CHAPTER 1

General introduction and thesis outline
INTRODUCTION

Doctors take the Hippocratic Oath. In the Dutch version of the Hippocratic Oath, they swear (promise) to practise the art of medicine as well as they can for the benefit of their fellow humans. Furthermore, doctors swears to promote health and to broaden their medical knowledge and acknowledge the boundaries of their possibilities. However, as new insights regarding doctors’ capabilities are constantly emerging, people’s perceptions of the phrases ‘as well as I can’ and ‘the boundaries of my possibilities’ in the Hippocratic Oath are evolving. For instance, in recent years, much research has been conducted into doctors’ ability to improve perioperative care, with current interest in more thoroughly preparing the patient preoperatively, so-called ‘prehabilitation’. Previous studies indicated that patients who are fitter preoperatively have better postoperative outcomes. Moreover, doctors’ task of promoting health often fades into the background when a patient presents with an illness. Prehabilitation can help to promote healthy behaviours in the long term, not just during the perioperative period. Would doctors not then be obligated to prepare patients for surgery as best they can? If yes, then what would be the best approach for prehabilitating patients? This thesis broadens the medical knowledge regarding possible improvements in perioperative care as well as explores and possibly extends the boundaries of doctors’ capabilities.

As the ageing population grows, the incidence of abdominal malignancies will also rise. Surgery is an important treatment modality for such malignancies, but it can be a challenge to patients’ homeostasis. Age- and disease-related psychophysiological changes and comorbidities negatively affect tolerance to surgery in older patients. Older patients, especially physical frail ones, are therefore more prone to complications. They require a specific preoperative risk stratification, and subsequently high-risk patients should be optimised.

Postoperative complications can be divided into surgical and nonsurgical, with the latter representing three-quarters of all postoperative complications. About 30% of nonsurgical complications are cardiopulmonary complications in elective major abdominal surgery. Cardiopulmonary complications lead to significantly increased morbidity, mortality, and length of hospital stay. In addition, hospital costs grow exponentially for patients with a complicated course. In recent years, attempts have been made to reduce postoperative complications with improvements in hospital structures and processes, including introduction of enhanced recovery programmes, and, within these programmes, the use of minimally invasive surgery, centralisation of care, and clinical auditing. Despite these improvements in perioperative care, the number of patients with complicated perioperative courses remains stable each
year, with 20 to 30% having severe complications after major abdominal surgery.\textsuperscript{15} In contrast, there is still room for improvement in reducing the perioperative risk by optimising the patient’s condition prior to surgery. The optimisation of the patient’s overall condition to strengthen their resilience against the stress of surgery is known as prehabilitation. Although prehabilitation can reduce the recurring high complication rates,\textsuperscript{2,4} it is not part of standard care. The reasons that prehabilitation is not embedded in the standard preoperative care path might be the varying results of prehabilitation programmes. Less significant improvements after prehabilitation programmes may be caused by both low attrition- and adherence rates. In addition, to improve physical fitness in a short period, high-intensity interval training seems to be most effective,\textsuperscript{16} and yet most studies have focused on moderate-intensity training. Another reason why prehabilitation is not embedded in the standard preoperative care path might be a lack of evidence for the (potential) financial benefits of prehabilitation programmes. This thesis addresses all of these obstacles. The implementation of multimodal prehabilitation programmes as standard care may be the final revolution in perioperative care that contribute to improved clinical outcome.

Part I - prehabilitation

Surgery is a major life event, and surgical stress may accelerate functional decline and reduce adaptive capacity. Prehabilitation may increase patients’ ability to cope with the stress of surgery by improving the capacity and functioning of the respiratory, cardiovascular, and/or musculoskeletal systems and thereby lowering the risk of postoperative morbidity and mortality. Several studies have shown a significant positive effect of prehabilitation on the postoperative outcome following abdominal surgery.\textsuperscript{2-5, 11, 17-19}

Multimodal approach

Initially, prehabilitation targeted only physical activity,\textsuperscript{4} but over time it has been transformed into a multimodal approach to prepare surgical candidates on multiple levels. As well as optimising preoperative physical exercise,\textsuperscript{6,11,20,21} positive effects on postoperative outcomes can be achieved by reducing preoperative malnutrition,\textsuperscript{22,23} anaemia,\textsuperscript{24-27} smoking,\textsuperscript{28} and alcohol abuse\textsuperscript{29}, and optimising both frailty\textsuperscript{30,31} and psychological resilience.\textsuperscript{32, 33}
Physical condition
The percentage of patients scheduled for major abdominal surgery who are unfit is around 30%. Despite this knowledge, some patients still enter surgery in an unfit state. The reasons for this situation may be that preoperative fitness is not objectively measured or that a training programme is not standardly provided or reimbursed. Patients who are unfit are particularly reluctant to train due to cost and transportation problems. Moreover, even if a training programme is offered free of charge, compliance is not yet optimal. Ferreira et al. have found that patients’ preferred exercise programmes are home-based and (semi-) supervised. The feasibility and effectiveness of a home-based (semi-) supervised exercise training programme for patients awaiting a liver or pancreatic resection are discussed later in this thesis.

Malnutrition
Nearly half of patients admitted to hospital are malnourished or at risk of malnutrition. Furthermore, a total of 80% of patients with pancreatic head cancer present with weight loss at diagnosis. Malnutrition leads to more perioperative complications. Patients at risk of malnutrition should be referred to a dietician to improve the perioperative outcome.

Iron-deficiency anaemia
Preoperative anaemia is a common problem amongst surgical patients. About 40% of patients who undergo major surgery have anaemia, mostly iron-deficiency anemia. Evidence suggests that preoperative anaemia is associated with higher rates of postoperative morbidity. This situation can be improved preoperatively with iron infusion. In a previous study of patients undergoing abdominal surgery, iron infusion was found to result in fewer blood transfusions and shorter hospitalisation times. However, literature supporting the effect of preoperative treatment of anaemia in reducing perioperative morbidity and mortality is limited.

Frailty
Frailty of patients leads to a higher risk of complications and a poorer quality of life after surgery. Around 37% of the patients in general surgery is frail. Frail elderly patients should be referred to the geriatrician to undergo a comprehensive geriatric assessment. In the assessment, deterioration in functioning in the broadest sense can be examined and adjustments made where possible. For example, medication for chronic illnesses can be adjusted and attention paid to delirium prevention and the social safety net. A structured geriatric assessment allows the care plan for frail patients to be optimised and morbidity to be better mitigated.
Smoking and alcohol consumption
Smoking increases the risk of cardiovascular, pulmonary, and wound complications after surgery. In addition to these complications, alcohol consumption has a negative impact on the immune system and increases the risk of bleeding. Thus, the importance of stopping smoking and alcohol consumption before major abdominal surgery should be more clearly emphasised in the preoperative work up. Patients who have been diagnosed with cancer and must undergo surgery will be more sensitive to lifestyle changes, and so it is expected that they, or at least some, will adopt healthier lifestyles sooner.

Psychological resilience
Psychological factors influence physiological and psychological outcomes after surgery. Therefore, it has been increasingly recognised that a prehabilitation programme should include psychological components. Patients who show signs of anxiety and/or depression should receive psychosocial support. Psychological interventions appear to affect immunologic function and certain patient-reported outcome measures after surgery. They result in patients being less anxious, yielding improvements in mental health, vitality, and self-perceived health after surgery. There is no clear postoperative effect, but demonstrable gains have been seen in postoperative functional capacity.

To incorporate a structured screening and assessment of these risk factors, the current preoperative care pathways must be reengineered. Although prehabilitation does not harm anyone, it has been suggested that a prehabilitation programme, as a care bundle, is most beneficial for high-risk patients.

Part II – Risk stratification
Adequate preoperative risk stratification is important in identifying high-risk patients. Those with a low cardiorespiratory fitness might benefit the most from exercise prehabilitation. Cardiorespiratory fitness can be described as the ability of the circulatory and respiratory systems to supply oxygen to skeletal muscles during sustained physical activity. Preoperative cardiorespiratory fitness has been found to have a consistent relation to postoperative outcome in major elective intra-abdominal surgery.

Cardiopulmonary exercise testing
Cardiopulmonary exercise testing (CPET) is an objective and precise method of evaluating a patient’s preoperative aerobic condition. CPET is increasingly used before major surgery to evaluate the risk of adverse perioperative events. In general, patients
with a lower oxygen uptake at the anaerobic threshold (AT) and/or a lower oxygen uptake at peak exercise (VO$_{2peak}$) have an increased risk of postoperative complications. CPET involves a test in which patients pedal against a ramped resistance on a home trainer whilst being monitored with specialised equipment which gathers information about CO$_2$ output and O$_2$ uptake (Figure 1).

The AT is the most repeatable measurement in CPET and is without a learning effect. When the aerobic metabolism is inadequate, the anaerobic metabolism compensates for the deficit and produces lactate. The venous lactate concentration then begins to rise. The hydrogen ion of the lactate is buffered by the HCO$_3^-$ in the blood. This buffering results in the production of CO$_2$ by the following chemical reaction: $\text{H}^+ + \text{HCO}_3^- \rightarrow \text{H}_2\text{CO}_3 \rightarrow \text{H}_2\text{O} + \text{CO}_2$. Therefore, the CO$_2$ output increases more rapidly than O$_2$ uptake. During an exercise test, the AT can be determined by measuring the breath-by-breath minute ventilation (VE), CO$_2$ output (VCO$_2$), and O$_2$ uptake (VO$_2$) using a facemask connected to a respiratory gas analysis device. Differences in VO$_2$ can be caused by one or more organs or systems. Surgery can also be regarded as a sort of exercise during which VO$_2$ rises. CPET is an effective measurement which provides an indication of whether the patient is in an adequate aerobic condition and able to tolerate this increase in VO$_2$ during surgery. Previous studies have shown that patients with an AT $\leq$11 ml/kg/min are classified as high-risk for postoperative complications.

Preoperative sarcopenia and myosteatosis
In recent years, awareness has grown of using body composition variables as predictors for postoperative outcomes. Studies have demonstrated that low muscle mass and function, referred to as sarcopenia, negatively affects postoperative outcomes after resection for colorectal liver metastasis. Moreover, preoperative sarcopenia is associated with poor overall survival in patients with various solid tumours. In addition, there is increasing evidence that preoperative low muscle radiation attenuation as a measure of muscle quality, also referred as myosteatosis, is an important prognostic factor for impaired outcome in patients with cancer.

C-reactive protein to albumin ratio
Emerging evidence has shown the potential value of a variety of systemic inflammation-based prognostic scores in pancreatic cancer. Serum elevation of C-reactive protein (CRP), an acute-phase protein, has been illustrated as a prognostic indicator in various neoplasms. Moreover, hypoalbuminemia brought about by malnutrition and related to cachexia has been reported to be correlated with an unfavourable prognosis of gastrointestinal tumours.
Figure 1. Laura van Wijk performing a CPET under the supervision of Mayella Kuikhoven (sports doctor).

This thesis investigates whether body composition variables such as abdominal muscle mass derived from the routinely performed preoperative abdominal CT scan and the ultimate preoperative CRP-to-albumin ratio can contribute to risk stratification in hepato-pancreato-biliary surgery.

Part III – Optimising perioperative care

Surgery-related muscle loss
One of the first geriatricians, Professor Jo Schreuder, said in the 1960s that ‘the bed is a mistake on four legs’. Sixty years later, however, this realisation has still not been sufficiently translated into effective policies to counteract in hospital immobilisation-induced muscle loss. In this context, previous studies have described that surgery-related loss of muscle quantity negatively affects postoperative outcomes.\textsuperscript{76-78} However, changes of muscle quality have not been fully investigated. This thesis addresses the identification of risk factors for surgery-related muscle loss after major abdominal surgery. A perioperative intervention targeting identified risk factors might prevent clinically relevant muscle loss and seems to be a promising strategy to reduce morbidity and mortality and improve quality of life after major abdominal surgery.
THESIS OUTLINE

Chapters 2 and Chapter 3, discuss, respectively, the results and protocol of the PRIOR (PRehabilitation In Own Residence) study, a multicentre study with a pre-test–post-test design. This study investigated the added value of a home-based high-intensity exercise training programme for the unfit patient who is scheduled to undergo a liver or pancreas operation. Insights into the effects of a high-intensity (semi-)supervised bimodal home-based exercise programme would be of great interest, as such a programme might be the most preferred and effective method for exercise prehabilitation.

To optimally prepare patients for oncologic liver or pancreatic surgery, a new preoperative care pathway was implemented in the University Medical Centre Groningen. In this care pathway, patients first attended a prehabilitation outpatient clinic and then had an appointment with the surgeon on the same day. At the clinic, patients were screened and assessed for six modifiable risk factors using a structured process which included digital questionnaires, a laboratory test, and functional tests. Chapter 4 evaluates the screening and assessment of the six patient related modifiable risk factors and measures the patient’s compliance rate with the recommended interventions. Chapter 5 describes the development of a flexible online tool to calculate the return on investment of a multimodal prehabilitation programme. The tool calculates the potential financial benefits of such a programme based on the difference in estimated complication-related in-hospital costs in the scenarios with and without a prehabilitation programme. Evidence that prehabilitation also has financial benefits may accelerate the implementation of these programmes in daily care.

CPET has been increasingly used for risk assessment before major surgery to evaluate the risk of adverse perioperative events. However, CPET is relatively expensive and time-consuming and requires well-trained personnel for an adequate interpretation of the results. It would be relevant in the search for time and cost savings to investigate whether the routinely performed preoperative abdominal CT scan can assist in (pre-)selection of unfit patients. Chapter 6 investigates the relationship between body composition variables derived from preoperative CT scans at the level of the third lumbar vertebra and CPET variables of aerobic fitness in older patients scheduled for colorectal surgery.

Since morbidity and mortality rates after pancreatic surgery are high, it is necessary to identify preoperative biomarkers which would enable better stratification of patients who may benefit from surgery. Chapter 7 investigates the prognostic value of the ultimate preoperative CRP-to-albumin ratio and the optimal cut-off value after resection.
for pancreatic ductal adenocarcinoma as compared with several established prognostic factors. Compelling evidence showing that this ratio has significant prognostic value could contribute to current prediction models and clinical decision-making.

Recent reports have suggested that surgery-related loss of muscle quantity is associated with decreased quality of life and postoperative outcomes. However, these studies only concern muscle quantity. There is minimal literature describing surgery-related changes in muscle quality. Chapter 8, presents risk factors for surgery-related loss of both muscle quantity and quality after liver resection for colorectal liver metastasis. In addition, the chapter describes the impact of surgery-related loss of muscle quantity and quality on overall survival in this population. Finally, chapter 9 describes the protocol of the ‘Muscle Power’ study, a prospective, observational cohort study which investigates the presence, impact, and risk factors of clinically relevant surgery-related muscle loss in cancer patients after major abdominal surgery using bedside ultrasound measurements, squeeze and force measurements, and quality-of-life and fatigue questionnaires. After the identification of risk factors for surgery-related muscle loss, perioperative intervention might prevent or reduce surgery-related muscle loss and subsequently improve postoperative outcomes in the future.

The summarising discussion in chapter 10 gives an overview of the findings presented in this thesis and highlights future perspectives.
REFERENCES


PART I

Prehabilitation