer waiting period may be perceived to promote tumor growth and increase the risk of metastases. It demands an effort of surgeons to reframe the patient's expectations and to make prehabilitation an integral part of the treatment. Furthermore, although an at-home exercise program may be logistically and economically more suitable, the execution of the exercises in the program was unsupervised and may have been of lower quality compared to training in a supervised setting. Additionally, despite the fact the workout and the recipes were developed together with patients, it was not possible to create a tailored program for each individual. Future research would benefit from the development of methodological frameworks for tailor-made lifestyle interventions. With the aid of technology such as Fit4SurgeryTV, it is possible to easily adapt the program according to the risk factors present and the patient's own preferences.

By the year of 2050, the world will be inhabited by over two billion people aged 60 years and older.[31] This transition from "baby-" to "granny" -boom will create a tremendous challenge for our health care systems. Therefore, it is in the interest of all parties to target high-risk patients in order to revert their frailty to resilience, especially prior to a surgical and other clinical intervention. This study illustrates that at-home digital prehabilitation is feasible in frail elderly scheduled for colorectal cancer surgery. A suitable next step would be to evaluate the effects of Fit4Surgery prehabilitation in a randomized setting. In short term, prehabilitation could result in fewer complications and faster recovery. In the long run, the perioperative period could serve as a pivotal time point in reverting complications of immobility.

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Summary

Summary

Towards resilience – prehabilitation in elderly with colorectal cancer

Part I – Frailty

The ageing society creates an increasing burden on our hospitals. Early risk prediction is essential in order to maintain high quality of care and to prevent complications. At the same time, it is in everybody's interest to reduce the administrative load of our health care processes as much as possible. In **Chapter 1**, we compared the first clinical impression of medical personnel with a validated screening tool predicting functional decline and mortality in elderly patients attending the first aid department. We included 238 patients among whom 42% experienced functional decline or death within 90 days. The ability of the first clinical impression was as good as the validated screening tool.

In **Chapter 2**, the concept of 'physical frailty' was further explored. In a population of elderly patients attending the radiology department for an abdominal CT-scan, muscle mass of the psoas major muscles, hand grip strength and functional state were measured. Among the included patients, 81 (46%) was diagnosed as being physically frail. However, the correlation between these groups was limited. Even more remarkable, the mortality of the physically frail group within one year was lower compared to their non-frail counterparts. This study illustrated that frailty is a complex and multifactorial syndrome and one should be conscious in reducing this problem to a single variable.

Regarding frailty in a surgical context, muscle mass remains not the only but an important parameter. It serves both as a protein reservoir and is indispensable in postoperative mobilization. In **Chapter 3**, we focused on the effect of physical frailty regarding the postoperative period in older patients with colorectal carcinoma. In a cohort of 373 elderly patients undergoing surgery for colorectal carcinoma, the relationship between muscle density on preoperative CT-scans and postoperative complications was assessed. After adjustment for confounding factors, muscle mass remained an independent predictor for anastomotic leakage, intensive care admission and prolonged hospital stay.

Besides decreased muscle mass, anaemia is also a known risk factor for

postoperative complications in patients with colorectal cancer. As such, low hemoglobin levels can result from a poor nutritional state, absolute blood loss from a tumor or as a symptom of progression of the severity of cancer. **Chapter 4** describes the results of a multicenter snapshot study in which the association between preoperative anaemia and postoperative complications and survival after three year was assessed in patients who underwent surgery for rectal cancer. After correction for confounding factors, anaemia remained an independent risk factor for decreased overall survival after three years.

Chapter 5, the last paper of Part I, was a study assessing the current screening methods for frail elderly that are being used in The Netherlands. The so called 'VMS' (security management bundle) is an obligatory screening instrument that has to be used when treating elderly patients in Dutch hospitals. This study focused specifically on older patients who were operated for colorectal carcinoma and we investigated whether the VMS-bundle was also an appropriate risk screening instrument for this group. The results showed that an increased VMS-score in elderly patients prior to colorectal surgery did not result in having an increased risk for postoperative mortality nor postoperative complications. Patients with a high VMS-score did have a prolonged hospital stay but the mortality rate did not differ compared to those with a lower VMS-score. It would be interesting to develop screening instruments that include more surgery specific risk factors.

Part II – Prehabilitation in colorectal surgery

Following the assessment of methods to map the vulnerability of the elderly patient, Part 2 focuses on the methods to revert frailty into resilience. In a surgical setting, this process of preoperative enhancement is defined as prehabilitation. Three elements of frailty and its possibility to revert its state preoperatively were assessed: physical condition, nutritional state and anaemia. In **Chapter 6**, a systematic review was performed to investigate the current evidence regarding preoperative physical training in older patients scheduled for colorectal cancer surgery. The results illustrated that the current number of studies performed in this field are hampered by a limited sample size and overall poor methodological quality. Frail patients are often excluded from studies, and the compliance of participating patients is low. Furthermore, there is often a focus on cardiorespiratory training and there are no specific programs for (frail) elderly patients. In a search performed in January 2016, none of the studies showed a significant reduction of complications

or hospital stay in older colorectal cancer patients by means of physical training.

In **Chapter 7**, a comparable systematic review was performed regarding the evidence on preoperative nutritional support in patients undergoing colorectal cancer surgery. Again, the number of studies was very limited, and the main focus was to add carbohydraterich products to a diet. Colorectal cancer patients are seldomly cachectic and thus would potentially profit more from selected dietary supplements such as protein or multivitamins.

Lastly, in **Chapter 8**, a study was performed to investigate the added value of peroperative intravenous iron compared to oral supplementation in patients suffering from iron deficiency anaemia secondary to colorectal carcinoma. In a cohort of 758 patients, the results illustrated that the administration of intravenous iron led to a significantly higher elevation of hemoglobin levels compared to its oral counterpart. Since a low hemoglobin level also reflects a patient's physical and nutritional state, intravenous iron could play an important role in the development of a prehabilitation program.

Part III – The Fit4Surgery approach

The results of the previous chapters illustrate that prehabilitation and especially reverting frailty by means of prehabilitation, is a complex challenge, requiring the collaboration of different disciplines. **Chapter 9** is a narrative review summarizing the current initiatives and describes the need for a collaborative initiative. The foundation Fit4Surgery was founded in 2016 and aims to gather evidence, connect experts and develop tools to facilitate prehabilitation programs worldwide. In this article, we emphasize that there is a need for the medical community to think beyond the evidence. As the FIT (Facts-Integration-Tools)-model describes, we need facts, but without integration with other fields or development of tools so that the evidence becomes operational for patients.

To conclude, in **Chapter 10**, we describe the Fit4SurgeryTV study, an at-home prehabilitation program that was specifically developed for frail elderly prior to colorectal cancer surgery. The pilot study assessed the feasibility of prehabilitation of this group who are at high risk for postoperative complications but who are, due to logistical and financial challenges, often excluded from participation in trials. We built a small television that offers a daily senior seven-minute workout

focusing on strength training. Twice a day, the program gives a suggestion for a protein rich snack. Every training and snack moment gives the patient medals that could be exchanged for a reward after the operation. The pilot was performed in 14 patients and the results showed a compliance rate of over 75%. Furthermore, most patients wanted to keep the television after the operation which suggests a window of opportunity to obtain long term reversal of frailty after a short term prehabilitation program.

Nederlandse Samenvatting

Weerbaarheid – Prehabilitatie bij oudere patiënten met darmkanker

Deel I – Kwetsbaarheid

Met de vergrijzing groeit eveneens het aantal ouderen dat zich presenteert in het ziekenhuis. Om de kwaliteit van de zorg zo optimaal mogelijk te houden en complicaties liever te voorkomen dan te behandelen, is vroegtijdige risicoscreening van belang. Tegelijkertijd trachten we de registratielast in de zorg te beperken. In **Hoofdstuk 1** werd de klinische blik van de medisch professional vergeleken met een gevalideerde vragenlijst. Na inclusie van 238 ouderen die zich op de spoedeisende hulp presenteerden, was bij 42% na 90 dagen sprake van functionele achteruitgang. Het vermogen van de klinische blik deze achteruitgang te voorspellen, bleek hierbij niet inferieur vergeleken met de gevalideerde vragenlijst.

In **Hoofdstuk 2** wordt het concept 'fysieke kwetsbaarheid' verder uitgediept. Bij oudere patiënten die zich op de afdeling radiologie aandienden voor het ondergaan van een CT-scan van de buik, werd de spiermassa, de handknijpkracht en de functionele status bekeken. Van alle geïncludeerde patiënten waren er 81 (46%) op één of meerdere domeinen fysiek kwetsbaar. Echter bleek de overlap tussen deze groepen gering en was er lagere mortaliteit na 1 jaar in de fysiek kwetsbare groep. Dit onderzoek geeft aan dat kwetsbaarheid een multifactorieel syndroom is waarbij de wens om dit te reduceren tot een ééndimensionale variabele mogelijk voorbarig is.

Aangezien spiermassa in het bijzonder van belang is in het perioperatieve proces, zowel als tractus ter mobilisatie en als eiwitreservoir in geval van complicaties, wordt in **Hoofdstuk 3** dieper ingegaan op de kwetsbaarheid van de patiënt met colorectaal carcinoom. Er werd bij 373 patiënten specifiek gekeken naar de relatie tussen spiermassa (preoperatief gemeten op CT) en postoperatieve complicaties. Na correctie voor diverse beïnvloedende factoren bleek een lage spiermassa een onafhankelijke voorspeller voor het krijgen van een naadlekkage, ic-opname en verlengde ziekenhuisduur.

Behoudens verminderde spiermassa is tevens bekend dat een laag hemoglobinegehalte ook geassocieerd is met een verhoogd risico op een ongewenst

postoperatief beloop. In **Hoofdstuk 4** werd middels een multicenter snapshot studie gekeken naar de associatie tussen preoperatieve anemie en postoperatieve complicaties en de overleving na drie jaar van patiënten die geopereerd werden aan een rectumcarcinoom. Het hemoglobinegehalte is representatief voor de grootte van de tumor en de algehele conditie van de patiënt. Deze studie toonde aan dat een laag hemoglobinegehalte op zichzelf ook een onafhankelijke voorspeller is voor een verminderde drie-jaars overleving van deze patiënten.

Tot slot werd in **Hoofdstuk 5** gekeken naar een screeningsmethode voor kwetsbare ouderen die reeds in Nederland geïmplementeerd is. De VMS (Veiligheidsmanagement)-screeningsbundel is een verplicht screeningsinstrument bij ouderen in Nederlandse ziekenhuizen. In deze studie keken we bij oudere patiënten die geopereerd werden voor colorectaal carcinoom of ook in deze groep de VMS een geschikt screeningsinstrument is. We toonden aan dat ouderen met een verhoogde VMS-score die colorectale chirurgie ondergaan geen verhoogd risico hebben op postoperatieve mortaliteit noch postoperatieve complicaties. Ze blijven echter wel vaker langer opgenomen en werden vaker ontslagen naar een verpleeg- of verzorgingstehuis dan patiënten met een lage VMS-score. Het is aangewezen om verder onderzoek te verrichten naar een screeningsinstrument dat meer toegespitst is op screening van risicopatiënten rondom chirurgie.

Deel II – Prehabilitatie in colorectale chirurgie

In vervolg op een inventarisatie van de methodes om kwetsbaarheid bij de oudere patiënt beter in kaart te brengen, hebben we ons in Deel 2 gericht op de mogelijkheden om die kwetsbaarheid om te zetten in weerbaarheid. Kwetsbaarheid valt onder te verdelen in verschillende dimensies die we onafhankelijk van elkaar hebben onderzocht. In **Hoofdstuk 6** hebben we een systematisch literatuuronderzoek verricht om te kijken wat de huidige stand van zaken is ten aanzien van prehabilitatie voor oudere patiënten met colorectaal carcinoom op het gebied van lichaamsbeweging. De studies die tot op heden verricht zijn includeerden slechts een gering aantal patiënten en waren van matige methodologische kwaliteit. Daarbij werden kwetsbare patiënten vaak geëxcludeerd voor deelname en was de therapietrouw laag. Geen van de studies kon derhalve een significante vermindering van complicaties of opnameduur aantonen.

In **Hoofdstuk 7** hebben we een vergelijkbaar systematisch literatuuronderzoek

verricht naar de bewijslast voor prehabilitatie bij patiënten met colorectaal carcinoom in de vorm van preoperatieve ondersteuning ten aanzien van de voedingstoestand. Hierbij was eveneens het aantal studies gering en lag de focus vooral op suppletie van koolhydraatrijke supplementen daar waar patiënten veelal niet aan absolute ondervoeding leden.

Vervolgens hebben we in **Hoofdstuk 8** gekeken naar de toegevoegde waarde van het preoperatief toedienen van intraveneus ijzer in vergelijking met orale suppletie bij patiënten met colorectaal carcinoom die tevens lijden aan een ijzergebreksanemie. Hierbij werd in een cohort van 758 patiënten aangetoond dat het toedienen van intraveneus ijzer significant meer stijging geeft van het hemoglobinegehalte. Aangezien een laag hemoglobinegehalte tevens een indicatie geeft van de voedingstoestand en invloed heeft op de fysieke conditie van de patiënt, zou intraveneus ijzer een belangrijke component kunnen vormen in een prehabilitatie programma.

Deel III – De Fit4Surgery benadering

Ten aanzien van het onderzoek dat uitgevoerd wordt op gebied van prehabilitatie kan gesteld worden dat de kennis momenteel veelal berust op experimentele studies. Tevens kan er nog winst behaald worden bij de samenwerking tussen verschillende disciplines en het creëren van een overkoepelend orgaan dat de huidige initiatieven verbindt en vertaalt naar implementeerbare programma's voor verschillende patiëntengroepen. In **Hoofdstuk 9** beschrijven we een overzicht van de huidige initiatieven wereldwijd en introduceren we het Fit4Surgery samenwerkingsverband. In dit overzicht beschrijven we de noodzaak voor de medische wereld om een stap verder te doen na het vergaren van bewijslast. In het zogenaamde FIT (Feiten, Integratie, Tools) -model wordt gesteld dat naast de feiten, de integratie met andere vakgebieden en de ontwikkeling van bruikbare tools voor patiënten, onontbeerlijk zijn voor succesvolle resultaten op gebied van prehabilitatie.

Tot slot beschrijven we in **Hoofdstuk 10** de resultaten van Fit4Surgery-TV, een prehabilitatie programma speciaal voor kwetsbare ouderen dat thuis te volgen is. Deze houten televisie werd met de vraagstelling of het juist voor deze groep die veel risico heeft op een gecompliceerd beloop, prehabilitatie haalbaar is. Een combinatie van dagelijkse krachttraining en adviezen ten aanzien van eiwitrijke

voeding werd in een pilot aangeboden aan 14 patiënten. Tevens kregen ze na elk oefenmoment een medaille die na afloop van de operatie ingewisseld kon worden voor een beloning. De studie was succesvol en 75% van de patiënten volgde het programma volledig. Voorts gaven deelnemers aan dat zij de televisie graag na de operatie zouden willen behouden om verder te oefenen. Dit biedt kansen om verder onderzoek te doen naar de mogelijkheden om korte termijn prehabilitatie om te zetten in lange termijn preventie van kwetsbaarheid bij ouderen.

Future Perspectives

The coming years will require a novel approach to the 'old' problems. Not surprisingly so, it appears that performing scientific research with elderly patients literally introduces fifty shades of gray. This thesis aimed to assess the possibilities to quantify and to optimize the overall condition of old patients undergoing surgery for colorectal cancer. We would love to have one golden bullet that indicates whether or not an operation would benefit the aged patient sitting in front of us. In the unfortunate event of a patient suffering from a poor preoperative condition, a quick-fix anti-aging program would be a dream. It is a very soothing thought that the body is too complex to respond to a quick fix. Thus, we may conclude that this thesis offers only a small glimpse, introducing more questions than answers.

As we age, we become more prone to be frail. All of our systems decline gradually. Our sight and our hearing become impaired, our walking speed and muscle strength decline and our cognitive ability to process and adapt becomes less agile. The reason for this inevitable process can easily be answered looking at nature. How we deal with it, however, is a question of humanity. Welfare has made it possible for us to live separated from our elderly family members. We can afford to put them in houses where they are being cared for, fed and cleaned by others. We lose connection and we do not see that their loneliness gradually transforms to frailty. And it is all too convenient to forget the frail and the old altogether which is illustrated in only 7% of all randomized trials worldwide focusing on the older patient.[1]

As we try to define frailty, we start from a highly specialized environment to define a risk factor. Physiotherapists will focus on decreased physical condition[2], dietary specialists on nutritional deficiencies[3], psychologists on mood disorders[4], etc. Even if we discuss a patient in a multidisciplinary setting, gastroenterologists and surgeons will still focus on the individual factors such as anaemia, surgical procedure, etc. Both the assessment of frailty and the methods for prehabilitation mentioned in this thesis are all a part of a partitioned state of health care. In the current system, this is the only way to financially and logistically treat a patient.[5] This poses a challenge for older patients who rarely fit into one specialism. Regarding a multifactorial condition such as frailty and its treatment in the preoperative period, collaboration rather than segregation would be an absolute condition in order for prehabilitation to work.[6]

This thesis hypothesized that it would be possible to focus specifically on the frail. By means of an at home training program in the weeks prior to surgery, it might be possible to revert the gradual decline of frailty. This is an individual approach, but it aims to enable patients to regain some physical condition in order to reconnect with society. By means of daily exercises that can be performed at home and easy-to-make recipes, both accompanied with a reward, we aimed to make a long-term goal graspable by means of small bite chunks.[7] This is only a small step to overcome the first threshold standing between society and the frail elderly patient. A bigger perspective and a collective approach are essential to create a sustainable and cost-effective model for the future.

The coming years will require a shift in health care thinking both from the perspective of the treating physician as of the patient. A hospital should not be a place where one ends up after being diagnosed with a disease. Maintenance of physical and cognitive health and thus maintenance of resilience should lie at the heart of the health care system. New technologies should not be considered as mere gadgets for the young and 'innovative', they should be combined with old social cohesions to maintain a healthy society.[8] Sharing information or making electronic medical records available for patients is not enough to truly emancipate.[9] The insights of medical research and the guidelines of best current medical practice should be incorporated in normal life by developing tools, both offline (e.g. support of a neighbor) and online (e.g. training program).

It might be an open door, but as a society, we are as strong as our weakest chain. Our ability to be aware of our interdependence of each other and to empower those who are more vulnerable to maintain a role in our society will define our development and will illustrate our level of empathy. As such, we might find it hard to imagine ourselves shambling behind a rollator through the busy traffic trying to get to a doctor's appointment. We might not see ourselves hardly hearing the news that we have to be operated on our rectal tumor. And we might not feel the sores of grade IV decubitus developing on our heels because no one had the time to elevate them. Therefore, we might as well start preparing for it now.

⃠ *This message was deleted.*

(This part of the future perspectives was deleted because of possible provocative or profane context.)

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Appendices

List op publications

List of contributing authors

PhD portfolio

Dankwoord

About the author

List of publications

In this thesis

1. Margadant CC, Bruns ERJ, Sloothaak DAM, van Duijvendijk P, van Raamt AF, van der Zaag HJ, Buskens CJ, van Munster BC, van der Zaag ES. Lower muscle density is associated with major postoperative complications in older patients after surgery for colorectal cancer. Eur J Surg Oncol 2016;42(11):1654–9.

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3. Bruns ERJ, van den Heuvel B, Buskens C, van Duijvendijk P, Festen S, Wassenaar EB, van der Zaag ES, Bemelman WA, van Munster BC The effects of physical prehabilitation in older patients undergoing colorectal surgery: a systematic review. Colorectal Disease 2016; 18, O267-O277

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11. Bruns ERJ, Doornewaard H, van Strijp D, Verhaegh WFJ, van der Zaag P, van Duijvendijk P, Wassenaar EB, Buskens CJ, Bemelman WA, van der Zaag ES. Combining fluorescent sentinel node mapping and genomic analysis in early stage colorectal cancer. *Submitted*

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Name PhD student: E.R.J. Bruns
PhD Period: 2015-2019
Name PhD supervisor: Prof. dr. W.A. Bemelman

	Year	Workload (ECTS)
PHD TRAINING		
General courses		
Basiscursus Regelgeving en Organisatie voor Klinisch Onderzoekers (BROK)	2015	0.9
Systematic Reviews	2015	0.7
Cohort Studies	2015	0.7
Practical Biostatistiscs	2015	1.1
Seminars, workshops and master classes		
Erasmus MC Masterclass	2018	0.7
Collegetours	2016-2017	1.5
CCA Next Board	2016-2018	3.0
NFU 'Registratie aan de Bron'	2016-2018	1.5
CCA retreat	2017	1.0
Presentations		
Poster ESCP Muscle mass & postoperative complications	2015	0.5
Poster ESCP Snapshot Anemia	2017	0.5
Oral presentation Chirurgendagen	2016	0.5
Symposium Chirurgendagen	2017	1.0
Gelre Wetenschapssymposium	201602017	1.0
Arts en Voeding Fit4Surgery	2018	0.5
NRC Live Health Care Cost	2017	0.5
(Inter)national conferences		
ESCP Dublin, Milan, Berlin	2015-2017	3.0
Alpine Colorectal Meeting, Wengen	2017	1.0
Chirurgendagen	2016-2017	2.0

TEACHING		
Lecturing		
Anatomy courses nurses Apeldoorn, AMC	2016-2018	2.0
Tutoring, Mentoring		
Curius mentor "Clinical reasoning"	2017	4.0
Paulien Kooijman	2015	2.0
Henk Jan Schuijt	2016	2.0
Tanja Argillander	2017	2.0
PARAMETERS OF ESTEEM		
Grants		
MLDS Innovation	2016	
Medtronic talent grant	2016	
STZ Innovation grant	2016	
Awards and Prizes		
Gelre Science Symposium "Best presentation"	2016	
Best Abstract Prehabilitation conference	2018	
Ernest W. Johnson Excellence in Research Writing In-Training Award	2019	

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<.>*

*Er is een limiet aan het aantal leestekens dat je kan gebruiken
om de stilte te verwoorden, in het bijzonder voor maanwandelaars
en diamanten potloodslijpers.

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Emma Bruns (1986, Wilrijk, Belgium) is a medical school graduate from the University of Amsterdam and is currently a surgical resident in training in Northwest hospital group in Alkmaar, The Netherlands.

Previously, she worked at the surgical department of hospitals in several countries (Bolivia, Nepal, Zambia). The ability to use creativity in environments of scarcity inspired her to make better use of the available resources in hospitals in her own country.

As a medical student, she started writing about her experiences inside and outside the hospital for NRC Handelsblad. In 2018, her first book “Mijn Buik Vol” (an interpretation of the original poems of surgeon Zachary Cope) was published.