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Targets for improving patient outcomes after major gastrointestinal cancer surgery: the value of perioperative care

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Citation

Kooten, R. T. van. (2023, June 15). *Targets for improving patient outcomes after major gastrointestinal cancer surgery: the value of perioperative care*. Retrieved from <https://hdl.handle.net/1887/3620458>

Version: Publisher's Version

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Chapter 1

General Introduction

Gastrointestinal carcinomas are malignancies originating from organs of the gastrointestinal tract, such as the esophagus, pancreas and colon. Major surgery is the cornerstone of curative treatment of primary malignancies of the gastrointestinal tract [1, 2]. With the increase in general life expectancy and consequently the rise in incidences of these types of malignancies has gone up, there has been a corresponding increase in the number of surgeries being performed.

The increase in overall survival due to improved oncological care has resulted in more patients having to live with the consequences of major gastrointestinal cancer surgery [3, 4]. For that reason, improving short- and long-term patient outcomes becomes more important, with the increasing focus on value-based healthcare and a more patient-centered approach to healthcare. Patient outcomes can be divided into short- and long-term outcomes. Short-term outcomes are often postoperative complications and mortality within 90 days after surgery. Long-term patient outcomes can be divided into two main categories, disease-specific outcomes, such as tumor recurrence and overall survival, and quality of life.

Short-term outcomes

Major gastrointestinal cancer surgery is accompanied by a high rate of major complications, up to 35% [5]. Complications are usually graded by the Clavien-Dindo classification, with IIIa and above being considered major complications (Table 1) [6].

Table 1 – Clavien-Dindo classification [6].

Grade	Definition
I	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic, and radiological interventions. Acceptable therapeutic regimens are: drugs as antiemetics, antipyretics, diuretics and electrolytes and physiotherapy.
II	Requiring pharmacological treatment with drugs other than such allowed for grade I complications. Blood transfusions and total parental nutrition are also included.
III	Requiring surgical, endoscopic or radiological intervention
IIIa	Intervention not under general anesthesia
IIIb	Intervention under general anesthesia
IV	Life-threatening complication requiring ICU-management
IVa	Single organ dysfunction (including dialysis)
IVb	Multiple organ dysfunction
V	Death of a patient

Postoperative complications are associated with increased short- and long-term morbidity and mortality, but also with increased length of hospital stay and healthcare costs [7]. Furthermore, postoperative complications are associated with a higher risk of tumor recurrence and thus decreased long-term survival [8, 9]. On one hand, because of an inflammatory response, that might enhance regrowth, on the other hand, it is thought that a postoperative complicated course might lead to the omission of adjuvant therapy and therefore leads to inferior oncological outcomes [10, 11].

The incidence of major complications can be decreased by improving surgical techniques. However, recent studies have implied that the peri-operative improvements may have a bigger impact on lowering postoperative complications [12]. A growing interest in perioperative research is currently focusing on the implementation and further improvement of enhanced recovery after surgery (ERAS) protocols [13]. ERAS protocols are guidelines for perioperative care, entailing elements such as prehabilitation, nutritional interventions, opioid-sparing analgesia and early mobilization [13]. Implementation of ERAS may lead to a reduction in overall complications by up to 50%, as shown in a meta-analysis [13, 14]. The identification of prognostic factors (e.g., malnourishment, frailty) for adverse events after major surgery might provide opportunities to optimize and personalize perioperative care. This could be done by striving to optimize adjustable prognostic factors (e.g., malnutrition) before the surgery, so-called prehabilitation, which might lead to a decreased risk for postoperative complications and mortality [15].

Long-term outcome: quality of life

As the number of long-term cancer survivors continues to rise together with the rise of a more patient-centered approach, a balance between disease-specific/oncological outcomes and quality of life is eminently important. Studies indicate that patients are only willing to risk an inferior functional outcome for better survival to a certain extent [16]. This influences (shared) decision-making regarding treatment options. Hence, quality of life after cancer surgery should be investigated, with emphasis on the factors influencing postoperative quality of life. This will help to inform patients and to gain insight into possible improvements in perioperative care. The postsurgical quality of life can be influenced by various factors, such as the occurrence of postoperative complications and the functional outcomes [17-20]. Several studies have shown that preoperative and short-term postoperative quality of life can predict long-term survival, indicating the importance of this field of research [21, 22]. An example of functional outcomes is the bowel function of patients after rectal cancer surgery. One year after rectal cancer surgery approximately 40% of the patients, complain of dysfunctional bowel functions, combined in the low-anterior resection syndrome (LARS) [19, 23-26].

LARS entails the following frequently ($\geq 35\%$) reported symptoms: clustering of bowel movement, incomplete evacuation, fecal incontinence, uncontrollable flatus, and urgency [27]. Additionally, the presence of a stoma can negatively influence health-related quality of life caused by stoma-related problems, such as sexual dysfunction, depression, constipation, negative body image, and difficulties while traveling leading to a lower quality of life [28, 29].

Preoperative treatment decision

The decision to engage in major gastrointestinal cancer treatment is usually not a straightforward one. Balancing between oncological outcomes and the risks of poor functional outcomes and complications, makes these treatment decisions particularly suitable for shared decision-making [30, 31]. Insights on the effects of various aspects of major cancer surgery on quality of life provide information that can be used by patients and physicians to assist in shared decision-making before engaging in treatment. It has been shown that explicit patient consideration before engaging in treatment is positively associated with long-term quality of life since it leads to a greater acceptance of treatment consequences [32]. Additionally, information on the development of long-term postoperative quality of life can be used for patient education before elective surgery on what to expect in the short- and long-term. Preoperative education of patients has been shown to reduce postoperative anxiety and postoperative pain [33, 34].

Aim of this thesis

The overall aim of this thesis is striving for the improvement of short- and long-term patient outcomes by providing leads for augmentation. By identifying prognostic factors and constructing prediction models for major complications and by gaining insights into long-term quality of life and the consequences of major gastrointestinal cancer surgery, this thesis should provide these leads.

Thesis Outline

The International Consortium for Health Outcomes Measurements (ICHOM) has constructed a set of various colorectal cancer-specific patient-centered outcome measures (Fig. 1) [35]. The outcome measures are based on expert opinion and patient experience and should represent patient outcomes that matter the most to patients undergoing colorectal cancer treatment. The various chapters in this thesis relate to these patient outcomes, except quality of death.



Figure 1 – ICHOM set of patient-centered outcomes measures for colorectal cancer [35].

Part I: Identification of risk factors for complications

A large number of studies have focused on reducing complications by improving surgical techniques. However, relatively few have addressed improving perioperative care. The latter contributes largely to the avoidance of complications and is responsible for shortened recovery after surgery, together with less morbidity and increased overall survival [12]. To enhance perioperative care and to be able to personalize preoperative care to prevent postoperative complications, for instance engaging in prehabilitation programs, preoperative patient selection is imperative [12, 14]. In **Chapters 2 and 3** an overview of prognostic factors for postoperative complications and postoperative mortality is given. Furthermore, with the upcoming data-driven approach to healthcare as well as the increasing availability of big data, machine learning models might be useful for accurate analysis [36]. Additionally, it is known that postoperative complications of CRC surgery are leading to more tumor recurrence and decreased long-term survival [37]. In **chapter 4** a comparison between the current gold standard, logistic regression, and machine learning is made for predicting postoperative complications in esophagogastric cancer surgery. As is shown in **chapters 2, 3 and 4**, malnutrition, frailty and low physical

performance are prognostic factors for a postoperative complicated course following major gastrointestinal surgery. Therefore **chapter 5** focuses on quantifying these factors in an easy-to-use manner by using the preoperative computer tomography (CT)-scan, by measuring cross-sectional abdominal muscle areas.

Part II: Late effects of major complications

Major gastrointestinal surgery might have a large impact on various patient outcomes (Fig 1.), but the question is how treatment of gastrointestinal malignancies affects daily life, daily functioning and health-related quality of life [38]. Therefore part II focuses on identifying various influential factors for long-term quality of life. In **chapter 6** an exploration of the impact on various aspects (e.g., social functioning, daily activities, sexual functioning) of long-term quality of life is performed. In **chapter 7** the impact of postoperative complications on the short and long-term quality of life is investigated. In **chapters 8 and 9** the presence of a stoma and dysfunctional bowel functioning and its relation to the quality of life after cancer surgery is investigated.

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