Time to prepare

Summary

With 1.8 million diagnosis per year, colorectal cancer is the second most frequent type of cancer in men and the third most frequent type of cancer in women worldwide. In 2019, a total of 12,907 patients were diagnosed with colorectal cancer in the Netherlands. As the number of elderly people in the Netherlands will continue to increase due to the ageing population in combination with increased life expectancy, it is expected that the number of patients with colorectal cancer will have increased by approximately 11% by the year 2032.

Surgical resection of the tumor with or without (neo)adjuvant chemotherapy or radiation therapy is the main curative treatment for patients with colorectal cancer. Despite advances in surgery, such as minimally invasive surgery and the introduction of the enhanced recovery after surgery care pathway (ERAS), the incidence of postoperative complications remains high. In the Netherlands, approximately 1 out 3 patients suffer from a postoperative complication after colorectal cancer surgery. Postoperative complications may severely impact postoperative recovery, (cancer-free) survival, and long-term quality of life and functioning of patients.

Instead of a *reactive* care pathway in which patients diagnosed with colorectal cancer apply a "sit, wait, and see" approach in the preoperative period, it might be better to *proactively* prepare a patient for the upcoming surgical intervention. A *proactive* approach aims to reduce the incidence, severity, and/or impact of postoperative complications and to accelerate and improve recovery by preoperatively optimizing modifiable risk factors for adverse postoperative outcomes. A modifiable risk factor that has been consistently inversely associated with the risk for adverse postoperative outcomes, such as complications, delayed recovery, and mortality, is a patient's preoperative aerobic fitness. The rationale behind this association is that aerobic fitness can be seen as a proxy for a patient's physiological reserve capacity that is needed to withstand the stress caused by the surgical procedure and anesthesia. Patients with a low preoperative aerobic fitness, and thus a lower physiological reserve capacity, might have a higher risk for adverse postoperative outcomes.

Prehabilitation involves screening and assessing for (modifiable) risk factors to subsequently optimize a patient's health status (i.e., reduce modifiable risk factors) using individualized interventions between cancer diagnosis and the start of cancer treatment in order to improve postoperative outcomes. However, with regard to the effectiveness and feasibility of such prehabilitation intervention some important questions might be relevant. Is there sufficient time available between cancer diagnosis and surgery for the execution of a prehabilitation program? How can adequate pretreatment screening and assessment of the anticipated risks be performed? What short-term physical exercise

training modality is most effective for improving preoperative aerobic fitness? Is tele-prehabilitation feasible in high-risk patients approaching colorectal surgery?

The rationale and objectives of the current thesis are outlined in **Chapter 1** using the *predictive, preventive, personalized, and participatory* (P4 Health) approach applied to patients with colorectal cancer preparing for surgery. Objectives of this thesis were 1) to explore a safe timeframe for prehabilitation (*preventive*), 2) to improve (uniformity of) preoperative risk assessment (*predictive*), 3) to evaluate the effectiveness of short-term physical exercise training interventions (moderate-intensity exercise training and high-intensity interval training) of current prehabilitation programs (*preventive*), and 4) to explore the feasibility of tele-prehabilitation as a new form of prehabilitation (*preventive, personalized, and participatory*).

Chapters 2 and 3 aimed to explore a safe time frame for prehabilitation in colorectal cancer. Implementation of cancer prehabilitation is challenging due to strict time restrictions between diagnosis and surgery dictated by treatment guidelines (maximal 35 days between diagnosis of colorectal cancer and first cancer treatment). The main concern of longer treatment intervals (time between diagnosis and surgery) would be tumor growth and increased risk for metastasis which could lead to early tumor recurrence and/or premature death. Therefore, it was questioned whether longer treatment interval was associated with decreased cancer-free and overall survival.

To answer this question, a systematic literature review (**Chapter 2**) was conducted concerning the association between the treatment interval and (cancer-free) survival in patients with colorectal cancer approaching surgery. The included studies were largely heterogeneous regarding treatment interval definitions, treatment interval time-intervals, and used outcome measures. Therefore, on the one hand, based on the systematic review, no optimal treatment delay could be recommended. On the other hand, the systematic review also did not support current time limits in colorectal cancer treatment guidelines. Therefore, a more personalized approach might be warranted as the risk-benefit ratio of a short treatment delay versus longer treatment delay including prehabilitation could be different depending on the anticipated preoperative risk (i.e., in high-risk patients).

In **Chapter 3** the safe timeframe for prehabilitation was further explored in a retrospective multicenter study investigating the association between the length of the treatment interval, and (cancer-free) survival. A total of 3376 patients with colon cancer approaching surgery were included. The study showed that a treatment interval up to 49 days (7 weeks) was not associated with worse cancer-free or overall survival in patients with

colon cancer approaching surgery. However, the occurrence of postoperative complications was associated with reduced overall survival, meaning that actions aiming at reducing (the impact of) postoperative complications could be more important than a short treatment interval. This extended "safe" timeframe of up to 49 days opens possibilities to better prepare high-risk patients for the upcoming stressor of surgery in order to improve postoperative outcomes.

As high-risk patients are expected to benefit most from prehabilitation, preoperative screening and multidisciplinary risk assessment are important *predictive* steps within a prehabilitation care pathway. The cardiopulmonary exercise test (CPET) is a versatile tool that can be used within multidisciplinary preoperative risk assessment. **Chapter 4** aimed to evaluate the inter-observer agreement of risk assessment by means of different CPET-derived variables among 26 sports physicians and/or exercise physiologists throughout the Netherlands. It was concluded that inter-observer agreement of the CPET-derived variables used for risk assessment was acceptable (intraclass correlation coefficient (ICC) ≥0.76). The results also showed that uniformity of the estimation of CPET-derived variables was higher (ICC ≥0.88) when clinicians used a guideline for the determination of risk assessment variables. In addition, effort-independent CPET-derived variables might be interesting variables that could be explored for future preoperative risk-assessment, as the results of the study in **Chapter 4** have shown that the inter-observer agreement of the slope of the relationship between the minute ventilation and carbon dioxide production (VE/VCO_2-slope) and the oxygen uptake efficiency slope (OUES) were excellent.

During a CPET, a patient exercises against an increasing intensity while respiratory gases are collected on a breath-by-breath base. To aid interpretation of the noisy raw breath-by-breath data, the data is averaged (a so-called data-averaging interval). **Chapter 5** explored whether differences in CPET data-averaging intervals influence the numerical values of CPET-derived variables used for preoperative risk assessment. Based on the results of this study, it was concluded that there was no evidence that the chosen data-averaging interval significantly affected the mean numerical values of the CPET-derived variables used for preoperative risk-assessment. These results were reassuring, as it enables professionals to use the data-averaging interval that best fits the properties of the test (i.e., length of the test or suspected pathology).

The two most commonly used CPET-derived variables for preoperative risk assessment are, oxygen uptake at peak exercise (VO_{2peak}) and at the ventilatory anaerobic threshold (VO_{2VAT}). Downsides of these variables are that the VO_{2peak} requires a maximal effort (which is not feasible for all patients), whereas the VO_{2VAT} is not determinable in all patients. Advantages of effort-independent variables like the VE/VCO_2-slope and OUES

are that they do not require a maximal effort and are determinable objectively in almost all patients **Chapter 6** involves a study that evaluated these two effort-independent CPET-derived variables that are under-investigated in the context of preoperative risk assessment. The study aimed to assess the association of VE/VCO_2-slope and OUES, with postoperative complications in patients who underwent colorectal surgery in four hospitals in the Netherlands. In multivariable logistic regression analysis, the VE/VCO_2-slope and OUES were found to be statistically significantly associated with postoperative complications. However, the association was not sufficiently accurate to estimate clinically relevant preoperative risk assessment thresholds with a predefined sensitivity of 80% and specificity of >50% for these variables. The VE/VCO_2-slope and OUES could be of added value, especially when known risk assessment variables such as the VO_{2peak} or VO_{2VAT} are not determinable. However, more research is needed to elucidate more specific risk-assessment thresholds for these new effort-independent CPET-derived variables independently, and/or in combination with other (CPET-derived) risk assessment variables.

Subsequent to the identification of preoperative (modifiable) risk factors by risk-assessment, an individualized prehabilitation program can be prescribed aiming at optimizing a patient's risk factors. Physical exercise training is the cornerstone of most prehabilitation programs. However, it is unclear what exercise modality is most effective for improving aerobic fitness in the short time period available for prehabilitation. **Chapter 7** is a critical appraisal of physical exercise training interventions aiming at improving aerobic fitness within the short timeframe (<6 weeks) that is available for prehabilitation in surgical oncology. More specifically, it was evaluated what the ability of moderate-intensity exercise training (MIET) and high-intensity interval training (HIIT) is to improve a patient's aerobic fitness as quantified by a CPET. The study highlighted several shortcomings in the current literature, such as inadequate reporting of a physical exercise program according to the frequency, intensity, time, type, volume, and progression (FITT-VP) principles, making it difficult to translate the results of these programs to clinical practice. Results indicated that short-term HIIT training programs elicited the greatest short-term improvements in aerobic fitness; nevertheless, more emphasis should be given to a patient's individual response to physical exercise training by adequately screening and assessing patients, individualized goal setting and exercise prescription based on the anticipated risk, adequately reporting of performed exercise, monitoring training progression and adjusting the physical exercise training program accordingly, and assuring high adherence,

In **Chapter 8**, the feasibility of a new form of personalized prehabilitation, tele-prehabilitation, was assessed. For patients at high-risk for postoperative complications, who often

are older and have comorbidities, participation in current hospital-based prehabilitation programs is challenging due to for example transportation issues and costs. Many patients therefore prefer home-based prehabilitation. A major pitfall of home-based prehabilitation is that adherence to unsupervised home-based prehabilitation is low (<70%). Home-based prehabilitation in combination with tele-monitoring could combine the benefits of hospital-based prehabilitation (e.g., supervision, higher adherence) with those of home-based prehabilitation (e.g., patient preference, no transportation issues, more autonomy). In a tele-prehabilitation study, a total of 11 (participation rate of 81%) high-risk patients (low preoperative aerobic fitness evaluated by a CPET) were included, of whom all managed to complete the program without any adverse events. Adherence regarding the physical exercise training program's frequency, intensity, and time was very good (91%, 84%, and 100%, respectively). The tele-prehabilitation program was well-appreciated by patients. When combining the appreciation with the quantitative evaluation of participation and adherence, it seems that tele-prehabilitation is feasible in high-risk patients scheduled for colorectal cancer surgery. Nevertheless, more research is needed to assess the (cost-)effectiveness of tele-prehabilitation with regard to improving aerobic fitness and postoperative outcomes.

Chapter 9 discusses the main findings and limitations of the studies presented in this thesis in the context of the preventive, predictive, personalized, and participatory (P4 Health) approach.

In conclusion, the extended "safe" time frame for prehabilitation offers possibilities for adequate screening and assessment of preoperative modifiable risk factors (*predictive*) and collaborative decision-making (*participatory*) regarding treatment, as well as regarding strategies to optimize these risk factors by means of *personalized* and *participatory* prehabilitation (*preventive*). The *predictive* value of the CPET can be enhanced by improving uniformity and by introducing new promising effort-independent risk assessment variables. However, more research is needed to establish thresholds for these effort independent CPET-derived variables. Lastly, tele-prehabilitation seems feasible in high-risk patients approaching colorectal surgery and contributes to more *personalized* and *participatory* prehabilitation**.**