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Preoperative risk assessment and prehabilitation to improve resilience in patients with colon or rectal cancer

Ruud Franssen

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Preoperative risk assessment and prehabilitation to improve resilience in patients with colon or rectal cancer

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CHAPTER 1

General Introduction

INTRODUCTION

Annually, approximately 12,000 men and women are diagnosed with colorectal cancer in the Netherlands, of whom more than 50% are 70 years or older (1). Prognosis after diagnosis largely depends on cancer stage at time of diagnosis, as 5-year survival decreases significantly from >90% for stage I disease to <15% for stage IV disease (1). In 2019, 95% of the men and women diagnosed with stage I-III colorectal cancer underwent surgery (2). When diagnosed with rectal cancer, the vast majority (76%) of the patients with stage II-III disease also received neoadjuvant chemotherapy and/or radiation therapy prior to surgery (2). In recent years, minimally invasive surgery has become the predominant approach in colorectal surgery. In 2019, approximately 82% of the colon resections were performed laparoscopically (3). With regard to rectal resections, approximately 71% were performed laparoscopically and/or robot-assisted, and 8% via a trans-anal endoscopic procedure (both minimally invasive surgical techniques) (3).

Despite advances in surgery such as minimally invasive surgery and the implementation of the enhanced recovery after surgery (ERAS) program that have led to improved postoperative outcomes (4), 30-day postoperative complication rates and mortality rates after colorectal surgery in the Netherlands remain high, being respectively approximately 30% and 3% (5). The occurrence of postoperative complications is associated with a longer length of hospital stay (6, 7), decreased disease-free and overall survival (8), and lower perceived quality of life and physical functioning (9). The major impact of colorectal cancer surgery is further highlighted by the observations that 50% of the patients still have diminished levels of physical functioning and higher levels of fatigue 3 months after surgery (10).

Patient-related preoperative risk factors that have been identified to be associated with a higher risk for postoperative complications in colorectal cancer surgery are: higher age, male sex, malnutrition, American Society of Anesthesiologists classification ≥III, anemia (hemoglobin level ≤7 mmol/L) (7, 11), prior myocardial infarction, and heart failure (11). In addition, having more than one risk factor increases the risk for poor postoperative outcomes significantly. A study by van Rooijen et al. showed that patients with more than one risk factor had a five-fold higher risk for severe postoperative complications compared to patients without any risk factor (7). Preoperative aerobic fitness as measured by means of a cardiopulmonary exercise test (CPET), and quantified as the oxygen uptake at peak exercise (VO_{2peak}) or oxygen uptake at the ventilatory anaerobic threshold (VO_{2VAT}), has been associated with postoperative complications in colorectal cancer surgery, advocating better postoperative outcomes for patients with a higher preoperative aerobic fitness (12-14). The before-mentioned preoperative risk factors

and/or a low aerobic fitness are all factors that have an impact on (or are reflective of) a person's physiological reserve capacity. Patients with a lower physiological reserve capacity might be less resilient to cope with perioperative stress caused by the surgical procedure and are therefore at increased risk for adverse postoperative outcomes (15, 16). Although it is acknowledged that factors, such as psychological wellbeing (17, 18) or nutritional status (19) might also severely influence the risk for adverse postoperative outcomes, the current thesis mainly focusses on identifying and optimizing "physical" factors in order to establish better postoperative outcomes.

THE PERIOPERATIVE STRESS RESPONSE AND MAINTAINING HOMEOSTASIS

Homeostasis is a physiological self-regulating mechanism by which an organism can maintain a dynamic internal equilibrium while adjusting to constantly changing external conditions (20). Under normal conditions, homeostasis is a dynamic steady state, but severe disturbances of homeostasis might occur due to psychological stress, physical exertion, injuries, or surgery leading to a stress response (21, 22). The perioperative stress response is a physiological and/or (patho)physiological response that consists of a *neuroendocrine-metabolic response* and an *inflammatory-immune response* (21).

Nociceptive impulses that arise from the tissue damage caused by the surgical procedure trigger a neuroendocrine-metabolic response by activating the hypothalamic-pituitary adrenal axis in order to re-establish homeostasis (see Figure 1) (21). Adrenalin and nor-adrenaline are released as an effect of hypothalamic activation of the sympathetic nervous system leading to mobilization of carbohydrate and fat stores (i.e., hepatic and muscle glycogenolysis and lipolysis) (21, 23). In addition to the fast response of the sympathetic nervous system, a slower endocrine response is initiated leading to glucocorticoid secretion by the adrenal cortex (21, 22). Growth hormone and glucocorticoid secretion increase hepatic glycogenolysis and cause hyperglycemia and insulin resistance (21, 23). The combined sympathetic nervous and endocrine response causes hyperglycemia and protein catabolism (i.e., proteolysis of skeletal muscle) (21, 22). The body uses the substrates mobilized by glycogenolysis, lipolysis, and proteolysis for wound healing and as an energy store (21). Blood flow to organs that are not prioritized for immediate physical action, such as the kidneys and gastrointestinal tract, is reduced, whereas blood flow to active muscles is increased alongside with higher rates of cellular metabolic activity (21). Activation of the sympathetic nervous system leads to increased heart rate, increased systemic vascular resistance, and increased arterial blood pressure. In addition, the release of vasopressin into the circulation by the pituitary gland in combination with the

release of aldosterone causes retention of fluid and salt (24). Combined, these responses maintain blood volume and cardiovascular homeostasis (24).

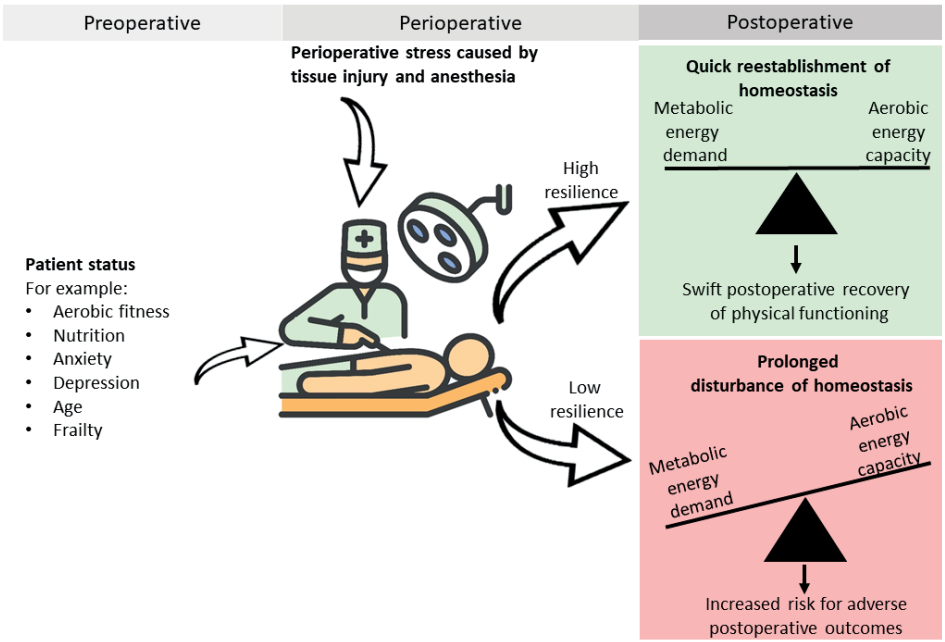

Figure 1. Perioperative stress response caused by the surgical intervention and anesthesia in relation to the ability of patients to cope with the stress response (resilience). Perioperative aerobic fitness and comorbidities might significantly alter the ability to adapt to the perioperative stress caused by the surgical trauma and anesthesia. Patients with a high physiological reserve capacity might be able to quickly re-establish the disturbance in homeostasis caused by the perioperative stress (green box). Patients with a low physiological reserve capacity might not be able to respond quickly to the perioperative stress and might have an increased risk for adverse postoperative outcomes (red box).

The *inflammatory-immune response* involves local and systemic inflammatory responses with the aim to reduce tissue damage, dispose infections, and initiate the healing process (24). Under physiological conditions, the (perioperative) stress-response and subsequent activation of the hypothalamic-pituitary adrenal axis is a survival mechanism designed to rapidly re-establish homeostasis. A coordinated activation of the hypothalamic-pituitary adrenal axis is key for an adequate physiological stress-response. An exaggerated, prolonged, or inadequate stress-response can lead to hypermetabolism, hypercatabolism, and a systemic inflammatory response (21, 24). The magnitude of the perioperative stress response is proportional to the duration and invasiveness of the surgery or trauma (21, 22). Hypothalamic-pituitary adrenal axis dysfunction is common in people with cardiopulmonary diseases, sedentary lifestyle, cardiovascular deconditioning, or psychosocial stress (25). In addition, hypothalamic-pituitary adrenal axis sensitivity decreases with age (25). Consequently, the perioperative stress response might be more pronounced and less coordinated with advancing age.

REDUCING PERIOPERATIVE STRESS

The *magnitude* of the perioperative stress response in combination with the *ability* of a patient to *adapt* to the disturbances in homeostasis (i.e., physiological reserve capacity) might be key factors in determining postoperative outcome (see Figure 2) (24). ERAS care pathways aim to reduce perioperative stress, thereby maintaining postoperative physiological function and accelerating recovery (26). The introduction of ERAS care pathways in colorectal surgery has significantly reduced the incidence of 30-day postoperative complications and readmissions (27, 28), as well as hospital length of stay (28). Until recently, the ERAS elements, such as the use of minimally invasive surgical techniques and avoiding preoperative fasting, have mainly focused on the direct perioperative period. Although ERAS attenuates the perioperative stress response, it might be too little and too late for high-risk patients to merely focus on the direct perioperative period (29). There may be more to be gained when preoperative modifiable risk factors are optimized before surgery (24). Cancer prehabilitation consists of a set of personalized, multimodal, needs-based interventions that are commenced directly after cancer diagnosis and before the start of cancer treatment, aiming at improving physiological, metabolic, and psychological resilience of an individual prior to an expected stressor, such as surgery (30). Improving aerobic fitness by means of physical exercise training is conceived to be the cornerstone of prehabilitation programs (31). However, evidence suggest that a more comprehensive multimodal approach, including interventions such as nutritional counseling, anxiety reduction, cessation of intoxications, and comorbidity optimization is most effective for improving postoperative outcomes (24, 32). Optimization of these preoperative risk factors takes time. In the Netherlands and in many other countries, time between diagnosis and start of the cancer treatment is constrained by treatment guidelines (33). Although poorly evidenced (33), these time limitations do pose a challenge with regard to the implementation of a comprehensive and effective prehabilitation program.

HOW MUCH TIME IS NEEDED AND AVAILABLE FOR PREHABILITATION?

It is clear that engaging with patients as early as possible within the preoperative care pathway opens possibilities for collaborative decision-making and maximizing preoperative resilience (34). It is less clear how much time is needed and available for prehabilitation. From a medical perspective, the main concern with longer diagnosis-to-surgery intervals would be tumor growth and increased risk for metastases, and therewith reduced cancer-free survival. Nevertheless, in combination with preventive

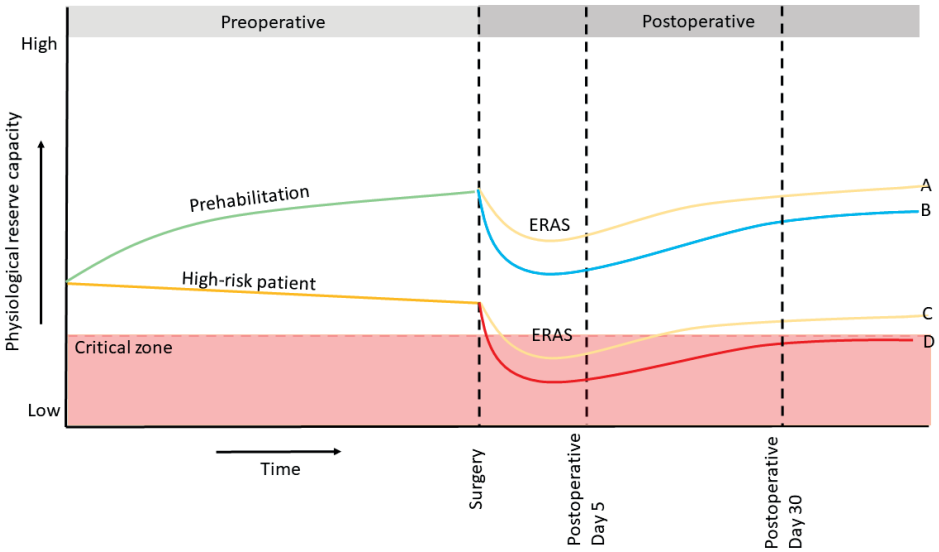

Figure 2. Schematic overview of perioperative interventions aiming at reducing the impact of, and/or optimizing the ability to cope with, the impact of the perioperative stress response in high-risk patients (low preoperative physiological reserve capacity). Prehabilitation aims to enhance the physiological reserve capacity of patients prior to surgery by reducing modifiable risk factors for adverse postoperative outcomes (such as low aerobic fitness, malnutrition, anemia). Enhanced recovery after surgery (ERAS) is a set of interventions aiming at minimizing the impact of perioperative stress response. Patients A and B participated in a prehabilitation program to improve their preoperative physiological reserve capacity. ERAS additionally minimizes the surgical stress response and the associated fall in physiological reserve capacity (patient A). Nevertheless, both patients A and B have an adequate physiological reserve capacity and do not have a high risk for adverse postoperative outcomes. Patients C and D did not participate in a prehabilitation program. ERAS reduces the fall in physiological reserve capacity (patient C). For both patients C and D, ERAS alone might insufficient, as these patients enter the critical zone and therefore have a higher risk for adverse postoperative outcomes and/or a delayed or even incomplete recovery after surgery.
Abbreviation: ERAS = enhanced recovery after surgery.

interventions such as prehabilitation, the opposite could also be true. In an observational study among 202 patients who underwent colorectal surgery, participation in a prehabilitation (median duration 29 days) program was associated with improved 5-year cancer-free survival (35). In the Netherlands, guidelines dictate that patients with colorectal cancer should receive treatment within 35 days after diagnosis (time point taken for "diagnosis" is the date of biopsy by which malignancy is confirmed). This short time-window between cancer diagnosis and surgical intervention might be especially challenging for the physical exercise intervention of the prehabilitation program as some studies show that prehabilitation can effectively improve aerobic fitness within three (36, 37) to four (38) weeks but others do not show improvement in aerobic fitness after four weeks of training (39). A possible explanation for the inability of latter study to improve aerobic fitness in a short timeframe is that the physical exercise volume (a combination of the physical exercise training's frequency, intensity, and time) might have been too low (40). Even within studies demonstrating that preoperative physical exercise training increases aerobic fitness, some patients improve their aerobic fitness

rapidly (high responders), whereas others do not (low- or non-responders). It is believed that true non-responders to physical exercise training do not exist (41). Nevertheless, not all patients respond to the same extent and some may need a higher training dose (e.g., longer duration, higher intensity) or different approach (i.e., other type of exercise, more or less rest in-between sessions) to be able to improve their aerobic fitness (41). In addition, it is possible that larger improvements in aerobic fitness can be reached when the period available for prehabilitation is extended beyond the current guideline-directed time constrains of 35 days. In a study by West et al. (42), patients with rectal cancer performing high-intensity interval training following neoadjuvant chemo-radiotherapy showed a trend towards improvement of VO_{2VAT} and VO_{2peak} after 3 weeks of training. However, larger and statistically significant improvements were seen after 6 weeks of training (between group difference for VO_{2VAT} +2.77 ml/kg/min 95% confidence interval (CI) 1.49 to 4.05 and for VO_{2peak} +3.90 ml/kg/min 95% CI 1.52 to 6.28). Moreover, a study in healthy older adults showed that high-intensity exercise training for a minimal duration of 4 to 6 weeks was needed for statistically significant improvements in respectively VO_{2VAT} and VO_{2peak} (43). Nevertheless, a randomized controlled trial (RCT) in patients preparing for abdominal surgery showed that VO_{2peak} can improve statistically significant following 4 weeks of high intensity interval training (HIIT) if sufficient physical exercise training volume is achieved (38). As described earlier, individual patients might respond faster of slower. In addition, even short duration prehabilitation might improve metabolic flexibility, which is the ability to rapidly respond and adapt to changes in metabolic demand, which could translate in better postoperative outcomes (44). To date, there is no consensus about how a short-term physical exercise intervention should be designed in terms of training frequency, intensity, time, type, volume, and progression. Even with longer duration prehabilitation, every patient is unique in the response to physical exercise training. The latter highlights the need for individualized physical exercise training prescriptions, frequent measuring (titration) of training progression, and adjusting the training prescription accordingly. A more flexible attitude with regard to the time between diagnosis and treatment initiation might be preferable, so that every individual patient can prepare optimally for the surgical intervention. The period between diagnosis and the start of cancer treatment should preferably not be a passive waiting period but instead be used as a proactive preparation period (45), in which the medical urgency to operate is outweighed against the initial risk for adverse outcomes and the potential to optimize modifiable risk factors. However, it is uncertain if, and to what extent, the treatment interval can be extended without compromising (cancer-free) survival.

EVERY PATIENT IS UNIQUE: *DOES ONE SIZE FITT ALL?*

For a prehabilitation program to be feasible and effective in improving postoperative outcomes, it is proposed that the prehabilitation program should be *predictive, preventive, personalized, and participatory (46). Predictive* means the prehabilitation program should incorporate formal risk assessment to identify an individual patient's risk for adverse postoperative outcomes and subsequently inform patients, their caregivers and healthcare professionals about the anticipated risks and possible preventive actions that can be taken. The prehabilitation program must be *preventive* as it aims to reduce the risk for individual patients at risk, in which it should be *personalized* to the needs, abilities, and goals of the patient. Personalization should be accomplished for both the content (e.g., type of exercise intervention, unimodal or multimodal) and context (e.g., hospital based, community-based, home-based) of the prehabilitation program. To be successful, every step of the preventive, predictive, and personalized approach should be executed in collaboration with the individual patient (collaborative decision-making) and his or her (in)formal caregivers to be *participatory* (34).

Predictive: *preoperative risk assessment*

Timely risk assessment is an essential part within the preoperative care pathway to provide patients and care providers with the necessary information about the risks and benefits of the surgical procedure and to come to a well-informed collaborative decision (34). Risk assessment should be multidisciplinary. Besides the evaluation of physical, nutritional, and physiological status, also other patient-related risk factors such as low hemoglobin levels (7, 47), intoxications (48), and geriatric status (49) should be assessed.

The CPET is the gold standard for the assessment of aerobic fitness. During a CPET, the patient exercises on a cycle ergometer against an increasing work rate until volitional maximal exertion. Respiratory gasses are collected at a breath-by-breath rate. In addition, blood pressure is measured by a sphygmomanometer and heart rate and rhythm is monitored by means of an electrocardiogram. The CPET provides a noninvasive objective evaluation of the integrated response of the cardiac, pulmonary, vascular, and muscular systems in response to an increasing work rate and can identify the dominant cause of exercise limitation (50). As such, the CPET is a versatile exercise test that can be used for multiple purposes, such as to identify the cause of an exercise limitation, estimate the likelihood of perioperative morbidity and mortality, inform shared decision-making, triage patients for perioperative care (i.e., ward or intensive care), direct preoperative preventive interventions (i.e., changes in medication), identify "unknown" co-morbidities, reveal contra-indications for physical exercise training, and guide physical exercise training prescription (i.e., personalization) as part of a preha-

bilitation program (50). The role of the CPET within preoperative risk assessment has been evaluated in a large international multicenter study (51). Preoperative aerobic fitness (a substitute for physiological reserve capacity) was assessed in 1,401 patients undergoing major non-cardiac surgery, thereby comparing subjective assessment using a physical activity questionnaire and objective assessment by means of a CPET (51). The study showed that subjective assessment by a physician did not accurately identify patients with poor preoperative aerobic fitness nor predicted postoperative morbidity or mortality (51). The authors concluded that a questionnaire such as the Duke activity status index (DASI) could be used for screening perioperative cardiac risk and the CPET to predict complications after major elective non-cardiac surgery (51). Within the literature, consistent cut-off points for CPET-derived variables are available that can be used for risk assessment of patients undergoing colorectal surgery (12-14, 52). Nevertheless, aerobic fitness, and thus quantification of aerobic fitness, is a dynamic metric that is subject to both analytical (i.e., measurement error or inter-rater variability) and biological variation (53). From a methodological perspective, efforts should be made to eliminate undesirable and/or unnecessary variation. Two of these possible sources of variation that could be minimized or avoided are the inter-observer variation in the interpretation of the preoperative CPET and variation due to data-averaging used for CPET interpretation. During CPET, breath-by-breath respiratory gasses are collected at a high sampling rate. To aid interpretation and to optimize graphical data display, different forms of data-averaging can be applied (54). Currently, it is unclear what the influence of the applied data-averaging method is on CPET variables used for preoperative risk assessment within patients and whether it affects risk assessment. The predictive value of preoperative CPET has been extensively studied in de past few decades, but the available literature has mainly focused on a few CPET-derived variables, such as VO_{2peak}, VO_{2VAT}, and the ratio of minute ventilation and carbon dioxide production at the ventilatory anaerobic threshold (VE/VCO_{2VAT}) (55). However, alternative variables may also have a prognostic value in some settings (16). Especially submaximal or effort-independent variables, such as the oxygen uptake efficiency slope (OUES) might have additional prognostic value (56) when a patient is unwilling or unable to exercise until volitional maximal exertion (16).

Preventive: *improving physical reserve capacity*

Prehabilitation is built on the notion that it is possible to "prepare" patients to better cope with the stress of surgery (29). It can be hypothesized that improving a patient's aerobic fitness preoperatively enables the patient to meet the increased oxygen demands postoperatively (15). Although research is scarce and from three decades ago, Older et al. observed an average increase in resting oxygen consumption of approximately 44% between the preoperative and postoperative period in 100 patients undergoing

major surgery (57). In order to meet these increased postoperative metabolic demands, a patient has to be able to increase his or her oxygen transport and utilization capacity. Failure to do so might increase the risk for postoperative complications. Indeed, West et al. showed that patients undergoing colorectal surgery who had a low aerobic fitness level had an increased risk for postoperative complications (12-14). From cross-sectional data, West et al. estimated that the odds for postoperative complications reduced by ~20% with every 1.0 mL/kg/min increase in VO_{2VAT} (13). Nevertheless, prehabilitation studies have shown heterogeneous results with regard to their ability to improve aerobic fitness and reduce postoperative complications which is probably at least partially explained by focusing on low-risk populations and design of excise interventions with a high risk of ineffectiveness (58). The first RCT that convincingly showed that prehabilitation could effectively improve aerobic fitness and subsequently reduce the incidence of postoperative complications was a trial by Barberan-Garcia et al. (59). The authors showed that multimodal prehabilitation, including HIIT in high-risk patients undergoing abdominal surgery reduced the incidence of postoperative complications by ~50% (59).

Personalized: *content and context*

Prehabilitation should be preceded by interdisciplinary risk assessment and the content of the prehabilitation program should be personalized accordingly. That is, patients might have different degrees of risk for any component of the prehabilitation program (60). Some patients might have a high risk based on their aerobic fitness, but a low risk based on their nutritional status. In this case, the primary focus (and resources) should be at improving aerobic fitness by means of physical exercise training. In addition to the personalization of the content, the context of prehabilitation should be taken into consideration.

The majority of the prehabilitation research that has been performed during the last decade has focused on hospital-based prehabilitation programs. A major challenge for hospital-based prehabilitation programs is that willingness to participate is often low due to personal (e.g., not interested, competing commitments), logistic (e.g., living too far away, travel expenses), and time-limitations (e.g., limited time between diagnosis and surgery) (61, 62). Frequent hospital visits were one of the barriers mentioned by patients that prevented engaging in a physical exercise training routine (63). Intuitively, an unsupervised home-based prehabilitation program will cause least disruption to the patient's life. Indeed, many patients report that they prefer home-based prehabilitation (64, 65). However, adherence to prehabilitation programs is higher in supervised programs (on average 98%) (66-68) compared to unsupervised programs (on average 70%) (69-71). Given the short timeframe between diagnosis and surgery in colorectal cancer, adherence is very important for a prehabilitation program to be effective. In addition

to community- and home-based prehabilitation, technologies like tele-monitoring might be able to overcome personal, logistical, and time-related barriers, thereby improving adherence. By using tele-monitoring (i.e., tele-prehabilitation), adherence can be measured more objectively and accurately, and patients can be coached and encouraged via tele-monitoring while performing their home-based training sessions. Tele-rehabilitation has already found its way into cardiac rehabilitation (72), but there is no evidence for the feasibility and effectiveness of tele-prehabilitation in high-risk patients preparing for colorectal surgery.

Participatory

The participatory aspect of prehabilitation is a vital element of the predictive, preventive, and personalized approach, as it refers to the willingness and abilities of patients to participate and adhere to prehabilitation (73). In a sense, the preoperative period provides a teachable moment when patients are faced with a potential life-threatening event that may persuade them to adapt to more healthy lifestyle behaviors (74). Nevertheless, prehabilitation can only be participatory if patients and their caregivers have an adequate level of health literacy (75). According to the World Health Organization, health literacy refers to people's knowledge, motivation, and competences to access, understand, appraise, and apply health information in order to make judgements and take decisions in everyday life concerning health care, disease prevention, and health promotion to maintain or improve quality of life during the life course. To understand and promote health literacy, the patient and his or her informal caregiver(s) have to be involved in the predictive, preventive, and personalized approach (73). By doing so, the patient is empowered to make adequate decisions and participate in every step of the patient journey between diagnosis and surgery (and beyond). Prehabilitation aims to improve a patient's physiological resilience against the pathophysiological stress caused by surgery and anesthesia in the period between diagnosis and surgery. This aim can only be achieved when the patient is motivated and able to actively participate in the whole prehabilitation program. Healthcare professionals should be aware of their important role in keeping patients informed and motivated for prehabilitation. Patients report that a recommendation by their physician is a great motivator for participating in a prehabilitation program (64, 65). The support of the multidisciplinary team, such as weekly telephone calls are also mentioned as a contributing factor for improving motivation (65). Another important aspect of a participatory approach is the physical location where a prehabilitation program is offered. Home-based prehabilitation is not only preferred by patients, but is also performed in a familiar context for the patient, with their social support system readily available for support. Involvement of patients and their caregivers, as well as data collection and feedback using tele-health (i.e., self-monitoring) enforce participatory aspects of preventive interventions (i.e., preha-

bilitation) (73). Nevertheless, careful planning and selection is needed with regard to tele-health, as it might not be acceptable and/or feasible for all patients (64).

The general aim of this thesis is to gather evidence in order to optimize physical exercise prehabilitation by exploring a safe timeframe for prehabilitation, by improving preoperative risk assessment by means of the CPET, by exploring the possible content of physical exercise prehabilitation and by exploring the feasibility of home-based teleprehabilitation. By doing so, this thesis contributes to the predictive, preventive, personalized, and participatory value of prehabilitation in patients with colorectal cancer preparing for surgery (see Figure 3).

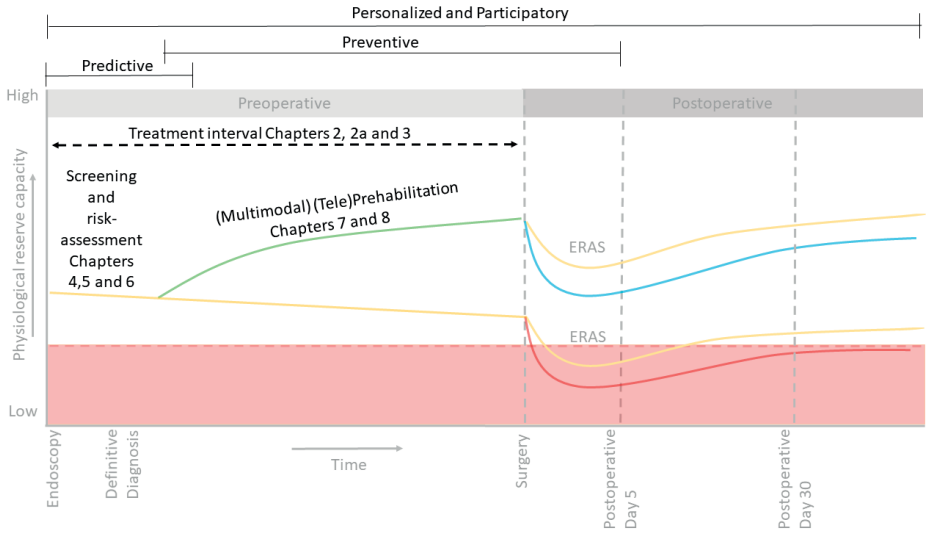

Figure 3. The patient journey of patients with stage I-III colorectal cancer as an outline of the content of this thesis. Abbreviation: ERAS = enhanced recovery after surgery.

Chapters 2, 2a, and **3** explore the safe timeframe available for prehabilitation by evaluating and discussing the association between treatment interval (time between diagnosis and surgery) and (cancer-free) survival in patients with colon or rectal cancer.

Chapters 4 and 5 address methodological issues related to the use, validity, and interpretation of the preoperative CPET with respect to risk assessment for aerobic fitness, whereas **chapter 6** evaluates new effort-independent CPET-derived variables that might be used to improve preoperative risk assessment of aerobic fitness in colorectal surgery.

Chapter 7 elaborates on the content of the physical exercise training module of a prehabilitation program and critically appraises current interventions.

Finally, **chapter 8** contains a quantitative evaluation of a feasibility study using multimodal tele-prehabilitation as a new method for providing home-based and personalized prehabilitation to high-risk patients with colorectal cancer preparing for surgery.

REFERENCES

1. (IKNL) IKN. NKR Cijfers 2022 [24-02-2023]. Available from: https://iknl.nl/nkr-cijfers.
2. (IKNL) IKN. Cijfers darmkanker [24-02-2023]. Available from: https://iknl.nl/kankersoorten/darmkanker/registratie#:~:text=Van%20de%20pati%C3%ABnten%20gediagnosticeerd%20met,chemotherapie%20gekregen%20na%20de%20operatie.
3. DCRA D-. DCRA, Jaarrapportage 2019 [24-02-2023]. Available from: https://dica.nl/jaarrapportage-2019/DCRA.
4. Group EC. The Impact of Enhanced Recovery Protocol Compliance on Elective Colorectal Cancer Resection: Results From an International Registry. Ann Surg. 2015;261(6):1153-9.
5. van den Bosch T, Warps AK, de Neree Tot Babberich MPM, Stamm C, Geerts BF, Vermeulen L, et al. Predictors of 30-Day Mortality Among Dutch Patients Undergoing Colorectal Cancer Surgery, 2011-2016. JAMA Netw Open. 2021;4(4):e217737.
6. Davies SJ, Francis J, Dilley J, Wilson RJ, Howell SJ, Allgar V. Measuring outcomes after major abdominal surgery during hospitalization: reliability and validity of the Postoperative Morbidity Survey. Perioper Med (Lond). 2013;2(1):1.
7. van Rooijen S, Carli F, Dalton SO, Johansen C, Dieleman J, Roumen R, et al. Preoperative modifiable risk factors in colorectal surgery: an observational cohort study identifying the possible value of prehabilitation. Acta Oncol. 2017;56(2):329-34.
8. Aoyama T, Oba K, Honda M, Sadahiro S, Hamada C, Mayanagi S, et al. Impact of postoperative complications on the colorectal cancer survival and recurrence: analyses of pooled individual patients' data from three large phase III randomized trials. Cancer Med. 2017;6(7):1573-80.
9. Brown SR, Mathew R, Keding A, Marshall HC, Brown JM, Jayne DG. The impact of postoperative complications on long-term quality of life after curative colorectal cancer surgery. Ann Surg. 2014;259(5):916-23.
10. Bor P, de Leeuwerk ME, Valkenet K, van Hillegersberg R, Veenhof C. Physical functioning and physical activity after gastrointestinal or bladder oncological surgery: An observational cohort study. Eur J Cancer Care (Engl). 2022:e13739.
11. Kirchhoff P, Clavien PA, Hahnloser D. Complications in colorectal surgery: risk factors and preventive strategies. Patient Saf Surg. 2010;4(1):5.
12. West MA, Asher R, Browning M, Minto G, Swart M, Richardson K, et al. Validation of preoperative cardiopulmonary exercise testing-derived variables to predict in-hospital morbidity after major colorectal surgery. Br J Surg. 2016;103(6):744-52.
13. West MA, Lythgoe D, Barben CP, Noble L, Kemp GJ, Jack S, et al. Cardiopulmonary exercise variables are associated with postoperative morbidity after major colonic surgery: a prospective blinded observational study. Br J Anaesth. 2014;112(4):665-71.
14. West MA, Parry MG, Lythgoe D, Barben CP, Kemp GJ, Grocott MP, et al. Cardiopulmonary exercise testing for the prediction of morbidity risk after rectal cancer surgery. Br J Surg. 2014;101(9):1166-72.
15. Bongers BC, Dejong CHC, den Dulk M. Enhanced recovery after surgery programmes in older patients undergoing hepatopancreatobiliary surgery: what benefits might prehabilitation have? Eur J Surg Oncol. 2021;47(3 Pt A):551-9.
16. Rose GA, Davies RG, Appadurai IR, Williams IM, Bashir M, Berg RMG, et al. 'Fit for surgery': the relationship between cardiorespiratory fitness and postoperative outcomes. Exp Physiol. 2022;107(8):787-99.

17. Abelson JS, Chait A, Shen MJ, Charlson M, Dickerman A, Yeo HL. Sources of distress among patients undergoing surgery for colorectal cancer: a qualitative study. J Surg Res. 2018;226:140-9.
18. Eddington HS, McLeod M, Trickey AW, Barreto N, Maturen K, Morris AM. Patient-reported distress and age-related stress biomarkers among colorectal cancer patients. Cancer Med. 2021;10(11):3604-12.
19. Hu WH, Cajas-Monson LC, Eisenstein S, Parry L, Cosman B, Ramamoorthy S. Preoperative malnutrition assessments as predictors of postoperative mortality and morbidity in colorectal cancer: an analysis of ACS-NSQIP. Nutr J. 2015;14:91.
20. Billman GE. Homeostasis: The Underappreciated and Far Too Often Ignored Central Organizing Principle of Physiology. Front Physiol. 2020;11:200.
21. Cusack B, Buggy DJ. Anaesthesia, analgesia, and the surgical stress response. BJA Educ. 2020;20(9):321-8.
22. Finnerty CC, Mabvuure NT, Ali A, Kozar RA, Herndon DN. The surgically induced stress response. JPEN J Parenter Enteral Nutr. 2013;37(5 Suppl):21S-9S.
23. Desborough JP. The stress response to trauma and surgery. Br J Anaesth. 2000;85(1):109-17.
24. Gillis C, Ljungqvist O, Carli F. Prehabilitation, enhanced recovery after surgery, or both? A narrative review. Br J Anaesth. 2022;128(3):434-48.
25. Manou-Stathopoulou V, Korbonits M, Ackland GL. Redefining the perioperative stress response: a narrative review. Br J Anaesth. 2019;123(5):570-83.
26. Gustafsson UO, Scott MJ, Hubner M, Nygren J, Demartines N, Francis N, et al. Guidelines for Perioperative Care in Elective Colorectal Surgery: Enhanced Recovery After Surgery (ERAS((R))) Society Recommendations: 2018. World J Surg. 2019;43(3):659-95.
27. Gustafsson UO, Hausel J, Thorell A, Ljungqvist O, Soop M, Nygren J, et al. Adherence to the enhanced recovery after surgery protocol and outcomes after colorectal cancer surgery. Arch Surg. 2011;146(5):571-7.
28. Bakker N, Cakir H, Doodeman HJ, Houdijk AP. Eight years of experience with Enhanced Recovery After Surgery in patients with colon cancer: Impact of measures to improve adherence. Surgery. 2015;157(6):1130-6.
29. West MA, Jack S, Grocott MPW. Prehabilitation before surgery: Is it for all patients? Best Pract Res Clin Anaesthesiol. 2021;35(4):507-16.
30. Carli F, Zavorsky GS. Optimizing functional exercise capacity in the elderly surgical population. Curr Opin Clin Nutr Metab Care. 2005;8(1):23-32.
31. Denehy L, Edbrooke L. The Role of Exercise Before Cancer Treatment. Semin Oncol Nurs. 2022:151330.
32. Waterland JL, McCourt O, Edbrooke L, Granger CL, Ismail H, Riedel B, et al. Efficacy of Prehabilitation Including Exercise on Postoperative Outcomes Following Abdominal Cancer Surgery: A Systematic Review and Meta-Analysis. Front Surg. 2021;8:628848.
33. Molenaar CJL, Winter DC, Slooter GD. Contradictory guidelines for colorectal cancer treatment intervals. Lancet Oncol. 2021;22(2):167-8.
34. Grocott MPW, Plumb JOM, Edwards M, Fecher-Jones I, Levett DZH. Re-designing the pathway to surgery: better care and added value. Perioper Med (Lond). 2017;6:9.
35. Trepanier M, Minnella EM, Paradis T, Awasthi R, Kaneva P, Schwartzman K, et al. Improved Disease-free Survival After Prehabilitation for Colorectal Cancer Surgery. Ann Surg. 2019;270(3):493-501.
36. Berkel AEM, Bongers BC, Kotte H, Weltevreden P, de Jongh FHC, Eijsvogel MMM, et al. Effects of Community-based Exercise Prehabilitation for Patients Scheduled for Colorectal Surgery With

High Risk for Postoperative Complications: Results of a Randomized Clinical Trial. Ann Surg. 2022;275(2):e299-e306.
37. Michel A, Gremeaux V, Muff G, Pache B, Geinoz S, Larcinese A, et al. Short term high-intensity interval training in patients scheduled for major abdominal surgery increases aerobic fitness. BMC Sports Sci Med Rehabil. 2022;14(1):61.
38. Woodfield JC, Clifford K, Wilson GA, Munro F, Baldi JC. Short-term high-intensity interval training improves fitness before surgery: A randomized clinical trial. Scand J Med Sci Sports. 2022;32(5):856-65.
39. Boereboom CL, Blackwell JEM, Williams JP, Phillips BE, Lund JN. Short-term pre-operative high-intensity interval training does not improve fitness of colorectal cancer patients. Scand J Med Sci Sports. 2019;29(9):1383-91.
40. Woodfield JC, Baldi JC, Clifford K. What is the minimal dose of HIIT required to achieve pre-operative benefit. Scand J Med Sci Sports. 2019;29(11):1841.
41. Montero D, Lundby C. Refuting the myth of non-response to exercise training: 'non-responders' do respond to higher dose of training. J Physiol. 2017;595(11):3377-87.
42. West MA, Loughney L, Lythgoe D, Barben CP, Sripadam R, Kemp GJ, et al. Effect of prehabilitation on objectively measured physical fitness after neoadjuvant treatment in preoperative rectal cancer patients: a blinded interventional pilot study. Br J Anaesth. 2015;114(2):244-51.
43. Herrod PJJ, Blackwell JEM, Boereboom CL, Atherton PJ, Williams JP, Lund JN, et al. The time course of physiological adaptations to high-intensity interval training in older adults. Aging Med (Milton). 2020;3(4):245-51.
44. Lobo DN, Pavel S, Gomez D, Greenhaff PL. Prehabilitation: high-quality evidence is still required. Br J Anaesth. 2022.
45. Levy N, Selwyn DA, Lobo DN. Turning 'waiting lists' for elective surgery into 'preparation lists'. Br J Anaesth. 2021;126(1):1-5.
46. Bongers BC, Punt IM, van Meeteren NL. On "Prehabilitation: The emperor's new clothes or a new arena for physical therapists?" Lundberg M, Archer KR, Larsson C, Rydwik E. Phys Ther. 2018;12:127-130. Phys Ther. 2019;99(7):953-4.
47. Huisman DE, Reudink M, van Rooijen SJ, Bootsma BT, van de Brug T, Stens J, et al. LekCheck: A Prospective Study to Identify Perioperative Modifiable Risk Factors for Anastomotic Leakage in Colorectal Surgery. Ann Surg. 2022;275(1):e189-e97.
48. Sharma A, Deeb AP, Iannuzzi JC, Rickles AS, Monson JR, Fleming FJ. Tobacco smoking and postoperative outcomes after colorectal surgery. Ann Surg. 2013;258(2):296-300.
49. Bessems SAM, Konsten JLM, Vogelaar JFJ, Csepan-Magyar R, Maas H, van de Wouw YAJ, et al. Frailty screening by Geriatric-8 and 4-meter gait speed test is feasible and predicts postoperative complications in elderly colorectal cancer patients. J Geriatr Oncol. 2021;12(4):592-8.
50. Levett DZH, Jack S, Swart M, Carlisle J, Wilson J, Snowden C, et al. Perioperative cardiopulmonary exercise testing (CPET): consensus clinical guidelines on indications, organization, conduct, and physiological interpretation. Br J Anaesth. 2018;120(3):484-500.
51. Wijeysundera DN, Pearse RM, Shulman MA, Abbott TEF, Torres E, Ambosta A, et al. Assessment of functional capacity before major non-cardiac surgery: an international, prospective cohort study. Lancet. 2018;391(10140):2631-40.
52. Lai CW, Minto G, Challand CP, Hosie KB, Sneyd JR, Creanor S, et al. Patients' inability to perform a preoperative cardiopulmonary exercise test or demonstrate an anaerobic threshold is associated with inferior outcomes after major colorectal surgery. Br J Anaesth. 2013;111(4):607-11.

53. Rose GA, Davies RG, Davison GW, Adams RA, Williams IM, Lewis MH, et al. The cardiopulmonary exercise test grey zone; optimising fitness stratification by application of critical difference. Br J Anaesth. 2018;120(6):1187-94.
54. Dumitrescu D, Rosenkranz S. Graphical Data Display for Clinical Cardiopulmonary Exercise Testing. Ann Am Thorac Soc. 2017;14(Supplement_1):S12-S21.
55. Otto JM, Levett DZH, Grocott MPW. Cardiopulmonary Exercise Testing for Preoperative Evaluation: What Does the Future Hold? Current Anesthesiology Reports. 2020;10(1):1-11.
56. Bongers BC, Berkel AE, Klaase JM, van Meeteren NL. An evaluation of the validity of the preoperative oxygen uptake efficiency slope as an indicator of cardiorespiratory fitness in elderly patients scheduled for major colorectal surgery. Anaesthesia. 2017;72(10):1206-16.
57. Older P, Smith R. Experience with the preoperative invasive measurement of haemodynamic, respiratory and renal function in 100 elderly patients scheduled for major abdominal surgery. Anaesth Intensive Care. 1988;16(4):389-95.
58. Thomas G, Tahir MR, Bongers BC, Kallen VL, Slooter GD, van Meeteren NL. Prehabilitation before major intra-abdominal cancer surgery: A systematic review of randomised controlled trials. Eur J Anaesthesiol. 2019;36(12):933-45.
59. Barberan-Garcia A, Ubre M, Roca J, Lacy AM, Burgos F, Risco R, et al. Personalised Prehabilitation in High-risk Patients Undergoing Elective Major Abdominal Surgery: A Randomized Blinded Controlled Trial. Ann Surg. 2018;267(1):50-6.
60. Davis JF, van Rooijen SJ, Grimmett C, West MA, Campbell AM, Awasthi R, et al. From Theory to Practice: An International Approach to Establishing Prehabilitation Programmes. Curr Anesthesiol Rep. 2022;12(1):129-37.
61. Berkel AEM, Bongers BC, van Kamp MS, Kotte H, Weltevreden P, de Jongh FHC, et al. The effects of prehabilitation versus usual care to reduce postoperative complications in high-risk patients with colorectal cancer or dysplasia scheduled for elective colorectal resection: study protocol of a randomized controlled trial. BMC Gastroenterol. 2018;18(1):29.
62. Woodfield J, Zacharias M, Wilson G, Munro F, Thomas K, Gray A, et al. Protocol, and practical challenges, for a randomised controlled trial comparing the impact of high intensity interval training against standard care before major abdominal surgery: study protocol for a randomised controlled trial. Trials. 2018;19(1):331.
63. Agasi-Idenburg CS, Zuilen MK, Westerman MJ, Punt CJA, Aaronson NK, Stuiver MM. "I am busy surviving" - Views about physical exercise in older adults scheduled for colorectal cancer surgery. J Geriatr Oncol. 2020;11(3):444-50.
64. Waterland JL, Ismail H, Amin B, Granger CL, Denehy L, Riedel B. Patient acceptance of prehabilitation for major surgery: an exploratory survey. Support Care Cancer. 2021;29(2):779-85.
65. Ferreira V, Agnihotram RV, Bergdahl A, van Rooijen SJ, Awasthi R, Carli F, et al. Maximizing patient adherence to prehabilitation: what do the patients say? Support Care Cancer. 2018;26(8):2717-23.
66. Dronkers JJ, Lamberts H, Reutelingsperger IM, Naber RH, Dronkers-Landman CM, Veldman A, et al. Preoperative therapeutic programme for elderly patients scheduled for elective abdominal oncological surgery: a randomized controlled pilot study. Clinical rehabilitation. 2010;24(7):614-22.
67. Dunne DF, Jack S, Jones RP, Jones L, Lythgoe DT, Malik HZ, et al. Randomized clinical trial of prehabilitation before planned liver resection. The British journal of surgery. 2016;103(5):504-12.
68. Bousquet-Dion G, Awasthi R, Loiselle SE, Minnella EM, Agnihotram RV, Bergdahl A, et al. Evaluation of supervised multimodal prehabilitation programme in cancer patients undergoing colorectal resection: a randomized control trial. Acta oncologica. 2018;57(6):849-59.

69. Kim DJ, Mayo NE, Carli F, Montgomery DL, Zavorsky GS. Responsive measures to prehabilitation in patients undergoing bowel resection surgery. The Tohoku journal of experimental medicine. 2009;217(2):109-15.
70. Gillis C, Li C, Lee L, Awasthi R, Augustin B, Gamsa A, et al. Prehabilitation versus rehabilitation: a randomized control trial in patients undergoing colorectal resection for cancer. Anesthesiology. 2014;121(5):937-47.
71. Carli F, Charlebois P, Stein B, Feldman L, Zavorsky G, Kim DJ, et al. Randomized clinical trial of prehabilitation in colorectal surgery. The British journal of surgery. 2010;97(8):1187-97.
72. Peretti A, Amenta F, Tayebati SK, Nittari G, Mahdi SS. Telerehabilitation: Review of the State-of-the-Art and Areas of Application. JMIR rehabilitation and assistive technologies. 2017;4(2):e7.
73. Sagner M, McNeil A, Puska P, Auffray C, Price ND, Hood L, et al. The P4 Health Spectrum - A Predictive, Preventive, Personalized and Participatory Continuum for Promoting Healthspan. Prog Cardiovasc Dis. 2017;59(5):506-21.
74. Esser T, Zimmer P, Schier R. Preoperative exercise and prehabilitation. Curr Opin Anaesthesiol. 2022;35(6):667-73.
75. Protheroe J, Nutbeam D, Rowlands G. Health literacy: a necessity for increasing participation in health care. Br J Gen Pract. 2009;59(567):721-3.

2

CHAPTER 2

The association between treatment interval and survival in patients with colon or rectal cancer: A systematic review

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ABSTRACT

Background

Surgery for colon or rectal cancer is associated with a high incidence of complications, especially in patients with a low aerobic fitness. Those patients might benefit from a comprehensive preoperative workup including prehabilitation. However, time between diagnosis and treatment is often limited due to current treatment guidelines. To date it is unclear whether the treatment interval can be extended without compromising survival.

Methods

A systematic review concerning the association between treatment intervals and survival in patients who underwent elective curative surgery for colon or rectal cancer was performed. A search up to December 2020 was conducted in PubMed, Cinahl, and Embase. Original research articles were eligible. Quality assessment was performed using the Downs and Black checklist.

Results

Eleven observational studies were included (897 947 patients). In colon cancer, treatment intervals that were statistically significant associated with reduced overall survival or cancer-specific survival ranged between >30 and >84 days. In rectal cancer only one out of four studies showed that treatment intervals >49 days was associated with reduced cancer-specific survival.

Conclusions

This systematic review identified that studies investigating the association between treatment intervals and survival are heterogeneous with regard to treatment interval definitions, treatment interval time-intervals, and used outcome measures. These aspects need standardization before a reliable estimate of an optimal treatment interval can be made. In addition, further research should focus on establishing optimal treatment intervals in patients at high risk for postoperative complications, as particularly these patients might benefit from extended diagnosis to treatment intervals permitting comprehensive preoperative preparation.

INTRODUCTION

The main curative treatment of colon and rectal cancer is surgical resection of the tumor, with or without (neo-)adjuvant treatment. Despite advances in surgery and anesthesia, complication rates for the main curative treatment of colorectal cancer, being surgical tumor resection, remain high (20-50%)[1-3]. Postoperative complications are associated with a delayed or inadequate recovery of physical fitness levels after surgery [4], reduced survival [5] and earlier cancer recurrence [6].

The time between first clinical presentation and cancer treatment is a complex pathway separated by several milestones. The term diagnostic interval is used to refer to the period between first clinical presentation and diagnosis. Time between diagnosis and first treatment is called treatment interval. Although the length of both the diagnostic interval and the treatment interval might impact survival, especially the latter is relevant in relation to optimizing a patient's physical fitness in anticipation of their cancer treatment [7].

Interventions aiming at optimizing a patient's physical fitness (including aerobic fitness) before the start of treatment (e.g., surgery) are called prehabilitation [8]. Two recent studies have shown that 3 to 6 weeks of prehabilitation in anticipation of abdominal surgery can effectively improve preoperative aerobic fitness and reduce postoperative complications by ~50% [9, 10]. However, there is an inter-individual variation in the response to prehabilitation with regard to improvements in aerobic fitness, implying that some patients might benefit more from a longer program duration [10, 11].

Nevertheless, most societies have strict treatment interval time-targets (34 days in the Netherlands [12]), that are not based on solid evidence [13], but leave a limited time window for a comprehensive preoperative workup. Extending the time interval between diagnosis and surgery could open a window for a comprehensive individualized and personalized prehabilitation program aiming at an optimal preparation of high-risk patients in anticipation of the upcoming stress of hospitalization and surgery.

Time between diagnosis and treatment seems trivial since the development of a colon or rectal adenocarcinoma may take 10 years or more [14]. However, with regard to the exponential growth of most malignancies, risk for metastasis could be the highest in these last few weeks [15, 16].

Although evidence is emerging, it remains unclear whether the treatment interval (TI) can be safely extended without compromising (cancer-free) survival. Therefore, the aim

of this systematic review was to evaluate if, and to what extent, TI can be extended in patients with colon or rectal cancer scheduled for elective surgery, without compromising overall, cancer-specific or cancer-free survival.

MATERIAL AND METHODS

A systematic review of the literature was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [17]. The search string (Supplemental File A) that was executed in the databases PubMed, Embase and Cinahl up to December 2020, included patients diagnosed with colon or rectal cancer who underwent elective curative surgical treatment (population), length of TI or short versus longer TI (exposure and comparator) and overall survival, cancer-specific survival or cancer-free survival (outcome). No filters were applied. In addition, reference lists of included studies were checked for additional relevant studies. Definition of TI was extracted from the articles. Original studies that assess TI on a continuous scale as well as studies using TI intervals, with survival as an outcome, written in English, German or Dutch were eligible. Studies in which patients participated in an intervention prior to cancer treatment and studies only focusing on diagnostic delay were excluded. Due to the differences between colon and rectal cancer with respect to cancer recurrence, tumor biology and pathology, and cancer treatment [18], studies that did not present separate analyses for colon and rectal cancer were excluded.

Title and abstract of the retrieved records, and subsequently full text articles were screened for eligibility, independently by two researchers (RF and MS) using Rayyan QCRI [19]. In case of disagreement between the reviewers, a third reviewer (MJ) was consulted.

Quality assessment of the studies was performed by two reviewers (RF and MS) independently using the Downs and Black checklist for non-randomized studies [20]. The Downs and Black checklist consists of 27 questions regarding quality of reporting, internal and external validity, and power of the included studies. Data extraction was performed by the first author (RF) and verified on accuracy and completeness by the second author (MS).

RESULTS

A total of 11 studies were included (see Figure 1 for the PRISMA flowchart of included studies).

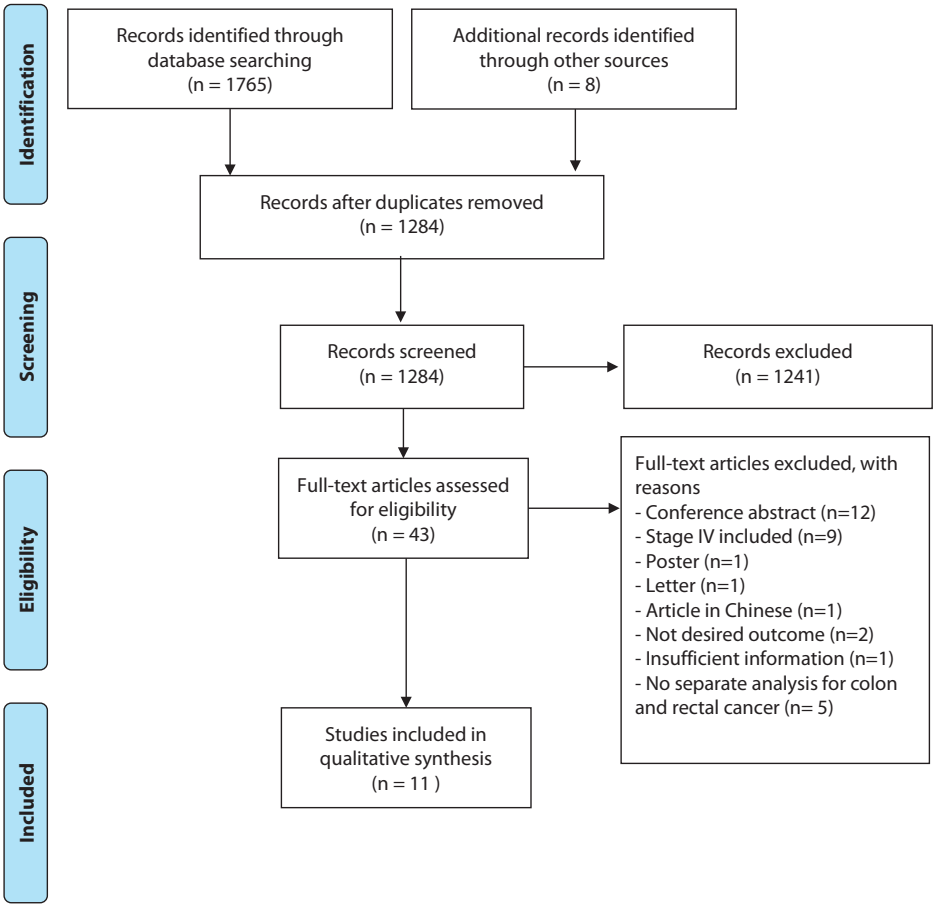

Figure 1. PRISMA flow diagram, displaying the selection of studies and reasons for exclusion.

The included studies had a total sample size of 897 947 patients, ranging from 266 in the smallest study[21] to 514 103 in the largest study [22]. Studies originated from different geographical locations: seven studies from the United States of America [22-28], one from the United Kingdom [29], two from The Netherlands [30, 31] and one from Mexico [21]. Studies were published between 2010 and 2020. Study designs comprised database reviews (n=5) [22, 26-29], retrospective (n=2)[23, 30] and prospective (n=3)[21, 24, 31] cohort studies, and a matched case-control study (n=1) [25]. Ten studies [21-30] analyzed colon cancers and four analyzed rectal cancer [25, 29-31], of which one study also analyzed tumors of the recto-sigmoid as a separate entity [29].

The start of TI (diagnosis) was not described clearly in six studies [22, 26-29, 31]. In other studies, the definition of the time point used as diagnosis differed. One study used the date of the first investigation defining malignancy [24], while some studies used date of colonoscopy or first specialist consultation as the date of diagnosis [21, 23, 30]. Others used the date of confirmed pathological diagnosis as date of 'diagnosis' [25]. End of TI was defined as the date of surgery in nine studies [21-29]. In the two remaining studies, end of TI was defined as the date of start of the earliest cancer treatment (either surgery, neoadjuvant radiotherapy and/or chemotherapy) [30, 31].

Follow-up duration was not stated in four studies [22, 27-29]. In the remaining studies, median follow-up ranged from 2.4 to 5.4 years. Outcome in the majority of the studies (7 out of 10) was overall survival (OS) [21-24, 26, 27, 30], two studies reported on relative survival (RS) [29, 31], one study reported on all cause death (ACD) and cancer-specific death (CSD) [25], and one study used cancer-specific mortality (CSM) [28]. Cancer-free survival (CFS) as an outcome was reported in four studies [24, 30, 31]. For readability of this manuscript, the term overall survival (OS) was used for the outcome measures OS and ACD. Cancer-specific survival (CSS) was used for RS, CSD and CSM, and CFS was used for the outcome measure CFS. A full overview of study characteristics of the included studies is presented in Table 1.

Methodological quality

As all studies were observational studies, no study reached the maximum score of 28 on the Downs and Black quality checklist. Quality scores ranged between 16 and 22. The greatest differences were seen in the items concerning reporting, ranging from a lowest score of six [22, 27] to a highest score of ten [23, 30], as well as in the items about confounding, ranging from a score of two [21] to a score of four [29, 30] (see Table 2).

Time to treatment initiation and survival in colon cancer

Associations between TI and OS or CSS in colon cancer were reported in ten studies [21-30], of which four studies [21, 24, 25, 30] found no association between TI and OS (Table 3). In contrast, six studies found a significant negative or a U-shaped association between TI and OS [22, 23, 26, 27] or CSS [28, 29]. Thresholds indicating that longer TI was associated with reduced OS or CSS ranged between >30 and >84 days.

CFS was reported as an outcome measure in two studies [24, 30]. No significant associations between TI and CFS was found, with a TI up to >120 days (Table 3).

Table 1. Characteristics of included studies

Author (year) country	Tumor site (stage)	Sample size (% female)	Age (years)	Study design, evidence level[32]	Start of, end of, and median treatment interval	Analysis	Analysis adjusted for	Follow-up period
Bagaria et al. (2018) USA [23]	Colon (stage I-III)	4 685 (47.6%)	Mean ± SD 71 ± 11	Retrospective cohort, 2b	**Start:** Diagnosis by colonoscopy **End:** Surgery **Median:** 11 days (range 1-256)	Cox HR	- Patient characteristics - Comorbidity - Tumor characteristics	Median, range 5.4, 1 day-24.6 years
Gleason et al. (2020) USA	Colon (stage I-III)	21 408 (56.6%)	n= 8 755 60-75 years n= 12 653 >75 years	Database review, 2b	**Start:** Diagnosis, not specified **End:** Surgery **Median:** 25 days	Cox HR	- Patient characteristics - Comorbidity - Tumor characteristics - Treatment characteristics	Not specified
Grass et al. (2020) USA [26]	Colon (stage I-III)	118 504 (52%)	Median, IQR 69, 59-78	Database review, 2b	**Start:** Diagnosis, not specified **End:** Surgery **Median:** 24 days (IQR 16-36)	Cox HR	- Socioeconomic state - Hospital - Year of diagnosis/ treatment	Median, 5.3 years
Kaltenmeier et al. (2019) USA [22]	Colon (stage I-III)	514 103 (52.6%)	Median, IQR 72, 61-80	Database review, 2b	**Start:** Diagnosis, not specified **End**: Surgery **Median:** 14 Days (IQR 4-27)	Cox HR	- Patient characteristics - Comorbidity - Tumor characteristics - Socioeconomic state - Hospital	Not specified
Kucejko el al (2020) USA [27]	Colon (stage I-III)	187 319 (53.3%)	Mean ± SD 68.5 ± 13.5	Database review, 2b	**Start:** Diagnosis, not specified **End:** Surgery **Median:** Not reported	Cox HR	- Patient characteristics - Tumor characteristics	Not specified
Lino Silva et al. (2019) Mexico [21]	Colon (stage I-III)	266 (51.1%)	Median, IQR 57, 47-68	Prospective cohort, 2b	**Start:** First specialist consultation **End:** Surgery **Median:** 38 days	Kaplan-Meier	Not applicable	Not specified

Table 1. Characteristics of included studies (*continued*)

Author (year) country	Tumor site (stage)	Sample size (% female)	Age (years)	Study design, evidence level[32]	Start of, end of, and median treatment interval	Analysis	Analysis adjusted for	Follow-up period
Wanis et al. (2017) USA [24]	Colon (stage I-III)	908 (50.2%)	n=47 <50 years n=101 50-59 years n=225 60-69 years n=293 70-79 years n=242 ≥80 years	Prospective cohort, 1b	**Start**: First investigation defining malignancy **End:** Surgery **Median:** 38 days (IQR 21-61)	Cox HR	- Patient characteristics (for DFS only) - Tumor characteristics - Treatment characteristics	Median 2.7 years
Gort et al. (2010) The Netherlands [31]	Rectum (stage I-III)	819 (38.2%) 755 [b]	Median, range 68, 25-92	Prospective cohort, 1b	**Start:** Diagnosis, not specified **End:** Cancer treatment (radiotherapy, surgery) **Median:** 40 days (IQR 28-53)	Cox HR	- Patient characteristics - Comorbidity - Tumor characteristics - Treatment characteristics	Median, IQR 4.4, 3.2-5.6 years
Pruitt et al. (2013) USA [25]	Colon and rectal (local-regional-distant) [a]	Colon: 2 634 (55.7%) Controls: 4 064 (61.1%)	n=287 66-69 years n=508 70-74 years n=618 75-79 years n=631 80-84 years n=590 ≥85 years	Matched case-control, 2b	Start: Confirmed pathologic diagnosis End: Surgery **Median:** Colon 13 days, Rectum 16 days.	Weighted logistic regression	- Patient characteristics - Comorbidity - Tumor characteristics - Treatment characteristics - Socioeconomic state - Hospital (for ACD only) - Year of diagnosis/ treatment	Median 29.9 months

Table 1. Characteristics of included studies (*continued*)

Author (year) country	Tumor site (stage)	Sample size (% female)	Age (years)	Study design, evidence level[32]	Start of, end of, and median treatment interval	Analysis	Analysis adjusted for	Follow-up period
Redaniel et al. (2014) UK [29]	Colon, recto-sigmoid and rectal (Dukes stage A and B)	Colon: 29 431 Recto-sigmoid: 4 249 Rectum 12 831 Total: 46 511 (43.9%)	n=921 15-44 years n=2 744 24-54 years n=8 628 55-64 years n=15 507 65-74 years n=18 711 ≥75 years	Database review, 2b	**Start:** Diagnosis by first event of highest priority, in declining priority: 1) histological or cytological confirmation; 2) admission to the hospital; 3) first consultation outpatient clinic **End:** Surgery **Median:** 30 days (IQR 18-42)	Cox eHR	- Patient characteristics - Tumor characteristics - Socioeconomic state	Not specified
Strous et al. (2019) The Netherlands [30]	Colon and Rectal (stage I-III)	Colon: 559 Rectum: 231 Total: 790 (45.7%)	Mean ± SD 70 ± 10	Retrospective cohort, 2b	**Start:** Date of biopsy **End:** Neoadjuvant treatment or Surgery **Median:** 32 days (IQR 26-43)	Cox HR	- Patient characteristics - Comorbidity - Tumor characteristics - Postoperative complications	Median, IQR 50, 32-75 months

[a]: Results displayed separately for disease stage.
[b]: Sample size for the CFS model is lower due to exclusion of patients who died within 30 days postoperatively, patients with metastasis within 3 months and patients without tumor-free margins.
Abbreviations: CI=confidence interval; IQR=interquartile range; SD=standard deviation; UK=United Kingdom; USA =United States of America.

Table 2. Results of the quality assessment of the included studies according to the Downs and Black checklist.

Author (year)	Reporting [a]	External validity [a]	Bias [a]	Confounding [a]	Power [a]	Total [b]
Bagaria et al. (2018) [23]	10	3	4	3	1	21
Gleason et sl. (2020)	7	3	4	3	1	18
Grass et al. (2020) [26]	7	3	4	3	1	18
Kaltenmeier el al. (2019) [22]	6	3	4	3	1	17
Kucejko et al. (2020) [27]	6	3	4	3	1	17
Lino Silva et al. (2019) [21]	7	3	4	2	1	17
Wanis et al. (2017) [24]	8	3	4	3	1	19
Gort et al. (2010) [31]	8	3	4	3	1	19
Pruitt et al. (2013) [25]	6	3	3	3	1	16
Redaniel et al. (2014) [29]	8	3	4	4	1	20
Strous et al. (2019) [30]	10	3	4	4	1	22

[a]: The maximal possible score for separate items of the Downs and Black checklist was: reporting 11; external validity 3; bias 7; confounding 6; power 1.
[b]: The total maximal possible score was 28.
Note: When the Downs and Black checklist referred to an intervention, this was conceived as exposed (a long time to treatment initiation) versus non-exposed (a short time to treatment initiation). Question 27 regarding power was scored on a binary scale: sufficient sample size (1) and insufficient sample size (0). Sample size was estimated based on the number of uncensored events in combination with the amount of predictor parameters that was corrected for in the survival analysis (one in ten rule).

Time to treatment initiation and survival in rectal cancer

In rectal cancer, three out of four studies did not find an association between TI and OS [25, 30] or CSS [25, 29]. One study [31] showed that patients with stage I-III rectal cancer who started treatment (surgery or neoadjuvant radiotherapy) >49 days after diagnosis had reduced CSS (Table 4).

With regard to CFS, one study[30] did not show a significant association between a TI of >35 days and CFS whereas another study[31] showed that a TI >49 days was associated with shorter CFS.

Table 3. Associations between time to treatment initiation and survival in patients with colon cancer

Author, (year)	Tumor stage	Associations of treatment intervals with survival		
Bagaria et al. (2018) [23]	I-III	*OS*		
		TI 1-7 days,	reference category	
		TI 8-14 days,	HR of 1.02 (95% CI 0.92-1.14)	
		TI 15-21 days,	HR of 1.03 (95% CI 0.90-1.17)	
		TI 22-28 days,	HR of 1.05 (95% CI 0.89-1.23)	
		TI 29-35 days,	HR of 1.12 (95% CI 0.92-1.36)	
		TI 36-42 days,	HR of 1.14 (95% CI 0.89-1.46)	
		TI 43-49 days,	HR of 1.11 (95% CI 0.79-1.56)	
		TI 50-53 days,	HR of 1.17 (95% CI 0.89-1.60)	
		TI 63-84 days,	HR of 1.07 (95% CI 0.73-1.57)	
		TI >84 days,	**HR of 1.47 (95% CI 1.02-2.11)**	
Gleason et al. (2020) [28]	I-III	CSM		
			Patients 60-75 years old	Patients >75 years old
		TI 0-10 days,	**HR of 1.98 (95% CI 1.64 – 2.41)**	**HR of 1.91 (95% CI 1.70 – 2.16)**
		TI 11-20 days,	**HR of 1.65 (95% CI 1.36 – 2.00)**	**HR of 1.74 (95% CI 1.55 – 1.97)**
		TI 21-30 days,	**HR of 1.50 (95% CI 1.23 – 1.81)**	**HR of 1.52 (95% CI 1.35 – 1.72)**
		TI 31-40 days,	HR of 1.1.1 (95% CI 0.89 – 1.38)	HR of 1.02 (95% CI 0.88 – 1.17)
		TI 41-50 days,	reference category	
		TI 51-60 days,	**HR of 1.34 (95% CI 1.04 – 1.71)**	HR of 1.08 (95% CI 0.91 – 1.28)
		TI 61-70 days,	HR of 1.03 (95% CI 0.75 – 1.42)	**HR of 1.37 (95% CI 1.13 – 1.66)**
		TI 71-80 days,	HR of 1.29 (95% CI 0.87 – 1.91)	**HR of 1.44 (95% CI 1.13 – 1.84)**
		TI 81-90 days,	HR of 1.49 (95% CI 0.93 – 2.37)	HR of 1.29 (95% CI 0.93 – 1.78)
		TI >90 days	**HR of 1.23 (95% CI 1.06 – 1.42)**	**HR of 1.72 (95% CI 1.44 – 2.06)**
Grass et al. (2020) [26]	I-III	*OS*		
		HR of 1.06 (95% CI 1.05 – 1.07)		
		HR represents increase in risk for every 14 days of extra TI >40 days (as a continuous variable)		

Table 3. Associations between time to treatment initiation and survival in patients with colon cancer (*continued*)

Author, (year)	Tumor stage	Associations of treatment intervals with survival		
Kaltenmeier et al. (2019) [22]	I-III	*OS*		
		TI < 7 days,	**HR of 1.56 (95% CI 1.45 – 1.68)**	
		TI 7-30 days,	reference category	
		TI 31-60 days,	**HR of 1.13 (95% CI 1.02 – 1.25)**	
		TI 61-90 days,	**HR of 1.49 (95% CI 1.19 – 1.85)**	
		TI 91-120 days,	**HR of 2.28 (95%CI 1.61 – 3.23)**	
		TI 121 – 180 days,	**HR of 2.46 (95% CI 1.48 – 4.09)**	
Kucejko el al.(2020) [27]	I-III	*OS*[a]		
			Patients up to 65 years old	Patients > 65 years old
		TI ≤ 14 days,	**HR of 1.38 (95% CI 1.32 – 1.44)**	**HR of 1.42 (95% CI 1.39 – 1.46)**
		TI 15 - 28 days,	reference category	
		TI 29 - 42 days,	HR of 0.99 (95% CI 0.92 – 1.05)	HR of 1.02 (95% CI 0.99 – 1.06)
		TI 43 - 84 days,	**HR of 1.22 (95% CI 1.13 – 1.31)**	**HR of 1.12 (95% CI 1.12 – 1.21)**
		TI > 84 days,	**HR of 1.68 (95% CI 1.46 – 1.93)**	**HR of 1.35 (95% CI 1.26 – 1.44)**
Lino Silva et al. (2019) [21]	I-III	*OS* Stage I: Not determined due to small sample size Stage II: TI 0-24 days TI 25-38 days TI 39-60 days TI >60 days Log-rank p=0.829 Stage III: TI 0-24 days TI 25-38 days TI 39-60 days TI >60 days Log-rank p=0.936		

Table 3. Associations between time to treatment initiation and survival in patients with colon cancer (*continued*)

Author, (year)	Tumor stage	Associations of treatment intervals with survival	
Wanis et al. (2017) [24]	I-III	*OS*	
		TI ≤30 days,	reference category
		TI 31-60 days,	HR of 0.91 (95% CI 0.66-1.26)
		TI 61-90 days,	HR of 0.82 (95% CI 0.53-1.26)
		TI 91-120 days,	HR of 0.78 (95% CI 0.34-1.81)
		TI >120 days,	HR of 0.90 (95% CI 0.48-1.70)
		CFS	
		TI ≤30 days,	reference category
		TI 31-60 days,	HR of 0.84 (95% CI 0.55-1.29)
		TI 61-90 days,	HR of 0.95 (95% CI 0.58-1.61)
		TI 91-120 days,	HR of 1.46 (95% CI 0.58-3.72)
		TI >120 days,	HR of 0.48 (95% CI 0.15-1.53)
Pruitt et al. (2013) [25]	local-regional-distant [a]	*ACD*	
		Local stage:	
		TI <7 days,	**adjusted OR of 1.43 (95% CI 1.04-1.96)**
		TI 7-14 days,	reference category
		TI 14-28 days,	adjusted OR of 1.18 (95% CI 0.86-1.62)
		TI ≥28 days,	adjusted OR of 1.15 (95% CI 0.80-1.64)
		Regional stage:	
		TI <7 days,	adjusted OR of 1.24 (95% CI 0.94-1.63)
		TI 7-14 days,	reference category
		TI 14-28 days,	adjusted OR of 1.13 (95% CI 0.85-1.49)
		TI ≥28 days,	adjusted OR of 1.06 (95% CI 0.75-1.50)
		CSD	
		Local stage:	
		TI <7 days,	adjusted OR of 1.14 (95% CI 0.69-1.89)
		TI 7-14 days,	reference category
		TI 14-28 days,	adjusted OR of 0.84 (95% CI 0.51-1.38)
		TI ≥28 days,	adjusted OR of 0.71 (95% CI 0.40-1.25)
		Regional stage:	
		TI <7 days,	adjusted OR of 1.26 (95% CI 0.95-1.67)
		TI 7-14 days,	reference category
		TI 14-28 days,	adjusted OR of 1.04 (95% CI 0.78-1.40)
		TI ≥28 days,	adjusted OR of 0.78 (95% CI 0.54-1.14)

Table 3. Associations between time to treatment initiation and survival in patients with colon cancer (*continued*)

Author, (year)	Tumor stage	Associations of treatment intervals with survival	
Redaniel et al. (2014) [29]	Dukes stage A and B	*RS*	
		TI <25 days,	**excess HR of 1.71 (95% CI 1.50-1.94)**
		TI 25-38 days,	reference category
		TI >38 days,	**excess HR of 1.19 (95% CI 1.02-1.38)**
Strous et al. 2019 [30]	I-III	*OS*	
		TI ≤35 days,	reference category
		TI >35 days,	HR of 1.29 (95% CI 0.90-1.86)
		CFS	
		TI ≤35 days,	reference category
		TI >35 days,	HR of 1.21 (95% CI 0.78-1.90)

[a]: The original study displayed results of two databases, results of the Medicare database are not displayed as also non-elective surgery was included. Presented data is from the NCDB database.

Abbreviations: ACD=all cause death; CFS=cancer-free survival; CI=confidence interval; CSD=cancer-specific death; DFS=disease-free survival; eHR=excess hazard ratio; HR=hazard ratio; IQR=interquartile range; OR=odds ratio; OS=overall survival; RER=relative excess risk; RS=relative survival; SD=standard deviation; TI = treatment interval; UK=United Kingdom; USA =United States of America.

Table 4. Associations between time to treatment initiation and survival in patients with rectal cancer

Author (year)	Tumor stage	Associations of treatment intervals with Survival	
Gort et al.(2010) [31]	**I**-III	*RS*	
		TI ≤49 days,	reference category
		TI >49 days**,**	**RER of 1.51 (95% CI 1.01-2.27)**
		CFS	
		TI ≤49 days,	reference category
		TI >49 days**,**	**HR of 1.44 (95% CI 1.06-1.96)**
Pruitt et al. (2013) [25]	Local-regional-distant [a]	*ACD*	
		Local stage:	
		TI <7 days,	adjusted OR of 1.50 (95% CI 0.90-2.51)
		TI 7-14 days,	reference category
		TI 14-28 days,	adjusted OR of 1.49 (95% CI 0.93-2.40)
		TI ≥28 days,	adjusted OR of 1.45 (95% CI 0.88-2.40)
		Regional stage:	
		TI <7 days,	adjusted OR of 1.11 (95% CI 0.70-1.76)
		TI 7-14 days,	reference category
		TI 14-28 days,	adjusted OR of 0.79 (95% CI 0.51-1.22)
		TI ≥28 days,	adjusted OR of 1.05 (95% CI 0.65-1.70)
		CSD	
		Local stage:	
		TI <7 days,	adjusted OR of 1.55 (95% CI 0.77-3.10)
		TI 7-14 days,	reference category
		TI 14-28 days,	adjusted OR of 1.52 (95% CI 0.80-2.92)
		TI ≥28 days,	adjusted OR of 1.63 (95% CI 0.83-3.18)
		Regional stage:	
		TI <7 days,	adjusted OR of 1.02 (95% CI 0.65-1.58)
		TI 7-14 days,	reference category
		TI 14-28 days,	adjusted OR of 0.83 (95% CI 0.54-1.26)
		TI ≥28 days,	adjusted OR of 0.74 (95% CI 0.46-1.19)
Redaniel et al.(2014) [29]	Dukes stage A and B	*RS*	
		Recto-sigmoid:	
		TI <25 days,	excess HR of 1.31 (95% CI 0.96-1.79)
		TI 25-38 days,	reference category
		TI >38 days,	excess HR of 1.03 (95% CI 0.74-1.45)
		Rectum:	
		TI <25 days,	excess HR of 1.17 (95% CI 0.97-1.39)
		TI 25-38 days,	reference category
		TI >38 days,	excess HR of 1.11 (95% CI 0.94-1.32)
Strous et al.(2019) [30]	I-III	*OS*	
		TI ≤35 days,	reference category
		TI >35 days,	HR of 0.86 (95% CI 0.46-1.61)
		CFS	
		TI ≤35 days,	reference category
		TI >35 days,	HR of 1.21 (95% CI 0.65-2.25)

Abbreviations: ACD=all cause death; CFS=cancer-free survival; CI=confidence interval; CSD=cancer-specific death; DFS=disease-free survival; eHR=excess hazard ratio; HR=hazard ratio; IQR=interquartile range; OR=odds ratio; OS=overall survival; RER=relative excess risk; RS=relative survival; SD=standard deviation; TI = treatment interval; UK=United Kingdom; USA =United States of America.

DISCUSSION

This systematic review aims to evaluate to what extent the TI can be safely extended without compromising survival in patients with colon or rectal cancer in order to identify a safe time frame for prehabilitation. In colon cancer, six out of ten studies showed a significant association between a longer TI and reduced OS or CSS. Of these, one study found an association with an excessively long TI of >84 days [23], and five studies with a TI ranging between >30 and >51 days [22, 26, 27, 29]. No associations were found between TI and CFS in patients with colon cancer [24, 30].

In rectal cancer, only one [31] out of four studies showed that patients had a better OS and CFS when treated (surgery or radiotherapy) within 49 days of diagnosis.

The associations between TI and OS or CSS in colon cancer are in contrast with a review investigating the effect of time from diagnosis to surgery on oncological outcomes in patients with colon cancer [14]. In this systematic review by Hangaard Hansen et al. [14], no associations were found between longer delays and reduced survival. Although their review was published in 2018, the current review managed to identify seven new studies that were not previously reviewed systematically. In addition, Hangaard Hansen et al. [14] also included patients with stage IV colon cancer. The inclusion of patients with stage IV disease might have attenuated a possible association, as these patients have markedly lower survival rate compared to patients with stage I-III colon cancer [33]. Regarding rectal cancer, the current review is the first to collectively examine studies investigating the association between TI and survival in rectal cancer as a unique entity.

Although some studies show that longer delays seem to be associated with reduced survival, there is no consensus on the length of the TI from which this association becomes significant. This inconsistency might be partially explained by the variety in time-points that were considered as diagnosis, and therefore as starting point of the TI. Duration of the TI might vary significantly between different starting points, such as date of biopsy or diagnosis by confirmed pathology. However, the lack of a consistent starting point of the TI does not fully explain the broad range of 31 to 84 days that is observed in colon cancer. The variety in findings does however identify a major pitfall in the current literature. Studies included in this systematic review were heterogeneous regarding their methodology, definition of TI, definition of TI time intervals, and used outcome measures (such as OS, RS, ACD, CFS, CSM). Therefore, comparison of studies is difficult and an optimal or maximal TI is difficult to establish. All of these key aspects need standardization before reliable estimates can be made regarding the association between TI and survival in patients with colon or rectal cancer. Another limitation of the

current review was that only a part of the interval between presentation of symptoms and first treatment was studied. Although the TI is of main interest with regard to the aim of this review, the association between TI and survival might be biased by the length of the diagnostic interval.

In colon cancer, four studies [22, 26, 27, 29] reporting reduced survival with longer TIs were large retrospective database studies (combined sample size of 866 437 patients). These database studies did not adjust for some relevant confounders such as comorbidity, adjuvant treatment and postoperative complications. Previous studies have shown that postoperative complications are related to both survival [5, 6, 30], cancer recurrence [6] and inadequate recovery of physical fitness postoperatively [4]. Also, three out of these four studies [22, 26, 27] used the same database that was complete for only 70% of newly diagnosed cancer cases. Although the latter must introduce some bias, it is impossible to determine how it exactly affects the results.

Some studies (n=4) showed that a very short TI (e.g., shorter than one week) was associated with reduced survival [22, 25, 34]. Although most studies explicitly stated that emergency surgery was excluded from the analysis, a very short TI probably represents patients with intestinal obstructions that were not designated as emergency surgery but still had higher priority. Previous research showed that patients with intestinal obstructions form a subgroup of patients with a short TI that also have a poorer prognosis [35]. In addition, one study found that a short TI of <30 days was associated with reduced CSS [28]. However, the association was lower when a complete preoperative workup, including endoscopy, CT scan of the pelvis and abdomen, and carcinoembryonic antigen, was performed. This indicates that the increased risk associated with a short TI, might be mitigated by a full preoperative oncologic workup. The authors concluded that ideal timing for surgery was between 3 and 6 weeks after diagnosis allowing time for the clinician to complete preoperative workup and for the patient to prepare for surgery and organize their social support network.

Perhaps, more emphasis could be given to how the TI can be used optimally in association with complications and survival, instead of focusing on a short TI. A study that did not observe an association between TI and OS, did contrastingly find a significant association between OS and variables associated with frailty, such as a higher age and postoperative complications[30] in colon cancer, and age and comorbidities[30] in rectal cancer. Although more research is needed, this could mean that the effect size of these risk factors is higher, and therefore probably more instrumental than a short TI. This is also emphasized in the study of Redaniel et al. [29], who indicated that factors

associated with frailty, such as a higher age and deprivation state, were associated with RS in patients with CRC independent of TI.

Prehabilitation aims to increase a patient's health between diagnosis and surgery in order to reduce postoperative complications and enhance recovery postoperatively [8]. In high-risk patients with colon or rectal cancer, there could be trade-off between the medical urgency to operate on and creating sufficient time preoperatively for an optimal preparation for surgery. Although not specifically aiming at high-risk patients, a recent Canadian study indeed showed that prehabilitation improved CFS in patients with colon and rectal cancer [36].

Studies aiming at identifying a safe window for prehabilitation, should give more emphasis to the association between TI and CFS, as it is a much more sensitive variable than OS given the relatively high 5-year survival rates in colon and rectal cancer. Only a few studies (n=3) investigated the association between CFS and TI [24, 30, 31]. In patient with colon cancer no association were observed between TI and earlier cancer recurrence whereas in patients with rectal cancer TI up to 49 days did not lead to reduced CFS. On the other hand, especially in elderly patients, OS might also be important, as elderly have increased odds of dying from other causes than cancer recurrence.

Future research could be improved by using a uniform definition for the start and end of the TI. In addition, length of the TI time intervals should be standardized in order to increase comparability between studies. With regard to the maximal time frame for prehabilitation, the start of the TI should ideally be set to the first investigation defining malignancy (such as endoscopy, computed tomography scan), as this is the first possible starting point for prehabilitation. In addition, perhaps multiple starting points can be reported to increase comparability between studies. Furthermore, studies should adjust for important confounders, such as postoperative complications, comorbidities and adjuvant treatment in addition to age, sex and tumor stage. Lastly, the association between TIs and (cancer free) survival should be specifically investigated in patients who have a high risk (based on low preoperative aerobic fitness) for postoperative complications, as these patients might benefit most from a comprehensive preoperative workup.

CONCLUSION

Studies are heterogeneous with regard to treatment interval definitions, treatment interval time-intervals and used outcome measures. *These key aspects need standardization before a reliable estimate can be made regarding an optimal TI.* Previous trials have

shown that prehabilitation with a program duration of 3-6 weeks, can effectively reduce postoperative complications. However, individual patients might benefit more from a more extensive time window. There is an urgent need for high-quality studies in large cohorts, in which colon and rectal cancer are studied separately with uniformly defined TI start and time-intervals. Moreover, subgroup analyses for patients with a high-risk of postoperative complications are needed in order to further clarify the association between TI and (cancer-free) survival in this subgroup of patients who are expected to benefit the most from a comprehensive preoperative prehabilitation program.

REFERENCES

1. Moug, S.J., et al., *Laparoscopic versus open surgery for colorectal cancer in the older person: A systematic review.* Ann Med Surg (Lond), 2015. **4**(3): p. 311-8.
2. Braga, M., et al., *Laparoscopic versus open colorectal surgery: a randomized trial on short-term outcome.* Ann Surg, 2002. **236**(6): p. 759-66; disscussion 767.
3. *Jaarrapportage 2018 DCRA*. 2018 09-11-2019]; Available from: https://dica.nl/jaarrapportage-2018/dcra.
4. Davies, S.J., et al., *Measuring outcomes after major abdominal surgery during hospitalization: reliability and validity of the Postoperative Morbidity Survey.* Perioper Med (Lond), 2013. **2**(1): p. 1.
5. Cienfuegos, J.A., et al., *The impact of major postoperative complications on long-term outcomes following curative resection of colon cancer.* Int J Surg, 2018. **52**: p. 303-308.
6. Law, W.L., et al., *The impact of postoperative complications on long-term outcomes following curative resection for colorectal cancer.* Ann Surg Oncol, 2007. **14**(9): p. 2559-66.
7. Weller, D., et al., *The Aarhus statement: improving design and reporting of studies on early cancer diagnosis.* Br J Cancer, 2012. **106**(7): p. 1262-7.
8. Silver, J.K. and J. Baima, *Cancer prehabilitation: an opportunity to decrease treatment-related morbidity, increase cancer treatment options, and improve physical and psychological health outcomes.* Am J Phys Med Rehabil, 2013. **92**(8): p. 715-27.
9. Barberan-Garcia, A., et al., *Personalised Prehabilitation in High-risk Patients Undergoing Elective Major Abdominal Surgery: A Randomized Blinded Controlled Trial.* Ann Surg, 2018. **267**(1): p. 50-56.
10. Berkel, A.E.M., et al., *Effects of Community-based Exercise Prehabilitation for Patients Scheduled for Colorectal Surgery With High Risk for Postoperative Complications: Results of a Randomized Clinical Trial.* Ann Surg, 2021.
11. Boereboom, C.L., et al., *Short-term pre-operative high-intensity interval training does not improve fitness of colorectal cancer patients.* Scand J Med Sci Sports, 2019. **29**(9): p. 1383-1391.
12. *Format transmural care pathway colorectal cancer*. 2017 01-17-2020]; 5:[Available from: https://shop.iknl.nl/shop/zorgpad-colorectaalcarcinoom/110209.
13. Molenaar, C.J.L., D.C. Winter, and G.D. Slooter, *Contradictory guidelines for colorectal cancer treatment intervals.* Lancet Oncol, 2021. **22**(2): p. 167-168.
14. Hangaard Hansen, C., et al., *The effect of time from diagnosis to surgery on oncological outcomes in patients undergoing surgery for colon cancer: A systematic review.* Eur J Surg Oncol, 2018. **44**(10): p. 1479-1485.
15. Burke, J.R., et al., *Tumour growth rate of carcinoma of the colon and rectum: retrospective cohort study.* BJS Open, 2020.
16. Amri, R., et al., *Treatment delay in surgically-treated colon cancer: does it affect outcomes?* Ann Surg Oncol, 2014. **21**(12): p. 3909-16.
17. Liberati, A., et al., *The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration.* Ann Intern Med, 2009. **151**(4): p. W65-94.
18. Paschke, S., et al., *Are Colon and Rectal Cancer Two Different Tumor Entities? A Proposal to Abandon the Term Colorectal Cancer.* Int J Mol Sci, 2018. **19**(9).
19. Ouzzani, M., et al., *Rayyan-a web and mobile app for systematic reviews.* Syst Rev, 2016. **5**(1): p. 210.
20. Downs, S.H. and N. Black, *The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions.* J Epidemiol Community Health, 1998. **52**(6): p. 377-84.

21. Lino-Silva, L.S., et al., *Overall survival of patients with colon cancer and a prolonged time to surgery.* J Surg Oncol, 2019. **119**(4): p. 503-509.
22. Kaltenmeier, C., et al., *Time to Surgery and Colon Cancer Survival in the United States.* Ann Surg, 2019.
23. Bagaria, S.P., et al., *Delay to Colectomy and Survival for Patients Diagnosed with Colon Cancer.* J Invest Surg, 2019. **32**(4): p. 350-357.
24. Wanis, K.N., S.V.B. Patel, and M. Brackstone, *Do Moderate Surgical Treatment Delays Influence Survival in Colon Cancer?* Dis Colon Rectum, 2017. **60**(12): p. 1241-1249.
25. Pruitt, S.L., et al., *Do diagnostic and treatment delays for colorectal cancer increase risk of death?* Cancer Causes Control, 2013. **24**(5): p. 961-77.
26. Grass, F., et al., *Impact of delay to surgery on survival in stage I-III colon cancer.* Eur J Surg Oncol, 2020. **46**(3): p. 455-461.
27. Kucejko, R.J., et al., *How Soon Should Patients With Colon Cancer Undergo Definitive Resection?* Dis Colon Rectum, 2020. **63**(2): p. 172-182.
28. Gleason, F., et al., *Early Elective Surgery After Colon Cancer Diagnosis has Higher Risk of Readmission and Death.* Ann Surg, 2020.
29. Redaniel, M.T., et al., *The association of time between diagnosis and major resection with poorer colorectal cancer survival: a retrospective cohort study.* BMC Cancer, 2014. **14**: p. 642.
30. Strous, M.T.A., M.L.G. Janssen-Heijnen, and F.J. Vogelaar, *Impact of therapeutic delay in colorectal cancer on overall survival and cancer recurrence - is there a safe timeframe for prehabilitation?* Eur J Surg Oncol, 2019. **45**(12): p. 2295-2301.
31. Gort, M., et al., *Actionable indicators for short and long term outcomes in rectal cancer.* Eur J Cancer, 2010. **46**(10): p. 1808-14.
32. *Oxford Centre for Evidence-Based Medicine—levels of evidence (March 2009).* 03-24-2020]; Available from: http://www.cebm.net/2009/06/oxford-centre-evidence-based-medicine-levels-evidence-march-2009/.
33. IKNL. *Cijfers over Kanker*. 25-04-2020]; Available from: https://www.cijfersoverkanker.nl/selecties/incidentie_darm/img5c0ce0cb85745.
34. Shin, D.W., et al., *Delay to curative surgery greater than 12 weeks is associated with increased mortality in patients with colorectal and breast cancer but not lung or thyroid cancer.* Ann Surg Oncol, 2013. **20**(8): p. 2468-76.
35. Fernandez, E., et al., *Symptom-to-diagnosis interval and survival in cancers of the digestive tract.* Dig Dis Sci, 2002. **47**(11): p. 2434-40.
36. Trepanier, M., et al., *Improved Disease-free Survival After Prehabilitation for Colorectal Cancer Surgery.* Ann Surg, 2019. **270**(3): p. 493-501.

SUPPLEMENTAL FILE 1. PUBMED SEARCH STRATEGY.

P
"colorectal-neoplasms"[MeSH] OR colorectal-neoplasm[tiab] OR colorectal-neoplasms[tiab] OR colorectal-neoplasia[tiab] OR colorectal-tumor[tiab] OR colorectal-tumors[tiab] OR colorectal-tumour[tiab] OR colorectal-tumours[tiab] OR colorectal-carcinoma[tiab] OR colorectal-carcinomas[tiab] OR colorectal-cancer[tiab] OR colorectal-cancers[tiab] OR colorectal-malignancy[tiab] OR colorectal-malignancies [tiab] OR colon-neoplasm[tiab] OR colon-neoplasms[tiab] OR colon-neoplasia[tiab] OR colon-tumor[tiab] OR colon-tumors[tiab] OR colon-tumour[tiab] OR colon-tumours[tiab] OR colon-carcinoma[tiab] OR colon-carcinomas[tiab] OR colon-cancer[tiab] OR colon-cancers[tiab] OR colon-malignancy[tiab] OR colon-malignancies [tiab] OR colonic-neoplasm[tiab] OR colonic-neoplasms[tiab] OR colonic-neoplasia[tiab] OR colonic-tumor[tiab] OR colonic-tumors[tiab] OR colonic-tumour[tiab] OR colonic-tumours[tiab] OR colonic-carcinoma[tiab] OR colonic-carcinomas[tiab] OR colonic-cancer[tiab] OR colonic-cancers[tiab] OR colonic-malignancy[tiab] OR colonic-malignancies [tiab] OR rectal-neoplasm[tiab] OR rectal-neoplasms[tiab] OR rectal-neoplasia[tiab] OR rectal-tumor[tiab] OR rectal-tumors[tiab] OR rectal-tumour[tiab] OR rectal-tumours[tiab] OR rectal-carcinoma[tiab] OR rectal-carcinomas[tiab] OR rectal-cancer[tiab] OR rectal-cancers[tiab] OR rectal-malignancy[tiab] OR rectal-malignancies [tiab] OR cancer-of-the-colon[tiab] OR cancer-of-the-rectum[tiab]
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"time-to-treatment"[MeSH] OR time-to-treatment[tiab] OR time-to-treatments[tiab] OR waiting-time[tiab] OR waiting-times[tiab] OR door-to-treatment-time[tiab] OR therapeutic-delay[tiab] OR therapeutic-delays[tiab] OR waiting-period[tiab] OR waiting-periods[tiab] OR waiting-time[tiab] OR waiting-times[tiab] OR wait-time[tiab] OR wait-times[tiab] OR wait-period[tiab] OR wait-periods[tiab] OR provider-delay[tiab] OR provider-delays[tiab] OR surgery-delay[tiab] OR surgery-delays[tiab] OR time-to-surgery [tiab] OR delayed-treatment[tiab] OR delayed-treatments[tiab] OR treatment-delay[tiab] OR treatment-delays[tiab] OR optimal-timing[tiab]
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"survival"[MeSH] OR survival[tiab] OR "mortality"[MeSH] OR mortality[tiab] OR death-rate[tiab] OR death-rates[tiab] OR progression[tiab] OR recurrence[tiab] OR Time-to-failure[tiab] OR "prognosis"[MeSH] OR prognosis[tiab] OR prognoses[tiab] OR "morbidity"[MeSH] OR morbidity[tiab] OR morbidities[tiab]

2ª

CHAPTER 2A

Letter to the editor: Can we really conclude that treatment delays are associated with poorer outcome in patients with colorectal cancer awaiting elective surgery?

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Dear editor, with great interest we read the systematic review by Whittaker et al. [1] published in Colorectal Disease. The study aims to explore the association between treatment delay (TD), and overall survival (OS) or disease free survival (DFS) in patients undergoing elective surgery for colorectal cancer (CRC). The authors concluded that elective surgery for CRC should not be postponed longer than 4 weeks. Although we endorse the importance of the aim of the study, we have some methodological concerns regarding this systematic review and meta-analysis.

Considering the wide heterogeneity in the definition of TD, it is questionable whether it is valid to perform a meta-analysis of the included studies. Although the end of the TD is generally clearly defined, the time-point used as diagnosis, which is mostly taken as starting point of TD, is defined less consistently. Definitions of diagnosis can vary from first investigation for defining malignancy to diagnosis confirmed by multidisciplinary team meeting [2]. From experience in our own hospital, these time-points can be as far as 7-14 days apart. In some studies, such as Kucejko et al. [3], diagnosis was not specified at all. Heterogeneity in the definition of TD makes it questionable whether it is valid to pool Hazard Ratios from the included studies in a meta-analysis.

Besides our concern about the methodology, we believe the conclusion is not sufficiently supported by the data presented. The authors state that elective surgery for CRC should not be postponed longer than 4 weeks. This interval seems to be chosen arbitrarily as this 4 week interval is not consistent with the intervals used in the included studies. For example, the study of Strous et al. [4] used a cutoff point of >5 weeks. In addition, with regard to the inconsistencies in definition of diagnosis, it is unclear how this maximum TD of 4 weeks (or any TD) should be interpreted (i.e., 4 weeks starting at what time-point).

The conclusion seems to be based on the association between TD and OS while the association between TD and DFS is far more interesting with regard to treatment delays and preparation for surgery. It is well known that OS is influenced by many factors. Some studies show that more frail patients often have a longer TD which might at least partially explain a possible association between a longer TD and OS [3]. As also acknowledged by the authors, not all included studies adjusted their analysis for patient factors associated with frailty [5]. As the main concern of longer treatment delays is tumor growth and risk for metastasis, DFS should be the main outcome of this systematic review.

We agree with the authors that TDs other than those that are needed for pre-treatment work-up or optimization of health should be avoided in order to provide optimal care and minimize patient distress. However, especially in patients at high risk for complica-

tions, interventions aimed at reducing complications might be more instrumental than aiming for short treatment delays. Perhaps a shift in thinking from "treatment-*delay*" to "optimization-period" would allow for more individualized "treatment-intervals".

REFERENCES

1. Whittaker, T.M., et al., *Delay to elective colorectal cancer surgery and implications for survival: a systematic review and meta-analysis.* Colorectal Dis, 2021.
2. Molenaar, C.J.L., et al., *Conflicting Guidelines: A Systematic Review on the Proper Interval for Colorectal Cancer Treatment*. World J Surg, 2021.
3. Kucejko, R.J., et al., *How Soon Should Patients With Colon Cancer Undergo Definitive Resection?* Dis Colon Rectum, 2020. **63**(2): p. 172-182.
4. Strous, M.T.A., M.L.G. Janssen-Heijnen, and F.J. Vogelaar, *Impact of therapeutic delay in colorectal cancer on overall survival and cancer recurrence - is there a safe timeframe for prehabilitation?* Eur J Surg Oncol, 2019. **45**(12): p. 2295-2301.
5. Grass, F., et al., *Impact of delay to surgery on survival in stage I-III colon cancer.* Eur J Surg Oncol, 2020. **46**(3): p. 455-461.

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CHAPTER 3

Treatment interval in curative treatment of colon cancer and its impact on (cancer free) survival in high-risk and non-high-risk patients

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CHAPTER 4

Inter-observer agreement of preoperative cardiopulmonary exercise test interpretation in major abdominal surgery

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ABSTRACT

Background

Accurate determination of cardiopulmonary exercise test (CPET) derived parameters is essential to allow for uniform preoperative risk assessment. The objective of this prospective observational study was to evaluate the inter-observer agreement of preoperative CPET-derived variables by comparing a self-preferred approach with a systematic guideline-based approach.

Methods

Twenty-six professionals from multiple centers across the Netherlands interpreted 12 preoperative CPETs of patients scheduled for hepatopancreatobiliary surgery. Outcome parameters of interest were oxygen uptake at the ventilatory anaerobic threshold ($\dot{V}O_{2VAT}$) and at peak exercise ($\dot{V}O_{2peak}$), the slope of the relationship between the minute ventilation and carbon dioxide production ($\dot{V}E/\dot{V}CO_2$-slope), and the oxygen uptake efficiency slope (OUES). Inter-observer agreement of the self-preferred approach and the guideline-based approach was quantified by means of the intra-class correlation coefficient.

Results

Across the complete cohort, inter-observer agreement intraclass correlation coefficient (ICC) was 0.76 (95% confidence interval (CI) 0.57-0.93) for $\dot{V}O_{2VAT}$, 0.98 (95% CI 0.95-0.99) for $\dot{V}O_{2peak}$, and 0.86 (95% CI 0.75-0.95) for the $\dot{V}E/\dot{V}CO_2$-slope when using the self-preferred approach. By using a systematic guideline-based approach, ICCs were 0.88 (95% CI 0.74-0.97) for $\dot{V}O_{2VAT}$, 0.99 (95% CI 0.99-1.00) for $\dot{V}O_{2peak}$, 0.97 (95% CI 0.94-0.99) for the $\dot{V}E/\dot{V}CO_2$-slope, and 0.98 (95% CI 0.96-0.99) for the OUES.

Conclusions

Inter-observer agreement of numerical values of CPET-derived parameters can be improved by using a systematic guideline-based approach. Effort-independent variables such as the $\dot{V}E/\dot{V}CO_2$-slope and the OUES might be useful to further improve uniformity in preoperative risk assessment in addition to, or in case $\dot{V}O_{2VAT}$ and $\dot{V}O_{2peak}$ are not determinable.

BACKGROUND

There is an increased focus on improving preoperative risk assessment and identification of the high-risk surgical patient scheduled for major surgery in order to guide shared clinical decision-making and patient management [1] by estimating the likelihood of postoperative morbidity and mortality [2]. CPET is an appealing test for preoperative risk assessment, as it provides an objective assessment of the integrative response to exercise of the cardiovascular, pulmonary, and neuromuscular system [3]. Previous research among patients with abdominal cancer has shown that preoperative CPET is an objective and reliable tool for identifying patients at high risk for complications [4-7].

The most frequently reported preoperative CPET-derived parameters that are used for risk assessment in major abdominal surgery are the oxygen uptake ($\dot{V}O_2$) at the ventilatory anaerobic threshold ($\dot{V}O_{2VAT}$), the ventilatory equivalent for carbon dioxide ($\dot{V}E/\dot{V}CO_2$) at the VAT ($\dot{V}E/\dot{V}CO_{2VAT}$), and the highest attained $\dot{V}O_2$ at peak exercise ($\dot{V}O_{2peak}$) [8, 9]. Downsides of these often-used risk assessment parameters are that a maximal effort is required to obtain a valid $\dot{V}O_{2peak}$, which is, depending on the used definition and population, not accomplished in 25-86% of the participants performing CPET [10, 11]. Methods of determining the submaximal $\dot{V}O_{2VAT}$ are complex [12] and there remains controversy about the underlying physiology of the $\dot{V}O_{2VAT}$ [12]. A previous study has shown that the $\dot{V}O_{2VAT}$ is not determinable in approximately 16% of the preoperative CPETs [13].

The use of submaximal indicators of aerobic capacity that are determinable in all patients could improve uniformity and reduce variety of preoperative risk assessment within and between hospitals. The slope describing the relation between minute ventilation and carbon dioxide production ($\dot{V}E/\dot{V}CO_2$-slope) is a submaximal parameter of ventilatory efficiency that can be used when $\dot{V}E/\dot{V}CO_{2VAT}$ is not determinable [2]. More recently, the oxygen uptake efficiency slope (OUES) has been introduced as an effort-independent indicator for aerobic capacity in patients undergoing major abdominal surgery [14]. The OUES is well correlated to both $\dot{V}O_{2VAT}$ [14] and $\dot{V}O_{2peak}$ [14, 15].

Although there is some research investigating the inter-observer agreement of the $\dot{V}O_{2VAT}$ and the $\dot{V}O_{2peak}$ in preoperative CPET [13], data on the inter-observer agreement of the preoperative $\dot{V}E/\dot{V}CO_2$-slope and OUES are lacking. In addition, it is unknown whether uniformity in determination of CPET-derived parameters can be improved by using a set of guidelines for CPET interpretation. Therefore, the aim of this study was to investigate the inter-observer agreement of determination of preoperative CPET parameters used for preoperative risk assessment in patients undergoing major abdominal surgery by using either a self-preferred or a systematic guideline-based approach.

METHODS

Study design

In this observational study, observers representing multiple centers across the Netherlands were asked to interpret 12 preoperative CPETs on two occasions, with at least four weeks between each interpretation session. The CPET order was shuffled between the interpretation sessions to prevent observers to be able to recall their previous CPET interpretation. At the first interpretation session, observers interpreted the CPETs using the method(s) they normally use, a self-preferred approach. At the second session, observers used a systematic guideline-based approach for CPET interpretation. The study was approved by the medical ethics committee of Zuyderland (METCZ20200160). Reporting was performed in accordance with the STROBE guidelines for observational studies [16].

Observers

Potential observers were recruited via the Netherlands Association of Sports Medicine (VSG) and a Dutch network of clinical exercise physiologists and were contacted by e-mail with the request to anonymously fill in a short questionnaire regarding CPET experience, CPET training, preferred CPET interpretation methods, and CPET experience in health-compromised populations. Subsequently, potential observers were asked whether they were potentially willing to participate in a study regarding inter-observer agreement of preoperative CPET interpretation. Potential observers were eligible if they were familiar with interpretation of CPETs in health-compromised populations. All participating observers provided informed consent before taking part in this study.

Data collection

Preoperative CPETs performed in patients scheduled for hepatopancreatobiliary surgery at the University Medical Centre Groningen were randomly selected from an existing database. The database consisted of CPETs performed on a cycle ergometer (Monark Exercise LC6, Vansbro, Sweden) in upright position using a breath-by-breath CPET system (Quark CPET, COSMED Srl, Rome, Italy) between March 2019 and March 2020. A detailed description of the CPET protocol can be found elsewhere [17]. The CPET protocol comprised a two-minute resting phase, a three-minute warm-up of unloaded cycling, and an incremental phase with constant work rate increments of 5, 10, or 15 W/min, depending on the patient's estimated physical fitness level and aimed at reaching a maximal effort within eight to twelve minutes. Throughout CPET, patients had to maintain a pedaling frequency between 60 and 80 revolutions/min. The protocol continued until the patient's pedaling frequency fell definitely below 60 revolutions/min, despite strong verbal encouragement. Patient data was anonymized and patient characteristics other than date of birth, sex, and body mass were concealed.

All CPETs were interpreted by the observers using the Omnia software version 1.6.8.0 (COSMED Srl, Rome, Italy) that was installed on a remote computer. Data display settings were set to 10-second average fixed time intervals. At least one week before each CPET interpretation session, observers received a short software manual. Before each CPET interpretation session, observers were contacted by telephone with oral instructions. In addition, a member of the research team (RF or AE) was available for assistance during each interpretation session. Observers were able to switch between tests as often as desired. During the first interpretation session, observers interpreted the CPETs by using their self-preferred approach. During the second interpretation session, observers used a systematic guideline-based approach for CPET interpretation. The guideline used in this study (see Additional file 1) was composed based on established CPET guidelines [2, 3, 14, 18-20]. Observers were asked to interpret the $\dot{V}O_{2VAT}$, $\dot{V}O_{2peak}$, and $\dot{V}E/\dot{V}CO_2$-slope up to the respiratory compensation point on both sessions, whereas they were asked to determine the OUES merely at the second interpretation session as the majority of the observers (73%) appeared not to be familiar with determination of the OUES.

Statistical analyses

Statistical analyses were performed using IBM SPSS Statistics version 26.0 (IBM, Chicago, IL, USA). A sample size calculation was performed using the sampicc function in STATA statistical software. Based on a previous study of Abbott et al., the estimated intraclass correlation coefficient (ICC) was 0.83 for $\dot{V}O_{2VAT}$ and 0.88 for $\dot{V}O_{2peak}$ [13]. It was hypothesized that the ICC values for the $\dot{V}E/\dot{V}CO_2$-slope and OUES would be markedly higher, as interpretation of these parameters is less complex. Starting from an ICC of 0.85 with an estimated full width of the 95% confidence interval (CI) of 0.11 below and above the point estimate, a minimum of 22 raters was required with a sample of 12 CPETs per rater. Descriptive analyses of the data were presented as mean ± standard deviation (SD) or 95% CI, or as median (interquartile range [IQR]), as appropriate based on the Shapiro-Wilk test. Data regarding non-determinable parameters was presented descriptively as percentages relative to the total number of observations per parameter. Inter-observer agreement was estimated for each of the CPETs outcome parameter by calculating the intraclass correlation coefficient (ICC) for the self-preferred approach and the systematic guideline-based approach separately. A two-way random model, single measures and absolute agreement ICC was calculated to estimate the inter-observer agreement. An ICC of 0 indicates no agreement and 1 indicates perfect agreement. ICC values were interpreted according to the classification of reliability, with values <0.50, 0.50-0.75, 0.75-0.90, and >0.90 representing poor, moderate, good, and excellent agreement, respectively [21]. In a primary analysis, ICCs of each CPET parameter separately were calculated for the total group of observers. Thereafter, ICCs were calculated for several subgroups of observers.

RESULTS

A total of 98 completed questionnaires were returned (response rate of 49%), of which 54 responders (55%) agreed to be contacted for further information concerning study participation. Eventually, 27 observers (28%) were willing to participate and provided informed consent. As one observer withdrew before the start of the study, 26 observers (27%) were included in the analyses. There was no loss to follow-up, meaning that all observers completed the 12 CPET observations on both interpretation sessions with a mean ± SD time between interpretation sessions of 66 ± 22 days.

Professions of the participating observers consisted of sports physicians (n=17), sports medicine residents (n=5), and clinical exercise physiologists (n=4). The median [IQR] duration of experience of the observers with CPET interpretation in general and CPET interpretation in health-compromised populations was 7.5 [9.0] and 6.0 [7.0] years, respectively. Observers interpreted 150 [114] CPETs annually (See Table 1).

Table 1. Observer characteristics.

	n (%)	Median [IQR]]
Sports physician	17 (64.4)	
Sports medicine resident	5 (19.2)	
Clinical exercise physiologist	4 (15.4)	
CPET experience (years)		7.5 [9.0]
Sports physician		10.0 [9.0]
Sports medicine resident		3.0 [2.0]
Clinical exercise physiologist		7.0 [11.0]
CPET experience in health-compromised populations (years)		6.0 [7.0]
Sports physician		7.0 [6.0]
Sports medicine resident		3.0 [2.0]
Clinical exercise physiologist		7.0 [11]
Quantity of observed CPETs annually		150 [114]
Sports physician		150 [100]
Sports medicine resident		100 [247]
Clinical exercise physiologist		226 [277]
Attended a formal CPET course	25 (96)	

Abbreviations: CPET = cardiopulmonary exercise testing; IQR = interquartile range.

The grand mean ± SD of all CPET observations for the complete cohort of observers using the self-preferred and guideline-based approach were respectively 12.1 ± 2.6 and 12.3 ± 2.6 mL/kg/min for $\dot{V}O_{2VAT}$, 17.4 ± 5.3 and 17.3 ± 5.4 mL/kg/min for $\dot{V}O_{2peak}$, and 30.7 ± 6.9 and 30.6 ± 7.1 for the $\dot{V}E/\dot{V}CO_2$-slope. The grand mean ± SD OUES normalized for body mass was 21.6 ± 6.1 for all observers using the guideline-based approach. There were no statistically significant differences in determined CPET parameters between the two approaches (See Table 2). Mean values for $\dot{V}O_{2VAT}$, $\dot{V}O_{2peak}$ and the $\dot{V}E/\dot{V}CO_2$-slope as interpreted by the observers using both approaches are presented in Table 2 for each interpreted CPET separately. Figure 1 (graph A, B and C) depicts the observed values of the CPET-derived parameters in each patient during the self-preferred approach. Based on the numerical $\dot{V}O_{2VAT}$ and $\dot{V}O_{2peak}$ values reported by the observers, there was no uniform classification whether a patient was considered a low-risk or high-risk patient in respectively 5 and 2 patients (Figure 1, graph A and B), as observations cross the line identifying the predefined risk thresholds. When using the systematic guideline-based approach, there was no uniform risk classification based on $\dot{V}O_{2VAT,}$ $\dot{V}O_{2peak}$, and the OUES in respectively 5, 0, and 1 patients (see Figure 2, graph A, B, and D).

Inter-observer agreement of preoperative CPET interpretation using a self-preferred approach

When using a self-preferred approach, the maximum number of observations per observed CPET parameter was 312 (26 observers × 12 CPETs). Regarding $\dot{V}O_{2VAT}$, 11 (4%) observations were missing, as observers reported them as not determinable. For the $\dot{V}E/\dot{V}CO_2$-slope, 26 observations (8.3%) were missing, as two observers (7.8%) were unfamiliar with $\dot{V}E/\dot{V}CO_2$-slope interpretation and therefore did not interpret this parameter. In addition, 2 $\dot{V}E/\dot{V}CO_2$-slope observations (<1%) were missing without a known reason. No observations were missing for $\dot{V}O_{2peak}$. See Figure 3 for an overview of the number of observations per parameter. As depicted in Figure 4, for the complete cohort of observers, the inter-observer agreement ICC was 0.76 (95% CI 0.57-0.93) for $\dot{V}O_{2VAT}$, 0.98 (95% CI 0.95-0.99) for $\dot{V}O_{2peak}$, and 0.86 (95% 0.75-0.95) for the $\dot{V}E/\dot{V}CO_2$-slope. Table 3 shows the inter-observer agreement ICC according to profession, the number of observed CPETs annually, the number of years of experience with CPET interpretation, and the number of years of experience with CPET interpretation in health-compromised populations.

Inter-observer agreement of preoperative CPET interpretation using a guideline-based approach

As there was no loss to follow-up of observers, the maximum number of observations when using a guideline-based approach also was 312 observations per CPET parameter. For $\dot{V}O_{2VAT}$, 13 observations (4%) were missing due to observers reporting the parameter as undeterminable. For $\dot{V}O_{2peak}$, 78 observations (25%) were missing because observers

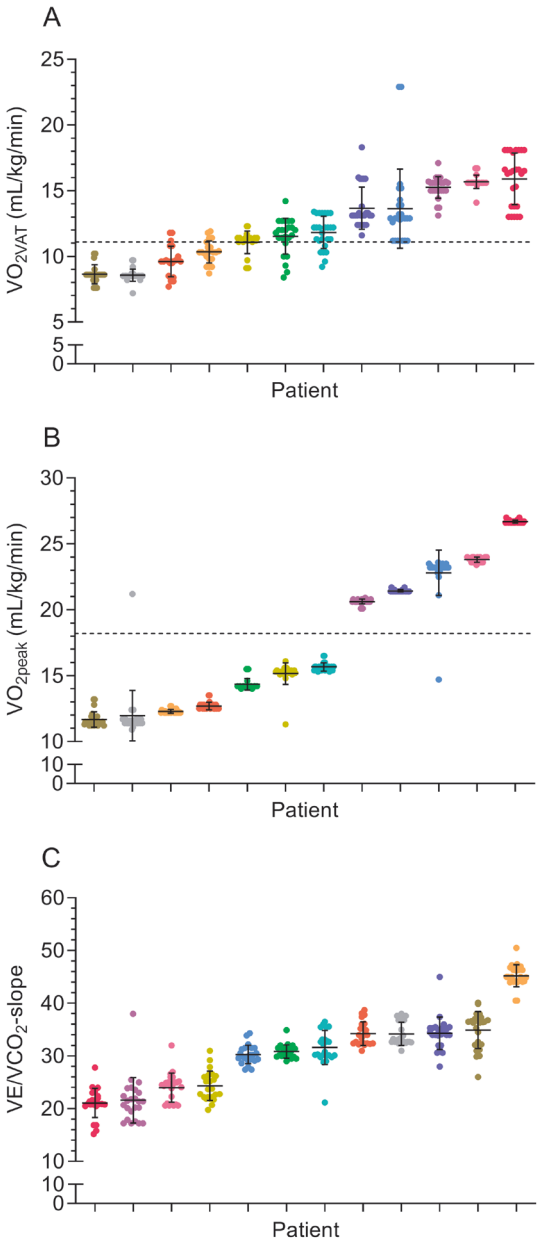

Figure 1. Observed values of the $\dot{V}O_{2VAT}$ (graph A), $\dot{V}O_{2peak}$ (graph B), and $\dot{V}E/\dot{V}CO_2$-slope (graph C) in each patient using the self-preferred approach ordered according to increasing value of the mean. Dots represent values determined by individual observers. Each vertical collection of dots represents an individual patient, in which each patient has a unique color throughout all graphs. Horizontal dotted lines represent known risk assessment thresholds defined as 11.1 mL/kg/min for $\dot{V}O_{2VAT}$[4] (graph A) and 18.2 mL/kg/min for $\dot{V}O_{2peak}$[4] (graph B). Error bars represent the SD of the mean.

Abbreviations: SD = standard deviation; $\dot{V}E/\dot{V}CO_2$-slope = slope of the relationship between the minute ventilation and carbon dioxide production; $\dot{V}O_{2peak}$ = oxygen uptake at peak exercise; $\dot{V}O_{2VAT}$ = oxygen uptake at the ventilatory anaerobic threshold.

Table 2. CPET-derived parameters using the self-preferred and guideline-based approach in individual patients.

Patient	SPA $\dot{V}O_{2VAT}$ (mL/kg/min)	GBA $\dot{V}O_{2VAT}$ (mL/kg/min)	Number of observations $\dot{V}O_{2VAT}$ (SPA; GBA)	SPA $\dot{V}O_{2peak}$ (mL/kg/min)	GBA Valid $\dot{V}O_{2peak}$ [a] (mL/kg/min)	Number of observations $\dot{V}O_{2peak}$ (SPA; GBA)	SPA $\dot{V}E/\dot{V}CO_2$-slope	GBA $\dot{V}E/\dot{V}CO_2$-slope	Number of observations $\dot{V}E/\dot{V}CO_2$-slope (SPA [b]; GBA)	GBA OUES/kg	Number of observations OUES (GBA)
1	11.1 ± 0.9	11.4 ± 0.8	26;25	15.2 ± 0.8	15.2 ± 0.1	26;26	24.3 ± 2.8	24.1 ± 1.3	24;26	17.4 (0.7)	26
2	13.6 ± 3.0	12.9 ± 1.0	26;26	22.8 ± 1.7	23.2 ± 0.5	26;18	30.3 ± 1.8	31.2 ± 1.1	24;26	24.8 (0.1)	26
3	9.6 ± 1.2	9.8 ± 1.4	22;22	12.7 ± 0.3	12.5 ± 0.1	26;21	34.2 ± 2.2	32.5 ± 1.0	22 [c];26	16.6 (0.3)	26
4	15.9 ± 2.0	16.3 ± 2.1	26;25	26.7 ± 0.1	26.5 ± 0.1	26;26	21.1 ± 2.8	21.3 ± 0.5	24;26	29.2 (0.4)	26
5	11.8 ± 1.2	11.7 ± 1.1	26;26	15.7 ± 0.3	15.3 ± 0.3	26;26	31.6 ± 3.2	32.4 ± 2.3	24;26	20.4 (1.5)	26
6	15.2 ± 0.8	15.5 ± 1.1	26;26	20.6 ± 0.2	20.6 ± 0.0	26;24	21.6 ± 4.3	21.2 ± 1.1	24;26	26.0 (2.1)	26
7	8.6 ± 0.7	9.0 ± 0.7	26;26	11.7 ± 0.6	11.3 ± 0.2	26;18	34.9 ± 3.5	36.1 ± 2.2	24;26	14.1 (0.3)	26
8	15.7 ± 0.5	15.9 ± 0.9	25;26	23.8 ± 0.2	23.5 ± 0.3	26;25	24.0 ± 2.7	24.4 ± 1.0	24;26	31.4 (0.7)	26
9	8.6 ± 0.5	8.8 ± 0.5	26;26	12.0 ± 1.9	11.4 ± 0.1	26;12	34.2 ± 2.2	32.7 ± 0.3	24;26	15.9 (0.0)	26
10	13.7 ± 1.6	13.9 ± 1.7	26;26	21.4 ± 0.1	21.4 ± 0.0	26;22	34.3 ± 3.1	34.5 ± 1.0	24;26	23.7 (0.8)	26
11	10.3 ± 0.8	10.5 ± 0.8	22;22	12.3 ± 0.1	12.3 ± 0.3	26;8	45.2 ± 2.1	46.1 ± 0.4	24;26	12.2 (0.2)	26
12	11.5 ± 1.4	11.5 ± 1.6	24;24	14.4 ± 0.4	14.3 ± 0.1	26;8	30.9 ± 1.3	31.1 ± 0.8	22 [c];26	23.3 (0.2)	26
Grand mean	12.1 ± 2.6	12.3 ± 2.6	25;25	17.4 ± 5.3	17.3 ± 5.4	26;20	30.7 ± 6.9	30.6 ± 7.1	24;26	21.6 (6.1)	26
Grand mean difference [d] (P-value)	-0.2 (P=0.903)			0.2 (P=0.946)			0.1 (P=0.977)				

Values are reported as mean ± SD.

[a]: Validity of the attained $\dot{V}O_{2peak}$ based on objective criteria of a maximal effort was only determined using the guideline-based approach.

[b]: Maximum number of observations was 24, as two observers were unfamiliar with interpretation of the $\dot{V}E/\dot{V}CO_2$-slope and therefore did not report this parameter.

[c]: Missing values of unknown origin.

[d]: Grand mean difference was calculated as SPA minus GBA.

Abbreviations: CPET = cardiopulmonary exercise testing; GBA = guideline-based approach; OUES = oxygen uptake efficiency slope; SD = standard deviation; SPA = self-preferred approach; $\dot{V}E/\dot{V}CO_2$-slope = slope of the relationship between the minute ventilation and carbon dioxide production; $\dot{V}O_{2peak}$ = oxygen uptake at peak exercise; $\dot{V}O_{2VAT}$ = oxygen uptake at the ventilatory anaerobic threshold.

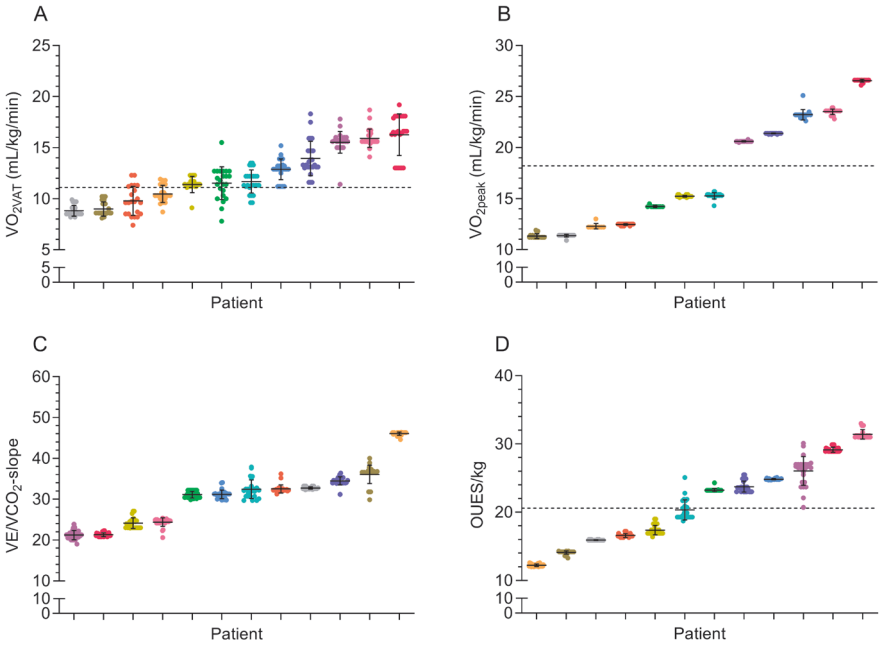

Figure 2. Observed values of the $\dot{V}O_{2VAT}$ (graph A), $\dot{V}o_{2peak}$ (graph B), $\dot{V}E/\dot{V}CO_2$-slope (graph C), and OUES/kg (graph D) in each patient using the guideline-based approach ordered according to increasing value of the mean. Dots represent values determined by individual observers. Each vertical collection of dots represents an individual patient, in which each patient has a unique color throughout all graphs. Horizontal dotted lines represent known risk assessment thresholds defined as 11.1 mL/kg/min for $\dot{V}O_{2VAT}$ [4] (graph A), 18.2 mL/kg/min for $\dot{V}O_{2peak}$[4] (graph B), and 20.6 for the OUES/kg[14] (graph D). Error bars represent the SD of the mean.

Abbreviations: OUES = oxygen uptake efficiency slope; SD = standard deviation; $\dot{V}E/\dot{V}CO_2$-slope = slope of the relationship between the minute ventilation and carbon dioxide production; $\dot{V}O_{2peak}$ = oxygen uptake at peak exercise; $\dot{V}O_{2VAT}$ = oxygen uptake at the ventilatory anaerobic threshold.

reported that no valid $\dot{V}O_{2peak}$ could be determined. Regarding the $\dot{V}E/\dot{V}CO_2$-slope and OUES, no observations were missing. Figure 3 depicts an overview of the number of observations per parameter. As depicted in Figure 4, for the complete cohort of observers, the inter-observer agreement ICC for $\dot{V}O_{2VAT}$ was 0.88 (95% CI 0.74-0.97), 0.99 (95% CI 0.99-1.00) for $\dot{V}O_{2peak}$, 0.97 (95% CI 0.94-0.99) for the $\dot{V}E/\dot{V}CO_2$-slope, and 0.98 (95% CI 0.96-0.99) for the OUES. Table 3 shows the inter-observer agreement ICC categorized according to profession, the number of observed CPETs annually, the number of years of experience with CPET interpretation, and the number of years of experience with CPET interpretation in health-compromised populations. There were no significant differences between categories.

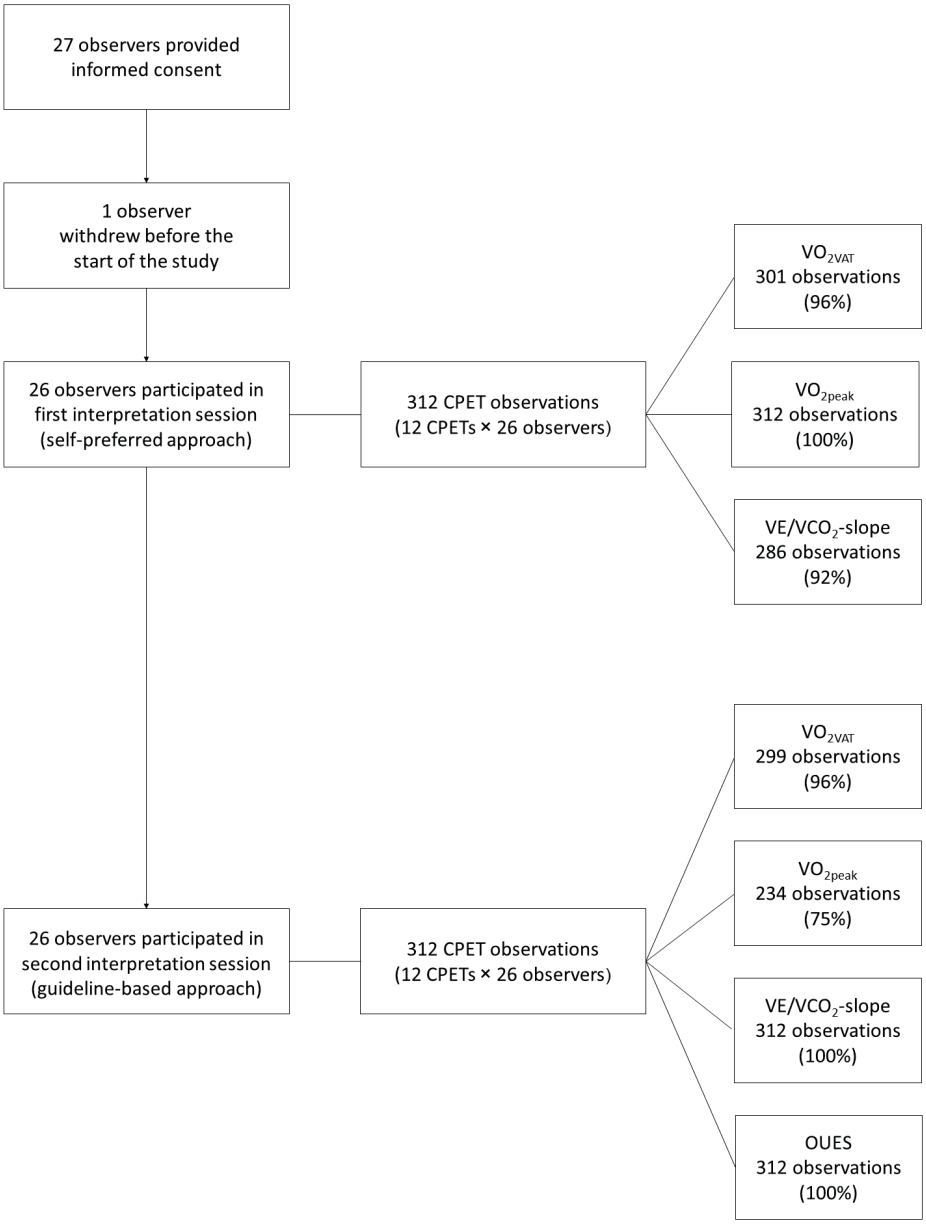

Figure 3. Flow diagram showing the number of study participants (observers) and the total number of observations per CPET-derived parameter for the self-preferred and the systematic guideline-based approach.

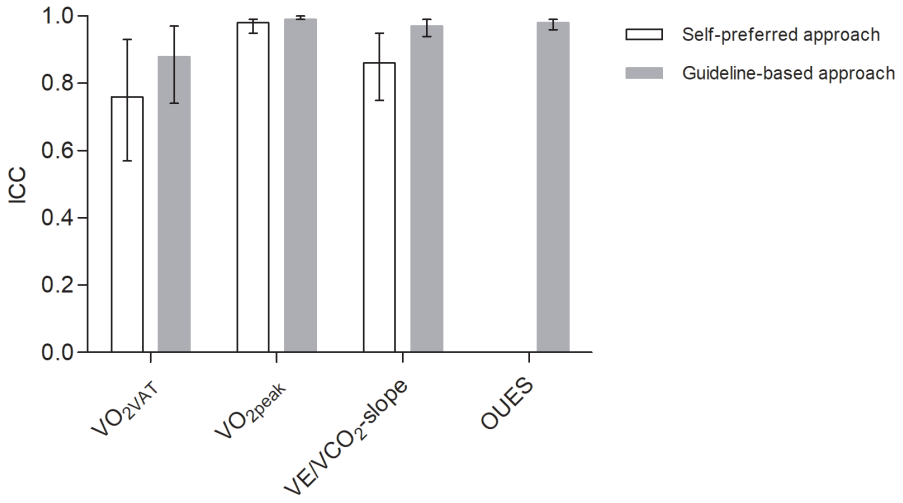

Figure 4. Intra-class correlation coefficient per CPET-derived parameter for the total group of observers.
Error bars represent the 95% CI.
Abbreviations: CI = confidence interval; OUES = oxygen uptake efficiency slope; $\dot{V}E/\dot{V}CO_2$-slope = slope of the relation between the minute ventilation and carbon dioxide production; $\dot{V}O_{2peak}$ = oxygen uptake at peak exercise, $\dot{V}O_{2VAT}$ = oxygen uptake at the ventilatory anaerobic threshold.

DISCUSSION

The aim of the current study was to determine the inter-observer agreement of preoperative CPET-derived risk assessment parameters by using either a self-preferred approach or a systematic guideline-based approach. When using a self-preferred approach, inter-observer agreement within the whole cohort of observers was moderate-to-good for $\dot{V}O_{2VAT}$, excellent for $\dot{V}O_{2peak}$, and good for the $\dot{V}E/\dot{V}CO_2$-slope. Inter-observer agreement when using a guideline-based approach was good for $\dot{V}O_{2VAT}$ and excellent for $\dot{V}O_{2peak}$, the $\dot{V}E/\dot{V}CO_2$-slope, and the OUES. This implies that inter-observer agreement of CPET-derived parameters might be improved by using a systematic guideline-based approach. These findings are important for improvement of preoperative risk assessment and future clinical guideline development.

High levels of inter-observer agreement are paramount to allow for reliable and uniform preoperative risk assessment to guide shared clinical decision-making and optimize patient management. $\dot{V}O_{2VAT}$ and $\dot{V}O_{2peak}$ are generally considered to be the most important preoperative risk assessment parameters that are consistently and independently associated with postoperative outcomes following major abdominal surgery [8]. The ICC value for the determined $\dot{V}O_{2VAT}$ using the self-preferred approach found in the current study was lower than the previously reported inter-observer agreement ICC value for

Table 3. Inter-observer agreement of CPET-derived parameters in subgroups of observers using the self-preferred and guideline-based approach.

	SPA $\dot{V}O_{2VAT}$ ICC (95% CI)	GBA $\dot{V}O_{2VAT}$ ICC (95% CI)	SPA $\dot{V}O_{2peak}$ ICC (95% CI)	GBA $\dot{V}O_{2peak}$ [a] ICC (95% CI)	SPA $\dot{V}E/\dot{V}CO_2$-slope ICC (95% CI)	GBA $\dot{V}E/\dot{V}CO_2$-slope ICC (95% CI)	GBA OUES [b] ICC (95% CI)
Profession							
Sports physician (n=17)	0.77 (0.57-0.93)	0.87 (0.74-0.97)	0.97 (0.99-1.0)	1.00 (1.00-1.00)	0.83 (0.70-0.94)	0.97 (0.94-0.99)	0.99 (0.97-0.99)
Sports medicine residents (n=5)	0.83 (0.66-0.94)	0.87 (0.71-0.97)	0.99 (0.99-1.00)	1.00 (0.99-1.00)	0.87 (0.75-0.96)	0.97 (0.97-1.00)	0.98 (0.96-0.99)
Clinical exercise physiologist (n=4)	0.66 (0.35-0.89)	0.76 (0.51-0.91)	0.87 (0.73-0.96)	0.99 (0.97-1.00)	0.97 (0.93-0.99)	0.97 (0.93-0.99)	0.97 (0.92-0.99)
CPET experience							
≤7 years (n=13)	0.81 (0.63-0.94)	0.87 (0.72-0.97)	0.98 (0.95-0.99)	1.00 (0.99-1.00)	0.88 (0.77-0.96)	0.98 (0.95-0.99)	0.99 (0.97-0.99)
7 years (n=13)	0.72 (0.50-0.92)	0.86 (0.71-0.96)	0.98 (0.95-0.99)	1.00 (1.00-1.00)	0.84 (0.71-0.94)	0.97 (0.93-0.99)	0.98 (0.95-0.99)
CPET experience in health-compromised populations							
≤6 years (n=12)	0.78 (0.60-0.92)	0.88 (0.75-0.97)	0.98 (0.95-0.99)	1.00 (1.00-1.00)	0.90 (0.82-0.97)	0.98 (0.96-0.99)	0.98 (0.97-1.00)
>6 years (n=14)	0.75 (0.54-0.93)	0.83 (0.67-0.95)	0.98 (0.95-0.99)	1.00 (1.00-1.00)	0.82 (0.67-0.93)	0.96 (0.92-0.99)	0.97 (0.96-0.99)
Number of CPETs interpreted annually							
≤150 (n=14)	0.75 (0.54-0.93)	0.88 (0.74-0.97)	1.00 (0.99-1.00)	1.00 (1.00-1.00)	0.82 (0.67-0.93)	0.98 (0.96-0.99)	0.98 (0.97-0.99)
>150 (n=12)	0.79 (0.62-0.93)	0.83 (0.69-0.94)	0.95 (0.90-0.98)	1.00 (0.99-1.00)	0.90 (0.81-0.97)	0.96 (0.92-0.99)	0.98 (0.95-0.99)

[a]: Interpret with caution, as ICC values are based on a small number of valid observations.

[b]: Only determined by using the guideline-based approach.

Abbreviations: CI = confidence interval; CPET = cardiopulmonary exercise testing; GBA= guideline-based approach; ICC = intraclass correlation coefficient; OUES = oxygen uptake efficiency slope; SPA= self-preferred approach; $\dot{V}E/\dot{V}CO_2$-slope = slope of the relationship between the minute ventilation and carbon dioxide production; $\dot{V}O_{2peak}$ = oxygen uptake at peak exercise; $\dot{V}O_{2VAT}$ = oxygen uptake at the ventilatory anaerobic threshold.

$\dot{V}O_{VAT}$ in the United Kingdom (0.76 versus 0.83 respectively) [13]. On the contrary, the ICC value for $\dot{V}O_{2peak}$ was higher in the current study compared to the UK study (0.98 versus 0.88, respectively). The lower ICCs for $\dot{V}O_{2VAT}$ found in the current study might be a reflection of the less extensive utilization of preoperative CPET and less uniformity of preoperative CPET interpretation and training in the Netherlands compared to the UK. The latter probably affects the inter-observer agreement of $\dot{V}O_{2VAT}$ to a greater extent than $\dot{V}O_{2peak}$, as methods for determining $\dot{V}O_{2VAT}$ are more complex than methods for $\dot{V}O_{2peak}$ determination [12].

Besides variation coming from inter-observer (dis)agreement, also other sources that add variability to the reported numerical values of CPET-derived parameters should be considered to improve uniformity of preoperative risk assessment. Other than inter-observer variation, data display methods, the used CPET protocol, measurement error, and within-patient physiological variation, are examples of sources that add variability to CPET-derived parameters. Although the present study showed that inter-observer agreement of $\dot{V}O_{2VAT}$ is good when using a systematic guideline-based approach, variation coming from other sources also needs to be minimized to allow for adequate and reliable preoperative risk assessment. In addition, taking these different sources of variation into account, a $\dot{V}O_{2VAT}$ of 10.9 mL/kg/min (considered a high-risk patient) in reality is probably not much different from an $\dot{V}O_{2VAT}$ of 11.3 mL/kg/min (considered a low-risk patient) [22]. As such, even with a good inter-observer agreement, perhaps less rigid thresholds should be considered for risk assessment as was already proposed by Rose et al. [23].

To improve inter-observer agreement and to allow for adequate and a more uniform preoperative risk assessment, more solid parameters that are identifiable in all patients, such as the $\dot{V}E/\dot{V}CO_2$-slope and the OUES might be of added value. The $\dot{V}E/\dot{V}CO_2$-slope is an effort-independent parameter that can be used in absence of the more frequently reported preoperative risk assessment parameter $\dot{V}E/\dot{V}CO_{2VAT}$ [24]. The OUES has been reported to be a valid (sub)maximal measure of aerobic capacity in patients undergoing colorectal surgery, and its predictive ability indicates that it might help discriminate patients at higher risk for postoperative complications [14]. Additionally, the OUES has been found to have excellent test-retest reliability in general surgical patients [25]. The ICC of the $\dot{V}E/\dot{V}CO_2$-slope and the OUES in our study was excellent and both parameters were objectively determinable in all patients.

The use of the effort-independent variable OUES in preoperative CPET might complement risk assessment, particularly when a parameter (e.g., $\dot{V}O_{2VAT}$) is not determinable, when risk assessment is inconclusive, or when a patient is unable and/or unwilling to

deliver a maximal effort. Nevertheless, although the OUES has been directly associated with postoperative complications [26] and mortality [15] in lung cancer patients, there is no evidence concerning a direct association of the preoperative OUES with postoperative complications and mortality in abdominal surgery. More research is needed to elucidate the exact association between the OUES and postoperative outcomes.

The current study has some limitations. First, participating observers were not selected randomly. It is possible that observers who are more confident of their CPET interpretation abilities were more willing to participate in the current study. Although it is difficult to estimate the actual effect of this possible selection bias, this could imply that the inter-observer agreement as presented in the current study might be an overestimation of inter-observer agreement in the total population of observers. Second, some observers (38%) were not familiar with the use of the software. Bias due to observers being not familiar with the software was expected to be minimal as the interpretation software that was used is very user-friendly and easy to comprehend. In addition, we accounted for this by providing a manual and an oral introduction before the start of the CPET interpretation sessions. Moreover, observers were free to switch between tests as much as desired, and a member of the study team was available online at all times to provide immediate assistance when needed. Nevertheless, any software-related bias would probably impact both approaches equally.

Strengths of this study consist of a relatively large number of observers that were willing to participate in both interpretation sessions. There was no loss to follow-up between the two interpretation sessions, meaning that all observers who interpreted the CPETs using the self-preferred approach also interpreted the CPETs using the systematic guideline-based approach. Therefore, differences between the two methods were not reliant on differences in participating observers between sessions.

Future research could focus on the influence of other sources of variation, such as data display intervals on the determination of CPET parameters in order to allow for uniform preoperative risk-assessment. In addition, more research is needed to elucidate the role of the OUES regarding preoperative risk assessment and its direct association with postoperative outcome measures.

CONCLUSIONS

The inter-observer agreement of $\dot{V}O_{2peak}$ is excellent, regardless of the approach that is used. A systematic guideline-based approach can further improve the inter-observer

agreement of the numerical values of CPET-derived parameters used for risk assessment. In patients who are unable to achieve a valid $\dot{V}O_{2peak}$, or when $\dot{V}O_{2VAT}$ is not determinable, the $\dot{V}E/\dot{V}CO_2$-slope and the OUES could be of added value as these are effort-independent parameters with excellent inter-observer agreement that are determinable in all patients. More research is needed to elucidate the exact role of the $\dot{V}E/\dot{V}CO_2$-slope and the OUES within preoperative risk assessment.

REFERENCES

1. Moonesinghe, S.R., et al., *Risk stratification tools for predicting morbidity and mortality in adult patients undergoing major surgery: qualitative systematic review.* Anesthesiology, 2013. **119**(4): p. 959-81.
2. Levett, D.Z.H., et al., *Perioperative cardiopulmonary exercise testing (CPET): consensus clinical guidelines on indications, organization, conduct, and physiological interpretation.* Br J Anaesth, 2018. **120**(3): p. 484-500.
3. American Thoracic, S. and P. American College of Chest, *ATS/ACCP Statement on cardiopulmonary exercise testing.* Am J Respir Crit Care Med, 2003. **167**(2): p. 211-77.
4. West, M.A., et al., *Validation of preoperative cardiopulmonary exercise testing-derived variables to predict in-hospital morbidity after major colorectal surgery.* Br J Surg, 2016. **103**(6): p. 744-752.
5. Lai, C.W., et al., *Patients' inability to perform a preoperative cardiopulmonary exercise test or demonstrate an anaerobic threshold is associated with inferior outcomes after major colorectal surgery.* Br J Anaesth, 2013. **111**(4): p. 607-11.
6. West, M.A., et al., *Cardiopulmonary exercise variables are associated with postoperative morbidity after major colonic surgery: a prospective blinded observational study.* Br J Anaesth, 2014. **112**(4): p. 665-71.
7. West, M.A., et al., *Cardiopulmonary exercise testing for the prediction of morbidity risk after rectal cancer surgery.* Br J Surg, 2014. **101**(9): p. 1166-72.
8. Moran, J., et al., *Role of cardiopulmonary exercise testing as a risk-assessment method in patients undergoing intra-abdominal surgery: a systematic review.* Br J Anaesth, 2016. **116**(2): p. 177-91.
9. Stubbs, D.J., L.A. Grimes, and A. Ercole, *Performance of cardiopulmonary exercise testing for the prediction of post-operative complications in non cardiopulmonary surgery: A systematic review.* PLoS One, 2020. **15**(2): p. e0226480.
10. Santa Mina, D., et al., *Aerobic capacity attainment and reasons for cardiopulmonary exercise test termination in people with cancer: a descriptive, retrospective analysis from a single laboratory.* Support Care Cancer, 2020. **28**(9): p. 4285-4294.
11. Berkel, A.E.M., et al., *Effects of Community-based Exercise Prehabilitation for Patients Scheduled for Colorectal Surgery With High Risk for Postoperative Complications: Results of a Randomized Clinical Trial.* Ann Surg, 2022. **275**(2): p. e299-e306.
12. Hopker, J.G., S.A. Jobson, and J.J. Pandit, *Controversies in the physiological basis of the 'anaerobic threshold' and their implications for clinical cardiopulmonary exercise testing.* Anaesthesia, 2011. **66**(2): p. 111-23.
13. Abbott, T.E.F., et al., *Inter-observer reliability of preoperative cardiopulmonary exercise test interpretation: a cross-sectional study.* Br J Anaesth, 2018. **120**(3): p. 475-483.
14. Bongers, B.C., et al., *An evaluation of the validity of the pre-operative oxygen uptake efficiency slope as an indicator of cardiorespiratory fitness in elderly patients scheduled for major colorectal surgery.* Anaesthesia, 2017. **72**(10): p. 1206-1216.
15. Yakal, S., et al., *Oxygen Uptake Efficiency Slope and Prediction of Post-operative Morbidity and Mortality in Patients with Lung Cancer.* Lung, 2018. **196**(2): p. 255-262.
16. von Elm, E., et al., *The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies.* Lancet, 2007. **370**(9596): p. 1453-7.
17. Berkel, A.E.M., et al., *Study protocol of a single-arm pre-post study to assess the preliminary effectiveness and feasibility of a home-based bimodal prehabilitation program on preoperative aerobic fitness*

in high-risk patients scheduled for liver or pancreatic resection. International Journal of Clinical Trials, 2020. **7**(2): p. 103-111.

18. Bjorke, A.C.H., T. Raastad, and S. Berntsen, *Criteria for the determination of maximal oxygen uptake in patients newly diagnosed with cancer: Baseline data from the randomized controlled trial of physical training and cancer (Phys-Can).* PLoS One, 2020. **15**(6): p. e0234507.
19. Dumitrescu, D. and S. Rosenkranz, *Graphical Data Display for Clinical Cardiopulmonary Exercise Testing.* Ann Am Thorac Soc, 2017. **14**(Supplement_1): p. S12-S21.
20. Mezzani, A., et al., *Standards for the use of cardiopulmonary exercise testing for the functional evaluation of cardiac patients: a report from the Exercise Physiology Section of the European Association for Cardiovascular Prevention and Rehabilitation.* Eur J Cardiovasc Prev Rehabil, 2009. **16**(3): p. 249-67.
21. Trevethan, R., *Intraclass correlation coefficients: clearing the air, extending some cautions, and making some requests.* Health Services and Outcomes Research Methodology, 2017. **17**(2): p. 127-143.
22. Older, P., *Anaerobic threshold, is it a magic number to determine fitness for surgery?* Perioper Med (Lond), 2013. **2**(1): p. 2.
23. Rose, G.A., et al., *The cardiopulmonary exercise test grey zone; optimising fitness stratification by application of critical difference.* Br J Anaesth, 2018. **120**(6): p. 1187-1194.
24. Otto, J.M., D.Z.H. Levett, and M.P.W. Grocott, *Cardiopulmonary Exercise Testing for Preoperative Evaluation: What Does the Future Hold?* Current Anesthesiology Reports, 2020. **10**(1): p. 1-11.
25. Phypers, B.J., et al., *Test-retest reliability of the oxygen uptake efficiency slope in surgical patients.* Anaesthesia, 2011. **66**(8): p. 659-66.
26. Kasikcioglu, E., et al., *Oxygen uptake kinetics during cardiopulmonary exercise testing and postoperative complications in patients with lung cancer.* Lung Cancer, 2009. **66**(1): p. 85-8.

SUPPLEMENTAL FILE 1. GUIDELINE FOR SYSTEMATIC INTERPRETATION OF PREOPERATIVE CARDIOPULMONARY EXERCISE TESTING.

Contents

1. Ventilatory anaerobic threshold

The determination of the ventilatory anaerobic threshold (VAT) – *synonyms: ventilatory threshold, gas exchange threshold, aerobic threshold, anaerobic threshold, and VT1* – is based on 3 criteria.

Criterion 1

Identify an increase in carbon dioxide production (VCO_2) relative to the oxygen uptake (VO_2) above the VAT by using the V-slope or modified V-slope method.

1. Go to the plot in which the VCO_2 (y-axis) and VO_2 (x-axis) are plotted against each other (see **Figure 1**).
2. Use:
   a. The *V-slope method:*

Identify the intersection of the regression lines **S1** (below the VAT) and **S2** (above the VAT) in the VCO_2-VO_2 relationship.

Or

   b. The *modified V-slope method:*

Move a line with a gradient of 1.0 from the lower right-hand corner of the graph towards the VCO_2-VO_2 relationship and identify the point at which this line first touches the curve of the relationship between VCO_2 and VO_2.

(Note: take outliers into account)

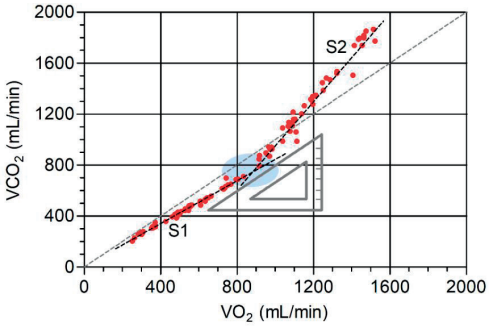

Figure 1. VCO_2 against VO_2.
S1 = slope below the VAT; S2 = slope above the VAT.

Criterion 2

Identify hyperventilation relative to the VO_2 using the ventilatory equivalents method.

1. Go to the plot in which the ventilatory equivalent for oxygen (VE/VO_2) and ventilatory equivalent for carbon dioxide (VE/VCO_2) (both on the y-axis) are plotted against time (x-axis) (see **Figure 2**).
2. Identify the point at which the VE/VO_2 ratio begins to rise after an initially flat or decreasing period and does not return to baseline.
3. For verification, go to the plot with the partial end-tidal oxygen tension ($P_{ET}O_2$) and partial end-tidal carbon dioxide tension ($P_{ET}CO_2$) (both on the y-axis) are plotted against time (x-axis) (see **Figure 3**): check whether $P_{ET}O_2$ starts to rise at this point after an initially flat or decreasing period and does not return to baseline.

(Note: take outliers into account)

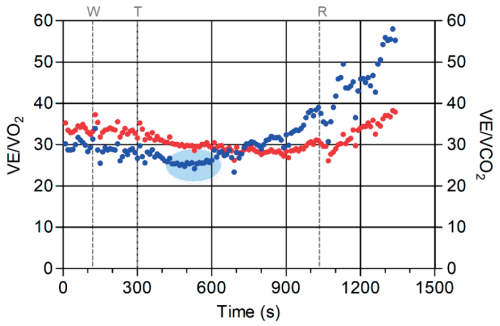

Figure 2. VE/VO_2 ● and VE/VCO_2 ● against time.
W = start warm-up; T = start test; R = start recovery.

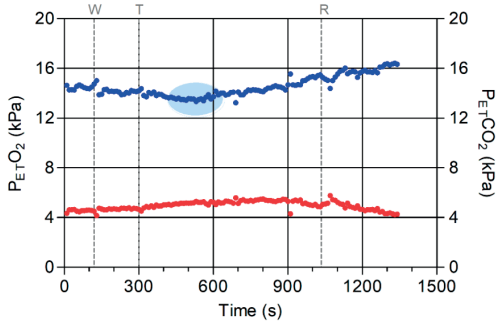

Figure 3. $P_{ET}O_2$ ● and $P_{ET}CO_2$ ● against time.
W = start warm-up; T = start test; R = start recovery.

Criterion 3

Check whether the VAT identified using criteria 1 and 2 is not caused by hyperventilation relative to VCO_2 using the ventilatory equivalents method.

1. Go to the plot in which VE/VO_2 and VE/VCO_2 (both on the y-axis) are plotted against time (x-axis) (see **Figure 2**).

2. Confirm that the VE/VCO_2 ratio remains constant or continues to decrease at the point at which VE/VO_2 starts to rise systematically.
3. For verification, go to the plot in which the $P_{ET}O_2$ and $P_{ET}CO_2$ (both on the y-axis) are plotted against time (x-axis) (see **Figure 3**): check if there is no reciprocal decrease in $P_{ET}CO_2$ at the point where $PETO_2$ starts to rise systematically.

(Note: take outliers into account)

Use the 3 criteria above to identify the point that best represents the VAT. (If you cannot identify a VAT based on these criteria, please select the option "VAT not determinable" in the drop-down menu of the Microsoft Excel document.)

2. Respiratory compensation point

The determination of the respiratory compensation point (RCP) – *synonyms: anaerobic threshold and VT2* – is based on 2 criteria.

Criterion 1

Identify the point at which the minute ventilation (VE) starts to increase more steep (respiratory compensation) in relation to the carbon dioxide production (VCO_2) due to metabolic acidosis.

1. Go to the plot in which VE (y-axis) and VCO_2 (x-axis) are plotted against each other (see **Figure 4**).
2. Identify the point where the slope of the relationship between VE and VCO_2 steepens.

(Note: take outliers into account)

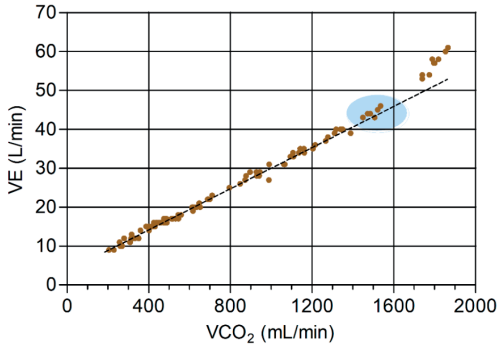

Figure 4. VE against VCO_2.

Criterion 2

Identify hyperventilation relative to the carbon dioxide production (VCO_2) using the ventilatory equivalents method.

1. Go to the plot in which the ventilatory equivalents for oxygen (VE/VO_2) and carbon dioxide production (VE/VCO_2) (both on the y-axis) are plotted against time (x-axis) (see **Figure 5**).
2. Identify the point at which the VE/VCO_2 ratio begins to rise after an initially flat or decreasing period and does not return to baseline.
3. For verification, go to the plot in which the partial end-tidal oxygen tension ($P_{ET}O_2$) and partial end-tidal carbon dioxide tension ($P_{ET}CO_2$) (both on the y-axis) are plotted against time (x-axis) (see **Figure 6**): at this point, $P_{ET}CO_2$ should begin to decline after an initially flat or increasing period.

(Note: take outliers into account)

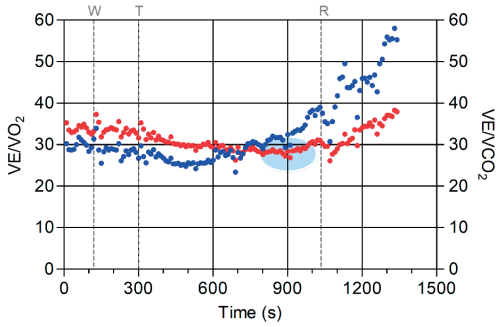

Figure 5. VE/VO_2 ● and VE/VCO_2 ● against time.
W = start warm-up; T = start test; R = start recovery.

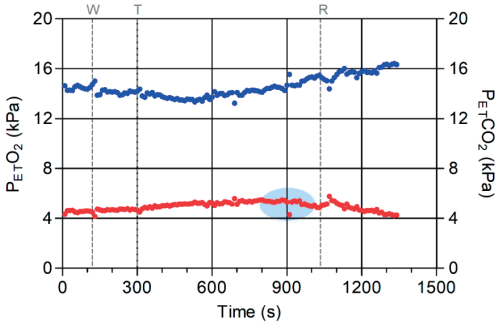

Figure 6. $P_{ET}O_2$ ● and $P_{ET}CO_2$ ● against time.
W = start warm-up; T = start test; R = start recovery.

Use the 2 criteria above to identify the point that best represents the RCP. (If you cannot identify an RCP based on these criteria, please select the option "RCP not determinable" in the drop-down menu of the Microsoft Excel document.)

3. Oxygen uptake at peak exercise

Determine the oxygen uptake (VO_2) at peak exercise (VO_{2peak}) using the following steps.

Criterion

Determine whether a *valid* VO_{2peak} was achieved.

1. Verify whether the VO_{2peak} was attained during a (near) maximal effort by checking if:
   a. The achieved respiratory exchange ratio at peak exercise (RER_{peak}) was ≥1.10

And/or

   b. The achieved heart rate at peak exercise (HR_{peak}) was >95% of predicted (*predicted* $HR_{peak} = 208 - (0.8 \times age\ in\ years)$)
2. When the abovementioned criteria for a maximal effort are met, go to the plot in which the VO_2 and VCO_2 (both on the y-axis) are plotted against time (x-axis) (see **Figure 7**) to determine the VO_{2peak} as the average VO_2 value over the last 30 seconds of the test.

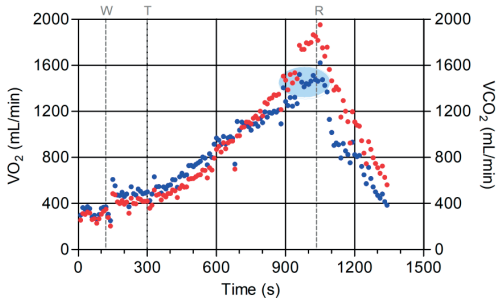

Figure 7. VO_2 ● and VCO_2 ● against time.
W = start warm-up; T = start test; R = start recovery.

Determine the VO_{2peak} (mL/min) averaged over the last 30 seconds of the test. (If the abovementioned criteria for a maximal effort are not met, select the option "no valid VO_{2peak}" in the drop-down menu of the Microsoft Excel document.)

4. Slope of the relationship between minute ventilation and carbon dioxide production

Determine the relationship between minute ventilation (VE) and carbon dioxide production (VCO_2), called VE/VCO_2-slope, up to the respiratory compensation point (RCP) using the following steps:

1. Go to the plot in which the VE (y-axis) is plotted against VCO_2 (x-axis) (see **Figure 8**).
2. Place the "lower limit" (**LL**) line of the VE/VCO_2-relationship at the point at which the work rate starts to increase.
3. Place the "upper limit" (**UL**) at the point at which the slope of the relationship between the VE and VCO_2 steepens (loss of linearity): if no RCP can be determined, the UL line should be placed at the end of the exercise phase (peak exercise).

(Note: take outliers into account)

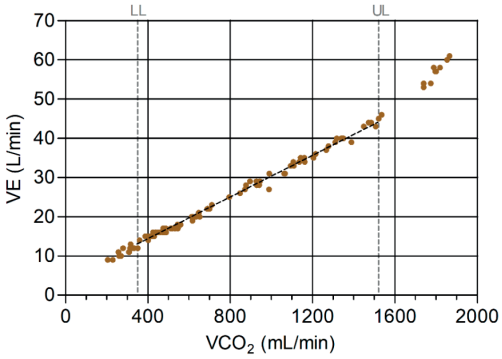

Figure 8. VE against VCO_2.
LL = lower limit; UL = upper limit.

The slope of the regression line describing the relationship of the VE with VCO_2 between the LL and UL represents the VE/VCO_2-slope.

5. Oxygen uptake efficiency slope

Determine the oxygen uptake efficiency slope (OUES) from the point at which the work rate starts to increase up to a plateau in oxygen uptake (VO_2) despite an increase in work rate (a 'true' VO_{2max}) or, in case no VO_2-plateau can be observed, up to the end of the exercise phase (peak exercise) using the following steps.

1. Go to the plot in which the VO_2 (y-axis) is plotted against the logarithm of the minute ventilation (Log VE) (x-axis) (see **Figure 9**).
2. Place the "lower limit" (**LL**) line at the first data point in the graph (left side), the start of the exercise phase.
3. Place the "upper limit" (**UL**) line at the start of the VO_2-plateau, or, in case there is no VO_2-plateau, at the end of the exercise phase (peak exercise).

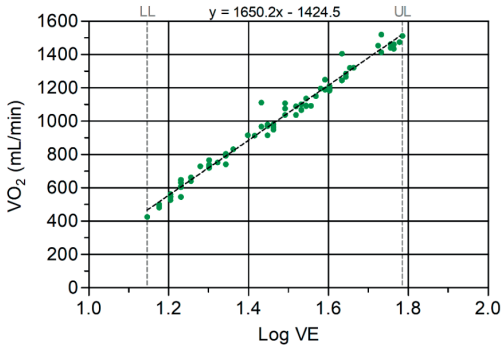

Figure 9. VO_2 against Log VE.
LL = lower limit; UL = upper limit.

The regression coefficient of the regression line between the LL en UL represents the OUES.

The OUES is determined with the formula: $VO_2 = (a \times \text{Log VE}) + b$.
The regression coefficient "a" (1650.2 in the example in Figure 8) represents the increase in oxygen uptake (VO_2) relative to the logarithm of the minute ventilation (VE) and is called the OUES.

6. References

American Thoracic Society; American College of Chest Physicians. ATS/ACCP statement on cardiopulmonary exercise testing. Am J Respir Crit Care Med. 2003;167:211-77.

Bjørke ACH, Raastad T, Berntsen S. Criteria for the determination of maximal oxygen uptake in patients newly diagnosed with cancer: baseline data from the randomized controlled trial of physical training and cancer (Phys-Can). PLoS One. 2020;15:e0234507.

Bongers BC, Berkel AE, Klaase JM, van Meeteren NL. An evaluation of the validity of the pre-operative oxygen uptake efficiency slope as an indicator of cardiorespiratory fitness in elderly patients scheduled for major colorectal surgery. Anaesthesia. 2017;72:1206-16.

Dumitrescu D, Rosenkranz S. Graphical Data display for clinical cardiopulmonary exercise testing. Ann Am Thorac Soc. 2017;14(Supplement_1):S12-S21.

Levett DZH, Jack S, Swart M, Carlisle J, Wilson J, Snowden C, Riley M, Danjoux G, Ward SA, Older P, Grocott MPW; Perioperative Exercise Testing and Training Society (POETTS). Perioperative cardiopulmonary exercise testing (CPET): consensus clinical guidelines on indications, organization, conduct, and physiological interpretation. Br J Anaesth. 2018;120:484-500.

Mezzani A, Agostoni P, Cohen-Solal A, Corrà U, Jegier A, Kouidi E, Mazic S, Meurin P, Piepoli M, Simon A, Laethem CV, Vanhees L. Standards for the use of cardiopulmonary exercise testing for the functional evaluation of cardiac patients: a report from the Exercise Physiology Section of the European Association for Cardiovascular Prevention and Rehabilitation. Eur J Cardiovasc Prev Rehabil. 2009;16:249-67.

5

CHAPTER 5

Influence of different data-averaging methods on mean values of selected variables derived from preoperative cardiopulmonary exercise testing in patients scheduled for colorectal surgery

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ABSTRACT

Introduction

Patients with a low cardiorespiratory fitness (CRF) undergoing colorectal cancer surgery have a high risk for postoperative complications. Cardiopulmonary exercise testing (CPET) to assess CRF is the gold standard for preoperative risk assessment. To aid interpretation of raw breath-by-breath data, different methods of data-averaging can be applied. This study aimed to investigate the influence of different data-averaging intervals on CPET variables used for preoperative risk assessment, as well as to evaluate whether different data-averaging intervals influence preoperative risk assessment.

Methods

A total of 21 preoperative CPETs were interpreted by two exercise physiologists using stationary time-based data-averaging intervals of 10, 20, and 30 seconds and rolling average intervals of 3 and 7 breaths. Mean values of CPET variables between different data averaging intervals were compared using repeated measures ANOVA. The variables of interest were oxygen uptake at peak exercise (VO_{2peak}), oxygen uptake at the ventilatory anaerobic threshold (VO_{2VAT}), oxygen uptake efficiency slope (OUES), the ventilatory equivalent for carbon dioxide at the ventilatory anaerobic threshold (VE/VCO_{2VAT}), and the slope of the relationship between the minute ventilation and carbon dioxide production (VE/VCO_2-slope).

Results

Between data-averaging intervals, no statistically significant differences were found in the mean values of CPET variables except for the ventilatory equivalent for carbon dioxide at the ventilatory anaerobic threshold (P=0.001). No statistically significant differences were found in the proportion of patients classified as high or low risk regardless of the used data-averaging interval.

Conclusion

There appears to be no significant or clinically relevant influence of the evaluated data-averaging intervals on the mean values of CPET outcomes used for preoperative risk assessment. Clinicians may choose a data-averaging interval that is appropriate for optimal interpretation and data visualization of the preoperative CPET. Nevertheless, caution should be taken as the chosen data-averaging interval might lead to substantial within-patient variation for individual patients.

Trial registration: Prospectively registered at ClinicalTrials.gov (NCT05353127)

INTRODUCTION

Preoperative aerobic fitness is independently associated with postoperative outcomes following major abdominal surgery (1). Consequently, cardiopulmonary exercise testing (CPET) is increasingly used within multimodal preoperative risk assessment (2), as it provides an objective, non-invasive, and accurate evaluation of a patient's aerobic fitness that represents the capacity to meet the increased oxygen demand following major abdominal surgery (3, 4). The advantage of CPET over other risk assessment tools is that CPET encompasses an integrative evaluation of the cardiovascular, pulmonary, and muscular system (5). In addition, CPET can be used to inform collaborative decision-making, to optimize comorbidities, to triage perioperative care (e.g., ward, intensive care), to advice on preoperative physical exercise training (e.g., risk assessment, contraindications), and to guide and personalize subsequent physical exercise training prescription (6).

During CPET, a patient exercises against a progressively increasing work rate until volitional exhaustion, while breath-by-breath respiratory gasses are analyzed. The large number of data-points that are collected by the breath-by-breath sampling rate can be a challenge for data visualization, as the signal can have high variability. Therefore, data-averaging is performed to optimize graphical data display and to aid CPET interpretation (see Figure 1). Although it is generally accepted that data-averaging methods influence the numerical value of CPET-derived variables, there is no consensus among existing guidelines on the best averaging method (7).

The most frequently used CPET-derived variables that are associated with postoperative complications in the current literature are the oxygen uptake at peak exercise (VO_{2peak}), the oxygen uptake at the ventilatory anaerobic threshold (VO_{2VAT}) (2, 6, 8), and the ventilatory equivalent for carbon dioxide at the ventilatory anaerobic threshold (VE/VCO_{2VAT}) (9). Measures that are less frequently used are the slope of the relationship between the minute ventilation and carbon dioxide production (VE/VCO_2-slope), that can be used as an alternative for the VE/VCO_{2VAT} if the VAT is undeterminable (8), and the oxygen uptake efficiency slope (OUES) (10).

Although preoperative risk assessment should be multimodal, CPET-derived thresholds are often used to recognize patients with a low aerobic fitness who have a high risk for adverse surgical outcomes. In major abdominal surgery, often used thresholds to identify patients at high-risk for postoperative complications are a VO2peak <18.2 mL/kg/min and/or a VO2VAT <11.1 mL/kg/min.(9). Studies in healthy individuals have shown that the numerical value of the VO_{2peak} can differ as much as ~10% depending on the

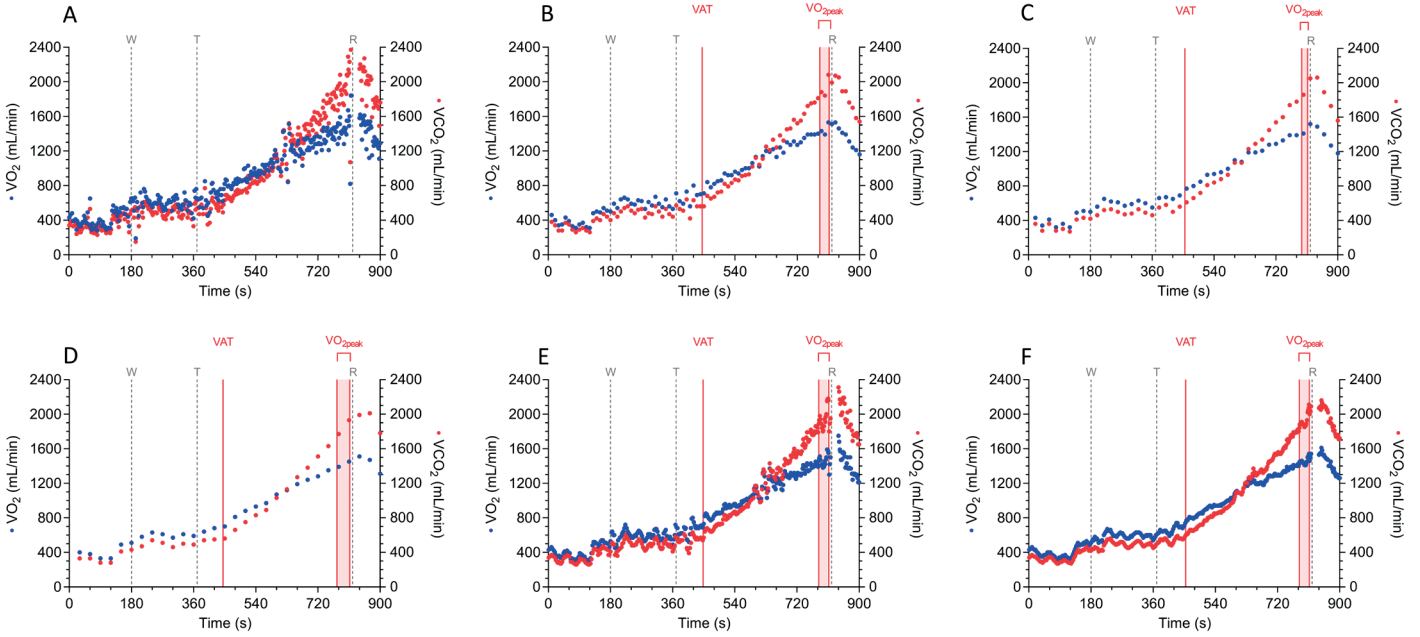


Figure 1. Visualization of the plot with oxygen uptake (VO_2) and carbon dioxide production (VCO_2) over time without data-averaging (graph A) and using the five different data-averaging intervals: a stationary time-based average of 10 seconds (graph B), 20 seconds (graph C), and 30 seconds (graph D), a rolling average interval of 3 breaths (graph E) and 7 breaths (graph F) in patient 21. See Supplemental file 1 for a graphical display of the Wasserman plots of patient 21 with the different data-averaging intervals.
Note that the number of data points is lower when stationary time-based averaging is used (and decreasing with longer data-averaging intervals) compared to when a rolling average is used. In addition, a lower number of data points leads to smoothing of the VO_2 and VCO_2 curves.
Abbreviations: VAT= ventilatory anearobic threshold; VCO_2= carbon dioxide production; VO_2 = oxygen uptake; VO_{2peak} = oxygen uptake at peak exercise.
Vertical grey dotted lines represent start of the warm-up phase (W), test phase (T), and recovery phase (R).

data-averaging method (11-13), indicating that data-averaging might significantly influence threshold determination and subsequently might affect preoperative risk assessment. To date however, there are no studies quantifying the extent to which differences in data-averaging influence the numerical value of preoperative CPET-derived variables such as VO_{2peak}, VO_{2VAT}, OUES, VE/VCO_{2VAT}, and VE/VCO_2-slope. Therefore, the primary aim of this study was to investigate the influence of different CPET data-averaging intervals on the numerical values of CPET-derived variables used for preoperative risk assessment in patients scheduled for elective colorectal cancer surgery. The secondary aim was to elucidate the impact of data-averaging intervals on the classification of patients into low or high risk for postoperative complications based on known risk assessment thresholds.

METHODS

This observational cross-sectional study was performed at the VieCuri Medical Center, a large teaching hospital in Venlo, the Netherlands. The current study was executed as a secondary analysis of data collected in a study (14) that was approved by the Medical Ethics Review Committee – Zuyderland/Zuyd (Heerlen, the Netherlands) under reference number METCZ20190150. Reporting was done using the STROBE guidelines for reporting of cross-sectional studies (15). The study protocol was prospectively registered at ClinicalTrials.gov (NCT05353127).

Participants

Data from consecutive patients considered for colorectal cancer surgery who were ≥18 years of age, had a score ≤7 metabolic equivalents of task on the veterans-specific activity questionnaire, and therefore performed preoperative CPET as a part of a teleprehabilitation study (14), were collected between July 2020 and September 2021. All patients signed informed consent. Preoperative CPET was conducted after diagnosis and before any intervention or treatment was initiated.

Preoperative cardiopulmonary exercise testing

Patients preoperatively performed incremental CPET up to volitional exertion in upright position on an electronically-braked cycle ergometer (Lode Corival, Lode BV, Groningen, the Netherlands). Prior to the test, patients were asked to refrain from vigorous physical activity, caffeine, and tobacco for 24 hours and meals for 2 hours, but to continue medication as usual. Seat height was adjusted to the participant's leg length. Before commencing CPET, forced vital capacity and forced expiratory volume in one second was obtained from maximal flow-volume curves (Ergostik, Geratherm Respiratory, Bad Kissingen, Germany) according to ATS/ERS standards (5). Subsequently, baseline cardio-

pulmonary values were assessed during a three-minute rest period while seated at the cycle ergometer, thereafter a three-minute warm-up phase took place that consisted of unloaded cycling. After the warm-up, work rate was increased by constant increments of 5, 10, 15, 20, or 25 W/min in a ramp-like manner, depending on the subject's estimated physical fitness level and aimed at reaching a maximal effort within eight to twelve minutes. Throughout CPET, subjects maintained a pedaling frequency between 60 and 80 revolutions/min. The protocol continued until the patient's pedaling frequency fell definitely below 60 revolutions/min, despite strong verbal encouragement, or when the patient met the criteria for exercise termination before symptom limitation as proposed in the ATS/ACCP statement on cardiopulmonary exercise testing (5).

During CPET, subjects breathed through a facemask (Hans Rudolph, Kansas City, MO, USA) connected to an ergospirometry system (Ergostik, Geratherm Respiratory, Bad Kissingen, Germany). Before every test, calibration for respiratory gas analysis measurements (ambient air and a gas mixture of 16% oxygen and 5% carbon dioxide) and volume measurements (three-liter syringe) took place. Expired gas passed through a flow meter (triple V volume transducer), an oxygen analyzer, and a carbon dioxide analyzer. The flow meter and gas analyzers were connected to a computer that calculated breath-by-breath minute ventilation, oxygen uptake, carbon dioxide production, and the respiratory exchange ratio. Raw unfiltered breath-by-breath data was retrogradely averaged over five different data display intervals.

Procedures

Preoperative CPET patient data was anonymized and patient characteristics other than anthropometric measures were concealed. A medical and clinical exercise physiologist (BB) and a clinical exercise physiologist (RF) determined VO_{2peak}, VO_{2VAT}, OUES, VE/VCO_{2VAT}, and the VE/VCO_2-slope in all CPETs by means of a predefined set of guidelines (see **Chapter 4** Supplemental file 1). A VO_{2peak} was conceived "valid" when objective criteria for maximal volitional exertion were reached defined as an RER ≥1.10 or reaching ≥95% of the predicted maximal heart rate at peak exercise. CPET interpretation was performed using Blue Cherry software version 1.3.3.3 (Geratherm Respiratory GmbH, Bad Kissingen, Germany), in which observers interpreted the CPET data together using TeamViewer software (TeamViewer GmbH, Göppingen, Germany). Final determination was based on consensus between the two observers. If the two observers were unable to reach consensus, a third observer (TT) was consulted. Data-averaging-intervals used were stationary time-based averages, calculated by averaging the breath-by-breath data over 10, 20, or 30 seconds and rolling averages calculated by averaging a fixed number of single breath measurements (i.e., 3 and 7), then discarding the first breath and adding a new

breath to obtain a new breath averaging block. Determination of the aforementioned CPET variables was repeated for all five different data-averaging intervals.

Apart from the CPET data, the preoperative patient characteristics age, sex, body mass index, smoking status (never, former, current), age-adjusted Charlson comorbidity index, American Society of Anesthesiologists classification, veterans-specific activity questionnaire score, hemoglobin levels (mmol/L), and tumor location were recorded to characterize the study population.

Sample size

A sample size calculation was performed with G*Power (16) for F-test repeated measures within factors. Based on a mean ± standard deviation (SD) value for VO_{2VAT} of 9.7 ± 2.3 mL/kg/min (based on preliminary analysis of the used data) for a mean difference between data-averaging methods of minimally 0.7 mL/kg/min, the estimated effect size is estimated at ~0.30. With an α of 0.05 and a β of 0.80, a minimum of 15 CPETs are needed to detect the estimated effect size.

Statistical analysis

Continuous data were checked for normality using the Shapiro-Wilks test. To assess the difference between different CPET data-averaging intervals, differences in mean numerical values of VO_{2peak}, VO_{2VAT}, OUES, VE/VCO_{2VAT}, and the VE/VCO_2-slope, between different data-averaging intervals were calculated and analyzed by means of within-factors repeated-measures analysis of variance (ANOVA). In case of a statistically significant difference between methods ($P<0.05$), post-hoc testing was performed using the Bonferroni correction to identify exact differences. Effect sizes were estimated by calculating the eta squared (i.e., sum of squares of the effect divided by the total sum of squares). To evaluate the influence of data-averaging intervals on preoperative risk assessment, individual numerical values for VO_{2peak}, VO_{2VAT}, OUES, and VE/VCO_{2VAT} were compared with known preoperative risk assessment thresholds. Patients were classified as high-risk when having a VO_{2peak} <18.2 mL/kg/min (9), VO_{2VAT} <11.1 mL/kg/min (9), OUES/kg <20.6 (10), and/or VE/VCO_{2VAT} >30.9 (9). Cochrane's Q-test was used to determine whether differences in preoperative risk assessment exist between data-averaging methods. Differences between data-averaging methods were assumed statistically significant when $P<0.05$.

RESULTS

A total of 21 CPETs of patients with colorectal cancer (see Table 1 for patient characteristics) were re-assessed using five different data-averaging intervals. Thus, a total of 105 CPETs (five data-averaging intervals × 21 CPETs) were evaluated. Mean ± SD duration of the CPET ramp phase was 586 ± 174 seconds (9:46 ± 2:54 min). A valid VO_{2peak} was reached in 70 (67.7%) of the evaluated CPETs. VO_{2VAT} and VE/VCO_{2VAT} were determinable in 104 out of 105 CPETs (99%). The OUES and VE-VCO_2-slope were determinable in all 105 CPETs.

Table 1. Baseline characteristics of subjects.

Characteristics	n=21
Age (years)	70.5 ± 12.5
Sex ratio (male; female)	12 (57%); 9 (43%)
Body mass index (kg/m^2)	28.6 ± 4.9
Age-adjusted Charlson comorbidity index	
≤3	10 (47.6%)
4-5	10 (47.6%)
6+	1 (4.8%)
ASA-classification	
I	4 (19.0%)
II	7 (33.3%)
III	9 (42.9%)
IV	1 (4.8%)
Hemoglobin level (mmol/L)	7.4 ± 1.2
Tumor location	
Colon	15 (71.4%)
Rectum	6 (28.6%)
Data are presented as mean ± standard deviation (SD) or as number (%).	

Mean values of the CPET-derived variables ranged from 14.5 mL/kg/min to 14.6 mL/kg/min for VO_{2peak}, from 9.3 mL/kg/min to 9.7 mL/kg/min for VO_{2VAT}, from 19.1 to 19.4 for OUES/kg, from 31.2 to 31.9 for VE/VCO_{2VAT}, and from 33.6 to 35.3 for VE/VCO_2-slope, dependent on the different data-averaging intervals. There was a significant difference in mean values of VO_{2peak} between groups with different data averaging intervals, but this difference did not remain significant after post-hoc testing. For the variable VE/VCO_{2VAT}, the 3 breaths rolling average interval was statistically significant different from the time-based 20 seconds (P=0.004) and 30 seconds (P=0.005) data-averaging interval, as well as from the rolling average of 7 breaths (P=0.021; see Table 2). The effect sizes for all variables were ≤0.009.

Table 2. Numerical values of CPET variables using different data-averaging intervals.

	Data-averaging interval					
	Stationary time-based average			Rolling average		P-value[a]
	10 seconds	20 seconds	30 seconds	3 breaths	7 breaths	
VO_{2peak} (mL/min)	1202 (1008-1396)	1194 (999-1389)	1193 (997-1390)	1201 (1008-1394)	1200 (1005-1396)	**0.040**[c]
VO_{2peak} (mL/kg/min)	14.6 (12.5-16.7)	14.5 (12.4-16.6)	14.5 (12.4-16.6)	14.6 (12.5-16.7)	14.6 (12.5-16.7)	**0.012**[c]
Valid VO_{2peak} (mL/kg/min)[b]	16.2 (13.7-18.7)	16.2 (13.6-18.7)	16.1 (13.5-18.8)	16.2 (13.6-18.8)	16.3 (13.7-18.7)	0.104
VO_{2VAT} (mL/min)	800 (684-916)	775 (656-895)	764 (669-859)	776 (668-884)	761 (669-851)	0.345
VO_{2VAT} (mL/kg/min)	9.7 (8.5-10.9)	9.4 (8.1-10.7)	9.3 (8.2-10.4)	9.5 (8.3-10.6)	9.3 (8.2-10.4)	0.435
OUES	1559 (1322-1795)	1559 (1338-1779)	1565 (1338-1792)	1582 (1354-1809)	1574 (1351-1798)	0.463
OUES/kg	19.1 (16.6-21.7)	19.2 (16.7-21.7)	19.3 (16.7-21.8)	19.5 (17.0-21.9)	19.4 (16.9-21.8)	0.479
VE/VCO_{2VAT}	34.2 (31.9-36.5)	34.6 (32.3-37.0)[d]	35.1 (32.6-37.5)[d]	33.6 (31.4-35.8)[d]	34.4 (32.0-36.8)[d]	**0.001**
VE/VCO_2-slope	31.4 (28.6-34.1)	31.8 (28.8-35.0)	31.2 (28.4-34.0)	31.8 (28.9-34.7)	31.8 (29.0-34.7)	0.608

Data are presented as mean and 95% confidence interval (CI), unless stated otherwise.

Abbreviations: OUES = oxygen uptake efficiency slope; VE/VCO_2-slope = the slope of the relationship between the minute ventilation and carbon dioxide production; VE/VCO_{2VAT} = ventilatory equivalent for carbon dioxide at the ventilatory anaerobic threshold; VO_{2peak} = oxygen uptake at peak exercise; VO_{2VAT} = oxygen uptake at the ventilatory anaerobic threshold.

[a]: as determined by repeated-measures ANOVA (within factors).

[b]: as determined by a respiratory exchange ratio at peak exercise ≥1.10 and/or a heart rate at peak exercise ≥95% of the predicted maximal heart rate based on the formula 208 – (0.8 × age in years).

[c]: did not remain significant after post hoc testing with Bonferroni correction.

[d]: the 3 breaths rolling average interval was statistically significant different from the stationary time-based interval of 20 seconds (P=0.004) and 30 seconds (P=0.005), as well as from the 7 breaths rolling average interval (P=0.021).

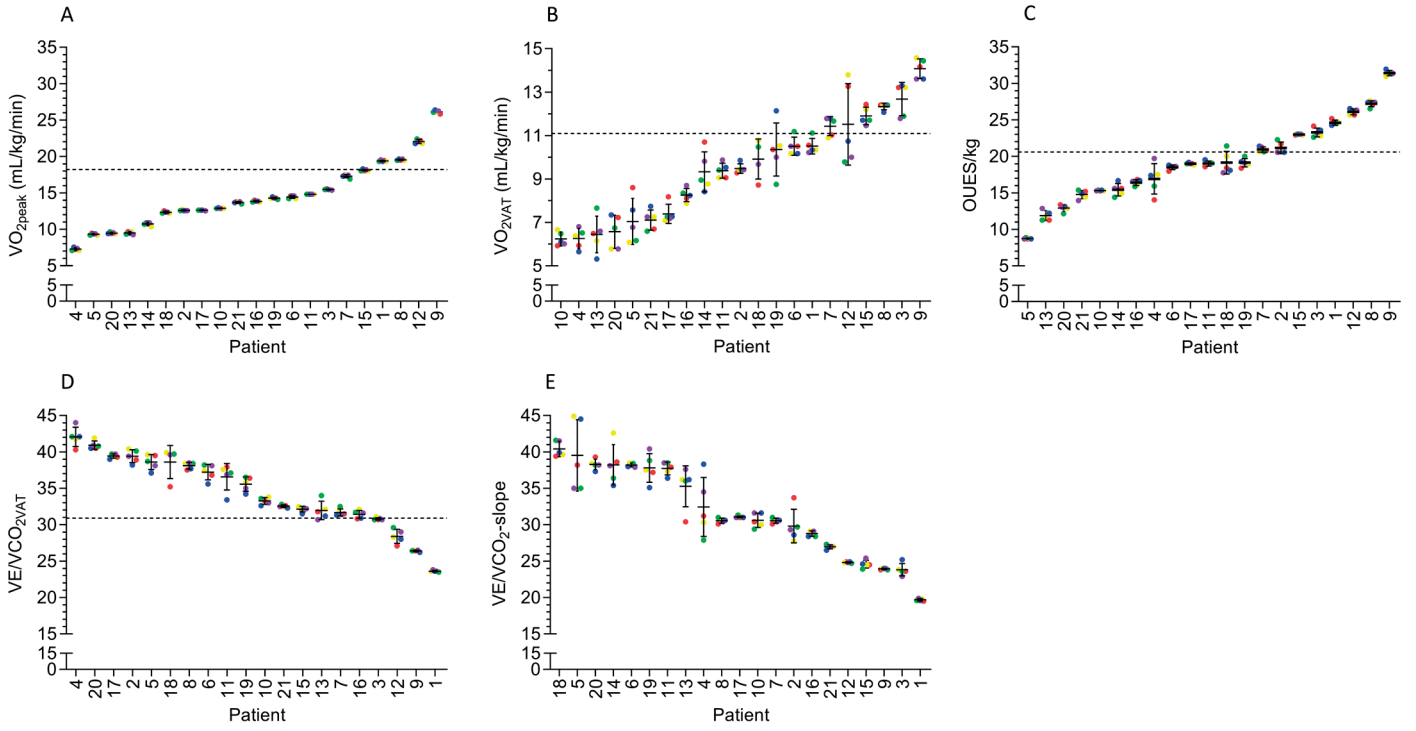


Figure 2. Variation in the observed values of VO_{2peak} (graph A), VO_{2VAT} (graph B), OUES (graph C), VE/VCO_{2VAT} (graph D), and the VE/VCO_2-slope (graph E) within individual patients.
Dots represent individual numerical value with a unique color for each data-averaging interval throughout the graphs (red = 10 seconds; yellow = 20 seconds; green = 30 seconds; blue = 3 breaths; purple = 7 breaths). Error bars represent the mean values and 95% confidence intervals. Horizontal dotted lines represent known risk assessment thresholds defined as 18.2 mL/kg/min for VO_{2peak} (graph A), 11.1 mL/kg/min for VO_{2VAT} (graph B), <20.6 for OUES (graph C), and >30.9 for VE/VCO_{2VAT} (graph D).
Note that individual values of patients often cross the risk threshold (dotted horizontal line). These patients might have a different risk estimation depending on the data-averaging interval.
Abbreviations: OUES = oxygen uptake efficiency slope; VE/VCO_2-slope = the slope of the relationship between the minute ventilation and carbon dioxide production; VE/VCO_{2VAT} = ventilatory equivalent for carbon dioxide at the ventilatory anaerobic threshold; VO_{2peak} = oxygen uptake at peak exercise; VO_{2VAT} = oxygen uptake at the ventilatory anaerobic threshold.

Figure 2 depicts within-patient variation in the numerical value of several CPET-derived variables using the five different data-averaging intervals. Although the numerical values for VO_{2peak} were consistent (maximal within patient difference, 0.4 mL/kg/min, or 5.6%), within patient variation could be as much as 4.0 mL/kg/min for VO_{2VAT} (40.8%), 5.7 for the OUES/kg (40.3%), 4.7 for VE/VCO_{2VAT} (13.4%), and 10.4 (37.3%) for VE/VCO_2-slope when using different data-averaging intervals (see Figure 2).

Table 3. Effect of different data-averaging intervals on classifying patients as having a high-risk for postoperative complications.

	Data-averaging interval					
	Stationary time-based average			Rolling average		
	10 seconds, n (%)	20 seconds n (%)	30 seconds (%) n (%)	3 breaths n (%)	7 breaths n (%)	P-value[a]
VO_{2peak}	17 (81%)	17 (81%)	17 (81%)	17 (81%)	16 (76%)	0.406
VO_{2VAT}	16 (76%)	16 (76%)	14 (67%)	14 (67%)	16 (76%)	0.615
OUES/kg	13 (62%)	13 (62%)	12 (57%)	14 (67%)	14 (67%)	0.231
VE/VCO_{2VAT}	16 (76%)	18 (86%)	17 (81%)	15 (71%)	16 (76%)	0.334

Data are presented as number (%).
Abbreviations: OUES = oxygen uptake efficiency slope; VE/VCO_{2VAT} = ventilatory equivalent for carbon dioxide at the ventilatory anaerobic threshold; VO_{2peak} = oxygen uptake at peak exercise; VO_{2VAT} = oxygen uptake at the ventilatory anaerobic threshold.
[a]: determined by Cochrane's Q-test.

DISCUSSION

To our knowledge, the current study was the first study that aimed to investigate whether the selection of different CPET data-averaging intervals would translate into differences in mean values of CPET-derived variables in patients with colorectal cancer who performed CPET for preoperative risk assessment. As CPET-derived variables are used to preoperatively classify patients into having a low or high risk for postoperative complications based on their CRF, the secondary aim of the current study was to investigate whether potential differences in the numerical values of CPET-derived variables would lead to differences in preoperative risk classification. Based on the mean values of the CPET-derived variables there were only statistically significant differences for the variables VO_{2peak} and VE/VCO_{2VAT} between different data-averaging intervals. For VO_{2peak}, the between-group difference did not remain significant after post-hoc analysis, whereas data-averaging group differences VE/VCO_{2VAT} were statistically significant between the 3 breaths moving average and the 20- and 30-second time-based interval, as well as the 7 breaths moving average.

For VO_{2peak}, the greatest observed difference between data-averaging groups was 0.1 mL/kg/min. Given that the coefficient of variation (a measure of reproducibility) for VO_{2peak} is estimated to be between ~5% and ~9% (5) (i.e., between ~0.7 mL/kg/min and ~1.3 mL/kg/min based on mean values of VO_{2peak} in the current study), the observed maximal difference of 0.1 mL/kg/min is not clinically relevant. The observation that this small difference in VO_{2peak} is not clinically relevant is further emphasized by the fact that no differences were found between the proportion of patients who were classified as low or high risk based on VO_{2peak} when using different data-averaging intervals in the current study. Provided that the critical difference of VE/VCO_{2VAT} in patients with colorectal cancer is assumed to be ~10% (17), the maximal mean difference of 1.5 (5%) measured in the current study is not deemed clinically relevant. The observation that differences in the mean values of the VE/VCO_2-slope are not clinically relevant is also supported by the very small effect size (0.009).

The main purpose of using data-averaging of CPET data is to reduce noise of breath-by-breath fluctuations and to aid CPET interpretation (5). In the current study there seem to be no clinically relevant differences in CPET-derived variables between different data-averaging intervals. This is a reassuring observation that opens possibilities to be flexible in the use of data-averaging intervals as long as the interval is within certain boundaries. That is, the type and duration of CPET can be taken into consideration when determining the optimal data-averaging interval (7). For example, using longer averaging intervals in longer tests, or using a rolling average for noisy data. On the other hand, longer intervals might mask dynamic pathophysiological processes such oscillatory breathing. In these circumstances shorter time-based intervals might be optimal (7). For preoperative exercise testing a stationary time-based average of 10 seconds, or a breath-based rolling average of 3 or 7 seconds might provide a good trade-off between de number of data-points and the duration of the test.

Although the literature is scarce with regard to the influence of data-averaging intervals on the determination of CPET-derived variables (and only available for VO_{2peak}), results of the current study are in line with a previous publication in which the effect of data-averaging intervals on VO_{2peak} in 22 healthy athletic subjects was investigated (18). The authors found that only a stationary time-based data-averaging interval of 60 seconds was significantly different from all other data-averaging intervals (10, 15, 20, and 30 seconds) (18). In a study evaluating VO_{2peak} values of 15 patients who were screened for heart transplant surgery (with comparable mean VO_{2peak} values as observed in the current study), no significant differences were found between stationary time-based data-averaging intervals of 15 and 30 seconds, and a 8 breaths rolling average interval (19). Moreover, only a 60-second stationary time-based data-averaging interval was

statistically significantly different from the aforementioned data-averaging intervals (19). These long data-averaging intervals (of 60 seconds or more) are probably not used very often in preoperative CPETs and are not recommend by current preoperative CPET guidelines (8).

Based on the results of this study, the recommendation in the preoperative CPET guideline to use a breath-based data-averaging interval of 3-5 breaths or a time-based data-averaging interval of ~20 seconds seems plausible when evaluating the mean (group level) values. Nevertheless, caution should be taken when evaluating individual patients, as different data-averaging intervals caused substantial variation in the numerical values of CPET-derived variables within patients. As depicted in Figure 2, individual values of patients could differ as much as ~40%. In individual patients, the chosen data-averaging interval could induce a shift of that patient from low to high risk or vice versa. This is an important observation, as risk assessment could influence surgical planning for individual patients (e.g., enrollment in prehabilitation program, referring to a higher care unit postoperatively) and the shared decision-making process. It is recognized that preoperative risk assessment is not solely based on risk thresholds determined by CPET, but rather consists of a composite assessment, taking into account the full CPET in combination with other preoperative risk factors such as, but not limited to, malnutrition, comorbidities, and geriatric status. Nevertheless, the influence of the data-averaging interval could be taken into consideration, especially in patients in which the CPET values are close to the risk classification cut-off point. In addition, instead of rigid cut-off points inducing black and white risk assessment, grey zones (intermediate risk) could be introduced to account for individual differences (17).

A limitation of the current study was that VO_{2peak} was determined over a ~30 second interval (5) regardless of the data-averaging interval that was used. The use of the fixed 30 second interval might have masked some of the variability caused by the data-averaging interval, explaining the very small differences of VO_{2peak} values between data averaging intervals. A strength of the current study is that variation other than variation coming from the data-averaging interval was minimized. Firstly, by repeating interpretation of the 21 CPETs that were retrospectively formatted using 5 different data-averaging intervals, as opposed to repeated testing of patients with different data averaging intervals. Secondly, to account for inter-observer variability, CPET interpretation was done by two clinical exercise physiologists, based on consensus, and by using a predefined set of guidelines (see **Chapter 4** Supplemental file 1). By doing so, the observed variation between groups of data-averaging intervals was exclusively caused by the used data-averaging interval and not by within-patient biological variation, measurement error, or inter-observer variability.

The current study opens possibilities for clinicians to be flexible in the data-averaging interval that is used for interpretation of the preoperative CPET. Current CPET literature does not provide clear and consistent guidance for clinicians about the choice of a data-averaging interval (7, 8). As different (patho)physiological patterns might require different data-visualization, future research could focus on investigating optimal data-visualization methods that best fit the aim of the CPET, the properties of the CPET, and the (patho)physiological process the clinician is willing to evaluate.

CONCLUSION

On a group level there appear to be no clinically relevant differences in the mean values of VO_{2peak}, VO_{2VAT}, OUES, VE/VCO_{2VAT}, and VE/VCO_2-slope between different data-averaging intervals used for interpretation of preoperative CPET in patients with colorectal cancer. In addition, the choice of data-averaging interval does not influence the proportion of patients classified as high or low risk for complications based on their exercise tolerance. Nevertheless, the chosen data-averaging interval might lead to substantial within patient variation for individual patients and should therefore be considered in patients in which the CPET values are close to the risk classification cut-off point.

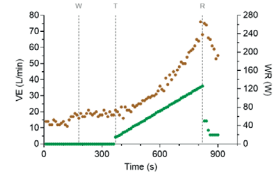
REFERENCES

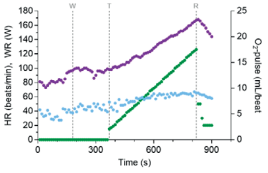
1. Moran J, Wilson F, Guinan E, McCormick P, Hussey J, Moriarty J. Role of cardiopulmonary exercise testing as a risk-assessment method in patients undergoing intra-abdominal surgery: a systematic review. Br J Anaesth. 2016;116(2):177-91.
2. Steffens D, Ismail H, Denehy L, Beckenkamp PR, Solomon M, Koh C, et al. Preoperative Cardiopulmonary Exercise Test Associated with Postoperative Outcomes in Patients Undergoing Cancer Surgery: A Systematic Review and Meta-Analyses. Ann Surg Oncol. 2021;28(12):7120-46.
3. Older P, Smith R, Courtney P, Hone R. Preoperative evaluation of cardiac failure and ischemia in elderly patients by cardiopulmonary exercise testing. Chest. 1993;104(3):701-4.
4. Bongers BC, Dejong CHC, den Dulk M. Enhanced recovery after surgery programmes in older patients undergoing hepatopancreatobiliary surgery: what benefits might prehabilitation have? Eur J Surg Oncol. 2021;47(3 Pt A):551-9.
5. American Thoracic S, American College of Chest P. ATS/ACCP Statement on cardiopulmonary exercise testing. Am J Respir Crit Care Med. 2003;167(2):211-77.
6. Otto JM, Levett DZH, Grocott MPW. Cardiopulmonary Exercise Testing for Preoperative Evaluation: What Does the Future Hold? Current Anesthesiology Reports. 2020;10(1):1-11.
7. Dumitrescu D, Rosenkranz S. Graphical Data Display for Clinical Cardiopulmonary Exercise Testing. Ann Am Thorac Soc. 2017;14(Supplement_1):S12-S21.
8. Levett DZH, Jack S, Swart M, Carlisle J, Wilson J, Snowden C, et al. Perioperative cardiopulmonary exercise testing (CPET): consensus clinical guidelines on indications, organization, conduct, and physiological interpretation. Br J Anaesth. 2018;120(3):484-500.
9. West MA, Asher R, Browning M, Minto G, Swart M, Richardson K, et al. Validation of preoperative cardiopulmonary exercise testing-derived variables to predict in-hospital morbidity after major colorectal surgery. Br J Surg. 2016;103(6):744-52.
10. Bongers BC, Berkel AE, Klaase JM, van Meeteren NL. An evaluation of the validity of the preoperative oxygen uptake efficiency slope as an indicator of cardiorespiratory fitness in elderly patients scheduled for major colorectal surgery. Anaesthesia. 2017;72(10):1206-16.
11. Dideriksen K, Mikkelsen UR. Reproducibility of incremental maximal cycle ergometer tests in healthy recreationally active subjects. Clin Physiol Funct Imaging. 2017;37(2):173-82.
12. Martin-Rincon M, Calbet JAL. Progress Update and Challenges on V . O2max Testing and Interpretation. Front Physiol. 2020;11:1070.
13. Martin-Rincon M, Gonzalez-Henriquez JJ, Losa-Reyna J, Perez-Suarez I, Ponce-Gonzalez JG, de La Calle-Herrero J, et al. Impact of data averaging strategies on VO2max assessment: Mathematical modeling and reliability. Scand J Med Sci Sports. 2019;29(10):1473-88.
14. Franssen RFW, Bongers BC, Vogelaar FJ, Janssen-Heijnen MLG. Feasibility of a tele-prehabilitation program in high-risk patients with colon or rectal cancer undergoing elective surgery: a feasibility study. Perioper Med (Lond). 2022;11(1):28.
15. von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP, et al. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. BMJ. 2007;335(7624):806-8.
16. Faul F, Erdfelder E, Lang AG, Buchner A. G*Power 3: a flexible statistical power analysis program for the social, behavioral, and biomedical sciences. Behav Res Methods. 2007;39(2):175-91.
17. Rose GA, Davies RG, Davison GW, Adams RA, Williams IM, Lewis MH, et al. The cardiopulmonary exercise test grey zone; optimising fitness stratification by application of critical difference. Br J Anaesth. 2018;120(6):1187-94.

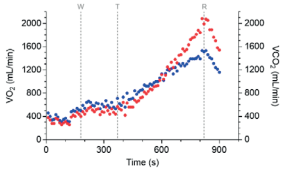
18. Midgley AW, McNaughton LR, Carroll S. Effect of the VO2 time-averaging interval on the reproducibility of VO2max in healthy athletic subjects. Clin Physiol Funct Imaging. 2007;27(2):122-5.
19. Johnson JS, Carlson JJ, VanderLaan RL, Langholz DE. Effects of sampling interval on peak oxygen consumption in patients evaluated for heart transplantation. Chest. 1998;113(3):816-9.

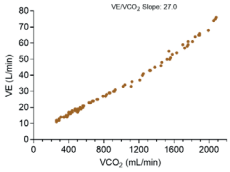
SUPPLEMENTAL FILE 1, GRAPHICAL DISPLAY OF THE WASSERMAN PLOTS OF PATIENT 21 WITH THE DIFFERENT DATA-AVERAGING INTERVALS.

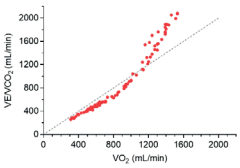
Data visualization using 10 seconds data-averaging

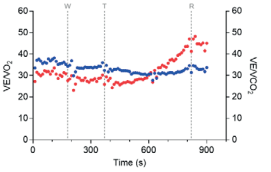


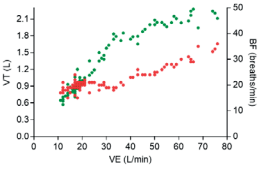


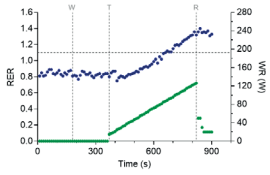


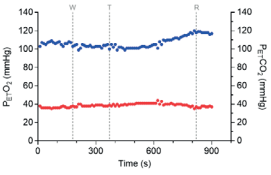


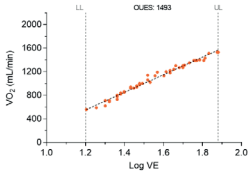




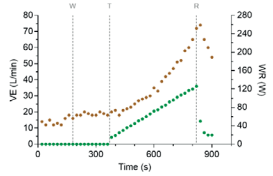


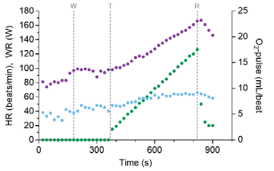


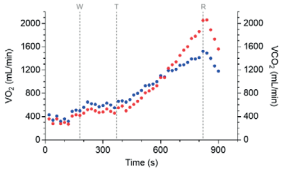


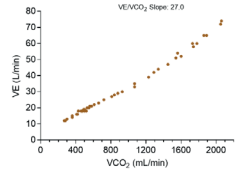


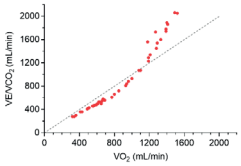
Data visualization using 20 seconds data-averaging

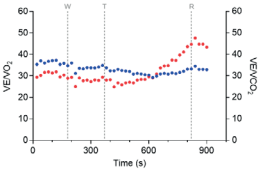


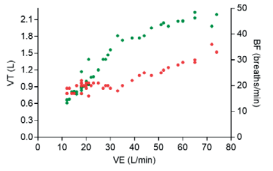


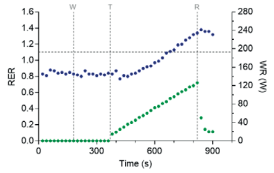


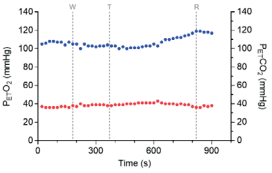


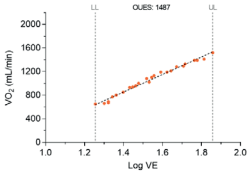




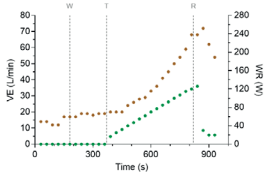


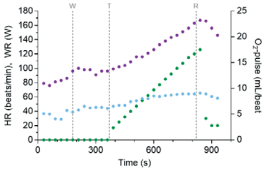


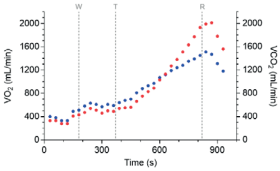


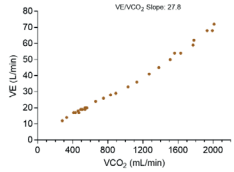


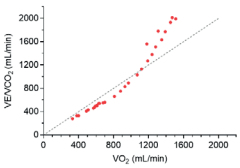
Data visualization using 30 seconds data-averaging

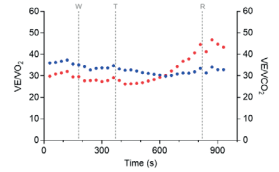


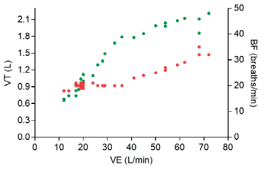


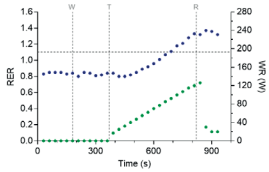


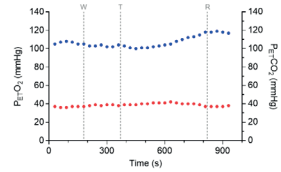


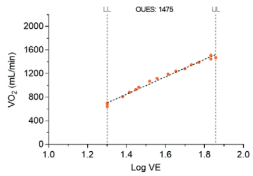




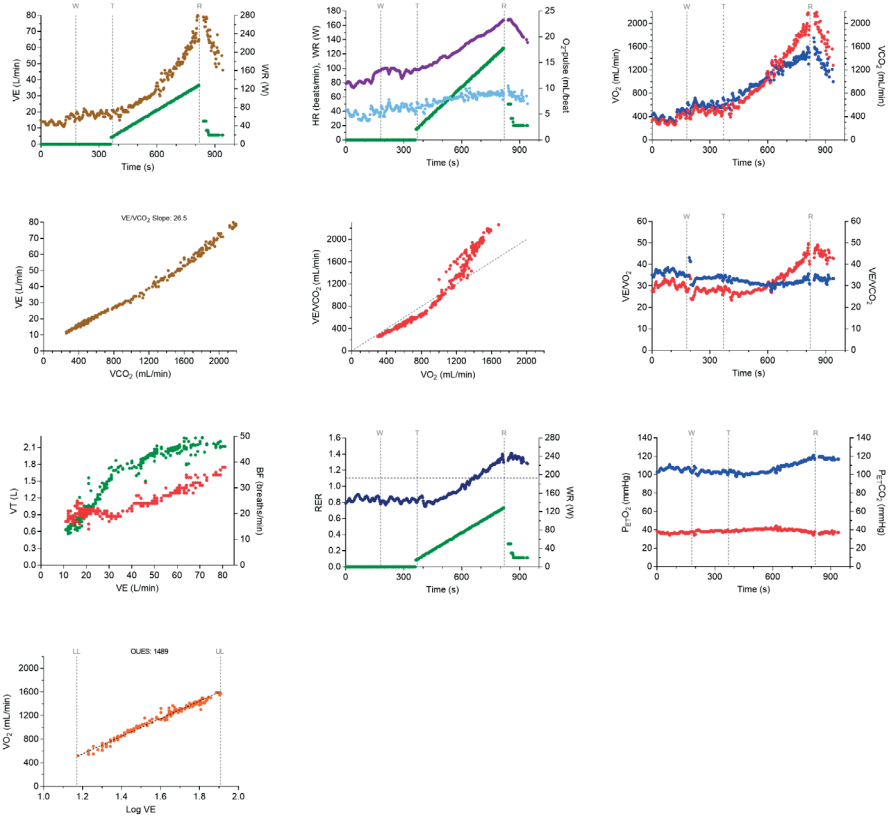




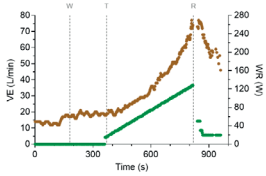


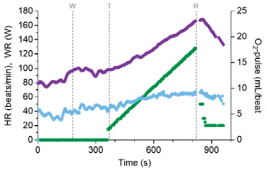


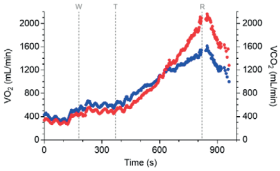
Data visualization using 3 breaths data-averaging

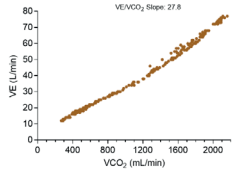


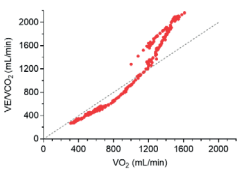
Data visualization using 7 breaths data-averaging

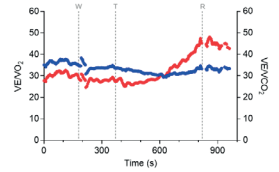


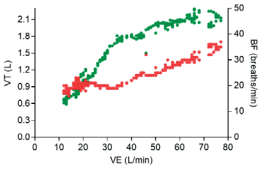


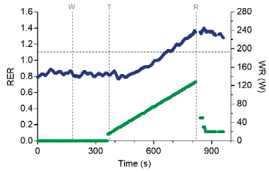


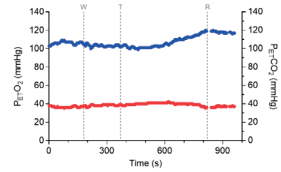


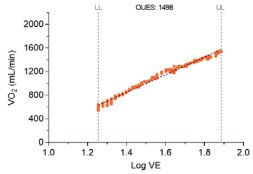












6

CHAPTER 6

A retrospective analysis of the association of effort-independent cardiopulmonary exercise test variables with postoperative complications in patients who underwent elective colorectal surgery

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**Shared first authorship*

Submitted

7

CHAPTER 7

Moderate-intensity exercise training or high-intensity interval training to improve aerobic fitness during exercise prehabilitation in patients planned for elective abdominal cancer surgery?

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Bart C. Bongers

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ABSTRACT

Low preoperative aerobic fitness is associated with an increased risk of postoperative complications and delayed recovery in patients with abdominal cancer. Surgical prehabilitation aims to increase aerobic fitness preoperatively to improve patient- and treatment-related outcomes. However, an optimal physical exercise training program that is effective within the short time period available for prehabilitation (<6 weeks) has not yet been established. In this comparative review, studies (n=8) evaluating the effect of short-term (<6 weeks) moderate-intensity exercise training (MIET) or high-intensity interval training (HIIT) on objectively measured aerobic fitness were summarized. The content of exercise interventions was critically appraised regarding the frequency, intensity, time, type, volume, and – monitoring of – progression (FITT-VP) principles. Three out of four studies evaluating HIIT showed statistically significant improvements in oxygen uptake at peak exercise (VO_{2peak}) by more than 4.9%, the coefficient of variation for VO_{2peak}. None of the two studies investigating short-term MIET showed statistically significant pre-post changes in VO_{2peak}. Although short-term HIIT seems to be a promising intervention, concise description of performed exercise based on the FITT-VP principles was rather inconsistent in studies. Hence, interpretation of the results is challenging, and a translation into practical recommendations is premature. More emphasis should be given to individual responses to physical exercise training. Therefore, adequate risk assessment, personalized physical exercise training prescription using the FITT-VP principles, full reporting of physical exercise training adherence, and objective monitoring of training progression and recovery is needed to ensure for a personalized and effective physical exercise training program within a multimodal prehabilitation program.

INTRODUCTION

There is a clear body of evidence showing that lower preoperative aerobic fitness is consistently and independently associated with a higher risk for postoperative complications following major abdominal cancer surgery [1-4]. Surgical prehabilitation involves targeted preventive interventions to improve a patient's health between the time of cancer diagnosis and the surgical procedure [5], in order to reduce the incidence, severity, and impact of postoperative complications, thereby accelerating and improving recovery [6]. The effectiveness of prehabilitation relies on the assumptions that 1) a patient's health status (not limited to, but also including aerobic fitness) can be improved in an often time-constrained preoperative setting, and 2) an improved health status translates into a reduced risk of postoperative complications and enhanced recovery.

Prehabilitation interventions should be designed using a multimodal perspective, thereby encompassing modalities such as physical exercise training, nutritional support, psychosocial support, alcohol consumption and/or smoking cessation [7], and anemia correction [8]. Physical exercise training is considered to be the main driver to improve aerobic fitness preoperatively. Intuitively, the process of increasing aerobic fitness seems to be straightforward; however, an effective physical exercise training program involves a complex interplay between sufficient overload and post-exercise recovery in order to promote supercompensation to subsequently improve aerobic fitness. To date, there is large heterogeneity between preoperative physical exercise training programs regarding program composition, mode of administration, and outcome measures of aerobic fitness [9], while the content of the programs seems to be based on a "one-size-fits-all" approach. Variation in the design and the quality of administering preoperative physical exercise training interventions may (partly) explain the variability in between-study estimates of effects.

As the period between cancer diagnosis and surgery is often time constrained (e.g., maximal 34 days in colorectal cancer) due to current treatment guidelines [10, 11], a preoperative physical exercise training program that is effective in a short time period is needed. Although aerobic fitness can be improved by moderate-intensity exercise training (MIET), high-intensity interval training (HIIT) has been introduced as a type of training that can improve aerobic fitness faster and more time-efficient [12]. As such, HIIT might on average be a physiologically more feasible option with respect to the effectiveness for a short-term preoperative optimization of aerobic fitness compared to MIET. The aim of the current comparative review is to provide evidence-based decision-support for choosing short -term MIET or HIIT as part of a multimodal prehabilitation program in patients scheduled for elective abdominal cancer surgery.

To achieve this aim, a literature search (Supplemental file 1) in the databases PubMed, CINAHL, and Embase (up to December 2020) has been conducted. Studies in patients with abdominal cancer or abdominal cancer survivors, in which short-term (defined as ≤6 weeks) unimodal MIET or HIIT were compared to either usual care or to each other, with the main outcome being aerobic fitness as measured by means of a cardiopulmonary exercise test (CPET), were included. The rationale to also include studies in abdominal cancer survivors was based on the expected low number of prehabilitation studies and the fact that the short time period between diagnosis and surgery is the main challenge in improving aerobic fitness. As such, we focused on short-term physical exercise training programs in populations with comparable subject characteristics with regard to age, comorbidities, and lifestyle. Studies investigating multimodal prehabilitation interventions, studies that combined MIET or HIIT with another type of training (e.g., resistance training, functional exercise training) and studies investigating physical exercise training programs during active cancer treatment (e.g., neoadjuvant chemo and/or radiation therapy were excluded. Moderate intensity was defined as exercise intensities between 64 and 76% of maximal heart rate (HR_{max}) [13],whereas high intensity was defined as efforts ≥80% of HR_{max} or equivalent [14].

The search identified eight studies of which six randomized controlled trials [15-20], one non-randomized controlled trial [21], and one single-arm pre-post study [22]. Six of these eight studies were prehabilitation studies [15-17, 20-22]. Three studies were performed in patients with colorectal cancer or colorectal cancer survivors [18, 19, 22], one study in patients with rectal cancer [21], two studies in patients with urological cancer [15, 17], and one study in patients with colorectal liver metastasis undergoing elective surgery [16]. Table 1 depicts relevant study characteristics. In order to add context to the included studies, subsequent sections are used to summarize basic background information concerning physical exercise training and program design. In addition, study results, study limitations, and future directions are discussed in the final sections.

Significance of maximal oxygen uptake for the quantification of preoperative aerobic fitness

Maximal oxygen uptake (VO_{2max}) as assessed during a progressive maximal CPET is generally considered as the gold standard for quantifying aerobic fitness [23]. VO_{2max} is determined by the integrative capacity of the pulmonary, cardiovascular, and muscular system to take in, transport, and utilize oxygen during maximal effort [24]. A true VO_{2max} requires a plateau in oxygen uptake (VO_2) despite an increasing exercise intensity, which is seldom seen [25]. Therefore, derivative indicators of aerobic fitness are often used. These indicators of aerobic fitness include 1) the highest achieved oxygen uptake (VO_2) at peak exercise (VO_{2peak}), which also requires a maximal effort but no VO_2 plateau, 2)

the submaximal VO_2 at the ventilatory anaerobic threshold (VAT) [3, 21, 26, 27]**.** The VAT demarks the transition from an almost entirely aerobic metabolism to anaerobic metabolism as an additional source of energy production to meet an increasing metabolic demand. It is assumed that an adequate preoperative aerobic fitness level is required to be able to cope with the surgically induced stress response, and the associated increased metabolic demands following major abdominal cancer surgery [28]. Therefore, patients with a low aerobic fitness have a higher risk for complications. In abdominal cancer surgery, patients with an VO_2 at the VAT <11 mL/kg/min are generally classified as high risk, although exact thresholds for identifying patients with a high risk for complications differ depending on type of surgery and type of outcome measure and are summarized by Older and Levett [1]. Particularly patients with a low preoperative aerobic fitness as determined by these CPET derived thresholds, who consequently have a high risk for postoperative complications, might benefit the most from preoperative interventions that improve their aerobic fitness.

Principles of physical exercise training prescription and adjustment

The process of developing a physical exercise training prescription consists of 1) assessing health and aerobic fitness levels, 2) interpretation of the assessment, 3) performing adequate risk assessment, 4) formulating a personalized and feasible exercise prescription based on previously selected aims, and 5) regular and structured assessment of progression and subsequent consideration of program adjustments [29, 30]. Training frequency, intensity, time, type, volume, and progression (FITT-VP principles) should be well-considered [29], along with recommendations as described by Hoogeboom et al. [31] in the international Consensus on Therapeutic Exercise aNd Training (i-CONTENT) tool.

Training **frequency** is typically described as the number of training sessions per week. Exact timing of training should be individualized, as it depends on several factors such as training intensity, training duration, recovery potential, training goals, and baseline aerobic fitness and periodization. Training **intensity** describes the effort that is associated with exercise that can be estimated using physiological performance parameters, preferably associated by using perception parameters. Ideally, training intensity is physiologically estimated based on the work rate at a given percentage of VO_{2peak} (or VO_2 at the VAT) as measured during a CPET [32]. However, work rate-based prescription will only be feasible when using specialized and calibrated fitness equipment. Other means involve heart rate monitoring, either using heart rate zones as derived from a CPET, a percentage of HR_{max} or heart rate reserve (HRR), and rating of perceived exertion (e.g., Borg scale) [12]. When using interval training with short intervals, work rate or rating of perceived exertion-based prescription is recommended as heart rate monitoring is

Table 1. General study characteristics.

Authors (year)	Study Design	Intervention versus control	Exercise training program duration	Study population / study period	Sample size	Age (years) [a]	Sex (% male)	Mean ± SD baseline VO_2 at the VAT (mL/kg/min)	Mean ± SD baseline VO_{2peak} (mL/kg/min)
Boereboom et al. (2016) [22]	Pre-post intervention study	HIIT (no control)	4 weeks	Colorectal cancer / preoperative	**HIIT** n=18	**HIIT** 67 ± 8	**HIIT** 72%	**HIIT** 14.0 ± 3.4	**HIIT** 23.9 ± 7.0
Blackwell et al. (2019) [17]	RCT	HIIT versus UC	4 weeks	Urological cancer / preoperative	**HIIT** n=19 **UC** n= 21	**HIIT** 71 ±2 **UC** 72 ±4	**HIIT** 100% **UC** 95%	**HIIT** 13.2 ± 1.9 **UC** 13.8 ± 2.8	**HIIT** 24.8 ± 5.2 **UC** 26.4 ± 5.7
Dunne et al. (2016) [16]	RCT	HIIT versus UC	4 weeks	Liver cancer / preoperative	**HIIT** n=20 **UC** n=17	**HIIT** median 61 (IQR 56-66) **UC** median 62 (IQR 53- 72)	**HIIT** 65% **UC** 76%	**HIIT** 11.2 ± 1.5 **UC** 11.4 ± 1.8	**HIIT** 17.6 ± 2.3 **UC** 18.6 ± 3.9
West et al. (2015) [21]	NRCT	HIIT versus UC	6 weeks	Rectal cancer / post-NACRT, preoperative	**HIIT** n=22 **UC** n=13	**HIIT** 64 (range 45-82) **UC** 72 (range 62-84)	**HIIT** 64% **UC** 69%	**HIIT** 10.2 (CI 9.15 to 11.37) **UC** 10.1 (CI 8.7 to 11.6)	**HIIT** 16.1 (CI 14.1 to 17.9) **UC** 15.7 (CI 13.2 to 18.2)
Banerjee et al. (2018) [15]	RCT	MHIIT versus UC	3 to 6 weeks	Bladder cancer / preoperative	**MHIIT** n=30 **UC** n=30	**MHIIT** 71.6 ± 6.8 **UC:** 72.5 ± 8.4	**MHIIT** 90% **UC** 87%	**MHIIT** 11.5 ± 2.1 **UC** 11.4 ± 2.6	**MHIIT** 19.2 ± 4.8 **UC** 20.4 ± 5.6
Kim et al. (2009) [20]	RCT	MIET versus UC	4 weeks	Colorectal cancer / preoperative	**MIET** n=14 **UC** n=7	**MIET** 55 ± 15 **UC** 65 ± 9	**MIET** 64% **UC** 57%		**MIET** 21.5 ± 10.1 **UC** 20.3 ± 4.6
Devin et al. (2016) [19]	RCT	HIIT versus MIET	4 weeks	Colorectal cancer / post-treatment	**HIIT** n=30 **MIET** n=17	**HIIT** 61.4 ± 11.1 **MIET** 61.6 ± 10.8	**HIIT** 60% **MIET** 47%		**HIIT** Median 22.8 (IQR 6) **MIET** Median 21.5 (IQR 8)

Table 1. General study characteristics. (*continued*)

Authors (year)	Study Design	Intervention versus control	Exercise training program duration	Study population / study period	Sample size	Age (years) [a]	Sex (% male)	Mean ± SD baseline VO_2 at the VAT (mL/kg/min)	Mean ± SD baseline VO_{2peak} (mL/kg/min)
Devin et al.[b] (2018) [18]	RCT	HIIT[2] versus MIET	4 weeks	Colorectal cancer / post-treatment	**HIIT**1 n=18 **HIIT**2 n=20 **MIET** n=19	**HIIT1** 60.7 ± 11.7 **HIIT2** 61.5 ± 10.2 **MIET** 59.8 ± 11.4	**HIIT1** 72% **HIIT2** 50% **MIET** 47%		**HIIT1** 23.2 (CI 21.8 to 24.5) **HIIT2** 23.5 (CI 22.2 to 24.8) **MIET** 23.4 (CI 22.1 to 24.7)

Abbreviations: CI = 95% confidence interval; HIIT = high-intensity interval training; IQR = interquartile range; MHIIT = moderate- to high-intensity interval training; MIET = moderate-intensity exercise training; NACRT = neoadjuvant chemoradiotherapy; NRCT = non-randomized controlled trial; RCT = randomized controlled trial; SD = standard deviation; UC = usual care (no exercise intervention).

[a]: values are presented as mean ± SD, unless stated otherwise.

[b]: the study of Devin et al. 2018 consisted of two groups receiving HIIT: the two HIIT protocols were equal for the first 4 weeks of training; thereafter, in a second cycle of 4 weeks, one group (HIIT1) continued to exercise three times per week, whereas group two (HIIT2) only trained once a week (only results of the first four weeks of training are displayed for both groups).

less useful when work intervals are <3 minutes due to the delayed cardiac response to exercise. According to the American College of Sports Medicine (ACSM), a minimal exercise intensity of 40% of HRR (maximal heart rate minus resting heart rate as measured after sitting for 5 minutes) is the threshold that should be exceeded for exercise to provide sufficient overload to improve aerobic fitness in deconditioned individuals (probably the majority of patients in need for prehabilitation). Training **time** indicates the duration of a single exercise training session, including warm-up and cool-down. In case of interval training, special consideration should be given to reporting the duration of the work and rest intervals separately. Training **type** defines the training modality, such as cycling, walking, running, continuous or interval exercise, functional exercises, or resistance training.

The product of training period (weeks), frequency (training sessions per week), intensity (e.g., percentage of VO_2 at the VAT or at peak exercise), and time (training session duration) is called training **volume**, which is usually expressed as the energy (in Kilojoules of Kilocalories) that is expended during an entire training program episode. Due to improvements in aerobic fitness as a result of training adaptations, training volume should be increased (by either increasing training frequency, intensity, and/or training time) to make sure an adequate overload is maintained throughout the complete program. This is known as **progression** of training. As sufficient progress in aerobic fitness should be the main outcome parameter of exercise prehabilitation, progression of training should frequently be assessed (referred to as "titration" [33]), preferably on a weekly base using a formal performance test [34]. Quantification of progression is essential to motivate responders, to timely identify non-responders, and to subsequently make necessary program adjustments concerning training frequency, intensity, and duration [34]. Based on the law of diminishing returns, the adaptive potential of physiologic function will diminish when training progresses, and improvements in aerobic fitness will plateau at some point [29]. This asymptotic response to exercise emphasizes another necessity for frequent formal monitoring of progression. The point at which improvements level-off despite progression of training might be important when considering optimal timing of surgical interventions.

In addition to the FITT-VP principles, **auto-regulation** is an important aspect of an individualized training program [35]. Auto-regulation refers to possibility of a patient to adjust a training session based on his state of recovery. Time needed to recover from a training session is highly individual and depends on factors as training volume, stress levels, sleep quality, nutrition, neuroendocrine- and immune system resilience, and environment. By using autoregulation, training load can be adjusted accordingly, allowing for higher training loads on days the patient is recovered well, whereas lower

training loads or rest could be prescribed on days the patient is still fatigued. To monitor recovery, several questionnaires exist, such as the perceived recovery status scale [36] and the wellbeing review [37]. These can be applied before every training session to give insight into the patient's preparedness to perform exercise.

How are high- and moderate-intensity exercise defined?

HIIT encompasses a broad spectrum of physical exercise training modalities characterized by brief periods of high-intensity exercise (work interval) interspersed with periods of (active) rest at a low intensity (rest interval). High-intensity intervals are defined as near maximal efforts that elicits heart rate to rise ≥80% of its maximum or equivalent [14]; however, this definition is imperfect, as perceived intensity of exercise is dependent on intensity multiplied by time. Duration of the work and rest intervals can vary significantly and are typically between 30 seconds and 4 minutes [38].

The term MIET involves types of exercise with intensities lower than HIIT that is usually performed in a continuous manner [14]. Though, several interval types are also possible. In order to improve aerobic fitness, a minimal duration of 20 minutes of continuous MIET is recommended [29].

There is evidence that especially skeletal muscle adaptations largely depend on exercise intensity, with higher intensities leading to more pronounced training-effects. The rationale behind this is that cellular stress caused by higher intensities leads to greater mitochondrial biogenesis and subsequent increased mitochondrial content [14]. By this cascade of events, oxidative capacity of the muscle is increased. There is less evidence available regarding the role of exercise intensity in mediating changes in skeletal muscle capillary density, maximal stroke volume, maximal cardiac output, and blood volume [14].

Evidence suggests that skeletal muscle mitochondrial adaptations [14] and improvements in VO_{2peak} in healthy individuals [14, 39], as well as clinical populations [38], are greater for HIIT than MIET with equal training volumes (the product of training frequency, intensity, and time). Hence, improvements in VO_{2peak} are comparable when the training volume of HIIT is lower. Especially in time-constrained periods, such as the period before abdominal cancer surgery, high training volumes might not always be feasible. HIIT therefore provides an attractive alternative to achieve training adaptations that improve aerobic fitness fast and more time efficient**.** A recent systematic review on HIIT in patients with cancer across all stages of therapy and aftercare, however not limited to exercise interventions <6 weeks (mean (SD) duration of 6 (3) weeks), was less conclusive. Although the authors found that HIIT was superior in improving aerobic

fitness compared to usual care, they found no evidence for additional benefits of HIIT above MIET for improvements in aerobic fitness [40]. In a recent randomized controlled trial comparing a multimodal 4-week prehabilitation program containing either MIET or HIIT [41], both groups increased their preoperative VO_2 at the VAT with respectively 1.71 mL/kg/min (+12.4%) and 1.97 mL/kg/min (+16.0%), with no significant between-group differences. Improvements in VO_{2peak} were statistically significant after HIIT (+1.95 mL/kg/min, +10.5%) but not after MIET (+0.45 mL/kg/min, +2.1%) with no significant difference between groups ($p = 0.080$) [41].

What is the ability of short-term HIIT or MIET to improve preoperative aerobic fitness in patients with abdominal cancer?

The effect of short-term HIIT on short-term improvement of preoperative aerobic fitness

Three studies [16, 17, 21] evaluating the effect of short-term HIIT compared to usual care (no exercise intervention) on aerobic fitness found significant improvements in VO_2 at the VAT and/or VO_{2peak} after 4 to 6 weeks of HIIT. One study without a control group [22] did not find significant changes in VO_2 at the VAT or VO_{2peak} after 4 weeks of HIIT. In the latter study, an uncontrolled pre-post intervention study, patients with colorectal cancer trained for 4 weeks prior to elective surgery. No significant improvements in aerobic fitness were found on the group level. However, there was a large heterogeneity in response to training between participants. A limitation of this study was the low adherence. Participants only attended a median of eight out of twelve intended exercise sessions. This low amount of attended HIIT sessions (40 minutes of HIIT with an estimated energy expenditure of 343 Kcal) might not have been sufficient training volume to improve VO_2 at VAT or VO_{2peak} [42]. This is further emphasized by the fact that essentially the same HIIT exercise prescription, though with higher exercise session attendance rates (and therefore higher training volumes), did manage to increase VO_2 at the VAT and VO_{2peak} in healthy adults (60 minutes of HIIT, with an estimated energy expenditure of 491 Kcal) [43] and in patients with urological cancer (55 minutes of HIIT with an estimated energy expenditure between 417 and 479 Kcal) [17]. In the latter study, four weeks of HIIT increased VO_2 at the VAT by 2.3 mL/kg/min (+17.4%) and VO_{2peak} by 2.2 mL/kg/min (+8.9%). Two other studies [16, 21] also showed beneficial effects of HIIT on aerobic fitness after 4 and 6 weeks of training. In patients awaiting liver resection for colorectal liver metastasis, a 4-week HIIT program improved VO_{2peak} by 2.0 mL/kg/min (+11.4%) [16]. West et al. [21] studied the effect of preoperative HIIT between neoadjuvant chemoradiotherapy (NACRT) and surgery in patients with rectal cancer. The HIIT group showed an improvement in VO_2 at the VAT and VO_{2peak} of respectively 2.1 mL/kg/min (+20.6%) and 2.7 mL/kg/min (+17.1%) after six weeks of training. In the study

of Dunne et al. [16], 18 out of 19 participants (~95%) in the exercise arm of the study attended all prescribed exercise sessions, whereas ~96% attended all 18 prescribed exercise sessions in the latter study of West et al. [21]. An overview of the used exercise prescription, performed physical exercise training, and outcomes can be found in Table 2, Table 3, and Figure 1 (graph A and B), respectively, as well as in Supplemental file 2.

The effect of short-term MIET or moderate to high-intensity interval training, on short-term improvement of preoperative aerobic fitness

Two studies investigated the effect of short-term MIET [20], or moderate- to high-intensity interval training [15] on objectively measured preoperative aerobic fitness in patients with abdominal cancer. In the study of Banerjee et al. [15], patients with bladder cancer followed a 3- to 6-week moderate- to high-intensity interval training program. Kim et al. [20] studied patients with colorectal cancer who participated in a 4-week daily, partly-supervised MIET program (Table 2). In both studies [15, 20], no significant group level improvements in VO_2 at the VAT or VO_{2peak} were found (Figure 1, graph A and B, and Supplemental file 2). However, the median number of attended sessions in the study of Banerjee et al. [15] was low and varied greatly between participants (median 8 sessions, range 1-10 sessions) (Table 3). This low amount and large range of attended exercise sessions, in combination with a training frequency of only 2 sessions per week, might not have provided sufficient overload to improve VO_2 at the VAT and VO_{2peak} rapidly. In the study of Kim et al. [20], merely ~74% of the sessions were attended, and attendance rates were based on self-report. Furthermore, the exercise intensity of 40% of the HRR was at the lower end of the minimal intensity needed to elicit improvements in aerobic fitness as recommended by the ACSM [29]. Although some progression was intended over the course of the 4-week exercise program, this progression was not based on objectively monitored training progression and recovery at the individual level, and the authors did not report actual adherence to the exercise prescription. Hence, the combination of low attendance rates in combination with the relatively low training intensity (low training volume) might not have led to sufficient overload.

The effect of short-term HIIT versus short-term MIET on short-term improvement of aerobic fitness

Currently, there seem to be no unimodal studies directly comparing short-term HIIT with short-term MIET in the preoperative setting. However, two studies evaluated the effect of short-term HIIT compared to MIET in colorectal cancer survivors (Table 2). In the first study performed in 2016, 4 weeks of HIIT was compared to 4 weeks of MIET. The HIIT group significantly increased VO_{2peak} with 3.5 mL/kg/min (+14.6%) after 4 weeks of training, whereas the MIET group did not significantly improve VO_{2peak} (+4.3%) [19] (Figure 1, graph C). In a second study performed in 2018, Devin et al. [18] compared two

Table 2. Exercise prescription according to the FITT-VP principles.

	Exercise protocol (FITT-VP principles)					
Authors (year)	F	I	T	T	V	P
Boereboom et al. (2016) [22]	**HIIT** 3-4 times a week	**HIIT** Work interval: 100-120% WR_{peak} Rest interval: unloaded cycling	**HIIT** Work interval: 5 × 1 minute Rest interval: 5 × 1.5 minutes	Cycling		Not reported
Blackwell et al. (2019) [17]	**HIIT** 3-4 times a week	**HIIT** Work interval: 110-120% WR_{peak} Rest interval: unloaded cycling	**HIIT** Work interval: 5 × 1 minute Rest interval: not reported	Cycling		Increase in WR after 6 sessions
Dunne et al. (2016) [16]	**HIIT** 3 times a week	**HIIT** Work interval: >90% VO_{2peak} Rest interval: <60% VO_{2peak}	**HIIT** Total: 30 minutes Work interval: Not reported Rest interval: Not reported	Cycling		Not reported
West et al. (2015) [21]	**HIIT** 3 times a week	**HIIT** Work interval: 50% of WR between VO_2 at the VAT and VO_{2peak} Rest interval: WR at 80% of VO_2 at the VAT	**HIIT** *First two sessions* Work interval: 4 × 2 minutes Rest interval: 4 × 3 minutes *After two sessions* Work interval: 6 × 2 minutes Rest interval: 6 × 3 minutes	Cycling		Responsive to exercise test in week 3
Banerjee et al. (2018) [15]	**MHIIT** 2 times a week	**MHIIT** Work interval: 70-85% of predicted HR_{peak} Rest interval: light resistance (50 W)	**MHIIT** Work interval: 6 × 5 minutes Rest interval: 6 × 2.5 minutes	Cycling		Not reported
Kim et al. (2009) [20]	**MIET** 7 times a week	**MIET** 40-65% HRR	**MIET** 50 minutes	Cycling (partially supervised)		Not reported
Devin et al. (2016) [19]	**HIIT** 3 times a week **MIET** 3 times a week	**HIIT** Work interval: 85-95% HR_{peak} Rest interval: 50-70% HR_{peak} **MIET** 70% HR_{peak}	**HIIT** Work interval: 4 × 4 minutes Rest interval: 4 × 3 minutes **MIET** 50 minutes	Cycling		**HIIT** Not reported **MIET** Not reported

Table 2. Exercise prescription according to the FITT-VP principles. (*continued*)

	Exercise protocol (FITT-VP principles)					
Authors (year)	F	I	T	T	V	P
Devin et al. (2018) [a] [18]	**HIIT** 3 times a week **MIET** 3 times a week	**HIIT** Work interval: 85-95% HR_{peak} Rest interval: 50-70% HR_{peak} **MIET** 70% HR_{peak}	**HIIT** Work interval: 4 × 4 minutes Rest interval: 4 × 3 minutes **MIET** 50 minutes	Cycling		**HIIT** Not reported **MIET** Not reported

Abbreviations: FITT-VP = frequency, intensity, time, type, volume, and progression; HIIT = high-intensity interval training; HR = heart rate; HR_{peak} = heart rate at peak exercise; HR_{max} = maximal heart rate; MIET = moderate-intensity exercise training; VAT = ventilatory anaerobic threshold; VO_2 = oxygen uptake; VO_{2peak} = oxygen uptake at peak exercise; WR= work rate; WR_{peak} = work rate at peak exercise.

[a]: the study of Devin et al. 2018 consisted of two groups receiving HIIT: the two HIIT protocols were equal for the first 4 weeks of training; thereafter, in a second cycle of 4 weeks, one group (HIIT1) continued to exercise three times per week, whereas group two (HIIT2) only trained once a week (only results of the first four weeks of training are displayed for both groups).

Table 3. Performed exercise according to the FITT-VP principles.

Authors (year)	Performed exercise (FITT-VP principles)					
	F	I	T	T	V	P
Boereboom et al. (2016) [22]	**HIIT** Sessions per week: not reported Total number of sessions: Median 8 (Range 6-14)	**HIIT** Not clearly reported Mean training workload 155W (± 55W) 100% of patients between 100-120% of WR_{peak}	**HIIT** Work interval: not clearly reported Rest interval: not clearly reported	Cycling		Not intended
Blackwell et al. (2019) [17]	**HIIT** Sessions per week: not reported Total number of sessions: Median 11 (IQR 10-12)	**HIIT** All participants achieved >85% of predicted HR_{max} during the sessions	**HIIT** Work interval: not reported Rest interval: not reported	Cycling		89% of participants increased WR with 10% after 6 sessions
Dunne et al. (2016) [16]	**HIIT** Sessions per week: not reported Total number of sessions: 94% of participants attended all (12) sessions	**HIIT** Not reported	**HIIT** Work interval: not reported Rest interval: not reported	Cycling		Not intended
West et al. (2015) [21]	**HIIT** Sessions per week: not reported Total number of sessions: 96% ± 5% of participants attended all (18) sessions	**HIIT** Not reported	**HIIT** Work interval: not reported Rest interval: not reported	Cycling		On group level improvement measured by interim CPET. Actual progression not clearly reported
Banerjee et al. (2018) [15]	**MHIIT** Sessions per week: not reported Total number of sessions: Median 8 (range 1-10)	**MHIIT** Average HR between 85% and 87% of predicted HR_{peak} or 90 and 92% of measured HR_{max} during CPET	**MHIIT** Work interval: in week 1, an average of 5.5 intervals achieved (range 3.5-6.0), in week 4, all patients achieved 6 intervals Rest interval: not reported	Cycling		Training load increased from 111 ± 5.5^2 W to 122 ± 5.8^2 W

Table 3. Performed exercise according to the FITT-VP principles. (*continued*)

Authors (year)	Performed exercise (FITT-VP principles)					
	F	I	T	T	V	P
Kim et al. (2009) [20]	**MIET** Sessions per week: not reported Total number of sessions: Mean 27 ±9, Compliance 74 ± 16%	**MIET** Not reported	**MIET** Not reported	Cycling (partially supervised)		Not intended
Devin et al. (2016) [19]	**HIIT** Sessions per week: not reported Total number of sessions: mean 97% of prescribed sessions were attended **MIET** Sessions per week: not reported Total number of sessions: mean 97% of prescribed sessions were attended	**HIIT** 91.7 ± 4.2%[2] of HR_{peak} **MIET** 73.4% ± 4.2 of HR_{peak}	**HIIT** Work interval: total 15.9 ± 0.1[2] min (97%) **MIET** 50 ± 0 min (100%)	Cycling		**HIIT** not intended **MIET** not intended
Devin et al. (2018) [a] [18]	**HIIT** Sessions per week: not reported Total number of sessions: mean 99.3% ± 2.2 and 99.9% ± 0.5 of prescribed sessions were attended **MIET** Sessions per week: not reported Total number of sessions: mean 100% ±0 of prescribed sessions were attended	**HIIT** [b] *Subgroup HIITT1* 90.6 ± 3.7% [a] of HR_{peak} and *Subgroup II HIIT2* 90.7 ± 4.3% [a] of HR_{peak} **MIET** 71.4 ± 8.3%[2] of HR_{peak}	**HIIT** [b] Work interval: *Subgroup HIITT1* 99.8 ± 0.4% [a] of prescribed *Subgroup II HIIT2* 100 ± 0% [a] of prescribed **MIET** 100 ± 0.0% of prescribed	Cycling		**HIIT** not intended **MIET** not intended

Abbreviations: FITT-VP = frequency, intensity, time, type, volume, and progression; HIIT = high-intensity interval training; HR = heart rate; HR_{peak} = heart rate at peak exercise; HR_{max} = maximal heart rate; MIET = moderate-intensity exercise training; VAT = ventilatory anaerobic threshold; VO_2 = oxygen uptake; VO_{2peak} = oxygen uptake at peak exercise; WR= work rate; WR_{peak} = work rate at peak exercise.

[a]: values are presented as mean ± SD, unless stated otherwise.

[b]: the study of Devin et al. 2018 consisted of two groups receiving HIIT: the two HIIT protocols were equal for the first 4 weeks of training; thereafter, in a second cycle of 4 weeks, one group (HIIT1) continued to exercise three times per week, whereas group two (HIIT2) only trained once a week (only results of the first four weeks of training are displayed for both groups

HIIT training protocols with MIET. The two HIIT protocols were identical for the first four weeks of training. Thereafter, a subgroup (HIIT1) continued to exercise three times per week, whereas another subgroup (HIIT2) only trained once a week (Table 2). As the aim of the current review was to evaluate the effect of short-term HIIT or MIET (i.e. within the available time period for prehabilitation), results displayed here only comprise the first 4 weeks of the exercise program. After the first 4 weeks of training, VO_{2peak} in both HIIT groups increased significantly (HIIT1 VO_{2peak} +4.2 mL/kg/min (+18.1%); HIIT2 VO_{2peak} +3.3 mL/kg/min (+14.1%)), whereas no significant group level changes in VO_{2peak} were seen in the group receiving MIET (+4.7%) [18] (Figure 1, graph C). Attendance rates in both studies of Devin et al. [18, 19] were >97% for HIIT and MIET in both studies.

Clinical relevance of preoperatively increasing aerobic fitness in abdominal cancer surgery

Exercise prehabilitation in high-risk patients (those with a low preoperative aerobic fitness) aims to preoperatively increase a patient's aerobic fitness, thereby increasing adaptive capacity to cope with the surgical stress response and reducing the risks of postoperative complications, a delayed recovery, and the associated socio-economic impact [28, 45]. A higher preoperative aerobic fitness has been found to be associated with a lower incidence of postoperative complications [4, 27]. Moreover, a higher preoperative aerobic fitness might reduce the impact of postoperative complications [6, 46].This is confirmed by a randomized controlled trial investigating the effect of a 3-week community-based supervised preoperative HIIT program and resistance training on postoperative complications in high-risk patients (preoperative VO_2 at the VAT <11 mL/kg/min) undergoing colorectal surgery [47]. In this study, an increase in VO_2 at the VAT of 1.0 mL/kg/min (+10.1%) and VO_{2peak} of 1.3 mL/kg/min (+8.8%) led to a reduction in postoperative complications of ~50%. In an RCT in patients scheduled for major abdominal surgery, a similar reduction of ~50% in postoperative complications was seen after a six-week prehabilitation program including HIIT [48]. Based on the law of diminishing returns, which states that improvements will level off when fitness levels improve, patients at high risk for complications (low preoperative aerobic fitness), as defined by a VO_2 at the VAT ≤11 mL/kg/min or an oxygen uptake at peak exercise VO_{2peak} ≤18 mL/kg/min, are likely to benefit most [34]. This holds especially true when preoperative aerobic fitness can be increased above these thresholds in high-risk patients [16]. Only one study in this review specifically included high-risk patients [21] and one study [16] separately reported on high-risk patients as a subgroup. In the RCT of Dunne et al. [16], patients trained before liver resection, of which five of the nine patients (56%) who met the definition of high-risk (VO_2 at the VAT ≤11 mL/kg/min) at baseline were no longer considered to be high-risk patients after a 4-week HIIT, as their aerobic fitness improved above the risk threshold. Nevertheless, although HIIT seems to be able to increase

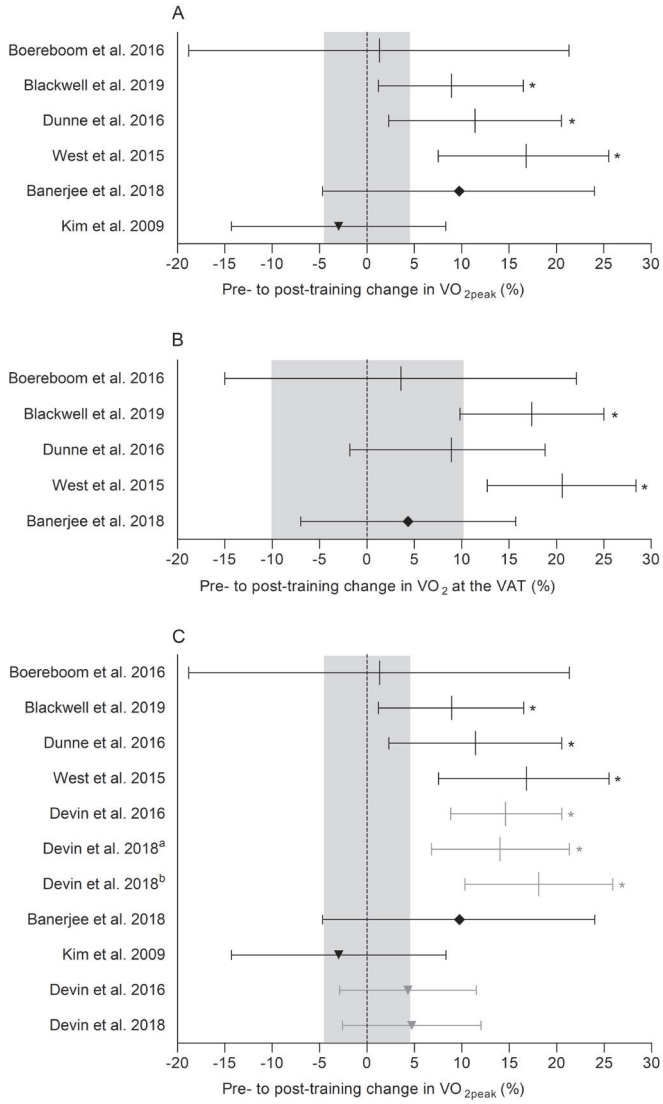

Figure 1. Relative pre- to post-training changes in VO_{2peak} (graph A) and VO_2 at the VAT (graph B) in studies evaluating short-term preoperative HIIT or MIET, as well as relative pre- to post-training changes in VO_{2peak} (graph C) in studies evaluating preoperative short-term HIIT or MIET (black bars) and in studies evaluating short-term HIIT and MIET in abdominal cancer survivors (grey bars).

Abbreviations: VAT = ventilatory anaerobic threshold; VO_2 = oxygen uptake; VO_{2peak} = oxygen uptake at peak exercise.

▌ = high-intensity interval training; ☐ = moderate- to high-intensity interval training; ☐ = moderate-intensity exercise training.

* = statistically significant ($P<0.05$).

Error bars represent the 95% confidence interval.

Grey area demarks the coefficient of variation of 4.9% for VO_{2peak} and 10.4% for VO_2 at the VAT [44].

[a, b]: Devin et al. 2018[a] and Devin et al. 2018[b] represent two subgroups within the same study that both performed HIIT, in which the two HIIT protocols were identical for the first four weeks of training: results displayed here only comprise the first 4 weeks of the exercise program.

aerobic fitness in a training episode as short as 4 weeks, longer training episodes will probably elicit greater improvements in aerobic fitness before the asymptotic response will start to level off, especially in patients with a low aerobic fitness. In patients with rectal cancer who participated in a 6-week preoperative physical exercise training after NACRT, VO_2 at the VAT and VO_{2peak} rapidly increased in the first three weeks following NACRT [21]. Despite a slightly less steep increase, aerobic fitness continued to increase between week 3 and 6 post-NACRT [21]. Although longer training episodes will lead to greater improvements, to date, optimal duration of individual preparation episodes are impossible to determine, as sufficient data is lacking. Nevertheless, future surgical planning should be a tradeoff between the medical urgency to operate and the time that is needed for optimal patient preparation in order to improve postoperative outcome.

Main limitations of the current literature and future perspectives

This comparative review aimed to evaluate current evidence concerning the effect of short-term (≤6 weeks) MIET and/or HIIT on objectively measured aerobic fitness. On a group level, short-term HIIT should probably be considered as more effective than MIET in the short preoperative period, as three out of four studies showed statistically significant improvements in VO_{2peak} after HIIT training that were >4.9%, the coefficient of variation of VO_{2peak} [44] (Figure 1 graph A). In contrast, the two studies that evaluated short-term preoperative MIET, pre-post changes in VO_{2peak} were not statistically significant and consistently smaller than the coefficient of variation (Figure 1 graph A). Although not performed in the preoperative period, the studies of Devin et al. in colorectal cancer survivors [18, 19] showed significant improvements in VO_{2peak} after short-term HITT, but not after short-term MIET (Figure 1 graph C). Improvements in VO_{2peak} of the MIET group only became significant after 8 weeks of training (data not shown) meaning it might take longer to improve aerobic fitness by means of MIET [18]. Nevertheless, the available studies mainly consisted of small (pilot) randomized controlled and/or single-arm trials. The largest study is this review included only 30 participants. As the aim of these small studies was probably more focused at feasibility than effectiveness of the physical exercise training intervention, studies seem inaccurate with regard to adequately reporting 1) all FITT-VP components of the physical exercise training prescription, 2) adherence to FITT-VP components of the physical exercise training program, and 3) objectively monitoring of individual (interim) training responses.

With regard to physical exercise training prescription (Table 2), all studies described their protocol in terms of frequency, intensity, time, and type. Except for MIET or HIIT, no variation existed with respect to type of training, as all included studies used a cycle ergometer to perform MIET and/or HIIT. Progression of training was merely reported in two studies [17, 20]. Only one study [21] used intermediate formal exercise testing

in order to objectively monitor individual training responses and adjusted the exercise prescription accordingly. Reporting of the actual performed exercise was rather incomplete as shown in Table 3. Applying training progression was only clearly reported in two studies (25%) [15, 17], and reported progression was rather generic instead of based on objectively measured individual training responses. None of the studies reported whether the exercise prescription was adjusted based on the recovery status of the patient. Overall, reporting of adherence to the exercise prescription was incomplete. As an adequate quantification of the actually performed FITT-VP is incomplete in most studies, the actual training dose, performed by the participants during the entire episode cannot be calculated. To allow for a better understanding between the performed dose of exercise and the response to exercise (e.g., improvement in aerobic fitness), as well as for an easier translation of scientific research into clinical practice, completely reporting the prescribed physical exercise training program, as well as adherence to its FITT-VP components on an individual patient's level is imperative.

Furthermore, by primarily focusing on group averages (such as, mean increase in VO_{2peak}), the variability in individual physical exercise training response is obscured. Although true non-responders to exercise do not exist [49], it is well known that there is large between-subject variation in response to physical exercise training [49, 50] and recovery [35]. Responders and non-responders among patients with colorectal cancer were briefly discussed in the study of Boereboom et al. [22]. Although 50% of the participants responded by improving their VO_{2peak}, the other half did not respond. The same trend was observed in the study of Dunne et al. [16], in which only 40% of the participants improved their VO_2 at the VAT. It was not reported whether variability in response to HIIT was affected by the performed total training volume, and therefore by the completed training dose, nor was the exercise prescription adjusted in accordance with the training response. Non-responders might actually become responsive to exercise when training volume (either training frequency, intensity, and/or time) is altered [49] or when another training type is applied [51]. To enable for timely identification of non-responders and to motivate responders, objective and frequent monitoring and quantification of training progression (titration) using performance tests is essential to be able to manipulate the components of the FITT-VP principles in such a way that it leads to an individualized effective physical exercise training program [34].

With regard to patient selection, most studies in this comparative review included relatively fit patients, and therefore estimates of effects might be attenuated. Considering the law of diminishing returns, as well as based on the a priori risk for postoperative complications, patients with a low aerobic fitness, as identified by CPET and quantified by a VO_2 at the VAT ≤11 mL/kg/min and/or VO_{2peak} ≤18 mL/kg/min, are expected to have

the greatest preoperative improvements in aerobic fitness and the greatest reduction in postoperative complication risk. Based on these criteria for determination of low aerobic fitness, only two [16, 21] out of the six included prehabilitation studies (two studies were performed in colorectal cancer survivors) included an, on the group level, high-risk patient group. In addition, self-selection bias seems an issue in prehabilitation trials, as there are indications that patients that are able and motivated to participate in exercise interventions are younger, have less comorbidities, and are more physically active (selection bias) compared to patients not willing to participate [52]. Therefore, those patients that need it most are probably the hardest to reach.

The context of all physical exercise programs included in this review was in the hospital. This inevitably excludes patients that are in greatest need for prehabilitation, as the most vulnerable patients are probably less mobile and therefore less likely to be able to attend hospital-based training sessions. Indeed, in the three studies [15-17] that reported on reasons for non-enrollment, between 26% and 73% of the participants declined participation due to travel distance to the hospital and therewith-associated costs. Evidence in sedentary middle-aged subjects suggests home-based HIIT is safe and can significantly increase aerobic fitness within 4 weeks [53]. Therefore, home- or community-based HIIT, possibly in combination with modern tele-monitoring techniques, could be a tempting alternative that might be able to ensure that patients are willing and able to participate in an efficient and effective preoperative physical exercise training program to improve their aerobic fitness, especially for high-risk patients with a low aerobic fitness.

Future development and reporting of preoperative physical exercise programs might be improved by using the i-CONTENT tool [31], by focusing on patients with a low aerobic fitness, by using individualized exercise prescriptions based on formal baseline assessments (i.e. CPET), by monitoring adherence to all FITT-VP principles, and by formally measuring training progression and recovery. The steps that can be taken to come to such an individualized approach are depicted in Figure 2. Substantial new data concerning preoperative optimization of aerobic fitness is expected in the near future. Within the domain of colorectal cancer alone, at least three prehabilitation trials are currently ongoing or have just finished [54-56]. Nevertheless, as randomized controlled trials in general have an excellent internal validity, their external validity or generalizability is often limited. Therefore, there is an urgent need for studies using real-life data to evaluate the effectiveness of different preoperative exercise training programs. In addition, studies investigating the feasibility and effectiveness of home-based HIIT with or without tele-monitoring for prehabilitation are needed.

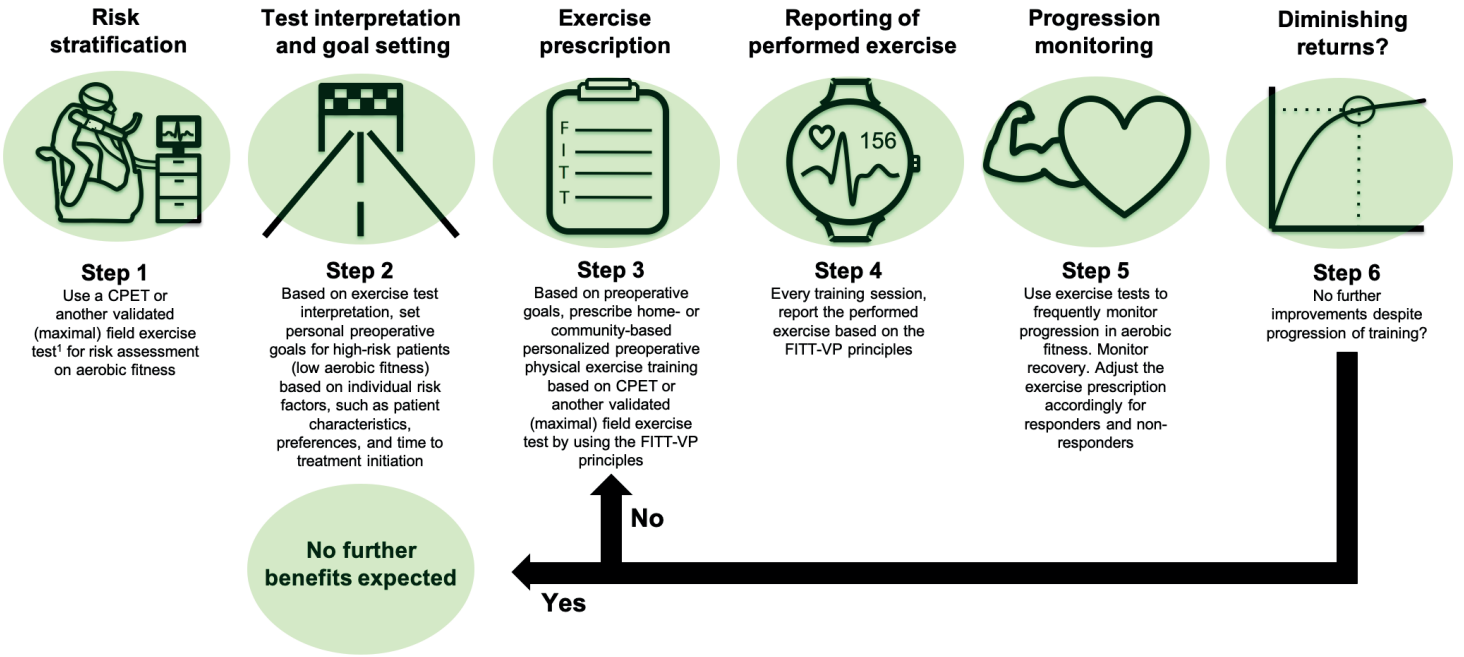

Figure 2. Proposed steps for the development and execution of a preoperative physical exercise training program to increase aerobic fitness.
Abbreviations: CPET = cardiopulmonary exercise test; FITT-VP = frequency, intensity, time, type, volume and progression of physical exercise training program.
[1] Such as: steep ramp test or incremental shuttle walk test.

CONCLUSION

Despite limited evidence in the preoperative period, HIIT seems to be a powerful stimulus to increase aerobic fitness at the group level within the often limited 4- to 6-week preoperative time window prior to abdominal cancer surgery. No evidence was found that short-term MIET alone could effectively improve aerobic fitness within this short time period. Nevertheless, one size does not fit all, and there is large heterogeneity in the response to physical exercise training. Therefore, adequate patient selection, personalized physical exercise training prescription using the FITT-VP principles, full reporting of physical exercise training adherence, and formal monitoring of training progression and recovery is needed to ensure for a personalized and effective short-term physical exercise training program embedded within a multimodal prehabilitation program.

REFERENCES

1. Older, P.O. and D.Z.H. Levett, *Cardiopulmonary Exercise Testing and Surgery.* Ann Am Thorac Soc, 2017. **14**(Supplement_1): p. S74-S83.
2. Moran, J., et al., *Role of cardiopulmonary exercise testing as a risk-assessment method in patients undergoing intra-abdominal surgery: a systematic review.* Br J Anaesth, 2016. **116**(2): p. 177-91.
3. West, M.A., et al., *Validation of preoperative cardiopulmonary exercise testing-derived variables to predict in-hospital morbidity after major colorectal surgery.* Br J Surg, 2016. **103**(6): p. 744-752.
4. West, M.A., et al., *Cardiopulmonary exercise variables are associated with postoperative morbidity after major colonic surgery: a prospective blinded observational study.* Br J Anaesth, 2014. **112**(4): p. 665-71.
5. Silver, J.K. and J. Baima, *Cancer prehabilitation: an opportunity to decrease treatment-related morbidity, increase cancer treatment options, and improve physical and psychological health outcomes.* Am J Phys Med Rehabil, 2013. **92**(8): p. 715-27.
6. Thomas, G., et al., *Prehabilitation before major intra-abdominal cancer surgery: A systematic review of randomised controlled trials.* Eur J Anaesthesiol, 2019. **36**(12): p. 933-945.
7. Scheede-Bergdahl, C., E.M. Minnella, and F. Carli, *Multi-modal prehabilitation: addressing the why, when, what, how, who and where next?* Anaesthesia, 2019. **74 Suppl 1**: p. 20-26.
8. Bartoszko, J., et al., *Association of preoperative anaemia with cardiopulmonary exercise capacity and postoperative outcomes in noncardiac surgery: a substudy of the Measurement of Exercise Tolerance before Surgery (METS) Study.* Br J Anaesth, 2019. **123**(2): p. 161-169.
9. Hijazi, Y., U. Gondal, and O. Aziz, *A systematic review of prehabilitation programs in abdominal cancer surgery.* Int J Surg, 2017. **39**: p. 156-162.
10. *Format transmural care pathway colorectal cancer*. 2017 01-17-2020]; 5:[Available from: https://shop.iknl.nl/shop/zorgpad-colorectaalcarcinoom/110209.
11. *National Cancer Waiting Times Monitoring Dataset Guidance version 10.0*. 09-01-2020].
12. Weston, M., et al., *High-intensity interval training (HIT) for effective and time-efficient pre-surgical exercise interventions.* Perioper Med (Lond), 2016. **5**: p. 2.
13. American College of Sports, M.
14. MacInnis, M.J. and M.J. Gibala, *Physiological adaptations to interval training and the role of exercise intensity.* J Physiol, 2017. **595**(9): p. 2915-2930.
15. Banerjee, S., et al., *Vigorous intensity aerobic interval exercise in bladder cancer patients prior to radical cystectomy: a feasibility randomised controlled trial.* Support Care Cancer, 2018. **26**(5): p. 1515-1523.
16. Dunne, D.F., et al., *Randomized clinical trial of prehabilitation before planned liver resection.* Br J Surg, 2016. **103**(5): p. 504-12.
17. Blackwell, J.E.M., et al., *High-intensity interval training produces a significant improvement in fitness in less than 31 days before surgery for urological cancer: a randomised control trial.* Prostate Cancer Prostatic Dis, 2020.
18. Devin, J.L., et al., *Cardiorespiratory Fitness and Body Composition Responses to Different Intensities and Frequencies of Exercise Training in Colorectal Cancer Survivors.* Clin Colorectal Cancer, 2018. **17**(2): p. e269-e279.
19. Devin, J.L., et al., *The influence of high-intensity compared with moderate-intensity exercise training on cardiorespiratory fitness and body composition in colorectal cancer survivors: a randomised controlled trial.* J Cancer Surviv, 2016. **10**(3): p. 467-79.

20. Kim, D.J., et al., *Responsive measures to prehabilitation in patients undergoing bowel resection surgery.* Tohoku J Exp Med, 2009. **217**(2): p. 109-15.
21. West, M.A., et al., *Effect of prehabilitation on objectively measured physical fitness after neoadjuvant treatment in preoperative rectal cancer patients: a blinded interventional pilot study.* Br J Anaesth, 2015. **114**(2): p. 244-51.
22. Boereboom, C.L., et al., *Short-term pre-operative high-intensity interval training does not improve fitness of colorectal cancer patients.* Scand J Med Sci Sports, 2019. **29**(9): p. 1383-1391.
23. Shephard, R.J., et al., *The maximum oxygen intake. An international reference standard of cardiorespiratory fitness.* Bull World Health Organ, 1968. **38**(5): p. 757-64.
24. Poole, D.C., D.P. Wilkerson, and A.M. Jones, *Validity of criteria for establishing maximal O2 uptake during ramp exercise tests.* Eur J Appl Physiol, 2008. **102**(4): p. 403-10.
25. Day, J.R., et al., *The maximally attainable VO2 during exercise in humans: the peak vs. maximum issue.* J Appl Physiol (1985), 2003. **95**(5): p. 1901-7.
26. Otto, J.M., D.Z.H. Levett, and M.P.W. Grocott, *Cardiopulmonary Exercise Testing for Preoperative Evaluation: What Does the Future Hold?* Current Anesthesiology Reports, 2020. **10**(1): p. 1-11.
27. West, M.A., et al., *Cardiopulmonary exercise testing for the prediction of morbidity risk after rectal cancer surgery.* Br J Surg, 2014. **101**(9): p. 1166-72.
28. Bongers, B.C., C.H.C. Dejong, and M. den Dulk, *Enhanced recovery after surgery programmes in older patients undergoing hepatopancreatobiliary surgery: what benefits might prehabilitation have?* Eur J Surg Oncol, 2020.
29. *ACSM's Resource Manual for Guidelines for Exercise Testing and Prescription*, in *ACSM's Resource Manual for Guidelines for Exercise Testing and Prescription*, D.P. Swain, Editor. 2014, Wolters Kluwer / Lippincott Williams and Wilkins. p. 468-479.
30. Hoogeboom, T.J., et al., *Therapeutic validity and effectiveness of preoperative exercise on functional recovery after joint replacement: a systematic review and meta-analysis.* PLoS One, 2012. **7**(5): p. e38031.
31. Hoogeboom, T.J., et al., *i-CONTENT tool for assessing therapeutic quality of exercise programs employed in randomised clinical trials.* Br J Sports Med, 2020.
32. Wolpern, A.E., et al., *Is a threshold-based model a superior method to the relative percent concept for establishing individual exercise intensity? a randomized controlled trial.* BMC Sports Sci Med Rehabil, 2015. **7**: p. 16.
33. Glasziou, P., L. Irwig, and D. Mant, *Monitoring in chronic disease: a rational approach.* BMJ, 2005. **330**(7492): p. 644-648.
34. Bongers, B.C., J.M. Klaase, and N.L.U. van Meeteren, *Prehabilitation vs Postoperative Rehabilitation for Frail Patients.* JAMA Surg, 2020.
35. Hayes, S.C., et al., *The Exercise and Sports Science Australia position statement: Exercise medicine in cancer management.* J Sci Med Sport, 2019. **22**(11): p. 1175-1199.
36. Laurent, C.M., et al., *A practical approach to monitoring recovery: development of a perceived recovery status scale.* J Strength Cond Res, 2011. **25**(3): p. 620-8.
37. McLean, B.D., et al., *Neuromuscular, endocrine, and perceptual fatigue responses during different length between-match microcycles in professional rugby league players.* Int J Sports Physiol Perform, 2010. **5**(3): p. 367-83.
38. Weston, K.S., U. Wisloff, and J.S. Coombes, *High-intensity interval training in patients with lifestyle-induced cardiometabolic disease: a systematic review and meta-analysis.* Br J Sports Med, 2014. **48**(16): p. 1227-34.

39. Milanovic, Z., G. Sporis, and M. Weston, *Effectiveness of High-Intensity Interval Training (HIT) and Continuous Endurance Training for VO2max Improvements: A Systematic Review and Meta-Analysis of Controlled Trials.* Sports Med, 2015. **45**(10): p. 1469-81.
40. Mugele, H., et al., *High-intensity interval training in the therapy and aftercare of cancer patients: a systematic review with meta-analysis.* J Cancer Surviv, 2019. **13**(2): p. 205-223.
41. Minnella, E.M., et al., *Effect of two different pre-operative exercise training regimens before colorectal surgery on functional capacity: A randomised controlled trial.* Eur J Anaesthesiol, 2020.
42. Woodfield, J.C., J.C. Baldi, and K. Clifford, *What is the minimal dose of HIIT required to achieve pre-operative benefit.* Scand J Med Sci Sports, 2019. **29**(11): p. 1841.
43. Boereboom, C.L., et al., *A 31-day time to surgery compliant exercise training programme improves aerobic health in the elderly.* Tech Coloproctol, 2016. **20**(6): p. 375-382.
44. Decato, T.W., et al., *Repeatability and Meaningful Change of CPET Parameters in Healthy Subjects.* Med Sci Sports Exerc, 2018. **50**(3): p. 589-595.
45. Barberan-Garcia, A., et al., *Post-discharge impact and cost-consequence analysis of prehabilitation in high-risk patients undergoing major abdominal surgery: secondary results from a randomised controlled trial.* Br J Anaesth, 2019. **123**(4): p. 450-456.
46. Van Beijsterveld, C.A., et al., *The association between preoperative physical functioning and short-term postoperative outcomes: a cohort study of patients undergoing elective hepatic resection.* HPB (Oxford), 2019. **21**(10): p. 1362-1370.
47. Berkel, A.E., et al., *Effects of community-based exercise prehabilitation for patients scheduled for colorectal surgery with high risk for postoperative complications: results of a randomized clinical trial,.* Annals of Surgery, 2020: p. Accepted for publication.
48. Barberan-Garcia, A., et al., *Personalised Prehabilitation in High-risk Patients Undergoing Elective Major Abdominal Surgery: A Randomized Blinded Controlled Trial.* Ann Surg, 2018. **267**(1): p. 50-56.
49. Montero, D. and C. Lundby, *Refuting the myth of non-response to exercise training: 'non-responders' do respond to higher dose of training.* J Physiol, 2017. **595**(11): p. 3377-3387.
50. Pickering, C. and J. Kiely, *Do Non-Responders to Exercise Exist-and If So, What Should We Do About Them?* Sports Med, 2019. **49**(1): p. 1-7.
51. Marsh, C.E., et al., *Fitness and strength responses to distinct exercise modes in twins: Studies of Twin Responses to Understand Exercise as a THerapy (STRUETH) study.* J Physiol, 2020.
52. de Souto Barreto, P., A.M. Ferrandez, and B. Saliba-Serre, *Are Older Adults Who Volunteer to Participate in an Exercise Study Fitter and Healthier than Non-Volunteers? The participation bias of the study population.* J Phys Act Health, 2012.
53. Blackwell, J., et al., *The efficacy of unsupervised home-based exercise regimens in comparison to supervised laboratory-based exercise training upon cardio-respiratory health facets.* Physiol Rep, 2017. **5**(17).
54. Woodfield, J., et al., *Protocol, and practical challenges, for a randomised controlled trial comparing the impact of high intensity interval training against standard care before major abdominal surgery: study protocol for a randomised controlled trial.* Trials, 2018. **19**(1): p. 331.
55. Berkel, A.E.M., et al., *The effects of prehabilitation versus usual care to reduce postoperative complications in high-risk patients with colorectal cancer or dysplasia scheduled for elective colorectal resection: study protocol of a randomized controlled trial.* BMC Gastroenterol, 2018. **18**(1): p. 29.
56. van Rooijen, S., et al., *Multimodal prehabilitation in colorectal cancer patients to improve functional capacity and reduce postoperative complications: the first international randomized controlled trial for multimodal prehabilitation.* BMC Cancer, 2019. **19**(1): p. 98.

SUPPLEMENTAL FILE 1. PUBMED SEARCH STRATEGY.

Population
("Neoplasms" [MeSH] OR neoplas*[tiab] OR cancer*[tiab]) AND ("Abdomen"[MeSH] OR abdom*[tiab] OR "Biliary Tract Neoplasms"[Mesh] OR biliary[tiab] OR bile-duct[tiab] OR "Intestinal Neoplasms"[Mesh] OR "Colorectal Neoplasms"[Mesh] OR intestin*[tiab] OR colon*[tiab] OR rect*[tiab] OR duoden*[tiab] OR ileum[tiab] OR ilea*[tiab] OR jejun*[tiab] OR "Stomach Neoplasms"[Mesh] OR stomach[tiab] OR gastric[tiab] OR "Liver Neoplasms"[Mesh] OR liver[tiab] OR hepat*[tiab] OR "Pancreatic Neoplasms"[Mesh] OR pancrea*[tiab] OR "Ovarian Neoplasms"[Mesh] OR ovar*[tiab] OR "Adrenal Gland Neoplasms"[Mesh] OR adren*[tiab] OR "Splenic Neoplasms"[Mesh] OR splen*[tiab] OR "Urologic Neoplasms"[Mesh] OR bladder[tiab] OR kidney[tiab] OR nephr*[tiab] OR nefr*[tiab] OR renal[tiab] OR urethr*[tiab] OR urolog*[tiab] OR urinary-tract[tiab] OR colorectal[tiab])
Intervention
("High-intensity Interval Training"[MeSH] OR high-intensity-interval[tiab] OR interval-training[tiab] OR interval-exercise[tiab] OR high-intensity-intermittent[tiab] OR HIIT[tiab] OR HIIE[tiab] OR sprint-interval-training*[tiab] OR prehabilitation[tiab] OR prehabilitative[tiab] OR pre-conditioning[tiab] OR preconditioning[tiab] OR "endurance training"[MeSH] OR endurance-training*[tiab] OR rehabilitation[tiab] OR "physical endurance"[MeSH] OR physical-endurance[tiab] OR MICT[tiab] OR MIE[tiab] OR moderate-intensity-exercise[tiab] OR exercise-training[tiab] OR physical-training[tiab] OR exercise-intervention*[tiab] OR exercise-program*[tiab])
Outcome
("physical endurance"[MeSH] or physical-endurance[tiab] OR aerobic-capacity[tiab] OR VO2peak[tiab] OR VO2-peak[tiab] OR Functional-capacity[tiab] OR anaerobic-threshold[tiab] OR ventilatory-anaerobic-threshold[tiab] OR VO2max[tiab] OR VO2-max[tiab] OR fitness[tiab] OR VO2[tiab] OR oxygen-uptake[tiab] OR aerobic-fitness[tiab] OR AT[tiab] OR VAT[tiab] OR VT1[tiab] OR cardiorespiratory-reserve[tiab] OR physical-capacity[tiab] OR cardiorespiratory-fitness[tiab])

SUPPLEMENTAL FILE 2.

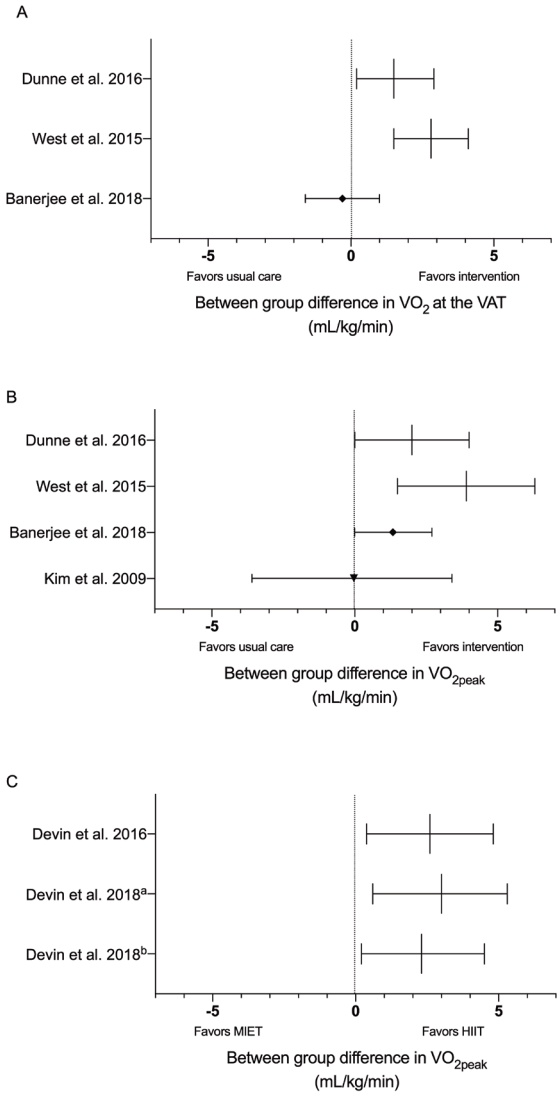

Figure 1. Between-group differences in oxygen uptake (VO_2) at the ventilatory anaerobic threshold (VAT) and peak exercise (VO_{2peak}) for the intervention group versus the usual care group (A and B), and VO_{2peaak} for HIIT versus MIET (C).
Abbreviations: HIIT = high-intensity interval training; MIET = moderate-intensity exercise training; VAT ventilatory anaerobic threshold; VO_2 = oxygen uptake; VO_{2peak} = oxygen uptake at peak exercise.
| = high-intensity interval training; ☐ = moderate- to high-intensity interval training; ☐ = moderate-intensity exercise training.
Errors bars represent the 95% confidence interval.
* = statistically significant (P<0.05).
Devin et al. 2018[a] and Devin et al. 2018[b] represent two subgroups within the same study that both performed HIIT. The two HIIT protocols were identical for the first four weeks of training. Results displayed here only comprise the first 4 weeks of the exercise program.

CHAPTER 8

Feasibility of a tele-prehabilitation program in high-risk patients with colon or rectal cancer undergoing elective surgery: a feasibility study

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ABSTRACT

Background

Prehabilitation appears to be an effective strategy to reduce postoperative complications and enhance recovery after colorectal surgery. Although many patients prefer (unsupervised) home-based prehabilitation, adherence can be problematic. Combining home- based prehabilitation with tele-monitoring might demonstrate a higher adherence than unsupervised prehabilitation; however, evidence on its feasibility and effectiveness in patients with colorectal cancer scheduled for elective surgery who are at high risk for postoperative complications is lacking. The aim of this study was to assess the feasibility of a bimodal tele-prehabilitation program in patients with colorectal cancer at high risk for postoperative complications.

Methods

High-risk patients (oxygen uptake at the ventilatory anaerobic threshold ≤11 mL/kg/min or oxygen uptake at peak exercise ≤18 mL/kg/min) with colorectal cancer were included in a home-based bimodal tele-prehabilitation program. The program consisted of a personalized tele-monitored moderate to high-intensity interval training intervention and nutritional counselling. Feasibility was measured by participation rate, dropout rate, adherence to the physical exercise training session's frequency, intensity, and time, and retention rate. Patient appreciation was measured by a patient appreciation questionnaire. Changes in preoperative physical fitness as secondary outcomes were quantified by time to exhaustion on a constant work rate (cycle) test, number of repetitions on the 30-second chair-stand test, and walking speed on the 4-meter gait speed test.

Results

The participation rate was 81%, there were no adverse events, and all participants managed to complete the tele-prehabilitation program (retention rate of 100%). Adherence with regard to the exercise program's frequency, intensity, and time was respectively 91%, 84%, and 100%. All participants appreciated the tele-prehabilitation program. Time to exhaustion on the constant work rate test improved (not statistically significant) from a pre-prehabilitation median score of 317 seconds to a post-prehabilitation median score of 412 seconds (p=0.24). Median number of repetitions on the 30-second chair-stand test improved from 12 to 16 (p=0.01).

Conclusions

Tele-prehabilitation seems feasible in high-risk patients with colorectal cancer, but efforts should be made to further improve adherence to physical exercise training intensity. More research is needed to establish the (cost-)effectiveness of tele-prehabilitation

regarding preoperative improvements in preoperative aerobic fitness and postoperative reduction of complications.

Trial registration: ISRCTN, ISRCTN64482109. Registered 09 November 2021 - Retrospectively registered, http://www.isrctn.com/ ISRCTN64482109

BACKGROUND

There is a growing amount of evidence showing that prehabilitation can effectively improve preoperative aerobic fitness and reduce the incidence of postoperative complications in patients who are referred for abdominal surgery [1] and surgery for colorectal cancer [2, 3] when aiming at patients at high risk for complications. Patients at high risk for postoperative complications after abdominal surgery often have a low aerobic fitness, are physically vulnerable, suffer from multimorbidity, are of older age [4], and depend on others for transport [5]. Therefore, for high-risk patients, participation in center-based prehabilitation is often difficult [6]. Among perceived barriers that hinder patients from participating in prehabilitation are the many hospital appointments [7, 8], finding time [2, 9], distance from the prehabilitation facility [10], and transportation issues [2, 9, 11].

Evidence from interviews among patients who underwent major abdominal surgery for cancer demonstrated that many patients prefer home-based prehabilitation [9, 12]. A home-based approach offers safety for patients who experience nausea, diarrhea, or physiological issues [12], provides flexibility towards medical/personal commitments [13], resolves transportation issues [13], and enhances social support [13]. In addition, home-based prehabilitation enables patients to combine prehabilitation with practical tasks and social activities of everyday life that are perceived as meaningful in the often short and stressful period between cancer diagnosis and treatment [12]. Considering the abovementioned needs and preferences of high-risk patients, a home-based approach might be desirable.

A disadvantage of (unsupervised) home-based prehabilitation as opposed to supervised hospital-based prehabilitation is that adherence can be problematic without supervision [14]. A systematic review reported mean adherence rates of >95% in studies evaluating hospital-based (supervised) prehabilitation opposed to only about 70% in studies evaluating (unsupervised) home-based prehabilitation [6]. As the preoperative period is often short and time-constrained (2-6 weeks), high-intensity physical exercise training with high exercise training adherence is of major importance for prehabilitation to be effective [15]. To improve adherence, prehabilitation should not only be personalized to a patient's aerobic fitness, everyday activities and preferences, but should also involve some degree of support and pressure to be motivational [8].

By using technologies like tele-monitoring (e.g., tele-prehabilitation,) the benefits of home-based and supervised prehabilitation might be combined. This way, adherence can be measured objectively and accurately, and patients can be coached, motivated,

and encouraged via tele-monitoring while performing their home-based individualized training sessions at a time and place of their preference. Evidence in patients with musculoskeletal conditions suggests that, compared to classic unsupervised home-based programs, tele-monitoring can improve adherence [16]. To date, a few studies have investigated feasibility of home-based tele-prehabilitation programs prior to colorectal cancer surgery [13, 17], and concluded that tele-prehabilitation was feasible, appreciated by patients and has the potential to improve physical fitness. However, these studies [13, 17] failed to report full feasibility as adherence to the physical exercise training's frequency, intensity, and time was lacking. Moreover, none of these studies [13, 17] specifically included patients at high risk for postoperative complications determined by preoperative cardiopulmonary exercise testing (CPET).

The aim of this pilot study was to investigate whether a home-based and tele-monitored prehabilitation program (tele-prehabilitation) is feasible in high-risk patients scheduled for colorectal cancer surgery. Secondary aims were to evaluate patient experiences and changes in preoperative aerobic fitness before and after the tele-prehabilitation program.

METHODS

Study design

The current pragmatic one-arm pilot feasibility study was carried out at VieCuri Medical Center, a large teaching hospital in Venlo, the Netherlands. The study was approved by the Medical Ethics Review Committee – Zuyderland/Zuyd (Heerlen, the Netherlands) under reference number METCZ20190150. Initially, the trial started in February 2020; however, due to restrictions caused by the worldwide COVID-19 pandemic, inclusion could only start in July 2020 and ended in September 2021. Reporting was done in accordance with the CONSORT statement extension to randomized pilot and feasibility trials [18].

Participants

A consecutive sample of potentially high-risk patients was recruited at the moment of suspected colorectal cancer by endoscopy. A few days after the endoscopy, patients were contacted by telephone to check for potential eligibility and willingness to participate. Patients were potentially eligible when they were ≥18 years of age, were able to operate a mobile phone, and had a score ≤7 metabolic equivalents of task (METs) on the veterans-specific activity questionnaire (VSAQ). These eligibility criteria were used as a pre-screening. Final eligibility was determined after CPET and final diagnosis, which was defined as an oxygen uptake (VO_2) at the ventilatory anaerobic threshold (VAT) ≤11 mL/kg/min or a valid VO_2 at peak exercise (VO_{2peak}) ≤18 mL/kg/min during CPET in com-

bination with confirmed diagnosis of colon or rectal cancer (stage I, II, or III) requiring elective resection with or without neoadjuvant treatment.

Intervention and assessments

A multimodal tele-prehabilitation program was embedded within the existing colorectal cancer pathway of VieCuri Medical Center. Therefore, no additional hospital visits were required for study purposes. Pre-prehabilitation measurements (T_0) were planned on the day of the appointment with the surgeon, approximately 2-5 days after final inclusion. In patients receiving neoadjuvant treatment, pre-prehabilitation measurements were performed concurrent with the first appointment with the surgeon after completing neoadjuvant treatment (approximately 4 weeks before surgery). Pre-prehabilitation (T_0) assessments consisted of evaluating aerobic fitness by time to exhaustion on a continuous work rate test at 80% of the peak work rate achieved during CPET. Additionally, lower limb muscle power and endurance was assessed by the number of repetitions on the 30-second chair-stand test and gait speed was measured using the 4-meter gait speed test. Post-prehabilitation (T_1), reassessment of the continuous work rate test, 30-second chair-stand test and the 4-meter gait speed test took place one or two days prior to surgery. In addition, participants filled out a patient appreciation questionnaire, based on the questionnaire of Dronkers et al. [19], and the systems usability questionnaire [20] after the post-prehabilitation assessment.

The tele-prehabilitation program consisted of a tele-monitored physical exercise training module and a nutritional support module. Encouraging smoking-cessation was part of usual care and was therefore not included explicitly in the tele-prehabilitation program.

Physical exercise training

The tele-monitored physical exercise training module was delivered by using *the mobile phone application of HC@Home (version* HC1.12a, *HC@Home B.V., Zwolle, the Netherlands) on a dedicated mobile phone (delivered to the patients for the duration of the tele-prehabilitation program) to which a heart rate monitor (Polar OH1, Polar Electro Inc., Kempele Finland) was connected. Personalized training zones were set based on the heart rate at the VAT and the respiratory compensation point as determined by CPET. Ideally, training sessions took place every other day and consisted of 30 minutes of aerobic moderate- to high- intensity interval training by a patient's preferred activity (i.e., walking, cycling, stair climbing, sit-to-stand exercises, push-ups, steps). Intervals consisted of 3 minutes of low-intensity exercise at a heart rate below the heart rate at the VAT and/or a 6-20 Borg rating of perceived exertion (RPE) score ≤11, interspersed by 3 minutes of high-intensity exercise at a heart rate just below the heart rate at the respiratory compensation point (approximately 70-85% of*

the heart rate at VO_{2peak}) or a Borg RPE score of 14-16. In-between training days, patients were advised to retain relative rest but still comply with the Dutch physical activity guidelines (e.g., >30 minutes of moderate-intensity physical activity). The abovementioned training protocol was used as a blueprint, which means that training frequency, intensity, time, type, volume, and progression were personalized according to CPET results (e.g., using shorter intervals in patients with a pulmonary exercise limitation), training heart rate, training Borg RPE score, recovery after training, and participant experiences and preferences. After the first face-to-face physical exercise training at home, which was supervised by a physical therapist specialized in physical exercise training in clinical populations, participants continued the home-based physical exercise training sessions independently. Involvement of a family member or (informal) caregiver during exercising was encouraged to promote motivation. The first face-to-face session was used to validate training zones and familiarize participants with the exercises and equipment. Performed training session's frequency, intensity, and time were automatically uploaded to an online platform, at which they could be reviewed by the physical therapist. A weekly phone call took place to monitor training progression and adjust the physical exercise program accordingly.

Nutritional counseling

Participants were screened for malnutrition using the patient-generated subjective global assessment short form (PG-SGA-SF) in combination with a comprehensive nutritional screening by a registered dietician. Preoperative nutritional counseling consisted of optimization of basic nutritional needs, as well as ensuring the recommended intake of protein, defined as 1.2-2.0 g/kg body mass [21]. After an initial intake assessment, follow-up counseling was provided by a weekly phone call between the dietician and the participants in order to monitor nutritional and protein intake, as well as to compare nutritional and protein intake against calculated needs. In addition, body mass was assessed based on self-report and participants were motivated to comply with the dietary advice.

Outcomes

The primary outcome of the study was feasibility as determined by 1) study participation rate combined with reasons for non-willingness or inability to participate, 2) the number and severity of adverse events related to the physical exercise training program, 3) adherence to the physical exercise training program, 4) study dropout rate and reasons for dropouts, and 5) retention rate. Secondary outcomes were 1) participant experiences as measured by the patient appreciation questionnaire, 2) user friendliness of the mobile phone application that was used for tele-prehabilitation assessed using the systems usability questionnaire [20], and 3) changes in physical fitness during the tele-prehabilitation program.

Statistical analyses

Statistical analyses were performed using IBM SPSS Statistics version 26.0 (IBM, Chicago, IL, USA). Participation rates were reported descriptively as numbers and percentages of the potentially eligible patients that were willing to participate in the current study. Dropout rates and adverse events were reported as numbers and as a proportion of participants enrolled in the study. Retention rate was expressed as a percentage and defined as the proportion of enrolled participants that completed the program. Adherence to the physical exercise training program with regard to training frequency, training intensity, and training time was determined as follows. For training frequency, observed training frequency was divided by the prescribed frequency and expressed as a percentage. Regarding training intensity, an exercise training session were designated as performed at an adequate intensity when, based on heart rate, at least 3 of the 5 prescribed high-intensity exercise bouts complied with the prescribed intensity, or when the training session intensity reported on the Borg RPE score was equal or higher than prescribed. The number of attended sessions in which the prescribed intensity was accomplished (based on either heart rate or Borg RPE score) was divided by the total number of attended sessions and presented as a percentage. For **training** time, the observed duration of the sessions was divided by the prescribed duration of the sessions and presented as a percentage. Adherence was deemed adequate if ≥80% as assessed individually for training frequency, training intensity, and training time. Participant appreciation of the tele-prehabilitation program, as scored by the patient appreciation questionnaire, and user friendliness of the mobile phone application of HC@Home, as scored by the systems usability questionnaire, were reported descriptively. A systems usability questionnaire score ≥73 was considered as good, and a score of ≥85 as excellent user-friendliness [22]. Continuous data representing changes in aerobic fitness during the tele-prehabilitation program were presented as median and interquartile range (IQR). Pre-post analysis was performed using the non-parametric Wilcoxon signed-rank test. A p-value <0.05 was considered statistically significant.

RESULTS

A total of 36 patients were contacted to check for eligibility and willingness to participate. The participation rate was 81%. Eventually, a total of 11 patients were eligible and were enrolled in the tele-prehabilitation program. Reasons for non-willingness or inability to participate and reasons for exclusion are depicted in Figure 1. Baseline characteristics of the included participants are listed in Table 1. There were no adverse events or dropouts as a result of the tele-prehabilitation program. One participant failed to perform the post-prehabilitation assessment and one patient was unable to perform adequately on the constant work rate test, both due to a feeling of general discomfort and nausea on the day of assessment.

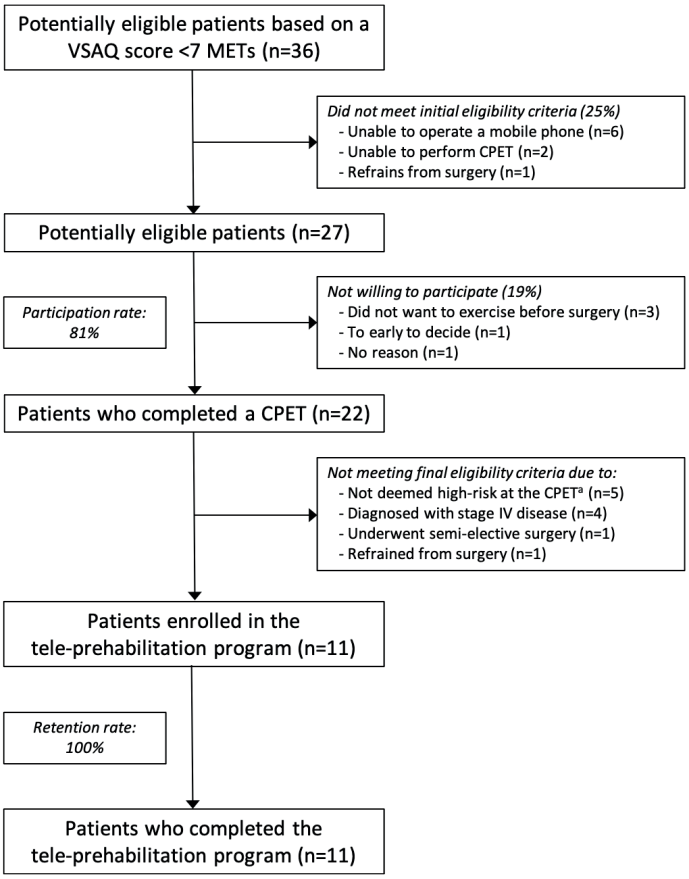


Figure 1. Flowchart of inclusion and participation

[a] High-risk is defined as an oxygen uptake (VO_2) at the ventilatory anaerobic threshold (VAT) ≤11 mL/kg/min or at peak exercise (VO_{2peak}) ≤18 mL/kg/min at the preoperative CPET.

Abbreviations: CPET = cardiopulmonary exercise test; METs = metabolic equivalent of task; VSAQ = veterans-specific activity questionnaire

Tele-prehabilitation program

The median time that elapsed between diagnosis (date of endoscopy) and surgery was 34 days (range 20-51) for participants with surgery as their first treatment (n=10; 91%). Median time between start of the physical exercise training program and surgery was 23 days (range 6-30) (Table 2). Adherence with regard to the tele-prehabilitation program's training frequency, intensity, and time (FIT) is depicted in Table 2. Combined, the participants performed a total of 109 out of 120 prescribed training sessions (91%). In addition, 9 out of 11 participants (81%) managed to adhere to ≥80% of the prescribed sessions. Mean ± SD training intensity reached throughout each entire training session was 78 ± 9% of the maximal heart rate during CPET and a score of 14 ± 1 on the 6-20 Borg RPE scale. Although participants were able to adhere to the prescribed exercise intensity

Table 1. Participant characteristics (n=11)

Characteristics	Included n=11
Age (years)	74 [68-78]
Sex ratio (male; female)	6;5
Living status	
Living alone	n=5 (45%)
Living with partner	n=6 (55%)
Body mass index (kg/m^2)	29.1 [24.6-33.1]
Smoking status	
Never	1 (9%)
Former	9 (82%)
Current	1 (9%)
Age-adjusted comorbidity index	
2-3	1 (9%)
4-5	3 (27%)
6+	7 (64%)
ASA-classification	
I	1 (9%)
II	3 (27%)
III	6 (55%)
IV	1 (9%)
VSAQ (METs)	4 [3-5]
VO_2 at the VAT (mL/kg/min)	9.3 [7.5-10.0]
VO_{2peak} (mL/kg/min)[a]	14.8 [12.7-15.6]
Hemoglobin level (mmol/L)	7.1 [6.7-8.7]
Albumin levels (g/L)	37 [35-40]
PG-SGA-SF score	
0	5 (45%)
2	2 (18%)
5+	4 (36%)
Tumor location	
Colon	8(73%)
Rectum	3(27%)
Tumor stage	
I	5 (46%)
II	3 (27%)
III	3 (27%)
Type of surgery	
Hemicolectomy	8 (73%)
Other	3 (27%)
Surgical approach	
Open	1 (9%)
Laparoscopic	8 (73%)
Endoscopic	1 (9%)
Conversion to open	1 (9%)
Received neoadjuvant treatment	1 (9%)

Data are presented as: number of patients (%) or median [IQR], unless stated otherwise.

[a] n=9, as a maximal effort was required based on a respiratory exchange ratio at peak exercise ≥1.10 and/or a heart rate at peak exercise >85% of predicted.

Abbreviations: ASA = American Society of Anesthesiologists; MET = metabolic equivalent of task; PG-SGA-SF = patient-generated subjective global assessment short form; VAT = ventilatory anaerobic threshold; VO_2 = oxygen uptake; VO_{2peak} = oxygen uptake at peak exercise; VSAQ = veterans-specific activity questionnaire.

Table 2. Performed training session frequency, intensity, and time, adherence, and changes in physical fitness of the physical exercise training module of the tele-prehabilitation program

Participant ID	**Frequency**	**Intensity**	**Time**	**Treatment initiation intervals**		**Change in physical fitness between pre- (T_0) and post-prehabilitation (T_1) assessment**								
	Number of sessions (% of prescribed)	Number of sessions with adequate intensity, Number (%)	Combined exercise duration of all sessions, minutes (% of prescribed)	Time from endoscopy to start prehabilitation (days)	Time from start prehabilitation to surgery (days)	Time to exhaustion on the constant work rate test (s)			Repetitions on the 30-second chair-stand test (number)			4-meter gait speed test (m/s)		
						T_0	T_1	Change (%)	T_0	T_1	Change (%)	T_0	T_1	Change (%)
1	19 (68%)	19 (100%)	640 (85%)	110[a]	58[a]	180	316	+136 (+76%)	10	14	+4 (+40%)	0.7	0.9	+0.2 (+29%)
2	5 (83%)	5 (100%)	159 (88%)	14	12	306	316	+10 (+3%)	14	18	+4 (+29%)	1.1	1.3	+0.2 (+18%)
3	13 (108%)	9 (69%)	254 (115%)	16	26	303	481	+178 (+59%)	8	10	+2 (+25%)	1.0	0.9	-+0.1 (-10%)
4	10 (91%)	9 (90%)	349 (95%)	12	25	581	773	+192 (+33%)	13	18	+5 (+38%)	1.3	1.1	-0.2 (-15%)
5	13 (100%)	11 (85%)	449 (112%)	21	30	606[b]	304[b]	-302 (-50%)[b]	10[b]	16[b]	+6 (+60%)[b]	1.3[b]	1.4[b]	-
6	12 (100%)	12 (100%)	407 (113%)	11	28	326	364	+38 (+6%)	16	17	+1 (+6%)	1.3	1.2	-0.1 (-8%)
7	10 (100%)	7 (70%)	312 (104%)	7	21	260	237	-23 (-9%)	10	10	0 (0%)	1.0	-	-
8	6 (100%)	4 (67%)	177 (98%)	14	13	783	657	-126 (-16%)	13	16	+3 (23%)	1.4	1.6	+0.2 (+14%)
9	6 (100%)	5 (83%)	183 (102%)	15	16	427	459	+32 (+8%)	12	15	+3 (+25%)	1.4	1.6	+0.2 (+14%)
10	2 (67%)	2 (100%)	68 (76%)	14	6	-	-	-	12	-	-	1.0	-	-
11	13 (100%)	8 (62%)	477 (111%)	12	27	307	668	+361 (+85%)	19	19	0 (0%)	1.4	1.3	-0.1 (-7%)[2]
Total	109 (91%)	91 (84%)	3475 (100%)											
Median				14[c] / 14[d]	23[c] / 25[d]	317	412	95 (+30%)	12	16	4 (+33%)	1.3	1.3	0.0 (0%)

[a] Participant received neoadjuvant treatment.

[b] Participant had a general feeling of discomfort during post-prehabilitation assessment and therefore did not perform adequately.

[c] All participants (n=11).

[d] Excluding the participant receiving neoadjuvant treatment (n=10).

Abbreviations: T_0 = pre-prehabilitation, T_1 = post-prehabilitation (1 or 2 days before surgery).

in 84% (91 out of 109) of the performed exercise sessions, only 63% of the participants were able to reach the prescribed intensity in ≥80% of their performed sessions. With regard to exercise session time (duration), all 11 participants managed to perform the prescribed exercise duration in ≥80% of the sessions. Duration of the performed physical exercise training sessions of all patients combined was 3475 minutes (100% of prescribed).

Participant appreciation of the tele-prehabilitation program is depicted in Table 3. All participants indicated that the tele-prehabilitation program prepared them well for the surgical intervention.

Table 3. Patient appreciation of the tele-prehabilitation program

	Strongly Disagree				Strongly Agree
	1	2	3	4	5
1. The aim of the intervention in preparation of the surgical treatment was clear to me.	-	-	-	-	11 (100%)
2. The perceived exertion during the cardiopulmonary exercise test was high.	1 (9%)	-	4 (36%)	3 (27%)	3 (27%)
3. In my opinion, the cardiopulmonary exercise test was useful.	-	-	1(9%)	-	10 (91%)
4. The perceived exertion during the home-based exercises was high.	1 (9%)	1 (9%)	2 (18%)	4 (36%)	3 (27%)
5. In my opinion the home-based exercises were useful.	-	-	-	1 (9%)	10 (91%)
6. I was motivated to perform the home-based exercises.	-	-	-	1 (9%)	10 (91%)
7. I experienced the home-based exercises as pleasant.	-	1 (9%)	1 (9%)	3 (27%)	6 (54%)
8. The home-based exercises were time-consuming.	7 (64%)	2 (18%)	1 (9%)	1 (9%)	-
9. The weekly evaluations by telephone were beneficial to me.	-	-	-	1 (9%)	10 (91%)
10. I experienced it be pleasant to be able to perform the exercises independently at home.	-	-	-	1 (9%)	10 (91%)
11. I think the tele-prehabilitation program prepared me well for the surgical treatment.	-	-	-	2 (18%)	9 (82%)

Data are presented as the number of patients (%).

Median systems usability questionnaire score was 85 (IQR 78-100). All 11 patients had a systems usability questionnaire score ≥73, indicating that the user friendliness of the mobile phone application was good. Six patients had a systems usability questionnaire of ≥85% indicating excellent user-friendliness (Figure 2).

Pre- and post-prehabilitation (preoperative) assessment of physical fitness was performed in 10 participants (91%) as shown in Figure 3. With regard to time to exhaustion on the constant work rate test, 7 participants (70%) had an equal or longer time

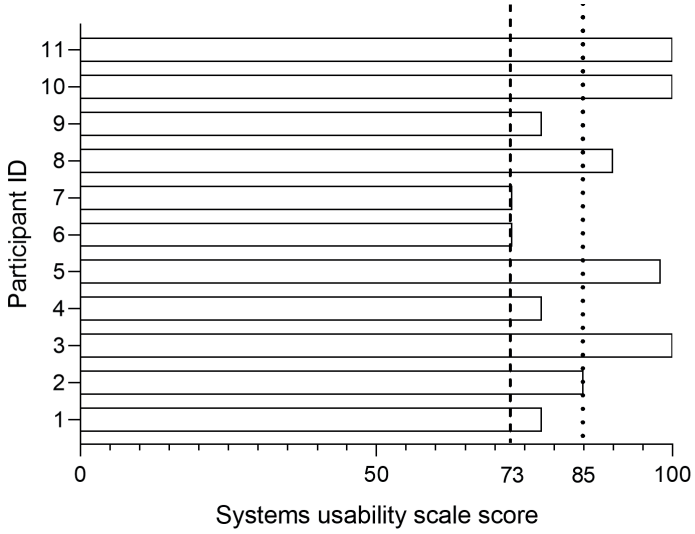


Figure 2. Participant's individual score on the systems usability scale.
Dashed and dotted line represent thresholds of respectively good (≥73) and excellent (≥85) usability of the mobile phone application used for tele-prehabilitation.

to exhaustion at the post-prehabilitation evaluation, whereas 3 patients (30%) had a shorter time to exhaustion. Of these 3 patients, 1 patient was unable to perform adequately on the constant work rate test after the tele-prehabilitation program due to general discomfort and nausea. From pre- to post-prehabilitation, time to exhaustion on the constant work rate test changed from a median of 317 s to a median of 412 s (p=0.24) and from a median of 307 s to a median of 459 s (p=0.07) with and without the participant with a general feeling of discomfort at the post-prehabilitation assessment, respectively. Following the tele-prehabilitation program, the number of repetitions at the 30-second chair-stand test significantly improved from a median of 12 to a median of 16 repetitions (p=0.01). No significant changes were observed in walking speed as measured by means of the 4-minute walk test (p=0.33).

DISCUSSION

The current study aimed to evaluate the feasibility of a home-based tele-prehabilitation program in high-risk patients with colon or rectal cancer scheduled for surgery. Tele-prehabilitation was deemed feasible, as willingness to participate was high (81%) and adherence was good (>80%). Patients felt the tele-prehabilitation prepared them well for surgery. Changes in physical fitness measured before and after the tele-prehabilitation program showed a trend towards improved physical fitness after tele-prehabilitation.

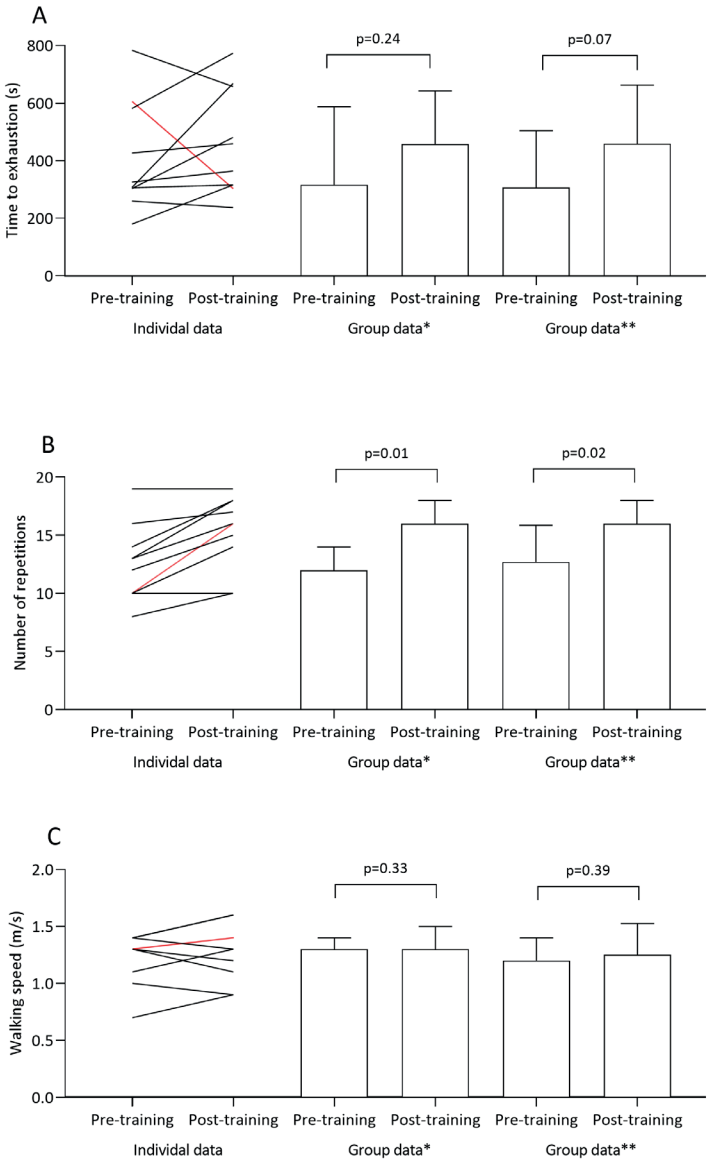


Figure 3. Preliminary changes in aerobic fitness before (pre-prehabilitation) and after (post-prehabilitation) the tele-prehabilitation program.
Graphs represent outcomes of the constant work rate test (A), the 30-second chair-stand test (B) and the 4-meter gait speed test (C).
Both individual data (left) and group data (right) are presented. For the group data, bars indicate median values with error bars representing the interquartile range. P-values indicate significance level tested with the non-parametric Wilcoxon signed-rank test.
* all patients that completed the post-prehabilitation (T_1) assessment (n=10).
** excluding the patient that had a general feeling of discomfort during post-prehabilitation (T_1) assessment (n=9), which is highlighted in red (participant ID 5) in the individual data plot.

There are no specific recommendations regarding the sample size of feasibility studies. Although only 11 participants were included in the current study, these participants were deemed representative for a larger population of patients with colorectal cancer with a high risk for postoperative complications, because participant characteristics are in line with participant characteristics in a larger randomized controlled trial in the same population [2].

The participation rate of 81% in the current study was comparable to the participation rate in previous tele-prehabilitation programs [13, 23] and a hospital-based [24] prehabilitation program (between 68% and 78%), and higher than a community-based [2] prehabilitation program (56%) before major abdominal surgery. A possible explanation for the observed high willingness to participate is that the tele-prehabilitation program was home-based, personalized, and indirectly supervised, thereby maximizing autonomy and lowering the threshold to participate.

One of the main challenges of "classic" (non-tele-monitored) unsupervised home-based prehabilitation is the often observed low exercise session adherence [6]. Previous studies have reported lower exercise session adherence in home-based (~70%) compared to hospital-based (>95%) prehabilitation programs [6]. Exercise session adherence (exercise frequency) in the current home-based tele-prehabilitation study was high (93% of prescribed) and almost comparable to supervised hospital-based prehabilitation programs (97-99%) [6]. Personalization of the tele-prehabilitation program and flexibility concerning planning of training sessions might have contributed to this high exercise session adherence, as autonomy is mentioned as one of the key factors that enable patients to participate in prehabilitation in the stressful and busy period between diagnosis and surgery [8]. In addition, it has been shown that some kind of supervision is essential for patients in order to stay motivated [8]. In this regard, home-based tele-prehabilitation might be superior to classic unsupervised home-based prehabilitation as the tele-monitoring in combination with weekly telephone calls might provide sufficient pressure and supervision for patients to keep motivated. In the current study it was noted that participants appreciated the weekly follow-up phone calls and reported them as useful.

Apart from adherence to training frequency alone, full adherence to a physical exercise training program should also be evaluated based on training intensity and training time [15]. Although overall adherence to the exercise intensity was >80%, only 7 participants (63%) managed to adhere to the prescribed intensity in ≥80% of the sessions. Exercise intensity is one of the key factors that contribute to the effectiveness to improve aerobic fitness in a short-term physical exercise program [15]; therefore, adherence to exercise

training intensity needs to be optimized. In the current study participants performed exercises unsupervised and tele-monitored after an initial home-based introduction session. It was noted that all participants reached the prescribed intensity during the first home-based supervised training session. In the following unsupervised training sessions, adherence to exercise training intensity was less consistent. This could mean that more direct supervision and encouragement is needed to adhere to the exercise intensity. Therefore, adherence concerning exercise intensity might be improved by adding a weekly supervised session (preferably home-based or by using video conferencing) in order to motivate and coach patients to adhere to the exercise program. In addition, direct feedback regarding the physical exercise training session intensity and duration provided by the mobile phone application might be helpful for patients to comply with the prescribed program.

In general, participants appreciated the tele-prehabilitation program. Most participants reported they experienced it pleasurable to perform exercises independently at home, they reported that the weekly telephone calls were helpful, and that the tele-prehabilitation program prepared them well for the surgical procedure. In addition, the usefulness of the smart phone application that was used for the tele-prehabilitation program, as rated by the systems usability questionnaire ranged from good to excellent. All participants managed to use the smart phone application independently (or with help of their buddy) after a short introduction session. These results are in accordance with a multimodal tele-prehabilitation study in patients with abdominal cancer that used commercially available wearables to improve physical fitness prior to surgery [23]. Patients in the latter study [23] reported that the wearables were easy to use and motivational to improve physical activity.

The current study has several limitations. Some patients were excluded for reasons that have to do with feasibility of tele-prehabilitation, such as being unable to operate a mobile phone (n=6, 17%) or being unable to perform a CPET (n=2, 6%). Although these excluded patients did not undergo CPET and therefore it is uncertain whether they would have been classified as high risk, the reasons for exclusion are specific for a tele-prehabilitation program. In addition, previous research has shown that patients that are unable to perform CPET should be treated as high-risk [25].

A major obstacle for the implementation of prehabilitation is the short diagnosis-to-surgery interval (median of 34 days, range 20-51 days). Combined with a relatively long interval between diagnosis and start of the prehabilitation (median of 14 days, range 7-21 days), this leaves limited time for a comprehensive prehabilitation program in patients who receive surgery as their first treatment. These time-limitations are often

caused by logistics (e.g., delayed final diagnosis and/or surgical planning) and time-constrains. Efforts should be made to use the available time as efficiently as possible, for example by starting screening, assessment, and prehabilitation directly after colorectal cancer diagnosis by endoscopy. Nevertheless, although essential for effective prehabilitation, these strict time-constrains are not strongly supported by evidence [26-28] and not specific towards tele-prehabilitation, but involve a broader problem that is generally seen in prehabilitation studies [29]. Another limitation that was observed in the current study was that in 3 participants (27%) heart rate could not be used as an indicator of exercise intensity due to chronotropic incompetence. Although this was partly covered by the use of the Borg RPE score, especially in non-real time monitored interventions such as tele-prehabilitation, the combination of perceived effort (i.e., Borg RPE) with a form of objective monitoring is of major importance due to the lack of direct supervision. Accelerometer-based [30, 31] or respiratory rate monitoring [32] might be alternative measures that can be used in addition to heart rate monitoring to provide an objective estimate of exercise intensity when heart rate monitoring is not feasible (e.g., participants with severe cardiac arrhythmia or chronotropic incompetence).

Strengths of the current tele-prehabilitation program are that the intervention was personalized and focused on high-risk patients, based on the CPET, and the use of an exercise intervention blueprint meaning the exercise intervention was adjusted based on the participant's preferences and characteristics. In addition, instead of attendance rates only, the current study reported full adherence (frequency, intensity, and time) to the physical exercise intervention. Another strength of the current study is that tele-prehabilitation was implemented within the current colorectal cancer treatment pathway and no additional study visits were required for participants.

In future research, attempts should be made to optimize adherence to the exercise training intensity of the tele-monitored physical exercise program, for example by using a combination of physically supervised and tele-monitored supervision. Furthermore, a larger prospective observational study could be designed to evaluate willingness to participate, adherence, and (cost-)effectiveness of prehabilitation when different forms of multimodal prehabilitation (e.g., tele-prehabilitation, community-based prehabilitation, and hospital-based prehabilitation) are presented to patients.

CONCLUSION

Results of this feasibility study have shown that a home-based tele-prehabilitation program is feasible and appreciated in high-risk patients undergoing surgery for colorectal

cancer. However, efforts should be made to further improve adherence towards exercise intensity. More research is needed to establish the (cost-)effectiveness of tele-prehabilitation with regard to improvements in preoperative aerobic fitness and reduction of postoperative complications before definitive conclusions can be drawn.

REFERENCES

1. Barberan-Garcia, A., et al., *Personalised Prehabilitation in High-risk Patients Undergoing Elective Major Abdominal Surgery: A Randomized Blinded Controlled Trial.* Ann Surg, 2018. **267**(1): p. 50-56.
2. Berkel, A.E.M., et al., *Effects of Community-based Exercise Prehabilitation for Patients Scheduled for Colorectal Surgery With High Risk for Postoperative Complications: Results of a Randomized Clinical Trial.* Ann Surg, 2022. **275**(2): p. e299-e306.
3. de Klerk, M., et al., *A multimodal prehabilitation program in high-risk patients undergoing elective resection for colorectal cancer: A retrospective cohort study.* Eur J Surg Oncol, 2021. **47**(11): p. 2849-2856.
4. van Rooijen, S., et al., *Preoperative modifiable risk factors in colorectal surgery: an observational cohort study identifying the possible value of prehabilitation.* Acta Oncol, 2017. **56**(2): p. 329-334.
5. Berkel, A.E.M., et al., *The effects of prehabilitation versus usual care to reduce postoperative complications in high-risk patients with colorectal cancer or dysplasia scheduled for elective colorectal resection: study protocol of a randomized controlled trial.* BMC Gastroenterol, 2018. **18**(1): p. 29.
6. Thomas, G., et al., *Prehabilitation before major intra-abdominal cancer surgery: A systematic review of randomised controlled trials.* Eur J Anaesthesiol, 2019. **36**(12): p. 933-945.
7. Agasi-Idenburg, C.S., et al., *"I am busy surviving" - Views about physical exercise in older adults scheduled for colorectal cancer surgery.* J Geriatr Oncol, 2020. **11**(3): p. 444-450.
8. Beck, A., et al., *What matters to you? An investigation of patients' perspectives on and acceptability of prehabilitation in major cancer surgery.* Eur J Cancer Care (Engl), 2021. **30**(6): p. e13475.
9. Ferreira, V., et al., *Maximizing patient adherence to prehabilitation: what do the patients say?* Support Care Cancer, 2018. **26**(8): p. 2717-2723.
10. Woodfield, J., et al., *Protocol, and practical challenges, for a randomised controlled trial comparing the impact of high intensity interval training against standard care before major abdominal surgery: study protocol for a randomised controlled trial.* Trials, 2018. **19**(1): p. 331.
11. Collaborative, P.-A.T., *SupPoRtive Exercise Programs for Accelerating REcovery after major ABdominal Cancer surgery trial (PREPARE-ABC): pilot phase of a multi-centre randomised controlled trial.* Colorectal Dis, 2021. **23**(11): p. 3008-3022.
12. Beck, A., et al., *Investigating the experiences, thoughts, and feelings underlying and influencing prehabilitation among cancer patients: a qualitative perspective on the what, when, where, who, and why.* Disabil Rehabil, 2022. **44**(2): p. 202-209.
13. Wu, F., et al., *The Feasibility and Effects of a Telehealth-Delivered Home-Based Prehabilitation Program for Cancer Patients during the Pandemic.* Curr Oncol, 2021. **28**(3): p. 2248-2259.
14. Lacroix, A., et al., *Effects of Supervised vs. Unsupervised Training Programs on Balance and Muscle Strength in Older Adults: A Systematic Review and Meta-Analysis.* Sports Med, 2017. **47**(11): p. 2341-2361.
15. Franssen, R.F.W., et al., *Moderate-intensity exercise training or high-intensity interval training to improve aerobic fitness during exercise prehabilitation in patients planned for elective abdominal cancer surgery?* Eur J Surg Oncol, 2022. **48**(1): p. 3-13.
16. Lambert, T.E., et al., *An app with remote support achieves better adherence to home exercise programs than paper handouts in people with musculoskeletal conditions: a randomised trial.* J Physiother, 2017. **63**(3): p. 161-167.
17. Bruns, E.R.J., et al., *Fit4SurgeryTV At-home Prehabilitation for Frail Older Patients Planned for Colorectal Cancer Surgery: A Pilot Study.* Am J Phys Med Rehabil, 2019. **98**(5): p. 399-406.

18. Eldridge, S.M., et al., *CONSORT 2010 statement: extension to randomised pilot and feasibility trials.* BMJ, 2016. **355**: p. i5239.
19. Dronkers, J.J., et al., *Preoperative therapeutic programme for elderly patients scheduled for elective abdominal oncological surgery: a randomized controlled pilot study.* Clin Rehabil, 2010. **24**(7): p. 614-22.
20. Myers, J., et al., *A nomogram to predict exercise capacity from a specific activity questionnaire and clinical data.* Am J Cardiol, 1994. **73**(8): p. 591-6.
21. Wischmeyer, P.E., et al., *American Society for Enhanced Recovery and Perioperative Quality Initiative Joint Consensus Statement on Nutrition Screening and Therapy Within a Surgical Enhanced Recovery Pathway.* Anesth Analg, 2018. **126**(6): p. 1883-1895.
22. Bangor, A., P.T. Kortum, and J.T. Miller, *An Empirical Evaluation of the System Usability Scale.* International Journal of Human–Computer Interaction, 2008. **24**(6): p. 574-594.
23. Waller, E., et al., *Prehabilitation with wearables versus standard of care before major abdominal cancer surgery: a randomised controlled pilot study (trial registration: NCT04047524).* Surg Endosc, 2022. **36**(2): p. 1008-1017.
24. Suen, M., et al., *Short-term multimodal prehabilitation improves functional capacity for colorectal cancer patients prior to surgery.* Asia Pac J Clin Oncol, 2021. **Epub ahead of print**.
25. Lai, C.W., et al., *Patients' inability to perform a preoperative cardiopulmonary exercise test or demonstrate an anaerobic threshold is associated with inferior outcomes after major colorectal surgery.* Br J Anaesth, 2013. **111**(4): p. 607-11.
26. Franssen, R.F.W., et al., *The Association Between Treatment Interval and Survival in Patients With Colon or Rectal Cancer: A Systematic Review.* World J Surg, 2021. **45**(9): p. 2924-2937.
27. Strous, M.T.A., M.L.G. Janssen-Heijnen, and F.J. Vogelaar, *Impact of therapeutic delay in colorectal cancer on overall survival and cancer recurrence - is there a safe timeframe for prehabilitation?* Eur J Surg Oncol, 2019. **45**(12): p. 2295-2301.
28. Molenaar, C.J.L., et al., *Conflicting Guidelines: A Systematic Review on the Proper Interval for Colorectal Cancer Treatment.* World J Surg, 2021. **45**(7): p. 2235-2250.
29. Boereboom, C.L., et al., *Short-term pre-operative high-intensity interval training does not improve fitness of colorectal cancer patients.* Scand J Med Sci Sports, 2019. **29**(9): p. 1383-1391.
30. Arvidsson, D., J. Fridolfsson, and M. Borjesson, *Measurement of physical activity in clinical practice using accelerometers.* J Intern Med, 2019. **286**(2): p. 137-153.
31. Jung, M.E., et al., *High-intensity interval training as an efficacious alternative to moderate-intensity continuous training for adults with prediabetes.* J Diabetes Res, 2015. **2015**: p. 191595.
32. Nicolo, A., C. Massaroni, and L. Passfield, *Respiratory Frequency during Exercise: The Neglected Physiological Measure.* Front Physiol, 2017. **8**: p. 922.

9

CHAPTER 9

General discussion

PREFACE

There is a transition in healthcare from the *reactive* treatment of disease to *proactive* care that is predictive, preventive, personalized, and participatory (P4 Health) [1]. Although the P4 Health model as introduced by the American biologist Leroy Hood is primarily a model used for primary prevention of disease [2], it can also be applied to tertiary prevention strategies such as prehabilitation. Cancer prehabilitation includes a set of proactive preventive interventions that take place between diagnosis and the beginning of cancer treatment and encompasses baseline assessments and targeted multimodal preventive interventions aiming at improving a patient's health in order to better cope with the treatment-induced stress response and subsequently reduce the incidence and severity of future impairments [3]. As such, the P4 Health approach was adopted in this thesis and applied to the field of prehabilitation in patients approaching colorectal surgery. *The aim of this thesis* was to optimize prehabilitation in this population by 1) exploring a safe timeframe for prehabilitation, 2) by improving preoperative risk assessment by means of cardiopulmonary exercise testing, 3) by evaluating what type of physical exercise training is most effective within the short timeframe between diagnosis and surgery, and 4) by exploring the feasibility of home-based tele-monitored prehabilitation in patients preparing for colorectal cancer (CRC) surgery. In this chapter, the main results of the thesis will be summarized and discussed in relation to existing evidence and clinical practice. Thereafter, strengths and limitations of the research in this thesis, as well as future directions and recommendations for future research and clinical practice will be provided.

SAFE TIMEFRAME FOR PREHABILITATION

In the Netherlands, as well as in many other countries, time between diagnosis and treatment initiation (treatment interval) in CRC is limited to 35 days due to strict treatment guidelines [4]. Although the treatment interval is often seen as a passive "waiting" period, this period opens a window of opportunity to *prepare* a patient for the upcoming surgical intervention [5]. To gain insight into a safe timeframe that can be used to prepare patients for their surgical procedure, a systematic review was conducted **(Chapter 2).**

The aim of the systematic review was to evaluate the association between the length of the treatment interval (time between diagnosis and treatment) and (cancer-free) survival. On the one hand, results of the systematic review did not provide evidence to support current short treatment intervals as dictated by current treatment guidelines in CRC surgery, thereby underpinning the notion that current short treatment intervals are

mainly based on social acceptability rather than medical urgency [6]. On the other hand, no clear recommendations regarding an optimal treatment interval could be provided based on the 11 studies that were included in our review, as studies were heterogeneous with regard to treatment interval definitions, treatment time intervals, and used outcome measures.

To further explore the association between treatment interval and (cancer-free) survival in patients with colon cancer, a retrospective cohort study was performed using data of 5 general hospitals in the south of the Netherlands between 2010 and 2016, thereby including 3376 patients **(Chapter 3)**. Subgroups were created for non-high-risk and high-risk patients. A patient was considered to have a high risk when they had an American Society of Anesthesiology (ASA) classification III and IV, or when they were aged >75 years and had a BMI <20 kg/m^2 or >30 kg/m^2, and/or a hemoglobin level <7.5 mmol/L. Results of this cohort study showed that a treatment interval of up to 49 days (7 weeks) was not associated with reduced cancer-free survival (CFS) or overall survival (OS), irrespective of the risk status of the patient. In contrast, occurrence of major postoperative complications was associated with reduced 1-year overall survival (non-high-risk hazard ratio (HR) 6.12; high-risk HR 6.84) and 5-year overall survival (non-high-risk HR 1.97; high-risk HR 2.47). The lack of association between treatment interval with CFS and OS in combination with the association between postoperative complications and OS could mean that strategies aiming at a reduction of the incidence and/or impact of postoperative complications might be more important with regard to improving CFS or OS than aiming for a very short treatment interval.

The results of our systematic review **(Chapter 2)** and observational study **(Chapter 3)** seem to be in contrast with a systematic review and meta-analysis by Whittaker et al. [7], which reported that treatment delays of more than 4 weeks could lead to poorer outcomes. Reasons for these discrepancies might lie in the heterogeneity of the literature that was reviewed by Whittaker et al., which was also outlined in a letter to the editor **(Chapter 2a)** in reply to their systematic review. In short, the chosen time-point for "diagnosis" was not uniform between studies, thereby allowing for variations in the treatment interval of up to 14 days. In addition, the treatment interval of 4 weeks was arbitrarily chosen by Whittaker et al., as the 4-week interval was not consistent with the intervals in the individual included studies, and the conclusion was solely based on an association between treatment delay and OS and not on CFS. As OS is affected by many factors, and the main concern of extending the treatment interval is tumor growth, a better outcome measure would have been CFS.

In line with our findings, a recent systematic review by Molenaar et al. [8] concluded that a uniform definition of treatment interval is lacking and that international guidelines are conflicting with regard to the length of the treatment interval. Moreover, Molenaar et al. [8] did not find decisive evidence that a longer length of the treatment interval is associated with poorer outcomes (i.e., tumor stage, CFS). Although it seems that, at the group level, an increase in the length of treatment interval up to 49 days does not lead to worse CFS, another factor of concern should be how patients feel about delaying surgery for the benefit of optimization of modifiable risk factors. It is well-understandable that many patients would prefer their tumor to be removed as soon as possible, as many patients experience "passive waiting" for surgery as fearful [9]. However, there is also evidence that thoughts and expectations of patients with regard to temporal aspects of diagnosis and treatment are open to contextualization by healthcare providers [10]. In addition, patients prefer a "preparing" strategy over a "waiting" strategy prior to surgery, because many believe that prehabilitation can attenuate the physical and mental deterioration before surgery [9].

The feeling of preparedness is further enhanced by sincere and personal guidance, and thorough and personalized information provision that is dosed throughout the preoperative and postoperative period [11]. This means that healthcare providers should discuss risks and benefits (based on formal risk assessment) with the patient and their caregivers in the form of collaborative decision-making to make optimal use of the time between diagnosis and surgery. Patients with a high risk for postoperative complications and/or a delayed recovery of physical functioning might benefit from a prolonged treatment interval to mitigate perioperative risks by participating in preventive interventions focused on their individual risk factors, whereas patients with a low risk might undergo surgical resection of the tumor as soon as possible with or without formal prehabilitation. Of course, efforts should be made to avoid unnecessary delays. In order to make optimal use of the available time, colorectal surgical pathways should be designed in such way that preparation for surgery (including risk assessment and prehabilitation) is initiated at the earliest time-point possible [12].

For adequate assessment of the risks (e.g., of delaying surgery) and benefits (e.g., improved psychophysiological resilience) of preventive actions, multidisciplinary preoperative risk assessment is an important step that should be initiated early after the decision to consider CRC surgery. By using multidisciplinary preoperative risk assessment as *predictive* healthcare, the patient and his or her caregivers can be timely informed about the patient's health status. As such, possible treatment options and their associated risks can be discussed to allow for collaborative decision-making concerning possible

preoperative *preventive* interventions (prehabilitation) that must be *personalized* to an individual patient's risk factors.

Clinical implications:

- On a group level, an extension of the treatment interval up to 49 days (7 weeks) does not lead to worse cancer-free and overall survival in patients with colon cancer.
- Possible extensions of the treatment interval should be based on collaborative decision-making following multidisciplinary risk assessment, as well as by evaluating patient preferences, modifiable risk factors, and the medical urgency for the surgical procedure.

Research implications:

- Continuous postoperative follow-up is needed to reveal subgroups (e.g., certain tumor types, patients with severe blood loss) of patients who might or might not benefit from a prolonged treatment interval in combination with prehabilitation regarding long term cancer-free and overall survival.

PREDICTIVE: *PREOPERATIVE RISK ASSESSMENT*

Risk assessment is an important *predictive* step in the preoperative care path. The cardiopulmonary exercise test (CPET) is the gold standard test that can be used to assess aerobic fitness as part of preoperative risk assessment [13]. To assess some methodological aspects of the preoperative CPET, two studies were conducted regarding uniformity of the determination of CPET-derived variables used for preoperative risk assessment **(chapter 4)** and the influence of data-averaging methods on the numerical value on these variables **(chapter 5)**.

To assess uniformity of preoperative risk assessment by means of CPET, a prospective observational study was completed among 26 professionals (sports physicians and clinical exercise physiologists) who interpreted 12 preoperative CPETs using two different approaches: a self-preferred approach and a guideline-based approach **(chapter 4)**. Variables of interest were, the oxygen uptake at the ventilatory anaerobic threshold (VO_{2VAT}), oxygen uptake at peak exercise (VO_{2peak}), the slope of the relationship between the minute ventilation and carbon dioxide production (VE/VCO_2-slope), and the oxygen uptake efficiency slope (OUES). The inter-observer agreement, as quantified by the intra-class correlation coefficient (ICC), was moderate-to-good-for VO_{2VAT} (ICC 0.76) and good for VO_{2peak} and VE/VCO_2-slope (ICC >0.80) when using the self-preferred approach. When

using a guideline-based approach for CPET interpretation, the ICC was good for VO_{2VAT} (ICC >0.80) and excellent for VO_{2peak}, VE/VCO_2-slope, and the OUES (ICC >0.90).

During a CPET, breath-by-breath respiratory gases are averaged using different data-averaging intervals in order to ease interpretation. The chosen data-averaging method might affect the numerical values of CPET-derived variables and the related preoperative risk assessment outcomes. Therefore, a study was conducted to explore the influence of different data-averaging methods on the numerical values of the VO_{2VAT}, VO_{2peak}, VE/VCO_{2VAT}, VE/VCO_2-slope, and OUES **(chapter 5)**. Two clinical exercise physiologists interpreted 21 preoperative CPETs of patients with CRC considered for surgery using 5 different data-averaging methods. At the group level there were no clinically relevant differences between data-averaging methods, meaning that the data-averaging interval did not greatly influence the mean values of the CPET-derived variables. Nevertheless, the results also showed that on an individual patient level the chosen data-averaging interval could lead to substantial variation in the numerical value of CPET derived variables.

The results of the studies in **Chapters 4 and 5** are reassuring, and indicative that the CPET has a high inter-observer reliability. Especially when a systematic guideline-based approach is used for preoperative CPET interpretation, the inter-observer agreement between professionals is good to excellent (ICC >0.80) for all variables **(chapter 4)**. The latter highlights the importance of a systematic approach for CPET interpretation given the complexity of CPET interpretation and the many different healthcare provides who might be involved in CPET interpretation across the Netherlands. In contrast to the United Kingdom [13], there are no (published) preoperative CPET guidelines and there is no centralized preoperative CPET education in the Netherlands. It would be undesirable when a patient is classified as having a high-risk for adverse postoperative outcomes in one hospital (or as assessed by one clinician) but not in another. An interesting observation from our study was that the VE/VCO_2-slope and OUES seem to be easier to determine accurately (e.g., compared to the VO_{2VAT}) as evidenced by their high ICC (>0.90); this makes them potentially interesting variables for future preoperative risk assessment [14].

The observation that data-averaging intervals do not seem to influence the numerical values of CPET variables used for preoperative risk assessment allows clinicians to use the data-averaging interval that best fits the test they are assessing. That is, a longer data-averaging interval can be used in tests with longer duration and/or a breath-based averaging method might be optimal to reveal pathophysiological mechanisms such as oscillatory breathing [15]. Although the two studies in **chapters 4 and 5** aimed to

evaluate and improve the methodology of the preoperative CPET, it needs to be noted that some degree of variation in CPET interpretation and execution will always exist and that it should be appreciated that any CPET-derived variable represents a dynamic metric influenced by analytical and biological variation [16]. To address these issues, Rose et al. already proposed to use risk zones for aerobic fitness (e.g., unfit when having a VO_{2VAT} <9.2 mL/kg/min, fit when having a VO_{2VAT} >13.6 mL/kg/min, and moderately fit in-between) instead of fixed risk thresholds for estimating preoperative risk [17]. In addition, clinicians should not determine the preoperative risk for adverse postoperative outcomes solely based on fixed thresholds but rather within the context of the whole CPET and health status of the patient.

Currently, mainly the CPET-derived variables VO_{2VAT} and VO_{2peak} have been associated with postoperative outcomes in colorectal surgery. These variables have some limitations as the submaximal variable VO_{2VAT} cannot be determined in all patients and not all patients are able to achieve a volitional maximal exercise making adequate interpretation of the VO_{2peak} difficult. Moreover, interpretation of only VO_{2VAT} and VO_{2peak} leads to substantial loss of physiological CPET data. Effort-independent preoperative CPET variables, such as the VE/VCO_2-slope and the OUES are determinable in all patients, do not require a maximal effort and, as highlighted in **chapter 4**, are easy to determine. To explore the predictive value of the VE/VCO_2-slope and the OUES with regard to preoperatively estimating 30-day postoperative complications in patients with CRC (n=102), a multicenter (n=4) observational study was conducted **(Chapter 6)**. The effort-independent CPET variables VE/VCO_2-slope and the OUES were statistically significant associated (respectively OR 1.08 and OR 0.94) with postoperative complications. However, in a receiver operator characteristics analysis, the independent association of the VE/VCO_2-slope and OUES/kg with postoperative complications was not accurate enough (AUC 0.64 for both variables) to retrieve any relevant cut-off points with the predefined sensitivity of 80% and specificity of 50%. This poor individual predictive value of CPET variables is consistent with current literature [18] and probably reflects the complex interaction between baseline physiology and postoperative outcomes. Further investigation of effort-independent variables in a larger dataset is warranted to allow for a more in-depth, multivariable analyses of certain subgroups of patients with disparate baseline physiology (e.g., sex, comorbidities, tumor types) and/or who underwent different (surgical) treatments. Even though, effort-independent variables such as the VE/VCO_2-slope and OUES/kg might be useful variables in patients who are unwilling or unable to exercise until volitional maximal exertion during a CPET and/or combined with other CPET-derived variables, such as VO_{2peak} and VO_{2VAT}. In general, a CPET should not be seen as a "pass" or "fail" test, as it is unlikely that one metric alone is able to adequately predict the risk for and resilience to adverse postoperative outcomes. Every patient has a unique profile of modifiable

and unmodifiable risk factors. Preoperative nutritional status, hemoglobin levels, psychological wellbeing, and intoxications also influence postoperative outcomes and should be implemented in preoperative risk assessment [19]. Preoperative risk estimates derived from CPET are primarily used to add weight to and to inform the process of collaborative decision-making. Thus, more shades of grey can be added by implementing CPET variables into a more comprehensive risk assessment model such as the Marsden Morbidity Index [20]. The Marsden Morbidity Index is a weighted risk score that includes several preoperative risk factors (including VO_{2VAT} and VO_{2peak}) in order to estimate the probability of postoperative morbidity (in this case at postoperative day 7). Future research is needed to establish the benefits of effort-independent variables, such as the VE/VCO_2-slope and OUES within such a model.

Besides estimating a patient's aerobic fitness to estimate the odds for adverse postoperative outcomes and recovery, it should be appreciated that the CPET is a versatile exercise test that can have many more roles within the preoperative workup, such as to inform collaborative decision-making, triage perioperative care (e.g., ward, intensive care), advice on preoperative interventions aiming at optimizing co-morbidities, identify previously unsuspected pathology, guide physical exercise training interventions (prehabilitation and rehabilitation), and guide intraoperative care [13]. Despite its many benefits, and contrasting with the United Kingdom, the CPET is still not widely implemented in preoperative care pathways in the Netherlands. Possible reasons are that a CPET is relatively costly and requires specialized equipment for respiratory gas analysis and personnel [13] that might not be available in all prehabilitation settings. Recently, a study showed that preoperative aerobic fitness (quantified as the achieved work rate at peak exercise normalized for body mass) estimated by a modified version of the steep ramp test (SRT) was inversely associated with the risk for postoperative complications (odds ratio 0.61, 95% confidence interval 0.41-0.93) in 304 patients scheduled for colorectal surgery [21]. This short-term, supramaximal test does not require respiratory gas analysis measurements and seems less demanding on the cardiopulmonary system than the CPET. Therefore, its widespread implementation for preoperative risk assessment is appealing. Furthermore, the SRT can be used in community settings or home-based settings for cardiorespiratory fitness monitoring before surgery [22]. As an example of its use, a short-term home-based high-intensity interval training program, in which training intensity was personalized every week based on SRT performance, has been found to significantly improve the preoperative aerobic fitness of high-risk patients who are scheduled to undergo hepatic or pancreatic surgery [23].

These promising findings require further investigation before implementation in routine clinical practice. Nevertheless, the SRT cannot replace the CPET given the before-

mentioned many roles it can fulfill. A form of triaging could be introduced to guide some patients (e.g., patients with cardiovascular or respiratory comorbidities or other relevant risk factors) towards CPET, while others who do not require the additional roles of the CPET can be safely tested for aerobic fitness using a practical field test requiring a maximal effort such as the SRT. Examples of screening tools that might be used for triaging are the 'physical activity readiness medical examination' (PARmed-X) and the 'physical activity readiness questionnaire' (PAR-Q) [24]. The PARmed-X and PAR-Q are easy to use screening tools that are used to determine the safety or possible risks of exercising based on your health history, current symptoms, and risk factors. Tools like the PARmed-X and PAR-Q could be further investigated and adapted (e.g., include cancer specific items such as signs of chemo-toxicity) for the purpose of preoperative triage.

Clinical implications:

- Preoperative CPET interpretation for adequate risk assessment should preferably be done by using a systematic guideline-based approach in order to reduce inter-observer variability.
- The CPET data-averaging interval does not influence preoperative risk assessment outcomes, meaning that clinicians can choose the data-averaging interval that best fits the properties of the test they are interpreting.
- The VE/VCO2-slope and the OUES could add weight to preoperative risk assessment in patients in whom the VO2VAT is difficult to determine and/or who are unable or unwilling to perform a volitional maximal effort.
- A CPET should not be seen as a "pass" or "fail" test, but should be used to add weight to, and inform the process of, collaborative decision-making.

Research implications:

- Effort-independent variables, such as the VE/VCO2-slope and the OUES, are promising variables to assist in preoperative risk assessment that should be further validated in combination with other risk assessment variables and/or biomarkers in a prospective study.
- The screening and selection of patients who would benefit from a comprehensive preoperative exercise test to assess aerobic fitness (the CPET) as opposed to more practical field exercise tests to estimate aerobic fitness (e.g., SRT) and to guide the physical exercise prescription needs further investigation.

PREVENTIVE: *PREHABILITATION*

Any modifiable risk factors identified during multidisciplinary preoperative risk assessment can be subject to preventive actions within a prehabilitation program. For patients with a low preoperative aerobic fitness, prehabilitation should preferably include a form of structured physical exercise training. The two most commonly used physical exercise training modalities in prehabilitation are moderate-intensity endurance training (MIET) and high-intensity interval training (HIIT). In a narrative review **(Chapter 7),** short-term (<6 weeks) MIET and HIIT physical exercise training programs were compared with respect to their ability to improve objectively measured aerobic fitness (VO_{2peak} or VO_{2VAT}) in patients with abdominal cancer and abdominal cancer survivors. Based on group means, HIIT seemed to be superior to MIET when aerobic fitness needs be improved within 4-6 weeks in patients with cancer. Six out of seven studies evaluating HIIT showed a statistically significant improvement in aerobic fitness (quantified as an improved VO_{2peak}) whereas no evidence was found that MIET resulted in any significant improvements of aerobic fitness within 6 weeks.

The observation that HIIT has the ability to improve aerobic fitness within the short timeframe available for prehabilitation was supported by a recent systematic review and meta-analysis [25], but challenged by another [26]. The latter, a systematic review and meta-analysis by Smyth et al. [26] concluded that there was insufficient evidence that HIIT could improve aerobic fitness prior to an oncologic resection. These contrasting findings might seem surprising; however, it needs to be noted that the review of Smyth et al. had severe methodological limitations that seriously influenced their results. In their meta-analysis, the authors compared VO_{2peak} after preoperative HIIT with the VO_{2peak} after a comparator condition (either moderate-intensity training or usual care), thereby not controlling for between-group baseline differences in VO_{2peak}. In all studies that were included by Smyth et al., the baseline VO_{2peak} values were numerically lower in the preoperative HIIT group compared to the MIET or usual care group. Consequently, although the preoperative HIIT group improved their VO_{2peak} to a greater extent in all studies, this effect was concealed in the meta-analysis by the higher baseline VO_{2peak} values of the moderate-intensity training or usual care group. When repeating the meta-analyses by comparing within-group changes in VO_{2peak}, HIIT indeed seemed to lead to greater improvements in preoperative aerobic fitness than moderate-intensity training or usual care (mean difference ± 1.82 mL/kg/min, Figure 1).

Recently, a randomized controlled trial (RCT) performed by Berkel et al. in high-risk patients with colorectal cancer scheduled for surgery demonstrated that 3 weeks of HIIT significantly improved preoperative aerobic fitness (VO_{2peak} +8.8% and VO_{2VAT} +10.1%)

and reduced the incidence of postoperative complications by ~50% [27]. An RCT [28] and an uncontrolled clinical trial [29] showed similar improvements in aerobic fitness after 4 weeks of HIIT in patients undergoing abdominal surgery. It is acknowledged that the efforts made in this thesis to elucidate the most "effective" physical exercise training intervention aiming at improving aerobic fitness in the short timeframe available for prehabilitation is only indicative and does not provide indisputable evidence. Hopefully, the identified pitfalls in current literature and the recommendations given regarding adequate patient selection, personalized physical exercise training prescription, full reporting of physical exercise training adherence, and formal monitoring of training progression and recovery in **Chapter 7** will lead to a better design and better reporting of the physical exercise training interventions in future prehabilitation studies, thereby contributing to the evidence base of exercise prehabilitation in general.

Clinical implication:

- HIIT seems more effective than MIET for short-term improvements (<6 weeks) in aerobic fitness in most patients scheduled for abdominal surgery.

Research implication:

- A randomized controlled trial that directly compares MIET to HIIT is needed to investigate what exercise modality is most effective for improving short-term aerobic fitness and subsequently improve postoperative outcomes.

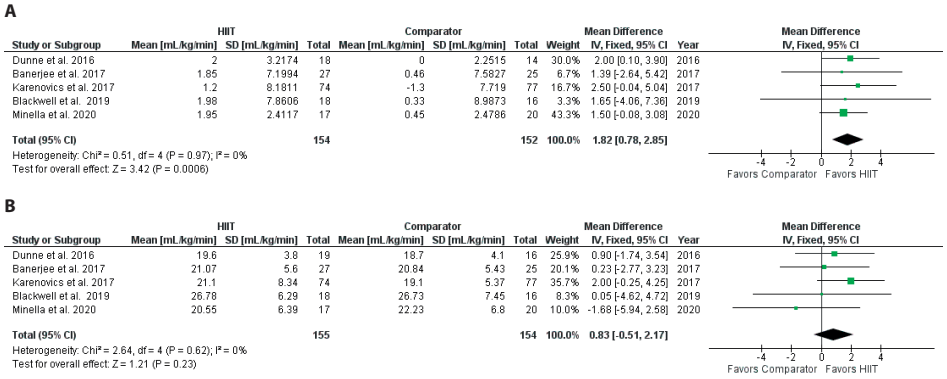


Figure 1. Mean change in the oxygen uptake at peak exercise (VO_{2peak}, in mL/kg/min) between high-intensity interval training (HIIT) and comparator (moderate-intensity training or usual care) groups of included studies. The square on the horizontal line represents the point estimate. The size of the square is determined by how much weight the study contributes to the pooled effect estimate. The diamond represents pooled effect estimates. a) meta-analyses as performed by Smyth et al. [26] based comparing post HIIT intervention VO_{2peak} between the intervention and control group, b) reanalysis based on within group mean differences in VO_{2peak} before and after the HIIT intervention.
Abbreviations: CI= confidence interval; HIIT = high intensity interval training; SD = standard deviation of the mean;

PERSONALIZED

Prehabilitation is a promising intervention, and evidence of its effectiveness regarding improving postoperative outcomes is emerging [30, 31]. Nevertheless, it is hard to reach a definitive conclusion based on current research [32, 33]. According to the 2018 Guidelines for Perioperative Care in Elective Colorectal Surgery, the evidence for multimodal prehabilitation to improve preoperative aerobic fitness is moderate, whereas the evidence to improve postoperative outcomes is weak [32]. As mentioned in **Chapter 7,** limitations in the current literature that might be partially responsible for the contrasting results are related to inadequate patient selection, a lack of personalized physical exercise prescription using the FITT-VP principles, incomplete reporting of the performed dose of physical exercise training, and no formal monitoring of training progression and recovery. Measures that help to quantify a patient's response to a stressor, such as heart rate variability (HRV) might be attractive to further personalize physical exercise prescription and to guide progression of training. Research in healthy subjects has shown promising results of HRV-guided physical exercise training [34]. HRV could be informative about whether a patient is ready to perform exercise or whether additional (active) rest is preferable (i.e., HRV-guided training).

In general, it is expected that high-risk patients are most likely to benefit from prehabilitation [32, 35]. However, current prehabilitation programs are mainly hospital-based, making it challenging for these vulnerable patients (i.e., often patients at higher age with low aerobic fitness, poor nutritional status, multimorbidity) to participate in prehabilitation programs [36-38]. Home-based prehabilitation could be an attractive alternative; however, self-reported adherence to unsupervised home-based prehabilitation is low (≤70%) [37]. In a feasibility study by Waterland et al. [39], 82 high-risk patients (mean baseline VO_{2peak} of 14 mL/kg/min) scheduled for major abdominal surgery (64% colorectal resection) were free to choose the location of the prehabilitation intervention. The majority of the patients (61%) completed the exercise sessions at home. Adherence was low as merely ~30% of the patients had a self-reported exercise session adherence >70%. Many patients prefer home-based prehabilitation [39-42], but also report that they need some degree of supervision and pressure to stay motivated [43]. Prehabilitation in combination with tele-monitoring might have the ability to improve accessibility to prehabilitation, as patients can exercise at home in the vicinity of their caregivers while receiving non-real-time support from a healthcare professional at a different location. Therefore, tele-prehabilitation can be of additive value regarding to the preventive, personalized, and participatory aspects of the P4 Health concept.

To investigate the feasibility of tele-prehabilitation in high-risk patients with colorectal cancer who are scheduled for elective surgery, a prospective study was performed **(Chapter 8)**. A total of 11 patients (participation rate of 80%) with a low preoperative aerobic fitness participated in the tele-prehabilitation of whom all (100%) managed to complete the prehabilitation program until the date of surgery. Adherence with regard to exercise training frequency, intensity, and time was high, respectively 91%, 84%, and 100%. These high adherence rates might indicate that tele-prehabilitation has the benefits of home-based prehabilitation (i.e., no fixed appointments, autonomy, safety), but also provides sufficient pressure and supervision for patients to be able to adhere to the prehabilitation intervention. Although preliminary and based on a small sample (n=11), patients in our study showed a trend toward improvement of their aerobic fitness levels (measured by a constant work rate (cycle) test and muscle function (measured by the 30-second chair-stand test). Tele-prehabilitation enforces self-efficacy and increases autonomy, as patients are less dependent on the schedule of the healthcare provides. Involvement and support of (in)formal caregivers is easier as tele-prehabilitation is concentrated in the patient's living environment. Although our tele-prehabilitation study was designed and planned before the worldwide Coronavirus disease 2019 (COVID-19) pandemic, restrictions due to COVID-19 probably led to wider adoption of eHealth within prehabilitation by both patients and healthcare providers, as is evidenced by the number of tele-prehabilitation studies that have evolved during the pandemic [44-48]. In accordance with our experience, many patients embrace the flexibility, accessibility, and social support of tele-prehabilitation [45]. Nevertheless, our tele-prehabilitation study only contained a small study sample and results should be interpreted as preliminary. The study showed that tele-prehabilitation could be considered as a form of personalization that might increase adherence and accessibility to prehabilitation, even in high-risk patients who often have a higher age and multiple comorbidities. Nevertheless, effectiveness with regard to the ability to improve aerobic fitness and subsequently reduce postoperative complications needs to be further investigated.

Implementation of eHealth solutions such as tele-prehabilitation might potentially lead to lower use of increasingly scarce resources (e.g., healthcare personnel, equipment, resources). Whether tele-prehabilitation truly proves to be less resource-intensive and more cost-effective needs to be established in future research. In addition, to allow for wider adoption of eHealth throughout the cancer continuum (from diagnosis to recovery), feasibility and effectiveness of remote screening and functional assessment could be further explored [49]. In addition, prehabilitation exclusively focusses on the preoperative period, which is only a small part of the patient's cancer care continuum [50]. If patients are familiarized with tele-monitoring equipment in the preoperative period, only very limited resources are required to extend preventive interventions

across the care continuum into the postoperative period (i.e., from tele-**pre**habilitation to tele-**re**habilitation).

Clinical implications:

- Tele-prehabilitation has the ability to combine high levels of participation and adherence with home-based prehabilitation and could therefore complement and/or be an attractive alternative to directly supervised hospital-based or unsupervised home-based prehabilitation programs.

Research implications:

- The potential (cost-)effectiveness of tele-prehabilitation should be further explored as an alternative method that can be used to improve accessibility of prehabilitation for high-risk patients.
- Efforts should be made to explore the feasibility and short-term (i.e., postoperative complications or functional recovery) and long-term (i.e., sustained healthy lifestyle or quality of life) effectiveness of eHealth throughout the cancer care continuum.

PARTICIPATORY

The participatory aspect of prehabilitation is very much about how to motivate patients to participate and adhere to the predictive, preventive, and personalized actions [2]. Patients, supported by their informal caregivers, need to be able and willing to participate and adhere to the program. To be easily accessible, the program should be planned, structured, executed, and monitored in collaboration with the patients, their family, and informal caregivers and within, or close to his or her living environment [51]. The period between diagnosis and cancer surgery can also be used to educate and inform patients and their informal caregivers about the upcoming treatment, thereby aiming at improving their health literacy. More importantly, the "safe" timeframe of up to 49 days **(Chapters 2-3)** enables possibilities for healthcare providers to discuss the risks and benefits of the treatment with their patients, as well as to execute possible preventive actions in order to reduce the risks associated with these treatments. As mentioned before, patient expectations related to timing of surgery are open to contextualization. This means that if patients are aware of the perioperative risks and preventive actions that might reduce these risks, they might be more confident to extend the treatment interval for the benefit of prehabilitation. Risk assessment is an essential step that is needed to provide important information for the process of collaborative decision-making. From health promotion research it is known that a patient's individual risk (as perceived by

the patient) is a strong motivator for adoption of health behaviors (i.e., prehabilitation) [52]. This further addresses the important role of multidisciplinary risk assessment (e.g., aerobic fitness using the CPET **(Chapters 4-6)**, nutritional assessment, medical assessment, psychological assessment) to inform patients about the anticipated risks and to guide and personalize multimodal prehabilitation. The home-based tele-prehabilitation program **(Chapter 8)** adds to the participatory concept as it is executed in a for the patient familiar and safe environment. Patients can be easily supported by their family and/or informal caregivers, but can still be encouraged [53] and receive feedback from their healthcare professionals to stay motivated.

STRENGTHS AND LIMITATIONS

The chapters in the current thesis were constructed using the P4 Health concept and therefore contain studies regarding different steps of the prehabilitation process from diagnosis to surgery. Topics range from estimating a safe timeframe for prehabilitation, to preoperative risk assessment (*predictive*), to the prehabilitation intervention itself (*preventive*). Collaboratively, these chapters add to *personalized* and *participatory* aspects of prehabilitation, which is essential for a wider adoption of the prehabilitation concept. The studies in the current thesis consist of multiple research designs such as, a systematic review **(Chapter 2)**, retrospective observational cohort studies **(Chapter 3 and 6**), translational observational studies (**Chapters 4 and 5)**, a narrative review **(Chapter 7**) and a pre-post intervention study **(Chapter 8)** in order to address the research aims as outlined in **Chapter 1** of this thesis. Sometimes, more than one research design was used to accomplish a specific aim. That is, to establish a "safe" timeframe for prehabilitation, a systematic literature review **(Chapter 2)** was conducted which was followed by an observational retrospective cohort study **(Chapter 3)** considering the association between treatment delay and (cancer-free) survival. By doing so, the gaps in the literature that were identified in the systematic review could be used in the design and reporting of the retrospective cohort study.

Nevertheless, some limitations need to be considered when interpreting the results of the current thesis. In general, the studies in the thesis mainly focused on the physical component of preoperative risk assessment and prehabilitation. Although this was anticipated, it needs to be noted that to utilize the full potential of prehabilitation interventions, multidisciplinary risk assessment and multimodal prehabilitation are essential.

The results of the studies in **Chapter 3** and **Chapter 6** were based on retrospective data. Confounding by indication is an important type of bias that is inevitable in retrospec-

tive studies. The study in **Chapter 4** was performed by re-interpreting CPET data of preoperative CPETs of patients who underwent hepatopancreatobiliary surgery. This population differs from patients approaching colorectal surgery who were investigated in the other parts of this thesis. However, these data were retrieved preoperatively and thus not affected by the surgical procedure. Moreover, the mean values of the CPET outcomes were comparable to those of potentially high-risk patient undergoing colorectal surgery. In addition, the CPET data was only used to establish inter-observer variability of professionals interpreting preoperative CPETs. Therefore, we do not believe this is a critical limitation as the results of this study **(Chapter 4)** are generalizable to a broader population of patients who had a preoperative CPET before abdominal surgery.

The influence of data-averaging methods on CPET derived variables was estimated by re-interpretation of preoperative CPET's by two clinical exercise physiologists **(Chapter 5)**. From a methodological perspective, this method is believed to be sound to reveal differences in numerical values of CPET-derived variables caused by the data-averaging interval (the aim of the study). From a clinical perspective, one should be aware that the analysis does not include any inter-individual differences in CPET interpretation (caused by the data-averaging method) that might occur when multiple clinicians are involved (real world practice).

The tele-prehabilitation study in **Chapter 8** merely included 11 participants and did not have a control group which precluded formal assessment of its effectiveness to improve preoperative aerobic fitness and postoperative complications. However, the goals of the study were to assess feasibility rather than effectiveness. The small study sample enabled us to do more in depth analyses of adherence to the prehabilitation intervention and to investigate between-patient differences. Although we investigated preliminary effectiveness with regard to the ability to improve aerobic fitness due to the pre-post design, additional effectiveness research is needed.

WHAT'S NEXT?

The current thesis provides insight into several aspects of the *predictive, preventive, personalized,* and *participatory* health approach applied to the field of prehabilitation. Nevertheless, not all questions have been answered and some new questions have emerged. The current thesis has shown that the treatment interval can probably be safely extended to benefit preventive measures. Prospective monitoring of the association between treatment interval and cancer-free survival with and without prehabilitation is needed to ensure that extensions of the treatment interval do not lead to worse

long-term outcomes and to further explore possible subgroups of patients who benefit or do *not* benefit from extended delays. The latter subgroup consists for example of patients who either do not respond to prehabilitation by improving their aerobic fitness within due time (e.g., patients with cancer cachexia, or factors causing increased anabolic resistance), or require urgent surgical treatment.

With future challenges in healthcare concerning discrepancies between demand and supply, increasing healthcare costs [54], and a fast growing number of people with newly diagnosed cancers [55], technology might play an important role with regard to the accessibility of healthcare [54]. The before-mentioned SRT might be a less resource-dependent alternative to CPET. However, given the extent of the healthcare challenges ahead, this might not be enough. For the predictive aspect of prehabilitation, technologies like accelerometry (i.e., activity monitors or mobile phone devices) that are scalable and easy to implement in the environment of the patient might be used for functional assessment; for example to estimate a patient's aerobic fitness level [56]. In the near future, it might even be possible to estimate a patient's aerobic fitness level from (retrospective) mobile phone data [57]. An easy to collect measure as heart rate variability could be used to guide the physical exercise prescription [34]. Future observational and qualitative research could focus on such technologies to assess feasibility and determine possible associations with postoperative complications and recovery. However, even if technologies are proven to be feasible and successful, it will be difficult to fully replace the CPET with all its different roles and the CPET might have a significant role in a comprehensive evaluation of certain patients (e.g., patients with multiple comorbidities or cardiovascular disease risk factors, patients experiencing chemo-toxicity).

Another application of technology regarding the preventive aspect of prehabilitation is the introduction of tele-prehabilitation. Tele-prehabilitation is a promising intervention, as the results in the current thesis have shown that was well accepted and feasible in a small group of high-risk patients preparing for colorectal cancer surgery. Nevertheless, it needs to be established whether tele-prehabilitation proves to be less resource-intensive than current prehabilitation programs. In addition, (cost-)effectiveness of tele-prehabilitation with respect to improving aerobic fitness and reducing postoperative complications should be further investigated. Preferably, a large cohort study should be set up in which patients can choose between different types of supervised prehabilitation (i.e., hospital-based, community-based, home-based, and tele-prehabilitation). By doing so, effectiveness between interventions can be evaluated and patient preferences can be monitored. In addition, in the light of the abovementioned challenges of future healthcare, it needs to be explored if and how tele-prehabilitation can contribute to efficiently use the available, and in the future increasingly limited, resources [54].

CONCLUSION

The results of this thesis indicate that the time between diagnosis and surgical treatment (treatment interval) of colorectal cancer can be safely extended for the benefit of prehabilitation without compromising cancer-free and overall survival. Whether or not the treatment interval is extended should be decided on an individual patient level and in collaboration with the patient and his or her relatives and based on multidisciplinary preoperative risk-assessment. The preoperative CPET is a valuable tool that can be used for preoperative risk assessment. In addition, the effort-independent CPET variables VE/VCO_2-slope and OUES are promising variables that could potentially complement preoperative risk assessment, especially in patients who are unable or unwilling to exercise until volitional maximal exertion. Regarding the physical exercise components of a prehabilitation program, HIIT seems to elicit the greatest improvements in aerobic fitness within the often short timeframe available for prehabilitation. Tele-prehabilitation is well accepted and feasible in high-risk patients scheduled for colorectal surgery and could be considered as a form of prehabilitation in addition to current home-based and hospital-based prehabilitation programs.

REFERENCES

1. Flores, M., et al., *P4 medicine: how systems medicine will transform the healthcare sector and society.* Per Med, 2013. **10**(6): p. 565-576.
2. Sagner, M., et al., *The P4 Health Spectrum - A Predictive, Preventive, Personalized and Participatory Continuum for Promoting Healthspan.* Prog Cardiovasc Dis, 2017. **59**(5): p. 506-521.
3. Silver, J.K. and J. Baima, *Cancer prehabilitation: an opportunity to decrease treatment-related morbidity, increase cancer treatment options, and improve physical and psychological health outcomes.* Am J Phys Med Rehabil, 2013. **92**(8): p. 715-27.
4. Molenaar, C.J.L., D.C. Winter, and G.D. Slooter, *Contradictory guidelines for colorectal cancer treatment intervals.* Lancet Oncol, 2021. **22**(2): p. 167-168.
5. Levy, N., D.A. Selwyn, and D.N. Lobo, *Turning 'waiting lists' for elective surgery into 'preparation lists'.* Br J Anaesth, 2021. **126**(1): p. 1-5.
6. Gort, M., et al., *Actionable indicators for short and long term outcomes in rectal cancer.* Eur J Cancer, 2010. **46**(10): p. 1808-14.
7. Whittaker, T.M., et al., *Delay to elective colorectal cancer surgery and implications for survival: a systematic review and meta-analysis.* Colorectal Dis, 2021. **23**(7): p. 1699-1711.
8. Molenaar, C.J.L., et al., *Conflicting Guidelines: A Systematic Review on the Proper Interval for Colorectal Cancer Treatment.* World J Surg, 2021. **45**(7): p. 2235-2250.
9. Gillis, C., et al., *Patients' perspectives of prehabilitation as an extension of Enhanced Recovery After Surgery protocols.* Can J Surg, 2021. **64**(6): p. E578-E587.
10. Malmstrom, M., et al., *It is important that the process goes quickly, isn't it?" A qualitative multi-country study of colorectal or lung cancer patients' narratives of the timeliness of diagnosis and quality of care.* Eur J Oncol Nurs, 2018. **34**: p. 82-88.
11. Cuijpers, A.C.M., et al., *The patient perspective on the preoperative colorectal cancer care pathway and preparedness for surgery and postoperative recovery-a qualitative interview study.* J Surg Oncol, 2022. **126**(3): p. 544-554.
12. Grocott, M.P.W., et al., *Re-designing the pathway to surgery: better care and added value.* Perioper Med (Lond), 2017. **6**: p. 9.
13. Levett, D.Z.H., et al., *Perioperative cardiopulmonary exercise testing (CPET): consensus clinical guidelines on indications, organization, conduct, and physiological interpretation.* Br J Anaesth, 2018. **120**(3): p. 484-500.
14. Otto, J.M., D.Z.H. Levett, and M.P.W. Grocott, *Cardiopulmonary Exercise Testing for Preoperative Evaluation: What Does the Future Hold?* Current Anesthesiology Reports, 2020. **10**(1): p. 1-11.
15. Dumitrescu, D. and S. Rosenkranz, *Graphical Data Display for Clinical Cardiopulmonary Exercise Testing.* Ann Am Thorac Soc, 2017. **14**(Supplement_1): p. S12-S21.
16. Rose, G.A., et al., *'Fit for surgery': the relationship between cardiorespiratory fitness and postoperative outcomes.* Exp Physiol, 2022. **107**(8): p. 787-799.
17. Rose, G.A., et al., *The cardiopulmonary exercise test grey zone; optimising fitness stratification by application of critical difference.* Br J Anaesth, 2018. **120**(6): p. 1187-1194.
18. Stubbs, D.J., L.A. Grimes, and A. Ercole, *Performance of cardiopulmonary exercise testing for the prediction of post-operative complications in non cardiopulmonary surgery: A systematic review.* PLoS One, 2020. **15**(2): p. e0226480.
19. Kirchhoff, P., P.A. Clavien, and D. Hahnloser, *Complications in colorectal surgery: risk factors and preventive strategies.* Patient Saf Surg, 2010. **4**(1): p. 5.

20. Nawoor-Quinn, Z., et al., *The Marsden Morbidity Index: the derivation and validation of a simple risk index scoring system using cardiopulmonary exercise testing variables to predict morbidity in high-risk patients having major cancer surgery.* Perioper Med (Lond), 2022. **11**(1): p. 48.
21. Cuijpers, A.C.M., et al., *Relation between preoperative aerobic fitness estimated by steep ramp test performance and postoperative morbidity in colorectal cancer surgery: prospective observational study.* Br J Surg, 2022. **109**(2): p. 155-159.
22. Bongers, B.C., *Steep ramp test protocol for preoperative risk assessment and short-term high-intensity interval training to evaluate, improve, and monitor cardiorespiratory fitness in surgical oncology.* J Surg Oncol, 2023.
23. van Wijk, L., et al., *Improved preoperative aerobic fitness following a home-based bimodal prehabilitation programme in high-risk patients scheduled for liver or pancreatic resection.* Br J Surg, 2022. **109**(11): p. 1036-1039.
24. Thomas, S.G., J.M. Goodman, and J.F. Burr, *Evidence-based risk assessment and recommendations for physical activity clearance: established cardiovascular disease.* Appl Physiol Nutr Metab, 2011. **36 Suppl 1**: p. S190-213.
25. Palma, S., et al., *High-intensity interval training in the prehabilitation of cancer patients-a systematic review and meta-analysis.* Support Care Cancer, 2021. **29**(4): p. 1781-1794.
26. Smyth, E., et al., *Preoperative high intensity interval training for oncological resections: A systematic review and meta-analysis.* Surg Oncol, 2021. **38**: p. 101620.
27. Berkel, A.E.M., et al., *Effects of Community-based Exercise Prehabilitation for Patients Scheduled for Colorectal Surgery With High Risk for Postoperative Complications: Results of a Randomized Clinical Trial.* Ann Surg, 2022. **275**(2): p. e299-e306.
28. Woodfield, J.C., et al., *Short-term high-intensity interval training improves fitness before surgery: A randomized clinical trial.* Scand J Med Sci Sports, 2022. **32**(5): p. 856-865.
29. Michel, A., et al., *Short term high-intensity interval training in patients scheduled for major abdominal surgery increases aerobic fitness.* BMC Sports Sci Med Rehabil, 2022. **14**(1): p. 61.
30. Falz, R., et al., *Effects and duration of exercise-based prehabilitation in surgical therapy of colon and rectal cancer: a systematic review and meta-analysis.* J Cancer Res Clin Oncol, 2022.
31. Waterland, J.L., et al., *Efficacy of Prehabilitation Including Exercise on Postoperative Outcomes Following Abdominal Cancer Surgery: A Systematic Review and Meta-Analysis.* Front Surg, 2021. **8**: p. 628848.
32. Gustafsson, U.O., et al., *Guidelines for Perioperative Care in Elective Colorectal Surgery: Enhanced Recovery After Surgery (ERAS((R))) Society Recommendations: 2018.* World J Surg, 2019. **43**(3): p. 659-695.
33. Lobo, D.N., et al., *Prehabilitation: high-quality evidence is still required.* Br J Anaesth, 2022.
34. Manresa-Rocamora, A., et al., *Heart Rate Variability-Guided Training for Enhancing Cardiac-Vagal Modulation, Aerobic Fitness, and Endurance Performance: A Methodological Systematic Review with Meta-Analysis.* Int J Environ Res Public Health, 2021. **18**(19).
35. Guo, Y., et al., *Effects of prehabilitation on postoperative outcomes in frail cancer patients undergoing elective surgery: a systematic review and meta-analysis.* Support Care Cancer, 2022. **31**(1): p. 57.
36. Berkel, A.E.M., et al., *The effects of prehabilitation versus usual care to reduce postoperative complications in high-risk patients with colorectal cancer or dysplasia scheduled for elective colorectal resection: study protocol of a randomized controlled trial.* BMC Gastroenterol, 2018. **18**(1): p. 29.
37. Thomas, G., et al., *Prehabilitation before major intra-abdominal cancer surgery: A systematic review of randomised controlled trials.* Eur J Anaesthesiol, 2019. **36**(12): p. 933-945.

38. Woodfield, J., et al., *Protocol, and practical challenges, for a randomised controlled trial comparing the impact of high intensity interval training against standard care before major abdominal surgery: study protocol for a randomised controlled trial.* Trials, 2018. **19**(1): p. 331.
39. Waterland, J.L., et al., *Prehabilitation in high-risk patients scheduled for major abdominal cancer surgery: a feasibility study.* Perioper Med (Lond), 2022. **11**(1): p. 32.
40. Waterland, J.L., et al., *Patient acceptance of prehabilitation for major surgery: an exploratory survey.* Support Care Cancer, 2021. **29**(2): p. 779-785.
41. Ferreira, V., et al., *Maximizing patient adherence to prehabilitation: what do the patients say?* Support Care Cancer, 2018. **26**(8): p. 2717-2723.
42. Agasi-Idenburg, C.S., et al., *"I am busy surviving" - Views about physical exercise in older adults scheduled for colorectal cancer surgery.* J Geriatr Oncol, 2020. **11**(3): p. 444-450.
43. Beck, A., et al., *What matters to you? An investigation of patients' perspectives on and acceptability of prehabilitation in major cancer surgery.* Eur J Cancer Care (Engl), 2021. **30**(6): p. e13475.
44. Drummond, K., et al., *Successes and challenges of implementing teleprehabilitation for onco-surgical candidates and patients' experience: a retrospective pilot-cohort study.* Sci Rep, 2022. **12**(1): p. 6775.
45. Wu, F., et al., *The Feasibility and Effects of a Telehealth-Delivered Home-Based Prehabilitation Program for Cancer Patients during the Pandemic.* Curr Oncol, 2021. **28**(3): p. 2248-2259.
46. Waller, E., et al., *Prehabilitation with wearables versus standard of care before major abdominal cancer surgery: a randomised controlled pilot study (trial registration: NCT04047524).* Surg Endosc, 2022. **36**(2): p. 1008-1017.
47. Seery, T., et al., *Patients' experiences of virtual prehabilitation during the COVID-19 pandemic.* Patient Educ Couns, 2022. **105**(2): p. 488-489.
48. Wu, F., R. Laza-Cagigas, and T. Rampal, *Understanding Patients' Experiences and Perspectives of Tele-Prehabilitation: A Qualitative Study to Inform Service Design and Delivery.* Clin Pract, 2022. **12**(4): p. 640-652.
49. Lambert, G., et al., *Teleprehabilitation during COVID-19 pandemic: the essentials of "what" and "how".* Support Care Cancer, 2021. **29**(2): p. 551-554.
50. Silver, J.K., *Cancer prehabilitation and its role in improving health outcomes and reducing health care costs.* Semin Oncol Nurs, 2015. **31**(1): p. 13-30.
51. Bongers, B.C., I.M. Punt, and N.L. van Meeteren, *On "Prehabilitation: The emperor's new clothes or a new arena for physical therapists?" Lundberg M, Archer KR, Larsson C, Rydwik E. Phys Ther. 2018;12:127-130.* Phys Ther, 2019. **99**(7): p. 953-954.
52. Ferrer, R. and W.M. Klein, *Risk perceptions and health behavior.* Curr Opin Psychol, 2015. **5**: p. 85-89.
53. Beck, A., et al., *Investigating the experiences, thoughts, and feelings underlying and influencing prehabilitation among cancer patients: a qualitative perspective on the what, when, where, who, and why.* Disabil Rehabil, 2022. **44**(2): p. 202-209.
54. Ministerie van Volksgezondheid, W.e.S., *Integraal Zorg Akkoord, Samen werken aan gezonde zorg*. September 2022.
55. J.Praagman, et al., *kanker in Nederland trends & prognoses tot en met 2032*. 2022, Intergraal kankercentrum Nederland.
56. Plasqui, G. and K.R. Westerterp, *Accelerometry and heart rate as a measure of physical fitness: cross-validation.* Med Sci Sports Exerc, 2006. **38**(8): p. 1510-4.
57. Eades, M.T., et al., *Smartphone-recorded physical activity for estimating cardiorespiratory fitness.* Sci Rep, 2021. **11**(1): p. 14851.

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**.**

Samenvatting

Met 1,8 miljoen diagnoses per jaar, staat het colorectaal carcinoom wereldwijd op de tweede plaats van meest voorkomende vorm van kanker bij mannen, en op de derde plaats bij vrouwen. In 2019 werden in Nederland 12.907 mensen gediagnosticeerd met een colorectaal carcinoom. Als gevolg van een vergrijzende populatie in combinatie een hogere levensverwachting, is het de verwachting dat het aantal mensen met een colorectaal carcinoom in het jaar 2032 met ongeveer 11% zal zijn toegenomen ten opzichte van 2019.

Chirurgische resectie van de tumor met of zonder (neo)adjuvante chemotherapie of radiotherapie is de primaire curatieve behandeling voor mensen met een colorectaal carcinoom. Ondanks ontwikkelingen binnen de chirurgie, zoals de introductie van het 'verbeterd herstel na een operatie' (**Eng.** Enhanced Recovery After Surgery) zorgpad, blijft het aantal mensen die een of meerdere postoperatieve complicaties krijgen na een chirurgische ingreep voor een colorectaal carcinoom hoog. Ongeveer 1 op de 3 patiënten in Nederland krijgt te maken met een postoperatieve complicatie na een operatie voor een colorectaal carcinoom. Postoperatieve complicaties hebben een grote invloed op het postoperatief herstel, (kankervrije) overleving, kwaliteit van leven en het lange-termijn functioneren van patiënten.

In plaats van een *reactief* zorgpad, waarin patiënten na de diagnose colorectaal carcinoom een afwachtende houding aannemen in de preoperatieve periode, is het wellicht beter om de patiënt *proactief* voor te bereiden op de grote operatie die gaat volgen. Een dergelijke *proactieve* aanpak heeft als doel om de incidentie en/of impact van postoperatieve complicaties te reduceren en het herstel te bevorderen door preoperatief modificeerbare risicofactoren voor nadelige postoperatieve uitkomsten te reduceren. Een modificeerbare risicofactor die consistent geassocieerd wordt met het risico op postoperatieve complicaties, vertraagd herstel of overlijden, is de preoperatieve aerobe fitheid van een patiënt. De rationale achter deze associatie is dat aerobe fitheid gezien kan worden als een proxy voor de fysiologische reservecapaciteit van een patiënt. Deze fysiologische reservecapaciteit is nodig om de stressrespons, veroorzaakt door de chirurgische procedure en anesthesie, te weerstaan. Patiënten met een lage aerobe fitheid, en dus een lage fysiologische reservecapaciteit, hebben een hoger risico op slechte postoperatieve uitkomsten.

Prevalidatie omvat het screenen en beoordelen van (modificeerbare) risicofactoren en het optimaliseren van de gezondheid door middel van gepersonaliseerde interventies in de tijdsperiode tussen de diagnose van kanker en de start van de behandeling. Op het gebied van de haalbaarheid en effectiviteit van een prevalidatieprogramma waren de volgende belangrijke vragen nog onbeantwoord, namelijk: 1) Is er voldoende tijd be-

schikbaar tussen de kankerdiagnose en de chirurgische behandeling voor het uitvoeren van een prevalidatie-programma? 2) Hoe kan er adequaat gescreend en getest worden op (modificeerbare) preoperatieve risicofactoren? 3) Welke fysieke trainingsmodaliteit is het meest effectief voor het verbeteren van de preoperatieve aerobe fitheid op korte termijn? 4) Is het haalbaar om tele-prevalidatie uit te voeren bij hoog-risico patiënten in voorbereiding op hun operatie voor colorectaal carcinoom?

De achtergrond en doelen van het huidige proefschrift zijn uitgezet in **Hoofstuk 1** aan de hand van het "*predictief, preventief, gepersonaliseerd* en *participatief* gezondheids-concept" (**Eng.** *predictive, preventive, personalized and participatory health,* ofwel P4 Health-concept). Doelen van dit proefschrift zijn: 1) op zoek te gaan naar een "veilige" tijdsspanne tussen diagnose en operatie (behandelinterval) waarin een prevalidatie-programma kan plaatsvinden, 2) het verbeteren van de (uniformiteit van de) preoperatieve risico-inschatting (*predictief),* 3) het evalueren van de effectiviteit van kortdurende fysieke trainingsinterventies (matig-intensieve training en hoog-intensieve interval training) die gebruikt kunnen worden binnen een prevalidatieprogramma (*preventief*), en 4) om te exploreren wat de haalbaarheid is van tele-prevalidatie als een nieuwe vorm van prevalidatie (*preventief, gepersonaliseerd en participatief*).

In **hoofstuk 2 en 3** werd onderzocht hoe lang de tijdsspanne is die "veilig" gebruikt kan worden voor de prevalidatie van patiënten met een colorectaal carcinoom. Het implementeren van een prevalidatieprogramma binnen de zorg voor patiënten met kanker is lastig vanwege restricties in de tijd tussen diagnose en start van de behandeling die zijn vastgelegd in behandelrichtlijnen (maximaal 35 dagen). De grootste zorg met betrekking tot het verlengen van het behandelinterval (de tijd tussen diagnose en de chirurgische ingreep) is het doorgroeien van de tumor en een verhoogd risico op metastases met als gevolg vroegtijdig terugkeren van de tumor en/of vroegtijdig overlijden. Een belangrijke vraag is dus: is een langer behandelinterval geassocieerd met een verminderde kankervrije of algehele overleving van patiënten met colorectaal carcinoom?

Om deze vraag te beantwoorden werd een systematische review van de literatuur uitgevoerd met betrekking tot de associatie tussen het behandelinterval en de (kankervrije) overleving bij patiënten met een colorectaal carcinoom die een chirurgische ingreep moesten ondergaan (**Hoofdstuk 2**). De geïncludeerde studies waren heterogeen met betrekking tot de definitie van het behandelinterval, de gebruikte indeling van behandelintervallen en de gebruikte uitkomstmaten. Enerzijds kon op basis van de systematische review geen optimaal behandelinterval aanbevolen worden. Anderzijds werd er echter ook weinig bewijs gevonden ter onderbouwing van de tijdsrestricties

die gehanteerd worden in de huidige behandelrichtlijnen. Een meer gepersonaliseerde aanpak met betrekking tot de lengte van het behandelinterval is daarom waarschijnlijk meer op zijn plaats. De winst-risicoverhouding van een kort versus lang behandelinterval in combinatie met prevalidatie verschilt mogelijk afhankelijk van de te verwachten perioperatieve risico's.

In **Hoofstuk 3** werd de "veilige" tijdsspanne die gebruikt kan worden voor prevalidatie verder uitgediept in een retrospectieve multicenterstudie, waarin de associatie tussen de lengte van het behandelinterval en (kankervrije) overleving werd onderzocht. In totaal werden 3.376 patiënten met een coloncarcinoom die in afwachting waren van een chirurgische ingreep geïncludeerd. Deze studie liet zien dat een behandelinterval tot 49 dagen (7 weken) niet geassocieerd is met een kortere kankervrije of algehele overleving. Het krijgen van een postoperatieve complicatie was wél geassocieerd met een kortere algehele overleving, hetgeen zou kunnen betekenen dat initiatieven die ten doel hebben om (de impact van) postoperatieve complicaties te verminderen mogelijk belangrijker zijn dan een zo kort mogelijk behandelinterval. De "veilige" tijdsspanne van 49 dagen maakt het mogelijk om met name hoog-risico patiënten beter voor te bereiden op de aankomende impact van de chirurgische ingreep om zo de postoperatieve uitkomsten te verbeteren.

Adequate preoperatieve screening en het maken van een multidisciplinaire risico-inschatting zijn belangrijke *predictieve* stappen binnen een prevalidatie-zorgpad, aangezien verwacht wordt dat hoog-risico patiënten het meest profiteren van prevalidatie. Een cardiopulmonale inspanningstest (CPET) is een veelzijdige test die gebruikt kan worden als onderdeel van een multidisciplinaire preoperatieve risico-inschatting. In **Hoofstuk 4** werd de interbeoordelaarsbetrouwbaarheid van de risicobeoordeling op basis van CPET-variabelen bij Nederlandse sportartsen en inspanningsfysiologen onderzocht. Geconcludeerd werd dat de interbeoordelaarsbetrouwbaarheid van CPET-variabelen die gebruikt worden voor het maken van risicobeoordeling acceptabel is (intra-klasse correlatiecoëfficiënt ≥ 0.76). De resultaten lieten ook zien dat de interbeoordelaarsbetrouwbaarheid van de bepaling van CPET-variabelen hoger was (intra-klasse correlatiecoëfficiënt ≥ 0.88) als clinici gebruik maken van een richtlijn voor de bepaling van variabelen voor een risico-inschatting. Daarnaast zijn inspannings-onafhankelijke CPET-variabelen mogelijk relevante variabelen om verder te onderzoeken op bruikbaarheid voor het maken van een preoperatieve risico-inschatting. De resultaten van **Hoofstuk 4** toonden namelijk ook aan dat de interbeoordelaarsbetrouwbaarheid van twee inspannings-onafhankelijke variabelen, namelijk de richtingscoëfficiënt van de relatie tussen het ademminuutvolume en koolstofdioxideproductie (VE/VCO_2-slope)

en de zuurstofopname efficiëntie helling (**Eng.** oxygen uptake efficiency slope (OUES)), uitmuntend waren.

Tijdens een CPET spant een patiënt zich in tegen een steeds groter wordende weerstand, terwijl ademgassen per ademteug worden verzameld. Om de interpretatie van de ruwe ademteug-data te vergemakkelijken, worden de data gemiddeld over een bepaalde tijdsperiode of een aantal ademteugen (ook wel een datamiddeling-interval genoemd). In **Hoofstuk 5** werd onderzocht of verschillen in het CPET-datamiddeling-interval van invloed zijn op de numerieke waarden van CPET-afgeleide variabelen die gebruikt worden voor het maken van een preoperatieve risico-inschatting. Op basis van de resultaten van deze studie kan geconcludeerd worden dat er geen bewijs is dat het gekozen datamiddeling-interval in belangrijke mate invloed heeft op de *gemiddelde* numerieke waarde van CPET-afgeleide variabelen die gebruikt worden voor het maken van een preoperatieve risico inschatting. Deze resultaten waren geruststellend, aangezien het de zorgprofessional in staat stelt een datamiddeling-interval te kiezen dat het beste past bij de te beoordelen test (bijvoorbeeld afhankelijk van de duur van de test of de te verwachte pathologie).

De twee meest gebruikte preoperatieve CPET-variabelen die gebruikt worden voor het maken van een preoperatieve risicobeoordeling zijn de zuurstofopname op maximale inspanning (VO_{2piek}) of op de ventilatoire anaerobe drempel (VO_{2VAD}). Nadelen van deze variabelen zijn dat voor het verkrijgen van een VO_{2piek} een maximale inspanning vereist is die niet haalbaar is voor alle patiënten en de VO_{2VAD} niet bij alle patiënten eenduidig te bepalen is. In **Hoofstuk 6** wordt een studie beschreven over twee inspanningsonafhankelijke CPET-variabelen die nog maar weinig onderzocht zijn in relatie tot het maken van een preoperatieve risico-inschatting, namelijk de VE/VCO_2-slope en de OUES. Voordelen van de VE/VCO_2-slope en de OUES zijn dat er geen maximale inspanning nodig is om ze te kunnen bepalen en dat ze objectief te bepalen zijn bij alle patiënten. Het doel van de studie was om de associatie van de preoperatieve VE/VCO_2-slope en de OUES met postoperatieve complicaties te onderzoeken in patiënten die colorectale chirurgie moesten ondergaan in vier ziekenhuizen in Nederland. Uit een multivariate logistische regressieanalyse bleek dat de VE/VCO_2-slope en de OUES statistisch significant geassocieerd waren met postoperatieve complicaties. Echter, deze associatie was niet sterk genoeg voor het bepalen van accurate klinische afkapwaarden met een van tevoren vastgestelde sensitiviteit >80% en specificiteit van >50%. De VE/VCO_2-slope en de OUES zouden van toegevoegde waarde kunnen zijn indien de VO_{2piek} of de VO_{2VAD} niet te bepalen zijn. Echter, er is meer onderzoek nodig om specifieke afkappunten te bepalen voor deze inspanning-onafhankelijke variabelen, zowel onafhankelijk als ook in

combinatie met andere (CPET-) variabelen die gebruikt worden voor het maken van een preoperatieve risico-inschatting.

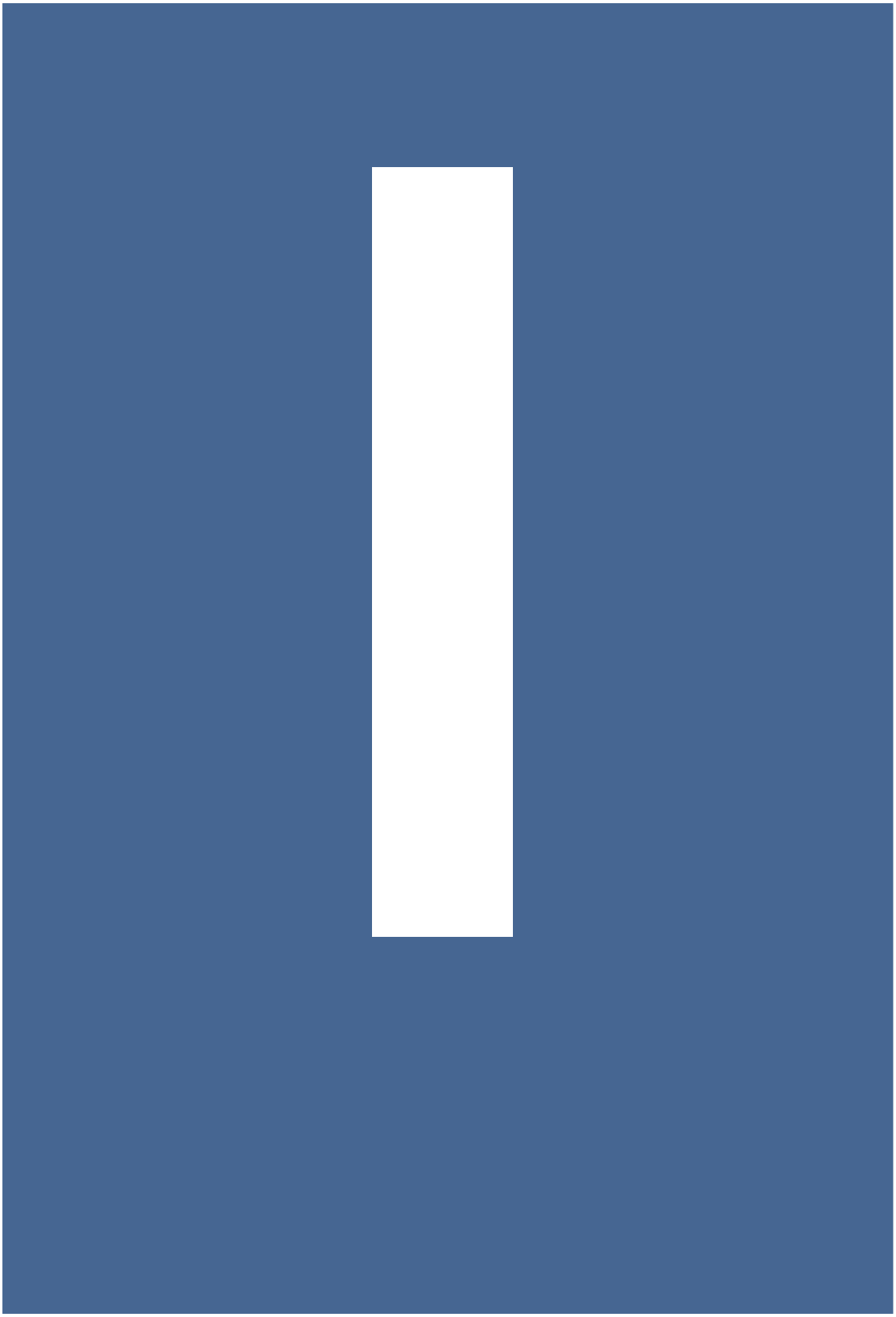
Als vervolg op de identificatie van preoperatieve (modificeerbare) risicofactoren door middel van risico-inschatting, kan een gepersonaliseerd prevalidatieprogramma opgesteld worden met als doel deze risico's te verlagen. Fysieke training is de hoeksteen van een prevalidatieprogramma. Het is echter onduidelijk welke fysieke trainingsmodaliteit het meest effectief is om de aerobe fitheid te verbeteren in de korte tijd die beschikbaar is voor prevalidatie. **Hoofdstuk 7** is een gedetailleerde beoordeling van fysieke trainingsinterventies die ten doel hebben de aerobe fitheid te verbeteren binnen de korte tijdspanne (< 6 weken) die beschikbaar is voor prevalidatie binnen de oncologische chirurgie. In het bijzonder is er gekeken naar de mogelijkheid van matig-intensieve training en hoog-intensieve intervaltraining (HIIT) voor het verbeteren van de aerobe fitheid, gemeten door middel van een CPET. De studie bracht verschillende tekortkomingen van de huidige literatuur aan het licht, zoals het inadequaat rapporteren van het fysieke trainingsprogramma volgens de frequentie, intensiteit, tijd, type, volume en progressie (FITT-VP) principes. Dit maakt het lastig om fysieke trainingsprogramma's te vertalen naar de klinische praktijk. De resultaten van de studie toonden aan dat, op groepsniveau, kortdurende HIIT-trainingsprogramma's de grootste korte termijn verbeteringen in aerobe fitness lieten zien. Er zou echter meer aandacht moeten zijn voor de individuele respons van een patiënt op een fysiek trainingsprogramma. Dit is mogelijk door het fysieke training programma te personaliseren, accuraat te rapporteren over de uitgevoerde fysieke training, progressie van de training te monitoren, de training aan te passen op basis van deze progressie, en door zorg te dragen voor een hoge therapietrouw.

In **Hoofstuk 8** werd de haalbaarheid van een nieuwe vorm van gepersonaliseerde prevalidatie, tele-prevalidatie, onderzocht. Met name voor patiënten die een hoog risico hebben op postoperatieve complicaties, vaak oudere patiënten met comorditeit, is deelname aan de huidige prevalidatieprogramma's die in het ziekenhuis uitgevoerd worden een uitdaging, onder andere door vervoersproblemen en kosten. Enerzijds geven veel patiënten aan een voorkeur te hebben voor prevalidatie in de thuisomgeving; anderzijds zijn er ook aanwijzingen dat de therapietrouw laag is (< 70%) als prevalidatie zonder supervisie in de thuisomgeving plaatsvindt. Thuisprevalidatie in combinatie met tele-monitoring kan mogelijk de voordelen van ziekenhuisprevalidatie (bijvoorbeeld hoge therapietrouw en supervisie) combineren met de voordelen van thuisprevalidatie (bijvoorbeeld voorkeur van de patiënt, geen problemen met vervoer, meer autonomie). In de tele-prevalidatie studie werden 11 deelnemers (deelnamepercentage van 81%) geïncludeerd. Alle deelnemers slaagden erin om het tele-prevalidatieprogramma te

voltooien. Therapietrouw met betrekking tot de frequentie, intensiteit en tijd van het fysieke trainingsprogramma was goed (respectievelijk 91%, 84% en 100%). De waardering voor tele-prevalidatie bij patiënten was ook goed. Tele-prevalidatie lijkt dus haalbaar in hoog-risico patiënten die in voorbereiding zijn op hun operatie voor een colorectaal carcinoom. Er is echter meer onderzoek nodig om de (kosten)effectiviteit met betrekking tot het verbeteren van de fysieke fitheid en postoperatieve uitkomsten bij tele-prevalidatie vast te stellen.

Hoofdstuk 9 bediscussieert de belangrijkste bevindingen en limitaties van de studies in dit proefschrift in de context van het *predictief, preventief, gepersonaliseerd* en *participatief* gezondheidsconcept.

Concluderend laten de resultaten uit dit proefschrift zien dat het behandelinterval bij hoog-risicopatiënten 'veilig' verlengd lijkt te kunnen worden om het risico op postoperatieve complicaties te verminderen middels prevalidatie. Dit verlengde behandelinterval kan gebruikt worden voor het screenen en testen van patiënten op preoperatief modificeerbare risicofactoren (*predictief*) en samen beslissen (*participatief*) over de medische behandeling, evenals voor het inzetten van interventies om preoperatieve risicofactoren te optimaliseren door middel van een *gepersonaliseerd* en *participatief* prevalidatieprogramma (*preventief*). Verder laten de resultaten zien dat de predictieve waarde van de CPET verbeterd kan worden door het optimaliseren van de uniformiteit van de beoordeling door het gebruik van een richtlijn voor CPET-interpretatie en door het gebruik van inspannings-onafhankelijke variabelen voor preoperatieve risico-inschatting. Er is echter aanvullend onderzoek nodig om klinisch relevante afkappunten voor deze inspannings-onafhankelijke variabelen vast te stellen. Tot slot lijkt tele-prevalidatie haalbaar bij hoog-risicopatiënten die zich voorbereiden op een chirurgische ingreep, en kan het bijdragen aan een meer *gepersonaliseerde* en *participatieve* vorm van prevalidatie.



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In the Netherlands, the population is greying (1). This coincides with an increasing number of people with one or more illnesses (2). As a result, the demand for healthcare is increasing at a faster rate than the healthcare sector can provide (3). In September 2022, a collaboration between affiliates of Dutch governmental organizations, medical societies, patient platforms, and healthcare insurance companies led to the publication of the Integral Health Agreement (Dutch, Integraal Zorgakkoord, IZA). The IZA highlights the need for a transition in healthcare that is needed to allow for future high-quality healthcare that is accessible and affordable for everyone (3). Future healthcare should be effective, resource efficient, and personalized, that is: in collaboration with the patient, organized around the patient, and with a focus on health instead of illness (3). Preventive actions, not only for primary prevention of diseases but also secondary prevention (e.g., colorectal cancer screening) and tertiary prevention strategies (e.g., prehabilitation) form important pillars within the IZA (3). Prehabilitation in cancer care refers to targeted preventive interventions to improve a patient's health between the time of cancer diagnosis and the start of treatment (e.g., surgery), in order to reduce the incidence, severity, and impact of (postoperative) complications and to accelerate and improve recovery (4). Sufficient time between diagnosis and surgery, adequate risk assessment to identify patients that could potentially benefit from prehabilitation (i.e., high-risk patients), and a patient-centered approach with regard to the content and context of prehabilitation are essential elements of personalized healthcare. Therefore, the aim of this thesis was to contribute to the accessibility and personalization of preoperative care in patients with colorectal cancer by exploring a safe timeframe for prehabilitation, by improving preoperative risk assessment using the cardiopulmonary exercise test (CPET), and by exploring whether prehabilitation can be personalized and organized around the patient by using eHealth. As such, this thesis also aligns with the IZA.

SCIENTIFIC RELEVANCE

This thesis provides evidence that, at the group level, treatment intervals up to and over 49 days (7 weeks after diagnosis) do not lead to reduced cancer-free survival **(Chapters 2 and 3)**. This safe timeframe of 7 weeks provides a window of opportunities for predictive actions (e.g., preoperative risk assessment) and preventive interventions (e.g., multimodal prehabilitation) based on collaborative decision-making. The established safe timeframe for prehabilitation should lead to a discussion about the strict wait time targets that are currently part of performance indicators of a hospital (5). Previous research has shown that prehabilitation can reduce postoperative complications by ~50% in high-risk patients (6). Therefore, especially in high-risk patients, and when medically deemed safe, priority could be given to optimization of modifiable risk factors by pre-

habilitation instead of applying as short as possible treatment intervals. The latter was already adopted in the "Position statement prehabilitation in patients with colorectal cancer undergoing surgery" of the Dutch Society of Surgery (7).

Regarding preoperative risk assessment to assess aerobic fitness by means of a CPET, several methodological issues were addressed in this thesis. Uniformity of risk assessment can be improved by using a set of guidelines for CPET interpretation and by using effort-independent CPET-derived variables such as the slope of the relationship between the minute ventilation and carbon dioxide production (VE/VCO_2-slope) and the oxygen uptake efficiency slope (OUES). The methodological recommendations regarding preoperative CPET interpretation given in **chapters 4 and 5** improve uniformity of risk assessment for aerobic fitness and should be adopted within future preoperative CPET guidelines and education. Uniformity of preoperative risk assessment is important, as the risk assessment procedure and the associated preventive interventions should not rely on the physician that is assessing the patient or the hospital where the assessment takes place. The findings that the effort-independent CPET variables VE/VCO_2-slope and OUES are associated to postoperative complications in patients approaching major elective colorectal surgery are novel. More research is needed to elucidate clinically relevant cut-off points of these variables alone or in combination with other (CPET) risk assessment variables. The introduced effort-independent CPET variables in the current thesis could mainly be of great benefit for patients who are unwilling or unable to perform a volitional maximal effort.

The recommendations given in **chapter 7** regarding adequate patient selection, personalized physical exercise training prescription, full reporting of physical exercise training adherence, and formal monitoring of training progression and recovery can be used for development of better physical exercise interventions within a prehabilitation program and to better reporting of the performed exercise. These factors will, if adopted well, lead to a lower risk of ineffectiveness of physical exercise interventions and better translation of physical exercise interventions into clinical practice.

Lastly, we showed that tele-prehabilitation might be an alternative (or complementary) to current hospital-based and community-based prehabilitation programs, as it was feasible and well-appreciated by high-risk patients undergoing colorectal cancer surgery. The evidence presented in this thesis about the feasibility of tele-prehabilitation in high-risk patients **(chapter 8)** contributes to personalization and accessibility of healthcare. Tele-prehabilitation might provide a bridge between the advantages of unsupervised exercise (e.g., no scheduled appointments, exercising at preferred time point) and supervised prehabilitation (e.g., high adherence, direct monitoring and supervision). In

addition, there are no geographical barriers and transportation issues, and expenses are reduced. Accelerated by the worldwide Corona virus pandemic, tele-prehabilitation (in oncology) has gained increasing interested as evidenced by the number of recently published and ongoing studies (8-12).

Research in this thesis has been shared in different (inter)national peer-reviewed journals. In addition, dissemination of the research took place during the annual scientific meetings of the VieCuri Medical Center, via various (inter)national conferences (e.g., the national prehabilitation congress 2022, World Congress of Prehabilitation Medicine 2023) and during meetings of the "Perioperative health" community of practice. The latter is a collaboration of scientific and clinical representatives of 14 hospitals in the Netherlands with the aim of improving perioperative care in the Netherlands.

SOCIETAL IMPACT

Although evidence is emerging and the fact that the concept fits well with the IZA goals, prehabilitation in colorectal cancer is still not collectively reimbursed by Dutch healthcare insurance companies. Recently, the Dutch Society of Surgery advised that, given the current evidence-base, prehabilitation should be implemented as best practice while simultaneously being evaluated regarding its real-world effectiveness (7). Especially in high-risk patients, the cost-benefit ratio of prehabilitation is expected to be high. Literature has shown that an estimated reduction of ~25% in complications would lead to a reduction of 2,253 Euro on in-hospital costs per patient. Given that the costs of supervised multimodal prehabilitation are estimated at 1,010 Euro per patient, this would lead to a 1,241 Euro cost saving per patient (13). A randomized controlled trial by Berkel et al. showed that the incidence of postoperative complications can even be reduced by as much as ~50% by prehabilitation in high-risk patients approaching colorectal surgery (6), which in turn would lead to even higher cost-reductions when focusing on these vulnerable patients. The latter underpins the importance of uniform and adequate risk assessment for future accessibility of future health care, as it provides tools to direct limited resources to patients who need it the most. Tele-prehabilitation has the potential to further reduce the costs of prehabilitation as potentially less hospital resources are required (e.g., facilities, personnel). The latter might also be beneficial with regard to the current and expected shortages in healthcare personnel and accessibility of healthcare (3). Nevertheless, ongoing research is needed to establish whether or not these assumptions prove to be true.

TO WHOM IS THIS THESIS RELEVANT?

The outcomes of this thesis are relevant for all patients approaching colorectal surgery, their relatives and informal caregivers, and involved healthcare professionals. The safe timeframe opens possibilities for patients and their informal caregivers to discuss anticipated risks and possibilities regarding optimal preparation for surgery with their physician or other involved healthcare professionals. To be able to make a well-balanced and collaborative decision, the patient and his or her informal caregivers, as well as the healthcare professionals, need to be aware of the risks involved, highlighting the need for adequate and uniform preoperative risk assessment. Although more research is needed regarding tele-prehabilitation, it has the potential to provide high-quality prehabilitation at the time and place that is preferred by the patient. One of the principles of the IZA is that future personalized healthcare is provided via eHealth if possible, and on-site if needed (3). Tele-prehabilitation in addition to home-based and community-based prehabilitation is a perfect example of how prehabilitation in the patient's living environment can be further adapted based on the needs and preferences of the patient and his or her (in)formal caregivers.

CONCLUSION

The results of the studies in this thesis should lead to a discussion about strict diagnosis-to-treatment time limitations enforced by current colorectal cancer treatment guidelines, and about ways to personalize the treatment interval based on the needs and preferences of individual patients. In addition, our recommendations with regard to preoperative CPET can lead to better and uniform risk assessment and they can also be embedded within future perioperative guidelines and education. Finally, the shift from hospital-based prehabilitation to community-based and home-based prehabilitation complemented with tele-prehabilitation will preferably lead to greater personalization and accessibility of prehabilitation, and contribute to lower costs as well as lower resource utilization in perioperative healthcare. Combined, it is believed that all these aspects have an impact on the predictive, preventive, personalized, and participatory value of prehabilitation in patients with colorectal cancer, as well as the principles outlined in the IZA. That is: future healthcare that is effective, resource efficient, personalized in collaboration with the patient, organized around the patient, and with a focus on health instead of illness.

REFERENCES

1. Statistiek CBvd. Bevolking; kerncijfers 2022 [28-09-2022]. Available from: https://www.cbs.nl/nl-nl/cijfers/detail/37296ned?dl=5B728.
2. Maatschappij CGe. Chronische aandoeningen en multimorbiditeit 2022 [28-09-2022]. Available from: https://www.vzinfo.nl/chronische-aandoeninginen-en-multimorbiditeit.
3. Ministerie van Volksgezondheid WeS. Integraal Zorg Akkoord, Samen werken aan gezonde zorg. September 2022.
4. Silver JK, Baima J. Cancer prehabilitation: an opportunity to decrease treatment-related morbidity, increase cancer treatment options, and improve physical and psychological health outcomes. Am J Phys Med Rehabil. 2013;92(8):715-27.
5. de Geus AJ, Ross-van Dorp CIJM. Wachttijden in de curatieve zorg 2003 [28-09-2022]. Available from: https://zoek.officielebekendmakingen.nl/kst-25170-31.html.
6. Berkel AEM, Bongers BC, Kotte H, Weltevreden P, de Jongh FHC, Eijsvogel MMM, et al. Effects of Community-based Exercise Prehabilitation for Patients Scheduled for Colorectal Surgery With High Risk for Postoperative Complications: Results of a Randomized Clinical Trial. Ann Surg. 2022;275(2):e299-e306.
7. Heelkunde NVv. Standpunt Prehabilitatie, Voorbereiding van patiënten met colorectaal carcinoom op de operatie. 2022(Conceptversie: 17-06-2022).
8. Drummond K, Lambert G, Tahasildar B, Carli F. Successes and challenges of implementing teleprehabilitation for onco-surgical candidates and patients' experience: a retrospective pilot-cohort study. Sci Rep. 2022;12(1):6775.
9. Lorca LA, Ribeiro IL, Pizarro M, Martinez M, Vivallos J. Functional results and feasibility of a teleprehabilitation program in patients who are candidates for elective colorectal cancer surgery during the COVID-19 pandemic. Asia Pac J Clin Oncol. 2023.
10. Piraux E, Caty G, Reychler G, Forget P, Deswysen Y. Feasibility and Preliminary Effectiveness of a Tele-Prehabilitation Program in Esophagogastric Cancer Patients. J Clin Med. 2020;9(7).
11. Wu F, Laza-Cagigas R, Rampal T. Understanding Patients' Experiences and Perspectives of Tele-Prehabilitation: A Qualitative Study to Inform Service Design and Delivery. Clin Pract. 2022;12(4):640-52.
12. Lambert G, Drummond K, Tahasildar B, Carli F. Virtual Prehabilitation in Patients With Cancer Undergoing Surgery During the COVID-19 Pandemic: Protocol for a Prospective Feasibility Study. JMIR Res Protoc. 2022;11(5):e29936.
13. Davis JF, van Rooijen SJ, Grimmett C, West MA, Campbell AM, Awasthi R, et al. From Theory to Practice: An International Approach to Establishing Prehabilitation Programmes. Curr Anesthesiol Rep. 2022;12(1):129-37.

Curriculum vitae

Ruud Fransicus Wilhelmina Franssen was born on August 9, 1984. After graduating from high school in 2000 (MAVO, Bouwens van de Boije College, Panningen) and completing the MTS at ROC ter AA in Helmond in 2004, he went on to study physiotherapy at Fontys University of Applied Sciences in Eindhoven. After graduating In 2008, he began working as a physiotherapist at Maxima Medical Center in Veldhoven, and in 2010 he started working at VieCuri Medical Center in Venlo.

Having a sincere interest in scientific research and exercise physiology, he decided to enroll in the part-time Master of Human Movement Sciences program at Maastricht University in 2014. He successfully completed the program in 2016.

In 2019, Ruud commenced his PhD research at VieCuri Medical Center in collaboration with Maastricht University (GROW, the school for oncology and reproduction). He conducted his research activities at VieCuri Medical Center in Venlo while simultaneously working as a physiotherapist and clinical exercise physiologist.

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