

# Time to prepare

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**Impact paragraph**



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 interest 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.

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