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

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Targets for Improving Patient Outcomes after Major Gastrointestinal Cancer Surgery

The value of peri-operative care

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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 (≥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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Part I: Identification of Prognostic Factors for Postoperative Complications

Chapter 2

Preoperative Risk Factors for Major Postoperative Complications After Complex Gastrointestinal Cancer Surgery: A Systematic Review

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List of abbreviations

ACS NSQIP; American College of Surgeons National Surgical Quality Improvement Program, CD; Clavien-Dindo, CRP; C-Reactive Protein, DICA; Dutch Institute for Clinical Auditing, ERAS; Enhanced Recovery After Surgery

Abstract

Patients undergoing complex gastrointestinal surgery are at high risk of major postoperative complications (e.g., anastomotic leakage, sepsis), classified as Clavien-Dindo (CD) ≥ IIIa. Identification of preoperative risk factors can lead to the identification of high-risk patients. These risk factors can also be used to design personalized perioperative care. This systematic review focuses on the identification of these factors. TheMedline and Embase databases were searched for prospective, retrospective cohort studies and randomized controlled trials investigating the effect of risk factors on the occurrence of major postoperative complications and/or mortality after complex gastrointestinal cancer surgery. Risk of bias was assessed using the Quality in Prognostic Studies tool. The level of evidence was graded based on the number of studies reporting a significant association between risk factors and major complications. A total of 207 eligible studies were retrieved, identifying 33 risk factors for major postoperative complications and 13 preoperative laboratory results associated with postoperative complications. The present systematic review provides a comprehensive overview of preoperative risk factors associated with major postoperative complications. A wide range of risk factors are amenable to actions in perioperative care and prehabilitation programs, which may lead to improved outcomes for high-risk patients. Additionally, the knowledge of this study is important for benchmarking surgical outcomes.

Introduction

Postoperative complications can occur after every type of surgery, and can lead to increased morbidity and mortality, as well as increased hospital length of stay and healthcare costs [1]. Complex gastrointestinal surgery (e.g., colorectal, gastric and esophagus resections) is associated with high complication rates [2, 3]. 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 shorter recovery time after surgery, together with less morbidity and increased survival. Some studies have suggested that perioperative care more accurately dictates outcomes and postoperative complications than surgery itself [4]. Perioperative care is currently being standardized in the form of enhanced recovery after surgery (ERAS) protocols, which provide guidelines for improved perioperative care. A meta-analysis by Vardhan et al. showed that the use of ERAS protocols reduces the rate of complications following major abdominal surgery by up to 50% [5]. The period of time before admission is used for screening for medical conditions that can negatively alter the surgical outcome (e.g., smoking and malnutrition). This can be particularly beneficial when the screening focuses on modifiable risk factors, which subsequently can be (partially) reversed (e.g., physical therapy, nutritional support).

Reduction of postoperative complications is also important in relation to long-term outcomes, especially in patients with cancer. The severity of complications is often graded using the Clavien-Dindo (CD) classification, a therapy-based complication severity classification [6]. It has been demonstrated that major complications (CD ≥ IIIa) are associated with postponement of adjuvant therapy and worse oncological outcomes, like local recurrences and shortened recurrence-free survival [7, 8]. The majority of studies addressing the prevention of postoperative complications have concentrated on operation-specific risk factors (e.g., anastomosis technique). However, for complex surgeries, the standard perioperative care protocols may not be adequate to reduce major complications for every individual patient.

Additionally, identifying risk factors for adverse outcomes is important for case-mix correction in benchmarking quality of care in nation-wide clinical auditing and surgical improvement programs, such as the Dutch Institute of Clinical Auditing (DICA) and American College of Surgeons National Surgical Quality Improvement Program (ACS NSQIP) [9, 10].

This review focuses on the identification of preoperative risk factors for major postoperative complications (CD ≥ IIIa) after major abdominal surgery with the construction of an intestinal anastomosis, which includes esophagectomy, gastrectomy, and colorectal surgery. Since, these types of surgery have technical similarities and are all high risk procedures. Furthermore, this study aims to identify the strengths and possible improvements in ERAS protocols.

Methods

The study protocol for this systematic review was registered with the PROSPERO database (CRD42020198812). This review adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (PRISMA).

Criteria for study eligibility

To evaluate the effect of preoperative factors on the incidence of major postoperative complications, studies were selected based on the type of surgery. Only studies addressing complex gastrointestinal cancer surgery (e.g., esophagectomy, gastrectomy, and colectomy), including the construction of an intestinal anastomosis, were selected. As an outcome, a study was required to report on the associations between major complications and an independent preoperative factor. Major complications were classified as CD ≥ IIIa or severe complications that were classified as such (e.g., anastomotic leakage, endoscopic intervention) [6]. Retrospective, prospective cohort studies, and randomized-controlled trials with full-text articles published in English or Dutch were assessed for eligibility. Case reports and case series (< 40 patients) were excluded. Only studies including adult patients (≥ 18 years of age) were selected, and animal studies were excluded.

Search method

The Medline and Embase electronic databases were searched to identify all relevant publications. Search terms included those from MeSH in PubMed and EMtree in Embase, as well as free text terms. Reference lists of identified studies will be checked for additional relevant studies. Included studies were restricted to those that were published between January 2005 and July 2021. Authors were contacted in case of full-text unavailability.

Study selection

Assessment of eligibility was performed independently by RB and RvK. Any disagreement regarding eligibility was resolved by discussion with MW as an arbitrator when necessary. The initial screening was based on title and abstract. Full texts were independently screened by two authors (RB and RvK). Again, disagreement was resolved by discussion with MW, who acted as an arbitrator. Study selection was performed using Endnote X9 (Clarivate Analytics, Philadelphia, PA, USA) and Rayyan QCRI (a mobile web app for systematic reviews).

Assessment of risk of bias

All eligible studies were independently assessed for potential risk of bias by RB and RvK, using the Quality in Prognostic Studies (QUIPS) tool for classification of prognostic factor studies [11]. Discrepancies were resolved by discussion, with MW as an arbitrator when necessary. The risk of bias in clinical trials was assessed in the following domains: study participation, study attrition, prognostic factor measurement, outcome measurement, adjustment bias, and statistical analysis bias. Each domain was graded as high, low, or unclear. The results of risk of bias screening are summarized in Supplementary File A.

Data extraction and management

Data extraction was performed by RvK, and subsequently verified by RB using a predefined, standardized form designed by RB and RvK. Any discrepancies were resolved through discussion.

Grading the level of evidence

The level of evidence regarding the association between a risk factor and major complications (CD ≥ IIIa) was scored using a grading system (Table 1) [12]. The score resulted from the number of studies conducting a multivariable analysis of the association and percentage of statistically significant results of these analyses.

Table 1 - Grading the level of evidence adapted from the grading score used by Lagarde et al. [12].

Level of evidence	Criteria
None	No significant evidence
Minor	Evidence significant from multivariable analysis form **one article**
Considerable	Evidence significant from multivariable analysis in **three or less** articles and/or in **less than 50%** of the articles describing this risk factor
Strong	Evidence significant from multivariable analysis in **more than three** articles and in **more than 50%** of all articles describing this risk factor
Very strong	Evidence significant from multivariable analysis **in ten or more** articles and **in more than 70%** of all articles describing this risk factor

Results

The literature search retrieved 207 eligible studies (Figure 1), all of which used an observational study design. An overview of the results reported in these studies on preoperative risk factors associated with major complications (i.e., CD ≥ IIIa) after major gastrointestinal cancer surgery is shown in Table 2, together with the type of surgery (lower or upper gastrointestinal surgery), and the level of evidence graded according to Table 1. The fourth column reports the number of studies, including the risk factor, in multivariable analysis and the percentage of significant results. This section is divided into six subsections: patient characteristics, comorbidities, intoxication, nutritional indicators, disease-related factors, and neoadjuvant therapy-related factors.

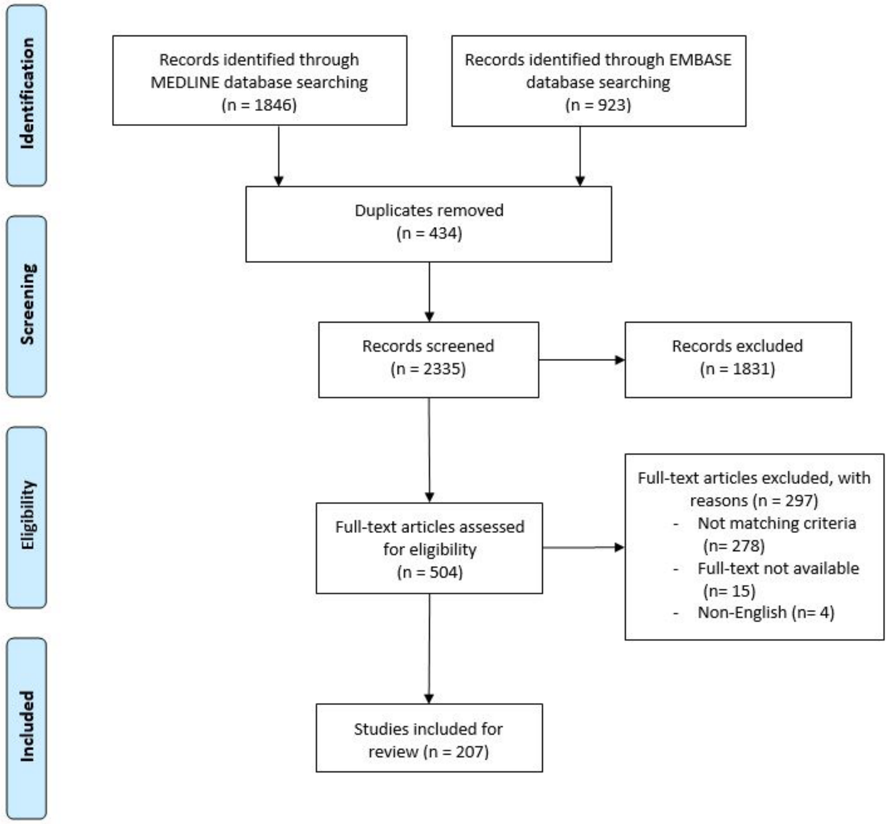

Figure 1 - PRISMA flowchart of study selection

Patient characteristics

Age and frailty

Age is an important risk factor. Many studies reported an independent association between older age and major complications and mortality (Table 2). The elderly are believed to exhibit less healing capacity, which leads to more postoperative complications [13, 14]. Another term reported in studies is "frailty", which is a physiological state of cumulative deficits (e.g., advanced age, poor physical performance), which render patients more susceptible to major complications [15]. In a large population-based retrospective cohort, Sparreboom et al. reported an association between frailty and anastomotic leakage [2]. Along with frailty, functional status, and activities of daily living dependency have demonstrated an association with postoperative complications and mortality (Table 2).

Table 2- This table represents all pre-operative risk factors for major complications (Clavien-Dindo (CD) ≥ IIIa) and mortality described in literature References used in this table are listed in Supplementary Information B. BMI= body-mass index; CD= Clavien-Dindo; HbA1c= glycated hemoglobin; Low= lower GI surgery; Up= upper GI surgery. *30-day mortality or in-hospital mortality.

Preoperative risk factors	Type of complications	Type of	Number of articles favoring (%)	Level of evidence	Reference(s)
Patient characteristics					
Age	Anastomotic leakage	Up & Low	10/22 (45)	Considerable	[2, 26, 66, 88-157]
	Intra-abdominal infection	Up	2/2 (100)	Considerable	
	Reoperation	Up & Low	2/2 (100)	Considerable	
	Venous thrombo-embolism	Up & Low	2/3 (67)	Considerable	
	Mortality*	Up & Low	17/20 (85)	Very strong	
	CD≥ IIIa	Up & Low	18/29 (62)	Strong	
Male gender	Anastomotic leakage	Up & Low	27/34 (79)	Very Strong	[2, 14, 26, 88, 89, 92, 95, 97, 102, 104, 105, 107, 111, 112, 114, 119-124, 126, 128, 129, 133, 137-140, 146, 149, 152, 156, 158-190]
	Pancreatic fistula	Up	1/2 (50)	Minor	
		Low	1/1 (100)	Minor	
	Intra-abdominal infection	Up & Low	3/5 (60)	Considerable	
	Reoperation	Up	1/1 (100)	Minor	
	Venous thrombo-embolism	Up	1/1 (100)	Minor	
	Mortality*	Low	5/6 (83)	Strong	
	CD ≥ IIIa	Up & Low	9/17 (53)	Strong	
American Society of Anesthesiologists (ASA) score	Anastomotic leakage	Up & Low	10/19 (53)	Strong	[2, 26, 88, 90, 91, 98, 99, 101, 102, 105, 110, 114, 120, 124, 126, 128-130, 133, 137-140, 144, 146, 148, 151-153, 162, 166, 170, 189, 191-196]
	Reintervention	Low	1/1 (100)	Minor	
	Mortality*	Up & Low	8/10 (80)	Strong	
	CD ≥ IIIa	Up & Low	6/15 (40)	Considerable	
	Mortality*	Up & Low	1/2 (50)	Minor	
Physical fitness	Anastomotic leakage	Low	1/2 (50)	Minor	[138, 160, 197, 198]
	CD ≥ IIIa	Up & Low	2/2 (100)	Considerable	
Frailty	Mortality	Up	2/2 (100)	Considerable	[92, 138, 153, 199]
	CD ≥ IIIa	Up & Low	2/3 (67)	Considerable	
Comorbidity					
Comorbidity	Anastomotic leakage	Up & Low	6/8 (75)	Strong	[2, 105-107, 129, 133, 146, 147, 149, 152, 162, 168, 200-203]
	Reoperation	Up & Low	2/2 (100)	Considerable	
	Respiratory failure	Up	1/1 (100)	Minor	
	Mortality*	Up & Low	3/3 (100)	Considerable	
	CD ≥ IIIa	Up	3/4 (75)	Considerable	

Table 2- Continued

Preoperative risk factors	Type of complications	Type of	Number of articles favoring (%)	Level of evidence	Reference(s)
	Anastomotic leakage	Up & Low	6/6 (100)	Strong	[136, 192, 193, 204-206]
Hypertension	Anastomotic leakage	Up & Low	2/3 (67)	Considerable	[135, 150, 155, 184, 207-209]
	CD ≥ IIIa	Up	3/3 (100)	Considerable	
	Anastomotic leakage	Up & Low	4/8 (50)	Strong	[100-102, 104, 114, 137, 140, 141, 154, 155, 170, 189, 190, 194, 202, 210-214]
	Acute respiratory distress syndrome (ARDS)	Up	1/1 (100)	Minor	
	Respiratory failure	Up	1/2 (50)	Minor	
	Mortality*	Up & Low	5/5 (100)	Strong	
	CD ≥ III	Up & Low	4/6 (67)	Strong	
	Anastomotic leakage	Up & Low	8/12 (75)	Strong	[100, 102, 104, 114, 117, 121, 131, 135-137, 154, 155, 158, 159, 170, 185, 194, 209, 210, 212, 213, 215-219]
	Duodenal stump fistula	Up	1/1 (100)	Minor	
	Respiratory failure	Up	1/1 (100)	Minor	
	Venous thrombo-embolism	Up	1/1 (100)	Minor	
	Mortality*	Up & Low	4/5 (80)	Strong	
	CD ≥ IIIa	Up & Low	8/11 (73)	Strong	
Chronic hepatic disease	Anastomotic leakage	Up	1/1 (100)	Minor	[102, 135, 140, 181, 215, 220, 221]
	Duodenal stump fistula	Up	1/1 (100)	Minor	
	Intra-abdominal infection	Up	1/1 (100)	Minor	
	Mortality*	Up & Low	2/2 (100)	Considerable	
	CD ≥ IIIa	Up	1/1 (100)	Minor	
Chronic kidney failure	Anastomotic leakage	Up	2/3 (67)	Considerable	[98, 102, 193, 209]
	Mortality*	Low	1/1 (100)	Minor	
Diabetes	Anastomotic leakage	Up & Low	9/18 (50)	Considerable	[26, 98, 104, 140, 158, 176, 182, 186, 194, 207, 208, 210, 212, 221-226]
	CD IV-V	Up	1/2 (50)	Minor	[100, 145]
Steroid use (chronically)	Anastomotic leakage	Up & Low	3/5 (60)	Strong	[98, 114, 129, 140, 165, 227, 228]
	Mortality*	Up & Low	2/2 (100)	Considerable	
Anti-coagulant therapy	Anastomotic leakage	Low	1/1 (100)	Minor	[189]
Prior abdominal surgery	Anastomotic leakage	Up & Low	3/5 (60)	Considerable	[2, 95, 142, 148, 167, 200]

Table 2- Continued

Preoperative risk factors	Type of complications	Type of	Number of articles favoring (%)	Level of evidence	Reference(s)
Intoxications					
Smoking	Anastomotic leakage	Up & Low	15/20 (75)	Very strong	[14, 25, 26, 98, 102, 114, 124, 129, 138, 142, 158, 160, 165, 166, 200, 201, 210, 220, 221, 229-232]
	Mortality*	Low	2/2 (100)	Considerable	
	CD ≥ IIIa	Up	2/2 (100)	Considerable	
	Anastomotic leakage	Low	4/6 (67)	Considerable	[124, 129, 138, 158, 166, 210, 232]
Nutritional indicators					
Overweight (BMI >25)	Anastomotic leakage	Up & Low	4/9 (44)	Considerable	[2, 49, 88, 94, 95, 104, 105, 111, 113-115, 122, 123, 133, 138, 146, 160, 163, 174, 180, 188, 195, 233-240]
	Pancreatic fistula	Up	2/2 (100)	Considerable	
	Intra-abdominal infection	Up & Low	3/5 (60)	Considerable	
	Reoperation	Up	1/1 (100)	Minor	
	Venous thrombo-embolism	Up & Low	1/3 (33)	Minor	
	Mortality*	Up & Low	2/4 (50)	Considerable	
	CD ≥ IIIa	Up	6/11 (55)	Strong	
Obesity (BMI >30)	Anastomotic leakage	Up & Low	6/7 (86)	Strong	[14, 114, 124, 140, 148, 165, 189, 207, 210, 233, 235, 238, 239, 241]
	Venous thrombotic-embolism	Up & Low	1/3 (33)	Minor	
	CD ≥ IIIa	Up & Low	1/3 (33)	Minor	
	Venous thrombo-embolism	Up & Low	1/3 (33)	Minor	
	CD ≥ IIIa	Low	1/1 (100)	Minor	
Sarcopenic obesity	CD ≥ IIIa	Up	1/1 (100)	Minor	[130]
Underweight (BMI <18,5)	Anastomotic leakage	Up & Low	1/2 (50)	Minor	[128, 184, 227, 235, 239]
Sarcopenia	Anastomotic leakage	Up & Low	2/3 (67)	Considerable	[242-247]
	Prolonged intubation	Up	1/1 (100)	Minor	
	CD ≥ IIIa	Up & Low	3/4 (75)	Strong	
Malnutrition/ preoperative weight loss	Anastomotic leakage	Up & Low	5/8 (63)	Strong	[106, 108, 114, 115, 130, 138, 140, 179, 210, 215, 248, 249] [144, 153, 198, 250]
	Duodenal stump fistula	Up	1/1 (100)	Minor	
	Mortality*	Up	2/2 (100)	Considerable	
	CD ≥ IIIa	Up	4/5 (80)	Strong	
High visceral fat area (VFA)	Anastomotic leakage	Up & Low	2/3 (100)	Considerable	[103, 234, 251-253]
	Intra-abdominal infection	Up	2/2 (100)	Considerable	
	Mortality*	Up	1/1 (100)	Minor	

Table 2- Continued

Preoperative risk factors	Type of complications	Type of	Number of articles favoring (%)	Level of evidence	Reference(s)
Perineal Fat Surface area (PRF) ≥ 40 cm²	CD ≥ III	Low	1/1 (100)	Minor	[124]
Disease related risk factors					
Tumor stage/ tumor size	Anastomotic leakage	Up & Low	9/16 (56)	Considerable	[2, 49, 90, 91, 95, 104, 105, 110, 113, 119, 120, 123, 131, 133, 137, 139, 144-146, 148, 152, 153, 159-161, 164, 172, 173, 176-178, 187, 191, 216-219, 225, 254-260]
	Postoperative hemorrhage	Up	2/2 (100)	Considerable	
	Intra-abdominal infection	Up & Low	2/3 (67)	Considerable	
	Major adverse cardiac event (MACE)	Up	1/1 (100)	Minor	
	Mortality*	Up & Low	2/4 (50)	Minor	
	CD ≥ IIIa	Up	13/22 (59)	Strong	
Preoperative	Anastomotic leakage	Low	1/3 (33)	Minor	[2, 126, 139, 147, 184, 261, 262]
	Mortality*	Up & Low	2/3 (67)	Considerable	
	CD ≥ IIIa	Up	1/1 (100)	Minor	
Neoadjuvant therapy-related risk factors					
	Anastomotic leakage	Up	1/1 (100)	Minor	[53, 149, 207, 263, 264]
	CD ≥ IIIa	Up	1/2 (50)	Minor	
	Mortality*	Up & Low	1/2 (50)	Minor	
	Anastomotic leakage	Low	4/7 (57)	Strong	[2, 105, 166, 175, 196, 256, 265, 266]
	Chylothorax	Up	1/1 (100)	Minor	
	Intra-abdominal complication (CD≥ IIIa)	Low	1/1 (100)	Minor	
	Anastomotic leakage	Up & Low	2/3 (67)	Considerable	[113, 114, 133, 153, 164, 195, 259, 267]
	CD ≥ IIIa	Up & Low	2/4 (50)	Considerable	
	Mortality*	Up & Low	1/2 (50)	Minor	
	Anastomotic leakage	Up & Low	4/7 (57)	Strong	[2, 105, 138, 184, 237, 268, 269]
Preoperative laboratory tests					
	Anastomotic leakage	Up & Low	2/4 (50)	Considerable	[104, 108, 128, 184, 210]
Platelet count increased	Anastomotic leakage	Low	1/1 (100)	Minor	[165]
Platelet count decreased		Low	1/1 (100)	Minor	[171]
White blood cell count (WBC) increased	Anastomotic leakage	Up & Low	1/2 (50)	Minor	[143, 210, 224]
	Venous thrombo-embolism	Low	1/1 (100)	Minor	
Neutrophil-to-lymphocyte Ratio (NLR)	Anastomotic leakage	Low	1/2 (50)	Minor	[160, 270]

Table 2- Continued

Preoperative risk factors	Type of complications	Type of	Number of articles favoring (%)	Level of evidence	Reference(s)
C-reactive protein (CRP) increased	Anastomotic leakage	Up & Low	2/2 (100)	Considerable	[121, 128, 158, 178, 186]
	CD ≥ IIIa	Up	2/3 (67)	Considerable	
CRP/Albumin ration (CAR)	Anastomotic leakage	Low	1/1 (100)	Minor	[142]
Increased creatinine	Anastomotic leakage	Up & Low	1/2 (50)	Minor	[104, 117, 139, 140, 208, 216]
	Mortality*	Up	1/2 (50)	Minor	
	CD ≥ IIIa	Up	1/2 (50)	Minor	
Decreased estimated glomerular filtration rate (eGFR)	CD ≥ IIIa	Up	1/1 (100)	Minor	[159]
Serum albumin	Anastomotic leakage	Up & Low	5/8 (63)	Strong	[26, 104, 123, 128, 130, 137, 139, 140, 151, 164, 168, 178, 183, 189, 190, 216, 232, 250, 263, 266]
	Mortality	Up	2/3 (67)	Considerable	
	CD ≥ IIIa	Up	5/10 (50)	Considerable	
Total protein decreased	Anastomotic leakage	Low	3/3 (100)	Considerable	[14, 121, 189, 190, 210]
	CD ≥ IIIa	Up & Low	2/2 (100)	Considerable	
Albumin-to-fibrinogen ratio (AFR)	CD>IIIa	Up	1/1 (100)	Minor	[186]
Increased HbA1c	Anastomotic leakage	Up	1/1 (100)	Minor	[220]

Male sex

A wide variety of studies have confirmed that male sex is a risk factor for major postoperative complications. Several theories have been proposed to address this issue. Historically, the incidence of smoking and alcohol consumption in the male population has been higher. However, these confounding variables have not been measured in many studies and, therefore, their effect on males may be overestimated [16]. Another theory is that differences in cortisol-induced sex hormones change after surgically induced stress, which could render males more susceptible to postoperative complications [17]. A third theory is that the narrower pelvis of male patients can make surgery for tumors located in this region technically more difficult [2, 14].

American Society of Anesthesiologists score

One of the most studied risk indicators in the context of predicting postoperative complications is the American Society of Anesthesiologists (ASA) score. Multiple studies found an independent association between ASA score and a higher incidence of anastomotic leakage and major complications [2, 18, 19]. Furthermore, the ASA score is a reliable predictor of 30-day mortality (Table 2).

Preoperative inflammatory biomarkers

Several studies described an association between elevated levels of preoperative inflammatory biomarkers (e.g., white blood cell count, C-reactive protein [CRP]) and postoperative complications (Table 2). Similarly, the neutrophil-to-lymphocyte ratio, a proxy measure of inflammation status in the body, is independently associated with an increased risk for major complications (Table 2). The association between preoperative inflammation and complications, however, is not yet fully understood.

Serum albumin is a negative acute-phase protein. It decreases during inflammation due to increased capillary leakage [20]. It is also known as a nutritional biomarker reflecting malnutrition (Section 3.4.1). In the Glasgow Prognostic Score, an inflammation-based prognostic score for cancer prognosis, albumin and CRP are combined to predict perioperative complications [21]. Similarly, You et al. proposed the albumin/fibrinogen ratio as a predictor of major complications (Table 2). Fibrinogen is an essential protein in the coagulation cascade as well as an acute-phase reaction protein in the response to systemic inflammation [22].

Comorbidities

Patients with ≥ 1 comorbidities and those using ≥ 5 drugs per day are more susceptible to complications [23]. Several studies have demonstrated that heart failure, hypertension, and renal insufficiency are independently associated with major complications and anastomotic leakage (Table 2). Vascular disease, particularly arterial calcifications, is an important risk factor for major complications, especially anastomotic leakage (Table 2). Furthermore, the relationship between major complications and diabetes is well understood, whereas hyperglycemia induces microvascular damage, yielding a reduced capacity for anastomotic healing [24] (Table 2).

Intoxication

Smoking

A history of smoking is a risk factor for the occurrence of postoperative complications after major abdominal surgery (Table 2). In a large retrospective cohort study, Sharma et al. estimated the increased risk for major postoperative complications and mortality after smoking to be 30% [16]. Quan et al. reported that the number of pack-years significantly influenced the risk for major complications [25]. Smoking is believed to induce microvascular damage, leading to decreased healing ability of the anastomosis, thereby leading to an increased rate of anastomotic leakage [26].

Alcohol consumption

Several studies have shown that habitual use of alcohol (≥3 units per day) increases the risk for postoperative complications (Table 2). Alcohol causes alcohol-induced liver and pancreatic disorders, as well as impaired immune capacity, hemostasis, and surgical stress response [27, 28]. Alcohol cessation before elective surgery significantly decreased postoperative complications [27, 28].

Nutrition-related risk factors

Malnutrition/preoperative weight loss

Among cancer patients, 63% experience weight loss before treatment. In those with gastric and esophageal cancers, this figure has been reported to be as high as 79% to 83% [29, 30]. Absolute weight loss can be an indication of malnutrition, which can also be measured according to nutritional indexes (*e.g.*, Prognostic Nutritional Index, Nutritional Risk Screening). A more advanced stage of malnutrition leads to cancer anorexia-cachexia syndrome—a hypercatabolic state characterized by weight loss and sarcopenia—which occurs in 15% to 40% of cancer patients [31, 32]. Malnutrition and preoperative weight loss were significantly associated with major complications and mortality (Table 2). Lack of nutrients has been implicated in decreased function of the immune, respiratory and cardiac systems, as well as decreased healing function [33, 34] and further deterioration due to a more catabolic metabolic state [13]. Collectively, this leads to an increased incidence of infectious complications as well as anastomotic leakage (Table 2). Low preoperative serum albumin levels are independently associated with an increased risk for major complications (Section 3.1.4).

Sarcopenia

Sarcopenia refers to the loss of skeletal muscle volume and/or strength, which have a close relationship, and primarily originates from malnutrition (Section 3.4.1). Sarcopenia is especially prevalent in patients with esophageal and gastric cancers (up to 56%), but also in elderly patients [35-37]. As shown in Table 2, sarcopenia was independently associated with worse surgical outcomes. The relationship between sarcopenia and major postoperative complications and mortality is due to reduced healing capacity resulting from a lack of nutrients and, therefore, a catabolic state.

Overweight and obesity

Obese and overweight patients are at higher risk for postoperative complications and mortality after major gastrointestinal surgery (Table 2). There are multiple theories addressing the association between overweight and major complications. First, obese patients often exhibit a significantly increased number of comorbidities, including diabetes, hyperlipidemia, coronary artery disease, and hypertension [38, 39]. Second, overweight and obesity are associated with an increased incidence of anastomotic leakage believed to be caused by a preoperative inflammatory state and increased insulin resistance, leading to decreased healing capacity [40, 41]. Third, increased visceral fat in those undergoing abdominal surgery may lead to more complications due to more technical difficulties (e.g., thicker mesocolon, increased abdominal wall pressure leading to decreased intraoperative visibility) [39, 42], which in turn leads to longer operation time and greater transfusion requirements [19]. Some retrospective studies have explored the relationship between visceral fat area, body mass index, and the impact of excessive abdominal fat tissue on surgical outcomes. However, whether visceral fat area is a better parameter than body mass index remains controversial [43].

Disease-related risk factors

Preoperative tumor complications

Of all preoperative tumor complications, anemia and iron deficiency are the most common. The prevalence of any degree of anemia has been suggested to be 50% to 75% in patients with colorectal cancer [44, 45]. Anemia leads to decreased healing capacity. Therewithal, patients receiving preoperative transfusion exhibited an increased rate of postoperative complications [46]. Blood transfusions appear to induce an immunosuppressive effect; therefore, a policy restricting transfusion is recommended [47]. Local preoperative tumor complications (e.g., bowel obstruction and tumor perforation) are independently associated with major complications (Table 2), theoretically, due to greater technical difficulty caused by an inflammatory response of the abdominal cavity and by the frailty of the tissue used for anastomosis and/or the spill of gastrointestinal fluids.

Advanced tumor stage

Advanced tumor stage, including those from poorly differentiated cancer types, lead to more extensive resections and technically more demanding surgery, followed by more intraoperative organ damage and postoperative complications [42, 48]. Second, extensive lymph node dissections and additional splenic resection, especially in gastric and esophageal resections, are high-risk procedures [49, 50]. Additionally, larger tumors and more extensive resections lead to more non-radical resections [51]. Furthermore, patients with a higher tumor grade or TNM stage are more likely to exhibit a form of systemic immune-inflammation, which is also associated with major complications [52] (Section 3.1.4).

Neoadjuvant therapy-related factors

Neoadjuvant therapy aims to reduce tumor volume to achieve R0 resections and mitigate—if not eliminate—micrometastases and, eventually, cancer recurrence. However, the use of neoadjuvant therapy is also associated with an increase in postoperative complications caused by a diminished healing capacity of damaged tissue (Table 2). Additionally, a possible decrease in psychological performance after neoadjuvant therapy may lead to impaired postoperative recovery [53]. Preoperative radiotherapy in those treated for rectal cancer has a high prevalence of postoperative complications and anastomotic leakage (Table 2). After neoadjuvant therapy, patients also experience postoperative cardiopulmonary complications more frequently [54]. Patients unable to complete neoadjuvant therapy often experience increased postoperative complications, which may be a confounder due to poor underlying health conditions [55].

Discussion

Results of the present study provide a comprehensive and structured overview of the associations between preoperative risk factors and major complications and mortality following complex gastrointestinal cancer surgery. Our findings provide unambiguous evidence supporting the association between age and major postoperative complications, as well as for the association between anastomotic leakage and male sex and smoking. Furthermore, substantial evidence has been provided regarding the association between major postoperative complications and age, male sex, comorbidities, malnutrition, sarcopenia and overweight/obesity. This study also provides strong evidence supporting an association between different comorbidities, obesity, malnutrition, decreased serum albumin, more advanced tumor stages, neoadjuvant radiotherapy, neoadjuvant chemotherapy and the occurrence of anastomotic leakage. Furthermore, strong evidence exists for an association between 30-day mortality and male sex, higher ASA score, and cardiac comorbidity. This systematic review also shows that risk factors for postoperative major complications in lower – and upper gastrointestinal cancer surgery show a substantial overlap.

The identification of risk factors may afford opportunities to optimize perioperative care by managing preoperative risk factors, thereby decreasing the risk for postoperative complications and mortality. This may reduce healthcare costs, in contrast to major complications, which lead to an increase in healthcare expenditures [1]. The described associations may contribute to focused and personalized preoperative care by enrolling patients with certain risk factors (e.g., frailty and malnutrition) into prehabilitation programs. Subsequently, identification of high-risk patients may prompt closer postoperative surveillance. Additionally, the identification of high-risk patients may also influence decision making regarding treatment options, for example, a 'watch and wait' strategy after clinical complete response to neoadjuvant therapy [56, 57].

Preoperative care

In literature, several prehabilitation programs have been described for modifiable risk factors, acting on the associations between preoperative factors and postoperative complications (Table 3). Preoperative control/management of these factors could improve postoperative outcomes. For example, adequate preoperative glycemic control in diabetic patients should lead to less postoperative hyperglycemia, which is associated with postoperative infectious complications and, could therefore, decrease the complication rate [58]. Furthermore, several prehabilitation programs incorporating for instance physical resistance training and nutritional support have been described in the literature (Table 3). Theoretically, these prehabilitation programs should lead to a reduction in postoperative complications, although there is limited evidence to support this [59, 60]. A limitation—present in the majority of research investigating preoperative interventions—could be that prehabilitation is not specifically targeted at patient-specific risk factors. Physical endurance training in a population >70 years of age with ASA III-IV, led to a 20% reduction in complications [61], indicating that preoperative care should be tailored to and specified for patients targeting their risk factors. Smoking cessation, which leads to a significant reduction in postoperative complications, is such an example [25, 62]. Currently, growing interest of perioperative research is focused on the implementation and further improvement of ERAS protocols, which may lead to a reduction in overall complications by up to 50%, as shown in a meta-analysis [5]. However, studies included in this systematic review have been published during the period in which ERAS protocols have been gaining interested and were widely implemented. This means that perioperative care has been improved and optimization of risk factors (e.g., malnutrition, smoking cessation) is standard in daily practice [63]. Also standard in ERAS protocols for gastrointestinal surgery is nutritional support, this is important for patients to cope with the metabolic and physiological stress inflicted by gastrointestinal cancer surgery and increased protein requirements [64]. In addition to nutritional support the so-called "Immunonutrition" which entails nutritional supplements (e.g., arginine, omega-3 fatty acids) is being studied, this is thought to lead to a reduction of surgical stress [65](Table 3). In the light of ERAS protocols studies have shown that an abbreviated period (2 h versus 12 h) of fasting leads to significantly reduced time-to-first-stool and complete oral intake [66, 67]. In the ERAS protocol for lower gastrointestinal surgery, bowel preparation is an important point of discussion because this could lead to changes in electrolyte levels, metabolic imbalance, and dehydration, especially in elderly and/or frail patients [68]. The suggestion to omit this from the protocol, if possible, especially in frail patients, is supported by a meta-analysis that revealed an advantage to no-bowel preparation with regard to anastomotic leakage, intra-abdominal infections, and wound infections [69]. In this context the role of perioperative prophylactic antibiotics usage is studied, which may have a preventive effect on surgical site infections, anastomotic leakage and mortality [70].

Table 3 – Table includes actable or improvable risk factors and subsequent in literature described prehabilitation options to reduce the risk of postoperative morbidity. References used in this table are listed in Supplementary Information B.

Risk factors	Prehabilitation	Reference
Physical performance	Resistance training	[47, 59, 61, 271-275]
	Endurance training	
	Physical therapy	
	Breathing exercises	
	Nutritional support	
	Immunonutrition	
Pulmonary comorbidity	Preoperative inspiratory muscle training	[276-279]
Malnutrition	Nutritional support	[63-65, 280-283]
	Oral nutritional supplements	
	Immunonutrition	
Sarcopenia	Nutritional support	[275, 284, 285]
	Resistance training	
	Nutritional supplements	
Smoking	Smoking cessation	[16, 25, 62, 286]
Alcohol consumption	Alcohol cessation	[28]
Iron deficiency anemia	Intravenous iron supplementation	[287]
Dental plaque	Preoperative oral management by dentist	[288, 289]

Intraoperative techniques and care

Furthermore, ERAS protocols have been further improved intraoperative care in terms of: minimally invasive surgery, pain management, temperature management and fluid administration [71]. During the publishing of the included studies minimally invasive surgery has become more standard procedure. Other intra-operative ERAS-principles that have been studied and implemented such as goal-directed fluid administration and use of fewer use of intra-operative vasopressors have been independently associated with decreased postoperative complications [71-73]. Also intra-operative normothermia has been shown to have a positive effect on prevention of postoperative infections [74].

The use of opioid-sparing analgesia has been shown to increase recovery time, but no reduction in postoperative complications [75].

Postoperative care

With the current increase in data-driven approaches in healthcare, the risk factors reported in Table 2 could be assessed in analysis of large datasets, in which the development of artificial intelligence may play an important role. Machine learning models usually demonstrate similar performance for predicting medical outcomes compared with logistic regression [76]. With increasingly larger datasets, machine learning holds the potential to unravel subtle associations that are not—or cannot—be identified using classic regression approaches. For suspected low-risk patients, machine learning has been suggested to support early discharge decisions [77]. Suspected high-risk patients may benefit from closer postoperative surveillance. Earlier detection of deterioration in patients may reduce the severity of complications and lessen the incidence of failure-to-rescue [78]. A proposed method for augmented postoperative surveillance involves wearable devices for constant postoperative monitoring [79]. These devices continuously transmit vital signs that alert healthcare personnel in case of deterioration.

Benchmarking surgical outcomes

Reduction of postoperative complications can also be established by clinical auditing and benchmarking of surgical outcomes [80, 81]. Auditing is used to measure quality of care using structure, process, and outcome indicators [82, 83]. The information provided by this review can be used for fair comparison of outcomes between different hospitals and institutions, which can only be established when using robust casemix models.

Limitations

The present study had some limitations. First, it provided only an overview of the associations between preoperative risk factors and major complications. As such, additional evidence is needed to confirm that these risk factors are causally related to poor surgical outcomes. Second, heterogeneous patient populations and study designs may have hindered adequate interpretation of the study results. The included studies were all conducted in an observational manner, and most of them were designed retrospectively. There was a wide variety between risk factor reporting between studies, not all risk factors (e.g., renal disease, pulmonary comorbidity) were defined within the studies therefore making interpretation difficult. A similar reporting absence was seen in the implementation and usage of ERAS protocols within the included patient population. ERAS protocols have been widely implemented in surgery in recent years, that's why we limited our study period to 2005.This type of study is subjected to bias, although we suspect that due to the large number of studies, this bias was limited.

However, all patients included in this study were preoperatively selected to be fit for surgery by expert opinion undergoing surgery, leading to allocation bias. This is a limiting factor for generalization of risk factor research in general. Although the present study provides an overview of all known risk factors, not all factors are described or necessarily applicable to every patient. Additionally, this study provides a theoretical overview; therefore, no quantitative effect of the specific risk factors is reported. An additional meta-analysis should be conducted to calculate the quantitative effects of each risk factor. Moreover, the inclusion of risk factors described in Table 2 was based on the significant outcomes in multivariable analysis. This selection was performed to minimize the risk of including confounding factors. However, this may have excluded risk factors studied in low-powered studies, which could also have led to the lack of research investigating risk factors. In the present study, both upper gastrointestinal and lower gastrointestinal cancer surgery were considered by examining esophageal, gastric, and colorectal resections in a large subset of patients undergoing these operations.

Conclusions

In conclusion, identification of improvable/modifiable risk factors exposes possibilities for augmentation of perioperative care, which may lead to improved surgical outcomes. Furthermore, the identified risk factors can lead to alteration and additions to already existing ERAS protocols, which have already resulted in improved perioperative care and reduction in complications [5, 63]. In addition, the identification of preoperative risk factors could lead to further improved and personalized perioperative care, thereby reducing major postoperative complications (e.g., risk factor-targeted prehabilitation). This study also contains important information to improve benchmarking of surgical outcomes in nation-wide clinical audits. The reduction of postoperative complications may prolong (recurrence-free) survival and lead to improved quality of life [84-87].

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Supplementary information A

Table S1 – Table showing the classification of study quality of all included studies using the QUIPS tool [1]. On the horizontal axis show the different assed domains per study. The vertical axis shows all included studies. The green bullet = little risk of bias, yellow = unclear risk of bias, red = high risk of bias.

	Study participation	Study attrition	Prognostic factor measurement	Outcome measurement	Adjustment for other prognostic factors	Statistical analysis and reporting
Abunasra 2005	+	?	+	+	+	+
Akiyoshi 2011(1)	+	?	+	−	+	+
Akiyosi 2011(2)	+	?	+	+	+	+
Aminian 2011	+	?	+	−	+	−
Amri 2013	+	?	+	+	+	−
Aoyama 2020	+	?	+	+	+	+
Baucom 2015	+	?	+	+	+	+
Bausys 2018	+	?	+	+	+	+
Beckmann 2017	+	?	+	+	+	+
Bertelsen 2010	+	+	+	+	+	+
Beuran 2018	+	?	+	−	−	−
Bickenbach 2013	+	?	+	+	+	−
Bisgard 2013	+	?	+	−	+	+
Blom 2012	+	?	+	+	−	−
Bludau 2015	+	?	+	+	+	+
Boccola 2011	+	?	+	+	+	+
Borggreve 2018	+	?	+	+	+	+
Brinkmann 2019	+	?	+	+	+	+
Chang 2014	+	?	+	+	+	−
Coimbra 2019	+	?	+	+	+	+
Cong 2009	+	?	+	+	+	−
Cooke 2009	+	?	+	−	+	+
Deguchi 2012	+	?	+	+	+	+
Der Hagopian 2018	+	?	+	+	−	−
Elliott 2017	+	?	+	+	+	+
Eom 2014	+	?	+	+	+	−
Eto 2016	+	?	+	+	+	+
Flynn 2020	+	?	+	+	+	+
Frasson 2015	+	?	+	+	+	+
Frasson 2016	+	?	+	+	+	+
Frouws 2017	+	?	+	+	+	?
Gessler 2016	+	+	+	+	+	+
Goense 2016	+	?	+	+	+	+
Gong 2014	+	?	?	+	+	−

	Study participation	Study attrition	Prognostic factor measurement	Outcome measurement	Adjustment for other prognostic factors	Statistical analysis and reporting
Gooszen 2018	+	+	+	−	+	+
Goto 2016	+	?	+	+	+	+
Guner 2018	+	?	+	+	+	+
Hall 2019	+	?	+	+	+	+
Hamai 2015	+	?	+	+	+	+
Harustiak 2015	+	?	+	+	+	+
Hayashi 2019	+	?	+	+	+	−
Herrod 2019	+	?	+	+	+	+
Horne 2020	−	?	+	+	+	+
Hu 2015	+	?	+	+	+	−
Huang 2015	+	?	+	+	+	+
Huang 2020	+	?	+	+	+	+
Iancu 2008	+	?	+	+	+	+
Ishino 2014	+	?	+	+	+	+
Iversen 2008	+	+	+	+	+	+
Jeong 2011	+	?	+	+	+	−
Jeong 2014	+	?	+	+	+	−
Jiang 2012	+	?	+	+	+	+
Jiang 2014	+	?	+	+	+	−
Jones 2015	+	?	+	+	+	+
Josse 2016	+	?	+	+	+	+
Juloori 2014	+	?	+	+	+	+
Jung 2012	+	?	+	+	+	−
Jung 2014	+	?	+	+	+	+
Kanaji 2016	+	?	+	+	+	+
Kang 2011	+	?	+	+	+	+
Kang 2016	+	?	+	+	+	+
Karup 2012	+	?	+	+	+	−
Kassis 2013	+	?	+	+	+	−
Katai 2005	+	?	+	+	+	+
Katsuno 2016	+	?	+	+	+	+
Kenig 2018	+	?	+	+	+	+
Kim 2003	+	?	+	+	+	+
Kim 2009	+	?	+	+	+	−
Kim 2015	+	?	+	+	+	−

	Study participation	Study attrition	Prognostic factor measurement	Outcome measurement	Adjustment for other prognostic factors	Statistical analysis and reporting
Kim 2016	+	?	+	+	?	+
Kim 2017	+	?	+	+	+	+
Klevebro 2019	+	?	+	+	+	−
Klose 2018	+	?	+	+	+	+
Kobayashi 2015	+	?	+	+	+	+
Koeter 2015	+	?	+	+	+	−
Konishi 2006	+	?	+	+	+	+
Kosuga 2017	+	?	+	+	+	+
Kouyoumdjian 2021	+	?	+	−	+	+
Kruhlikava 2017	+	?	+	+	+	+
Kruschewski 2007	+	?	+	+	+	+
Kumagai 2011	+	?	+	+	+	+
Kumagai 2014	+	?	+	+	+	+
Kumar 2011	+	?	?	+	+	?
Kvasnovsky 2016	+	?	+	+	+	+
Lagarde 2008	+	?	+	+	+	+
Landi 2016	+	?	+	+	+	−
Leake 2013	+	?	+	−	+	+
Lee 2012	+	?	+	+	+	−
Lee 2016 (1)	+	?	+	−	+	+
Lee 2016 (2)	+	?	+	+	+	−
Lee 2016 (3)	+	?	+	+	+	−
Lee 2017	+	?	+	+	+	−
Lee 2018	+	?	+	+	+	+
Li 2016	+	?	+	+	+	+
Li 2017	+	?	+	+	+	+
Li 2021	+	?	+	+	+	+
Lim 2016	+	?	+	+	+	+
Lindner 2017	+	?	+	+	−	−
Liou 2018	+	?	+	+	+	+
Lipska 2006	+	?	+	+	+	+
Lo 2008	+	?	+	+	+	+
Lu 2018	+	?	+	+	+	+
Manfredi 2017	+	?	+	+	+	+
Marinello 2016	+	?	+	?	?	+

Table S1 –Continued

	Study participation	Study attrition	Prognostic factor measurement	Outcome measurement	Adjustment for other prognostic factors	Statistical analysis and reporting
Martin 2015	+	?	+	+	+	+
Marusch 2005	+	?	+	−	+	+
Matsui 2021	+	?	+	+	+	+
Matsumoto 2016	+	?	+	+	+	+
Merkow 2008	+	?	+	+	+	+
Miki 2014	+	?	+	+	+	+
Milgrom 2014	+	?	−	+	+	−
Mitzman 2018	+	?	+	−	+	+
Miyakita 2017	+	?	+	+	+	−
Morita 2011	+	?	+	+	+	−
Mungo 2015	+	?	+	+	+	+
Mungo 2017	+	?	+	+	+	+
Nakagawa 2017	+	?	+	+	+	−
Nevo 2018	+	?	+	+	+	+
Nikolian 2017	+	?	+	+	+	+
Nishikawa 2018	+	+	+	+	+	+
Nobuoka 2008	+	?	+	+	+	−
Nordholm-Carstensen 2019	+	+	+	+	+	+
Norero 2019	+	?	+	+	+	+
Ohkura 2018	+	?	+	+	+	+
Ojima 2009	+	?	+	+	+	+
Okabe 2019	−	?	+	+	+	+
Okada 2019	+	?	+	+	−	+
Okamura 2016	+	?	+	+	+	−
Okamura 2017	+	?	+	+	+	+
Onerup 2019	+	+	+	+	+	+
Orsenigo 2014	+	?	+	+	+	+
Oshi 2018	+	?	+	+	+	−
Ostenfeld 2015	+	+	+	+	+	+
Ozer 2010	+	?	+	+	+	+
Park 2013	+	?	+	+	+	+
Parthasarathy 2017	+	?	+	+	+	+
Pellino 2018	+	?	+	+	+	+
Poelemeijer 2018	+	?	+	+	+	+
Quan 2019	+	?	+	+	+	+

	Study participation	Study attrition	Prognostic factor measurement	Outcome measurement	Adjustment for other prognostic factors	Statistical analysis and reporting
Ragg 2009	+	?	+	+	+	+
Reilly 2014	+	?	+	+	+	+
Rencuzogullari 2017	+	?	+	+	+	+
Saito 2019	+	?	+	+	+	+
Salem 2017	+	?	+	+	+	−
Sato 2020	+	?	+	+	−	+
Schlottmann 2018	+	?	+	+	+	+
Schreckenbach 2018	−	?	+	+	+	+
Shen 2019	+	?	+	+	+	+
Shichonohe 2019	+	?	+	+	+	+
Shinji 2018	+	?	+	+	+	+
Smit 2016	+	?	+	+	+	+
Song 2014	+	+	+	+	+	+
Souwer 2020	+	?	+	+	+	+
Sparreboom 2018	+	+	+	+	+	+
Stromark 2016	+	?	+	+	+	+
Sugisawa 2012	+	?	+	+	+	+
Sunpawerawong 2012	+	?	+	+	+	−
Tackeuchi 2016	+	?	+	+	+	+
Takeuchi 2015	+	?	+	+	+	−
Tan 2013	+	+	+	+	?	−
Tanaka 2015	+	?	+	+	+	+
Tanaka 2016	+	?	+	+	+	+
Tegels 2014	+	?	+	+	+	+
Tian 2017	+	?	+	+	?	−
Tokunuga 2009	+	?	+	+	+	+
Tran 2015	+	?	+	+	+	−
Tu 2016	+	?	+	+	+	+
Tu 2017 (1)	+	?	+	+	+	+
Tu 2017 (2)	+	?	+	+	+	+
Ushiku 2015	+	?	+	+	+	+
Van Daele 2016	+	?	+	+	+	+
Van Leersum 2014	+	+	+	+	+	+
Van Rossum 2015	+	?	+	?	+	+

	Study participation	Study attrition	Prognostic factor measurement	Outcome measurement	Adjustment for other prognostic factors	Statistical analysis and reporting
Verweij 2016	+	?	+	+	+	+
Veyrie 2007	+	?	+	+	+	+
Wang 2017	+	?	+	−	+	+
Wang 2019 (1)	+	?	+	+	+	+
Wang 2019 (2)	+	?	+	+	+	+
Wang 2020	+	?	+	+	+	+
Wantanbe 2014	+	?	+	−	+	+
Wightmann 2017	+	?	+	+	+	+
Xiao 2019 (1)	+	?	+	+	+	+
Xiao 2019 (2)	+	?	+	+	+	+
Xie 2017	+	?	+	+	+	+
Xu 2020	+	?	+	+	+	−
Yang 2017 (1)	+	?	+	+	+	−
Yang 2017 (2)	+	?	+	+	+	−
Yasui 2017	−	?	+	+	+	+
Yeh 2005	+	?	+	+	+	+
Yoshida 2014	+	?	−	+	+	+
Yoshida 2016	+	?	+	+	+	+
Yoshida 2018	+	?	+	+	+	+
You 2019	+	?	+	+	+	+
Yu 2019 (1)	−	?	+	+	+	+
Yu 2019 (2)	+	?	+	+	+	+
Yun 2017	+	?	?	+	+	+
Zaimi 2018	+	+	+	+	+	−
Zhang 2016	+	?	+	+	?	−
Zhang 2018	+	?	+	+	+	+
Zhao 2016	+	?	?	+	+	+
Zheng 2018	+	?	+	+	+	+
Zheng 2019	+	?	+	+	+	+
Zhou 2015	+	?	+	+	+	+
Zingg 2011	+	?	?	+	+	+

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Supplementary Information B

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2

Chapter 3

Patient-Related Prognostic Factors for Anastomotic Leakage, Major Complications and Short-term Mortality Following Esophagectomy for Cancer: A Systematic Review and Meta-analysis

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List of abbreviations

ASA, American Society of Anesthesiologists; ERAS, Enhanced Recovery After Surgery; OR, Odds Ratio; QUIPS, Quality in Prognostic Studies.

Abstract

Objective: To identify preoperative patient-related prognostic factors for anastomotic leakage, mortality and major complications in patients undergoing oncological esophagectomy.

Summary of Background Data: Esophagectomy is a high-risk procedure with an incidence of major complications around 25% and short-term mortality around 4%.

Methods: We systematically searched theMedline and Embase databases for studies investigating the associations between patient-related prognostic factors and anastomotic leakage, major postoperative complications (Clavien-Dindo ≥ IIIa) and/or 30-day/in-hospital mortality after esophagectomy for cancer.

Results: Thirty-nine eligible studies identifying 37 prognostic factors were included. Cardiac comorbidity was associated with anastomotic leakage, major complications and mortality. Male sex and diabetes were prognostic factors for anastomotic leakage and major complications. Additionally, ASA-score >III and renal disease were associated with anastomotic leakage and mortality. Pulmonary comorbidity, vascular comorbidity, hypertension and adenocarcinoma tumor histology were identified as prognostic factors for anastomotic leakage. Age >70 years, habitual alcohol usage and a BMI 18.5-25 were associated with increased risk for mortality.

Conclusion: Various patient-related prognostic factors are associated with anastomotic leakage, major postoperative complications and postoperative mortality following oncological esophagectomy. This knowledge may define casemix adjustment models used in benchmarking or auditing and may assist in selection of patients eligible for surgery or tailored perioperative care.

Introduction

Esophageal carcinoma is the seventh most common and sixth most lethal malignancy worldwide [1]. Its incidence is rising rapidly in the Western world which might be a result of the obesity epidemic and the associated higher prevalence of gastro-esophageal reflux disease. Currently, the 5-year survival rate of curatively treated esophageal carcinoma patients approximates 40-50% [2, 3]. This curative treatment consists of neoadjuvant chemo(radio)therapy followed by surgical resection. However, esophagectomies are highly invasive procedures associated with significant postoperative morbidity. The incidence of major postoperative complications ranges around 26-31% with failure-to-rescue rates of around 18-19% [4, 5]. Reduction of (severe) complications might reduce recovery time, length of hospital stay, readmission rates and hospital costs, and increase long-term quality of life. In addition, recurrence-free and overall cancer-related survival are negatively affected by postoperative complications [6, 7].

The implementation of enhanced recovery after surgery (ERAS) protocols reduces postoperative complication rates [8]. Further reduction of major complications may be achieved by tailor-made perioperative care using personalized prehabilitation programs. In addition, benchmarking surgical outcomes in national clinical audits might lead to a further decrease of surgical morbidity [9, 10]. An audit measures quality of care using structure, process, and outcome indicators and feeds benchmarked results back to clinicians [11, 12]. Reduction of hospital variation may enhance outcomes at population level [13]. In auditing, knowledge on patient-related prognostic factors predicting adverse outcomes is essential in order to establish casemix models enabling fair hospital comparison.

We aimed to identify patient-related prognostic factors for major postoperative complications (Clavien-Dindo ≥ IIIa), anastomotic leakage, and 30-day/in-hospital mortality after esophageal cancer surgery [14].

Methods

The study protocol was registered in the PROSPERO database (CRD42020204787). This systematic review and meta-analyses adhered to the Preferred Reporting Items for Systematic Reviews guidelines.

Criteria for study eligibility

All studies including patients undergoing curatively intended esophagectomy for cancer, describing patient-related prognostic factors for 1) anastomotic leakage, 2) major postoperative complications (Clavien-Dindo ≥ IIIa) and/or 3) 30-day/in-hospital mortality were considered for inclusion. Studies including patients undergoing salvage or palliative surgery were excluded. No restrictions regarding neoadjuvant therapy or tumor stage were applied. Only retrospective or prospective cohort studies and randomized-controlled trials with full-text articles published in English or Dutch were included. Case reports and case series (< 40 patients) were excluded. Studies including children (< 18 years of age) or animals were excluded. No restrictions as to study publication status were applied. In case of overlapping cohorts, the study reporting on the highest number of relevant outcome measures and/or patients was included.

Search method

To identify all relevant publications, the Medline and Embase electronic databases were searched systematically from inception to the 19th of April 2021. Search terms included controlled MeSH terms in PubMed and EMtree terms in EMBASE, as well as free text terms. No restrictions for date of publication were applied. Reference lists of identified review articles were checked for additional relevant studies. Authors were contacted in case of full-text unavailability.

Study selection

Study selection was performed individually by DMV and RTvK. Initial screening was based on title and abstract. Disagreements regarding eligibility were resolved by discussion, with MWJMW acting as arbitrator when necessary. Thereafter, full texts were independently screened by DMV and RTvK. Again, MWJMW acted as arbitrator in case of disagreement. Reasons for exclusion were documented. A flowchart of study selection is depicted in Figure 1. Endnote X9 (Clarivate Analytics, Philadelphia, PA, USA) and Covidence were used during the selection process.

Assessment of risk of bias

All included studies were independently assessed for potential risk of bias by DMV and RTvK, using the Quality in Prognostic Studies (QUIPS) tool for classification of prognostic factor studies [15]. Discrepancies were resolved by discussion, with MWJMW as arbitrator. The risk of bias in studies was assessed on the following domains: study participation, study attrition, prognostic factor measurement, outcome measurement, adjustment bias, and statistical analysis bias. Each domain was graded as high, low or unclear. The results are summarized in Supplementary Information B.

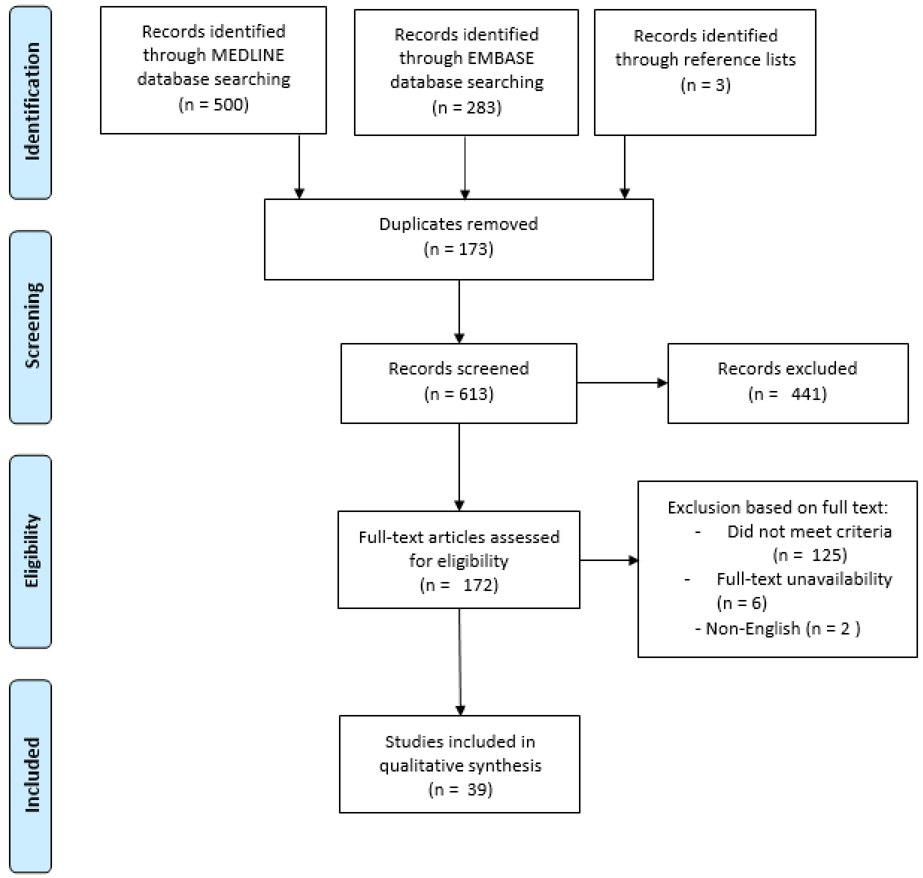

Figure 1 – PRISMA flowchart of study selection

Data extraction and management

Data extraction was performed by RTvK and subsequently checked by DMV. The data extraction was performed in a predefined Excel-sheet, designed by DMV and RTvK. The sheet was piloted in at least one included study. Discrepancies regarding data extraction were resolved by discussion, MWJMW acted as arbitrator when necessary. Subsequently, data was imputed in RevMan 5. The following data was extracted: 1) general study information (author, journal, year of publication, dataset, methodology, treatment regimen, patient characteristics), 2) investigated patient-related prognostic factors, 3) outcome measure incidence or odds Ratios (OR) and accompanying 95% confidence intervals (CI) of outcomes in different prognostic factor groups.

Data analyses

Following data extraction, the homogeneity between the included studies was assessed using the Higgins I^2 statistic, with an I^2>50% considered heterogeneous. Random-effect modelling was used to calculate pooled univariable OR and accompanying 95% CI for anastomotic leakage, major complications and 30-day/in-hospital mortality. A two-sided $p<0.05$ was considered statistically significant. Analyses were conducted using RevMan 5 (Cochrane).

Results

After removal of duplicates, the literature search resulted in a total of 613 studies potentially eligible for inclusion. After title and abstract, and full-text screening 39 studies met inclusion criteria (Figure 1). The risk of bias of the included studies is depicted in Supplementary File 3. All included studies were observational. The main study characteristics are presented in Table 1. A total of 37 different patient-related prognostic factors for severe complications, anastomotic leakage and/or 30-day/in-hospital mortality were described in 48.853 patients and used in the current meta-analyses (Table 1). Eleven studies described prognostic factors for major complications, 31 for anastomotic leakage, and 12 for 30-day/in-hospital mortality.

Anastomotic leakage

A total of 37 prognostic factors for anastomotic leakage were described in 31 studies, all were included in the meta-analyses (Table 2). Ten factors were significantly associated with anastomotic leakage, one protective factor was identified.

Renal disease was the most prominent prognostic factor for anastomotic leakage with an OR of 3.02 (95% CI 2.03-4.50; *P* <0.01). In addition, vascular comorbidity (OR 1.53; 95% CI 1.13-2.05; *P* <0.01), diabetes (OR 1.40; 95% CI 1.05-1.88; *P* <0.01), pulmonary comorbidity (OR 1.32; 95% CI 1.11-1.57; *P* <0.01), hypertension (OR 1.26; 95% CI 1.04-1.52; *P* 0.02) and cardiac comorbidity (OR 1.24; 95% CI 1.07-1.42; *P* <0.01) were significantly associated with anastomotic leakage. American Society of Anesthesiologists (ASA) score ≥ III also significantly increased the risk of anastomotic leakage (OR 1.49; 95% CI 1.13-1.97; *P* 0.04). Males were at greater risk for anastomotic leakage than females (OR 1.20; 95% CI 1.03-1.40; *P* 0.02). Anastomotic leakage occurred more often after surgery for adenocarcinoma compared to squamous cell carcinoma (OR 1.45; 95% CI 1.06-1.99; *P* 0.02).

An increased HBa1c was also associated with anastomotic leakage (OR 2.14; 95% CI 1.21-3.78; *P* <0.01) but was only described by one study [16]. Therefore, meta-analysis was not possible.

Patients receiving neoadjuvant chemotherapy were at lower risk for anastomotic leakage (OR 0.88; 95% CI 0.78-0.98; *P* 0.04).

An analysis of studies only including minimally invasive esophagectomy did show no significant associations (Supplementary Information A).

Major complications

A total of 23 prognostic factors for major postoperative complications (CD ≥ IIIa) were described in 11 studies and were used in the meta-analyses (Table 3). Of these factors, four were significantly associated with major complications, of which male sex was the most prominent (OR 4.50; 95% CI 1.21-16.64; *P* 0.02). In addition, cardiac comorbidity (OR 1.53; 95% CI 1.25-1.87; *P* <0.01) and diabetes (OR 1.93; 95% CI 1.14-3.26; *P* 0.01) were significantly associated with major complications. The presence of any comorbidity was also associated with major complications but was described by only one study (OR 1.69; 95% CI 1.12-2.55; *P* 0.01). A time interval between neoadjuvant therapy and surgery of < 8 weeks was associated with fewer major complications (OR 0.68; 95% CI 0.50-0.93; *P* 0.01).

Mortality

Fifteen prognostic factors for 30-day/in-hospital mortality were identified in 12 studies and used for meta-analyses (Table 4). Of these factors, six were significantly associated with increased mortality rates. ASA ≥ III (OR 2.77; 95% CI 1.80-4.26; *P* <0.01), cardiac comorbidity (OR 2.40; 95% CI 1.72-3.35; *P* <0.01), an age of 70 years and older (OR 2.06; 95% CI 1.66-2.56; *P* <0.01) and a BMI between 18.5 and 25 (OR 1.41; 95% CI 1.11-1.78; *P* <0.01) were significantly associated with higher risk of mortality. In addition, habitual alcohol usage (OR 3.10; 95% CI 2.26-4.25; *P* <0.01) and renal disease (OR 2.85; 95% CI 1.71-4.74; *P* <0.01) were significantly associated with increased mortality rates but were described by only one study. Overweight (BMI 25-30) (OR 0.40; 95% CI 0.30-0.53; *P* <0.01) and an interval between neoadjuvant therapy and surgery of < 8 weeks (OR 0.54; 95% CI 0.35-0.85; *P* <0.01) were associated with lower mortality rates.

Table 1- Baseline characteristics of included studies. AL; anastomotic leakage, GEJ; gastro-esophageal junction, MI; minimally invasive, ACC; adenocarcinoma, CRT; chemoradiotherapy, CTx; chemotherapy, RT; radiotherapy, SCC; squamous cell carcinoma. *Major complications are defined as Clavien-Dindo ≥ IIIa.

Author (year)	Country	Study type	Inclusion period	Number of patients	Histology (ACC*/SCC*)	Localization	Neo-adjuvant therapy	MI*/ Open/ Both	Trans-thoracic / Transhiatal	Location of anastomosis	Type of anastomosis	AL	Major complications*	30-day Mortality	Investigated prognostic factors
Alexiou (1998) [48]	UK	Observational	1987-1997	523	ACC and SCC	Cervical, Intrathoracic and GEJ	0%	100% Open	-	Thoracic	-	29 (5.5%)	-	-	Age
Aoyama (2020) [49]	Japan	Observational	2005-2018	122	ACC and SCC	Intrathoracic	-	-	-	Cervical	-	44 (36,1%)	-	-	Age, sex, smoking, alcohol usage, tumor stage
Berkelmans (2015) [50]	The Netherlands	Observational	2013-2014	89	ACC and SCC	-	CRT 73 (82.0%), CTx 4 (4.5%)	100% MI	Both	-	-	15 (16.9%)	-	-	Sex, neoadjuvant therapy, ASA-score, any comorbidity, cardiovascular comorbidity, pulmonary comorbidity, vascular comorbidity, diabetes, renal disease, steroid use, BMI
Borggreve (2018) [51]	The Netherlands	Observational	2003-2015	406	ACC 309 (76.1%), SCC 92 (22.7%)	-	CRT 153 (37.7%), CTx 122 (30.0%)	Both	Both	-	Hand sewn and stapled	104 (25.6%)	-	-	Sex, histology, neoadjuvant therapy, ASA-score, cardiovascular comorbidity, pulmonary comorbidity, diabetes, smoking
Busweiler (2018) [52]	The Netherlands and Sweden	Observational	2012-2014	2.509	ACC 1.787 (71.2%), SCC 415 (16.5%)	Cervical, intrathoracic and GEJ	CRT 1.857 (74.0%), CTx 285 (11.4%)	Both	Both	Cervical and thoracic	-	311 (12.4%)	-	59 (2.4%)	Age, sex, ASA-score

Table 1- Continued

Author (year)	Country	Study type	Inclusion period	Number of patients	Histology (ACC*/SCC*)	Localization	Neo-adjuvant therapy	MI*/ Open/ Both	Trans-thoracic / Transhiatal	Location of anastomosis	Type of anastomosis	AL	Major complications*	30-day Mortality	Investigated prognostic factors
Daele, V. (2016) [53]	Belgium	Observational	2005-2014	412	ACC 203 (49.3%), SCC 209 (50.7%)	Intrathoracic and GEJ	RT 195 (47.3%), CTx 228 (55.3%)	Both	Transthoracic	Thoracic	Stapled	12 (3.0%)	-	-	Age, sex, histology, neoadjuvant radiotherapy, neoadjuvant chemotherapy, ASA-score, , cardiovascular comorbidity, diabetes, renal disease, hypertension, previous surgery, smoking, preoperative weight loss
Filip (2015) [54]	Italy	Observational	2008-2012	167	ACC 105 (62.9%), SCC 58 (34.7%)	Cervical, intrathoracic and GEJ	CRT 131 (78.4%)	Both	-	-	-	-	20 (12.0%)	-	Sex, tumor localization, histology, neoadjuvant therapy, ASA-score, cardiovascular comorbidity, pulmonary comorbidity, vascular comorbidity, diabetes, renal disease, hepatic disease, HIV, preoperative weight loss
Fjederholt (2017) [55]	Denmark	Observational	2003-2012	557	ACC 557 (100.0%)	GEJ	-	-	Both	-	-	42 (7.5%)	-	-	Sex, ASA-score, Charlson index, smoking, tumor stage
Fogh (2011) [56]	USA	Observational	1994-2005	260	-	Intrathoracic and GEJ	CRT 260 (100%)	-	-	-	-	32 (12.3%)	-	14 (5.4%)	Age, sex
Gao (2019) [57]	China	Observational	2016-2017	96	-	Intrathoracic and GEJ	Unspecified38 (39.6%)	100% MI	Both	-	Hand sewn and stapled	12 (12.5%)	-	-	Age, sex, neoadjuvant therapy, comorbidity, pulmonary comorbidity, diabetes, hypertension, alcohol

Table 1- Continued

Author (year)	Country	Study type	Inclusion period	Number of patients	Histology (ACC*/SCC*)	Localization	Neo-adjuvant therapy	MI*/ Open/ Both	Trans-thoracic / Transhiatal	Location of anastomosis	Type of anastomosis	AL	Major complications*	30-day Mortality	Investigated prognostic factors
Goense (2016) [58]	The Netherlands	Observational	2012-2015	167	ACC and SCC	Intrathoracic and GEJ	CRT 8 (4.8%), CTx 145 (86.8%)	100% MI	Both	-	Hand sewn and stapled	40 (24.0%)	-	-	Sex, neoadjuvant therapy, ASA-score, cardiovascular comorbidity, pulmonary comorbidity, vascular comorbidity, diabetes, renal disease, hypertension, smoking
Gooszen (2018) [26]	The Netherlands	Observational	2011-2015	3.348	ACC 2.600 (77.7%), SCC 663 (19.8%)	Intrathoracic and GEJ	CRT 776 (23.2%), CTx 239 (7.1%)	Both	-	Cervical and thoracic		656 (19.6%)	-	-	Sex, tumor localization, histology, neoadjuvant therapy, ASA-score, cardiovascular comorbidity, pulmonary comorbidity, vascular comorbidity, diabetes, neurological comorbidity, hypertension, previous surgery, tumor stage
Hall (2019) [59]	USA	Observational	2005-2015	915	ACC 682 (74.5%), SCC 73 (8.0%)	Intrathoracic and GEJ	621 (67.8%)	Both	-	-	-	127 (13.9%)	-	-	Sex, histology, neoadjuvant radiotherapy, ASA-score, ADL-dependency, cardiovascular comorbidity, pulmonary comorbidity, bleeding disorder, diabetes, renal disease, steroid use, smoking, preoperative weight loss, tumor stage

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Table 1- Continued

Author (year)	Country	Study type	Inclusion period	Number of patients	Histology (ACC*/SCC*)	Localization	Neo-adjuvant therapy	MI*/ Open/ Both	Trans-thoracic / Transhiatal	Location of anastomosis	Type of anastomosis	AL	Major complications*	30-day Mortality	Investigated prognostic factors
Janowak (2015) [61]	USA	Observational	2009-2013	168	-	-	CRT 93 (55.4%)	Both	Both	-	-	-	58 (35.0%)	-	Age, sex, neoadjuvant therapy, ASA-score, cardiovascular comorbidity, pulmonary comorbidity, diabetes, renal disease, smoking, BMI
Kassis (2013) [62]	USA	Observational	2001-2011	7.595	-	-	3 478 (45.8%)	Both	Both	-	-	804 (10.6%)	-	-	Sex, neoadjuvant therapy, ASA-score, cardiovascular comorbidity, vascular comorbidity, diabetes, renal disease, previous surgery, hypertension, steroid use, history of malignancy, smoking, BMI
Kathiravetpillai (2016) [63]	The Netherlands	Observational	2001-2014	190	-	-	CRT 100%	Both	-	-	-	50 (26.3%)	39 (20.5%)	9 (4.7%)	Interval neoadjuvant and surgery
Klevebro (2019) [19]	Sweden	Observational	2010-2017	2.332	-	-	-	Both	-	-	-	312 (13.3%)	1383 (59.3%)	42 (1.8%)	Cardiovascular comorbidity, pulmonary comorbidity
Koeter (2015) [64]	The Netherlands	Observational	2009-2011	53	ACC 49 (92.5%), SCC 4 (7.5%)	-	CRT 100%	Both	-	Cervical	Hand sewn and stapled	13 (24.5%)	-	-	Sex, histology, ASA-score, comorbidity
Koyanagi (2016) [65]	Japan	Observational	2014-2015	40	ACC 4 (10.0%), SCC 36 (90.0%)	Cervical, intrathoracic and GEJ	15 (30.0%)	Both	Both	Cervical	Hand sewn and stapled	7 (17.5%)	-	-	Sex, tumor localization, histology, neoadjuvant therapy, smoking, tumor stage
Kruhilikava (2017) [24]	Denmark	Observational	2003-2010	285	-	-	-	-	-	-	-	24 (8.4%)	62 (21.8%)	7 (2.5%)	BMI
Markar (2013) [66]	USA	Observational	1991-2011	500	-	-	-	-	-	-	-	18 (3.6%)	-	3 (0.6%)	Age

Table 1- Continued

Author (year)	Country	Study type	Inclusion period	Number of patients	Histology (ACC*/SCC*)	Localization	Neo-adjuvant therapy	MI*/ Open/ Both	Trans-thoracic / Transhiatal	Location of anastomosis	Type of anastomosis	AL	Major complications*	30-day Mortality	Investigated prognostic factors
McBee (2020) [67]	USA	Observational	2016-2018	1.260	ACC and SCC	Cervical, intrathoracic and GEJ	-	Both	-	-	-	171 (13,6%)	-	34 (2,7%)	BMI≥30
Miki (2016) [68]	Japan	Observational	2000-2015	158	-	Cervical, intrathoracic and GEJ	CTx 35 (22.2%)	100% MI	-	-	-	-	30 (23.4%)	-	Age, sex, tumor localization, neoadjuvant therapy, pulmonary comorbidity, diabetes, BMI<25
Mitzman (2018) [69]	USA	Observational	2009-2016	9.389	-	-	-	Both	-	-	-	-	-	321 (3.4%)	BMI
Miyawaki (2020) [70]	Japan	Observational	2013-2017	188	ACC and SCC	-	-	-	Transthoracic	Cervical	Hand sewn	29 (15,4%)	-	-	Sex, neoadjuvant therapy pulmonary comorbidity, diabetes, hypertension, tumor stage
Murphy (2013) [71]	USA	Observational	2002-2008	191	-	-	-	Both	-	-	-	16 (8.4%)	-	-	Comorbidity, smoking, alcohol, tumor stage
Okamura (2016) [16]	Japan	Observational	2011-2015	300	ACC and SCC	-	-	Both	-	Cervical	Hand sewn and stapled	35 (11.7%)	-	-	Age, sex, histology, neoadjuvant therapy, cardiovascular comorbidity, pulmonary comorbidity, diabetes, neurological comorbidity, hepatic disease, hypertension, smoking, HBa1c
Rutegard (2016) [72]	Sweden	Observational	2001-2005	567	ACC 466 (82.2%), SCC 149 (26.7%)	Cervical, intrathoracic and GEJ	33 (5.8%)	-	Both	Thoracic	-	-	154 (25.0%)	-	Sex, histology, neoadjuvant therapy, any comorbidity, tumor stage
Rutegard (2016) [73]	Sweden	Observational	2001-2005	559	ACC 449 (80.3%), SCC 110 (19.7%)	Cervical, intrathoracic and GEJ	29 (5.2%)	-	Both	Thoracic	Hand sewn and stapled	44 (7.9%)	-	-	Sex, histology, neoadjuvant therapy, any comorbidity, tumor stage

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Table 1- Continued

Author (year)	Country	Study type	Inclusion period	Number of patients	Histology (ACC*/SCC*)	Localization	Neo-adjuvant therapy	MI*/ Open/ Both	Trans-thoracic / Transhiatal	Location of anastomosis	Type of anastomosis	AL	Major complications*	30-day Mortality	Investigated prognostic factors
Saito (2019) [74]	Japan	Observational	2007-2015	90	ACC 3 (3.3%), SCC 87 (96.7%)	-	CTx 29 (32.2%)	100% MI	Both	-	-	-	32 (35.6%)	-	Sex, histology, neoadjuvant therapy, ASA-score, cardiovascular comorbidity, diabetes, smoking, alcohol, BMI, tumor stage
Salem (2016) [75]	USA	Observational	2010-2013	129	-	-	-	100% MI	-	-	-	5 (3.9%)	-	-	BMI
Sato (2020) [76]	Japan	Observational	2013-2019	248	ACC 213 (85.9%), SCC 21 (8.5%)	-	-	Both	-	Thoracic	-	38 (15,3%)	-	-	Sex, histology, neoadjuvant therapy, pulmonary comorbidity, diabetes, hypertension, tumor stage
Scarpa (2015) [77]	Italy	Observational	2008-2012	181	-	-	-	Both	Both	-	-	8 (4.4%)	20 (11.0%)	2 (1.1%)	Age
Schlottmann (2018) [78]	USA	Observational	2000-2014	5.243	-	-	-	-	-	-	-	297 (5.7 %)	-	-	Age
Shichinohe (2019) [79]	Japan	Observational	2009-2012	483	-	-	-	-	-	-	-	54 (11.1%)	132 (27.3%)	-	Sex, malnutrition
Takeuchi (2014) [80]	Japan	Observational	2011	5.354	ACC and SCC	Cervical, intrathoracic and GEJ	1.005 (18.8%)	Both	Both	Both	-	-	-	244 (4.6%)	Sex, neoadjuvant therapy, ASA-score, renal disease
Werf, V.d. (2018) [23]	The Netherlands	Observational	2011-2016	3.091	ACC and SCC	Intrathoracic and GEJ	CRT 3.091 (100%)	Both	Both	Cervical and thoracic	Hand sewn and stapled	341 (11.0%)	185 (6.0%)	106 (3.4%)	Interval neoadjuvant and surgery
Zhao (2017) [81]	China	Observational	2010-2016	273	SCC 273 (100.0%)	-	0%	100% MI	-	-		19 (7.0%)	25 (9.2%)	0 (0.0%)	Age

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Table 2 – Results of meta-analyses identifying patient-related prognostic factors for anastomotic leakage. ASA-score; American Society of Anesthesiologists score, BMI; Body Mass Index, CRT; Chemoradiotherapy, Ctx; Chemotherapy, OR; Odds Ratio, RT; Radiotherapy.

Prognostic factor	Number of studies	Number of patients	OR (95% CI)	I^2 (%)	Forest plot (OR)
Patient characteristics					
ASA-score ≥ III	8	13.233	**1.49 [1.13, 1.97]**	64	
Male	17	16.209	**1.20 [1.03, 1.40]**	9	
Age ≥ 70	6	1.399	0.85 [0.51, 1.42]	34	
Nutritional factors					
BMI > 30	6	9.773	1.10 [0.71, 1.71]	65	
BMI 25-30	2	414	0.85 [0.34, 2.14]	9	
BMI < 18.5	1	285	1.10 [0.24. 5.00]	-	
BMI 18.5 – 25	2	414	0.85 [0.38, 1.90]	0	
Malnutrition	3	1.910	1.49 [0.94, 2.36]	24	
Preoperative laboratory tests					
Increased HbA1c	1	300	**2.14 [1.21, 3.78]**	-	
Comorbidity					
Alcohol	4	597	1.54 [0.91, 2.60]	0	
Smoking	9	10.705	**1.19 [0.97, 1.44]**	58	
History of malignancy	1	415	1.86 [0.66, 5.22]	-	
Steroid use	4	9.013	2.30 [0.50, 10.63]	76	
Hypertension	7	12.414	**1.26 [1.04, 1.52]**	37	
Previous surgery	3	11.355	**1.09 [0.95, 1.24]**	0	
Hepatic comorbidity	**1**	**300**	**3.29 [0.97, 11.16]**	-	
Neurologic comorbidity	2	3.648	1.34 [0.44, 4.09]	0	
Renal disease	4	11.355	3.02 [2.03, 4.50]	0	
Diabetes	11	13.923	1.40 [1.05, 1.88]	66	
Vascular comorbidity	4	10.955	**1.53 [1.13, 2.05]**	32	
Bleeding disorder	1	915	0.97 [0.37, 2.53]	-	
Pulmonary comorbidity	7	7.713	1.32 [1.11, 1.57]	0	
Cardiac comorbidity	6	14.896	1.24 [1.07, 1.42]	0	
Charlson index ≥ 2	1	557	**1.74 [0.91, 3.33]**	-	
Any comorbidity	5	988	1.66 [0.97, 2.85]	15	

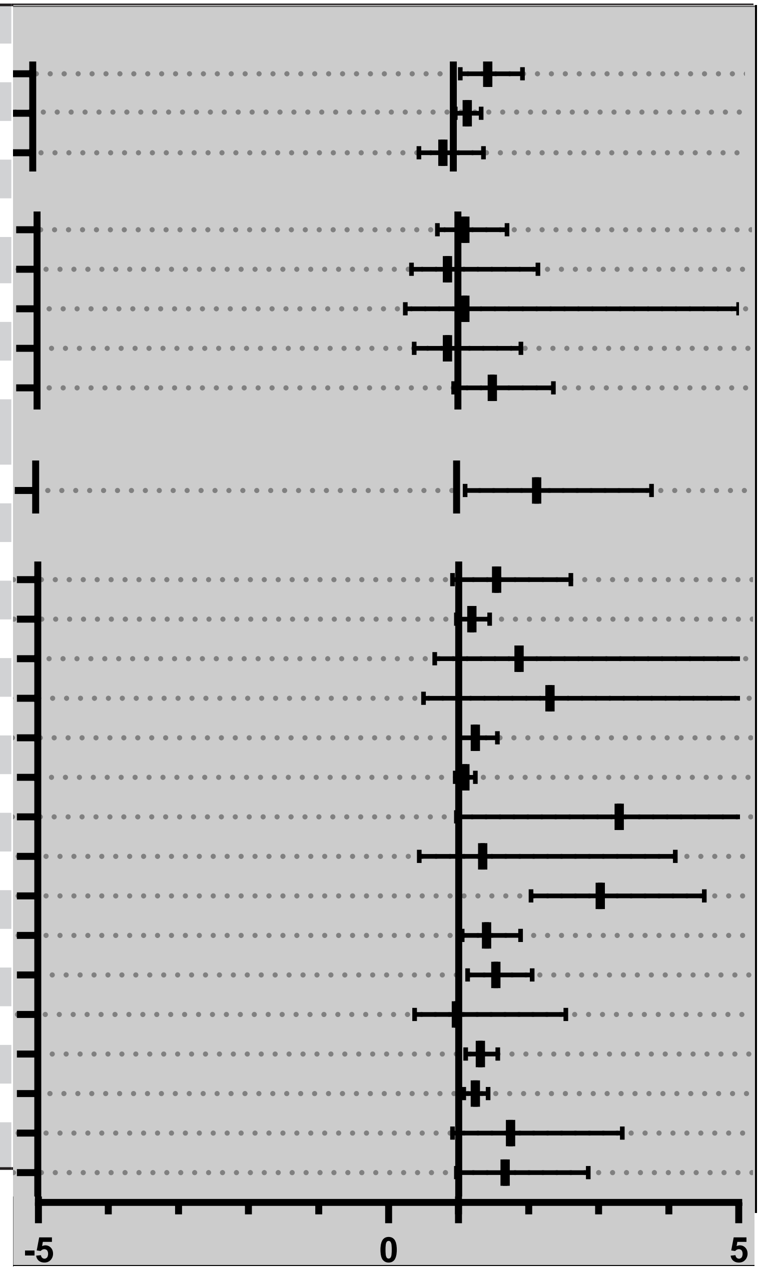

Table 2- Continued

Prognostic factor	Number of studies	Number of patients	OR (95% CI)	I² (%)	Forest plot (OR)
Tumor characteristics					
N3	2	3.905	1.15 [0.70, 1.90]	0	
N1-2	4	4.860	0.96 [0.82, 1.13]	0	
T4	2	3.905	0.84 [0.50, 1.41]	0	
T2-3	5	5.048	1.10 [0.86, 1.42]	0	
Tumor stage III-IV	3	790	0.89 [0.45, 1.75]	16	
Adenocarcinoma	8	6.537	**1.45 [1.06, 1.99]**	0	
Intrathoracic tumour	2	3.388	1.20 [0.94, 1.52]	0	
Neoadjuvant therapy					
Interval neoadjuvant and surgery < 8 weeks	2	3.281	0.85 [0.62, 1.16]	18	
Neoadjuvant Ctx	9	13.517	**0.88 [0.78, 0.98]**	0	
Neoadjuvant RT	3	9.110	0.78 [0.48, 1.25]	73	
Neoadjuvant CRT	6	4.417	1.02 [0.84, 1.24]	0	
Any neoadjuvant therapy	10	5.935	0.81 [0.63, 1.04]	13	

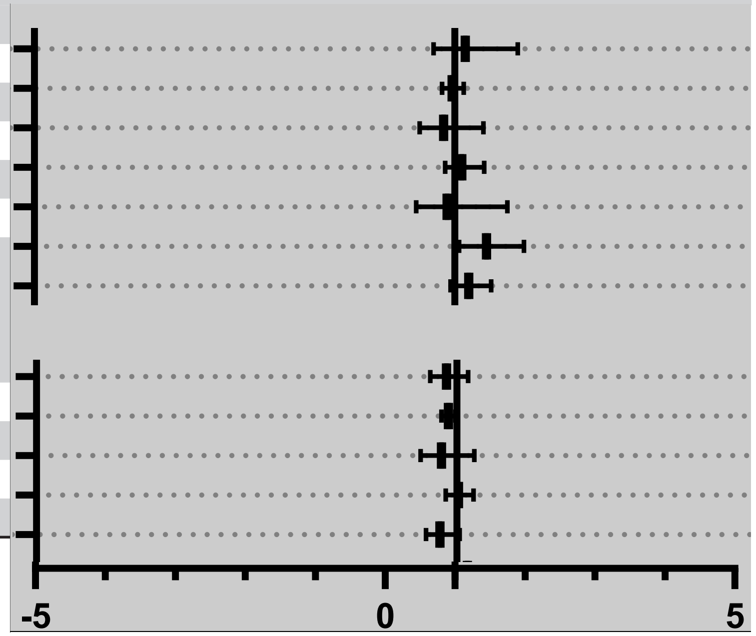

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Table 3 – Results of meta-analyses identifying patient-related prognostic factors for major complications (Clavien-Dindo ≥ IIIa). ASA-score; American Society of Anesthesiologists score, BMI; Body Mass Index, , Ctx; Chemotherapy, CRT; Chemoradiotherapy, OR; Odds Ratio.

Prognostic factor	Number of studies	Number of patients	OR (95% CI)	I^2 (%)
Patient characteristics				
ASA ≥ III	3	425	1.46 [0.85, 2.51]	0
Male	5	1.150	**4.50 [1.21, 16.64]**	88
Age ≥ 70	5	1.347	0.80 [0.60, 1.07]	0
Nutritional factors				
BMI > 30	2	453	0.50 [0.03, 8.38]	96
BMI < 18.5	2	375	1.29 [0.57, 2.94]	0
BMI 18.5 – 25	2	453	0.67 [0.43, 1.05]	0
Malnutrition	2	650	1.42 [0.92, 2.20]	0
Comorbidity				
Alcohol	1	90	1.09 [0.41, 2.86]	-
Smoking	2	258	1.45 [0.59, 3.58]	48
Hepatic comorbidity	1	167	1.39 [0.29, 6.80]	-
Renal disease	1	168	1.80 [0.65, 4.93]	-
Diabetes	4	583	**1.93 [1.14, 3.26]**	0
Vascular comorbidity	1	167	0.93 [0.11, 7.83]	-
Pulmonary comorbidity	4	2.825	0.66 [0.34, 1.28]	70
Cardiac comorbidity	4	2.757	**1.53 [1.25, 1.87]**	0
Any comorbidity	1	567	**1.69 [1.12, 2.55]**	-
Tumor characteristics				
Stage III-IV	2	657	0.93 [0.66, 131]	0
Intrathoracic tumor	2	325	1.54 [0.77, 3.08]	0
Adenocarcinoma	3	824	1.09 [0.52, 2.29]	35
Neoadjuvant therapy				
Neoadjuvant Ctx	2	248	1.27 [0.67. 2.41]	0
Neoadjuvant CRT	2	335	0.96 [0.50, 1.82]	11
Neoadjuvant therapy	5	1.150	1.01 [0.69, 1.48]	0
Interval neoadjuvant and surgery < 8 weeks	2	3.281	**0.68 [0.50, 0.93]**	0

Forest plot (OR)

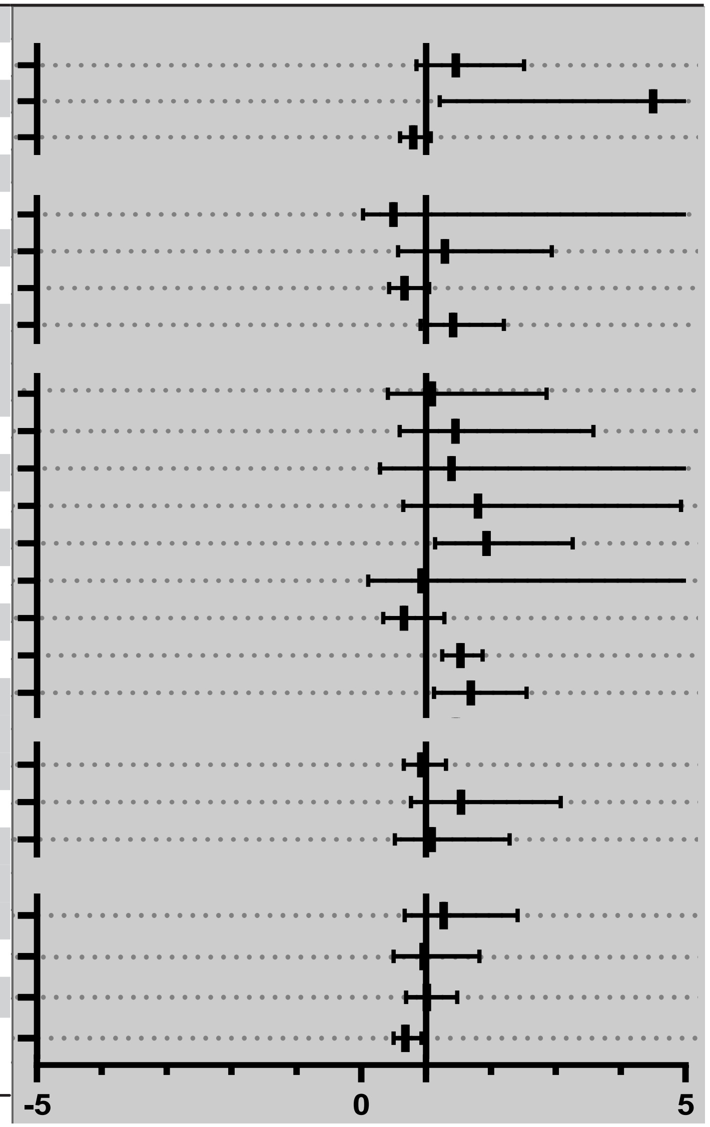
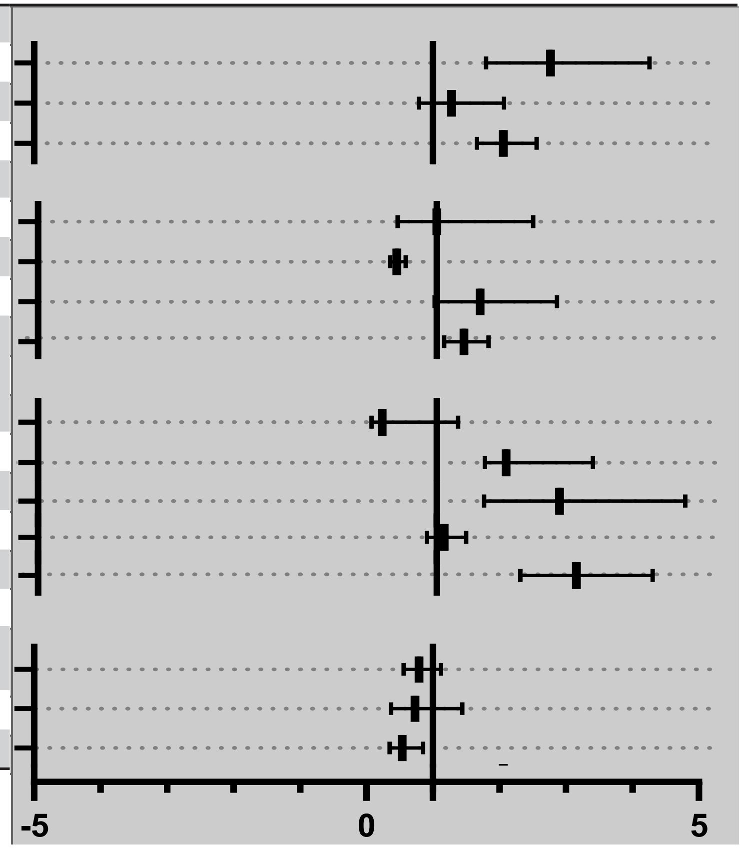


Table 4 - Results of meta-analyses identifying patient-related prognostic factors for 30-day mortality/in-hospital. ASA-score; American Society of Anesthesiologists score, BMI; Body Mass Index, Ctx; Chemotherapy, OR; Odds Ratio, RT; Radiotherapy.

Prognostic factor	Number of studies	Number of patients	OR (95% CI)	I^2 (%)	Forest plot (OR)
Patient characteristics					
ASA ≥ III	2	7.863	**2.77 [1.80, 4.26]**	0	
Male	2	7.858	1.28 [0.79, 2.07]	-	
Age ≥ 70	4	6.193	**2.06 [1.66, 2.56]**	0	
Nutritional factors					
BMI > 30	3	10.934	1.00 [0.41, 2.45]	75	
BMI 25-30	2	9.674	**0.40 [0.30, 0.53]**	0	
BMI < 18.5	2	9.674	1.65 [0.97, 2.81]	0	
BMI 18.5 – 25	2	9.674	**1.41 [1.11, 1.78]**	0	
Comorbidity					
Pulmonary comorbidity	1	2.332	0.18 [0.02, 1.32]	-	
Cardiac comorbidity	2	7.686	**2.40 [1.72, 3.35]**	0	
Renal disease	1	5.354	**2.85 [1.71, 4.74]**	-	
Smoking	1	5.354	1.11 [0.85, 1.44]	-	
Alcohol	1	5.354	**3.10 [2.26, 4.25]**	-	
Neoadjuvant therapy					
Interval neoadjuvant and surgery < 8 weeks	2	3.281	**0.54 [0.35, 0.85]**	0	
Neoadjuvant RT	1	5.354	0.73 [0.37, 1.44]	-	
Neoadjuvant Ctx	1	5.354	0.79 [0.56, 1.12]	-	



Discussion

This study is the first systematic review and meta-analyses describing prognostic factors for anastomotic leakage, major complications and 30-day/in-hospital mortality following esophageal cancer surgery. Thirty-nine studies were included, providing a comprehensive and quantitative overview of the available literature. After analyses of 37 potential prognostic factors described in literature, renal disease, vascular comorbidity, diabetes, pulmonary, hypertension, cardiac comorbidity, ASA-score ≥ III, male sex and adenocarcinoma tumor histology were prognostic factors for anastomotic leakage. Patients receiving neoadjuvant chemotherapy had a lower risk for anastomotic leakage. Male sex, cardiac comorbidity and diabetes were prognostic factors for major complications. In the current study, age >70 years, ASA-score ≥ III, cardiac comorbidity and a BMI of 18.5-20 were prognostic factors for mortality whereas a BMI of 25-30 appeared preventive of mortality. A time interval of < 8 weeks between neoadjuvant therapy and surgery was associated with lower major complication and mortality rates.

Patient characteristics

Although the observed associations were heterogenous, this study shows that male sex was associated with both higher anastomotic leakage and major complication rates. This might be a result of the higher incidence of smoking and alcohol consumption in the male population [17]. Another theory described in literature is that cortisol-induced sex hormones vary among men and women, making males more susceptible to postoperative complications after surgically induced stress [18]. In the current study, older patients are at higher risk for postoperative mortality than younger patients; age did not seem to impact anastomotic leakage and major complication rates. This might be caused by an increased susceptibility for failure to rescue in the elderly [5]. In the elderly, a decreased preoperative performance status as demonstrated by a higher ASA-score and/or comorbidities, such as cardiac and pulmonary comorbidity, might result in worse short-term outcomes [19].

Comorbidity

As shown in this study, comorbidity is a prognostic factor for the occurrence of postoperative complications. The presence of comorbidities might, besides poorer physical performance, also implicate a greater presence of artery calcifications, which was shown by Goense et al. to be independently associated with anastomotic leakage [20]. Additionally, the association between diabetes and major complications is well understood, as hyperglycemia induces microvascular damage which subsequently reduces healing capacity [21].

Body mass index (BMI)

This study showed that a BMI of 18.5-20 is associated with postoperative mortality. Patients with a BMI between 25 and 30, however, tended to have a lower risk for mortality. Previous studies have shown that preoperative weight loss and a lower BMI make patients more susceptible for failure to rescue [4, 5]. Patients with a higher BMI at baseline might have more physical reserves (i.e., less prone for catabolism), which prevents short-term adverse events. An even higher BMI (>30) was not protective for mortality. This might be caused by the difficulty of surgery in the obese due to the high amount of visceral fat compromising intraoperative visibility and making the surgery more challenging [22].

Neoadjuvant therapy

The current study also shows lower leakage rates after administration of neoadjuvant therapy. As the administration of neoadjuvant therapy is the standard of care for esophageal cancer, it may only be omitted in frail patients unable to withstand systemic therapy. This might explain the lower anastomotic leakage rates in patients undergoing neoadjuvant therapy compared to patients not receiving preoperative systemic therapy. Another prognostic factor observed in this study was the interval between neoadjuvant therapy and surgery. This study shows that an interval of >8 weeks is associated with increased major complication and mortality rates. The higher rate of adverse events in patients with a prolonged interval may be subjected to selection bias. Van de Werf et al. showed that more frail patients had a longer interval [23]. In these frail patients, the interval might have been used for preoperative optimization. Another explanation may be that the interval is prolonged due to toxicity and/or slower recovery from neoadjuvant therapy. However, especially in patients undergoing chemoradiotherapy, the longer interval might also complicate surgery because of increased postradiation scarring with increasing interval lengths.

Tumor histology

As shown in this study adenocarcinoma tumor histology is a prognostic factor for anastomotic leakage after esophagectomy. A theory is that based on the differences in pathogenesis of adenocarcinoma and squamous carcinoma patient characteristics are different. For instance, adenocarcinoma is more common in overweight and obese patients and in patients with more alcohol usage both are risk factors for anastomotic leakage [24]. However, squamous cell carcinoma is more common in patients with habitual alcohol usage and smoking [25]. Another difference between adenocarcinoma and squamous cell carcinoma is the localization, since adenocarcinoma is typically located more proximal. This localization is more suitable for a cervical anastomosis, which is associated with a higher frequency of anastomotic leakage [26].

Surgical techniques

Given the differences in incidence and severity of anastomotic leakage of a cervical and intrathoracic anastomosis, the risk-factors for anastomotic leakage might also differ based on anastomotic location [26]. Additionally, minimally invasive surgery is being used more in daily practice, unfortunately many studies do not report open and minimally invasive procedures separately. Therefore, this meta-analysis was unable to make distinctions between different surgical techniques (e.g., location of anastomosis, minimally invasive surgery), since the included studies did not allow for stratified analyses.

Perioperative care

The identification of prognostic factors for adverse events after esophagectomy may provide opportunities to optimize perioperative care by treating or optimizing these prognostic factors preoperatively and thereby decreasing surgical risk. Reduction of postoperative morbidity and mortality may in turn reduce healthcare costs [27]. Therefore, reduction of postoperative morbidity impacts healthcare on both patient, hospital and national level. The prognostic factors described in the current study may contribute to focused and personalized preoperative care by enrolling patients with certain prognostic factors into (tailor-made) prehabilitation programs. Currently, more generalized perioperative care programs are being studied and implemented in the form of ERAS protocols [28]. As part of the ERAS protocols, lifestyle interventions (e.g., alcohol cessation) are introduced in daily practice [29-31]. In addition, there is more focus on preoperative malnutrition and impaired physical capacity, which are shown to be negative prognostic factors for postoperative complications in this meta-analysis [32]. Intra and postoperative care are also being standardized in ERAS protocols (e.g., fluid therapy, opioid-sparing analgesia) [33].

The reduction of postoperative complications is important because complications are associated with reduced overall survival. Additionally, the reduction of complications positively impacts (progression-free) survival [34]. It is thought that infectious complications lead to proinflammatory cytokine release, which are related with tumor progression and metastasis [35]. One might even argue that resection could be reconsidered in patients with multiple prognostic factors as definitive chemoradiotherapy might be a more suited curative treatment option for such patients [36, 37]. However, one should keep in mind the reduced survival after definitive chemoradiotherapy.

With the use of neoadjuvant therapy, a window for preoperative optimization is opened. A systematic review showed that (p)rehabilitation programs for esophageal cancer patients can improve objective measures of physical fitness. However, effects on postoperative outcomes were less eminent [38]. Nonetheless, preoperative exercise programs have shown to significantly impact health related quality of life [39]. Several studies report that well designed randomized controlled trials on prehabilitation programs are needed in order to prove their beneficial effects on short-term postoperative outcomes [38, 40]. They should focus on optimizable preoperative prognostic factors (e.g., malnutrition or vitamin deficiencies). Esophageal cancer patients are at high risk for malnutrition due to the anatomical localization of the tumor. Therefore, nutritional interventions are important in preoperative prehabilitation [41]. This is supported by the results of the current study showing that patients with a low BMI have increased risk of postoperative mortality. Slightly overweight patients even had reduced mortality rates. These results indicate that malnourishment and depletion of essential food substances are an important and modifiable prognostic factor in esophageal cancer surgery.

Identification of high-risk patients may indicate that changes in postoperative care are needed, for example, closer postoperative surveillance or delayed enteral feeding in high-risk patients. Closer postoperative surveillance might for instance be done by using wearable devices for continuous postoperative monitoring, even on the regular hospital ward. This might lead to more timely recognition and identification of postoperative adverse events subsequently leading to earlier treatment and lower failure-to-rescue rates [42, 43].

The identified prognostic factors for major adverse outcomes after surgery are vital in clinical auditing. Comparing hospitals and providing clinicians with benchmarked outcome information is an important quality-improvement tool [44]. For fair hospital comparison, benchmarked information should be corrected for differences in casemix among hospitals. The current study provides prognostic factors for three major adverse events after esophagectomy that should be used for casemix correction in clinical audits like the Dutch Upper Gastrointestinal Cancer Audit (DUCA) [45].

Limitations

This study had some limitations. Firstly, it provided an overview of multiple studies creating a heterogeneous patient population. Additionally, definitions of prognostic factors (e.g., renal disease, cardiac comorbidity) used in literature are heterogeneous, making interpretation difficult. In addition, neo-adjuvant therapy is currently standard of care, however, this is not yet incorporated in all studies, compromising the external validity of the current study. As discussed, ERAS protocols influence postoperative outcomes which may interfere with the results of this meta-analysis. However, none of the included studies reported on the use of ERAS protocols. The observational study design used in all of the included studies may have hindered adequate interpretation of results. Additionally, most of the included studies were retrospective. Therefore, the current study is subjected to bias. However, it is suspected that due to the high number of included studies and patients, this bias was limited. In current prognostic factor research, several limitations are known, such as: publication bias, reporting bias, poor statistical analysis, and inadequate replication of findings [46]. These meta-analyses used pooled data to calculate univariable ORs, which do not correct for potential confounding factors. Additionally, this study focusses on pre-operative prognostic factors, whereas surgical factors, such as the type of anastomosis or surgery may also contribute to the risk of postoperative major complications. Lastly, continuous variables such as BMI and age are being reported as categorical variables which is subjected to bias and may make risk estimates less useful [47].

Future research should be directed towards prospective studies with well-documented prognostic factors. Additionally, well-designed randomized-controlled trials investigating the impact of preoperative prehabilitation programs for modifiable prognostic factors on surgical outcomes and quality of life. This should pave the way to enhanced personalized perioperative care.

In conclusion, this systematic review and meta-analysis identified 37 prognostic factors that are associated with adverse events after esophageal cancer surgery. Cardiac comorbidity was identified as prognostic factor for all three studied adverse outcomes (anastomotic leakage, major complications and mortality). Male sex and diabetes were identified as prognostic factors for anastomotic leakage and major complications. ASA-score >III and renal disease were shown to be associated with anastomotic leakage and mortality. Pulmonary comorbidity, vascular comorbidity, hypertension and adenocarcinoma were prognostic factors for anastomotic leakage. Older age (>70), habitual alcohol usage and an intermediate BMI were associated with increased risk for mortality. These factors should be used in casemix correction models in national clinical audits. In addition, they also enable further research for accurate pre-operative patient selection and personalized peri-operative care ultimately aiming to reduce surgical morbidity and improve postoperative quality of life.

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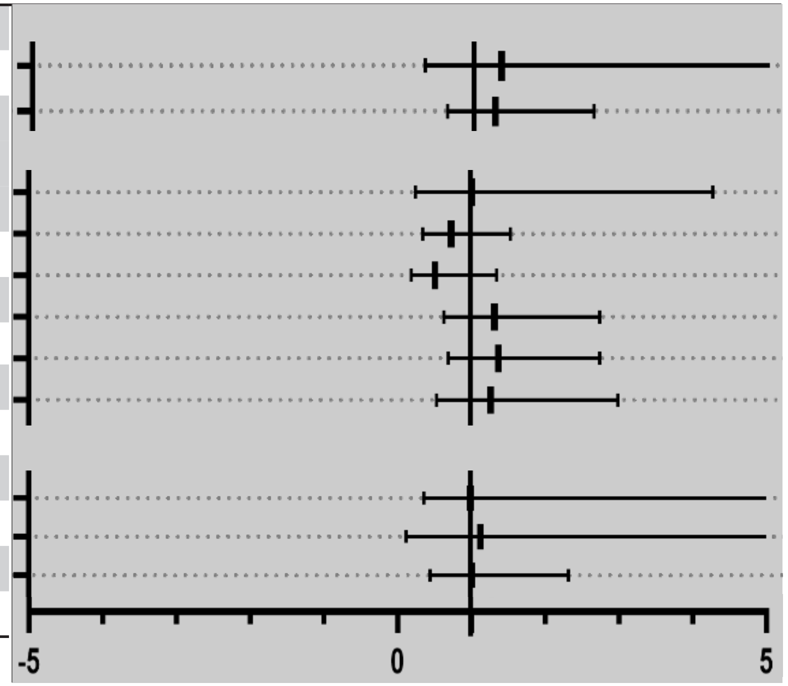
3

Supplementary Information A

Table S1 – Results of meta-analyses identifying patient-related prognostic factors for anastomotic leakage after minimally invasive esophagectomy. ASA-score; American Society of Anesthesiologists score, BMI; Body Mass Index, CRT; Chemoradiotherapy, Ctx; Chemotherapy, OR; Odds Ratio, RT; Radiotherapy.

Prognostic factor	Number of studies	Number of patients	OR (95% CI)	I^2 (%)
Patient characteristics				
ASA ≥ III	2	256	1.36 [0.33, 5.67]	86
Male	3	352	1.28 [0.63, 2.62]	0
Comorbidity				
Renal disease	2	256	1.01 [0.24, 4.28]	0
Diabetes	3	352	0.73 [0.34, 1.53]	0
Vascular comorbidity	2	256	0.51 [0.19, 1.35]	0
Pulmonary comorbidity	2	256	1.32 [0.63, 2.77]	0
Cardiac comorbidity	2	256	1.37 [0.69, 2.74]	0
Any comorbidity	2	256	1.26 [0.53, 2.99]	0
Neoadjuvant therapy				
Neoadjuvant Ctx	2	256	0.99 [0.36, 2.71]	0
Neoadjuvant CRT	2	256	1.13 [0.12, 10.62]	38
Neoadjuvant therapy	3	352	1.01 [0.44, 2.32]	0

Forest plot (OR)

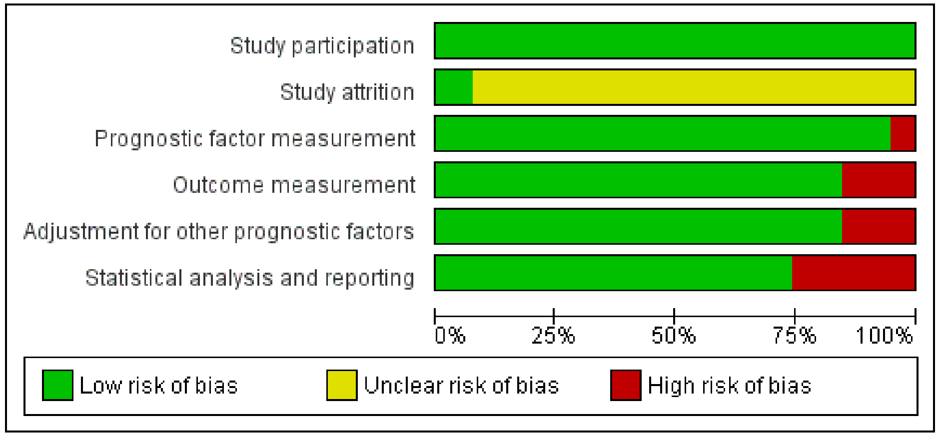


Supplementary Information B

	Study participation	Study attrition	Prognostic factor measurement	Outcome measurement	Adjustment for other prognostic factors	Statistical analysis and reporting
Alexiou 1998	+	+	+	+	−	+
Aoyama 2020	+	?	+	+	+	+
Berkelmans 2015	+	+	+	+	−	+
Borggreve 2018	+	?	+	+	+	+
Busweiler 2018	+	?	+	+	+	+
Daele, V. 2016	+	?	+	+	+	+
Filip 2015	+	?	+	+	+	+
Fjederholt 2017	+	?	+	+	+	+
Fogh 2011	+	?	+	+	+	+
Gao 2019	+	?	+	+	+	+
Goense 2016	+	?	+	+	+	+
Goozen 2018	+	+	+	−	+	+
Hall 2019	+	?	+	+	+	+
Harustiak 2016	+	?	+	+	+	+
Janowak 2015	+	?	+	+	+	+
Kassis 2013	+	?	+	−	+	−
Kathiravetpillai 2016	+	?	−	−	+	+
Klevebro 2019	+	?	+	+	+	−
Koeter 2015	+	?	+	+	+	−
Koyanagi 2016	+	?	−	+	−	−
Kruhilikava 2017	+	?	+	+	+	+
Markar 2013	+	?	+	−	−	−
McBee	+	?	+	−	+	+
Miki 2016	+	?	+	+	+	+
Mitzman 2018	+	?	+	−	+	+
Miyawaki 2020	+	?	+	+	+	+
Murphy 2013	+	?	+	+	+	+
Okamura 2016	+	?	+	+	+	−
Rutegard (1) 2012	+	?	+	+	+	−
Rutegard (2) 2012	+	?	+	+	+	+
Saito 2019	+	?	+	+	+	+
Salem 2016	+	?	+	+	+	−
Sato 2020	+	?	+	+	+	+
Scarpa 2015	+	?	+	+	−	−
Schlottmann 2018	+	?	+	+	+	+
Shichinohe 2019	+	?	+	+	+	+
Takeuchi 2014	+	?	+	+	+	+
Werf, V.d. 2018	+	?	+	+	+	+
Zhao 2017	+	?	+	+	−	−

Table S1 - Table showing the classification of study quality of all included studies using the Quality In Prognosis Studies (QUIPS) tool [1]. On the horizontal axis show the different assed domains per study. The vertical axis shows all included studies. The green bullet = low risk of bias, yellow = unclear risk of bias, red = high risk of bias.

Table S2 – Summary table showing an overview of classification of study quality of all included studies using the QUIPS tool as shown in table S1.



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3

Chapter 4

Conventional Regression Analysis and Machine Learning in Prediction of Anastomotic Leakage and Pulmonary Complications after Esophagogastric Cancer Surgery

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List of abbreviations

ARDS; Acute Respiratory Distress Syndrome, ASA; American Society of Anesthesiologists, AUC; Area Under the Curve, CI; Confidence Interval, DUCA; Dutch Upper Gastrointestinal Cancer Audit, ERAS; Enhanced Recovery After Surgery, GLM; Generalized Linear Model, KNN; k-Nearest Neighbors, OR; Odds Ratio, ROC; Receiver Operating Characteristics, SVM; Support Vector Machine.

Abstract

Background and Objectives: With the current advanced data-driven approach to health care, machine learning is gaining more interest. The current study investigates the added value of machine learning to linear regression in predicting anastomotic leakage and pulmonary complications after upper gastrointestinal cancer surgery.

Methods: All patients in the Dutch Upper Gastrointestinal Cancer Audit (DUCA) undergoing curatively intended esophageal- or gastric cancer surgery in 2011-2017 were included. Anastomotic leakage was defined as any clinically or radiologically proven anastomotic leakage. Pulmonary complications entailed: pneumonia, pleural effusion, respiratory failure, pneumothorax and/or acute respiratory distress syndrome. Different machine learning models were tested. Nomograms were constructed using logistic regression.

Results: Between 2011-2017, 4,228 patients underwent surgical resection for esophageal cancer of which 18% developed anastomotic leakage and 30% a pulmonary complication. Of the 2,199 patients with surgical resection for gastric cancer, 7% developed anastomotic leakage and 15% a pulmonary complication. In all cases, linear regression had the highest predictive value with area under the curves (AUCs) varying between 61.9-68.0, but the difference with machine learning models did not reach statistical significance.

Conclusion: Machine learning models can predict postoperative complications in upper gastrointestinal cancer surgery, but they do not outperform the current gold standard, linear regression.

Introduction

The incidence of esophageal cancer in the western world has increased over the past decades and is currently the seventh most common malignancy worldwide and accounts for 5% of the cancer-related mortality in 2018. Although the incidence of gastric cancer decreased over the last years, it is still the fifth most common malignancy worldwide and was responsible for 8% of the cancer-related mortality in 2018. [1] Curative treatment of these upper gastrointestinal cancers consists in most cases of (neo)adjuvant therapy and surgical resection. These resections are complex procedures. Present-day, the 5-year survival rates of resectable esophageal- and gastric carcinoma lie around 28-42%. [2]. Although in centers of excellence, postoperative mortality is around 2%, the overall-complication rate of around 60-65% after esophagectomy is high compared to most procedures for gastrointestinal malignancies. [3] Of all severe postoperative complications, anastomotic leakage and pulmonary complications are the most common. [2-5] The incidence of major complications (Clavien-Dindo ≥ IIIa) is 20-31%, with a failure-to-rescue rate of 13-25%. [6, 7] Postoperative complications are associated with higher tumor recurrence and lower overall (cancer-related) survival. [8] Reduction of postoperative complications will enhance recovery, lead to fewer readmissions and may increase long-term quality of life.

With the present increase of data-driven approaches in healthcare, preoperative risk factors can be appraised by analyzing large datasets. Machine learning holds the potential to unravel subtle associations that are not—or cannot—be identified using conventional regression analyses. In the current literature, no consensus exists on the added value of machine learning in predicting postoperative outcomes. [9, 10]

The aim of this study is twofold. First, to investigate the added value of machine learning methods in predicting postoperative outcomes after esophageal- and gastric carcinoma surgery and compare it to conventional regression analyses. Second, to use the best performing method to develop a predictive model for anastomotic leakage and cardiopulmonary complications after esophagectomy and gastrectomy.

Methods

Data source and study population

Data were retrieved from the Dutch Upper GI Cancer Audit (DUCA). A prospective nationwide audit, initiated in 2011, containing all patients undergoing surgery with the intention of resection for esophageal- or gastric cancer in the Netherlands. [11] Participation in the DUCA has been incorporated as a mandatory quality standard, leading to data completeness of 99.8% and accuracy of 94%-100%. Validation of completeness and accuracy of this data registration has been performed by external data verification. [3] All Dutch hospitals register detailed patient, tumor, and treatment characteristics, pathology, 30-day morbidity, and 30-day/in-hospital mortality. [12]

Patient selection

Patients that underwent elective surgery with curative intent for primary esophageal- or gastric cancer were selected. Only patients with histologically proven adenocarcinoma or squamous cell carcinoma, a known surgery date between 2011 and 2017 and a recorded surgical technique were included. Patients with surgery with palliative or prophylactic intent and patients with non-epithelial tumors were excluded. Additionally, patients with missing essential values (age, sex, length, weight, surgical approach, American Society of Anesthesiologists (ASA)-score, preoperative therapy and TMN-stage) were excluded.

Definitions of complications

The studied postoperative outcomes were anastomotic leakage and pulmonary complications in patients with esophageal carcinoma, and anastomotic leakage in patients with gastric carcinoma. Anastomotic leakage was defined as any clinically or radiologically proven anastomotic leakage. Pulmonary complications entailed: pneumonia, pleural effusion, respiratory failure, pneumothorax and/or acute respiratory distress syndrome (ARDS).

Statistical analysis For each outcome, the dataset was randomly divided in training (75%) and testing (25%) data. All models used variables documented in the Dutch Upper GI Cancer Audit (DUCA), which covers patient characteristics, comorbidity, treatment characteristics and outcome [13]; a total of 28 prognostic variables were included. The following machine learning models, which are frequently described in literature, were used: k-Nearest Neighbors (KNN), support vector machine (SVM), Neural Networks, Random Forest, AdaBoost and SuperLearner. [14-16] These models were compared with linear regression, for which a generalized linear model (GLM) was used. Background information on the models used can be found in table 1. Afterwards, nomograms were constructed using a regression model fit. The predictive strength of the models was measured by the Area Under the Receiver Operating Characteristics (ROC) Curve (AUC). Odds ratios (OR) with 95% confidence intervals and P-values were reported for each variable to assess the impact on the risk of all patient characteristics. All analyses were done using R version 3.6.1 in RStudio. The Caret packages were used for pipelining and data splitting. ROC curves and AUC scores were calculated using the pROC package, plots were made using the ggplot2 package. The rms package was used to make the nomograms.

Table 1 - Explanation of the models used

Logistic Regression
Describes the relationship between a discrete binary outcome and one or several predictor variables. The outcome is expressed as the log odds of one class over the other. This can be transformed to odds or probabilities.
Lasso Regression
The difference between the logistic regression model and the lasso model is that the lasso model can exclude coefficients that have little weight in the solution. This may increase interpretability.
k-Nearest Neighbour (kNN)
Predicts new instances of a class by looking at *k* other instances in the neighborhood. The predictor variables are transformed by centering and scaling to improve numerical stability. For each outcome a separate kNN model is fit.
Neural Networks (NN)
The inspiration for NN comes from the architecture of the human brain. The idea is that artificial neurons send the next neuron a signal based on the input they are receiving. A network of artificial neurons is called a neural network. A NN consists of layers. The first being an input layer (the predictor variables), followed by one or more hidden layers (the artificial neurons) and finally resulting in an output layer (the prediction). For each outcome in the data a NN is fit.
Support Vector Machine (SVM)
A classification (and regression) algorithm that can classify non linearly separable data by constructing a hyperplane (or a set of hyperplanes) in high dimensional space. A SVM tries to find a hyperplane that best separates two groups. This is the hyperplane whose distance to the nearest element of each class is the largest. For data that is not linearly separable the kernel trick is used. This is a method of adding dimensions to the data while at the same time keep the calculations feasible. For each outcome a *polynomial* (kernel) SVM and a *radial* (kernel) SVM is fit.
Random Forest
A random forest is an ensemble of decision trees. The model is trained with a technique called bootstrap aggregation (bagging). Bagging reduces variance and avoids overfitting in ensemble methods. With this technique many bootstrap samples are taken and a decision tree is trained on each sample. The outcome of all trees together is averaged, which leads to the final outcome. For each outcome a random forest is trained.
Adaboost
Boosting is similar to a random forest. The main differences are that the trees are now built sequentially and the results are averaged along the way. Boosting is an ensemble method that combines weak classifiers to output a single strong predicted response. The technique is considered to be an improvement over random forests in some occasions. For each outcome an Adaboost.m1 model is trained.
Super Learner
The super learner finds an optimal weighted combination of candidate learners. The candidate learners can be any prediction algorithm. The super learner itself is a prediction algorithm as well. The performance of the candidate learners is assessed by cross-validation. For each outcome a super learner model is trained. The candidate learners consist of all models mentioned above. With the exception of Adaboost.m1, which is replaced by XGBoost (an alternative boosting algorithm).

Results

Study population

Between 2011 and 2017, 8,173 patients were included in the DUCA. Of these, 6,427 were included in the final dataset (figure 1). Of the excluded patients, 403 were a result of missing essential values; the outcomes of these patients were not significantly different from those included. In total, 4,228 patients underwent a surgical resection for esophageal carcinoma, of which 2,540 had a postoperative complication (60%). Of the 2199 patients with a resection for gastric carcinoma, 883 patients had a postoperative complication (40%). Patient characteristics are described in table 2, and figure 2 presents an overview of the type of postoperative complications.

Esophageal carcinoma

Anastomotic leakage occurred in 31% (799 of 4,228) patients following esophagectomy and pulmonary complications in 54% (1380 of 4228), figure 2. From all prediction models, the generalized linear model had the highest AUC, both for anastomotic leakage (61.9; 95%CI 57.9-65.9) and for pulmonary complications (64.4; 95%CI 60.9-67.9), figures 3a and 3b. Closely followed by the machine learning models: Neural Networks (AUC 61.7; 95%CI 57.7-65.6), LASSO (AUC 61.7; 95%CI 57.7-65.7) and SuperLearner (AUC 61.7; 95%CI 57.7-65.8) for anastomotic leakage. And the machine learning model LASSO (AUC 64.3; 95%CI 60.9-67.8) for pulmonary complications. For preoperative prediction, nomograms, based on a generalized linear model, have been constructed for anastomotic leakage (figure 5a) and pulmonary complications (figure 5b). For anastomotic leakage: steroid use, advanced tumor stage, distant metastasis, surgical approach and preoperative weight loss factors with the most prognostic value. For pulmonary complications, these are weight loss, ASA III/IV, advanced tumor stage, type of resection and location of anastomosis.

Gastric carcinoma

After gastrectomy, anastomotic leakage was reported in 18% (156 of 2,199) patients. Generalized linear model had the highest AUC (68.0; 95%CI 60.2-75.8) (Figure 4), followed by the machine learning model Neural Networks (AUC 67.9; 95%CI 60.4-75.5). A nomogram for the preoperative prediction of anastomotic leakage after gastric resection is displayed in figure 5c. Tumor histology and lymph node involvement are factors with the most prognostic value.

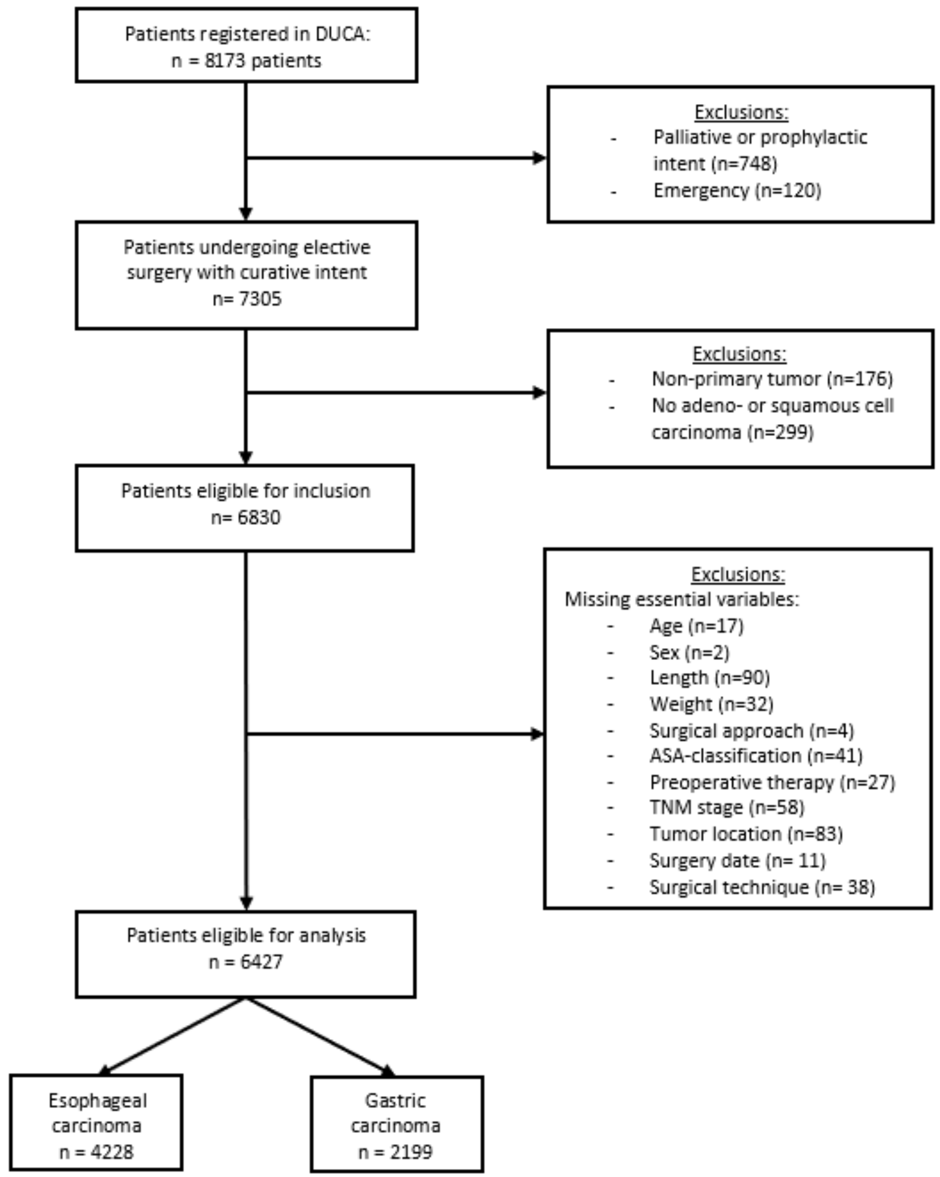


Figure 1 - Patient selection

Table 2 - Patient characteristics

	Esophageal cancer resection		Gastric cancer resection	
	(n = 4,228)		(n = 2,199)	
Age, median (IQR)	66	(59-71)	70	(62-77)
Gender				
Male	3,272	(77%)	1,366	(62%)
Female	956	(23%)	833	(38%)
BMI				
< 20	276	(7%)	170	(8%)
20-24	1,614	(38%)	949	(43%)
25-29	1,663	(39%)	789	(36%)
≥ 30	675	(16%)	291	(13%)
Comorbidity				
None	998	(24%)	433	(20%)
Yes	3,229	(76%)	1,764	(80%)
Of which cardiac	978	(30%)	676	*(31%)*
diabetes	639	(20%)	375	*(17%)*
pulmonary	769	(18%)	352	*(16%)*
thrombotic	173	(5%)	154	*(7%)*
Unknown	1	(<1%)	2	(<1%)
Preoperative weight loss				
None	1,138	(27%)	639	(29%)
1-5 kg	1,184	(28%)	543	(25%)
6-10 kg	891	(21%)	473	(22%)
11-15 kg	279	(7%)	146	(7%)
16-20 kg	106	(3%)	55	(3%)
21-35 kg	56	(1%)	24	(1%)
Unknown	574	(14%)	319	(15%)
Previous surgery*				
No	2,943	(70%)	1,313	(60%)
Yes	1,276	(30%)	882	(40%)
Unknown	9		4	
Histology				
Adenocarcinoma	3,383	(80%)	2195	(>99%)
Squamous cell carcinoma	845	(20%)	4	(<1%)
Type of surgery				
Transhiatal	1,395	(33%)	-	
Transthoracic	2,833	(67%)	-	
McKeown	1,353	(48%)		

Table 2 - Continued

	Esophageal cancer resection		Gastric cancer resection	
	(n = 4,228)		(n = 2,199)	
Total gastrectomy	-		924	(42%)
cTNM-7 stage				
Stage 0	6	(<1%)	16	(1%)
Stage I	566	(13%)	465	(21%)
Stage II	1,116	(26%)	842	(38%)
Stage III	2,155	(51%)	185	(8%)
Stage IV	40	(1%)	39	(2%)
Stage X	345	(8%)	652	(30%)
Neoadjuvant treatment				
None	314	(7%)	848	(39%)
Chemotherapy	286	(7%)	1,316	(60%)
Chemoradiotherapy	3,628	(86%)	35	(2%)
ASA-score				
I	712	(17%)	305	(14%)
II	2,592	(61%)	1,237	(56%)
III	908	(22%)	639	(29%)
IV	16	(<1%)	18	(1%)
Steroid use				
No	4,093	(97%)	2,118	(96%)
Yes	107	(3%)	46	(2%)
Unknown	28	(1%)	35	(2%)

** Thoracic- and/or abdominal surgery*

4

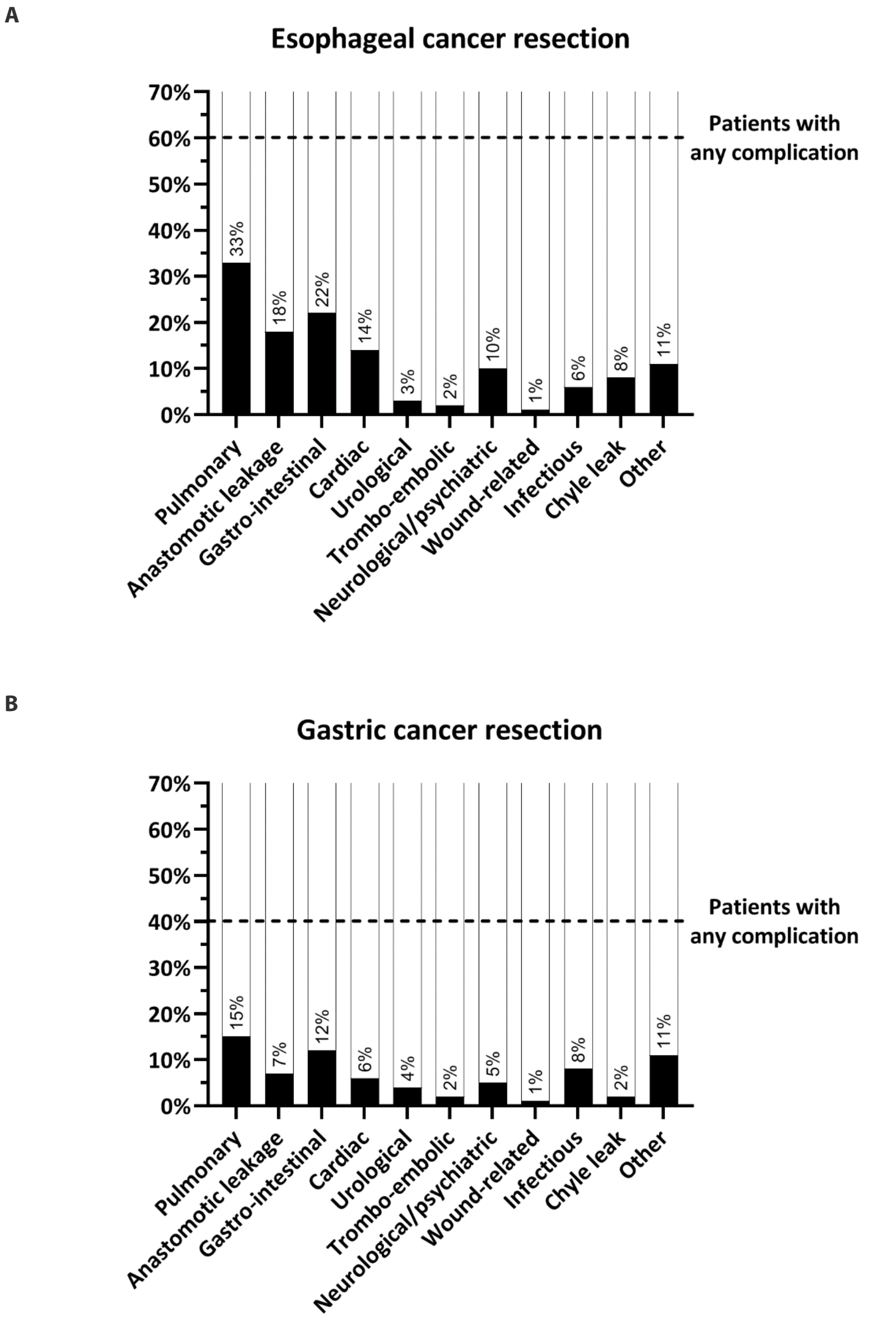
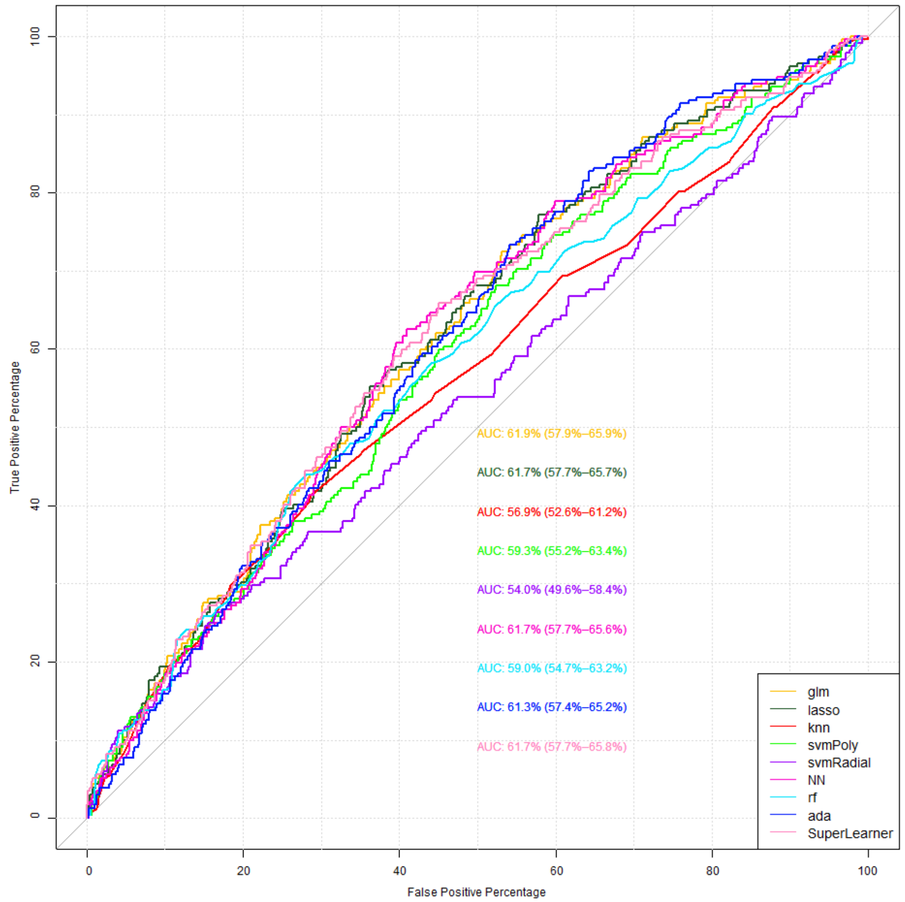
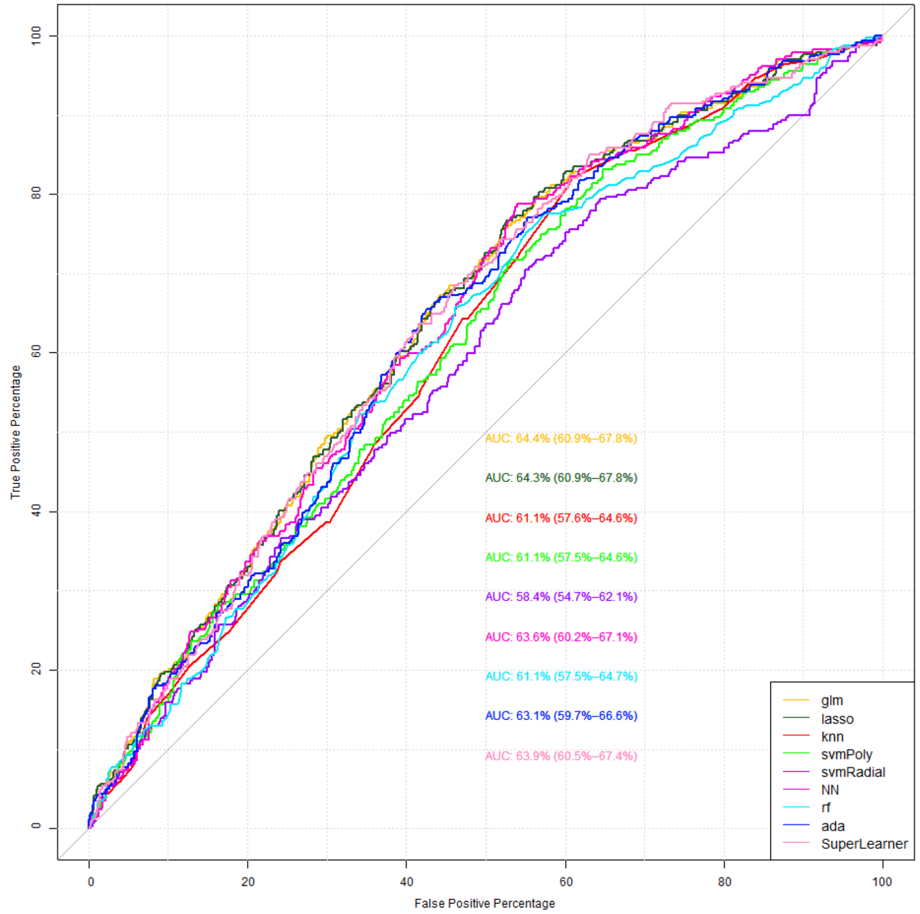


Figure 2 - Type of complications after surgery after (A) esophagectomy and (B) gastrectomy



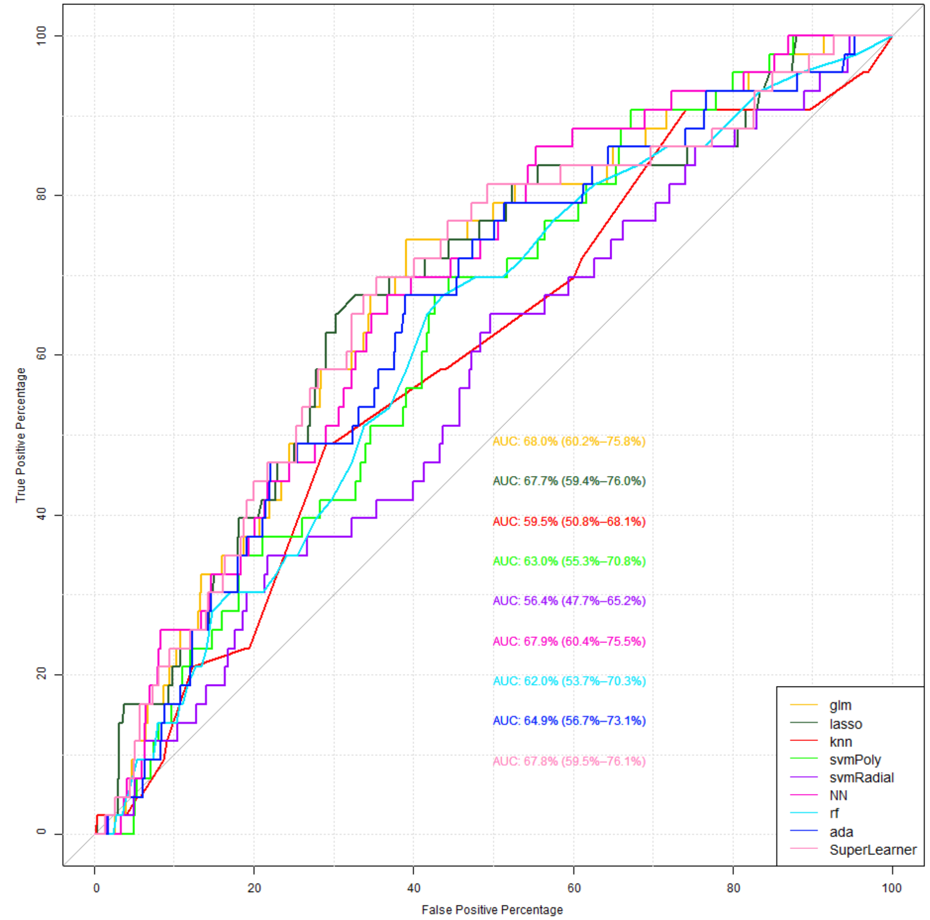
	AUC% (95% CI)
Generalized Linear Model	61.9 (57.9-65.9)
Lasso	61.7 (57.7-65.7)
kNN	56.9 (52.6-61.2)
Neural Networks	61.7 (57.7-65.6)
SvmPoly	59.3 (55.2-63.4)
SvmRadial	54.0 (49.6-58.4)
Random Forest	59.0 (54.7-63.2)
Adaboost	61.3 (57.4-65.2)
SuperLearner	61.7 (57.7-65.8)

Figure 3a - Anastomotic leakage after esophageal cancer resection



	AUC% (95% CI)
Generalized Linear Model	64.4 (60.9-67.8)
Lasso	64.3 (60.9-67.8)
kNN	61.1 (57.6-64.6)
Neural Net	63.6 (60.2-67.1)
SvmPoly	61.1 (57.5-64.6)
SvmRadial	58.4 (54.7-62.1)
Random Forest	61.1 (57.5-64.7)
Adaboost M1	63.1 (59.7-66.6)
SuperLearner	63.9 (60.5-67.4)

Figure 3b - Pulmonary complications after esophageal cancer resection



	AUC% (95% CI)
Logistic Regression	68.0 (60.2-75.8)
Lasso	67.7 (59.4-76.0)
kNN	59.4 (50.8-68.1)
Neural Net	67.9 (60.4-75.5)
SvmPoly	63.0 (55.3-70.8)
SvmRadial	56.4 (47.7-65.2)
Random Forest	62.0 (53.7-70.3)
Adaboost M1	64.9 (56.7-73.1)
SuperLearner	67.8 (59.5-76.1)

Figure 4 - Anastomotic leakage after gastric cancer resection

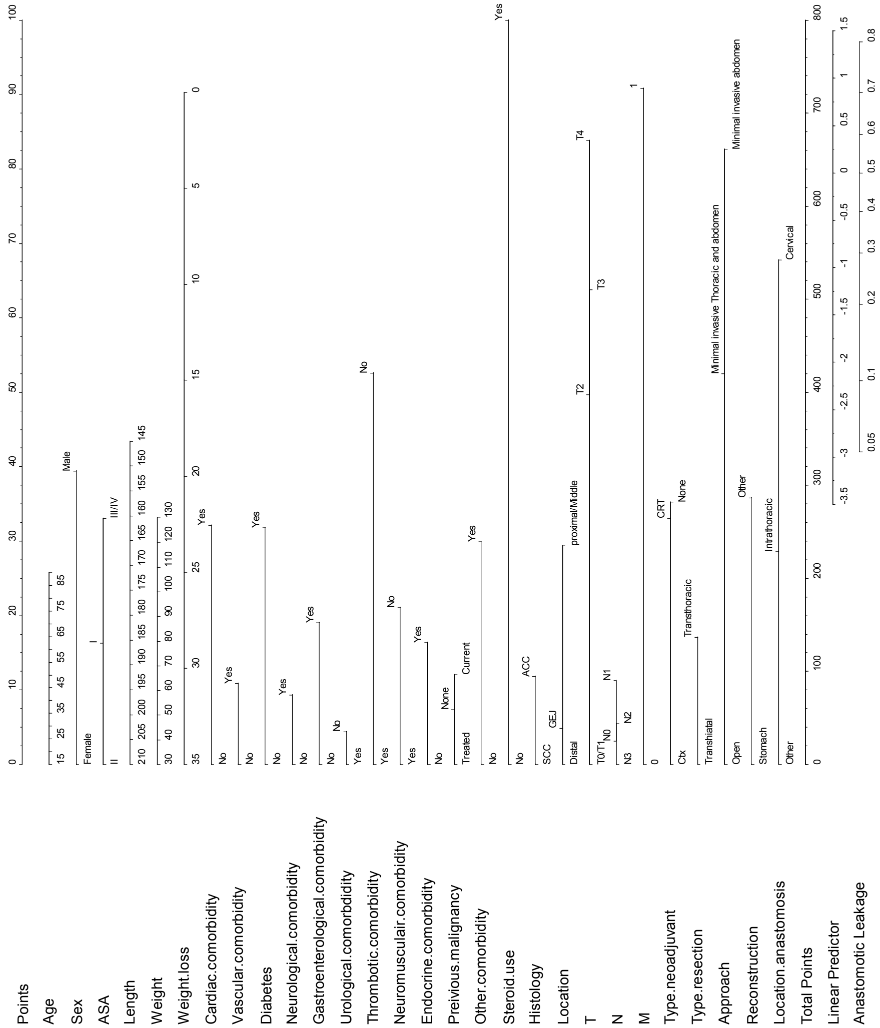


Figure 5a - Nomogram for the prediction of anastomotic leakage after esophageal cancer resection. AUC: 61.9%

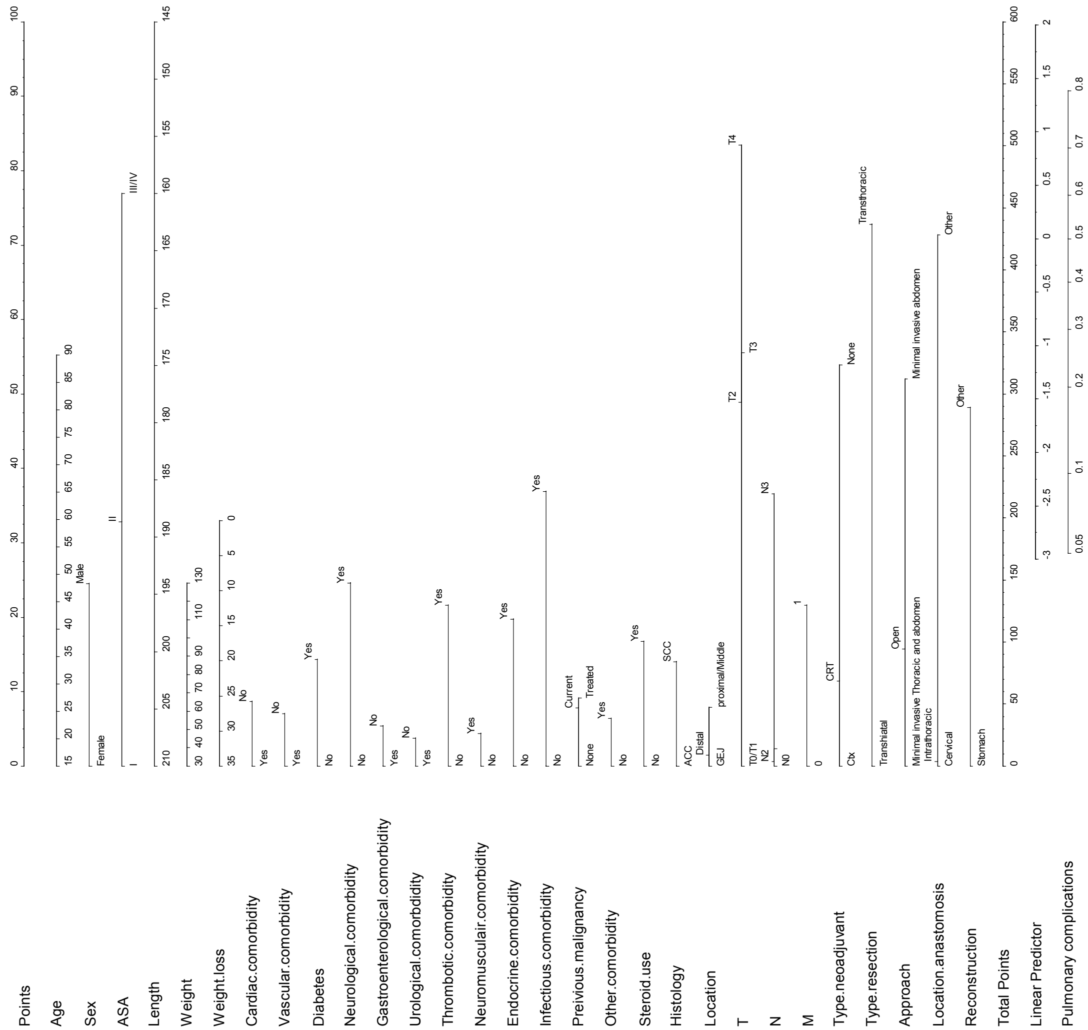


Figure 5b- Nomogram for the prediction of pulmonary complications after esophageal cancer resection. AUC: 64.4%

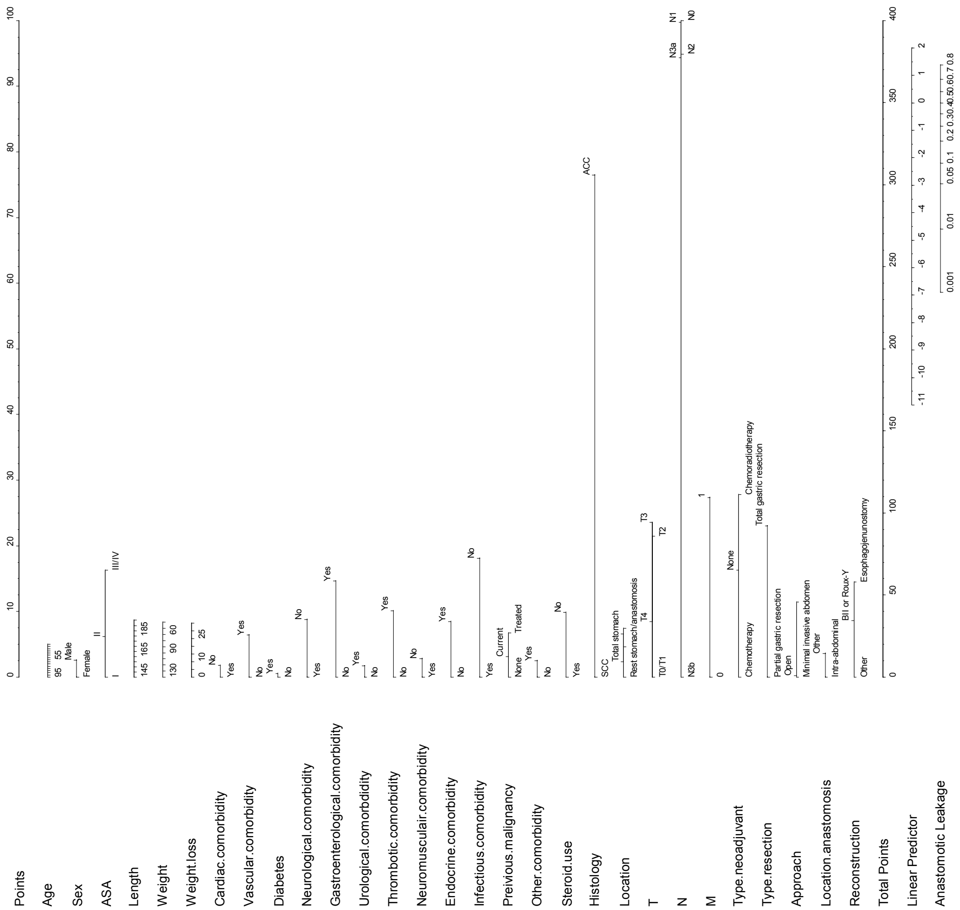


Figure 5c- Nomogram for the prediction of anastomotic leakage after gastric cancer resection. AUC: 68.1%

Discussion

This study presents the development of various (machine learning) models for the prediction of anastomotic leakage and pulmonary complications in a population-based cohort of 4,228 patients that underwent esophagectomy and 2,199 patients that underwent gastrectomy in the Netherlands. Linear regression had the highest accuracy of all models for the prediction of anastomotic leakage after esophagectomy and gastrectomy, as well as for pulmonary complications after esophagectomy. Of the machine learning models, the Neural Networks had the highest accuracy for predicting anastomotic leakage after esophageal cancer surgery and after gastric cancer surgery. LASSO had the highest accuracy of the machine learning models for the prediction of pulmonary complications following esophageal cancer surgery. Furthermore, highest accuracy of all studied models was 68.0%, suggesting that none of the models had superior predictive ability for postoperative complications in this patient cohort.

It is thought that for the development of machine models, a large population is necessary to adequately train the models. For example, the study of Nudel et al. included over 436,000 patients and 40 different variables. In their study, artificial neural networks and gradient boosting machines outperformed the traditional linear regression in predicting anastomotic leakage after weight loss surgery. [10] However, a study that included merely 321 patients successfully designed a support vector classification model to predict postoperative complications in patients undergoing gastrectomy, using 23 clinical features. Their model had an accuracy of 78% in external validation. Like in the current study, age and tumor stage were the most predictive for the development of complications. [17]. With a broad array of machine learning models available, it is difficult to decide which model to use for each particular outcome. The systematic review of Elfanagely et al. reviewed 45 papers published between 2015 and 2020. [18] They concluded that machine learning in surgical research is still in its infancy, but these early-published papers show potential. However, they found great heterogeneity exists between the different studies; various models are being used, and different variables and outcomes are being investigated.[18] They have also shown large variation in sample sizes, ranging from 71 to 130,945, implying that sample size is not the only factor for successful machine learning models. However, it might be possible that a certain publication and confirmation bias is present in the current literature, which could be deceiving.

In line with current literature, our study has demonstrated that ASA-score ≥III is associated with anastomotic leakage and pulmonary complications. [17, 19] Both patients with advanced age and high ASA-classification are thought to have lower healing capacity causing higher susceptibility to postoperative complications. Patients with a more advanced tumor stage may require more extensive resections and technically more demanding surgery to reach an R0 resection. This may lead to more intraoperative organ damage and subsequent postoperative complications. [20] Furthermore, lymph node involvement and, therefore, extensive lymph node dissections and possibly additional splenic resection are high-risk procedures. [21] As shown in this study, chronic use of steroids preoperatively is associated with postoperative complications, which is thought to be due to a reduced healing capacity. [22, 23]

In daily practice, it is difficult to estimate the surgical risk and make treatment decisions based on individual predictive factors. Therefore incorporating multiple factors into prediction models can be used to combine information in a simple and more useful manner. [24] However, the use of these models is often limited since they are often created in a selected patient population or specialized centers, making generalization hard; hence this study used a nationwide population-based cohort. [25, 26] Furthermore, clinical judgment and expertise are still needed for correct interpretation and usage of clinical prediction models. With the current more data-driven approach to health care and the availability of nationwide clinical audits, big data becomes available, eliminating this limitation of generalization of models. In addition, with big data, the interest in machine learning for prediction models has increased. In our study, linear regression was superior to the machine learning models. Another study, which used a more extensive amount of variables, did show favor for machine learning models. [10] However, one could question the use in daily clinical practice when using more extensive models, which subsequently leads to more administrative burden to include all variables unless being automated. Furthermore, in some machine learning models (e.g., neural networks) individual prognostic factors are not known, in contrast to inear regression. As demonstrated in this study, linear regression can be used to construct nomograms, which are easy to use in daily practice and might expose improvable prognostic factors (e.g., weight loss, steroid use) for postoperative complications. Subsequently, nomograms can easily be formed into web-based models of mobile phone applications, which might increase usability in daily practice.

As part of the currently ongoing implementation and standardization of perioperative care into enhanced recovery after surgery (ERAS) protocols, preoperative optimization of patients has gained interest. [27] Research towards improving perioperative care for upper gastrointestinal surgery also focuses on identifying preoperative high-risk patients and developing prehabilitation programs for these patients. Upper gastrointestinal cancer patients are at high risk for malnutrition due to the anatomical localization of the tumor. Therefore, nutritional interventions are important in preoperative prehabilitation. [28] Prehabilitation programs for patients with esophageal carcinoma have been shown to improve objective measures of physical fitness but are less clear on postoperative outcomes. [29] However, good physical fitness and nutritional status are widely recognized as a protective factor against postoperative complications. It has shown to lead to sooner return to bowel function, oral feeding and restored metabolic equilibrium and is therefore currently being standardized and implemented into ERAS protocols. [27, 30] This may indicate that prehabilitation programs might have to be more specific towards certain risk factors.

Although our study provides insight on a different aspect of the clinical applicability of machine learning models, it has some limitations. The use of Dutch national audit data, DUCA, might lead to less generalizability to other countries. However, in The Netherlands, participation in the DUCA has been incorporated as a mandatory quality standard, leading to an exceptionally complete and reliable database. Voluntary participation of some other audits and registries could give a distorted view if their participation did not concern all patients. External validation of the models did not occur in this study. However, the accuracy of the models was tested using a random internal sample of 25% of patients. Another limitation of the study is that the experience and expertise of the individual centers and/or surgeons could not be included. Hospital volume is thought to be a predictor of mortality after high-risk surgery. [31] Patients treated in high-volume hospitals benefit from more experience and more advanced expertise. However, according to the DUCA research regulations, no data is provided that can be used to derive individual hospitals. If these restrictions are lifted in the future, this variable could be implemented in the model to improve accuracy. Additionally, accuracy may be improved by adding more variables, which are currently not in the the DUCA registry, such as preoperative laboratory results (e.g., C-reactive protein (CRP), albumin) [32] and other predictors such as smoking and alcohol usage [33, 34] were not included in our models, whereas these variables may serve as strong preoperative predictors. The use of intraoperative variables such as intraoperative hypotension or blood transfusion may improve predictive accuracy of the model. However, these factors cannot be used during patient selection for prehabilitation programs or for surgery. [35-37] Additionally, the anastomotic leakage rate of 18% following esophagectomy in the Netherlands is relatively high compared to other countries, an explanation is the learning curve for new techniques (e.g., minimally invasive) in recent years. Around 2010 minimally invasive surgery was introduced and many surgeons changed from a McKeown to an Ivor Lewis technique. [38] Furthermore, both clinically and radiologically proven anastomotic leakages were included. Finally, all patients included in this study were selected to be fit for surgery by expert opinion preoperatively, leading to allocation bias. However, occurrence of this type of bias is unavoidable in this type of study.

Conclusion

This study demonstrates that the studied machine-learning models are able to predict postoperative complications in upper gastrointestinal cancer surgery, but they are not superior to the current gold standard, logistic regression. However, the accuracy of all studied models was relatively low. Furthermore, the use of prediction models does serve a purpose for preoperative risk estimation and treatment decisions, but clinical expertise is still needed. Additionally, identifying predictive individual factors within prediction models (e.g., malnutrition) may improve perioperative care and might lead to improved preoperative physical fitness of patients, which can improve ERAS protocols and therewith surgical outcomes.

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Chapter 5

Computer Tomography-based Preoperative Muscle Measurements as Prognostic Factors for Anastomotic Leakage Following Oncological Sigmoid and Rectal Resections

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List of Abbreviations

ASA; American Society of Anesthesiology, AUC; Area Under the Curve, BMI; Body Mass Index, CE; Contrast Enhanced, CRT; Chemoradiotherapy, CT; Computed Tomography, LAR; Low-Anterior Resection, OR; Odds Ratio, PMI; Psoas Muscle Index, ROC; Receiver Operating Characteristics, ROI; Region Of Interest, SMI; Skeletal Muscle Index, TAMA; Total Abdominal Muscle Area, TPA; Total Psoas Area

Abstract

Background

Oncological sigmoid and rectal resections are accompanied with substantial risk of anastomotic leakage. Preoperative risk assessment and patient selection remains difficult, highlighting the importance of finding easy-to-use parameters. This study evaluates the prognostic value of contrast enhanced (CE) computed tomography (CT)–based muscle measurements for predicting anastomotic leakage.

Methods

Patients that underwent oncological sigmoid and rectal resections in the LUMC between 2016-2020 were included. Preoperative CE-CT scans, were analyzed using Vitrea software to measure total abdominal muscle area (TAMA) and total psoas area (TPA). Muscle areas were standardized using patient's height into: psoas muscle index (PMI) and skeletal muscle index (SMI) (cm^2/m^2).

Results

In total 46 patients were included, of which 13 (8.9%) suffered from anastomotic leakage. Patients with anastomotic leakage had a significantly lower PMI (22.1 vs. 25.1, $p<0.01$) and SMI (41.8 vs. 46.6, $p<0.01$). After adjusting for confounders (age and comorbidity), lower PMI (OR: 0.85, 95%CI 0.71-0.99, $p=0.03$) and SMI (OR: 0.93, 95%CI 0.86-0.99, $p=0.02$) were both associated with anastomotic leakage.

Conclusion

This study showed that lower PMI and SMI were associated with anastomotic leakage. These results indicate that preoperative CT-based muscle measurements can be used as prognostic factor for risk stratification for anastomotic leakage.

Introduction

Rectosigmoid resections are associated with a high risk of postoperative complications causing morbidity and mortality [1, 2]. Major complications occur in 15-18% of the patients, with anastomotic leakage being the most frequent with an incidence of up to 10% [3-5]. However, risk stratification is challenging, given that multiple studies have shown that a wide variety of factors correlate with risk of postoperative complications [6]. This highlights the importance of accurate prediction models, that use robust clinical parameters to assess frailty and the associated surgical risk for these patients [6, 7]. This is particularly important given that, with the increasing age of patients undergoing this type of surgery, the number of frail older adult patients increases [8]. Preoperative selection of frail patients and subsequent targeted interventions, such as physical prehabilitation programs, have been shown to be potentially beneficial, leading to a reduction of postoperative complication rates [9-11].

Recently, some studies are reporting that skeletal muscle and psoas muscle volumes can be used as a proxy for patient frailty [7]. Low skeletal muscle volume or psoas muscle volume is defined as sarcopenia, which can be relatively easily assessed using computed tomography (CT). Studies have shown that CT-based measurements of abdominal muscles, including the psoas muscle, have potential in predicting adverse outcome in surgical patients [12, 13].

This study explores the potential prognostic value and clinical use of CT-based preoperative muscle measurements, such as skeletal muscle index (SMI) and psoas muscle index (PMI) in an attempt to predict anastomotic leakage after oncological rectosigmoid resections.

Methods

Study Population and Treatment

All patients who underwent sigmoid or rectal resection for primary colorectal cancer in the Leiden University Medical Center (LUMC) between January 2016 and December 2020 were retrospectively included in this study. Exclusion criteria were: (temporary) construction of stoma during primary surgery, emergency surgery, palliative intended surgery, distant metastasis at time of diagnosis of the primary tumor and endoscopic resection. Patient characteristics (e.g., age, comorbidity) and clinical data (e.g., type of surgery, complications) were collected from the electronic medical record and the LUMC cancer registry. This study was approved by the Medical Ethics Committee of the LUMC (ID number G21.093).

Computer Tomography-based Measurements

All included patients had a preoperative contrast enhanced (CE) abdominal CT in portal venous phase of no more than 3 months before surgery. Analysis of CT-scans was performed using Vitrea (version 7.14.2.227, Canon Medical, USA). Muscle areas were determined by manually segmenting a region of interest (ROI) in the skeletal- and psoas muscles on the portovenous phase of the CE-CT images. The CT slice at the level of the inferior part of L3 was chosen for analysis, which is conform the criteria of previous studies [7, 13]. Subsequently, the skeletal muscles and psoas muscle areas determined from the segmented ROIs (mm^2) [7, 13, 14]. Total abdominal muscle area (TAMA) was categorized into specific abdominal muscle groups; psoas muscles, back muscles (erector spinae and quadratus lumborum muscles), lateral muscle (external- and internal oblique and transversus abdominis) and rectus abdominis (Fig. 1). Additionally, total psoas area (TPA) was calculated by the sum of both psoas muscles. Two researchers (RTK, CJR) independently performed the image segmentation after ensuring an interobserver variability correlation of at least 0.8 in a training set, under supervision of a radiologist (ANC). Disagreements regarding measurements were resolved by discussion, with ANC acting as a third observer when necessary. The muscle areas were adjusted by patient's height (m) in order to standardize the measurement between patients. The height normalized muscle areas (muscle indices) of the psoas and skeletal muscles (TAMA), PMI and SMI were used for further analysis. The units for muscle areas were cm^2 and muscle indexes, cm^2/m^2.

Anastomotic leakage

All complications that occurred during 90 days after surgery were registered and reviewed. Anastomotic leakage was defined as a defect of the intestinal wall or abscess at the site of the colorectal anastomosis, diagnosed or confirmed by contrast enema, furthermore, an abscess around the anastomosis, for which endoscopic, percutaneous or operative re-intervention was required.

Statistical analysis

Odds ratios (OR) with 95% confidence intervals and P-values were reported for each variable to assess the impact of all patient- and treatment characteristics, multivariable analysis was conducted using clinically-relevant variables. Mann-Whitney U and chi-squared test were used to assess patient- and treatment characteristics. A P-value of <0.05 was considered statistically significant. The Spearmans ρ correlation coefficient was used to assess interobserver variability in CT muscle surface area scoring. To show clinical use of CE CT-based muscle parameters nomograms were constructed based on regression model using the rms package in R. The predictive strength of the prediction models used to construct the nomograms was measured by the Area Under the Receiver Operating Characteristics (ROC) Curve (AUC). All analyses were done using R version 4.1.2 in RStudio. ROC curves and AUC scores were calculated using the pROC package, plots were made using the ggplot2 package.

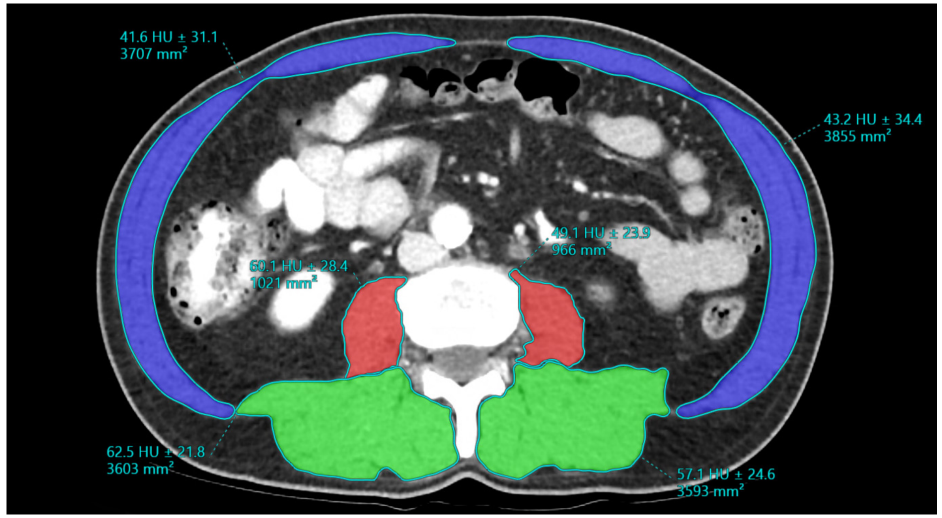

Figure 1 – Example Vitrea software for contrast-enhanced (CE) computed tomography (CT)-based muscle measurements. Regions of interest (ROI) were drawn and categorized into specific muscle groups; psoas muscles (Red), back muscles (erector spinae and quadratus lumborum muscles) (Green), lateral muscle (external- and internal oblique and transversus abdominis) and rectus abdominis (Blue).

Results

Patient characteristics

A total of 215 patients underwent a sigmoid or rectal resection between 2016 and 2020 of which 48 were excluded because a CT scan was not present (Fig. 2). Additionally, patients with emergency surgery (n=3) and patients with stoma construction during primary surgery (n=18) were excluded. Of the in total 146 included patients 13 (8.9%) suffered from anastomotic leakage. There was a significant difference between the group of patients that suffered from anastomotic leakage and the group that did not with respect to age and the use of minimally invasive techniques (Table 1). There were no significant differences observed in comorbidities.

Computer Tomography-based measurements

Results showed that the manual segmentation (Fig. 1) of the muscles on CT images were highly reproducible, with the Spearmans ρ correlation coefficient >0.87. (Table 2).

Muscle measurements

Patients that suffered anastomotic leakage had significantly lower preoperative TPA (median: 77.5 cm^2 vs. 59.6 cm^2, p=0.02) and lower TAMA (median: 144.2 cm^2 vs. 111.8 cm^2, p=0.01) (Table 3). Additionally, comparing the PMI and SMI between both groups, both parameters were significantly lower in the anastomotic leakage groups (p<0.01).

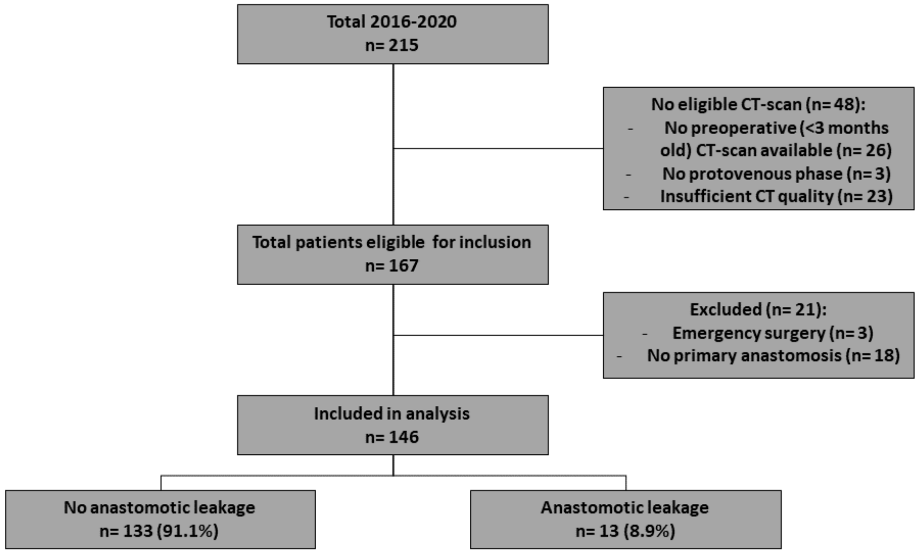

Figure 2 – Flowchart of patient inclusion

Uni- and multivariable analysis

An higher age (OR: 1.07, 95%CI 1.01-1.13, p=0.02) and lower PMI (OR: 0.87, 95%CI 0.77-0.99, p=0.03) and SMI (OR: 0.94, 95%CI 0.88-0.99, p=0.04) were in univariable analysis significantly associated with anastomotic leakage (Table 4). After adjusting for confounders (age and comorbidity), a lower PMI (OR: 0.85, 95%CI 0.71-0.99, p=0.03) and SMI (OR: 0.93, 95%CI 0.86-0.99, p=0.02) were both significantly associated with the occurrence of anastomotic leakage.

Nomograms

For preoperative prediction of anastomotic leakage regression model-based prediction models, using clinically- and statistically relevant parameters (age, gender, comorbidity, chemoradiotherapy and SMI or PMI), were made. The prediction model using PMI had an AUC of 79.8% (Fig. 3A) and using SMI as muscle parameter had an AUC of 79.0% (Fig. 3B), respectively. Additionally, clinically usable nomograms were constructed using these prediction models with using PMI (Fig. 4A) as muscle parameter and one using SMI (Fig. 4B).

Table 1 – Patient characteristics

	No anastomotic leakage	**Anastomotic leakage**	***p*-value**
	n=133 (91.1%)	**n= 13 (8.9%)**	
Age (median)	59 (50-71)	68 (37-86)	**<0.01**
Gender (male)	80 (60.2%)	5 (38.5%)	0.22
ASA score			
1-2	26 (19.5%)	3 (23.1%)	0.95
3-4	12 (9.0%)	10 (76.9%)	
Comorbidity	74 (55.6%)	10 (76.9%)	0.24
BMI (median)	25.0 (19.5-41.3)	25.9 (17.5-34.7)	0.93
MUST-score			
0 (low risk)	81 (60.9%)	3 (23.1%)	
1 (medium risk)	4 (3.0%)	2 (15.4%)	**<0.01**
2 (high risk)	1 (0.8%)	1 (7.7%)	
Missing	47 (35.3%)	7 (53.8%)	
pT-stage			
0	1 (0.8%)	0 (0.0%)	
1-2	58 (43.6%)	6 (46.2%)	0.69
3-4	74 (55.6%)	7 (53.8%)	
pN-stage			
0	81 (60.9%)	9 (69.2%)	0.74
≥1	52 (39.1%)	4 (30.8%)	
Neo-adjuvant chemoradiotherapy (CRT)	23 (17.3%)	4 (30.8%)	0.41
Type of surgery			
Low-anterior resection (LAR)	64 (48.1%)	9 (69.2%)	0.25
Sigmoid resection	69 (51.9%)	4 (30.8%)	
Minimally invasive			
Open	4 (3.0%)	2 (15.4%)	**<0.01**
Laparoscopic	129 (97.0%)	11 (84.6%)	

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Table 2 - Interobserver variability, The Spearmans ρ correlation coefficient

	Coefficient	p-value
Total Abdominal Muscle Area (TAMA)	0.99	**<0.01**
Total Psoas Area (TPA)	0.95	**0.01**
Psoas left	0.89	**0.04**
Psoas right	0.87	0.05
Psoas Muscle Index (PMI)	0.91	**0.03**
Skeletal Muscle Index (SMI)	0.99	**<0.01**

Table 3 - Preoperative contrast enhanced (CE) computed tomography (CT) muscle measurements

	No anastomotic leakage n=133 (91.1%)	Anastomotic leakage n= 13 (8.9%)	*p*-value
Total Psoas Area (TPA) (cm²) (median)	77.5 (37.7-196.3)	59.6 (39.7-101.4)	**0.01**
Total Abdominal Muscle Area (TAMA) (cm²) (median)	144.2 (70.1-377.1)	111.8 (73.8-191.1)	**0.02**
Psoas Muscle Index (PMI) (cm²/m²) (mean)	25.05 (14.7-64.1)	22.1 (14.2-28.7)	**<0.01**
Skeletal Muscle Index (SMI) (cm²/m²) (mean)	46.6 (27.-123.1)	41.8 (26.5-54.1)	**<0.01**

Table 4 – Logistic regression analysis odds ratio (OR) for anastomotic leakage.

	OR	*p*-value	Adjusted OR*	*p*-value
Age	1.07 (1.01-1.13)	**0.02**	-	
Sex (male)	0.41 (0.13-1.33)	0.14		
ASA score**			-	
1	Ref	-	Ref	
2	0.82 (0.21-3.25)	0.78	0.99 (0.21-4.56)	0.99
3	0.72 (0.07-7.68)	0.79	0.81 (0.06-10.34)	0.87
Comorbidity	2.58 (0.68-9.79)	0.16	-	
Type of surgery				
Low Anterior Resection (LAR)	Ref	-	Ref	
Sigmoid resection	0.63 (0.18-2.15)	0.46	0.45 (0.12-1.62)	0.21
T-stage				
1	Ref	-	-	
2	0.56 (0.1-3.6)	0.57	0.33 (0.05-2.41)	0.28
3	0.47 (0.08-2.68)	0.42	0.28 (0.04-1.99)	0.21
4	1.62 (0.19-13.93)	0.66	0.78 (0.08-8.18)	0.84
Neoadjuvant therapy	2.13 (0.60-7.50)	0.24	1.43 (0.37-5.51)	0.61
BMI	0.99 (0.86-1.14)	0.90	0.97 (0.84-1.11)	0.66
Psoas Muscle Index (PMI)	0.87 (0.77-0.99)	**0.03**	0.85 (0.71-0.99)	**0.03**
Skeletal Muscle Index (SMI)	0.94 (0.88-0.99)	**0.04**	0.93 (0.86-0.99)	**0.02**

* Adjusted for age, comorbidity, ** ASA; American Society of Anesthesiologists

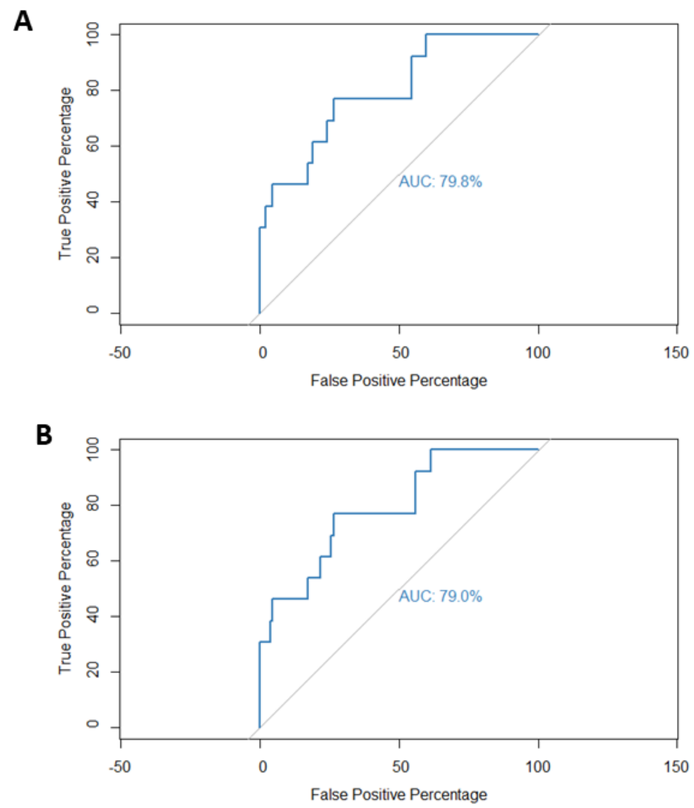

Figure 3- ROC curve of logistic regression predictions model used to construct nomogram A) using PMI as muscle parameter, B) using SMI as muscle parameter.

Discussion

This study investigated the value of CT-based cross-sectional measurements of abdominal and psoas muscles as a prognostic factor for anastomotic leakage after curative intended oncological sigmoid or rectal resection. Cross sectional measured abdominal and psoas muscle area were significantly lower in patients that suffered from anastomotic leakage. Furthermore, both PMI and SMI are both prognostic factors for anastomotic leakage following sigmoid and rectal resection.

Recent studies have shown an association between lower muscle volumes and short-term surgical outcomes after colorectal surgery [7, 12, 13]. Literature reports that cross-sectional lumbar muscle areas are well correlated with muscle mass in the whole body [15, 16]. However, analysis of CT images using a single-muscle approach such as the psoas major muscle, might be less laborious and therefore more realistic in a clinical setting, validation is however still lacking [17]. As shown by Jones et al. TPA and TAMA on the L3 level correlates well with clinical outcomes. [7]. However these reports also showed that TAMA was more reproducibly measured by CT-analysis than TPA. This is also observed in our study as the interobserver variability is higher in the TPA.

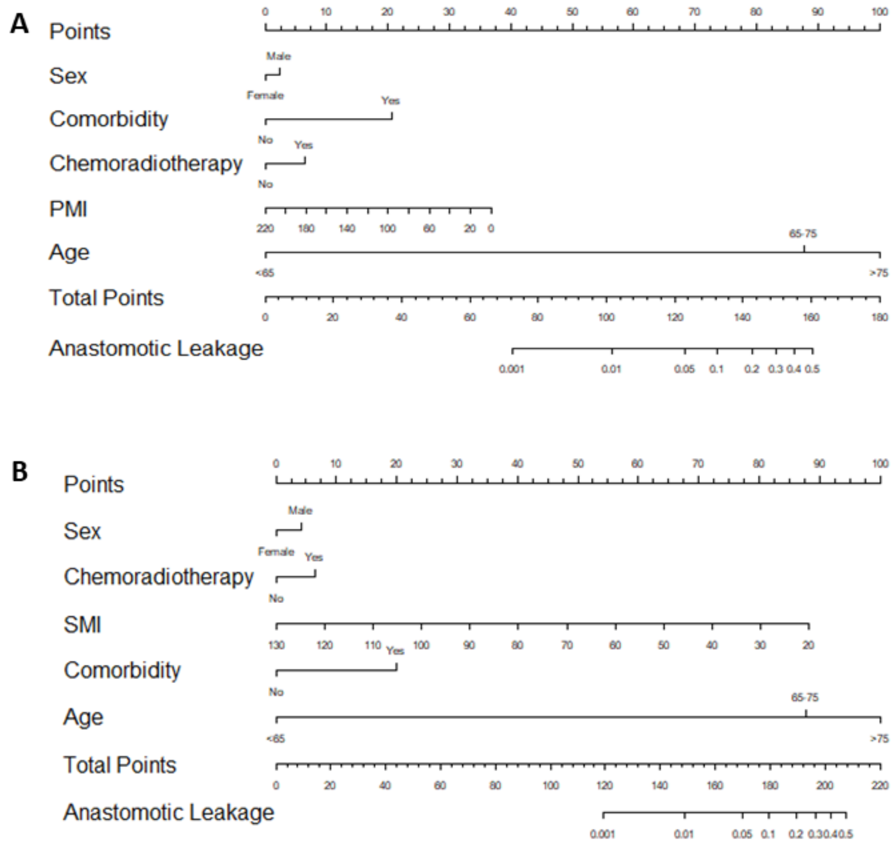

Figure 4 – Nomogram prediction the risk of anastomotic leakage constructed using logistic regression model. A) Using psoas muscle index (PMI) as muscle parameter, the model had an area under the curve (AUC) of 79.8% (Fig. 4A) B) using skeletal muscle index (SMI) as muscle parameter, the model had an AUC of 79.0% (Fig. 4B)

The association between low muscle mass and anastomotic leakage might be partly explained by frailty, since previous studies have shown an association between frailty and anastomotic leakage following colorectal surgery as well [7, 18, 19]. However, there is no consensus on markers for determining patient frailty at this time, identification of frail patients is still difficult [20, 21].

Skeletal muscle depletion is defined as a decrease in muscle mass and it occurs when protein degradation exceeds protein synthesis. Potential causes of muscle atrophy are aging, malnutrition, long-term immobilization, as well as various serious and often chronic diseases, such as chronic heart failure, chronic obstructive lung disease, renal failure, AIDS, sepsis, anorexia nervosa and muscular dystrophies among others. Furthermore, skeletal muscle depletion may be the result from cancer too, as part of the cancer-cachexia syndrome [22-24]. Cancer cachexia is a wasting syndrome characterized by weight loss, anorexia, asthenia and anemia. The pathogenicity of this syndrome is multifactorial, due to a complex interaction of tumor and host factors leading to muscle protein breakdown, thus to cachexia-related sarcopenia [23, 25]. Several studies have shown a clear correlation between lower muscle mass and an increased inflammatory state due to tumor-cachexia and frailty [26, 27]. This might explain the association between sarcopenia and anastomotic leakage as well since a more katabolic and inflammatory state may hamper healing capacity in tissues such as bowel tissue resulting in anastomotic leakage [28, 29].

Additionally, aging in patients might explain this association, since CT-based muscle measurement may be more accurate than just age, since it is more representative for biological age compared to calendar age. Ageing leads to trunk muscle attenuation, but such age-related differences vary widely between muscle groups [30]. Thicknesses of rectus abdominis, internal oblique and external oblique muscles were 36% to 48% smaller for older than younger adults [31]. Additionally, trunk muscle deficits with increasing age may have important implications for physical function, disability, pain, and risk of injury in older adults [32].

Accurate prediction of postoperative complications and especially anastomotic leakage could improve preoperative patient selection, treatment decision and shared-decision making. An important dilemma in patients undergoing sigmoid or rectal resection is whether or not to construct a anastomosis and/or (temporary) stoma [33]. An important consideration is the risk of anastomotic leakage since a (temporary) diverting stoma can reduce the rate of clinical symptomatic anastomotic leakage [6, 34]. Furthermore, measuring a low muscle mass on the preoperative CE-CT could be an indication for prehabilitation programs, since low muscle mass may be reversible [9, 11, 35]. Especially, in rectal cancer patients undergoing neo-adjuvant chemo(radio)therapy, whereas there is a greater window of preoperative optimization by physical exercise, which has been shown to be safe and feasible [36]. Prehabilitation programs have been shown to objectively improve physical fitness [37]. Additionally, since patients with lower skeletal muscle mass may experience more chemotherapy toxicity, this might be used in shared decision making and treatment planning as well [38, 39].

LimitationsAlthough this study provides insights in the used of CT-based muscle measurements, this study has some limitations. Since, patients included in this study were selected to be fit for surgery by expert opinion, this may lead to allocation bias. Additionally, some patients were excluded because of unavailability of CT examinations or insufficient quality. However, the occurrence allocation bias is unavoidable in this type of retrospective study. Due to the relatively low sample size an validation of the prediction models was not possible. Furthermore, this was a single center study in an academic teaching hospital where comorbidity/competing risks were possibly not fully known by applied comorbidity classification, this affect generalizability.

Conclusion

In this exploratory analysis, low SMI and PMI were predictive for anastomotic leakage and show potential in treatment planning, shared decision making and engaging in prehabilitation programs. Since abdominal CT scans are routinely being performed for preoperative staging and treatment planning, they can easily be used to quantify muscle volumes without additional examinations or costs.

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5

Part II: Consequences of major gastrointestinal surgery

Chapter 6

Patient Perspectives on Consequences of Resectable Colorectal Cancer Treatment: a Qualitative Study

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List of Abbreviations

EORTC; European Organization for Research and Treatment of Cancer, ICHOM; International Consortium for Health Outcomes Measurement, LARS; Low-Anterior Resection Syndrome, VHBC; Value-Based Health Care

Abstract

Background: Colorectal cancer is diagnosed in approximately 500,000 patients each year in Europe, leading to a high number of patients having to cope with the consequences of resectable colorectal cancer treatment. As treatment options tend to grow, more information on these treatments' effects is needed to properly engage in shared decision-making. This study aims to explore the impact of resectable colorectal cancer treatment on patients' daily life.

Methods: Patients (≥18 years) who underwent an oncological colorectal resection between 2018 and 2021 were selected. Purposeful sampling was used to include patients who differ in age, comorbidity, (neo-)adjuvant therapy, postoperative complications and stoma presence. Semi-structured interviews were conducted, guided by a topic guide. Interviews were fully transcribed and subsequently thematically analyzed using the framework approach. Analyses were done by using the predefined themes: 1) daily life and activities, 2) psychological functioning, 3) social functioning, 4) sexual functioning and 5) healthcare experiences.

Results: Sixteen patients with a follow-up between 0.6 and 4.4 years after surgery were included in this study. Participants reported several challenges they experience due to poor bowel functioning, stoma presence, chemotherapy-induced neuropathy, fear of recurrence and sexual dysfunction, however, they were reported not to interfere much with daily life.

Conclusion: Colorectal cancer treatment leads to several challenges and treatment-related health deficits. This is often not recognized by generic patient-reported outcome measures, but the findings on treatment-related health deficits presented in this study, contain valuable insights which might contribute to improving colorectal cancer care, shared decision making and value based healthcare.

Introduction

In Europe, colorectal cancer is diagnosed in approximately 500,000 patients each year, leading to a high number of patients that has to live with the consequences of colorectal cancer treatment [1]. The cornerstone of colorectal cancer treatment is surgical resection, which encompasses invasive and high-risk procedures with a total complication rate of up to 30% and 30-day mortality of about 2% [2-4]. Currently, patient psychological and functional outcomes next to oncological outcomes after resectable colorectal cancer treatment are gaining more interest, due to increased overall survival, improved oncological care and more awareness of the sequelae of cancer survivorship [5, 6]. Together with an increasing trend towards shared decision-making, (recurrence-free) survival is not the only important factor taken into account during treatment planning and patient counseling, but also the anticipated quality of life after treatment [7]. Since this post-treatment quality of life should also be part of the decision-making process regarding treatment options, treatment decisions may be impacted. Therefore, treatment options such as, "watch and wait" after clinical complete response to neoadjuvant therapy may be preferred [8]. To adequately engage in shared decision-making, information on how surgical treatment of colorectal cancer affects daily life and quality of life after colorectal cancer surgery is essential. Colorectal cancer surgery may lead to a decreased quality of life, as well as decreased daily functioning and decreased physical functioning [9]. However, a previous study of our group showed that quality of life returns to a level similar to the preoperative level one-year after surgery, which seems paradoxical since various treatment-related health deficits may arise [10].

Earlier studies have shown that coping mechanisms in patients with malignant diseases might be leading to a relative underestimation of the effect of treatment-related health deficits on patient-reported quality of life [11, 12]. Insight into long-term consequences of colorectal cancer treatment for daily life and explicit patient consideration on treatment decisions might positively influence the long-term quality of life and lead to a higher acceptance of possible consequences. Additionally, rehabilitation programs might be more focused on these consequences [13].

This study aims to explore the impact of resectable colorectal cancer treatment on patients' daily life. With a qualitative approach more in-depth information on patients' perspectives might be obtained. The major themes from the cancer-specific European Organization for Research and Treatment of Cancer (EORTC) qlq-C30 questionnaire are studied [14]. These themes are often affected by colorectal cancer treatment. Furthermore, the findings of this explorative study could expose outcomes with a high burden on patients' daily life. Ultimately, this information can be used for patient information, shared-decision making and treatment planning . Also, the knowledge gained by this study may provide leads for the optimization of long-term postoperative care and rehabilitation programs in colorectal cancer patients.

Methods

Setting

A purposive sample was retrieved from a cohort of patients who underwent surgery for colorectal cancer between 2018 and 2021 at the Leiden University Medical Center (LUMC), a tertiary teaching hospital in the Netherlands. Purposeful sampling was used to include patients of a different age, comorbidity, (neo-)adjuvant therapy, postoperative complications and stoma presence.

Participants

Patients (≥18 years) after curative intended colorectal resection for primary carcinoma were approached during follow-up appointments. To be eligible, participants had to understand and speak Dutch. Patients were included until no further pertinent information and themes were forthcoming from at least three interviews, suggesting that data saturation was reached [15, 16].

Ethics approval

The Medical Ethics Committee Leiden Den Haag Delft assessed the study protocol for this study (ref. no. N21.168) and concluded that no formal review was needed, as this study was not conducted under the Medical Research Involving Human Subjects Act (WMO). All study participants were given verbal and written information about the study and signed an informed consent form.

Semi-structured interviews

To learn more about the perspectives of patients towards the effects of oncological colorectal treatment on their daily functioning, a qualitative approach was used [17-19]. For the semi-structured interviews, a topic guide was developed. The topics were based on the cancer- EORTC qlq-C30 questionnaire and an expert-opinion; 1) daily life and activities, 2) psychological functioning, 3) social functioning, 4) sexual functioning and 5) healthcare experiences [14]. Semi-structured interviews were selected as a method, because it offers flexibility to gather in-depth perspectives and leads to rich thematically-structured narratives with participants [18]. The interviews were conducted online via Zoom by one investigator, a trained medical doctor involved in surgical oncology (RTK).

Analysis

The interviews were fully audio-taped and manually transcribed. A theoretical thematic analysis of the transcripts was performed together by two researchers (RTK, BAMS) to identify patterns in the data[17]. The analysis was done by using the framework approach, and followed the following sequential steps: (1) familiarizing with the data, (2) developing a coding scheme , based on the aforementioned themes, using ATLAS. ti 9, (3) coding of the transcripts, the coding scheme was applied independently by two coders and discussed until an agreement was reached, (4) summarizing the data for data interpretation [19]. The researchers met regularly and discussed the coding scheme as it developed during data analysis.

Results

Participants

In total, 16 patients participated in this study, 9 were male and ages ranged from 54 to 79, (Table 1). Patients were interviewed between 0.6 and 4.4 years after surgery. Six participants had a primary tumor located in the colon and 10 had a rectum-located tumor. Six participants received neo-adjuvant therapy and 3 received adjuvant chemotherapy. A stoma was constructed in 7 participants of which 3 were closed at time of the interview. Major complications, requiring a reoperation, occurred in 6 participants of which 3 experienced an anastomotic leakage.

Daily life and activities

Multiple participants reported to have poor bowel functioning with increased stool frequencies: "*I have stool at least 10 times a day*" (P16). This influences their daily life, for example their work and their mobility: "*I visit other companies for work and you prefer not to go to the toilet there, but I often have to go*" (P16) and "*When I'm on the road, I always think: am I nearby or can I be at a toilet within ten minutes?*" (P4) and "*Two hours is really the maximum that I can walk, because then I have to go to the toilet.*" (P2) To avoid these unwanted situations, some participants reported that they pay extra attention to their diet: "*When I eat a lot of legumes and herbs, then it gets really wrong.*" (P4) and "*I have to be careful with oil*" (P14).

Having a stoma is also reported to present certain challenges in daily life. It took a while for most participants to get used to. In the beginning, they felt unsecure and had several problems, such as uncontrollable flatus and stoma bag leakages. Fortunately, at the time of the interviews, most patients reported to experience almost no stoma-related fecal leakage, but still have a fear of getting a stoma bag leakages. Furthermore, participants reported that they did not want to be dependent on nurses or family "*you*

Table 1 – Study participant characteristics. * At time of the interview

ID	Age* (years)	Gender	Comorbidities	Tumor stage	Time since surgery * (years)	Type of Surgery	Stoma	Postoperative complications	Reoperation	(Neo-) adjuvant therapy
P1	69	Male	Hypertension, Obesity, Hypercholesteremia	cT3bN0/ ypT2N1M0	2.1	Laparoscopic abdominoperineal resection	Colostoma	Urinary retention	No	Neo-adjuvant chemotherapy and radiotherapy
P2	56	Female	Abdominal surgery	pT4aN2b	3.5	Laparoscopic sigmoid resection	-	-	No	Adjuvant chemotherapy
P3	54	Female	Orofacial surgery	pT3N0	1.1	Laparoscopic low-anterior resection	Colostoma	Anastomotic leakage, Pulmonary embolism	Yes	
P4	68	Female	-	cT2N1M0/ ypT0N0	3.9	Laparoscopic low-anterior resection	-	-	No	Neoadjuvant brachytherapy
P5	75	Male	Diabetes Mellitus type II, Hypertension, Hypercholesterolemia	pT3N1b	2.5	Laparoscopic sigmoïd resection	-	-	No	Adjuvant chemotherapy
P6	69	Female	Cataract surgery	pT3N0	3.0	Laparoscopic low-anterior resection	Colostoma	Anastomotic leakage, abdominal abscess, SIADH	Yes	-
P7	57	Male	-	pT2N1M0	0.7	Laparoscopic hemicolectomy left	-	-	No	Adjuvant chemotherapy
P8	62	Female	COPD, Hypertension	pT3N0	4.2	Open transverse colectomy	Colostoma (reversed after 1 year)	Hemorrhage	Yes	-
P9	77	Male	Urolithiasis	pT2N0	4.4	Laparoscopic Hemicolectomy right	-	-	No	-
P10	67	Female	Appendectomy	pT1N0	3.2	Laparoscopic low-anterior resection	-	-	No	-

Table 1 – Continued

ID	Age* (years)	Gender	Comorbidities	Tumor stage	Time since surgery * (years)	Type of Surgery	Stoma	Postoperative complications	Reoperation	(Neo-) adjuvant therapy
P11	79	Male	Nephrectomy, multinodular goiter	pT2N0	0.6	Laparoscopic sigmoid resection	-	-	No	-
P12	74	Male	Cystoprostatectomy	pT2N1b	0.6	Open abdominoperineal resection	Colostoma	Small bowel perforation	Yes	-
P13	54	Male	-	cT3N1/ ypT1N0	3.2	Laparoscopic low-anterior resection	-	-	No	Neo-adjuvant chemotherapy and radiotherapy
P14	57	Female	Hypertension	cT3N1/ ypT2N0	3.3	Laparoscopic low-anterior resection	-	-	No	Neo-adjuvant radiotherapy
P15	70	Male	Diabetes Mellitus type II, Hypertension, Peripheral venous insufficiency	cT3N1/ ypT3N1c	2.6	Laparoscopic low-anterior resection	Ileostoma (reversed after 3 months)	Ureter perforation	Yes	Neo-adjuvant chemotherapy and radiotherapy
P16	63	Male	Hypertension	cT3aN2M0/ ypT2N0	4.2	Laparoscopic low-anterior resection	Ileostoma (reversed after 6 months)	Anastomotic leakage, Urinary retention	Yes	Neo-adjuvant chemotherapy and radiotherapy

can tell me how to do it, because I want to do it myself; I have to accept it and I have to deal with it" (P3). Participants reported that they learned to cope with a stoma: "*I always say, it never makes you happy, that you have it, but I can deal with it quite well*" (P6) and "*Sometimes I even forget that I have a stoma*" (P1).

Additionally, some participants complain about chemotherapy-induced neuropathy in their feet, which greatly influences their ability to walk: "*It's mainly my right foot. Because of that foot I will probably also walk slightly different, which causes problems in my knees and my back*" (P2). Furthermore, chemotherapy-induced neuropathy of the hands is reported not only to cause pain, but also to affect activities in daily life: "*Before I get my hands on small objects, I sometimes have to make multiple attempts, because I don't feel it well*" (P7).

Most participants reported that it took a while before they were fully recovered from surgery "*The surgery itself was not such a problem for me, because I thought: that's part of it, but in the end it took quite a while before I was fully recovered*" (P10). After full recovery most participants reported that not much has changed in daily life: "*In the end nothing has really changed in my daily life*" (P15). Although almost all of the patients face some negative influences of the treatment on their daily lives, in some cases it did positively change their general perspective on life: "*I look at what I can do, there is a solution for everything*" (P4) and *"I can still live and be a happy person"* (P5).

Psychological functioning

The interviews showed that colorectal cancer treatment may have an impact on a patient's psychological functioning. Multiple participants reported that, after colorectal cancer treatment, the fear of cancer recurrence plays a major role in their daily living, "*Once you are diagnosed with rectal cancer, the fear of recurrence is always on the back of your mind*" (P12). Consequently, as part of this fear, participants are more aware of anything they feel within their bodies: "*You are more aware of things you feel, this makes you worry more*" (P8). Also, their confidence in their own body and physical health is sometimes decreased "*When I feel something in my body I keep wondering if this is normal or if I should visit the doctor*" (P2). Not only do participants experience fear towards their own bodies, the follow-up hospital visits are also reported as frightening events: *"Every time I have a CT scan or blood test, it is still exciting for me"* (P8).

Some participants also reported changes in their mindset after the treatment, for instance: participants are more consciously enjoying their lives, are better in dealing with work-related issues and are more aware of their goals in life: "*I do not make a big fuss about some things anymore, for example at work*" (P16) and "*I have more plans, I want to get more out of life now*" (P15). Additionally, participants reported changes in their perspectives towards themselves: "*I have learned a lot about myself, you can do more than you think*" (P6) and "*I am more aware of my own body*" (P8).

Furthermore, postoperative complications, such as hemorrhage and anastomotic leakage, have been reported by the participants as influential on their mental health: "*Especially with an emergency reoperation, you are upset for a while. That has had quite a big influence, but it is now going great again*" (P12) and "*I still suffer from flashbacks, for instance when I have to go to the toilet at 2am I remember that was the moment when the bleeding started back then*" (P8).

It was also reported that some participants do cope differently with their disease, for example some are hesitant to speak about their colorectal cancer treatment: "*I do not really like to speak about my colon cancer, because I do not feel the need to discuss this with other people, since they always have an 'irrelevant' story about someone else with cancer*" (P12). Others say it helps them to talk about it "*I'd like to talk about it because it relieves me*" (P13). Participants with a stoma reported that they are usually open about having a stoma: "*I'm not ashamed of it at all, but I don't want to confront people with it*" (P1).

Social functioning

A few participants reported that the diagnoses of colorectal cancer and treatment had no influence on their social functioning: "*Actually, little has changed in that respect*" (P4). Some participants report that they felt supported: "*You discover how many dear friends and people you have around you*" (P2) and "*I knew he would always be there for me. He did a fantastic job*" (P8). Some relationships were deepened seeing another side of each other "*The bond with my children has definitely deepened after treatment*" (P6), and some reported that this was even more with people who also had to deal with cancer: "*They know a bit more about what I went through, than people who have never had to deal with it*" (P13).

Stoma may lead to specific challenges, as participants with a stoma reported that the fear of stoma-related stool leakage or uncontrollable flatulence does influence social functioning "*During social appointments I am sometimes afraid that the stoma will leak, then you are not relaxed*" (P3).

Sexual functioning

Participants, male and female, reported several challenges regarding sexual functioning as a consequence of their colorectal cancer treatment, while some were not sexually active anymore. Erectile dysfunction and being unable to ejaculate was reported as a major issue *"I do not get a good erection anymore and ejaculation is not possible at all. I do have medication for this, but it is not the same as it was before surgery"* (P1). As medication for erectile dysfunction might offer some solution, several participants reported that the loss of the ability to spontaneously engage in sexual activities is a burden on their sexual functioning. Furthermore, bowel functioning might interfere with sexual functioning "*I am a bit more hesitant, because I am afraid of losing stool*" (P10), along these lines a stoma might have a negative impact as well "*In the beginning, the stoma frightened us*" (P8). Abdominal scars after laparotomy is also reported to be of influence on sexual functioning. When issues arise, participants stated that talking about this with their partners was very helpful "*We talk well about sexuality, therefore it has not become a problem*" (P15). Contrastingly, some other participants do report not to experience any difficulties or changes regarding sexuality: "*nothing really changed*" (P7).

Healthcare and treatment experiences

Participants reported several factors which they consider as important during colorectal cancer treatment, and which might impact daily life during treatment, and follow-up. Good explanation about the surgical treatment and perioperative care is reported as very important: "*The explanations by the doctors about the surgery were good, luckily because I like to know everything*" (P3), "*Whenever I had a question it was answered*" (P7) and "*Before surgery, I knew what was going to happen and the possible consequences*" (P11). Additionally, involvement and openness of medical personal was reported as important: "*You can call the stoma nurses at any time to solve some issues that might occur*" (P1) and "*The enormous concern and dedication of the surgeon helped me a lot and felt very supportive*" (P6) . Others reported to find it difficult to find answers to their questions: "*I would like to know if the symptoms I experience are normal*" (P9).

Conversely, also negative experiences regarding doctor-patient communication after complications have been reported: **"***The surgeon who operated on me the first time never spoke to me after the complication, which I thought was a pity*" (P16). Furthermore, the way of communication might affect patient-doctor communication: "*Due to COVID-19 most of the appointments were by phone, therefore you cannot really discuss all your questions*" (P2). Waiting on results is reported as a factor on mental health: "*I have been waiting for 3 months on the results of genetic tests, which was quite long which bothered me*" (P2). Other negative factors that have been reported were: "*Usually I can sleep anywhere, but in the hospital, it was very bad*" (P12) and "*I had a pulmonary embolism which was detected quite late, this was a pity because, in hindsight, as I understood the symptoms were very clear*" (P3).

Discussion

This study aimed to explore and gain insights into patient perspectives on the consequences of colorectal cancer treatment for their daily life. Health deficits as consequence of colorectal cancer treatment that were reported were poor bowel functioning, the presence of a stoma, chemotherapy-induced neuropathy of hands and feet due to chemotherapy, sexual dysfunction and fear of recurrence. Poor bowel functioning impacted daily life and activities, since patients reported to use the bathroom more frequently and had to pay more attention to their diet. Whereas, patients with a stoma reported to be afraid of stoma-related fecal leakage and uncontrollable flatus from their stoma in social situations. Patients who suffered from chemotherapy-induced neuropathy in hands and feet reported altered sensory functioning and pain during activities. Sexual dysfunction is reported to be a result of erectile function loss or ejaculation function loss. Also, the presence of a stoma or abdominal scars affected sexual functioning. Some patients reported to have an increased fear of recurrence when their follow-up appointment is coming up, and some reported that they trust their body less than before the diagnosis. Furthermore, social functioning is rarely affected. Also, coping style mechanisms seem to be different between patients: some patients do feel the need to talk about their situation, whereas others prefer not to speak about their colorectal cancer. However, overall, patients reported that daily life remains fairly unaffected by colorectal cancer treatment, since patients experience only minor interference with daily life. These findings suggest that various coping mechanisms are in place.

As witnessed from a prior conducted study by our group, patients report that over time their quality of life seems to be returning to preoperative levels, suggesting that they face no or minor challenges or treatment-related health deficits [10]. However, as also shown in the current study and other literature, patients who underwent colorectal cancer treatment may still experience various challenges and health deficits. These challenges and health deficits differ based on the treatment they received [20-23]. The findings of this study suggest that most challenges that are frequently reported after colorectal surgery are bowel related. The functional bowel complaints which these patients reported, were similar to the ones that are described in literature as low-anterior resection syndrome (LARS). However, the LARS-score was not formally determined in this study [24, 25]. It has been shown that quality of life in patients reporting LARS is significantly impaired [26, 27]. Still, patients with a stoma also reported specific stoma-related challenges, such as worrying about stool leakages and uncontrollable flatulence, which is consistent with previous literature [28].

In line with a prior study, postoperative complications can in some cases affect the doctor-patient relationship. This urges, amongst other reasons, preoperative counseling of patients with information of the risks of surgery [29]. A noticeable complaint that was frequently reported by patients in our study that underwent (neo-)adjuvant chemotherapy, was peripheral neuropathy. In accordance with existing literature, patients reported that symptoms decrease over time, but a large proportion of patients keeps experiencing complaints [30-32]. These complaints of chemotherapy-induced peripheral neuropathy do, however, not affect global health status, but impair physical- and role functioning [31].

Another domain that is reported to be affected in this study, and in accordance with literature, is sexual functioning, which may be decreased as a result of colorectal cancer treatment [22]. As previously studied, sexual dysfunction may be caused by both surgery and radiotherapy. Additionally, the presence of a stoma is also described to negatively affect sexual activity in this study as well as in previous research [33-35].

Furthermore, previous studies have shown that coping strategies, to cope with treatment-related health deficits and challenges, differ between patients. This is similar to what was witnessed under the psychological functioning theme in this study [36]. Previous studies in both patients with ovarian carcinoma and colorectal carcinoma showed that patient may have various coping strategies, and that coping might even be enhanced as result of cancer survivorship [11, 12, 37]. The coping style that is used by patients might explain the underestimation of the effect of treatment-related health deficits (e.g., poor bowel function, chemotherapy-induced neuropathy) on quality of life, since patients are able to live a modified life with the use of various strategies and self-management techniques to maintain their quality of life [38]. Additionally, there is considerable individual variation between patients on how these self-management strategies are undertaken [39].

The knowledge acquired by this study on challenges that patients face after treatment could be taken in to account by making treatment decisions and by implementation of new treatment strategies [40, 41].For example, recently, studies have reported a complete mesocolic excision as a new surgical technique for right-sided colon cancer, which entails a more extensive procedure to ensure adequate lymphatic resection [42]. While an alternative strategy might be to make the colonic resection more precise and potentially less extensive by performing a sentinel node procedure instead of a complete mesocolic excision [43]. In theory, a less extensive resection might lead to a lower rate of postoperative complications and better functional bowel outcome [44]. Additionally, in case multiple treatment options exist, information on postoperative consequences of the treatment on quality of life and the associated treatment-related health deficits may entail important information for patients during shared decision-making. Furthermore, as shown in this study, some patients reported that good preoperative education on the consequences of colorectal cancer treatment is important to them. Explicit patient consideration of their treatment and certain trade-offs are shown to have a positive effect on long-term quality of life, as it leads to increased acceptance of treatments' consequences [13, 26]. As shown in this study, after colorectal cancer treatment, patients may face various treatment-related health deficits in various domains (e.g., psychological, social, physical) [20]. In addition, these patients have an increased risk of other health issues, such as adverse effects of treatments and psychosocial challenges [45, 46]. Therefore, optimizing post-treatment psychological-, sexual-, nutritional-, and cognitive functioning of colorectal cancer survivors could be an integral part of rehabilitation programs. However, some treatment-related health deficits may not be treatable, reliable outcome data on these sequelae may render important knowledge to incorporate in preoperative patient education and in shared decision-making.

Value based-health care

The insights of this study are important in light of the newly introduced management strategy value-based healthcare (VBHC). An important element of VBHC is measuring outcomes and costs for every patient [47, 48]. To measure patient outcomes uniformly, a standard set of patient-centered outcomes was developed by The International Consortium for Health Outcomes Measurement (ICHOM), including survival and disease control, disutility of care, degree of health, and quality of death [49]. Using both generic and disease-specific questionnaires. Trying to streamline implementation of the patient-reported outcome measurements, some have suggested only to use generic quality of life assessment strategies. However, this study shows that one must be cautious in only using these generic patient-reported outcome sets and quality of life questionnaires, since these might give a too limited image of the actual quality of life of a patient. As this study shows, colorectal cancer patients might still experience challenges and treatment-induced health deficits, [37, 50].

Strengths and limitations

First, in this study, differences in complaints were witnessed between sub-groups. However, to study significant differences between sub-groups, a quantitative study design is more applicable. Despite this, this study gives valuable insights into the quality of life and influential factors on daily life after colorectal cancer treatment. A strength of this study is, due to the qualitative approach of this study, complementary and more in-depth insights are gathered that add to previous quantitative studies [51]. Second, this was a single-center study in an academic teaching hospital with relatively advanced/complex cases, which might affect the generalizability. To overcome this issue, purposeful sampling was used to include patients with a different age, comorbidity, (neo-)adjuvant therapy, postoperative complications and stoma presence, therefore patient characteristics and complication rates are not representable for the general population. Third, interviews were held online and via Zoom, since interviews were partly conducted during the COVID-19 pandemic. This might have influenced the quality of the conversations with the participants. However, Shapka et al. showed no differences in quality between face-to-face and online conducted interviews [52]. Therefore, we expect that our method of interviewing did not majorly affect our results. Last, the sample size in this study is small, but data saturation was reached. This means that no more forthcoming information or themes were gained in the last three interviews, as described by Hennink et al [16].

Conclusion

In conclusion, this explorative study shows that patients who underwent treatment for resectable colorectal cancer, face several challenges and treatment-related health deficits in the long-term, but that these challenges and health deficits lead to only minor interference with daily life. The reported minor interference might suggest coping mechanisms are in place. Frequently reported health deficits after colorectal cancer treatment are the presence of a stoma, poor bowel function, chemotherapy-induced neuropathy, fear of tumor recurrence and sexual dysfunction. The results of this study offer in-depth insights into patient perspectives on the consequences of colorectal cancer treatment. These insights are important in appreciation of generic quality of life questionnaires, in which post-treatment health deficits may be less clearly noticeable and therefore may be underestimated.

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Chapter 7

The Impact of Postoperative Complications on Short- and Long-Term Health-Related Quality of Life After Total Mesorectal Excision for Rectal Cancer

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List of Abbreviations

EORTC; European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core, HRQoL; health-related quality of life, RSCL; Rotterdam Symptom Checklist, TME; total mesorectal excision.

Abstract

Background: Survival for rectal cancer patients has improved over the past decades. In parallel, long-term health-related quality of life (HRQoL) is gaining interest.This study focuses on the effect of complications following rectal cancer surgery on HRQoL and survival.

Methods: The TME-trial (1996-1999) randomized patients with operable rectal cancer between surgery with preoperative short-course radiotherapy and surgery. Questionnaires including the Rotterdam Symptom Checklist were sent at 6 time points within the first 24 months and after 14 years the EORTC QLQ-C30 and EORTC QLQ-CR29 questionnaires. Differences in HRQoL and survival between patients with and without complications were analyzed.

Results: A total of 1207 patients were included, of which 482 (39.9%) patients experienced complications, surgical complications occurred in 177 (14.6%) patients, non-surgical complications in 197 (16.3%) and 108 patients (8.9%) had a combination of both types of complications. Three months after surgery, patients with a combination of surgical- and non-surgical complications, especially patients with anastomotic leakage, had the worst HRQoL. Twelve months postoperative HRQoL returned to a similar level as before surgery, regardless of complications. In patients who survived 14 years, no significant differences in HRQoL were seen between patients with and without complications. However, patients with complications did have lower overall survival.

Conclusion: This study shows that survival and short-term HRQoL are negatively affected by complications. Twelve months after surgery HRQoL had returned to the preoperative level regardless, of complications. Also, in patients that survived 14 years, there was no effect of complications on HRQoL detected.

Introduction

Colorectal cancer is one of the most common types of cancer in western countries with increasing incidence, of which approximately a third is located in the rectum. Fortunately, survival has improved substantially [1-3]. The cornerstone of rectal cancer treatment is surgery, which is a complex procedure and is associated with a high rate of overall postoperative complications, 36-59 % [4, 5]. Postoperative complications are associated with increased morbidity and mortality, as well as increased hospital length of stay and healthcare costs. Another major issue in rectal cancer treatment is local recurrence. The Dutch TME-trial demonstrated that reduction from 10.9% to 5.6% of local recurrence rates was achieved by adding short-course preoperative radiotherapy to the standard treatment [6]. Preoperative radiotherapy may increase postoperative complications [7], although the addition of preoperative radiotherapy does not seem to lead to a decreased health-related quality of life (HRQoL) [8].

Currently, the overall 5-year survival of rectal cancer lies around 75-80% [9]. Together with an increasing trend towards value-based health care and shared decision-making, recurrence-free – and long-term survival are not the only important factors that have to be considered during treatment planning, but also other factors such as quality of life. Furthermore, studies indicate that patients are only willing to risk an inferior functional outcome for better survival to a certain extent [10]. This impacts decision-making regarding treatment options, for example, watching and waiting after clinical complete response to neoadjuvant therapy [11]. Therefore, HRQoL after rectal cancer should be investigated as well as factors influencing this, both to inform patients and to gain insight into possible improvements of perioperative care.

This study aims to objectify the difference in short- and long-term HRQoL between uncomplicated and complicated postoperative recovery after total mesorectal excision (TME) surgery for rectal cancer. The hypothesis is that postoperative complications lead to a decreased HRQoL. Furthermore, the differences in overall survival between patients with- and without postoperative complications are studied.

Methods

Study Population and Treatment

Between January 1996 and December 1999 patients with resectable rectal cancer were enrolled in the Dutch multicentre TME-Trial, [12-15]. The trial was approved by the medical ethics committees of all the participating hospitals. During this trial, patients were randomly allocated to TME surgery or preoperative radiotherapy followed by

TME surgery. Eligibility criteria were a clinically resectable adenocarcinoma with an inferior tumor margin below the level of S1/S2 and within 15 cm from the anal verge, without evidence of distant metastases. Patients were excluded from analysis when not having filled out the baseline HRQoL questionnaire or when deceased within 30 days after surgery. Patients assigned to preoperative radiotherapy received a total dose of 25 Gy in five fractions delivered by a three- or four-field technique over 5–7 days. The clinical target volume included the primary tumor and the mesentery containing the sacral, perirectal, and internal iliac nodes up to the S1/S2 junction. The perineum was also included in this volume if an abdominoperineal resection (APR) was planned. Otherwise, the lower field border was 3 cm above the anal verge. All patients underwent surgery following the TME principle [12, 16]. Following our previous report, survival was calculated from the day of surgery [12]. The status, alive, of patients, was censored at the time of the last follow-up.

Health-related quality of life (HRQoL) assessment

HRQoL was measured using different questionnaires on 7 different time points. Preoperatively and 3, 6, 12, 18 and 24 months after surgery the Rotterdam Symptom Checklist (RSCL) was used supplemented with questions concerning sexual functioning as reported previously (Table A.1) [13, 14, 17, 18]. In July - August 2012, after a median follow-up of 14.4 years after surgery the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core (EORTC) questionnaires: cancer-specific QLQ-C30 and colorectal- cancer-specific QLQ-CR29 was sent by mail to the surviving patients [19, 20]. In all questionnaires, a four-point Likert scale was used and subsequently all responses were linearly converted to 0–100 scales.

Complications

All complications that occurred during admission were registered and reviewed, of which the following definitions were used. Surgical complications are considered complications directly related to the surgical intervention (e.g., anastomotic leakage. Non-surgical complications are complications not directly related to the surgical intervention (e.g., urinary tract infection). Anastomotic leakage included all leakages clinically diagnosed or confirmed by contrast enema, furthermore, an abscess around the anastomosis was also recorded as anastomotic leakage. Rare complications were classified as other.

Statistics

Linear mixed models with random patient intercepts and time (categoric) and treatment group as fixed factors were used to obtain estimates for the subscales of the RSCL of each of the scheduled time points, to account for drop-out. At each time point, the difference in quality of life between groups was tested by Wald's tests, using linear mixed-effects model the "lme" package. A univariable Poisson regression analysis was carried out using the "lme" package to analyze the effect of individual variables on HRQoL. Cox regression analysis were carried out using the "survival" and "survminer" packages. Analysis were performed in R Version 3.6.3.

Results

Patient characteristics

A total of 1530 patients were selected of which 323 were excluded because of the following reasons: ineligible at randomization (n= 50), no resection (n= 37), no informed consent for HRQL questionnaires (n=89), 30-day mortality (n=41) and no baseline HRQL forms returned (n= 106), leaving 1207 patients for analysis (Figure 1). Patient, tumor and treatment characteristics are listed in Table 1. In total 482 (39.9%) patients suffered from complications, of which urinary tract infection (n= 106) was the most common followed by pulmonary complication (n= 85), anastomotic leakage (n= 79) and abdominal wound infection (n= 75) (Table A.2). Patients were divided into four separate groups based on the type of complications: no complications, surgical complications, non-surgical complications or a combination of surgical and non-surgical complications. There was a significant difference between the different groups in age, the distance of the tumor to the anal verge and stoma formation during primary surgery. There were no significant differences observed in comorbidities (Table 1). Response to the HRQoL questionnaires did not significantly differ between the groups at any time point (Table 2).

Survival after TME surgery

The 5-year overall survival was 67.5%, the 10-year overall survival was 51.6% in the study cohort (Figure 2A). When leaving out the condition for 30-day survival the 5-year survival was lower in the patients with both surgical- and non-surgical complications, 5-year survival was 45.5% and 56.5% respectively (Figure 2B). Decreased survival after surgery was associated with postoperative complications, the 5-year and 10-year overall survival were poorest in patients with both surgical- and non-surgical complications 56.5% and 40.7% respectively (adjusted HR: 1.37, 95%CI 1.04-1.78) (Table 3).

Health-related Quality of life (0-24 months)

The HRQoL measured by the global health status, activity level and physical level was lower after 3 months compared to the preoperative measurements but after approximately 12 months the levels were back to the preoperative level for all groups (Table A.3, Figure 3). In the patients with a combination of both surgical and non-surgical complications the impact of surgery was significantly larger ($p<0.05$) in the first 12 months after surgery. Likewise, patients that suffered from anastomotic leakage had a significantly decreased global health status and activity level (Table A.4, Figure A.1). A decrease in male sexual functioning and psychological distress was seen after surgery, these changes were comparable in all subgroups.

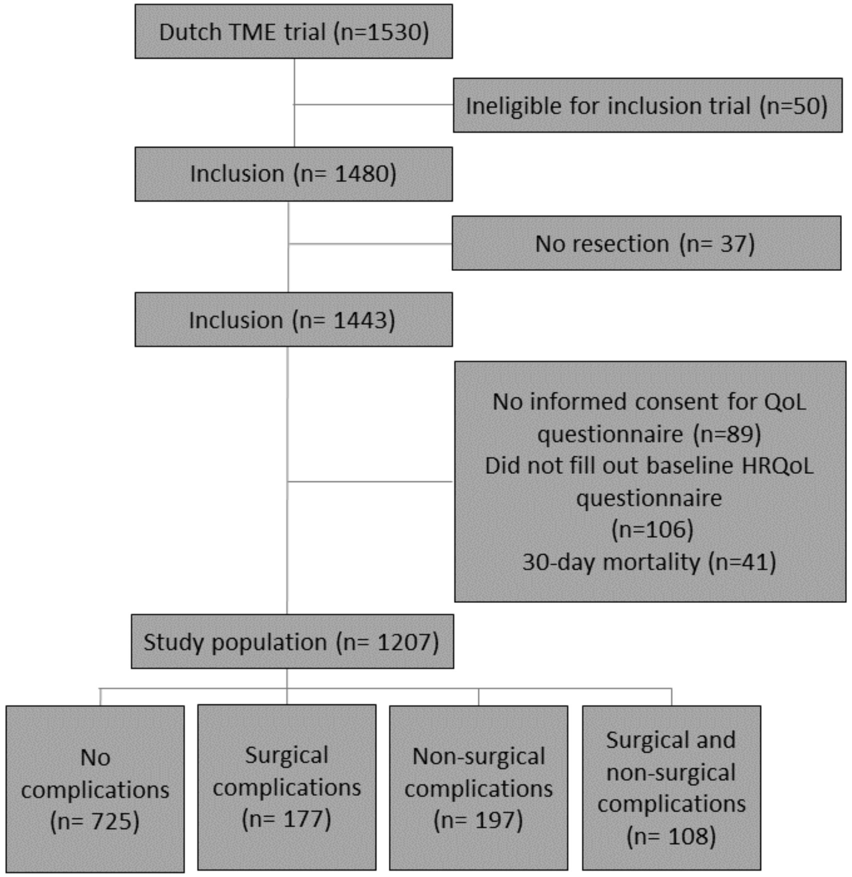

Figure 1 – Flowchart of patient selection for study

Impact of individual variables

Univariate regression analysis was performed to identify influential factors for postoperative overall health and the activity level at the 3 month, 12 month and 24 month time point (Table 4). A combination of surgical and non-surgical complications was significantly associated with a decreased global health (RR: 0.88, 95%CI 0.80-0.97) and activity level (RR: 0.84, 95%CI 0.70-0.98) 3 months after TME surgery. Anastomotic leakage was also significantly associated with a decreased global health status 3 months after surgery (RR: 0.91, 95%CI 0.82-1.00). Additionally, a more advanced tumor stage (RR: 0.98, 95%CI 0.95-0.99) and Hartmann resection (RR: 0.82, 95C%CI 0.70-0.95) were associated with a decreased global health status 12 months after surgery.

Table 1 – Patient, tumor- and treatment characteristics

Characteristics (n= 1248)	**No complications (n= 725 (60.1%))**	**Surgical complications (n= 177 (14.6%))**	**Non-surgical complications (n= 197 (16.3%))**	**Surgical and non-surgical complications (n= 108 (8.9%))**	***p*-value**
Median age [range]	64 [23-88]	65 [41-86]	66 [26-92]	67 [43-88]	**<0.01**
Male	447 (61.7%)	123 (69.5%)	121 (61.4%)	76 (70.4%)	0.09
Mean BMI at baseline	25.4 [16.2-53.1]	26.1 [18.4-45.9]	25.4 [17.1-45.4]	25.4 [17.7-35.3]	0.13
Comorbidities					
Any comorbidity	195 (26.9%)	39 (22.0%)	55 (27.9%)	20 (18.5%)	0.36
Hypertension	104 (14.3%)	24 (13.6%)	27 (13.7%)	6 (5.5%)	0.38
Cardiac comorbidity	35 (4.8%)	8 (4.5%)	7 (3.3%)	7 (6.5%)	0.21
Pulmonary comorbidity	23 (3.2%)	4 (2.3%)	6 (3.0%)	4 (3.7%)	0.65
Diabetes	46 (6.3%)	14 (7.9%)	6 (3.0%)	4 (3.7%)	0.15
Previous abdominal surgery	50 (6.9%)	10 (5.6%)	11 (5.6%)	7 (6.5%)	0.66
Chronic drug use	164 (22.6%)	36 (20.3%)	44 (22.3%)	17 (15.7%)	0.50
TNM stage					0.80
0	14 (1.9%)	5 (2.8%)	4 (2.0%)	0 (0.0%)	
I	221 (30.5%)	52 (29.4%)	67 (34.0%)	33 (30.6%)	
II	193 (26.6%)	48 (27.1%)	43 (21.8%)	32 (29.6%)	
III	262 (36.1%)	60 (33.9%)	74 (37.6%)	36 (33.3%)	
IV	35 (4.8%)	12 (6.8%)	9 (4.6%)	7 (6.5%)	
Distance to anal verge					**0.01**
<5	203 (28.0%)	69 (39.0%)	54 (27.4%)	41 (38.0%)	
5-10	303 (41.8%)	72 (40.7%)	76 (38.5%)	40 (37.0%)	
>10	219 (30.2%)	35 (19.8%)	67 (34.0%)	27(25.0%)	
Unknown	0 (0,0%)	1 (0.6%)	0 (0.0%)	0 (0.0%)	
Neo-adjuvant RT					0.32
Yes	345 (47.6%)	89 (50.3%)	104 (52.8%)	60 (55.6%)	
No	380 (52.4%)	88 (47.7%)	93 (47.2%)	48 (44.4%)	
Operation type					**<0.01**
LAR	490 (67.6%)	92 (52.0%)	135 (68.5%)	64 (59.3%)	
APR	203 (28.0%)	82 (46.3%)	41 (20.8%)	41 (38.0%)	
Hartmann	32 (4.4%)	3 (1.7%)	21 (10.7%)	3 (2.8%)	
Stoma					**<0.01**
None	210 (29.0%)	45 (25.4%)	48 (24.4%)	35 (32.4%)	
Diverting	312 (43.0%)	50 (28.2%)	107 (54.3%)	32 (29.6%)	
Permanent	203 (28.0%)	82 (46.3%)	41 (20.8%)	41 (38.0%)	
Missing	0 (0.0%)	0 (0.0%)	1 (0.5%)	0 (0.0%)	

Table 2 – Questionnaire response per time point. Percentages are calculated using the patients that were alive at the time of the questionnaire.

Completed questionnaires	No complications	Surgical complications	Non-surgical complications	Surgical and non-surgical complications	Overall	*p*-value
Baseline	725 (100.0%)	177 (100.0%)	197 (100.0%)	108 (100.0%)	1207 (100.0%)	
3 months	672 (93.1%)	161 (92.0%)	182 (92.9%)	101 (90.2%)	1205 (92.6%)	0.22
6 months	662 (92.3%)	157 (91.3%)	174 (90.6%)	93 (86.1%)	1086 (91.3%)	0.20
12 months	623 (90.2%)	145 (88.4%)	167 (88.8%)	87 (85.3%)	1022 (89.3%)	0.31
18 months	590 (87.7%)	137 (89.0%)	155 (86.6%)	77 (81.1%)	959 (87.1%)	0.34
24 months	543 (83.8%)	129 (86.0%)	146 (83.0%)	74 (84.1%)	892 (84.0%)	0.81
14 years	251 (76.3%)	57 (82.9%)	66 (82.5%)	25 (71.4%)	400 (77.8%)	0.44

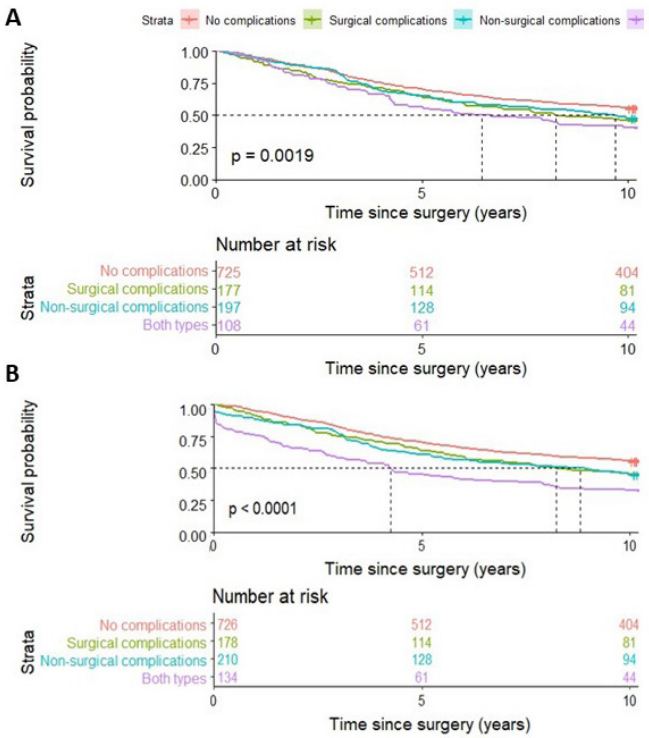

Figure 2- Overall survival probability analysis using Cox regression, subgroups are patient without complications, with surgical complications, non-surgical complications, and patients with a combination of surgical- and non-surgical complications. A) represents survival cure of patients included in HRQoL analyses, B) represents the survival curve without conditional-survival.

Table 3- Survival analysis of using Cox regression. *Adjusted for age, sex, TNM-stage

	Univariate Cox		Multivariate Cox	
	HR (95%CI)	**P-value**	**HR (95%CI)**	**P-value**
Age	1.03 (1.02-1.04)	**<0.01**		
Male sex	0.76 (0.64-0.91)	**<0.01**		
BMI	0.99 (0.97-1)	0.67		
Level of education	0.79 (0.49-1.27)	0.34		
Type of complications				
No complications	ref		ref	
Surgical complications	1.33 (1.06-1.67)	**0.01**	1.23* (0.92-1.55	0.07
Non-surgical complications	1.24 (0.99-1.55)	0.06	1.18* (0.95-1.48)	0.14
Both surgical and non-surgical complications	1.56 (1.19-2.03)	**<0.01**	1.37* (1.043-1.78)	**0.02**
Anastomotic leakage	1.10 (0.80-1.52)	0.54	1.12* (0.81-1.54)	0.49
Type of surgery				
LAR	ref		ref	
APR	1.23 (1.03-1.46)	**0.02**	1.20* (1.00-1.43)	**<0.05**
Hartmann	1.86 (1.33-2.60)	**<0.01**	1.45* (1.04-2.04)	**0.03**
TNM-stage	1.91 (1.74-2.10)	**<0.01**		
Stoma				
No stoma	ref		ref	
Diverting	1.23 (1.00-1.51)	**<0.05**	1.12* (0.92-1.38)	0.27
Permanent	1.33 (1.07-1.65)	**0.01**	1.25* (1.0-1.56)	**<0.05**
Neoadjuvant RT	0.99 (0.85-1.17)	0.98		
Any comorbidity	1.00 (1.00-1.00)	0.99		
Previous malignancy	3.67 (0.38-35.2)	0.26		
Chronic medication	0.55 (0.09-3.3)	0.51		

Health-related Quality of life (14 years)

After a median follow-up of 14 years, 429 patients filled out the quality of life questionnaires, which entails 84.0% of the patients that survived. Global health status was not significantly different between the different (sub)groups with and without complications (Table A.5). We do see significant changes in constipation, urinary frequency, which are more common in the patients after both surgical and non-surgical complications.

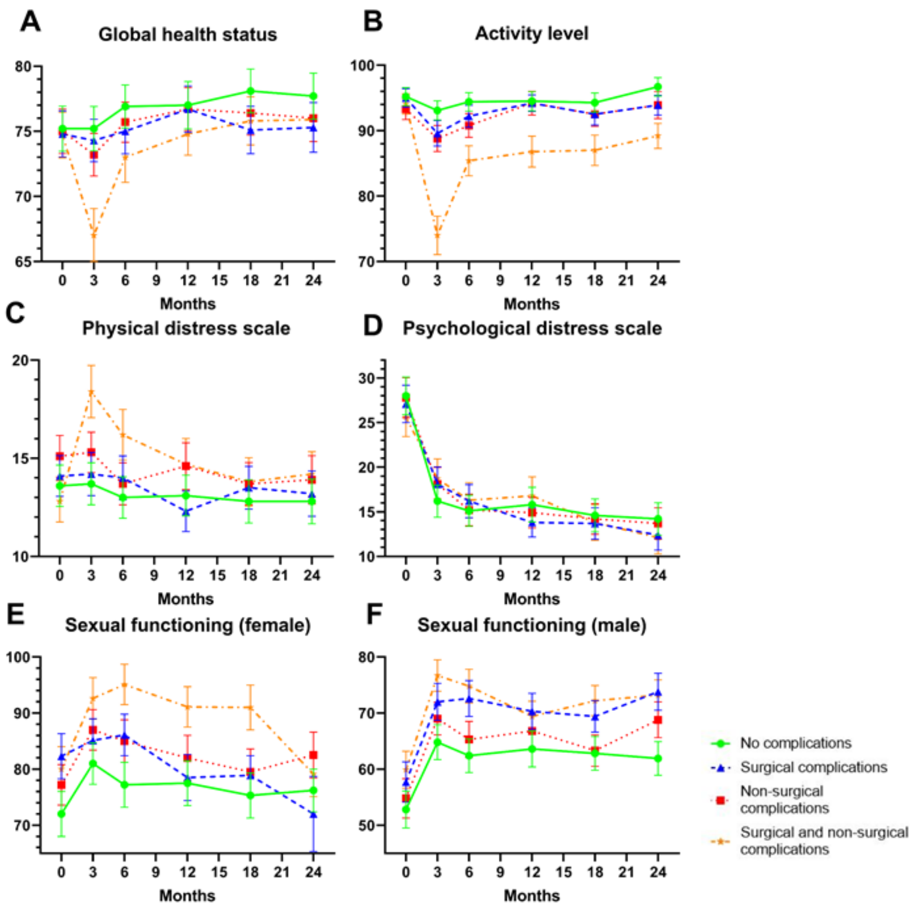

Figure 3 – Health-related quality of life measured by the Rotterdam Symptoms Check List questionnaire on six time points, preoperatively, 3, 6, 12, 18 and 24 months postoperative. Overall health, a higher score is a better health, for all other scores a higher score is more problems. A) Global health status, B) Activity level, C) Physical distress scale, D) Psychological distress scale, E) Sexual functioning (female), F) Sexual functioning (male). The scores of Overall health and Activity Scale are 0-100, a higher score means a better health. For the other subscale the scores are linearly transformed (0-100) a higher score is indicating more distress. Raw results are shown in Table A.3.

Table 4 – Univariable regression analysis of the effect of variables on Global health status and Activity level, measured by the Rotterdam Symptom Checklist at 3 months, 12 months, and 24 months after surgery. * Ileostoma of colostoma present at time of the questionnaire.

	3 Months		12 Months		24 Months	
Global Health Status	**Unadjusted RR (95%CI)**	**P-value**	**Unadjusted RR (95%CI)**	**P-value**	**Unadjusted RR (95%CI)**	**P-value**
Age	1.00 (1.00-1.00)	0.27	1.00 (1.00-1.00)	0.39	1.00 (1.00-1.00)	0.20
Sex	0.99 (0.94-1.04)	0.66	0.97 (0.93-1.02)	0.27	0.97 (0.92-1.02)	0.28
BMI at baseline	1.00 (0.99-1.01)	0.73	0.99 (0.99-1.00)	0.08	0.99 (0.98-1.00)	**<0.05**
Level of education	1.01 (0.99-1.02)	0.41	1.01 (0.99-1.02)	0.28	1.01 (0.99-1.02)	0.49
Type of complications						
No complications	1.00		1.00		1.00	
Surgical complications	0.99 (0.92-1.05)	0.72	1.00 (0.93-1.06)	0.92	0.97 (0.90-1.00)	0.39
Non-surgical complications	0.97 (0.91-1.04)	0.40	1.00 (0.93-1.06)	0.92	0.98 (0.91-1.04)	0.52
Both surgical and non-surgical complications	0.88 (0.80-0.97)	**<0.01**	0.97 (0.89-1.06)	0.51	0.98 (0.89-1.07)	0.61
Anastomotic leakage	0.91 (0.82-1.00)	**0.04**	0.95 (0.86-1.04)	0.32	0.94 (0.84-1.04)	0.21
Type of surgery						
LAR	1.00		1.00		1.00	
APR	1.04 (0.99-1.09)	0.08	0.99 (0.94-1.04)	0.78	0.99 (0.94-1.05)	0.84
Hartmann	0.91 (0.80-1.02)	0.13	0.82 (0.70-0.95)	**<0.01**	0.89 (0.76-1.03)	0.13
TNM-stage	0.98 (0.96-1.00)	0.07	0.98 (0.95-0.99)	**<0.05**	0.98 (0.96-1.01)	0.20
Stoma*	1.02 (0.99-1.05)	0.13	1.00 (0.97-1.03)	0.87	1.00 (0.97-1.03)	0.98
Neoadjuvant RT	1.02 (0.98-1.07)	0.34	1.01 (0.97-1.06)	0.55	1.00 (0.95-1.05)	0.97

Table 4 – Continued

	3 Months		12 Months		24 Months	
Activity level						
Age	1.00 (0.99-1.00)	0.07	1.00 (0.99-1.00)	0.06	1.00 (0.99-1.00)	0.13
Sex	0.96 (0.88-1.03)	0.28	0.97 (0.89-1.05)	0.39	0.95 (0.87-1.04)	0.25
BMI at baseline	1.00 (0.99-1.01)	0.83	1.00 (0.99-1.01)	0.71	1.00 (0.98-1.01)	0.64
Level of education	1.01 (0.99-1.03)	0.34	1.01 (0.99-1.03)	0.43	1.01 (0.99-1.03)	0.29
Type of complications						
No complications	1.00		1.00		1.00	
Surgical complications	0.97 (0.86-1.08)	0.61	1.00 (0.89-1.11)	0.97	0.99 (0.88-1.11)	0.92
Non-surgical complications	0.97 (0.86-1.07)	0.51	0.98 (0.87-1.09)	0.72	0.97 (0.85-1.08)	0.60
Both surgical and non-surgical complications	0.84 (0.70-0.98)	**<0.05**	0.94 (0.79-1.08)	0.40	0.96 (0.80-1.11)	0.58
Anastomotic leakage	0.92 (0.77-1.07)	0.32	0.96 (0.81-1.12)	0.96	0.99 (0.82-1.15)	0.87
Type of surgery						
LAR	1.00		1.00		1.00	
APR	1.00 (0.92-1.08)	0.99	1.00 (0.92-1.09)	0.93	0.99 (0.90-1.08)	0.90
Hartmann	0.95 (0.77-1.13)	0.57	0.94 (0.75-1.13	0.55	0.95 (0.74-1.17)	0.67
TNM-stage	0.99 (0.96-1.03)	0.73	0.99 (0.95-1.03)	0.76	0.99 (0.95-1.04)	0.73
Stoma*	1.00 (0.95-1.05)	0.97	1.00 (0.95-1.05)	0.97	1.00 (0.94-1.05)	0.92
Neoadjuvant RT	1.02 (0.94-1.09)	0.67	1.00 (0.93-1.08)	0.95	1.00 (0.92-1.08)	0.94

Discussion

The HRQoL, as measured by our approach, of patients that survived 12 months after TME surgery for rectal cancer is comparable with the preoperative status and no significant differences were witnessed between patients with an uncomplicated and complicated recovery. However, short-term postoperative recovery was affected in patients with complicated TME surgery, especially when there was a combination of surgical and non-surgical complications and in case of anastomotic leakage. Nevertheless, in patients who survived 1 year up to 14 years after surgery no significant HRQoL differences were seen between uncomplicated and complicated surgery, suggesting the deficit of HRQoL as a result of complications is temporary. Nonetheless, this study showed that postoperative complications negatively impact overall survival, this effect was the highest in patients that suffered a combination of surgical and non-surgical complications.

The results of the short-term postoperative HRQoL are in line with a previously conducted study about patients undergoing oncological colorectal surgery, as they did observe a decrease in physical functioning after complications requiring reoperation [21]. However, they showed no effect of postoperative complications on the global health status, while in our study there was a significant difference shown between patients without complications and patients with both surgical- and non-surgical complications in the first year after surgery. A similar pattern was reported after surgery for diverticular disease: a significant decrease of physical functioning was associated with postoperative complications, while no significant effects on global health perception were seen [22]. As reported by Sharma et al. postoperative complications were significantly associated with increased anxiety, depression and poorer functional wellbeing.[23]. This is not supported by our study, since we see a high preoperative psychological distress and a decrease in psychological distress after surgery which is comparable in both patients with and without postoperative complications. This might be the result of improved preoperative informing and counseling of patients over the past decades, leading to patients having lower preoperative anxiety [23]. Additionally, a study on HRQoL after oncological esophagectomy showed no significant difference on short- or long-term HRQoL after postoperative complications or anastomotic leakage compared to an uncomplicated postoperative course [24]. However, in a study measuring HRQoL after restorative proctocolectomy a difference in HRQoL in patients with and without postoperative pelvic sepsis was observed [25]. The differences in outcome between these studies might be subjected to the patient population, especially benign versus malignant, or the different questionnaires used in the studies. It might be related to the coping style which might differ between different patient populations, since patients with malignant diseases might be more resilient and cope differently with health deficits following postoperative complications, leading to a relative underestimation of the effect of complications on HRQoL [26, 27]. Time points of measuring HRQoL were not equal in all studies, however, most studies measured HRQoL within the first 2 years after surgery. Only Constantinides et al. measured HRQoL at 3-6 years after surgery [22]. This may lead to different outcomes as this study shows that HRQoL is subjected to time.

This study has shown that patients with postoperative complications have lower overall survival. These outcomes are in line with previous studies [28-30]. Furthermore, anastomotic leakage has been shown to be associated with increased local recurrence which impacts survival as well [28]. Several mechanisms might explain this, first the overall survival might be affected by postoperative complications causing an impaired health status [31]. Additionally, it is thought that a systemic inflammatory response after complications leads to decreased (recurrence-free) survival. This inflammatory response is responsible for the release of pro-inflammatory cytokines and growth factors that subsequently might stimulate the growth of residual cancer cells [32, 33].

This study is based on data obtained during a multicenter randomized-controlled trial on preoperative short-course radiotherapy and TME surgery vs. TME surgery alone. Since there was no significant difference in the postoperative complication rate between irradiated- and non-irradiated patients, making this study data is representable for this research question as well. However, our study was not designed to answer whether radiotherapy does increase postoperative complications. Furthermore, previous studies have shown that patients with preoperative radiotherapy may have an impaired activity level in the first two years after surgery, no effect on HRQoL was shown 14 years postoperative [13, 17]. Additionally, the more recent RAPIDO trial, reported no influence of (neo-)adjuvant therapy on long term HRQoL in rectal cancer patients [34].

The current improvements in overall survival of rectal cancer patients result in a larger population that has to live with the physical-, psychological- and societal consequences of rectal cancer surgery, such as having a stoma, bowel dysfunction, physical and psychological stress [35, 36]. The results of this study give insights in the impact of postoperative complications after rectal cancer surgery on the development of HRQoL overtime after postoperative compilations. This information may serve in optimizing patient information and shared decision-making before engaging treatment [37]. Additionally, information on the postoperative HRQoL development can be used for preparatory education of patients planned for 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 [38, 39]. Furthermore, this study gives leads for alteration of (p)rehabilitation programs that should be focusing on enhancing activity and physical fitness and in case of postoperative complications rehabilitation programs might be directed on regaining activity level and physical fitness. The use of prehabilitation programs seems to be especially effective in high-risk patients, therefore preoperative detection of high-risk patients will be needed [40, 41].

A limitation of this study is that postoperative complications are significantly associated with lower survival. This may cause bias in HRQoL measurements, especially 14 years after surgery. Furthermore, between surgery and the 14 year postoperative HRQoL questionnaires other events may have occurred which may have influenced the HRQoL, leading to a possible underestimation of the effect of complications. Furthermore, rectal cancer care has evolved over the past years leading to improvements in treatment, advanced diagnostics and early detection by screening contributing to improved survival. Also, treatment and detection of postoperative complications have been improved, which may lead to a lower burden of postoperative complications. The strength of this study is the high response (77.8%) of long-term follow-up (14 years) HRQoL questionnaires. To our knowledge, this study has currently the longest follow-up of all studies on the impact of complications after rectal surgery. However, although the TME trial is a well-designed and documented RCT, this study has been conducted in 1996-1999 and since then perioperative care and surgical techniques have been improved. Currently, postoperative outcomes after colorectal surgery are improved due to progress in surgical techniques and perioperative care. A major improvement in perioperative care is the introduction of Enhanced Recovery After Surgery (ERAS) protocols. ERAS protocols have been proven to reduce postoperative complications and mortality [42-44]. Preadmission exercise interventions, incorporated in ERAS protocols, are associated with a positive impact on HRQoL [45]. The progress in surgical techniques is marked by the introduction of minimally-invasive surgery. However, in a meta-analysis no clinically significant difference was found in postoperative HRQoL between laparoscopic surgery and open colorectal surgery [46]. Despite, the absence of a significant effect on HRQoL, minimally invasive surgery is thought to lead to a faster postoperative recovery and less use of parenteral and oral analgesics [47, 48]. There are no significant differences between laparoscopic and open surgery regarding intra-operative or postoperative complications [49, 50].

In conclusion, this study did show a decreased overall survival after postoperative complications. Furthermore, this study presents that short-term HRQoL is affected in patients with a combination of surgical and non-surgical complications and in patients with anastomotic leakage. Moreover, after 12 months HRQoL in all patients returned to the pretreatment level. No significant effects of postoperative complications were seen on long-term HRQoL (24 months and 14 years) in patients with- and without postoperative complications. These results suggest that the effects of postoperative complications on the HRQoL are temporary.

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Supplementary Information

Table A.1 - Overview of the items included in the Rotterdam Symptom Checklist (RSCL) and the sexual functioning scale [13].

Items containing HRQoL questionnaires
RSCL physical symptom distress (23 items)
1 Lack of appetite
2 Tiredness
3 Sore muscle
4 Lack of energy
5 Low back pain
6 Nausea
7 Difficulty sleeping
8 Headaches
9 Vomiting
10 Dizziness
11 Decreased sexual interest
12 Abdominal (stomach) aches
13 Constipation
14 Diarrhea
15 Acid indigestion
16 Shivering
17 Tingling of hands or feet
18 Difficulty concentrating
19 Sore mouth/pain when swallowing
20 Loss of hair
21 Burning/sore eyes
22 Shortness of breath
23 Dry mouth
RSCL psychologic distress scale (7 items)
1 Irritability
2 Worrying
3 Depressed mood
4 Nervousness
5 Despairing about future
6 Tension
7 Anxiety

Table A.1 - Continued

RSCL activity level scale (8 items)
1 Care for myself (wash, etc.)
2 Walk about the house
3 Light housework/household jobs
4 Climb stairs
5 Heavy housework/household jobs
6 Walk out of doors
7 Go shopping
8 Go to work
Sexual Functioning (4 items)
1 Feeling sexual attractive
2 Sexually interested
3 Sexual pleasure
4 Sexual satisfaction

Table A.2- Overview of complications.

	Surgical complications (n= 177 (14.6%))	Non-surgical complications (n= 197 (16.3%))	Surgical and non-surgical complications (n= 108 (8.9%))
Surgical complications			
Abdominal wound dehiscence	13	-	16
Perineal wound dehiscence	31	-	11
Wound infection abdomen	48	-	27
Wound infection perineal	26	-	11
Intestinal necrosis	2	-	3
Anastomotic leakage	41	-	38
Hemorrhage	23	-	12
Intestinal fistula	7	-	9
Stoma complication	11	-	7
Intestinal perforation	1	-	6
Non-surgical complications			
Urinary tract infection	-	65	41
Abdominal abscess	-	27	16
Sepsis	-	17	34
Infected hematoma	-	5	3
Pulmonary complication	-	50	35
Renal complication	-	1	5
Neurological complication	-	11	8
Thromboembolism	-	8	9
Cardiac complications	-	22	10
Delirium	-	18	8
Multi-organ failure	-	1	2
Tension complication	-	4	0
Line sepsis	-	12	3
Cholecystitis	-	5	7

Table A.3 – Raw results of health-related quality of life measured by the Rotterdam Symptoms Check List questionnaire on six time points, preoperative, 3, 6, 12, 18 and 24 months postoperative, graphical presentation of results is shown in Figure 3. The scores of Overall health and Activity Scale (0-100), a higher score means a better health. For the other subscale the scores are linearly transformed (0-100) a higher score is indicating more distress.

	No complications (n=725 (60.1%))	Surgical complications (n= 177 (14.6%))	Non-surgical complications (n=197 (16.3%))	Surgical and non-surgical complications (n= 108 (8.9%))	*p*-value
Overall health					
Preoperative	75.2	74.8	75.0	74.7	
3 Months	75.2	74.3	73.2	67.0	
6 Months	76.9	75.0	75.7	73.0	0.48 α
12 Months	77.0	76.7	76.7	74.8	
18 Months	78.1	75.1	76.4	75.8	
24 Months	77.7	75.3	76.0	75.9	
Activity level					
Preoperative	95.2	95.0	93.3	94.1	
3 Months	93.1	89.6	88.8	74.0	
6 Months	94.4	92.2	90.8	85.4	**<0.01** α, γ, δ, ε
12 Months	94.5	94.2	92.0	86.8	
18 Months	94.3	92.5	91.6	87.0	
24 Months	96.7	93.9	90.8	89.2	
Physical distress scale					
Preoperative	13.6	14.1	15.1	12.8	
3 Months	13.7	14.2	15.3	18.4	
6 Months	13.0	14.0	13.7	16.2	**<0.01**
12 Months	13.1	12.3	14.6	14.7	
18 Months	12.8	13.5	13.7	13.8	
24 Months	12.8	13.2	13.9	14.2	
Psychological distress scale					
Preoperative	28.0	27.1	27.8	25.6	
3 Months	16.2	18.1	18.1	18.7	
6 Months	15.1	16.2	15.2	16.3	0.77
12 Months	15.8	13.8	14.9	16.8	
18 Months	14.6	13.7	14.2	13.8	
24 Months	14.2	12.4	13.7	12.1	

Table A.3 – Continued

Sexual functioning (male)					
Preoperative	52.8	57.7	54.8	59.9	
3 Months	64.8	72.0	69.0	76.7	
6 Months	62.4	72.6	65.3	74.8	0.43 α
12 Months	63.6	70.3	66.8	69.4	
18 Months	62.8	69.4	63.3	72.2	
24 Months	61.9	73.8	68.8	73.2	
Sexual functioning (female)					
Preoperative	72.0	82.3	77.2	80.0	
3 Months	81.0	85.1	87.0	92.6	
6 Months	77.2	86.1	85.0	95.1	0.66
12 Months	77.6	78.5	82.0	91.1	
18 Months	75.3	78.9	79.5	91.0	
24 Months	76.2	72.0	82.5	79.1	

α: statistically difference between no complication and both surgical and non-surgical complications
β: statistically difference between no complication and surgical complications
γ: statistically difference between no complications and non-surgical complications
δ: statistically difference between surgical complications and both surgical and non-surgical complications
ε: statistically difference between non-surgical complications and both surgical and non-surgical complications

Table A.4- Overview of HRQoL subscale patients with and without anastomotic leakage

	No complications (n=726)	Anastomotic leakage (n=88)	*p*-value
Global health			
Preoperative	75.2	77.0	
3 Months	75.2	68.0	<0.01
12 Months	77.0	56.9	
24 Months	77.7	72.6	
Activity level			
Preoperative	95.2	96.8	
3 Months	93.1	81.7	<0.01
12 Months	94.5	89.3	
24 Months	96.7	91.9	
Physical scale			
Preoperative	13.6	14.4	
3 Months	13.7	16.2	0.85
12 Months	13.1	14.2	
24 Months	12.8	13.5	
Psychological scale			
Preoperative	28.0	26.8	
3 Months	16.2	16.1	<0.01
12 Months	15.8	14.9	
24 Months	14.2	12.8	

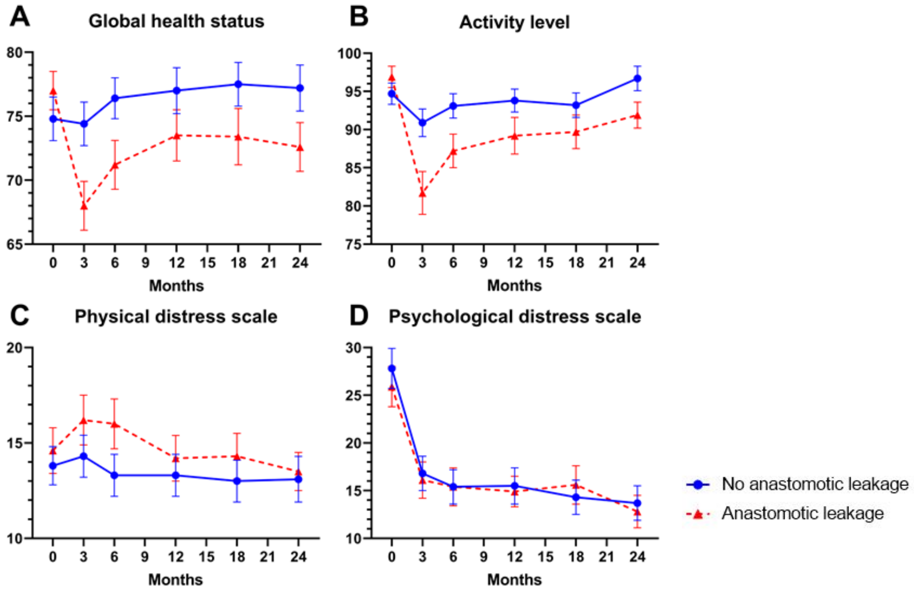

Figure A.1- Health-related quality of life in patients with anastomotic leakage (AL) and without AL. Measured by the Rotterdam Symptoms Check List questionnaire on six-time points, preoperative, 3, 6, 12, 18 and 24 months postoperative. Overall health, a higher score is better health, for all other scores a higher score is more problems. A) Global health status, B) Activity level, C) Physical distress scale, D) Psychological distress scale. The scores of overall health and Activity Scale are 0-100, a higher score means better health. For the other subscale, the scores are linearly transformed (0-100) a higher score is indicating more distress.

Table A.5 – Health-related quality of life measured by EORTC QLQ C30 and 29, 14 years after surgery. * higher is more symptoms, # higher is better functioning. Percentages given in the top row are calculated form the total of patients that were alive (n=511) at the time of the questionnaire.

	No complications (n=251 (49.1%))	Surgical complications (n=57 (11.1%))	Non-surgical complications (n=66 (12.9%))	Both surgical and non-surgical complications (n=25 (4.9%))	*p*-value
EORTC QLQ-C30					
Global Health status#	78.4	81.5	74.3	76.9	0.23
Physical functioning#	76.7	77.9	74.0	77.6	0.35
Role functioning #	78.2	78.8	74.2	77.8	0.13
Emotional functioning#	84.0	89.2	82.9	88.0	0.15
Cognitive functioning#	86.3	84.4	82.6	82.7	0.74
Social functioning#	86.0	85.5	83.8	84.6	0.54
Fatigue*	24.9	25.1	28.5	21.8	0.34
Nausea and vomiting*	3.3	1.6	4.6	13.3	0.25
Pain*	15.0	11.6	15.3	12.3	0.46
Dyspnea *	13.3	11.7	19.1	18.5	0.35
Insomnia *	24.6	16.9	24.5	25.3	0.30
Appetite loss *	6.4	2.7	11.9	4.0	0.07
Constipation *	14.5	8.2	18.8	20.8	**0.02**
Diarrhea *	10.5	7.2	14.4	7.3	0.21
Financial difficulties *	4.6	7.1	7.0	5.1	0.26
EORTC QLQ-C29					
Body image#	88.1	90.6	88.4	86.4	0.94
Anxiety#	83.5	81.9	77.3	83.3	0.48
Weight#	86.9	90.6	85.4	88.9	0.51

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Table A.5 – Continued

	No complications (n=251 (49.1%))	Surgical complications (n=57 (11.1%))	Non-surgical complications (n=66 (12.9%))	Both surgical and non-surgical complications (n=25 (4.9%))	*p*-value
Sexual interest (male) [#]	57.8	52.1	49.2	69.4	0.22
Sexual interest (female) [#]	65.7	85.2	70.1	48.2	0.14
Urinary frequency*	26.2	30.5	34.6	37.2	**0.02**
Blood and mucus in stool*	1.9	4.7	3.5	6.0	0.28
Stool frequency (stoma)	12.5	11.8	11.1	10.8	0.95
Stool frequency (no stoma) *	22.3	24.2	27.8	27.1	0.65
Urinary incontinence*	12.8	10.3	16.4	18.7	0.27
Dysuria *	1.6	0.0	1.5	1.3	0.48
Abdominal pain*	4.3	8.5	11.1	5.1	**<0.01**
Buttock pain*	7.1	10.9	11.0	15.4	0.05
Bloating*	9.7	10.9	12.6	8.0	0.49
Dry mouth*	15.8	18.4	24.9	24.0	0.06
Hair loss*	1.8	4.0	3.5	3.8	0.45
Taste*	3.7	3.4	6.5	10.3	0.17
Flatulence (stoma) *	21.0	24.0	17.9	17.7	0.84
Flatulence (no stoma) *	31.7	36.8	40.0	29.6	0.20
Fecal incontinence (stoma) *	14.9	5.4	12.8	12.5	0.06
Fecal incontinence (no stoma) *	14.0	21.8	23.1	3.7	0.08
Sore skin (stoma) *	11.6	7.3	14.1	5.9	0.61
Sore skin (no stoma) *	8.9	6.9	11.7	14.8	0.71

Table A.5 – Continued

	No complications (n=251 (49.1%))	Surgical complications (n=57 (11.1%))	Non-surgical complications (n=66 (12.9%))	Both surgical and non-surgical complications (n=25 (4.9%))	*p*-value
Embarrassment (stoma) *	10.4	10.4	12.8	3.9	0.52
Embarrassment (no stoma) *	21.2	26.4	29.2	18.5	0.54
Impotence*	57.4	59.0	63.8	66.7	0.84
Dyspareunia *	22.7	22.2	16.7	6.7	0.69

Chapter 8

Stoma Versus Anastomosis After Sphincter-Sparing Rectal Cancer Resection; the Impact on Health-Related Quality of Life

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List of Abbreviations

APE; abdominoperineal excision, ASA; American Society of Anesthesiologists, DCRA; Dutch ColoRectal Audit, EORTC; European Organization for Research and Treatment of Cancer, HRQoL; health-related quality of life, LAR; Low-Anterior Resection, LARS; Low-Anterior Resection Syndrome, POLARS; Pre-Operative LARS score, PROM; patient-reported outcome measure

Abstract

Background: Surgical resection is the mainstay of curative treatment for rectal cancer. Post-operative complications, low anterior resection syndrome (LARS) and the presence of a stoma may influence the quality of life after surgery. This study aimed to gain more insights into the long-term trade-off between stoma and anastomosis.

Methods: All patients who underwent sphincter-sparing surgical resection for rectal cancer in the Leiden University Medical Center and the Reinier de Graaf Gasthuis between January 2012 and January 2016 were included. Patients received the following questionnaires: EORTC-QLQ-CR29, EORTC-QLQ-C30, EQ-5D-5L and the LARS-score. A comparison was made between patients with a stoma and without a stoma after follow-up.

Results: Some 210 patients were included of which 149 returned the questionnaires (70.9%), after a mean follow-up of 3.69 years. Overall quality of life was not significantly different in patients with and without stoma after follow-up using the EORTC-QLQ-C30 ($p=0.15$) or EQ-5D-5L ($p=0.28$). However, after multivariate analysis, a significant difference was found for the presence of a stoma on global health status ($p=0.01$) and physical functioning ($p<0.01$). Additionally, there was no difference detected in the quality of life between patients with major-LARS or a stoma.

Conclusion: This study shows that, after correction for possible confounders, a stoma is associated with lower global health status and physical functioning. However, no differences were found in health-related quality of life between patients with major-LARS and patients with a stoma. This suggests that the choice between stoma and anastomosis is mainly preferential, and that shared decision-making is required.

Introduction

With an estimated 704,000 new patients worldwide each year, rectal cancer has become the eighth most diagnosed cancer type in the world in 2018 [1]. Approximately 3,300 new patients are diagnosed with rectal cancer in the Netherlands every year [2]. Of these patients 63.6% receive a (temporary) stoma [3]. Nowadays, the treatment of rectal cancer is adopting a more multimodal approach, but surgical resection is still the cornerstone of curative treatment [4]. Over the past decades, the 5-year survival has gone up to 75-80% [5]. The increased survival over the past decades and enlarged focus on value-based healthcare account for the growing interest in the quality of life after cancer treatment [6-8]. An example is the shift from abdominoperineal excision (APE) to sphincter-sparing techniques with low anastomosis in order to maintain organ preservation and bowel continence [9]. The ongoing upswing in overall survival after rectal cancer surgery brings about new dilemmas such as stoma presence, bowel dysfunction and psychological and physical stress [10, 11].

After rectal cancer resection, surgeons are left with the decision on how to reconstruct. Should an anastomosis be constructed with- or without a defunctioning stoma or should a definitive stoma be made? For this choice two considerations are key. First of all the risk of anastomotic leakage, its consequences, and whether a patient is able to cope with them [12]. An anastomotic leak can be a fatal insult to a frail patient. The other important consideration is the risk of a poor functional outcome. Approximately 41% of patients without a stoma after a sphincter-sparing surgical resection for rectal cancer experience major low anterior resection syndrome (LARS) one year after surgery [13]. LARS is described as a "disorder of bowel function after rectal resection, leading to a detriment in quality of life" [14, 15]. Frequently (≥35%) reported symptoms are: clustering of bowel movement, incomplete evacuation, faecal incontinence, uncontrollable flatus and urgency [16]. LARS has been shown to have a detrimental influence on short- and long-term health-related quality of life [17, 18]. Factors that have a negative impact on functional outcomes after rectal resection are low anastomosis, temporary stoma or a stoma before surgery and (neo-)adjuvant radiotherapy. A definitive stoma may prevent these adverse functional outcomes. However, also stoma-related complications such as parastomal hernia, retraction, prolapse and stoma necrosis must be considered [19, 20]. This also goes for temporary stoma's as they can significantly increase mid- to long-term morbidity and cause readmissions and re-interventions. Furthermore, up to 28.5% of temporary stoma's are never reversed [21].

Post-operative complications, poor functional outcomes and the presence of a stoma in patients may all influence the quality of life after surgery, making the decision between the formation of a (temporary) stoma or anastomosis a difficult one [22]. This decision should always be made together with the patient. Information on quality of life after rectal cancer surgery is vital for shared decision-making [23]. This study aims to determine the influence of a stoma on the health-related quality of life (HRQoL) after rectal cancer surgery and gain more insights into the trade-offs between stoma and anastomosis on the long run. In addition, the difference in HRQoL between patients with major-LARS and a stoma is analyzed, using patient-reported outcome measures (PROMs).

Methods

Study population and treatment

The Medical Ethics Committee Leiden Den Haag Delft assed this study protocol and concluded no formal review was needed, as this study is not being conducted under the Medical Research Involving Human Subjects Act (WMO). Consecutive patients who underwent surgical resection for rectal cancer in the Leiden University Medical Center, Leiden, The Netherlands and the Reinier de Graaf Gasthuis, Delft, The Netherlands, between January 2012 and January 2016 with at least 1.5-years follow-up were reviewed for the current study. All patients signed an informed consent form before a review of their medical records and sending questionnaires. Patients that gave informed consent, but did not return the questionnaires were called at least twice. These patients were excluded form analyses, but their characteristics were included in (Table S.1). Inclusion criteria were: patients with a primary tumor of stage I-III located in the rectosigmoid and rectum treated with surgical resection. Patients who underwent emergency surgery, palliative intended surgery or who were treated with an APE were excluded. Additionally, patients with <90% completed questionnaires were excluded. Data regarding 30-day morbidity and mortality were extracted from the Dutch ColoRectal Audit (DCRA), a nationwide clinical audit [24]. The remaining data were extracted from the electronic patient record.

Baseline characteristics and outcomes

Distance from anus was measured during coloscopy. Short-term endpoints were: 90-day major complications, readmissions, and reinterventions. Major complications were defined according to the Clavien-Dindo classification as ≥ IIIA [25]. The HRQoL of patients was assessed as the primary outcome. Secondary outcomes at one- and 2-years after surgery were unplanned re-admissions and re-interventions after the initial 30-day postoperative period.

Health-related quality of life (HRQoL) assessment

After at least 1.5 years of follow-up, patients were asked to fill in the HRQoL questionnaires (EORTC QLQ-CR29, EORTC QLQ-C30, and EQ-5D-5L) [26-28]. In all questionnaires, a four-point Likert scale was used and subsequently, all responses were linearly converted to 0–100 scales.

Statistical analyses

The statistical analysis was performed with SPSS Statistics version 24. Patients were divided into two groups, patients who had a stoma at the time of follow-up and patients without a stoma at the time of follow-up. Chi-square test was used for categorical variables, the Mann-Whitney U test was used for numeric variables. Multivariate analysis using the linear regression was performed to correct for possible confounding with correction for Charlson comorbidity index and tumor recurrence. For sub-analysis, the population was divided into a group with major-LARS and a group of patients with a stoma. After using the EQ-5D-5L questionnaire, a crosstab was made. The p-value of the VAS score was calculated using the Mann-Whitney U test. The p-values of mobility, self-care, usual activity, pain and anxiety were calculated with Pearson's chi squared test. A p-value of 0.05 was considered statistically significant. In line with current evidence, a HRQoL score difference of >5% was considered clinically significant [29]. Outcomes were assumed significant if both statistically-and clinically significant.

Results

Patient characteristics

A total of 254 patients were eligible for the study, of which 44 (17.3%) refused to participate. Of the 210 patients that provided informed consent 149 (70.9%) filled out the questionnaires after a mean follow-up of 3.69 (range: 1-8) years (Figure 1). The 61 patients (29.1%) that did consent to take part in the study, but did not return the questionnaires were on average older in both the stoma and no stoma group, other patient characteristics were comparable with those of patients that have returned the questionnaires (Table S.1). At the time of follow-up 23 included patients (15.4%) had a stoma, of which 20 were a colostoma. In total 103 (69.1%) patients underwent a low anterior resection (LAR) with primary anastomosis, 30 (20.1%) a LAR with a defunctioning stoma and 16 (10.7%) a Hartmann resection (Table 1). In 46 patients (30.9%) a stoma was constructed during primary surgery and 9 (6.0%) in patients during a reintervention. Thirty-two patients (21.4%) had a temporary stoma, of which 2 were closed more than a year after surgery. Patients who still had a stoma at the time of follow-up were older (p=0.03), had a lower tumor (p=<0.01), received more frequent neoadjuvant therapy (p=0.03) and had more major postoperative complications (p=0.03). Patients with a stoma had significantly more unplanned readmissions in both the first (p <0.01) and the second year of follow-up (p=0.03) (Table 2). Moreover, significantly more unplanned reinterventions were performed in the stoma group in both the first (p <0.01) and second-year (p <0.01) of follow-up.

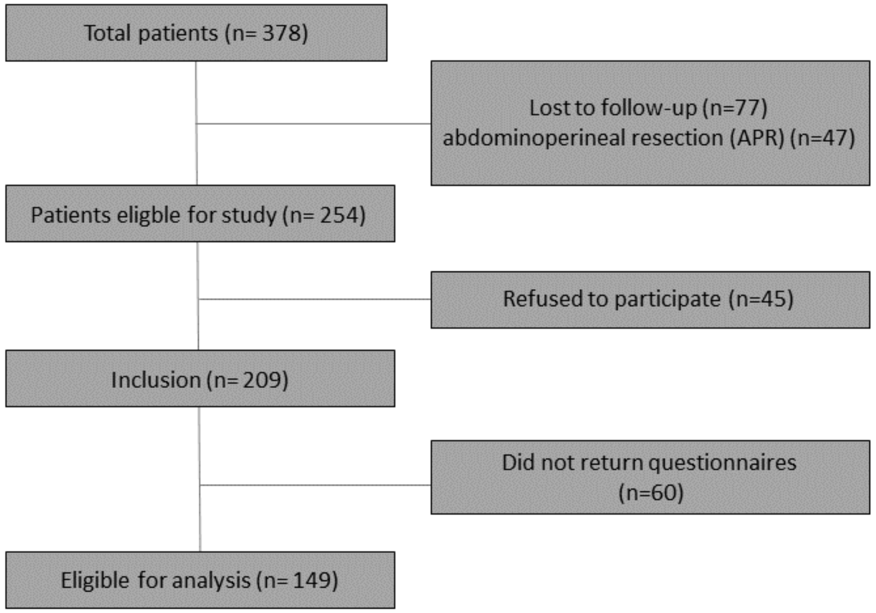

Figure 1 - Flowchart patient inclusion

Health-Related Quality of Life

The overall quality of life more than 2 years after surgery was not significantly different between patients with and without a stoma, not in the EQ-5D-5L (p=0.28) nor in the EORTC-QLQ-C30 (p=0.15) (Figure 2, Table S.2, Table S.4). However, patients with a stoma reported significantly lower physical functioning (p=0.03), significantly more problems with self-care (p=0.03) and usual activity (p=<0.01). Moreover, patients who received a stoma had significantly more complaints of nausea and vomiting (p=0.02), dry mouth (p=0.03), hair loss (p=0.02), sore skin (p<0.01), impotence (p=0.01) and lower body image (p=0.03). Additionally, patients with a stoma reported more financial difficulties (p=0.02).

In a multivariate analysis a stoma present at follow-up was associated with a lower global health status (RR: 0.93, 95%CI 0.88-0.99, p=0.04) and physical functioning (RR: 0.91, 95CI% 0.86-0.96, p <0.01) (Table S.5, S.6). Also a higher cT-score (RR: 0.97, 95%CI 0.95-0.99, p<0.01) and neoadjuvant chemoradiotherapy (RR: 0.94, 95%CI 0.98-0.99, p=0.02) were associated with a lower global health status (Table S.5).

Table 1 - Patient characteristics.

		Stoma		
		No N=126 (84.6%)	**Yes N=23 (15.4%)**	**p-value**
Age (years)	Mean (range)	64.6 (40-85)	69.1 (56-81)	**0.03**
Gender %	Male	84 (66,7%)	12 (52.2%)	0.18
	Female	42 (33.3%)	11 (47.8%)	
BMI	Mean	26.40	26.50	0.45
ASA	I-II	119 (94.4%)	20 (87.0%)	0.19
	III-IV	7 (5.6%)	3 (13.0%)	
Comorbidity	Yes	76 (60.3%)	13 (56.5%)	0.73
	No	50 (39.7%)	10 (43.5%)	
Charlson Comorbidity index	2-6	109 (86.5%)	21 (91.3%)	0.53
	7-11	17 (13.5%)	2 (8.7%)	
Previous abdominal surgery	Yes	31 (24.6%)	8 (34.8%)	0.31
	No	95 (75.4%)	15 (65.2%)	
Tumor location	Distal	12 (9.5%)	5 (21.7%)	**<0.01**
	Middle 1/3	33 (26.2%)	14 (60.9%)	
	Proximal	80 (63.5%)	4 (17.4%)	
	Unknown	1 (0.8%)	0 (0.0%)	
Tumor cStage	I	14 (11.1%)	1 (4.3%)	0.83
	II	28 (22.2%)	5 (21.7%)	
	III	82 (65.1%)	17 (73.9%)	
	IIII	1 (0.8%)	0 (0.0%)	
	Unknown	1 (0.8%)	0 (0.0%)	
Neoadjuvant therapy	Radiotherapy	21 (16.7%)	7 (30.4%)	**0.03**
	Chemoradiation	27 (21.4%)	9 (39.2%)	
	None	78 (61.9%)	7 (30.4%)	
Minimal invasive	Yes	122 (96.8%)	22 (95.5%)	0.77
	No	4 (3.2%)	1 (4.3%)	
Type of initial surgery	LAR	99 (78.6%)	4 (17.4%)	**<0.01**
	LAR with diverting stoma	26 (20.6%)	4 (17.4%)	
	Hartmann	1 (0.8%)	15 (65.2%)	
Stoma formation	During primary surgery	27 (21.4%)	19 (82.6%)	**<0.01**
	During reintervention	5 (4.1%)	4 (17.4%)	
	No	94 (74.5%)	0 (0.0%)	
Major complications*	Yes	16 (12.7%)	7 (30.4%)	**0.03**
	No	110 (87.3%)	16 (69.6%)	
Follow-up in years	Mean (range)	3.6 (1-7)	4.4 (2-8)	0.06

* Major complications are defined as a Clavien-Dindo ≥ IIIa

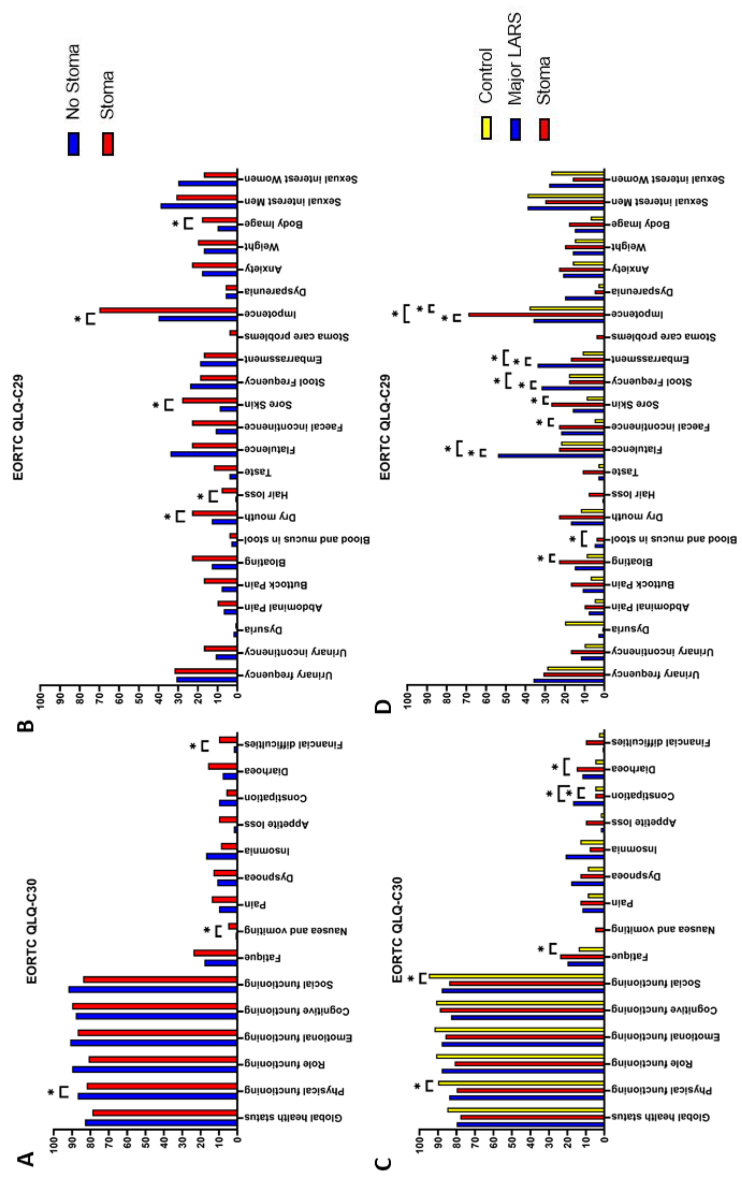

Figure 2 - Patient Reported Outcomes (PROMs). A) EORTC-QLQ-C30, comparison between patients with stoma (red) and patients without stoma (blue) at follow up. B) Patient Reported Outcomes (PROMs) using EORTC-QLQ-CR29, comparison between patients with stoma and patients without stoma at follow up. C) EORTC-QLQ-C30, comparison between patients with stoma (red), patients major Low Anterior Resection Syndrome (LARS) (blue) and control patients, without a stoma or major LARS (yellow) at follow up. D) EORTC-QLQ-CR29, comparison between patients with stoma and patients major Low Anterior Resection Syndrome (LARS) control patients, without a stoma or major LARS (yellow) at follow up.
* p-value <0.05

Male sex (RR: 0.95, 95%CI 0.92-0.99, p=0.01), higher ASA-score (RR: 0.92, 95%CI 0.89-0.96, p<0.01), a higher cN-score(RR: 0.97, 95%CI 0.95-0.99, p=0.01) and Hartmann procedure (RR: 0.90, 95%CI 0.84-0.96, p<0.01) were significantly associated with a lower reported physical functioning (Table S.6).

Major-LARS and health-related quality of life

A sub-analysis was done for patients that did not have a stoma at follow-up and reported major-LARS (n=30, 23.8%). No difference was found in global health status between major-LARS patients and patients with a stoma (p=0.50). Furthermore, no significant difference was found for any of the five functioning scales of the EORTC-QLQ-C30 (Figure 2, Table S.7). Within the EORTC-QLQ-CR29, major-LARS patients reported more problems with flatulence (p=<0.01) and stool frequency (p=0.03) (Figure 2, Table S.8). Moreover, patients with a major-LARS had more complaints of embarrassment compared to patients with a stoma (p=0.02).

Table 2- One- and two-year endpoints. Patients were divided by having a stoma at the time of follow-up. Unplanned readmission and unplanned reinterventions did not include stoma reversal-related admissions and soma reversal interventions.

		Stoma		
		No N=126	Yes N=23	p-value
1-year endpoints				
Unplanned readmission	**Yes**	18 (14.3%)	9 (39.1%)	<0.01
	No	108 (85.7%)	14 (60.9%)	
Unplanned re-intervention	**Yes**	6 (4.8%)	7 (30.4%)	<0.01
	No	120 (95.2%)	16 (69.6%)	
2-year endpoints				
Unplanned readmission	**Yes**	24 (19.0%)	10 (43.5%)	<0.01
	No	102 (81.0%)	13 (56.5%)	
Unplanned re-intervention	**Yes**	9 (7.1%)	9 (39.1%)	<0.01
	No	117 (92.9%)	14 (60.9%)	

Discussion

This study evaluated the HRQoL in patients with an anastomosis or a stoma two years or more after sphincter-sparing rectal resection for cancer. It shows that postoperative global health status and physical functioning are negatively associated with the presence of a stoma in these patients after adjusting for possible cofounders (Charlson comorbidity index, tumor recurrence). In contrast, no clinically significant differences in HRQoL were found between patients with a stoma and patients with an anastomosis and major-LARS. Patients with major-LARS had more complaints of embarrassment than patients with a stoma. Patients with a stoma had a significantly higher unplanned readmission and reintervention rate in the first two years after surgery.

Earlier studies showed ambiguous results for the influence of a stoma on HRQoL. A Cochrane review found that, out of the 26 studies included, only 10 reported significantly poorer HRQoL in patients with a permanent stoma [30]. Therefore, the authors concluded their study did not allow for firm conclusions about whether patients with or without permanent colostoma have a superior HRQoL after rectal cancer surgery. One explanation for a reduced quality of life with a stoma can be stoma-related problems. Vonk-Klaasen et al. demonstrated in their systematic review that stoma-related problems, defined as sexual problems, feeling depressed, constipation, body image, difficulties while traveling, and worry about stoma noises lead to a lower HRQoL [22]. Furthermore, differences in body image were observed, which were most likely caused by the presence of a stoma. In addition, significantly more male patients with a stoma complained about impotence. It should be noted here, that the patients with a stoma were significantly older and that some patients were not sexually active anymore at time of surgery. Some of the above reported differences may therefore be at least partly due to the influence of age.

When comparing patients with poor functional outcomes and patients with a stoma this study did not show differences in HRQoL. Most studies on HRQoL of patients with major-LARS, only compared patients with and without major-LARS. These studies agree that major-LARS is associated with a decreased HRQoL [14, 15, 31, 32]. However, also patient- and treatment characteristics (e.g., age, radiotherapy, low anastomosis) of patients that develop major-LARS are likely to influence HRQoL [31, 33]. In this study patients with major-LARS had significantly more complaints of embarrassment than patients with a stoma, which can be an important issue to discuss with a patient when a high risk of major-LARS is anticipated. The Pre-Operative LARS score (POLARS) can be used to make an estimation of LARS score to predict the postoperative functional outcome [34].

The current study showed that patients with a stoma had significantly more readmissions and reinterventions. These results are in line with current literature [19, 35]. Additionally, stoma-related complications (e.g., bulge, peristomal hernia) were shown to be associated with a decrease in HRQoL, which could have impacted the results of this study [19, 36]. The increased number of readmissions and reinterventions in patients with a stoma as well as stoma-related complications are also relevant in the tradeoff between a stoma or an anastomosis.

A factor that should be taken into account when comparing different studies on quality of life after rectal cancer surgery is the timing of measuring PROMs [37]. Compared to the population norm, HRQoL improves three to six months after surgery with patients reaching role-, physical- and emotional functioning [38, 39]. Studies suggest that HRQoL improvement during this period is caused by fewer defecation or stoma-related complaints, as well as the reversal of temporary stomas, which possibly contributes to this positive effect [39-41]. Furthermore, the age of patients might be an important factor in HRQoL studies after rectal cancer surgery. Recent studies have shown that younger patients (<65 years) are more affected in their quality of life than elderly patients [38, 39]. Several other studies have shown that the overall quality of life in colorectal cancer survivors is comparable to that of the population norms, suggesting that cancer survivors are very resilient and cope well with their treatment [38, 39, 42]. Colorectal cancer survivors have persisting concerns, such as having to adapt to living with a stoma, these concerns consist of clothing difficulties, dietary changes and bowel functioning [43]. How well patients cope with these problems hugely influences their quality of life and should be considered regarding PROMs. Additionally, comparison of patients with an anastomosis or a stoma may be troubled by confounding by indication, i.e. the choice for a stoma is influenced by the (perceived) risk of adverse postoperative outcomes. In this study, this is reflected by the fact that patients with a stoma had a more advanced age, lower tumor location and received more neoadjuvant therapy. In general, advancing age goes hand in hand with a declining HRQoL [44]. This preoperative patient selection and the subsequent difference in patient characteristics and treatment decisions are inevitable in retrospective HRQoL research.

As stated, the decision between an anastomosis and a (temporary) stoma after sphincter-sparing rectal cancer surgery is motivated by the risk of adverse events (e.g., anastomotic leakage) and the expected functional outcomes [12, 33, 45]. However, since this decision is usually not a straightforward one, caused by the lack of a clinically 'best choice', considering the risks of poor functional outcome, makes this decision preference-sensitive and therefore particularly relevant for shared decision-making [34, 46, 47]. The presented HRQoL effects of a stoma and major-LARS in this study might provide information that can be used as patient information to assist in shared decision-making. Furthermore, explicit patient consideration of the trade-off between anastomosis or a stoma might positively influence the long-term quality of life and lead to a higher acceptance of possible consequences [48].

Limitations

The fact that this study excluded all patients that underwent an APE, could be scrutinized. However, with a classic-APE, there is no decision to be made between a stoma or an anastomosis, as the latter is not an option. Furthermore, APE-patients typically have lower rectal tumors with invasion of the sphincter complex or sphincter insufficiency, which is associated with typical and worse pre-operative symptoms [35, 49]. Nonetheless, patients could have been excluded that had intersphincteric-APEs as an alternative for a Hartmann. In these patients, the same considerations about an anastomosis or a stoma could have been made, but surgeons could have been reluctant to leave the rectal stump. The decision whether to perform an APE as an alternative to a low Hartmann is an ongoing debate, the main reason this is done is to avoid the risk of staple line rupture and subsequent leakage and pelvic abscesses as well as persisting mucus production and diversion proctitis [50, 51]. However, an APE is associated with additional risks of perineal wound complications [52]. In our hospitals, the rectal stump is typically left in place except in very low resections. Another limitation of this study was the small sample size, especially in the stoma group. The latter could have been consequential to the exclusion of APE patients as mentioned above and stoma reversal before follow-up and answering the PROM questionnaires. An additional limitation is that the sample size did not allow for sub-analysis of patients with an ileostoma and a colostoma or stoma formation during primary surgery and stoma formation during reintervention. Furthermore, a limitation is the variation in follow-up. In this study, we included all patients operated from 2012 until 2016. The follow-up and time of receiving the questionnaires after operation varied between two and seven years. However, to our knowledge, this is the first study to make a comparison of long-term HRQoL between patients with a stoma and major-LARS.

Conclusion

This study shows that, after correction for possible confounders, a stoma is associated with a lower global health status and physical functioning. However, no clinically significant difference was found in HRQoL between patients with major- LARS and patients with a stoma. This suggests that the choice between stoma and anastomosis is mainly preferential and should be made together with the patient. This study offers leads for improved patient information and enhanced shared decision-making before rectal cancer surgery.

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Supplementary Information

Table S.1 - Patient characteristics of non-responders

		Stoma	
		No N=53 (86.9%)	Yes N=8 (13.1%)
Age (years)	**Mean (range)**	68.3 (37-85)	75.4 (63-84)
Gender %	**Male**	31 (58.5%)	4 (50%)
	Female	22 (41.5%)	4 (50%)
BMI	**Mean**	25.8	25.6
ASA	**I-II**	50 (94.3%)	6 (75.0%)
	III-IV	3 (5.7%)	2 (25.0%)
Comorbidity	**Yes**	35 (66.0%)	7 (85.5%)
	No	18 (34.0%)	1 (12.5%)
Charlson Comorbidity index	**2-6**	47 (88.7%)	5 (62.5%)
	7-11	6 (11.3%)	3 (37.5%)
Previous abdominal surgery	**Yes**	16 (30.2%)	2 (25.0%)
	No	37 (69.8%)	6 (75.0%)
Tumor location	**Distal**	5 (9.4%)	2 (25.0%)
	Middle 1/3	22 (41.5%)	6 (75.0%)
	Proximal	26 (49.1%)	0 (0.0%)
	Unknown	0 (0.0%)	0 (0.0%)
Tumor cStage	**I**	3 (5.7%)	0 (0.0%)
	II	17 (32.1%)	3 (37.5%)
	III	32 (60.4%)	5 (62.5%)
	IIII	1 (1.9%)	0 (0.0%)
	Unknown	0 (0.0%)	0 (0.0%)
Neoadjuvant therapy	**Radiotherapy**	12 (22.6%)	3 (37.5%)
	Chemoradiation	8 (15.1%)	1 (12.5%)
	None	33 (62.3%)	4 (50.0%)
Minimal invasive	**Yes**	48 (90.6%)	6 (75.0%)
	No	5 (9.4%)	2 (25.0%)
Type of initial surgery	**LAR**	35 (66.0%)	0 (0.0%)
	LAR with diverting stoma	18 (34.0%)	3 (37.5%)
	Hartmann	0 (0.0%)	5 (62.5%)
Major complications*	**Yes**	10 (18.9%)	1 (12.5%)
	No	43 (81.1%)	7 (87.5%)
Follow-up in years	**Mean (range)**	3.8 (1-6)	4.0 (1-6)

* Major complications defined as Clavien-Dindo ≥ IIIa.

Table S.2 - Patient Reported Outcomes (PROMs) using EORTC-QLQ-C30, comparison between patients with stoma and without a stoma. *A value of 0 is considered as a low quality of life, a value of 100 is considered as a maximum quality of life. #A value of 0 is considered as a low level of complication, a value of 100 is considered as a maximum level of complication of functioning

	Stoma		
	No N=126	**Yes N=23**	**p-value**
Global health status *	82.87	78.62	0.15
Physical functioning *	88.63	80.87	**0.03**
Role functioning *	89.52	81.16	0.09
Emotional functioning *	90.79	86.60	0.41
Cognitive functioning *	88.27	89.85	0.97
Social functioning *	92.40	84.06	0.06
Fatigue #	17.95	24.15	0.11
Nausea and vomiting #	0.79	5.07	**0.02**
Pain #	9.60	13.77	0.27
Dyspnoea #	11.20	13.04	0.82
Insomnia #	16.67	8.69	0.25
Appetite loss #	2.11	10.14	0.15
Constipation #	9.60	5.79	0.32
Diarrhoea #	8.33	15.94	0.24
Financial difficulties #	1.60	10.14	**0.02**

Table S.3 - Patient Reported Outcomes (PROMs) using EORTC-QLQ-CR29. A value of 0 is considered as a low level of a complication, a value of 100 is considered as a maximum level.

	Stoma		
	No N=126	**Yes N=23**	**p-value**
Urinary frequency	31.32	31.88	0.77
Urinary incontinency	11.11	17.39	0.21
Dysuria	2.17	1.45	0.79
Abdominal pain	6.99	10.15	0.87
Buttock pain	8.06	17.39	0.07
Bloating	12.63	23.19	0.06
Blood and mucus in stool	3.63	4.35	0.59
Dry mouth	13.44	23.19	**0.03**
Hair loss	0.81	8.70	**0.02**
Taste	3.79	11.59	0.06
Flatulence (without stoma)	33.88		-
Faecal incontinence (without stoma)	11.29		-
Sore skin (without stoma)	9.92		-
Stool frequency (without stoma)	23.83		-
Embarrassment (without stoma)	19.01		-
Flatulence (with stoma)		23.19	-
Faecal incontinence/leakage (with stoma)		23.19	-
Sore skin (with stoma)		27.54	-
Stool frequency/bags change (with stoma)		18.84	-
Embarrassment (with stoma)		17.39	-
Stoma care problems	-	4.35	-
Impotence	39.99	69.70	**0.01**
Dyspareunia	6.45	5.56	1.00
Anxiety	17.60	23.19	0.37
Weight	16.53	20.29	0.90
Body image	9.99	18.36	**0.03**
Sexual interest Men	38.89	30.55	0.33
Sexual interest Women	29.72	16.67	0.16

Table S.4 - Patient Reported Outcomes (PROMs) using EQ-5D-5L, Patient Reported Outcomes (PROMs) using EORTC-QLQ-C30, comparison between patients with stoma and without a stoma. A value of 1 is considered as no problems, a value of 2 as slight problems, a value of 3 as moderate problems, a value of 4 as severe problems and a value of 5 as unable to.

		Stoma			
		No N=123	Yes N=22	Total N=145	p-value
Mobility	**1**	90 (73.2%)	13 (59.1%)	103 (71.0%)	0.35
	2	22 (17.9%)	7 (31.8%)	29 (20.0%)	
	3	9 (7.3%)	1 (4.5%)	10 (6.9%)	
	4	2 (1.6%)	1 (4.5%)	3 (2.1%)	
	5	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Self-care	**1**	118 (95.9%)	18 (81.8%)	136 (93.8%)	**0.03**
	2	3 (2.4%)	3 (13.6%)	6 (4.1%)	
	3	2 (1.7%)	1 (4.5%)	3 (2.1%)	
	4	0 (0.0%)	0 (0.0%)	0 (0.0%)	
	5	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Usual activity	**1**	98 (79.7%)	10 (45.5%)	108 (74.5%)	**<0.01**
	2	15 (12.2%)	6 (27.3%)	21 (14.5%)	
	3	8 (6.5%)	5 (22.7%)	13 (9.0%)	
	4	2 (1.6%)	1 (4.5%)	3 (2.1%)	
	5	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Pain or discomfort	**1**	72 (58.5%)	13 (59.1%)	85 (58.6%)	0.36
	2	37 (30.1%)	9 (40.9%)	46 (31.7%)	
	3	11 (9.0%)	0 (0.0%)	11 (7.6%)	
	4	3 (2.4%)	0 (0.0%)	3 (2.1%)	
	5	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Anxiety or Depression	**1**	104 (84.6%)	15 (68.2%)	119 (82.1%)	0.13
	2	14 (11.3%)	6 (27.3%)	20 (13.8%)	
	3	5 (4.1%)	1 (4.5%)	6 (4.1%)	
	4	0 (0.0%)	0 (0.0%)	0 (0.0%)	
	5	0 (0.0%)	0 (0.0%)	0 (0.0%)	
VAS	**mean**	82.85	76.41		0.28

Table S.5 – Individual factors influencing the global health status, measured by the EORTC-QLQ-C30.

Global Health Status	Univariate	p-value	Multivariate*	p-value
Age	1.00 (1.00-1.00)	0.23	-	
Male sex	0.98 (0.95-1.02)	0.36	0.98 (0.95-1.02)	0.33
ASA-score	0.98 (0.95-1.02)	0.33	1.00 (0.96-1.03)	0.81
Charlson Comorbidity index	0.98 (0.95-0.99)	**<0.01**	-	
Stoma at follow-up	0.95 (0.90-1.00)	**0.04**	0.93 (0.88-0.99)	**0.01**
Comorbidity	1.01 (0.97-1.04)	0.66	-	
Major complications#	0.99 (0.92-1.02)	0.69	0.98 (0.91-1.01)	0.10
Tumor recurrence	0.86 (0.80-0.93)	**<0.01**	-	
Neoadjuvant chemoradiotherapy	0.96 (0.91-1.01)	0.12	0.94 (0.89-0.99)	**0.02**
Adjuvante chemotherapy	1.01 (0.98-1.04)	0.46	1.02 (0.96-1.08)	0.56
cT-score	0.94 (0.92-0.96)	**<0.01**	0.97 (0.95-0.99)	**<0.01**
cN-score	0.98 (0.96-1.01)	0.16	0.98 (0.96-1.00)	0.11

*Corrected for: Charlson comorbidity index, tumor recurrence. #Major complications defined as Clavien-Dindo ≥ IIIa.

Table S.6 – Individual factors influencing the physical functioning, measured by the EORTC-QLQ-C30.

Physical Functioning	Univariate	p-value	Multivariate*	p-value
Age	0.99 (0.99-1.00)	**<0.01**	-	
Male sex	0.96 (0.92-0.99)	**0.02**	0.95 (0.92-0.99)	**0.01**
ASA-score	0.91 (0.88-0.94)	**<0.01**	0.92 (0.89-0.96)	**<0.01**
Charlson Comorbidity index	0.97 (0.96-0.99)	**<0.01**	-	
Stoma at follow-up	0.91 (0.86-0.96)	**<0.01**	0.91 (0.86-0.96)	**<0.01**
Comorbidity	0.94 (0.91-1.98)	**<0.01**	-	
Major complications#	1.00 (0.96-1.04)	0.68	0.99 (0.95-1.04)	0.81
Tumor recurrence	0.98 (0.93-1.02)	0.6	-	
Neoadjuvant chemoradiotherapy	0.98 (0.93-1.03)	0.45	0.97 (0.92-1.02)	0.17
Adjuvant chemotherapy	1.01 (0.98-1.04)	0.6	1.01 (0.95-1.07)	0.77
cT-score	0.99 (0.97-1.01)	**0.19**	0.98 (0.96-1.01)	0.13
cN-score	0.97 (0.95-0.99)	**0.02**	0.97 (0.95-0.99)	**0.01**

*Corrected for: Charlson comorbidity index, tumor recurrence. #Major complications defined as Clavien-Dindo ≥ IIIa

Table S.7 - Patient Reported Outcomes (PROMs) using EORTC-QLQ-CR30, comparison between patients with stoma and with major Low Anterior Resection Syndrome (LARS). *A value of 0 is considered as a low quality of life, a value of 100 is considered as a maximum quality of life. #A value of 0 is considered as a low level of complication, a value of 100 is considered as a maximum level of complication.

	Control N=96	Major Lars N=30	Stoma N=23	p-value
Global health status *	84.81	80.83	78.62	0.39
Physical functioning *	89.75$^{\beta}$	84.26	80.87	0.13
Role Functioning *	90.72	88.89	81.16	0.41
Emotional functioning *	92.20	88.89	86.60	0.49
Cognitive functioning *	90.72	83.33	89.85	0.09
Social functioning *	94.51$^{\beta}$	88.33	84.06	**0.02**
Fatigue #	14.34$^{\beta}$	20.00	24.15	0.32
Nausea and vomiting #	0.21	0.56	5.07	**<0.01**
Pain #	8.86	12.22	13.77	0.96
Dyspnoea #	8.75	18.39	13.04	0.14
Insomnia #	12.91	21.11	8.69	0.42
Appetite loss #	2.08	2.22	10.14	0.14
Constipation #	5.00$^{\alpha}$	17.24$^{\beta}$	5.79	**0.01**
Diarrhoea #	5.49$^{\alpha}$	12.64	15.94	**0.01**
Financial difficulties #	2.53	1.11	10.14	**<0.01**

α: statistically different from Major Lars
β: statistically different from Stoma

Table S.8 - Patient Reported Outcomes (PROMs) using EORTC-QLQ-C29, comparison between patients with stoma and with major Low Anterior Resection Syndrome (LARS). A value of 0 is considered as a low level of a complication, a value of 100 is considered as a maximum level.

	Control N=96	Major LARS N=30	Stoma N=23	p-value
Urinary frequency	29.37	36.11	31.88	0.24
Urinary incontinency	10.42	12.64	17.39	0.41
Dysuria	20.81	3.45	1.45	0.43
Abdominal pain	5.42	8.89	10.15	0.41
Buttock pain	7.08	11.11	17.39	0.10
Bloating	9.17$^{\beta}$	15.55	23.19	0.12
Blood and mucus in stool	0.83$^{\alpha}$	5.00	4.35	**<0.01**
Dry mouth	12.50	17.78	23.19	0.58
Hair loss	0.83	1.11	8.70	0.92
Taste	3.33	3.45	11.59	0.54
Flatulence (without stoma)	22.81$^{\alpha}$	54.02	-	**<0.01**
Faecal incontinence (without stoma)	5.26$^{\alpha,}$	22.99	-	**<0.01**
Sore skin (without stoma)	9.21	16.09	-	0.19
Stool frequency (without stoma)	18.86$^{\alpha}$	32.18	-	**0.01**
Embarrassment (without stoma)	11.40$^{\alpha}$	34.48	-	**<0.01**
Flatulence (with stoma)	-	-	23.19	**-**
Faecal incontinence/leakage (with stoma)	-	-	23.19	**-**
Sore skin (with stoma)	-	-	27.54	**-**
Stool Frequency/bags change (with stoma)	-	-	18.84	**-**
Embarrassment (with stoma)	-	-	17.39	**-**
Stoma care problems	-	-	4.35	-
Impotence	38.89$^{\alpha\beta}$	36.23$^{\beta}$	69.70	**0.69**
Dyspareunia	3.17	20.00	5.56	0.08
Anxiety	16.25	21.11	23.19	0.43
Weight	15.83	16.67	20.29	0.79
Body Image	7.99$^{\beta}$	15.55	18.36	**<0.01**
Sexual interest Men	39.10	39.13	30.55	0.94
Sexual interest Women	27.54	28.57	16.67	0.45

α: statistically different from Major Lars
β: statistically different from Stoma

Chapter 9

The Impact on Health-Related Quality of a Stoma or Poor Functional Outcomes After Rectal Cancer Surgery in Dutch Patients: a Prospective Cohort Study

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List of Abbreviations

APR; abdominoperineal resection, ASA; American Society of Anesthesiologists, EORTC; European Organization for Research and Treatment of Cancer, HRQoL; health-related quality of life, LARS; Low-Anterior Resection Syndrome, NKR; Netherlands Cancer Registry, POLARS; Pre-Operative LARS score, PLCRC; Prospective Dutch Colorectal Cancer, PROFILES; Patient Reported Outcomes Following Initial treatment and Long-term Evaluation of Survivorship

Abstract

Background: As the survival of patients with rectal cancer has improved in recent decades, more and more patients have to live with the consequences of rectal cancer surgery. An influential factor in long-term Health-related Quality of Life (HRQoL) is the presence of a stoma. This study aimed to better understand the long-term consequences of a stoma and poor functional outcomes.

Methods: Patients who underwent curative surgery for a primary tumor located in the rectosigmoid and rectum between 2013 and 2020 were identified from the nationwide Prospective Dutch Colorectal Cancer (PLCRC) cohort study. Patients received the following questionnaires: EORTC-QLQ-CR29, EORTC-QLQ-C30, and the LARS-score at 12 months, 24 months and 36 months after surgery.

Results: A total of 1,170 patients were included of whom 751 (64.2%) had no stoma, 122 (10.4%) had a stoma at primary surgery, 45 (3.8%) had a stoma at secondary surgery and 252 (21.5%) patients that underwent abdominoperineal resection (APR). Of all patients without a stoma, 41.4% reported major low-anterior resection syndrome (LARS). Patients without a stoma reported significantly better HRQoL. Moreover, patients without a stoma significantly reported an overall better HRQoL.

Conclusion: The presence of a stoma and poor functional outcomes were both associated with reduced HRQoL. Patients with poor functional outcomes, defined as major LARS, reported a similar level of HRQoL compared to patients with a stoma. In addition, the HRQoL after rectal cancer surgery does not change significantly after the first year after surgery.

Introduction

In recent decades, the 5-year survival of rectal cancer patients has increased to approximately 80%, leading to more patients having to deal with the consequences of rectal cancer treatment [1]. The cornerstone of rectal cancer treatment is still surgical resection [2]. These consequences of rectal cancer surgery are, for instance, stoma presence, bowel dysfunction, psychological and physical stress [3-5]. Of all the surgically treated rectal cancer patients in the Netherlands, 63.6% receive a (temporary) stoma [6]. The decision on whether or not to make a stoma during rectal surgery can be difficult [7]. This decision between an anastomosis or a stoma is mainly based on two considerations. Firstly, the risk of postoperative complications (e.g., anastomotic leakage) as can lead to morbidity and mortality [8, 9]. A (temporary) stoma has been shown to reduce the rate of symptomatic anastomotic leakage and re-operations Secondly, dysfunctional bowel functions, often defined as major Low-anterior Syndrome (LARS), may have a detrimental effect on the quality of life and should therefore be taken into account [10-12]. Major LARS is reported in 42 % of the patients one year after rectal surgery [13]. Several patient characteristics (e.g., age, gender) and treatment characteristics (e.g., low tumor, neoadjuvant radiotherapy) are prognostic factors for major LARS [14].

The presence of a stoma and poor bowel functions in patients can both affect the quality of life after rectal cancer surgery, therefore the trade-off between the formation of a (temporary) stoma or anastomosis should be explored further [15]. This study aims to determine the influence of a stoma and poor functional outcomes on the health-related quality of life (HRQoL) after rectal cancer surgery in a nation-wide population-based study.

Methods

Study population and treatment

Patients who underwent surgical resection for a primary carcinoma in the rectosigmoid and rectum between 2013 and 2020 were retrieved from the ongoing nationwide Prospective Dutch Colorectal Cancer (PLCRC) cohort study [16]. this study collected clinical data and patient-reported outcome measurements (PROMs) from colorectal cancer patients; a total of 59 centers in The Netherlands participated. PROMs were retrieved within the Patient Reported Outcomes Following Initial treatment and Long-term Evaluation of Survivorship (PROFILES) registry [17]. Patients were included at any time during their rectal cancer treatment, therefor a cross-sectional study design was used. Three separate cohorts of 1-, 2- and 3-years after surgery were constructed and analyzed separately. Clinical data were obtained from the Netherlands Cancer Registry (NKR). All patients signed an informed consent form before their medical records were reviewed and sending questionnaires were sent. Inclusion criteria were: patients with a primary tumor of stage I-III located in the rectosigmoid and rectum treated with surgical resection. Patients who underwent emergency surgery or palliative intended surgery were excluded.

Health-related quality of life assessment

The following PROMs were completed by the patients: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core (EORTC) questionnaires: cancer-specific QLQ-C30 and colorectal- cancer-specific QLQ-CR29 and Low-Anterior Resection Syndrome (LARS)-questionnaire at 12 months, 24 months and 36 months after surgery [18-20]. A four-point Likert scale was used in all questionnaires after which all responses were linearly converted to 0–100 scales.

Statistical analyses

Patients were divided into four groups, patients without a stoma 1 year after surgery, patients with a stoma 1 year after surgery constructed during primary surgery, patients with a stoma 1 year after surgery constructed during secondary surgery and patients who underwent an APR resection. The chi-square test was used for categorical variables, the Mann-Whitney U test was used for numeric variables, a post-hoc Bonferroni test was used to correct for multiple testing. For sub-analysis, patients with a stoma were divided into a group of patients with- and without major-LARS. Major LARS was defined as a LARS-score ≥30.

Results

Patient characteristics

A total of 1,545 patients were identified from the PLCRC registry of whom 355 (23.0%) were excluded because they had not filled-out any questionnaire (Fig. 1). In addition, 20 (1.3%) patients were excluded because essential variables were missing. Patients were divided into four groups; patients without a stoma (64.2%), patients with Low Anterior Resection (LAR) and a stoma constructed at primary surgery (10.4%), patients with a stoma constructed at secondary surgery or a temporary stoma present at 1-year (3.8%) and patients that underwent an APR (21.5%) (Table 1).

Patient with a stoma constructed during primary surgery were older than the other groups, including patients that underwent APR. Furthermore, patients with a stoma and APR had a lower located tumor, compared to patients without a stoma, and received significantly more neo-adjuvant therapy. In addition, patients with a stoma constructed during secondary surgery were significantly more affected by anastomotic leakage.

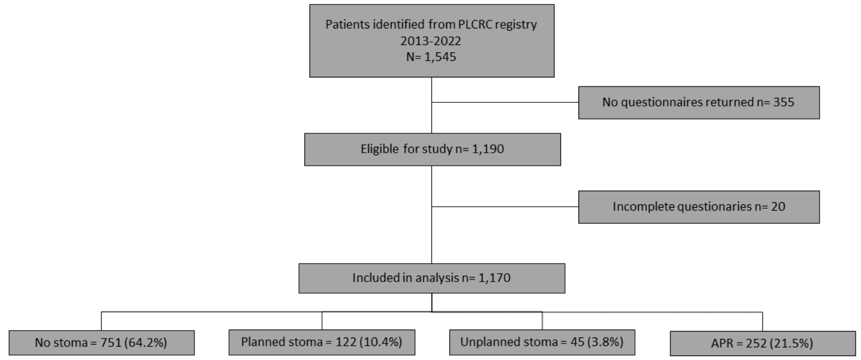

Figure 1 – Flowchart of patient selection

Health-Related Quality of Life (12 months)

Patients without a stoma reported an overall better HRQoL compared to patients with a stoma measured by the EORTC qlq-C30 questionnaire (Fig. 2, Table S.1). Furthermore, stoma patients who underwent APR reported better HRQoL outcomes than stoma patients after LAR. No significant differences were seen in HRQoL when comparing patients with a stoma constructed during primary or during secondary surgery. Witnessed by the EORTC qlq-CR29 questionnaire, patients with a stoma constructed during secondary surgery reported more problems in stoma care compared to patients with a stoma constructed during primary surgery (Table S.2). Another significant finding was that the body image is worse in patients with a stoma compared to patients without a stoma.

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Table 1 – Patient characteristics

		No stoma	Stoma at primary surgery	Stoma at secondary surgery	APR	p-value
		n=751 (64.2%)	n=122 (10.4%)	n=45 (3.8%)	n=252 (21.5%)	
Age (years)	**Mean**	63.2	69.3	62.7	64.7	**<0.01**
Gender %	**Male**	484 (64.4%)	85 (69.7%)	32 (71.1%)	167 (66.3%)	0.39
	Female	267 (35.6%)	37 (30.3%)	13 (28.9%)	85 (33.7%)	
BMI	**Mean**	26.1	26.6	28.5	26.3	0.07
ASA	**I-II**	638 (85.0%)	96 (78.7%)	34 (75.6%)	213 (84.5%)	0.20
	III-IV	101 (13.4%)	23 (18.9%)	9 (20.0%)	36 (14.3%)	
	Unknown	12 (1.6%)	3 (2.5%)	2 (4.4%)	3 (1.2%)	
Tumor location	**0-5cm**	165 (22,0%) β γ δ	69 (56,6%)	17 (37,8%)	223 (88,5%)	**<0.01**
	5.1-10cm	277 (36,9%)	36 (29,5%)	20 (44,4%)	18 (7,1%)	
	10.1-15cm	145 (19,3%)	12 (9,8%)	5 (11,1%)	3 (1,2%)	
	>15cm	27 (3,6%)	0 (0,0%)	1 (2,2%)	0 0,0%	
	Unknown	137 (18,2%)	5 (4,1%)	2 (4,4%)	8 (3,2%)	
pT-score	**0**	52 (6,9%)	11 (9,0%)	4 (8,9%)	36 (14,3%)	0.64
	I	124 (16,5%)	10 (8,2%)	6 (13,3%)	27 (10,7%)	
	II	239 (31,8%)	42 (34,4%)	9 (20,0%)	88 (34,9%)	
	III	304 (40,5%)	57 (46,7%)	24 (53,3%)	90 (35,7%)	
	IV	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	
	Unknown	32 (4,3%)	2 (1,6%)	2 (4,4%)	11 (4,4%)	
Neoadjuvant therapy	**Radiotherapy**	170 (22.6%) β γ δ	30 (24.6%)	15 (33.3%)	47 (18.7%)	**<0.01**
	Chemoradiation	146 (19,4%)	48 (39.3%)	15 (35.6%)	146 (57.9%)	
	None	435 (57.9%)	44 (36.1%)	14 (31.1%)	59 (23.4%)	
Approach	**Open**	15 (2.0%)	6 (4.9%)	0 (0.0%)	22 (8.7%)	0.96
	Laparoscopic	564 (75.1%)	74 (60.7%)	31 (68.9%)	146 (57.9%)	
	Robot-assisted	166 (22.1%)	42 (34.4%)	14 (31.1%)	83 (32.9%)	
	Unknown	6 (0.8%)	0 (0.0%)	0 (0.0%)	1 (0.4%)	
Anastomotic leakage	**Yes**	44 (5.9%) β γ δ	0 (0.0%)	17 (37.8%)	0 (0.0%)	**<0.01**

ASA, American Society of Anesthesiologists,
α: statistically different from group no stoma
β: statistically different from group stoma at primary surgery
γ: statistically different from group stoma at secondary surgery
δ: statistically different from group APR

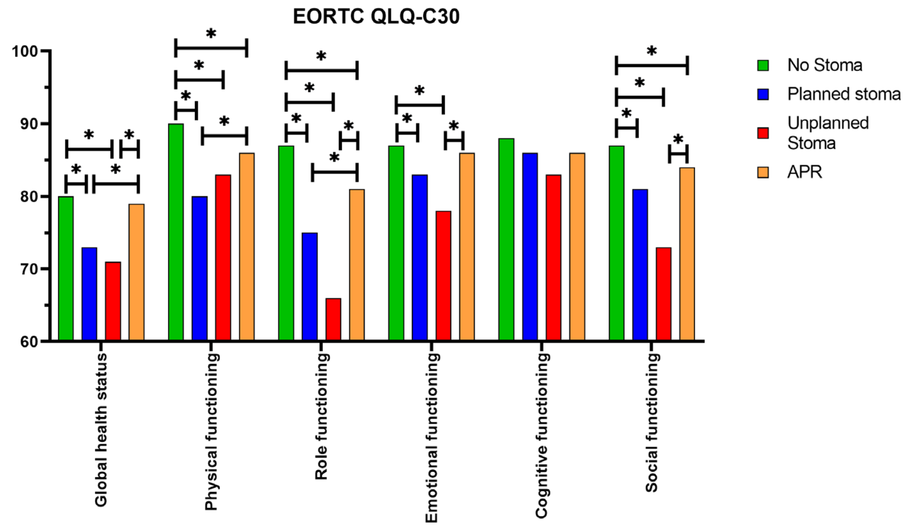

Figure 2 – Health-related quality of life over time 12 months after surgery, measured using EORTC QLQ-C30 and EORTC QLQ-CR29. Complete overview of data is shown in Table S.1 and Table S.2.

Functional outcome and health-related quality of life

Patients without a stoma were divided into two groups based on their LARS-score, patients with a LARS-score ≥30 (33.1%) were defined as major LARS (Table S.3). Major LARS patients had a tumor located lower in the rectum and received more neoadjuvant therapy compared with patients without or with minor LARS. Overall, patients without a stoma reported a better HRQoL (Fig. 3, Table S.4). Patients with major LARS did not report a significantly better HRQoL, expect for physical functioning, compared to patients with a stoma. Body image was significantly worse in patients with a major LARS than in patients without major LARS, but significantly better compared to stoma patient (Table S.5).

Health-related quality of life (HRQoL) over time (12-36 months)

The group of patients (n=311) who completed all questionnaires, at time-points: 12 months, 24 months and 36 months after surgery, were analyzed (Table S.6). As shown in Figure 4, the HRQoL does not change significantly between 12months and 36 months after surgery.

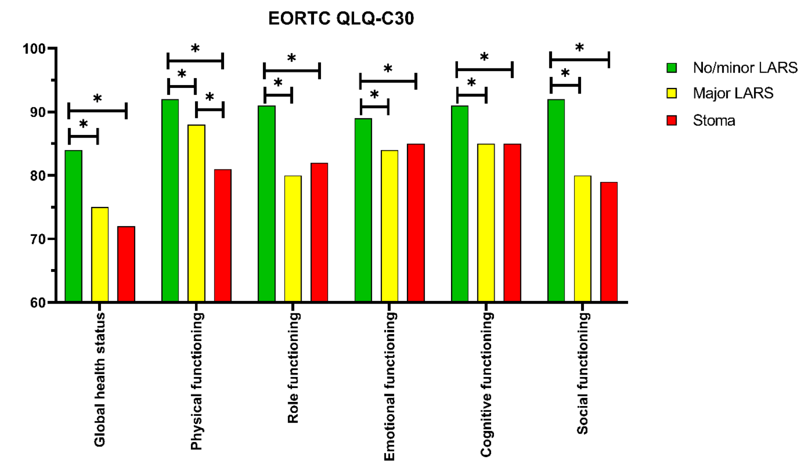

Figure 3 – Health-Related Quality of Life (HRQoL) 12 months after surgery, using the EORTC QLQ-C30 questionnaire, patients were divided into three groups. Patient characteristics are shown in Table S.3 and the complete overview of HRQoL data is shown in Tables S.4 and S.5.

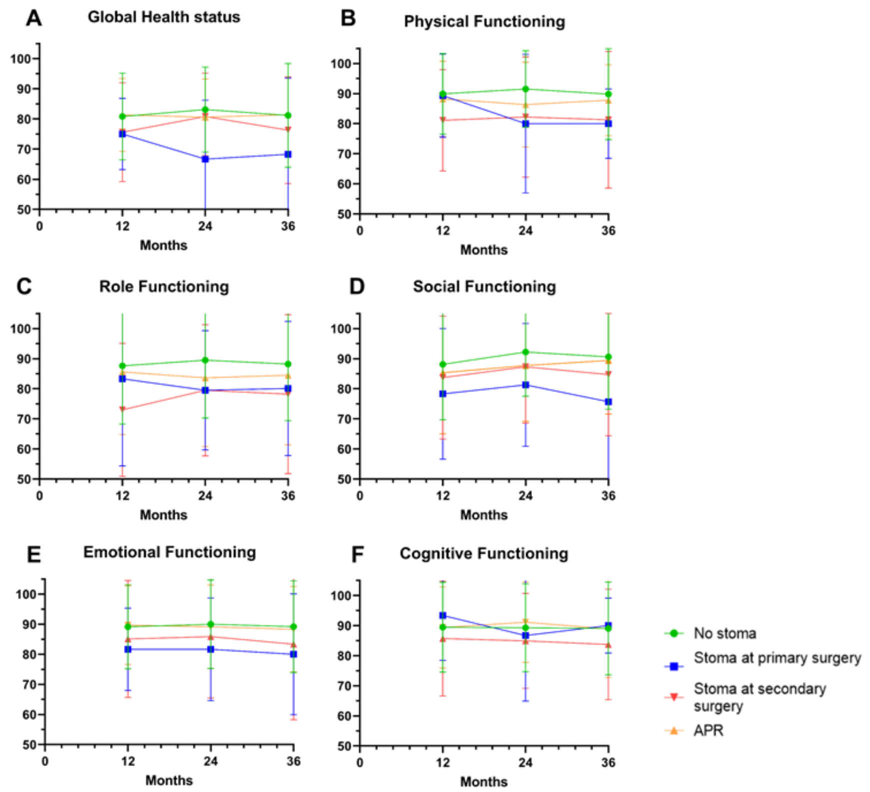

Figure 4 – Health-related quality of life (HRQoL), using the EORTC-QLQ-C30 questionnaire, over time in the first 36 months after surgery in patients who filled out all three questionnaires (t=12, t=24, t=36), patient characteristics are shown in (Table S.6)

Discussion

This study presents a comparison in the HRQoL between patients with and without a stoma and poor functional outcome after rectal cancer surgery. The presence of a stoma and poor functional outcomes were both associated with a reduced HRQoL. A primary colostoma, can be constructed after APR and after LAR. Reported physical functioning was better in patient with a colostoma after APR. HRQoL after rectal cancer surgery did not change significantly after the first year postoperatively over the next two years.

Previous studies have also shown a reduced HRQoL in patients with a stoma or major LARS [15, 21]. However, some studies reported ambiguous results for the influence of a stoma on HRQoL. A Cochrane review by Pachler et al. included 26 studies, of which only 10 reported a significantly reduced HRQoL in patients with a permanent colostoma [22]. Moreover, as shown, patients without a stoma can be divided into two groups based on the functional outcomes measured by LARS score. Outcomes of this study were in line with other studies, as these studies agree that poor bowel function is associated with reduced HRQoL [19, 23, 24]. The differences between patients with a stoma during primary or secondary surgery stoma have not been widely studied. It has been shown that postoperative complications and anastomotic leakage can affect postoperative HRQoL [25, 26]. Additionally, there is a direct independent association between postoperative complications, a permanent stoma and failure to close a (temporary) stoma [27, 28]. Additionally, postoperative distant metastasis are associated with failure to close a (temporary) stoma [27, 28]. The differences in HRQoL between patients with a LAR and stoma and patients that underwent an APR, might be the result of an APR reducing the risk of pelvic abscesses, persisting mucus production and diversion proctitis and therefore impacting HRQoL, however an APR is associated with increased morbidity and a perineal wound [29, 30]. Furthermore, Bakker et al. showed that patients that underwent a LAR with primary stoma, were significantly older and had more comorbidities, therefore differences in HRQoL might be subjected to worse patient characteristics [31].

Knowledge of postoperative HRQoL after the rectal cancer surgery provides essential information regarding treatment options to aid in shared decision-making. Since explicit patient consideration regarding treatment options is positively associated with long-term quality of life and improved acceptance [32]. An important treatment option is whether to construct a stoma, which is usually not a foregone conclusion [7, 33]. When deciding between an anastomosis and a (temporary) stoma in rectal cancer surgery, two factors are being considered. Firstly, the risk of postoperative complications, especially anastomotic leakage and secondly the expected functional outcomes [8, 9, 14, 34]. The risk of poor functional outcomes can be estimated using the POLARS score, based on prognostic factors, such as: age, gender, tumor location, stoma and preoperative radiotherapy [14, 35]. In addition, anastomotic leakage can be estimated as well using patient- and treatment characteristics (e.g., comorbidity, gender, tumor location) [9, 36, 37]. Better information to improve postoperative patient education on stoma care leads to an increased HRQoL and lower healthcare costs [38, 39].

Limitations

Although this study reports valuable results, it has some limitations. First, due to the lack of patients with more than 1 year of follow-up in the database, a cross-sectional approach was used. This hampers an accurate analysis of the development of HRQoL overtime. Second, the data on considerations and subsequent decision on when to construct a stoma and why a stoma was not reversed were not available. A prospective study might be needed to further investigated the decision towards stoma construction and their consequences. Moreover, comparison of patients with and without a stoma is subjected to confounding by indication, as the choice to construct a (planned) stoma is based on patient- and treatment characteristics. This effect is apparent by the differences in age, tumor location and neoadjuvant therapy between these groups. These factors may also influence HRQoL and thereby inherently bias comparisons [40]. There is an ongoing debate about the indication to perform an APR as alternative to a low Hartmann resection, therefore indication for APR might differ from other countries [29, 30]. Unfortunately, we had no information on whether APRs were intersphincteric or extralevator APRs.

Conclusion

This study shows the impact of a stoma and poor functional outcomes on HRQoL after rectal cancer surgery. The presence of a stoma and poor functional bowel outcomes were both associated with a decreased HRQoL. Patients with poor functional bowel outcomes, defined as major LARS, report a similar level of HRQoL compared to patients with a stoma. Additionally, HRQoL after rectal cancer surgery does not change significantly after the first year post surgery. Information on the effect of treatment decisions and surgical outcomes on the long-term HRQoL of patient undergoing rectal cancer surgery is essential for patient education and shared-decision making.

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Supplementary Information

Table S.1 - Health-related quality of life (HRQoL) 12 months after surgery measured using EORTC-QLQ-C30.

EORTC-QLQ-C30	No stoma	Stoma at primary surgery	Stoma at secondary surgery	APR	p-value
	n= 751 (64.2%)	n= 122 (10.4%)	n= 45 (3.8%)	n= 252 (21.5%)	
Global Health status	80.1 β,γ	73.4 δ	71.9 δ	79.0	**<0.01**
Physical functioning	90.9 β,γ,δ	80.1 δ	83.0	86.0	**<0.01**
Role Functioning	87.6 β,γ,δ	75.1 δ	66.3 δ	81.5	**<0.01**
Emotional functioning	87.4 β,γ	83.4	78.2 δ	86.9	0.08
Cognitive functioning	88.8	86.7	83.7	86.3	0.09
Social functioning	87.6 β,γ,δ	81.7	73.9 δ	84.2	**<0.01**
Fatigue	17.4 β,γ,δ	25.1	27.0	20.5	**<0.01**
Nausea and vomiting	2.4 δ	2.5	4.5	1.3	0.24
Pain	9.0 δ	12.7	14.8	12.3	**<0.01**
Dyspnea	8.1	10.1	12.1	9.7	0.37
Insomnia	17.7	18.3	23.5	19.2	0.68
Appetite loss	4.1 β	8.7 δ	8.3	3.3	**<0.01**
Constipation	9.4 β,γ,δ	4.4	2.3	3.7	**<0.01**
Diarrhea	11.6 γ,δ	9.6 δ	4.7	4.6	**<0.01**
Financial difficulties	4.2 β,δ	8.2	8.3	6.8	**0.02**

α: statistically different from group No stoma
β: statistically different from group stoma at primary surgery
γ: statistically different from group stoma at secondary surgery
δ: statistically different from group APR

Table S.2 – Health-related quality of life (HRQoL) 12 months after surgery measured using EORTC-QLQ-CR29.

EORTC-QLQ-CR29	No stoma	Stoma at primary surgery	Stoma at secondary surgery	APR	p-value
	n= 751 (64.2%)	n= 122 (10.4%)	n= 45 (3.8%)	n= 252 (21.5%)	
Urinary frequency	26.9 β	32.0 γ	21.9 δ	31.7	**<0.01**
Urinary incontinency	7.8 β	12.0	9.6	13.7	**<0.01**
Dysuria	1.7	2.7	5.9	2.8	0.09
Abdominal pain	9.8	10.4	5.9 δ	10.8	0.42
Buttock pain	13.2	15.3	13.3	18.4	**<0.01**
Bloating	15.4 γ,δ	15.6 γ	5.9 δ	12.2	**<0.01**
Blood and mucus in stool	3.7	4.0 δ	4.4	1.5	**<0.01**
Dry mouth	14.1	14.8	16.3	13.4	0.80
Hair loss	2.5	4.4	9.6	2.2	**0.01**
Taste	4.1 β	8.5	8.9	5.3	**<0.01**
Flatulence (no stoma)	40.0	-	-	-	-
Fecal incontinence (no stoma)	12.9	-	-	-	-
Sore skin (no stoma)	13.8	-	-	-	-
Stool frequency (no stoma)	29.9	-	-	-	-
Embarrassment (no stoma)	24.5	-	-	-	-
Flatulence (stoma)	-	27.3	20.7 δ	28.9	0.08
Fecal incontinence/leakage (stoma)	-	10.9	15.6	9.4	0.40
Sore skin (stoma)	-	13.9 γ	25.9 δ	14.9	**0.02**
Stool Frequency/ bags change (stoma)	-	12.1	14.8	11.8	0.94
Embarrassment stoma)	-	24.0	24.4	20.7	0.58
Stoma care problems	-	4.9	8.9 δ	3.5	**<0.01**
Impotence	32.8 β, δ	46.2 γ, δ	28.1 δ	61.4	**<0.01**
Dyspareunia	17.9 δ	45.8	45.5	34.5	**<0.01**
Anxiety	24.7 β,γ,δ	30.3	34.8 δ	25.5	**0.02**
Weight	14.1	14.6	21.5	14.7	0.60
Body image	11.9 β,γ,δ	23.4	27.3	23.2	**<0.01**
Sexual interest Men	47.0 β, δ	31.2	39.6	36.0	**<0.01**
Sexual interest Women	30.4	19.5	20.3	26.2	**<0.01**

α: statistically different from group No stoma
β: statistically different from group stoma at primary surgery
γ: statistically different from group stoma at secondary surgery
δ: statistically different from group APR

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Table S.3 - Patient characteristics.

		No/minor LARS	Major LARS	Stoma	p-value
		n=447 (48.7%)	n=304 (33.1%)	n=167 (18.2%)	
Age (years)	**Mean**	63.61	62.53	67.5 α β δ	**<0.01**
Gender %	**Male**	300 (68.2%)	184 (59.2%)	117 (70.1%)	**0.04**
	Female	140 (31.8%)	127 (40.8%)	50 (29.9%)	
BMI	**Mean**	26.06	26.26	27.1	0.07
ASA*	**I-II**	373 (85.6%)	265 (86.0%)	130 (77.8%)	0.99
	III-IV	60 (13.8%)	41 (13.3%)	32 (19.2%)	
	Unknown	3 (0.8%)	2 (0.7%)	5 (3.0%)	
Tumor location	**0-5cm**	63 (14.3%) β γ δ	102 (32.8%)	86 (51.5%)	**<0.01**
	5.1-10cm	162 (36.8%)	115 (37.0%)	56 (33.5%)	
	10.1-15cm	86 (19.5%)	59 (19.0%)	17 (10.2%)	
	>15cm	20 (4.5%)	7 (2.3%)	1 (0.6%)	
	Unknown	109 (24.8%)	28 (9.0%)	6 (3.6%)	
pT-score	**0**	16 (3.6%) β	36 (11.6%)	15 (9.0%)	**0.02**
	I	69 (15.7%)	55 (17.7%)	16 (9.6%)	
	II	138 (31.4%)	101 (32.5%)	54 (30.5%)	
	III	196 (44.5%)	108 (34.7%)	81 (48.5%)	
	IV	0 (0.0%)	0 (0.0%)	0 (0.0%)	
	Unknown	21 (4.8%)	11 (3.5%)	4 (2.4%)	
Neoadjuvant therapy	**Radiotherapy**	83 (18.9%) β γ δ	87 (28.0%)	71 (42.5%)	**<0.01**
	Chemoradiation	58 (13.1%)	88 (28.3%)	48 (28.7%)	
	None	299 (68.0%)	136 (43.7%)	48 (28.7%)	
Approach	**Open**	10 (2.3%)	5 (1.6%)	6 (3.6%)	0.29
	Laparoscopic	337 (76.6%)	227 (73.0%)	105 (62.9%)	
	Robot-assisted	91 (20.7%)	75 (24.1%)	56 (33.5%)	
	Unknown	2 (0.5%)	4 (1.3%)	0 (0.0%)	
Anastomotic leakage	**Yes**	19 (4.3%) γ δ	25 (8.0%) γ δ	55 (32.9%)	**<0.01**

*ASA, American Society of Anesthesiologists
α: statistically different from group No/minor LARS
β: statistically different from group Major LARS
γ: statistically different from group Stoma

Table S.4 – Health-related quality of life (HRQoL) 12 months after surgery in patients with no or minor Low-Anterior Syndrome (LARS) and patients with major LARS, measured using EORTC-QLQ-C30.

EORTC-QLQ-C30	No/minor LARS	Major LARS	Stoma	p-value
	n=447 (59,5%)	n=304 (40.5%)	n= 167 (14.2%)	
Global Health status	84.1 β,γ	75.0	73.0	**<0.01**
Physical functioning	92.6 β γ	88.8 γ	80.9	**<0.01**
Role Functioning	91.3 β,γ	80.5 δ	72.7	**<0.01**
Emotional functioning	89.6 β,γ	84.4	82.0	**<0.01**
Cognitive functioning	91.3 β,γ	85.	85.9	**<0.01**
Social functioning	92.9 β,γ	80.5	79.6	**<0.01**
Fatigue	13.6 β,γ	22.6	25.6	**<0.01**
Nausea and vomiting	1.6	3.3	3.0	**0.17**
Pain	6.7 β,γ	12.0	13.3	**<0.01**
Dyspnea	7.7	8.8	10.6	**0.40**
Insomnia	14.1 β	22.3	19.7	**<0.01**
Appetite loss	2.6 β,γ	6.0	8.6	**<0.01**
Constipation	8.5 γ	11.0 γ	3.8	**<0.01**
Diarrhea	5.7 β,γ	20.2 γ	8.3	**<0.01**
Financial difficulties	2.5 β,γ	6.0	8.2	**<0.01**

α: statistically different from group No/minor LARS
β: statistically different from group Major LARS
γ: statistically different from group stoma at primary surgery
δ: statistically different from group stoma at secondary surgery

Table S.5 – Health-related quality of life (HRQoL) 12 months after surgery, measured using EORTC-QLQ-CR29.

EORTC-QLQ-CR29	No/minor LARS	Major LARS	Stoma	p-value
	n=447 (59,5%)	n=304 (40.5%)	n= 167 (14.2%)	
Urinary frequency	24.0 β,γ	30.5	29.2	**<0.01**
Urinary incontinency	6.5 β,γ	9.3	11.4	0.05
Dysuria	1.1 β	2.5	3.6	0.05
Abdominal pain	7.3 β	13.4	9.2	**<0.01**
Buttock pain	7.2 β,γ	21.7 γ	14.8	**<0.01**
Bloating	11.0 β,γ	22.0 γ	13.0	**<0.01**
Blood and mucus in stool	2.3 β	5.7	4.1	**<0.01**
Dry mouth	11.7 β	17.4	15.2	**0.01**
Hair loss	1.9 δ	3.3	5.8	0.03
Taste	2.4 β,γ	6.1	8.6	**<0.01**
Flatulence (no stoma)	31.3	52.5	-	**<0.01**
Fecal incontinence (no stoma)	4.9	23.9	-	**<0.01**
Sore skin (no stoma)	8.3	21.6	-	**<0.01**
Stool frequency (no stoma)	21.1	42.4	-	**<0.01**
Embarrassment (no stoma)	13.2	40.2	-	**<0.01**
Flatulence (stoma)	-	-	25.5	0.06
Fecal incontinence (stoma)	-	-	12.2	0.30
Sore skin (stoma)	-	-	17.2	**0.01**
Stool frequency (stoma)	-	-	12.9	0.43
Embarrassment (stoma)	-	-	24.2	0.93
Stoma care problems	-	-	5.9	0.13
Impotence	29.2 β,γ	38.8	40.9	**<0.01**
Dyspareunia	18.2	17.7	45.7	0.05
Anxiety	21.9 β,γ	28.5	31.5	**<0.01**
Weight	12.2 β	16.3	16.5	0.08
Body image	7.8 β,γ	17.2 γ	24.5	**<0.01**
Sexual interest Men	49.2 γ	44.3 γ	33.5	**<0.01**
Sexual interest Women	37.1 β,γ	23.7	19.7	**<0.01**

α: statistically different from group No/minor LARS
β: statistically different from group Major LARS
γ: statistically different from group Stoma

Table S.6 – Patient characteristics of those who completed all questionnaires at t=12, t=24 and t=36

		No stoma	Stoma at primary surgery	Stoma at secondary surgery	APR	p-value
		n=205 (65.9%)	n=43 (13.8%)	n=5 (1.6%)	n=58 (18.6%)	
Age (years)	**Mean**	64.69	68.63	59.00	64.88	**0.02**
Gender %	**Male**	142 (69.3%)	29 (67.4%)	3 (60.0%)	35 (60.3%)	0.63
	Female	63 (30.7%)	14 (32.6%)	2 (40.0%)	23 (39.7%)	
BMI	**Mean**	26.01	27.21	23.89	25.86	0.47
ASA	**I-II**	179 (87.3%)	33 (76.7%)	3 (60.0%)	53 (91.4%)	0.16
	III-IV	23 (11.2%)	7 (16.3%)	2 (40.0%)	3 (5.2%)	
	Unknown	3 (1.5%)	3 (7.0%)	0 (0.0%)	2 (3.4%)	
Tumor location	**0-5cm**	36 (17.6%) β ,	19 (44.2%)	0 (0.0%)	51 (87.9%)	**<0.01**
	5.1-10cm	77 (37.6%)	15 (34.9%)	3 (60.0%)	4 (6.9%)	
	10.1-15cm	51 (24.9%)	5 (11.6%)	1 (20.0%)	2 (3.4%)	
	>15cm	4 (2.0%)	1 (2.3%)	0 (0.0%)	0 (0.0%)	
	Unknown	37 (18.0%)	3 (7.0%)	1 (20.0%)	1 (1.7%)	
pT-score	**0**	22 (10.7%)	4 (9.3%)	0 (0.0%)	11 (19.0%)	0.07
	I	32 (15.6%)	5 (11.6%)	0 (0.0%)	5 (8.6%)	
	II	58 (28.3%)	16 (37.2%)	0 (0.0%)	22 (37.9%)	
	III	84 (41.0%)	17 (39.5%)	4 (80.0%)	18 (31.0%)	
	IV	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	
	Unknown	9 (4.4%)	1 (2.3%)	1 (20.0%)	2 (3.4%)	
Neoadjuvant therapy	**Radiotherapy**	42 (20.5%) δ	14 (32.6%)	1 (20.0%)	8 (13.8%)	**<0.01**
	Chemoradiation	52 (25.4%)	14 (32.6%)	1 (20.0%)	37 (63.8%)	
	None	111 (54.1%)	15 (34.9%)	3 (60.0%)	13 (22.4%)	
Approach	**Open**	4 (2.0%)	1 (2.3%)	1 (20.0%)	1 (1.7%)	0.06
	Laparoscopic	162 (79.0%)	25 (58.1%)	2 (40.0%)	41 (70.7%)	
	Robot-assisted	39 (19.0%)	17 (39.5%)	2 (40.0%)	16 (27.6%)	
	Unknown	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Anastomotic leakage	**Yes**	10 (4.9%)	10 (23.3%)	0 (0.0%)	0 (0.0%) α β γ	**<0.01**

α: statistically different from group No stoma
β: statistically different from group stoma at primary surgery
γ: statistically different from group stoma at secondary surgery
δ: statistically different from group APR

Chapter 10

Summary
General Discussion
Future Perspectives
Conclusion

Summary

Part I: Identification of Prognostic Factors for Postoperative Complications

Major gastrointestinal surgery is associated with high rates of postoperative complications, leading to increased length of hospitalization, morbidity and healthcare costs [1-3]. **Chapter 2**, shows a comprehensive overview of the literature describing prognostic factors which are associated with major postoperative complications and 30-day mortality after upper- and lower-gastrointestinal cancer surgery. In total 207 studies were included, identifying 33 risk factors for major postoperative complications and 13 preoperative laboratory results associated with major postoperative complications. This study showed strong associations between age, male sex, comorbidities, malnutrition, sarcopenia and overweight/obesity, and the occurrence of major postoperative complications (Clavien-Dindo ≥IIIa) [4]. Additionally, strong evidence was shown supporting an association between male sex, comorbidity, obesity, malnutrition, smoking, decreased serum albumin, advanced tumor stages, neoadjuvant therapy, and the occurrence of anastomotic leakage. Furthermore, an association between 30-day mortality and male sex, higher ASA score, and cardiac comorbidity is shown. This overview may contribute to personalized preoperative care by searching for modifiable factors, such as poor physical performance, smoking, alcohol consumption, iron deficiency anemia and malnutrition [5-9]. These factors may be suitable for preoperative optimization during preoperative prehabilitation programs and thus reduce postoperative complications.

Additionally, in **Chapter 3** a meta-analysis was performed for prognostic factors for major complications and mortality after esophageal cancer surgery. This systematic review and meta-analysis included 39 studies and identified 37 prognostic factors that are associated with anastomotic leakage, major complications and mortality after esophageal cancer surgery. Of these prognostic factors renal disease, vascular comorbidity, diabetes, pulmonary, hypertension, cardiac comorbidity, ASA-score ≥ III, male sex and adenocarcinoma tumor histology were significantly associated with anastomotic leakage. Patients receiving neoadjuvant chemotherapy had a lower risk for anastomotic leakage. Male gender, cardiac comorbidity and diabetes were associated with major complications (Clavien-Dindo ≥IIIa) [4]. Furthermore, age >70 years, ASA-score ≥ III, cardiac comorbidity and a BMI of 18.5-20 were significantly associated with 90-day mortality, whereas a BMI of 25-30 appeared preventive of mortality.

However, in daily practice, it might be difficult to estimate the surgical risk of individual patients and subsequently make treatment decisions, based on individual prognostic factors found in population studies. Therefore incorporating multiple factors into a generalizable prediction model might offer a solution to combine the information in a simple and more useful manner [10]. Altogether, with the current more data-driven approach to healthcare and the availability of nationwide clinical audits, big data becomes available. In addition, with big data, the interest in machine learning for prediction models has increased. **Chapter 4** described the construction of machine learning-based prediction models to predict postoperative complications, anastomotic leakage and pulmonary complications, after esophageal- and gastric cancer surgery. The machine learning models that are most frequently described in literature were used: k-Nearest Neighbors (KNN), support vector machine (SVM), Neural Networks, Random Forest, AdaBoost and SuperLearner [11-14]. Additionally, a comparison between machine learning models and the current golden standard, regression model was performed. **Chapter 4** showed that machine-learning models were able to predict postoperative complications, anastomotic leakage and pulmonary complications, after esophageal- and gastric cancer surgery, however, machine-learning models did not outperform a linear regression model.

In search of a modifiable prognostic factor that is cheap and easily available, **Chapter 5** entailed an explorative study of the use of contrast-enhanced (CE) computed tomography (CT)-based muscle measurements in the prediction of anastomotic leakage after oncological sigmoid and rectal resections. Using Vitrea software preoperative transversal CE-CT scans of patients were analyzed and total abdominal muscle area (TAMA) and total psoas area (TPA) at the inferior level of the L3 vertebrae was measured. Subsequently, muscle areas were standardized using the patient's height into psoas muscle index (PMI) and skeletal muscle index (SMI) (cm2/m2). **Chapter 5** showed that a lower PMI and SMI are both associated with the occurrence of anastomotic leakage after oncological sigmoid or rectal resection. This association might be explained by the fact that a low muscle mass indicates frailty, which causes muscle depletion [15]. These results indicate that preoperative CT-based muscle measurements can be used as a prognostic factor for preoperative risk stratification for anastomotic leakage.

Part II: Consequences of Major Gastrointestinal Surgery

As major gastrointestinal surgery is an invasive procedure, long-term effects of these types of surgery are to be expected [16]. This poses the question of how (surgical) treatment of gastrointestinal cancer impacts the long-term quality of life and daily life. Knowledge of long-term quality of life is essential to be able to counsel patients and shared decision-making. To gain more insights into the long-term quality of life after colorectal cancer surgery, we performed a qualitative study (**Chapter 6**) evaluating the long-term consequences of resectable colorectal cancer treatment. Semi-structured interviews were conducted, guided by a predefined topic guide. A total of 16 patients were interviewed, these interviews entailed the predefined themes: daily

life and activities, psychological functioning, social functioning, sexual functioning and healthcare experiences. This study showed that patients who underwent colorectal cancer treatment for resectable colorectal cancer report minor interference with their daily life, although they face several challenges and treatment-related health deficits in the long-term. Which challenges patients face depend on the kind of treatment (e.g., (neo-)adjuvant therapy, type of resection) that they underwent and treatment outcomes (e.g., complications, stoma construction). Frequently reported factors influencing daily life were: poor bowel function, the presence of a stoma, chemotherapy-induced neuropathy, fear of tumor recurrence and sexual dysfunction. Even though patients reported a good quality of life, they reported several challenges and treatment-related health deficits, this suggests that cancer survivorship might have led to increased resilience and mechanisms to cope with these challenges and health deficits [17, 18]. Therefore, the results of this study offer enhanced insights into patient perspectives on the challenges after colorectal cancer treatment and provide leads for patient education, postoperative rehabilitation and patient guidance programs to further improve long-term patient outcomes.

Additionally, **Chapter 7** studied the impact of postoperative complications following rectal cancer surgery on quality of life. For this study, the Rotterdam Symptom Checklist was sent at 6 timepoints (preoperatively and 3, 6, 12, 18 and 24 months after surgery), additionally the EORTC QLQ-C30 and EORTC QLQ-CR29 questionnaires were sent 14 years postoperative. This study showed that survival and short-term quality of life were negatively affected by postoperative complications. However, twelve months after surgery quality of life returns to a level similar to before surgery, regardless of complications within 30 days after surgery. These results are comparable to the results reported in **Chapter 6**. Furthermore, in patients that survived 14 years, there was no long-term effect of postoperative complications from the peri-operative trajectory on quality of life detected. These results suggest that the negative effects of postoperative complications on the quality of life are temporary.

As shown in **Chapter 6**, the presence of a stoma and poor bowel functioning were both reported to be influential on daily life, therefor in **Chapters 8 and 9,** westudied the impact of a stoma and poor bowel functioning after rectal cancer surgery on the quality of life. **Chapter 8** is based on a retrospective cohort of 149 patients who underwent sphincter-sparing resection for rectal cancer between 2012 and 2016 were recruited from the LUMC and Reinier de Graaf Gasthuis. Whereas, **Chapter 9** was based on patients who underwent surgery for a primary tumor located in the rectosigmoid and rectum between 2013-2020. These patients were identified from the nationwide Prospective Dutch Colorectal Cancer cohort study (PLCRC). Poor bowel functioning was defined as major Low-Anterior Resection Syndrome (LARS) [19]. Frequently (≥35%) reported symptoms of major LARS are: clustering of bowel movement, incomplete evacuation, fecal incontinence, uncontrollable flatus and urgency [20]. Results of both **Chapters 8 and 9** showed that the presence of a stoma and major LARS were both associated with reduced quality of life, regardless of postoperative complications. Notwithstanding, a postoperative complication, such as anastomotic leakage is often the cause of the construction of a stoma. Patients with poor functional outcomes, defined as major LARS, reported a similar level of quality of life compared to patients with a stoma. An additional finding was that the quality of life following rectal cancer surgery did not change significantly after the first year post-surgery.

General Discussion

Gastro intestinal oncologic treatment and especially surgery is often a high impact and riskful trajectory. Finding ways to limit this impact and risk is of paramount importance in itself but even more since the number of patients with cancer is increasing. Additionally survival after major gastrointestinal cancer surgery goes up due to improved oncological care and patients live longer with the consequences, such as physical-, psychological- and societal impairments after surgery and (neo-)adjuvant therapy. Therefore gathering data on short and long-term outcomes such as postoperative complications as well as short- and long-term quality of life and functional outcomes, is becoming increasingly important [21-23]. The current thesis identifies multiple targets for the improvement of short-term and long-term patient outcomes.

Prognostic factors for postoperative complications

The identification of prognostic factors for postoperative complications and mortality after major gastrointestinal surgery may contribute to surgical risk assessment and subsequent patient selection. Patients with high surgical risk may require different treatment decisions, for instance, “watch-and-wait” or the use of a defunctioning ileostoma in case of colorectal surgery [24, 25]. Surgical risk assessment and subsequent adequate perioperative care could significantly decrease in-hospital mortality [26]. Therefore, surgical risk assessment might also offer leads for personalized perioperative care and shared decision-making [27]. Furthermore, the identification of prognostic factors for postoperative complications may provide targets for preoperative optimization and prehabilitation to reduce postoperative morbidity. Reduction of complications might lower the length of recovery time, length of hospital stay, readmission rates and hospital costs, and increase long-term quality of life [28, 29]. Therefore, the reduction of postoperative complications impacts healthcare on patient-, hospital- and national levels.

Modifiable prognostic factors

Identification of specific prognostic factors is important to weigh the pros and cons before engaging in high-risk surgery. Furthermore, prognostic factors, especially improvable/modifiable factors offer possibilities for augmentation of perioperative care and enrollment in prehabilitation programs, which might ultimately lead to improved patient outcomes [30, 31]. In particular, with the use of neoadjuvant therapy, a time window for preoperative optimization and prehabilitation programs is opened. An example of a modifiable prognostic factor is diabetes since adequate preoperative glycemic control may lead to fewer postoperative hyperglycemic events and therefore reduces the risk of infectious complications [32]. However, some prognostic factors might seem unmodifiable but may be modifiable after all, due to confounding factors. For instance, males have a higher risk of postoperative complications, but historically the incidence of smoking and alcohol consumption in the male population has been higher, these confounding factors are not being measured and corrected for in many studies, therefore, the effect of male gender on postoperative complications may be modifiable [9]. Another theory on why males are more at risk for postoperative complications is that their more narrow pelvic anatomy, makes surgery for tumors located in this region (e.g., rectum) technically more difficult [3, 33]. The latter might become less of an issue with the introduction of new techniques, such as robot-assisted surgery. Therefore, one should be critical towards prognostic factors and possible confounders.

Clinical use of prognostic factors

In daily practice, it might be difficult to estimate the surgical risk and make treatment decisions based on multiple individual prognostic factors. Therefore, clustering multiple factors into a prediction model might offer a solution in a simple and useful manner [10]. Altogether, with the current more data-driven approach to healthcare and the availability of nationwide clinical audits, big data becomes available. This has also led to a growing interest in machine learning. Whereas some studies have shown superior prediction models using machine learning models compared to conventional regression-based models, one could question publication bias [12, 34]. In our study, linear regression was superior to the machine learning models. Furthermore, several studies that have shown a positive outcome towards using machine learning often used a great number of preoperative variables and patients to build their models. One could question the use in daily clinical practice when using these extensive models, which subsequently leads to more administrative burden to include all variables unless extraction of variables is automated [34, 35]. An additional shortcoming of some machine learning models (e.g., neural networks) is that the influence of individual prognostic factors is not always known, in contrast to for instance linear regression, making the identification of modifiable prognostic factors impossible.

Furthermore, there is a need for easy-to-use clinical parameters that can be used in the prediction of postoperative complications. An example that is gaining interest in current research, is the preoperative contrast-enhanced computed tomography (CE-CT)-based muscle measurements [36, 37]. Since a CE-CT is standard in the routine preoperative work-up of gastrointestinal cancer patients, there are no extra examinations or costs associated with obtaining this prognostic factor. Furthermore, multiple studies, including this thesis, have shown a positive association between low muscle volume and postoperative complications (e.g., anastomotic leakage) [38]. The association between low muscle mass and anastomotic leakage might be explained by frailty since previous studies have shown an association between frailty and anastomotic leakage following colorectal surgery as well [38, 39]. Therefore, the identification of low muscle volume using CE-CT-based muscle measurements might offer a solution to determining frailty. In several studies, a clear correlation between low muscle mass and an increased inflammatory state due to tumor-cachexia and frailty has been shown [40, 41]. This might explain the association between low muscle mass and anastomotic leakage as well, hence a more katabolic and inflammatory state may negatively influence the healing capacity of bowel tissue resulting in anastomotic leakage [42, 43].

Complications and survival

Short-term mortality caused by complications is often defined as failure-to-rescue [44]. A high risk of failure-to-rescue may reflect a compromised physiological reserve for surviving critical illness inflicted by complications [45]. Additionally, long-term (recurrence-free) survival is negatively impacted by complications, due to an improved risk of tumor-recurrence [46]. On one hand, postoperative complications may increase the risk of omission and delay of adjuvant therapy and therefore increasing the risk of tumor-recurrence [47]. On the other hand, infectious complications are shown to be associated with tumor recurrence, most likely due to a pro-inflammatory response with the release of cytokines and growth factors [48]. Also, surgery itself leads to the suppression of cell-mediated immunity, and possible diffusion of tumors, therefore increasing the recurrence potential [49].

Long-term consequences of major gastrointestinal surgery

Long-term patient outcomes in terms of quality of life and treatment-related health deficits are gaining interest with the introduction of value-based healthcare, a new strategy to redefine healthcare. Value-based health care is a conceptual framework, with the founding principle of defining value by measuring patient outcomes relative to the total costs of care [50, 51]. To measure patient outcomes uniformly, a standard set of patient-centered outcomes was developed by The International Consortium for Health Outcomes Measurement (ICHOM), including survival and disease control, disutility of care, degree of health, and quality of death [52]. Another reason to proceed into gaining more insights into long-term patient outcomes is that previous studies have suggested that patients are only willing to risk an inferior functional outcome for better survival to a certain extent [53]. This should be taken into consideration in shared decision-making and treatment decisions. Other treatments may be more preferred by patients, for example, watching and waiting after clinical complete response to neoadjuvant therapy [25, 54]. To make optimal treatment decisions, the anticipated quality of life after gastrointestinal cancer treatment has to be known, as well as the factors influencing this, both to inform patients and to gain insight into possible improvements in perioperative care. As a result of major gastrointestinal cancer treatment, patients may face various treatment-related health deficits. As shown in this thesis factors impacting the quality of life were postoperative complications, poor bowel functioning, the presence of a stoma, chemotherapy-induced neuropathy, fear of recurrence and sexual dysfunction. Which health-deficits patients depend on the type of treatment, but also treatment outcomes (e.g., complications, stoma presence) [55-58]. However, studies have also shown that in the long-term the overall quality of life after cancer treatment seems to be relatively unaffected [55]. Suggesting that, cancer survivorship might enhance resilience and coping strategies [17, 18]. This may lead to a relative underestimation of the impact of cancer treatment and treatment-related health deficits (e.g., poor bowel function, chemotherapy-induced neuropathy), when measuring the quality of life using conventional questionnaires [58, 59]. Since patients can live a modified life with the use of various strategies and self-management techniques to maintain their quality of life. However, there is considerable individual variation between patients on how these self-management strategies are undertaken, therefore personalized patient guidance and rehabilitation are recommended [60, 61].

Postoperative complications

Short-term outcomes, such as postoperative complications, may have an impact long-term outcomes, as a decrease in physical functioning after major complications has been shown [62, 63]. Furthermore, postoperative complications are significantly associated with anxiety and depression [64]. Additionally, complications, such as anastomotic leakage after colorectal surgery might lead to the construction of a stoma which influences postoperative quality of life as well [65]. Several studies on long-term (>1 year) postoperative quality of life showed no significant difference in global health status after postoperative complications or anastomotic leakage compared to an uncomplicated postoperative course [62, 63, 66].

Stoma and bowel functioning

Frequently reported challenges after colorectal surgery is bowel related, either due to the presence of a stoma or due to functional bowel complaints. Both poor functional bowel outcomes and the presence of a stoma have a negative impact on quality of life [65, 67, 68]. The decision to construct a (temporary) stoma after colorectal cancer surgery is based on three key factors, the location of the tumor, the risk of anastomotic leakage and the risk of poor functional bowel outcomes. If the tumor location is appropriate for sphincter-sparing resection, the risk of anastomotic leakage should be considered when deciding whether or not to construct a (temporary) stoma [69]. As anastomotic leakage may be a fatal insult to the patient, therefore preoperative surgical risk assessment has to be performed. The other important consideration is the risk of a poor bowel functional outcome. Poor bowel functioning in patients without a stoma is commonly described in literature as low-anterior resection syndrome (LARS) [19]. The general definition of LARS in literature is: "*A disorder of bowel function after rectal resection, leading to a detriment in quality of life*" [19, 70]. Of all patients who underwent sphincter-sparing surgical resection for rectal cancer approximately 41% experience complaints of major LARS.

Since a stoma has disadvantages, such as stoma-related complications (e.g., parastomal hernia, bulge) and decrease quality of life, routine use of a defunctioning stoma in colorectal surgery is debated [23]. As a solution, the selective use of defunctioning stoma in high-risk patients has been proposed and proven feasible [24, 71]. Furthermore, patient- and treatment characteristics (e.g., age, radiotherapy, tumor location) may be used, for instance by applying the Pre-Operative LARS score (POLARS), to predict the anticipated LARS-score, thus the functional bowel outcome [72]. Subsequently, the combination of the surgical risk prediction and the predicted functional bowel outcomes together may be used in shared decision-making to ultimately decide whether or not to construct a (temporary) stoma. Such decisions are usually not straightforward, caused by the lack of a clinically 'superior choice', making such treatment decisions particularly relevant for shared decision-making [27, 73].

Future Perspectives

Preoperative risk assessment

With the availability of nationwide clinical audits, big data comes available for the creation of generalizable prediction models [74, 75]. As will be the upcoming and further development of artificial intelligence and machine learning algorithms [12]. These prediction models can support clinical knowledge by making treatment decisions, especially detecting modifiable prognostic factors (e.g., frailty, malnutrition). Prediction models can identify high-risk patients, and for those patients, treatments might require adjustment, for instance using a (defunctioning) stoma or less invasive treatment strategies. Perioperative care needs to be adjusted in the case of high-risk patients since failure to identify high-risk surgical patients could significantly increase in-hospital mortality rates, due to inappropriate perioperative care [26]. However, for this to work in daily practice without leading to an administrative burden, automatization of extracting important parameters, such as patient characteristics, laboratory and imaging results, is necessary. Also, combining various available data sources is currently still an obstacle in modern-day medical research and daily practice. The availability of information on a patient's longitudinal pre-disease health status and a patient's health care perspectives might give additional information to use in preoperative decision-making. Eventually, preoperative surgical risk assessment may also be used to enhance preoperative patient education and with the patient deciding on the treatment, which is most appropriate, considering the patient's individual preferences.

Frailty

With the current aging population and advancing surgical techniques, more surgeries on elderly patients are being performed and it's probable that this trend will continue in the future. While cancer survival has improved over the past few decades, larger survival improvements have been observed in younger adult patients (<75 years) than older adult patients (≥75 years) [76]. Age has also shown to be an important prognostic factor for postoperative adverse outcomes, postoperative complications and mortality [2]. Postoperative complications result in an increase of mortality in the first year after surgery [77]. However, as chronological age progresses, the heterogeneity in interindividual health status and biological age, increases [78, 79]. To address the biological health heterogeneity in clinical practice, the term "frailty" is used to distinguish between either end of the spectrum of clinically recognizable physical state. With the aging population, the preoperative detection of frailty becomes a crucial part of personalized risk assessment to facilitate optimal perioperative care. The current golden standard to define frailty, is by using the comprehensive geriatric assessment (GSA), an assessment of multiple geriatric domains (e.g., somatic, psychosocial, functional). However, this assessment suffers from a limited consensus regarding methodology and is very time-consuming [80]. Therefore, an easy-to-use preoperative risk assessment and detection of frail patients will be necessary. Several biological, routinely measured, parameters have been proposed as determinants of patient frailty, biochemical, radiologic, and histologic parameters have been proposed and have to be further investigated to implement in clinical practice [81-84]. As shown in this thesis, contrast-enhanced (CE)-CT-based muscle measurements might offer an easy-to-use clinical parameter to detect frailty.

Personalized perioperative care

This thesis offers targets, methods for the identification of (modifiable) prognostic factors for postoperative complications and insights in treatment consequences. This may be used to enhance and personalize perioperative care. Some studies have

suggested that perioperative care dictates postoperative complications more than surgery itself [85]. Therefore, perioperative care is currently being standardized into enhanced recovery after surgery (ERAS) protocols [86]. ERAS protocols have been shown to be able to reduce postoperative complications up to 50% [87]. The preadmission phase of ERAS focuses on an improved physical state of a patient before surgery, for instance, by lifestyle interventions, such as alcohol- and smoking cessation and physical prehabilitation, which are currently introduced in daily practice [88-90]. However, using preoperative risk assessment with an explicit focus on the detection of modifiable prognostic factors may aid in personalizing and improving preoperative care further for high-risk patients.

Preoperative optimization of modifiable prognostic factors (e.g., poor physical fitness, malnutrition) in dedicated prehabilitation programs has been described in literature, such as physical resistance training, nutritional support, cessation of smoking and cessation of alcohol intake [6, 9, 90, 91]. In theory, these prehabilitation programs are assumed to lead to a reduction in postoperative complications, although there is limited evidence to support this [92, 93]. For instance, physical prehabilitation programs have been shown to objectively improve physical fitness, however, the effects on postoperative outcomes were less eminent [5, 92]. The lack of evidence to support the ability to reduce complications by prehabilitation programs might be the result of these programs do not specifically target specific (modifiable) prognostic factors associated with postoperative complications. When a preoperative physical fitness prehabilitation program was applied in a high-risk population, >70 years of age with ASA III-IV, this led to a 20% reduction in postoperative complications [6]. This suggests that preoperative care should be targeting modifiable prognostic factors and individualized prehabilitation programs are required to establish a significant and cost-effective reduction in postoperative complications. Along these lines, several studies report that well-designed randomized controlled trials on prehabilitation programs are needed in order to prove their beneficial effects on short-term postoperative outcomes [5, 94]. These studies need to focus on a multimodal approach toward modifiable prognostic factors (e.g., malnutrition or poor physical status). After detection of modifiable prognostic factors patients may need to be referred for tailored preoperative optimization to a specialist on that specific factor, for instance, a physiotherapist in case of poor physical fitness, a dietician in case of malnutrition and a psychologist in case of anxiety. In the Netherlands primary care and general practitioners might have a coordinating role in this, since they are already familiar with the patient, but it also offers convenience for the patients as it is often closer to home, which might enhance compliance.

Identification of high-risk patients may indicate the need for intensified and personalized postoperative care. For example, closer postoperative surveillance or delayed enteral feeding in high-risk patients. Closer postoperative surveillance might, for instance, be done by using wearable devices for continuous postoperative monitoring of vital signs, even on the regular surgical ward [95, 96]. This has been shown to lead to more timely recognition and identification of postoperative adverse events, subsequently leading to earlier goal-directed therapy, for instance, antibiotic treatment in case of septic complications, and lower failure-to-rescue rates [95, 97].

Rehabilitation programs

Patients who underwent gastrointestinal cancer treatment may face various treatment-related health deficits in multiple domains (e.g., phycological, social, physical) [55]. As shown in this thesis, patients who suffer from major postoperative complications do suffer from physical impairments leading to a lower level of self-care. Therefore, postoperative rehabilitation programs for these patients may have to be directed toward regaining activity level and physical fitness. Besides direct treatment-related health deficits (e.g., abdominal wound, stoma), patient with postoperative complications have an increased risk of other health issues too, including physical difficulties, sexual dysfunction and psychosocial challenges [98, 99]. Hence, post-treatment psychological-, sexual-, nutritional-, and cognitive functioning of cancer survivors need to be an integral part of the multidisciplinary rehabilitation programs. In order to improve long-term quality of life post-treatment rehabilitation has to be in place for gastrointestinal cancer survivors. Since patients learn to cope with certain treatment-induced health deficits, they still might benefit from rehabilitation programs [17, 18]. Therefore, close attention has to be paid to any health deficits that could occur during or after treatment to offer rehabilitation programs. However, some treatment-induced health deficits may not be treatable, this may result into important information to incorporate into preoperative patient education and shared decision-making.

Shared decision-making

The results described in this thesis offer insights into the impact of major gastrointestinal cancer surgery on quality of life. Information on patient outcomes, short- and long-term, has to be incorporated in treatment decision-making, shared-decision making and preoperative patient education. Healthcare professionals have to keep long-term patient outcomes, quality of life and functional outcomes in mind while proposing oncological treatment decisions. Additionally, these insights in treatment consequences may serve in optimizing patient information and be used during preoperative patient education and in shared decision-making [73, 100]. Using information about treatment consequences in pre-treatment patient education may lead to more understanding. Furthermore, explicit patient consideration of treatment decisions may lead to a higher quality of life post-treatment [101]. Preoperative education of patients has also been shown to reduce postoperative anxiety and postoperative pain [102, 103].

Conclusion

Improving patient outcomes is a challenging process encompassing multiple factors and a multimodal approach. First of all, the importance of improving short-term patient outcomes, reducing postoperative complications, is important in itself, but will also contribute to enhance overall survival and quality of life after surgery. An improvement in preoperative risk assessment and subsequent personalization of perioperative care may lead to a reduction of postoperative complications and mortality. Furthermore, preoperative risk assessment may support clinical knowledge in making treatment decisions and it can be used to identify (modifiable) prognostic factors for postoperative complications. Especially identification of modifiable prognostic factors may be important, because those are possibly optimizable before surgery. Preoperative optimization of modifiable prognostic factors can be done by enrolling patients in prehabilitation programs and should lead to an enhanced physical status, which may result in improved short-term patient outcomes. Moreover, high-risk patients might benefit from personalized or intensified postoperative care, such as closer postoperative surveillance. The complete omission of adverse treatment effects, such as postoperative complications and construction of (temporary) stomas, after major gastrointestinal cancer surgery seems like a utopia. Therefore, knowledge of treatment consequences and treatment-related health deficits remains of utmost importance. This knowledge on treatment consequences and treatment-related health deficits may be used in preoperative education and decision-making, both for patients and healthcare professionals. Especially, if multiple treatment options are available knowledge on treatment consequences of the treatment options is important for shared decision-making. Healthcare professionals can use knowledge of treatment consequences and treatment-related health deficits by making treatment decisions and in the development of new treatment strategies. Additionally, knowledge on postoperative treatment-related health deficits can facilitate the enhancement of postoperative patient guidance and rehabilitation programs. Some treatment-related health deficits may be (partly) treatable, whereas others are not treatable. Especially, those that are not treatable can become vital information in preoperative patient education and shared decision-making. In conclusion, the targets for improving perioperative care presented in this thesis may be used to further improve short- and long-term patient outcomes of resectable gastrointestinal cancer survivors.

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Appendices

Dutch-language Summary (Nederlandse Samenvatting)
List of Publications
Curriculum Vitae
Acknowledgements (Dankwoord)

Nederlandse Samenvatting

Achtergrond en Doel

Gastro-intestinale carcinomen zijn kwaadaardige tumoren die ontstaan uit organen van het maagdarmkanaal, zoals de slokdarm en dikke darm. De hoeksteen van in opzet genezende behandeling voor primaire tumoren van het maagdarmkanaal is een complex gastro-intestinale operatie. Gezien de algemene levensverwachting en daarmee ook de incidentie van dit soort tumoren is gestegen, worden er meer van dit type operaties uitgevoerd. Samen met de toename van de totale overleving door de verbeterde oncologische zorg leidt dit ertoe dat meer patiënten moeten leven met de gevolgen van een complexe oncologische gastro-intestinale operatie. Daarom wordt het verbeteren van de resultaten voor de patiënt op de korte- en lange termijn belangrijker. Dit is mede in gegeven door de toenemende focus op patiëntgerichte benadering van de gezondheidszorg en de opkomst van value-based healthcare. Value-based healthcare is een conceptueel raamwerk, met als basisprincipe waarde te definiëren door patiëntuitkomsten te meten in verhouding tot de totale zorgkosten. Patiëntuitkomsten kunnen worden onderverdeeld in korte- en lange termijn uitkomsten. Korte termijn uitkomsten worden vaak gedefinieerd als complicaties en mortaliteit binnen 90 dagen na de operatie. Patiëntuitkomsten op de lange termijn kunnen ook worden onderverdeeld in twee hoofdcategorieën: ziekte-specifieke uitkomsten en kwaliteit van leven. Ziekte-specifieke uitkomsten, zijn uitkomsten zoals tumor recidieven en algehele overleving van patiënten. De kwaliteit van leven richt zich op het dagelijks leven, eventuele beperkingen en de functionele uitkomsten na een behandeling.

Het doel van dit proefschrift is het streven naar verbetering van de patiëntuitkomsten op korte- en lange termijn, door middel van het beiden van aanknopingspunten voor verbetering van de zorg rondom een operatie. Enerzijds door de identificatie van (aanpasbare) prognostische factoren voor ernstige complicaties na een operatie en deze vervolgens te gebruiken in predictiemodellen, maar ook door inzicht te verwerven in de kwaliteit van leven op lange termijn en de gevolgen van complex oncologische gastro-intestinale chirurgie.

Deel I: Identificatie van prognostische factoren voor complicaties na operatie

Complex gastro-intestinale chirurgie gaat gepaard met hoge kans op complicaties, wat leidt tot gezondheidsschade, langere ziekenhuisopnames en hogere zorgkosten. **Hoofdstuk 2** geeft een uitgebreid overzicht van de in de literatuur beschreven prognostische factoren die geassocieerd zijn met ernstige complicaties en mortaliteit binnen 30 dagen na oncologische dikke darm, slokdarm en maag operaties. In totaal werden er 207 studies geïncludeerd, uit deze studies werden 33 prognostische factoren en 13 preoperatieve bloedwaardes geïdentificeerd, welke geassocieerd zijn met ernstige postoperatieve complicaties. Deze studie toonde sterke associaties aan tussen hogere leeftijd, mannelijk geslacht, co-morbiditeit (o.a. hoge bloedruk, diabetes), ondervoeding, lage spiermassa en overgewicht/obesitas, en het optreden van ernstige complicaties (Clavien-Dindo ≥IIIa). Bovendien werd er sterk bewijs geleverd ter ondersteuning van een verband tussen mannelijk geslacht, co-morbiditeit, obesitas, ondervoeding, roken, verlaagd albumine in het bloed, gevorderde tumor stadia en chemo- en/of radiotherapie voorafgaande aan de operatie en het optreden van naadlekkage na de operatie. Bovendien, is er een verband gevonden tussen mortaliteit binnen 30 dagen na operatie en mannelijk geslacht, hogere ASA-score en cardiale ziekte. Dit overzicht kan bijdragen aan gepersonaliseerde zorg rondom de operatie door te zoeken naar aanpasbare factoren, zoals slechte fysieke fitheid, roken, en ondervoeding. Deze factoren kunnen geschikt zijn voor optimalisatie voorafgaande aan de operatie, in zo genoemde prehabilitatie programma's en zo leiden tot een vermindering van complicaties en mortaliteit na de operatie.

Daarnaast werd in **Hoofdstuk 3** een meta-analyse uitgevoerd naar prognostische factoren voor ernstige complicaties en mortaliteit na oncologische slokdarm operaties. Deze systematische literatuur review en meta-analyse omvatte 39 studies en identificeerde in totaal 37 prognostische factoren die zijn geassocieerd met naadlekkage, ernstige complicaties en mortaliteit na slokdarm operatie. Van deze prognostische factoren waren nierziekte, vasculaire ziekte, diabetes, pulmonale aandoening, hoge bloeddruk, hartaandoening, ASA-score ≥ III, mannelijk geslacht en adenocarcinoom histologie significant geassocieerd met naadlekkage. Patiënten die voorafgaande aan de operatie chemotherapie kregen, hadden een lager risico op naadlekkage. Mannelijk geslacht, een hart aandoening en diabetes waren geassocieerd met ernstige complicaties (Clavien-Dindo ≥IIIa). Bovendien waren leeftijd >70 jaar, ASA-score ≥ III, een hart aandoening en een BMI van 18.5-20 significant geassocieerd met mortaliteit binnen 90 dagen, terwijl een BMI van 25-30 was geassocieerd met een lager risico op mortaliteit.

Echter, in de dagelijkse praktijk kan het moeilijk zijn om het chirurgische risico van individuele patiënten in te schatten op basis van individuele prognostische factoren die zijn geïdentificeerd in verschillende studies. Het combineren van meerdere prognostische factoren in een generaliseerbaar predictiemodel kan daarom een uitkomst bieden om de informatie op een eenvoudige manier te presenteren. Met de huidige meer data-driven kijk op de gezondheidszorg, alsmede de toenemende beschikbaarheid van "big data". Door het beschikbaar komen van big data groeit ook de interesse in machine learning voor het maken van predictiemodellen. **Hoofdstuk**

A

4 beschrijft het maken van predictiemodellen op basis van machine learning voor complicaties, naadlekkage en longcomplicaties na oncologische slokdarm- en maag operatie. In deze studie werden machine learning modellen gebruikt die het vaakst in de literatuur worden beschreven: k-Nearest Neighbours (KNN), support vector machine (SVM), Neural Networks, Random Forest, AdaBoost en SuperLearner. Daarnaast werd een vergelijking uitgevoerd tussen de machine learning modellen en de huidige gouden standaard, een lineair regressie model. **Hoofdstuk 4** toonde aan dat machine learning modellen in staat zijn om complicaties na oncologische slokdarm- en maag chirurgie te voorspellen, maar dat deze machine learning modellen niet beter presteerden een lineair regressiemodel.

Ingegeven door de vraag naar een aanpasbare prognostische factor, die goedkoop en gemakkelijk te bepalen is, is in **Hoofdstuk 5** een verkennend onderzoek naar het gebruik van computertomografie (CT)-scan gebaseerde spiermetingen. Met behulp van Vitrea-software werden CT-scans van voor de operatie geanalyseerd en middels deze scans werden spieroppervlaktes op het niveau van de 3e lumbale wervel gemeten. Vervolgens werden spiergebieden gestandaardiseerd met behulp van de lengte van de patiënt. **Hoofdstuk 5** laat zien dat een lagere spiermassa significant is geassocieerd met het optreden van naadlekkage na oncologische endeldarm operatie. Deze associatie zou verklaard kunnen worden door het feit dat een lage spiermassa duidt op kwetsbaarheid, “frailty”, wat spierverlies veroorzaakt. De resultaten van deze studie geven aan dat CT-scan gebaseerde spiermetingen voorafgaande aan de operatie eenvoudig en goedkoop kunnen worden gebruikt als een prognostische factor voor risico inschatting voor het krijgen van naadlekkage na endeldarm operatie. Daarnaast bied deze studie aanknopingspunten voor mogelijke prehabilitatie programma’s voor fysieke fitheid, wat kan leiden tot een verminderde kans op naadlekkage.

Deel II: Consequenties van complexe gastro-intestinale chirurgie

Aangezien complex gastro-intestinale operaties invasieve procedures zijn, zijn lange termijn effecten van dit soort operaties te verwachten. Dit roept de vraag op hoe chirurgische behandeling van gastro-intestinale tumoren de kwaliteit van leven en het dagelijks leven op de lange termijn beïnvloedt. Kennis van de kwaliteit van leven en functionele uitkomsten op de lange termijn is essentieel om patiënten te kunnen voorlichten en voor shared decision-making. Om meer inzicht te krijgen in de kwaliteit van leven op lange termijn na darmkanker operaties, hebben we een kwalitatief onderzoek uitgevoerd (**Hoofdstuk 6**), waarin de lange termijn gevolgen van operabele darmkanker behandeling werden onderzocht. Er werden semi-gestructureerde interviews bij patiënten afgenomen, aan de hand van een vooraf gedefinieerde onderwerpen lijst. De onderwerpen die aanbod kwamen tijdens de interviews hadden betrekking op de thema's: dagelijks leven en activiteiten, psychisch functioneren, sociaal functioneren, seksueel functioneren gezondheidszorg ervaringen. Deze studie gaf aan dat patiënten die een behandeling ondergingen darmkanker slechts lichte verstoring van hun dagelijks leven bemerkte. Dit terwijl ze op de lange termijn met verschillende uitdagingen en behandeling gerelateerde gezondheidsproblemen werden geconfronteerd. Voor welke uitdagingen patiënten komen te staan, hangt af van het soort behandeling (bijv. chemotherapie, type operatie) die ze hebben ondergaan en de behandel uitkomsten (bijv. complicaties, stoma formatie). Veel voorkomende factoren die het dagelijks leven beïnvloeden zijn: slechte darmfunctie, de aanwezigheid van een stoma, chemotherapie geïnduceerde neuropathie, angst voor terugkeer van de kanker en seksuele disfunctie. Hoewel patiënten een goede kwaliteit van leven rapporteerden, rapporteerden ze verschillende uitdagingen en behandelings-gerelateerde gezondheidsproblemen. Dit suggereert dat het overleven van kanker mogelijk heeft geleid tot coping mechanismen om met deze uitdagingen en gezondheidstekorten om te gaan. Deze resultaten bieden vernieuwde en verbeterde inzichten in de perspectieven van de patiënt op de uitdagingen na de behandeling van darmkanker. Daarmee bieden de resulaten aanknopingspunten voor patiëntenvoorlichting, postoperatieve revalidatie en patiënt begeleidingsprogramma's om de langetermijnresultaten voor patiënten nog verder te verbeteren.

Daarnaast bestudeerde **Hoofdstuk 7** de impact van complicaties na oncologische endeldarm operatie op de kwaliteit van leven. Voor deze studie werd de Rotterdam Symptom Checklist op 6 tijdstippen aan deelnemende patiënten toegezonden (voor operatie, en 3, 6, 12, 18 en 24 maanden na de operatie), daarnaast werden de EORTC QLQ-C30 en EORTC QLQ-CR29 vragenlijsten 14 jaar na de operatie verzonden. Deze studie toonde aan dat de overleving en de kwaliteit van leven op korte termijn negatief werden beïnvloed door complicaties. Twaalf maanden na de operatie keert de kwaliteit van leven echter terug naar een vergelijkbaar niveau met vóór de operatie, ongeacht complicaties binnen 30 dagen na de operatie. Deze resultaten zijn vergelijkbaar met de resultaten van **Hoofdstuk 6**. Bovendien werd er bij patiënten die 14 jaar overleefden geen lange termijn effecten van complicaties op de kwaliteit van leven gedetecteerd. Deze resultaten suggereren dat de negatieve effecten van complicaties op de kwaliteit van leven van tijdelijke aard zijn. Deze studie geeft aan dat een postoperatief rehabilitatie traject met name voor patiënten met complicaties belangrijk kan zijn.

Zoals in **Hoofdstuk 6** werd beschrijven, hebben de aanwezigheid van een stoma en een slechte darm functie beide een negatieve invloed op het dagelijks leven. **Hoofdstuk 8** is gebaseerd op een retrospectief cohort van 149 patiënten die tussen 2012 en 2016 een sfincter-sparende resectie ondergingen voor endeldarm kanker. Daarnaast was **Hoofdstuk 9**, met dezelfde vraagstelling, gebaseerd op patiënten die tussen 2013-2020 een oncologische endeldarm operatie ondergingen, geïdentificeerd uit het landelijk Prospectief Landelijk CRC cohort (PLCRC). In beide studies werd een slechte darmfunctie gedefinieerd als major Low-Anterior Resection Syndrome (LARS). Vaak gemelde symptomen van major LARS zijn: clustering van stoelgang, onvolledige evacuatie, fecale incontinentie, oncontroleerbare flatus en aandrang. De resultaten van zowel **Hoofdstuk 8** als van **Hoofdstuk 9** toonden aan dat de aanwezigheid van zowel een stoma en als major LARS beide geassocieerd waren met verminderde kwaliteit van leven, ongeacht complicaties. Desondanks is een complicatie, zoals een naadlekkage, vaak wel de aanleiding om een stoma aan te leggen. Patiënten met slechte functionele uitkomsten, rapporteerden een vergelijkbare kwaliteit van leven als patiënten met een stoma. Een bijkomende bevinding was dat de kwaliteit van leven na een oncologische endeldarm operatie niet significant veranderde na het eerste jaar na de operatie. Deze resultaten kunnen worden gebruikt tijdens patiëntenvoorlichting, maar ook bij shared decision-making.

Discussie en Toekomstige Perspectieven

Risico inschatting voor de operatie

Door de beschikbaarheid van "big data" daarnaast de opkomende en verdere ontwikkeling van artificial intelligence (AI) en machine learning-algoritmen groeien de mogelijkheden voor het creëren van generaliseerbare voorspellingsmodellen. Deze predictiemodellen kunnen de klinische kennis ondersteunen en helpen bij het opsporen van aanpasbare prognostische factoren (bijv. kwetsbaarheid, ondervoeding). Vervolgens kunnen bij hoog risico patiënten de behandeling worden gewijzigd, zoals het gebruik van een ontlastend stoma, of kunnen minder ingrijpende behandelstrategieën worden gebruikt. Verder kan de zorg rondom de operatie worden aangepast bij hoog risico patiënten, zoals intensievere monitoring van vitale functies na de operatie. Om dit echter in de dagelijkse praktijk te laten werken zonder tot extra administratieve lasten te leiden, is automatisering van het extraheren informatie omtrent prognostische factoren, zoals patiëntkenmerken en laboratoriumuitslagen, noodzakelijk. Ook het combineren van verschillende beschikbare databronnen is momenteel nog een obstakel in het moderne medische onderzoek en de dagelijkse praktijk. Bovendien kan de beschikbaarheid van informatie omtrent de longitudinale gezondheidsstatus van een patiënt voorafgaande aan het optreden van de ziekte en de perspectieven van een patiënt op de gezond aanvullende informatie opleveren die kan worden gebruikt bij het nemen van behandel beslissingen. Daarnaast moeten chirurgische risico inschatting en functionele uitkomst voorspellingen worden gebruikt tijdens het maken van behandelbeslissingen, patiënten voorlichting, shared decision-making en gepersonaliseerde perioperatieve zorg.

Kwetsbaarheid

Met de huidige vergrijzing en voortschrijdende chirurgische technieken worden en zullen er meer operaties worden uitgevoerd bij ouderen. Hoewel de overleving van kanker de afgelopen decennia is verbeterd, zijn er grotere overlevingswinsten waargenomen bij jongere volwassen patiënten (<75 jaar) dan bij oudere volwassen patiënten (≥75 jaar). Er is aangetoond dat leeftijd een belangrijke prognostische factor is voor complicaties en mortaliteit na operatie. Bovendien zijn complicaties verantwoordelijk voor oversterfte in het eerste jaar na de operatie. Naarmate de chronologische leeftijd toeneemt, neemt ook de heterogeniteit van de interindividuele gezondheidsstatus, de biologische leeftijd toe. Derhalve wordt klinische detectie van kwetsbaarheid, "frailty", voorafgaande aan de operatie belangrijker. Zowel, voor een goede risico inschatting als voor het maken van passende behandel beslissingen en gepersonaliseerde perioperatieve zorg. De huidige gouden standaard om kwetsbaarheid te definiëren is echter het gebruik van de comprehensive geriatric assessment (GSA), een beoordeling van meerdere geriatrische domeinen. Deze tijdsintensieve assessment heeft weinig consensus en is niet geheel gebruiksvriendelijk. Daarom bied een eenvoudig te gebruiken parameter, zoals de in deze thesis beschreven CT-scan gebaseerde spiermetingen om kwetsbare patiënten te identificeren mogelijk uitkomst. Gezien, verschillende biologische parameters voor kwetsbaarheid reeds routinematig worden gemeten, kan dit uitkomst bieden in het detecteren van kwetsbaarheid van de patiënt. Er bestaan verschillende biochemische, radiologische en histologische parameters die op kwetsbaarheid kunnen duiden, welke dit precies zijn en hoe dit in de praktijk gebruikt kan worden moet verder worden onderzocht.

Gepersonaliseerde perioperatieve zorg

Dit proefschrift biedt aanknopingspunten voor het verbeteren en personaliseren van de zorg rondom een operatie. Dit is belangrijk omdat, wanneer chirurgische patiënten met een hoog risico niet als zodanig worden geïdentificeerd, de mortaliteit in het ziekenhuis aanzienlijk kan toenemen als gevolg van inadequate perioperatieve zorg. Derhalve hebben studies gesuggereerd dat de zorg rondom een operatie meer van invloed is op het ontwikkelen complicaties dan de operatie zelf. Daarom wordt de zorg rondom de operatie momenteel gestandaardiseerd in de zogenaamde Enhance Recovery After Surgery (ERAS)-protocollen. Het is aangetoond dat ERAS-protocollen complicaties na operatie tot 50% kunnen verminderen. De fase voor opname voor operatie van ERAS-protocollen richt zich met name op een verbetering van de fysieke toestand van een patiënt vóór de operatie, bijvoorbeeld door leefstijl interventies, zoals stoppen met roken en roken en fysieke training, die momenteel in de dagelijkse praktijk worden geïntroduceerd. Bovendien kan een risico inschatting en specifiek de detectie van aanpasbare prognostische factoren helpen bij het verbeteren van de zorg rondom de operatie. In de literatuur zijn verschillende prehabilitatie programma's beschreven voor het optimaliseren van aanpasbare prognostische factoren, zoals fysieke training, diëtetiek ondersteuning, het stoppen met roken en het stoppen met alcoholgebruik. Theoretisch zouden deze prehabilitatie programma's moeten leiden tot een vermindering van complicaties, hoewel er slechts beperkt bewijs is om dit te ondersteunen. Van fysieke prehabilitatie programma's is aangetoond dat het leid tot een objectief verbeterde fysieke fitheid, maar de effecten op het verminderen van complicaties is minder groot. Het gebrek aan bewijs, kan het gevolg zijn van het feit dat de onderzochte prehabilitatie programma's niet specifiek gericht zijn op prognostische factoren die verband houden met postoperatieve complicaties. Maar, wanneer een hoog risico cohort met patiënten van 70 jaar en ouder met onderliggende zekers een fysiek prehabilitatie programma onderging, leidde dit wel tot een 20% vermindering van complicaties. Dit suggereert dat zorg voorafgaande aan de operatie gericht moet zijn op specifieke factoren en dat er geïndividualiseerde prehabilitatie programma's nodig zijn om te leiden tot een groot genoeg effect om een significante, en kosteneffectieve, reductie van complicaties te weeg te brengen. Daarom rapporteren verschillende studies dat er goed opgezette trials naar prehabilitatie programma's nodig zijn om een positief effect op complicaties aan te tonen. Deze onderzoeken moeten zich direct richten op een multimodale aanpak van beïnvloedbare preoperatieve prognostische factoren, zoals onder andere ondervoeding of een slechte fysieke toestand. Na detectie van aanpasbare prognostische factoren tijdens de risico inschatting kan het nodig zijn patiënten door te verwijzen naar een specialist op die specifieke factor, bijvoorbeeld een fysiotherapeut in geval van een slechte lichamelijke conditie, een diëtist in geval van ondervoeding en een psycholoog in geval van angstklachten. In Nederland kan de eerstelijnszorg, onder andere huisartsen, hierin een rol spelen aangezien zij de patiënt al kennen, daarnaast biedt dit ook gemak voor de patiënt omdat het vaak dichter bij huis is en daardoor de therapietrouwheid kan vergroten.

Het identificeren van patiënten met een hoog risico kan aanleiding geven voor geïntensiveerde en gepersonaliseerde zorg na de operatie. Bijvoorbeeld, nauwere bewaking van vitale waardes of uitgestelde voeding. Strengere bewaking van vitale waardes kan bijvoorbeeld worden gedaan door middel van wearables, deze kunnen na de operatie continue vitale parameters, zoals hartslag en bloeddruk, meten. Dit kan zelfs op de reguliere chirurgische afdeling. Verschillende studies hebben aangetoond dat dit kan leiden tot een snellere herkenning complicaties, wat vervolgens leidt tot een eerdere behandeling hiervan. Een voorbeeld hiervan is het eerder starten van antibiotica in het geval van een infectieuze complicatie. Dit zal uiteindelijk ook moeten leiden tot een lager percentage mortaliteit na complicaties.

Rehabilitatie programma's

Patiënten die een behandeling voor een gastro-intestinale tumor hebben ondergaan, kunnen te maken krijgen met verschillende behandelings-gerelateerde gezondheidsproblemen, in verschillende domeinen, zoals psychologisch, sociaal of fysiek. Zoals beschreven dit proefschrift, lijden patiënten die ernstige complicaties hebben gehad aan fysieke beperkingen die leiden tot een slechter functioneren en verminderde fysieke gezondheid in het eerste jaar na de operatie. Naast directe behandelings-gerelateerde gezondheidsproblemen, zoals bijvoorbeeld een operatiewond of een stoma, hebben deze patiënten ook een verhoogd risico op andere gezondheidsproblemen, waaronder psychosociale problemen en seksuele problemen. Daarom moet het psychologisch-, seksueel-, voedings- en cognitief functioneren van patiënten tijdens en na behandeling van gastro-intestinale tumoren een integraal onderdeel zijn van multidisciplinaire revalidatie programma's. Ondanks dat patiënten leren omgaan met door de behandeling veroorzaakte gezondheidsproblemen, kunnen ze nog steeds baat hebben bij dergelijke revalidatie programma's. Daarom moet er aandacht worden besteed aan eventuele gezondheidstekorten die optreden tijdens of na de behandeling om revalidatie programma's op aan te passen. Sommige door behandeling veroorzaakte gezondheidstekorten zijn echter niet behandelbaar, dit kan wel belangrijke informatie bevatten om op te nemen in patiënt voorlichting en bij gedeelde besluitvorming.

Shared decision-making

De resultaten van dit proefschrift bieden inzicht in de impact van complexe oncologische gastro-intestinale chirurgie op de kwaliteit van leven op de korte- en lange termijn. Informatie over de resultaten van de patiënt, op korte- en lange termijn, moet worden opgenomen in de besluitvorming over behandeling en voorlichting van patiënten voorafgaande aan de behandeling. Enerzijds moeten artsen rekening houden met de lange termijn resultaten van de patiënt, de kwaliteit van leven en de functionele resultaten bij oncologische behandelvoorstellen. Daarnaast kunnen deze inzichten omtrent de gevolgen van de behandeling dienen bij het optimaliseren van patiënten informatie en kan het worden gebruikt tijdens shared decision-making. Het gebruik van informatie over de gevolgen van de behandeling tijdens de voorlichting van patiënten voorafgaande aan de behandeling zou kunnen leiden tot meer begrip, en bovendien zou expliciete overweging van de patiënt bij behandel beslissingen leiden tot een hogere kwaliteit van leven na de behandeling. Er is ook aangetoond dat voorlichting van patiënten leid tot een afname van angst en pijn na de operatie.

Conclusie

Het verbeteren van patiëntuitkomsten is een uitdagend proces dat meerdere factoren en een multimodale aanpak behelst. Allereerst is het belang van het verbeteren van de patiëntresultaten op korte termijn, het verminderen van postoperatieve complicaties, op zichzelf belangrijk, maar het draagt ook bij aan het verbeteren van de algehele overleving en kwaliteit van leven na een operatie. Verbetering van de risico inschatting voor de operatie en het vervolgens personaliseren van de zorg rondom de operatie kan leiden tot een vermindering van postoperatieve complicaties en mortaliteit. Bovendien kan de risico predictie de klinische kennis ondersteunen bij het nemen van behandelbeslissingen en het identificeren (aanpasbare) prognostische factoren voor postoperatieve complicaties. Met name aanpasbare prognostische factoren zijn van belang om te identificeren gezien deze mogelijk vóór de operatie kunnen worden geoptimaliseerd. Aanpasbare prognostische factoren kunnen vervolgens worden gebruikt in prehabilitatie programma's om de fysieke toestand van een patiënt te verbeteren en zo de uitkomsten voor de patiënt te verbeteren. Bovendien kunnen patiënten met een hoog risico baat hebben bij gepersonaliseerde en geïntensiveerde zorg na de operatie. Echter, het volledig uitbannen van nadelige behandelingseffecten, complicaties na complexe oncologische gastro-intestinale operaties en het aanleggen van (tijdelijke) stoma's, lijkt een utopie. Daarom blijft informatie over de gevolgen van het groot belang. Bovendien kan kennis over behandel consequenties en behandelings-gerelateerde gezondheidsproblemen worden gebruikt bij besluitvorming omtrent behandelingen, zowel door patiënten als door zorgprofessionals. Vooral indien er meerdere behandelopties beschikbaar zijn, is kennis over de behandel consequenties van de behandelopties belangrijk voor gedeelde besluitvorming. Bovendien kunnen zorgprofessionals kennis over behandelingsgevolgen en behandeling gerelateerde gezondheid problemen gebruiken bij het kiezen van behandelingen en bij de ontwikkeling van nieuwe behandelingen. Bovendien kan kennis over behandeling gerelateerde gezondheid problemen de verbetering van patiënten begeleiding en revalidatie programma's na de operatie helpen te verbeteren. Sommige behandeling gerelateerde gezondheid problemen zijn (deels) behandelbaar, andere niet. Vooral kennis omtrent degenen die niet behandelbaar zijn, kan essentiële informatie vormen bij preoperatieve patiëntenvoorlichting en gedeelde besluitvorming. Concluderend kunnen de aanknopingspunten voor het verbeteren van de zorg rondom operatie die in dit proefschrift zijn gepresenteerd gebruikt worden om de patiëntuitkomsten op korte- en lange termijn na complexe oncologische gastro-intestinale operaties te verbeteren.

List of Publications

The Early Survival Gap Between Younger and Older Adults with Resected Colon Carcinoma is Governed by Frailty

Cor J. Ravensbergen, *Robert T. van Kooten*, Yara van Holstein, Yaren Zügül, Stijn A.S.L.P. Crobach, Hein Putter, Koen C.M.J. Peeters, Willem Grootjans, Ana Navas Cañete, Marije Slingerland, Simon P. Mooijaart, Frederiek van den Bos, Wilma E. Mesker, Rob A.E.M. Tollenaar

Submitted

Patient Perspectives on Consequences of Resectable Colorectal Cancer Treatment: a Qualitative Study

Robert T. van Kooten, Bianca A.M. Schutte, Dorine J. van Staalduinen, Jetty H.L. Hoeksema, Fabian A. Holman, Chantal van Dorp, Koen C.M.J. Peeters, Rob A.E.M. Tollenaar, Michel W.J.M. Wouters

Colorectal Dis., 2023

Patient and staff experience evaluation in Remote Patient Monitoring; what to measure and how? A systematic review

Valeria Pannunzio, Maria H.C. Morales Ornelas, *Robert T. van Kooten*, Pema Gurung, Hine J. A. van Os, Michel W.J. Wouters, Rob A.E.M. Tollenaar, Maaike Kleinsmann, Dirk. Snelders, Douwe E. Atsma

Submitted

The Impact on Health-Related Quality of a Stoma or Poor Functional Outcomes After Rectal Cancer Surgery in Dutch Patients: a Prospective Cohort Study

Robert T. van Kooten, Jelle P.A. Algie, Rob A.E.M. Tollenaar, Michel W.J.M. Wouters, Hein Putter, Koen C.M.J. Peeters, Jan Willem T. Dekker

Eur J Surg Oncol., 2023

Computed Tomography-based Preoperative Muscle Measurements as Prognostic Factors for Anastomotic Leakage Following Oncological Sigmoid and Rectal Resections

Robert T. van Kooten, Cor J. Ravensbergen, Sophie C.D. van Büseck, Willem Grootjans, Koen C.M.J. Peeters, Fabian A. Holman, Jan W.T. Heemskerk, Michel W.J.M. Wouters, Ana Navas Cañete and Rob A.E.M. Tollenaar

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The Impact of Postoperative Complications on Short- and Long-Term Health-Related Quality of Life After Total Mesorectal Excision for Rectal Cancer

Robert T. van Kooten, M. Elske van den Akker-Marle, Hein Putter, Elma Meershoek-Klein Kranenbarg, Cornelis J.H. van de Velde, Michel W.J.M. Wouters, Rob A.E.M. Tollenaar, Koen C.M.J. Peeters

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Stoma versus anastomosis after sphincter-sparing rectal cancer resection; the impact on health-related quality of life

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Preoperative Risk Factors for Major Postoperative Complications After Complex Gastrointestinal Cancer Surgery: A Systematic Review

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Multi-OMIC profiling of survival and metabolic signaling networks in cells subjected to photodynamic therapy

Ruud Weijer, *Robert T. van Kooten*, Séverine Clavier, Esther A. Zaal, Maud M. E. Pijls, Klaas Vermaas, René Leen, Aldo Jongejan, Perry D. Moerland, Antoine H.C. van Kampen, André B.P. van Kuilenburg, Celia R. Berkers, Simone Lemeer, Michal Heger

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Curriculum Vitae

Robert Thomas van Kooten was born in Wageningen on the 19th of June 1993 and grew up in Veenendaal. After attending Atheneum at the Rembrandt College in Veenendaal, he was not enrolled in the study of Medicine and therefore decided to study, as back-up, Econometrics at the University of Amsterdam instead. A year later, in 2012, he was luckily able to make the switch to Medicine at the University of Amsterdam.

During the first year of his study, Robert did an internship in a nursing home, Henriette Roland Holst Huis in Amsterdam after which he kept working there for the next six years of his study. Additionally, in his second year of studying Medicine, he first came in contact with surgical research at the Department of Experimental Surgery at the Amsterdam Medical Center (AMC). The subject of this research was photodynamic therapy for extrahepatic cholangiocarcinoma, especially concentrating on cell death and the subsequent immune response. Furthermore, Robert was chairman of the second board of the Vereniging Chirurgie voor Medisch Studenten (VCMS), AMC, which focused on extracurricular surgical masterclasses and workshops for medical students.

After obtaining his medical degree in 2018, he started as ANIOS at the department of surgical oncology at the Netherlands Cancer Institute - Antoni van Leeuwenhoek Hospital, in Amsterdam. In 2019 he started working at the Leiden University Medical Center (LUMC) as a PhD candidate at the Department of Surgery, under the supervision of Prof. Dr. Rob Tollenaar, Prof. Dr. Michel Wouters and Dr. Koen Peeters. During the COVID-19 pandemic, next to his PhD trajectory, Robert was part of the OnCovid project team, a team of medical professionals formed from NVvH and SONCOS that worked together with amongst others: DICA, NZa and IKNL on the continuation of oncological care during the COVID-19 pandemic. In January 2023, with his PhD almost finished, he returned to clinics as ANIOS Surgery at Alrijne hospital, Leiderdorp.

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