General introduction
Annually around 20,000 patients in the Netherlands undergo major abdominal surgery for both benign and malignant disease. Major abdominal surgery may be defined as all digestive resections with reconstruction by means of anastomosis and/or stoma. Twenty percent of these patients will suffer a major complication in their postoperative course, requiring invasive treatment such as endoscopic treatment, percutaneous drainage, reoperation and intensive care management.

Major complications cause patients to have to stay in hospital or in an intensive care unit for a longer period and these patients are at increased risk of morbidity and mortality. Moreover, an increased risk for long-term mortality and increased risk for cancer recurrence is reported. Finally, major complications are also associated with increased costs in a large cohort including general and vascular surgery.

Research on the impact of major complications in patients who undergo major abdominal surgery is limited and should address important questions such as the long-term effects of major complications and impact on hospital costs.

In order to decrease the amount of major complications and its consequences preventive measures start with an adequate indication for treatment, taking into account an optimal diagnostic workup and all personal aspects of the patient.

Regarding surgical innovations two important advances have already been implemented in order to reduce the amount of trauma, such as increased use of minimally invasive techniques and fast track perioperative care.

The introduction of minimally invasive surgical techniques has resulted in less perioperative blood loss, faster postoperative recovery and a shorter length of hospital stay in colorectal surgery. In esophageal surgery the implementation of minimally invasive techniques has lead to a marked decrease in pulmonary complications. Alongside these minimally invasive surgical approaches, the implementation of fast track perioperative care has further improved postoperative recovery. With these perioperative measures and surgical innovations taken into account major complications still occur in up to 20% of patients.

Studies have shown that early goal-directed treatment of complications improves outcomes regarding morbidity and mortality. In order to facilitate early treatment for complications diagnostic quality control algorithms in the early postoperative phase are necessary.

Early diagnosis of postoperative complications can be quite challenging, since clinical examination, biochemical testing and even additional imaging techniques can be rather non-specific due to effects of surgery itself. In the first days after surgery clinical risk assessment may have a low predictive value for major complications such as anastomotic leak. Therefore, biochemical markers are increasingly used to follow the postoperative period. Markers such as C-reactive protein, interleukins 6 and 8 and procalcitonin are
raised the first postoperative days due to surgical trauma. Currently the median time from surgery to diagnosis of complications is eight days.\textsuperscript{16, 17} Indicating room for improvement.

Early postoperative computed tomography scans show a large overlap between uncomplicated patients and patients with anastomotic leak, with free air and fluid also seen often in uncomplicated postoperative patients.\textsuperscript{18}

A standardized postoperative quality control algorithm, based on biochemical markers would further help the current Fast Track policy. Fast Track patients are often discharged as early as the fifth postoperative day if no postoperative complications are seen.\textsuperscript{8} With a median time from surgery to diagnosis of complications of eight days it is imperative that the risk of complications is assessed prior to discharge. These perspectives encouraged the initiative to research quality control algorithms in major abdominal surgery, aiming for both early diagnosis and treatment of complications as well as implementation of safe discharge criteria.

**AIM OF THE THESIS**

The aim of this thesis was to assess the role of quality control in major abdominal surgery and to assess the optimal postoperative quality control algorithm in order to early diagnose and treat the postoperative complications and to allow for safe discharge.

**OUTLINE OF THE THESIS**

**Part 1: Quality control in major abdominal surgery**

**H1** Quality control in major abdominal surgery

**H2** Value of a step-up diagnosis plan by CRP and CT scan to diagnose and manage postoperative complications after major abdominal surgery

The first part of this thesis explores quality control in digestive surgery. In chapter 1, all pre-, peri- and postoperative mechanisms are described that are of influence for optimal quality control in surgery. Ranging from an optimal diagnostic workup, adequate pre-assessment of patients before surgery, to a good indication for a personalized surgical treatment coordinated in a multidisciplinary meeting. Moreover perioperative and postoperative quality control mechanisms such as the use of markers are broadly discussed. This chapter further emphasizes the need for postoperative quality control algorithms in surgery.
Chapter 2 assesses which postoperative measurements and assessments should be implemented in a quality control algorithm after major abdominal surgery. In an observational cohort study the relationship between major complications and postoperative clinical and biochemical markers is explored. Interestingly clinical parameters can be rather non-specific, whereas C-reactive protein showed a strong association with major postoperative complications.

**Part 2: C-reactive protein and quality control**

**H3** What is CRP; biochemical and clinical aspects

**H4** C-Reactive protein in diagnosing postoperative complications after major abdominal surgery, proposal for a prediction model for early assessment of major complications

**H5** Predictive value of C-reactive protein for major complications after major abdominal surgery: a systematic review and pooled-analysis

**H6** Acute phase proteins in intra-peritoneal drain fluid: to drain or not to drain

**H7** C-reactive protein and Interleukin-6 in perianastomotic exudate in diagnosis of major complications after major abdominal surgery

Our observational study revealed C-reactive protein levels are highly correlated with major postoperative complications. The second part of the thesis further studies the use of C-reactive protein to predict postoperative complications. Chapter 3 describes the biochemical aspects of C-reactive protein with a historical overview. The inflammatory response, caused by surgical trauma, explains the physiological postoperative rise in C-reactive protein production in the liver. In the case of postoperative complications a further increase in CRP production is seen, caused by the increased inflammatory response.

Postoperative CRP levels depict a wide range of values. In chapter 4 the relationship between CRP and major complications is further explored in a large cohort, aiming to determine a cut-off for CRP above which additional examination for complications should be performed. A CRP value above 140 mg/L on the third postoperative day has been calculated as a marker for major complications, indicating additional CT-scan examination of the patient.

Chapter 5 consists of a systematic review of the literature for CRP as a marker for complications in order to obtain an optimal cut-off. Available studies are rather heterogeneous, limiting the possibility for a general conclusion. Raw data was obtained from seven separate studies, allowing for a pooled analysis of C-reactive protein levels in 1427 patients. Supporting the finding from our cohort study, the optimal cut-off was again found to be 140 mg/L on the third postoperative day.
Measured CRP levels depict information on the inflammatory state of the patient. As it is routinely measured in peripheral blood samples it is non-specific for location. In chapter 6 and 7 the measurement of CRP in peri-anastomotic drain fluid is explored, aiming to obtain local information on the inflammatory state around the anastomosis and in the intra-abdominal compartment, which may aid in narrowing the differential diagnosis in the assessment of patients at risk of major postoperative complications.

**Part 3: Quality control in specific patient groups**

- **H8** The effect of gender, age and BMI on postoperative C-reactive protein levels after major abdominal surgery.
- **H9** C-reactive protein in predicting postoperative complications Are there differences in open and minimally invasive colorectal surgery.
- **H10** C-reactive protein as a marker for postoperative complications. Are there differences in emergency and elective colorectal surgery?

In this part the postoperative CRP levels in specific patient groups were studied, as well as the application of a cut-off for CRP and whether this should be adjusted in different patient groups.

Factors as gender, age and BMI are evaluated in the context of postoperative major complications. Moreover differences in postoperative CRP levels are assessed in patients having major complications after laparoscopic or open colectomies, but also differences are assessed in elective or emergency colorectal interventions.

**Part 4: Implications of major complications**

- **H11** Long-term survival after complications following major abdominal surgery
- **H12** Major abdominal surgery in octogenarians: Should high age affect surgical decision-making?
- **H13** Hospital cost-analysis of complications after major abdominal surgery.
- **H14** The PRECious trial. PREdiction of Complications, A step-up approach, CRP first followed by CT-scan imaging to ensure quality control after major abdominal surgery: study protocol for a stepped-wedge trial

The consequences of major complications are evaluated in two different perspectives; a) The effect of major complications on long-term survival of patients, and b) the effect of major complications in octogenerians is assessed.

Finally, an evaluation is made of the direct costs of an uncomplicated and complicated patient. In the time of cost-efficiency adjustments this evaluation can help for determining the quality of surgical treatments.
All this information directs us to the design of a study protocol for a stepped-wedge trial, the PRECious trial in which a prospective stepped-wedge study is performed. In the case of CRP levels higher than 140 mg/l on the 3\textsuperscript{th} or 4\textsuperscript{th} postoperative day a CT scan is performed. Prospective evaluation of this data, gathered in different hospitals will indicate the value of this algorithm.
REFERENCES