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

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Summary

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Dankwoord



SUMMARY

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

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

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

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

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

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

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

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

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

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

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

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