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

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9 General discussion

GENERAL DISCUSSION

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

9.1 FINDINGS OF THIS THESIS

Part I – Identifying preoperative frailty

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

Part II – Identifying relevant postoperative outcome

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

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

Part III – The effect of prehabilitation

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

9.2 IDENTIFYING PREOPERATIVE FRAILTY

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

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

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

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

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

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

9.3 IDENTIFYING RELEVANT POSTOPERATIVE OUTCOMES

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

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

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

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

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

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

9.4 THE EFFECT OF PREHABILITATION

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

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

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

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

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

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

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

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

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

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

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

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

9.5 FUTURE PERSPECTIVE

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

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

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

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

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