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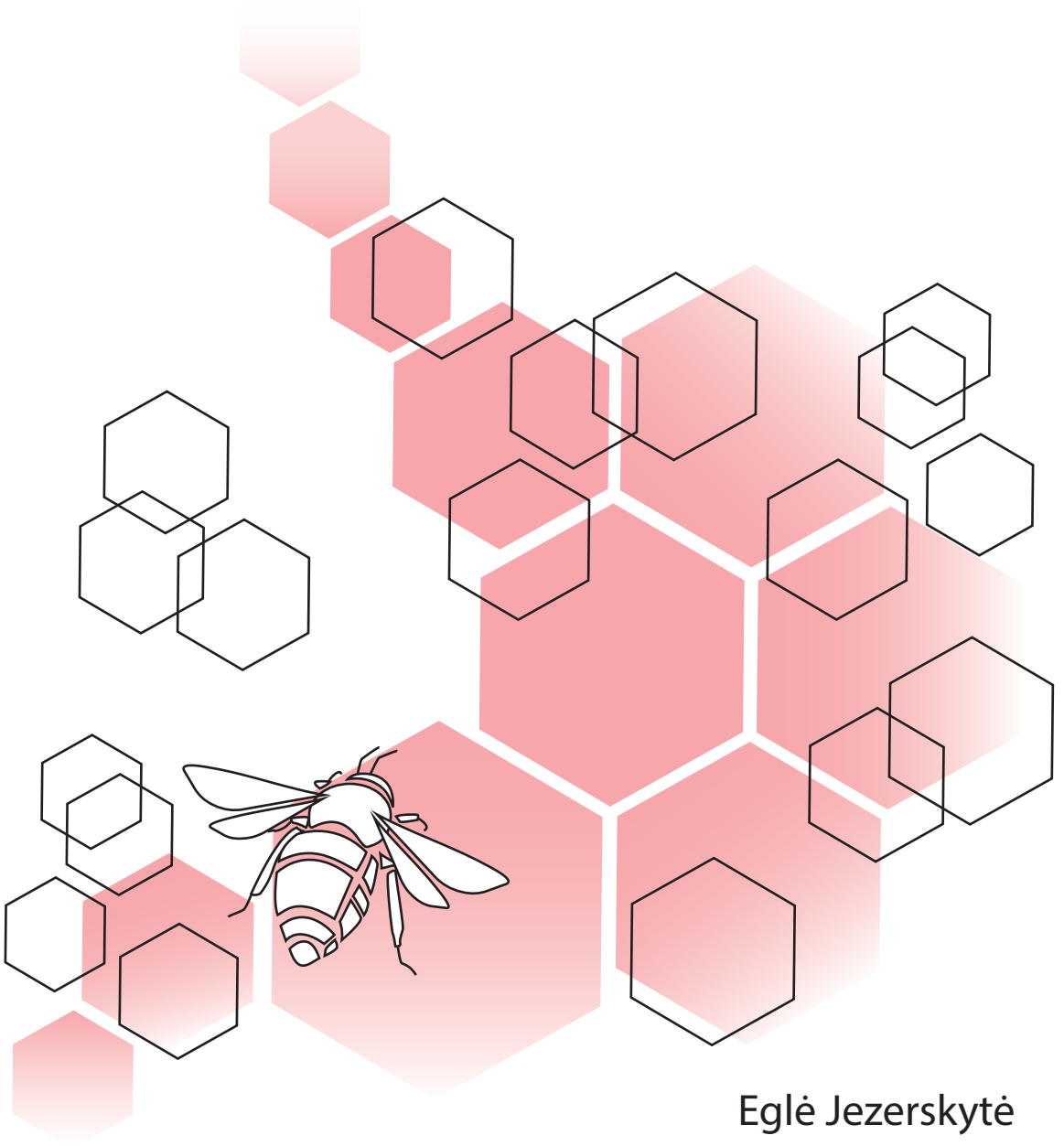

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Faculteit der Geneeskunde

Voor mijn ouders

“Labiausiai žmoguje vertinu augimo jausmą”
Arūnas Jezerskis

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Chapter 1

General introduction and outline of the thesis

GENERAL INTRODUCTION

Esophageal and gastric cancer management

In 2018, over 572.000 patients were diagnosed with esophageal cancer and over 1.000.000 patients were diagnosed with gastric cancer worldwide [1]. Several risk factors have been identified that contribute to the occurrence of esophageal and gastric cancer, such as gastroesophageal reflux disease, H. pylori infection, smoking, alcohol consumption, old age, male gender and obesity [2-4]. These risk factors differ for esophageal and gastric cancer, as gastroesophageal reflux disease and male gender are established risk factors for esophageal cancer, while H. pylori infection is a risk factor for gastric cancer.

Despite the fact that esophageal cancer ranks sixth and gastric cancer third in terms of cancer related mortality in men worldwide, in patients treated with curative intent both perioperative morbidity and mortality have decreased and long-term survival has improved over the recent years [5-7]. This can be explained by the development of perioperative care programs including prehabilitation, minimally invasive surgical techniques and Enhanced Recovery After Surgery programs [8-10]. Furthermore, the introduction of perioperative chemotherapy for particularly patients with gastric cancer and neoadjuvant chemoradiotherapy or perioperative chemotherapy for patients with esophageal or gastroesophageal junction cancer has contributed to improved long-term outcomes [11-13].

In the Netherlands as well as in other countries, all patients are discussed in a pre- and post-treatment multidisciplinary team meeting. Many aspects, such as tumor location, length and extent, patients' condition and comorbidities are taken into consideration when a treatment approach is chosen. Often several surgical approaches are possible in one patient. Both a total gastrectomy and an esophagectomy can be performed in a patient with gastroesophageal junction cancer. An esophagectomy in patients with a distal esophageal or gastroesophageal junction cancer can either be performed transhiatal or transthoracic, and a transthoracic esophagectomy can be performed with either a cervical (McKeown) or intrathoracic (Ivor Lewis) anastomosis. Evidence for the optimal surgical procedure regarding surgical morbidity, quality of life and long-term survival is still scarce and decisions on treatment are now made at the discretion of the (surgical) team. One randomized controlled trial investigated transhiatal versus transthoracic esophagectomy for distal esophageal and gastro-esophageal junction cancer [14]. Significantly lower postoperative morbidity has been found following a transhiatal esophagectomy. However, only a non-significant trend towards an improved survival following the transthoracic procedure was observed, which might have been due to the limited sample size. Currently, two randomized controlled trials are comparing the other described clinical decision-making challenges. One investigates the difference in postoperative morbidity, mortality and quality of life between minimally invasive esophagectomy with a cervical or an intrathoracic anastomosis [15]. Another trial

investigates the difference in survival, postoperative complications, quality of life and cost-effectiveness between transthoracic esophagectomy and a transhiatal total gastrectomy in patients with gastroesophageal junction cancer [16].

Quality of Life after surgery in patients with Esophagogastric cancer

The primary goal of surgery with curative intent is an optimal oncologic outcome consisting of a radical resection, accompanied by minimal surgical morbidity resulting in prolonged long-term survival. In addition, as long-term survival of esophagogastric cancer patients improves, long-term health related quality of life (HR-QoL) has gained attention as another important aspect to consider. The HR-QoL can be evaluated using patient-reported questionnaires. For cancer patients, a range of such questionnaires is available, but the most widely used questionnaires in Europe are the European Organization for Research and Treatment of Cancer (EORTC) HR-QoL questionnaires [17]. The EORTC Quality of Life Group has devised various HR-QoL questionnaires that are, among others, specifically validated for patients with cancer in general (EORTC QLQ-C30 [18]), and for patients with specific tumor sites, including distal esophageal (EORTC QLQ-OES18 [19, 20]) and gastroesophageal junction cancer (EORTC QLQ-OG25 [21]). HR-QoL can be influenced by many factors, including characteristics of the patient, such as age and gender, characteristics of the disease, such as type of cancer, stage of the disease, and characteristics of the treatment, such as type of (neo)adjuvant treatment, surgical approach, and the occurrence of complications. In this thesis, we focus primarily on the influence of treatment on HR-QoL.

It is well established that HR-QoL decreases after esophagogastric surgery and that it restores to baseline within one year after surgery [22]. In addition, several studies have investigated the difference in HR-QoL between various surgical approaches in patients with esophagogastric cancer. In gastroesophageal junction cancer, superior HR-QoL was found after a total gastrectomy [23-25] compared to an esophagectomy while another study showed similar HR-QoL after either operation [26]. In patients with distal esophageal or gastroesophageal junction cancer, similar HR-QoL was found following a McKeown and an Ivor Lewis esophagectomy in two studies [27, 28] and one study found better HR-QoL following Ivor Lewis esophagectomy [24]. Following transthoracic and transhiatal esophagectomy in patients with distal esophageal or gastroesophageal junction cancer, similar HR-QoL results were found in several studies [29-31], and one study found a better HR-QoL following transhiatal compared to transthoracic surgery [32]. In addition, patients who endured complications following an esophagectomy were found to report worse HR-QoL compared to patients without postoperative complications [33-36]. However, most of these studies were performed before the implementation of minimally invasive surgery and neoadjuvant treatment or were single center studies with a limited number of patients. When survival is gained at the expense of complications, or when treatments are equivalent in terms of postoperative outcomes such as complications and survival, HR-QoL becomes

an important outcome to consider during the clinical decision-making process, particularly when different surgical options are possible. It is therefore important to investigate how patients experience their QoL following different surgical procedures.

Information needs of patients with Esophageal and Gastric cancer

Good information provision to patients is important, and dependent on the phase of the disease trajectory. Information provision concerns, among others, information on diagnosis, treatment options, and treatment details such as side-effects or morbidity from the proposed treatment. The information needs of cancer patients may differ and can be influenced by many factors, such as gender, age, marital status, level of education, experienced HR-QoL and occurrence of postoperative complications [37-41]. The level of received information can be evaluated in cancer patients using questionnaires, such as the EORTC information module, the EORTC-INFO25 [42]. Overall, patients report to need information about clinical and HR-QoL outcomes not only during treatment, yet also during the post-treatment period [37, 43, 44]. Bidirectional associations have been found between information needs and HR-QoL in patients with various types of cancer [38, 45]. Also, a multicenter study found that female cancer patients inquired more information about psychosocial support compared to male patients [38]. However, the knowledge about the information needs of esophageal and gastric cancer patients is scarce.

One study compared information needs of patients with esophageal cancer who received either curative or palliative treatment [46]. Patients in the curative treatment group reported to be more satisfied with the information provided, to be more informed about the disease and to want more information compared to patients in the palliative treatment group. Also, the information needs of Dutch and Italian patients with esophageal cancer have been compared [47]. Dutch patients were found to report a higher level of satisfaction with the information received at diagnosis, whereas Italian patients were found to report more satisfaction with the received information about the disease, albeit only during the neoadjuvant treatment period. However, no previous studies have investigated the impact of gender and postoperative complications on the information needs in patients with esophagogastric cancer. As postoperative complications are common in this group (42-65%) [48, 49], examining the information needs of this particular group of patients, could help with providing adequate information on what to expect during the postoperative period.

OUTLINE OF THE THESIS

This thesis focusses on the HR-QoL, information needs, postoperative complications and long-term survival after esophageal and gastric cancer surgery.

In **chapter 2** we evaluated the difference in long-term HR-QoL between patients with gastroesophageal junction cancer following an Ivor Lewis esophagectomy or a total gastrectomy. In addition, we examined the differences in incidence of postoperative complications (anastomotic leakage, atrial fibrillation and pulmonary complications) and oncologic results (c/ypTNM stage, histology, R0 resection rate, (positive) lymph node count). In **chapter 3** the difference in long-term HR-QoL following a McKeown and an Ivor Lewis esophagectomy for a distal esophageal or gastroesophageal junction cancer was investigated. The HR-QoL of patients in both groups was compared to the HR-QoL of the general population, and a subgroup analysis of HR-QoL in patients with no or minor postoperative complications (Clavien-Dindo grade 0-2) was performed. In **chapter 4** transthoracic and transhiatal surgical approaches were compared in terms of long-term HR-QoL in patients with distal esophageal or gastroesophageal junction cancer. In this study we also compared the HR-QoL of the included patients with that of the general population. Furthermore, as neoadjuvant therapy and minimally invasive approach were found to influence HR-QoL [50-52], the difference in long-term HR-QoL between transthoracic and transhiatal esophagectomies was investigated in subgroups of patients following neoadjuvant therapy and after minimally invasive surgery. In addition, the long-term HR-QoL following a cervical or intrathoracic anastomosis after transthoracic esophagectomy was studied. **Chapter 5** provides an overview of information needs of esophageal and gastric cancer patients following esophagogastric surgery. This study focused on the difference in information needs between patients with and without postoperative complications in time cohorts at 6-12 months, at 18-24 months and 3-5 years after surgery. Also, the difference in information needs between male and female patients, and the association between information needs and three HR-QoL domains (global quality of life (EORTC-QLQ-C30), eating restrictions (EORTC-QLQ-OG25) and anxiety (EORTC-QLQ-OG25)), were investigated in the baseline cohort (assessed prior to surgery), and the 6-12 months, 18-24 months and 3-5 years follow-up cohorts. In **chapter 6**, the influence of postoperative complications on HR-QoL over time at 3-, 6-, 9-, 12-, 18- and 24-months postoperatively in patients with esophageal cancer was investigated. The change in HR-QoL over time compared to baseline was also investigated in patients with and patients without postoperative complications, separately. In addition, the difference in short- and long-term HR-QoL was investigated between patients with and without anastomotic leakage, between patients with anastomotic leakage grade 2-3 versus patients with no anastomotic leakage or anastomotic leakage grade 1, and between patients with a cervical versus an intrathoracic anastomosis. In **chapter 7**, the differences in long-term survival, postoperative morbidity, mortality and pathology results in patients with gastroesophageal junction cancer following

an esophagectomy and a total gastrectomy at a population level were investigated. Both 3-year overall survival and 3-year conditional survival (survival after exclusion of 30-day and in-hospital mortality) were studied. In **chapter 8 & 9** (Summary and Discussion), the results of the studies included in this thesis are summarized and reviewed, the need for future studies is outlined, the methodological limitations are addressed and the clinical implications are discussed.

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Chapter 2

Long-term quality of life after total gastrectomy versus Ivor Lewis esophagectomy

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ABSTRACT

Background

There is scarce evidence on whether a total gastrectomy or an Ivor Lewis esophagectomy is preferred for gastroesophageal junction (GEJ) cancers regarding effects on morbidity, pathology, survival and health-related quality of life (HR-QoL). The aim of this study was to investigate the difference in long-term HR-QoL in patients undergoing total gastrectomy versus Ivor Lewis esophagectomy in a tertiary referral center.

Methods

Patients with a follow-up of > 1 year after a total gastrectomy or an Ivor Lewis esophagectomy for GEJ/cardia carcinoma completed the EORTC QLQ-C30 and EORTC QLQ-OG25 questionnaires. 'Problems with eating', 'reflux' and 'nausea & vomiting' were the primary HR-QoL endpoints. The secondary endpoints were the remaining HR-QoL domains, postoperative complications and pathology results.

Results

30 patients after gastrectomy and 71 after esophagectomy were included. Mean age was 63 years. Median follow-up was two years (range 12-84 months). Patients after gastrectomy reported less 'choking when swallowing' and 'coughing' (β=-5.952, 95% CI -9.437 – -2.466; β=-13.084, 95% CI -18.525 – -7.643). More lymph nodes were resected in esophagectomy group (p=0.008). No difference was found in number of positive lymph nodes, R0 resection or postoperative complications.

Conclusion

After a follow-up of > 1 year 'choking when swallowing' and 'coughing' were less common after a total gastrectomy. No differences were found in postoperative complications or radicality of surgery. Based on this study no general preference can be given to either of the procedures for GEJ cancer. These results support shared decision making when a choice between the two treatment options is possible.

INTRODUCTION

In 2018, esophageal and gastric cancer were diagnosed in over 570.000 and 1.033.000 patients, respectively worldwide [1]. Only a small percentage of patients present with a gastroesophageal junction (GEJ) or cardia carcinoma, defined as a tumor involving the GEJ with the epicenter within 2 cm of the cardia (true GEJ tumor) or a tumor of the gastric cardia without esophageal involvement (cardia cancer). The actual incidence of these specific cancers however, is unknown. The Dutch Upper Gastrointestinal (GI) Cancer audit shows that in 2018, 174 patients were operated for GEJ cancer in the Netherlands, which also includes patients with cardiac tumors [2]. Treatment of gastroesophageal junction tumors is challenging. The therapy for these cancers usually consists of neoadjuvant chemoradiotherapy or perioperative chemotherapy followed by surgery. Different surgical approaches exist: both a total gastrectomy with a Roux-Y reconstruction or an esophagectomy with gastric tube reconstruction can be performed. An esophagectomy can be executed both transhiatally and transthoracically, with either an intrathoracic or cervical anastomosis. Additionally, the operative approach can be open, minimally invasive or hybrid. There is no substantial evidence which is the preferred procedure in terms of postoperative morbidity, mortality, pathology, health-related quality of life (HR-QoL), survival or health care costs [3-6]. In addition, the results could be conflicting for the different outcome parameters: an esophagectomy might result in a better long-term survival at the cost of a worse quality of life compared to a gastrectomy or vice versa. Furthermore, not all patients value these outcome parameters the same, as for some patients, survival is more important and for others quality of life. These issues complicate surgical decision making even more.

Functional complaints after Upper GI surgery such as reflux and nausea are common, posing a challenge in maintaining QoL. Therefore, it is of great importance to examine the effects of these operations in terms of functional complaints and HR-QoL in addition to short-term morbidity and long-term survival.

Few studies compared QoL following a total gastrectomy and a transthoracic esophagectomy using different HR-QoL questionnaires [7-10]. Three out of four of these studies show better HR-QoL after a total gastrectomy, with better global health, role, social functioning and less fatigue [8], better physical functioning and less dyspnea and reflux [9] and less gastrointestinal symptoms [7]. The follow-up time in these studies varied from three months to two years. However, these studies either had a low response rate (34.5% and 52.5%) [9, 10], a small sample size (N=27 and N=53) [7, 8] or patients with a distal esophageal cancer were not excluded [8]. The aim of this study was to investigate the differences in long-term HR-QoL domains in a large series of patients with a true GEJ or cardia carcinoma undergoing a total gastrectomy with a Roux-Y reconstruction versus a transthoracic esophagectomy

with gastric tube reconstruction with an intrathoracic anastomosis (Ivor Lewis) in a tertiary referral center.

METHODS

Study population

All patients following surgery for GEJ or cardia cancer defined as a tumor involving the GEJ with the epicenter within 2 cm of the cardia (true GEJ tumor) or a tumor in the gastric cardia without esophageal involvement (cardia cancer) attending the Amsterdam UMC (Location AMC) were asked to participate in the study when they visited the outpatient clinic between 2014 and 2018. Theoretically, all of these patients could have undergone either an esophagectomy or a gastrectomy for their GEJ/cardia tumor. Patients were included if they had undergone a total gastrectomy or an Ivor Lewis esophagectomy for a GEJ or cardia carcinoma with a minimum follow-up of one year (operated between 2010 and 2017). Patients with metastases, patients following a transhiatal esophagectomy, patients with a cervical anastomosis, patients with a recurrence or who died during follow-up were excluded. Also, patients after salvage esophagectomy or patients with a jejunal or colonic interposition were excluded. Official ethical approval for this study was waived by the Institutional Review Board of Amsterdam UMC (location AMC). This paper adheres to the STROBE guidelines for the reporting of prospective studies [11].

(Neo)adjuvant therapy

Patients scheduled for an esophagectomy were generally treated with neoadjuvant chemoradiotherapy according to the CROSS scheme [12], and patients for a gastrectomy were treated with perioperative chemotherapy consisting of EOX (epirubicine, oxaliplatin and capecitabine), based on the MAGIC study [13]. Some of the patients in the gastrectomy group received adjuvant chemoradiotherapy because of their participation in the CRITICS trial [14]. If the stomach involvement was more than 3 cm as evaluated by upper GI endoscopy perioperative chemotherapy instead of neoadjuvant chemoradiotherapy was administered to esophagectomy patients. A diagnostic laparoscopy was performed for advanced T stages (>T3) if the bulk of the tumor was located in the stomach before initiation of neoadjuvant therapy [15].

Surgery

The treatment plan including the surgical procedure was determined during the weekly Multi-Disciplinary Team meeting of the Amsterdam Gastrointestinal oncology outpatient clinic (GIOCA - Gastrointestinal oncologic center Amsterdam). If more than 2 cm ingrowth in the esophagus was seen and a gastric tube could still be performed (determined during diagnostic laparoscopy), an esophageal resection with gastric tube reconstruction was performed. If ingrowth in the stomach was extensive to a level that a gastric tube could

not be created, and ingrowth in the esophagus was limited, a gastrectomy was performed. If clinical lymph node metastases were present in locoregional lymph node stations that did not have an overlap between the esophageal and gastric cancer classification systems, this also influenced the choice for the surgical approach. Excluded were patients that had extensive tumor expansion in both the esophagus and stomach necessitating an esophagogastric resection with colonic interposition. In case of a total gastrectomy, a modified D2 lymphadenectomy was performed, including complete omentectomy with a Roux-Y reconstruction. In case of an esophagectomy a 2-field lymphadenectomy was performed, including the paratracheal lymph node stations and a gastric tube reconstruction with an intrathoracic anastomosis. Operations were performed using an open as well as a minimally invasive approach.

Follow-up

Outpatient clinic visits were scheduled every 3 months the first year and every 6 months the 2^{nd} – 4^{th} year, and once yearly until the 5^{th} postoperative year. No imaging was performed unless clinically indicated, in accordance with the Dutch guideline [16]

Baseline characteristics and perioperative morbidity

Clinical data were obtained from a prospectively maintained database of all operated patients with an esophageal or gastric cancer in the Amsterdam UMC (location AMC). This database includes patient and tumor characteristics such as age, gender, American Society of Anesthesiologists (ASA) classification and neoadjuvant therapy, details on surgical procedure and perioperative complications.

Health-related Quality of Life

The European Organization for Research and Treatment of Cancer (EORTC) quality of life questionnaires (EORTC QLQ-C30 and EORTC QLQ-OG25) were handed out during the outpatient clinic visits [17-19]. These questionnaires are validated for evaluating HR-QoL in cancer patients and patients with gastroesophageal cancer, respectively. The EORTC QLQ-C30 contains one global health score, five functional scores (physical, role, social, cognitive and emotional functioning) and nine symptom scores (fatigue, nausea and vomiting, pain, dyspnea, insomnia, appetite loss, constipation, diarrhea, financial difficulties). The EORTC QLQ-OG25 contains one functional score (body image) and 15 symptom scores (dysphagia, reflux, odynophagia and problems with eating with others, pain and discomfort, anxiety, problems with eating, dry mouth, trouble with taste, trouble with swallowing of saliva, choking when swallowing, trouble with coughing, trouble with talking, weight loss, hair loss).

All questions employ 4 response categories ranging from 1 (not at all) to 4 (very much), with the exception of two questions representing global health, whose response options ranged from 1 (very poor) to 7 (excellent). Questionnaire scores were linearly transformed

into scores ranging from 0 to 100 (best global health or functioning or worst symptoms) according to the scoring manual of the EORTC QoL Group [20].

Endpoints

The primary endpoints were three HR-QoL domains: 'nausea and vomiting', 'reflux' and 'problems with eating'. These domains were chosen during a consensus discussion between two surgeons, a medical psychologist and a PhD candidate (SSG, MIBH, MAGS & EJ). The 'nausea and vomiting', 'reflux' and 'problems with eating' domains were chosen because these symptoms occur most frequently during follow-up according to recent literature and professional experience [21]. The secondary endpoints were the remaining HR-QoL domains, postoperative complications (such as anastomotic leakage, atrial fibrillation and pulmonary complications) according to the ECCG criteria [22], Clavien-Dindo grade and pathology results (c/ypTNM stage, histology, R0 resection rate, (positive) lymph node count). All endpoints were measured after a follow up of more than one year.

Statistical analysis

Descriptive statistics were used for analysis of baseline and pathology characteristics as well as postoperative complications. These parameters were reported as proportions for binary or categorical variables, as means with standard deviations (SD) for parametric continuous variables, and as medians with interquartile ranges (IQR) for non-parametric continuous variables. Characteristics of both groups and postoperative morbidity outcomes were compared using the Mann-Whitney U test (for non-parametric continuous variables) or Student's t test (for parametric continuous variables) and the Chi^2 or Fisher's exact test for categorical data. Univariable linear regression analysis was performed to analyze QoL (sub)domain differences between the gastrectomy and esophagectomy groups. QoL (sub)domains with $p < 0.10$ were selected subsequently to be included in a multivariable linear regression analysis. The following variables were tested for confounding and effect modification: gender, age, ASA score and neoadjuvant therapy (yes/no). A variable was considered a confounder, if the β of remission changed more than 10%. The variable that resulted in the highest change in β was added first. The other variables were then again tested for confounding until the correlation coefficient of remission did not change >10% (adjusted model). Effect modification was tested using interaction terms. No significant effect modification for the tested variables was found. Results were presented with a mean difference between both groups and corresponding 95% confidence interval (CI). All P-values were based on a 2-sided test. Given the many outcomes the number of statistical tests relative to the sample size is large. Therefore, a stringent P-value below 0.01 was considered statistically significant. A difference in mean values of HR-QoL domains of more than 10 points between the two procedures was considered clinically relevant according to EORTC guideline [19]. Statistical analyses were performed in SPSS Statistics version 24.

RESULTS

Demographic and clinical characteristics

One-hundred-twenty-six eligible patients were asked to complete the questionnaires. The response rate was 80.2%, resulting in 101 included patients, 30 in the gastrectomy group and 71 in the esophagectomy group (Figure 1). Baseline characteristics of the study population are depicted in Table 1. Mean age was 63 years. Most patients were male (83.2%). Gender, ASA classification and comorbidities did not statistically differ between treatment groups. As expected, perioperative chemotherapy was applied more often in the gastrectomy group and neoadjuvant chemoradiotherapy more in the esophagectomy group. A minimally invasive operation was performed in 23 patients (76.6%) in the gastrectomy group and in 67 patients (94.4%) in the esophagectomy group (p = 0.015). Median follow-up was 24 months (range 12-84 months) in the gastrectomy group and also 24 months (range 12-72 months) in the esophagectomy group.

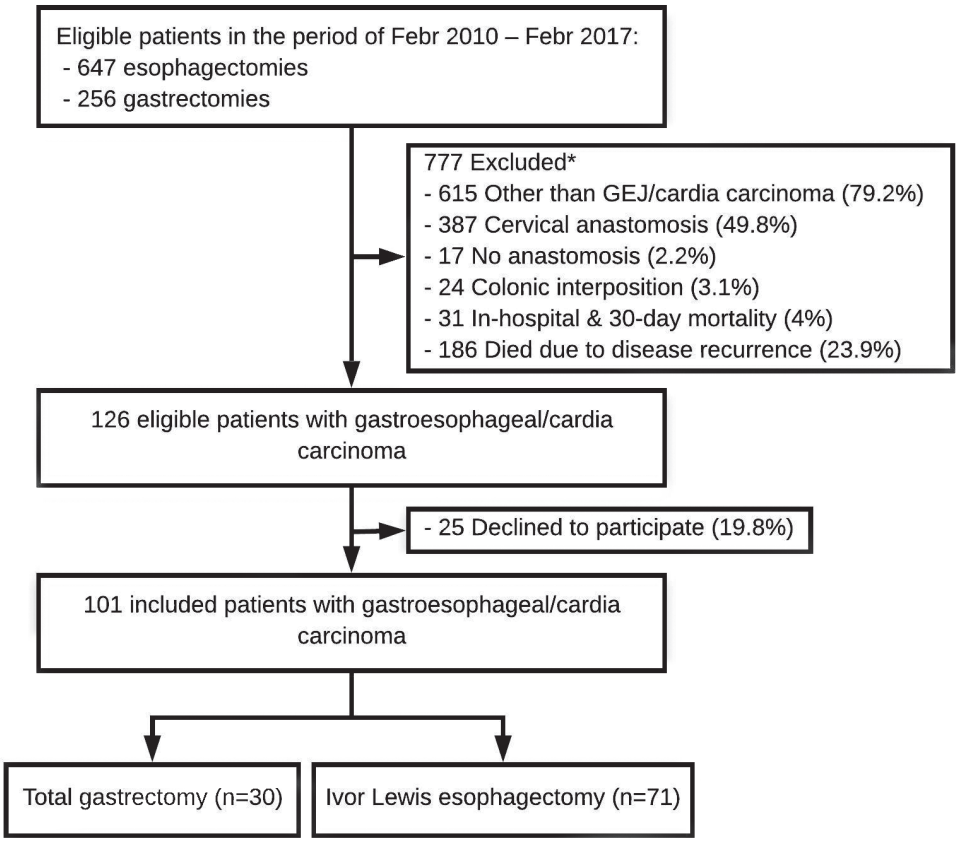

Figure 1: Study Flow Chart.

*=Excluded subcategories are not mutually exclusive.

Table 1: Baseline characteristics of patients with a junctional or cardia carcinoma operated with either total gastrectomy or Ivor Lewis esophagectomy in the period of 2010 – 2017.

			Total gastrectomy		Ivor lewis esophagectomy		Total		P-value
N			30		71		101		
Age (yrs)	**Mean, y, range**		65.9	(45-82)	61.8	(43-79)	63	(43-82)	**0.015**
Gender	**Male**		26	(89.7)	58	(81.7)	84	(83.2)	**0.541**
Follow-up	**Median, months, range**		24	(12-84)	24	(12-72)	24	(12-84)	**0.263**
Tumor location	**GEJ**		4	(13.3)	69	(97.2)	73	(72.3)	**<0.001**
	Cardia		26	(86.7)	2	(2.8)	28	(27.7)	
Comorbidity	**No**		9	(30)	35	(49.3)	44	(43.6)	**0.074**
	Cardiovascular		19	(63.3)	30	(42.3)	49	(48.5)	
	Pulmonal		4	(13.3)	4	(5.6)	8	(7.9)	
	Metabolic		8	(26.7)	11	(15.5)	19	(18.8)	
ASA classification	**1**		2	(6.7)	19	(26.8)	21	(20.8)	**0.057**
	2		19	(63.3)	31	(43.7)	50	(49.5)	
	3		9	(30)	21	(29.6)	30	(29.7)	
Neo-adjuvant therapy	**No**		5	(16.7)	8	(11.3)	13	(12.9)	**0.520**
	Yes	**Chemotherapy**	24	(80)	5	(7.0)	29	(28.7)	**<0.001**
		Chemoradiotherapy	1	(3.3)	58	(81.7)	59	(58.4)	
Approach	**Open**		7	(23.3)	4	(5.6)	11	(10.9)	**0.015**
	Minimally invasive		23	(76.6)	67	(94.4)	90	(89.1)	
cT	**T0**		1	(3.3)	1	(1.4)	2	(2)	**0.618**
	T1		4	(13.3)	8	(11.3)	12	(11.9)	
	T2		8	(26.7)	18	(25.4)	26	(25.7)	
	T3		16	(53.3)	43	(60.6)	59	(58.4)	
	T4		1	(3.3)	1	(1.4)	2	(2)	
cN	**N0**		14	(46.7)	34	(47.9)	48	(47.5)	**0.710**
	N1		10	(33.3)	25	(35.2)	35	(34.7)	
	N2		5	(16.7)	9	(12.7)	14	(13.9)	
	N3		1	(3.3)	3	(4.2)	4	(4)	
cM	**cM0**		30	(100)	71	(100)	101	(100)	**na**
Adjuvant therapy	**No**		5	(16.7)	51	(71.8)	56	(55.4)	**<0.001**
	Yes	**Chemotherapy**	20	(66.7)	19	(26.8)	39	(38.6)	**0.610**
		Chemoradiotherapy	3	(10)	1	(1.4)	4	(4.0)	

Data are presented as n (%) unless otherwise indicated. na=not applicable. cTNM staging classification before the treatment (AJCC 8th edition).

ENDPOINTS

Primary endpoints

The results of the multivariable analysis of HR-QoL domains are presented in table 2. Additional data of univariable analysis is given in Online Resource. The difference between the mean scores of the 'problems with eating' domain was more than 10 points, which makes the difference clinically relevant. However, no significant difference was found in 'problems with eating', 'reflux' or 'nausea and vomiting' between the gastrectomy and esophagectomy groups.

Secondary endpoints: remaining HR-QoL domains

Of the remaining HR-QoL domains, patients after total gastrectomy reported significantly 'less choking when swallowing' (p=0.001) and 'trouble with coughing' (p<0.001). These differences were also clinically relevant according to EORTC as the difference in mean scores was more than 10 points in both domains. No significant differences were found in 'global health', any of the functioning scores, 'fatigue', 'pain', 'dyspnea', 'insomnia', 'appetite loss', 'constipation', 'diarrhea', 'financial difficulties', 'dysphagia', 'odynophagia', 'pain and discomfort', 'anxiety', 'eating with others', 'dry mouth', 'trouble with taste' or 'swallowing saliva', 'trouble with talking', 'weight loss' and 'hair loss' between the gastrectomy and esophagectomy groups.

Table 2: Multivariable analysis of difference in EORTC QLQ-30 and QLQ-OG25 questionnaire' domains between patients treated with gastrectomy (N=30) and Ivor Lewis esophagectomy (N=71).

	Covariates	B	95% CI		P-value
			Lower	Upper	
Insomnia	Total gastrectomy	-6.452	-11.922	-0.981	0.021
	Gender	-	-	-	-
	Age	-	-	-	-
	Neoadjuvant therapy	-	-	-	-
	ASA*				
	ASA score (2)	16.734	3.669	29.799	0.013
	ASA score (3)	14.148	0.086	28.21	0.049
Appetite loss	Total gastrectomy	4.426	-1.504	10.356	0.142
	Gender	-	-	-	-
	Age	0.332	-0.275	0.938	0.281
	Neoadjuvant therapy	-	-	-	-
	ASA*				
	ASA score (2)	6.489	-7.591	20.568	0.363
	ASA score (3)	-2.426	-17.545	12.693	0.751
Diarrhea	Total gastrectomy	3.948	-1.505	9.401	0.154
	Gender	-	-	-	-
	Age	-	-	-	-
	Neoadjuvant therapy	-	-	-	-
	ASA*				
	ASA score (2)	5.974	-7.049	18.997	0.365
	ASA score (3)	0.606	-13.411	14.623	0.932
Dysphagia	Total gastrectomy	3.024	-0.028	6.077	0.052
	Gender	-	-	-	-
	Age	-	-	-	-
	Neoadjuvant therapy	-	-	-	-
	ASA*				
	ASA score (2)	5.111	-2.178	12.401	0.167
	ASA score (3)	2.872	-4.974	10.718	0.469
Eating	Total gastrectomy	5.366	0.595	10.137	0.028
	Gender	-	-	-	-
	Age	0.338	-0.156	0.832	0.177
	Neoadjuvant therapy	-	-	-	-
	ASA*				
	ASA score (2)	-	-	-	-
	ASA score (3)	-	-	-	-

Table 2: Continued

	Covariates	B	95% CI		P-value
			Lower	Upper	
Odynophagia	Total gastrectomy	4.810	1.010	8.611	0.014
	Gender	-	-	-	-
	Age	-	-	-	-
	Neoadjuvant therapy	-	-	-	-
	ASA*				
	ASA score (2)	6.249	-2.835	15.334	0.175
	ASA score (3)	7.348	-2.386	17.081	0.137
Dry mouth	Total gastrectomy	2.908	-2.77	8.586	0.312
	Gender	-	-	-	-
	Age	0.201	-0.379	0.782	0.493
	Neoadjuvant therapy	-	-	-	-
	ASA*				
	ASA score (2)	13.786	0.304	27.268	0.045
	ASA score (3)	1.904	-12.573	16.381	0.795
Choked when swallowing	Total gastrectomy	-5.952	-9.437	-2.466	**0.001**
	Gender	-	-	-	-
	Age	-	-	-	-
	Neoadjuvant therapy	-	-	-	-
	ASA*				
	ASA score (2)	-	-	-	-
	ASA score (3)	-	-	-	-
Trouble with coughing	Total gastrectomy	-13.084	-18.525	-7.643	**<0.001**
	Gender	-	-	-	-
	Age	-	-	-	-
	Neoadjuvant therapy	-	-	-	-
	ASA*				
	ASA score (2)	12.52	-0.416	25.455	0.058
	ASA score (3)	10.675	-3.482	24.832	0.138
Weight loss	Total gastrectomy	4.132	-1.181	9.445	0.126
	Gender	-	-	-	-
	Age	0.666	0.117	1.214	0.018
	Neoadjuvant therapy	-	-	-	-
	ASA*				
	ASA score (2)	-	-	-	-
	ASA score (3)	-	-	-	-

*=Relative to reference (ASA = 1). Bold values represent significance. B=regression coefficient, CI=confidence interval. Ivor Lewis esophagectomy is the reference to which total gastrectomy is compared.

Secondary endpoints: perioperative morbidity

The occurrence of postoperative complications did not significantly differ between the two groups (Table 3). Especially, no significant difference in atrial fibrillation, anastomotic leakage, pneumonia and Clavien-Dindo classification was found between the gastrectomy and the esophagectomy group.

Table 3: Postoperative complications of patients (N=101) with a GEJ or cardia carcinoma operated with either total gastrectomy or Ivor Lewis esophagectomy in the period of 2010 – 2017.

		Total gastrectomy N = 30		Ivor Lewis esophagectomy		P-value
Postoperative complications	**No**	16	(53.3)	39	(54.9)	**0.883**
	Yes	14	(46.7)	32	(45.1)	
	Atrial fibrillation	2	(6.7)	14	(19.7)	**0.139**
	Anastomotic leakage	7	(23.3)	6	(8.5)	**0.054**
	Pneumonia	3	(10.0)	7	(9.9)	**0.983**
	Other	12	(40.0)	27	(38.0)	**0.852**
Clavien-Dindo classification	**Grade 1**	0		7	(9.9)	**0.262**
	Grade 2	3	(10.0)	11	(15.5)	
	Grade 3A	3	(10.0)	9	(12.7)	
	Grade 3B	0		1	(1.4)	
	Grade 4A	6	(20.0)	7	(9.9)	
	Grade 4B	0		3	(4.2)	

Data are presented as n (%) unless otherwise indicated. Clavien-Dindo classification grade 5 is excluded from this study.

Secondary endpoints: pathology results

Pathology results are displayed in table 4. Most patients in both groups presented with an adenocarcinoma (98 patients). In the gastrectomy group 26 patients had a cardia carcinoma, and 4 patients had a GEJ tumor. In the esophagectomy group 69 patients had a GEJ tumor and 2 patients had cardia carcinoma. cT3 and cN0 were most often seen in both groups. In both the gastrectomy and esophagectomy group, one patient had an R1 resection (3.3% vs 1.4%, p=0.508). In the esophagectomy group significantly more lymph nodes were resected (p=0.008), however no difference in lymph node metastases was found. In addition, there were no significant differences in tumor regression grade.

Table 4: Pathology results of patients (N=101) with a junctional or cardia carcinoma operated with either total gastrectomy or Ivor Lewis esophagectomy in the period of 2010 – 2017.

		Total gastrectomy N = 30		Ivor Lewis esophagectomy N = 71		P-value
Histologic type	Adenocarcinoma	28	(93.3)	70	(98.6)	**0.508**
	Other	2	(6.6)	1	(1.4)	
(y)pT	T0	4	(13.3)	16	(22.5)	**0.373**
	T1	6	(20.0)	21	(29.6)	
	T2	4	(13.3)	3	(4.2)	
	T3	13	(43.3)	31	(43.7)	
	T4	3	(10.0)	0		
(y)pN	N0	16	(53.3)	43	(60.6)	**0.692**
	N1	9	(30.0)	19	(26.8)	
	N2	2	(6.7)	4	(5.6)	
	N3	3	(10.0)	5	(7.0)	
(y)pM	cM1	0		0		**na**
Radicality	R0	29	(96.7)	70	(98.6)	**0.508**
	R1	1	(3.3)	1	(1.4)	
Lymph nodes	Median (range)	22	(12-41)	29	(4-56)	**0.008**
Lymph node metastases	Median (range)	0	(0-12)	0	(0-16)	**0.241**
Tumor response after neoadjuvant therapy	Total	4	(13.3)	17	(23.9)	**0.970**
	Partial	14	(46.7)	29	(40.9)	
	None	7	(23.3)	17	(23.9)	

Data are presented as n (%) unless otherwise indicated. c/pM metastases. na = not applicable.

DISCUSSION

This study describes the difference in long-term quality of life in disease-free patients who underwent either a total gastrectomy or an Ivor Lewis esophagectomy for GEJ or cardia cancer. We found no significant difference in the primary endpoint HR-QoL domains 'problems with eating', 'reflux' and 'nausea and vomiting'. Of the secondary HR-QoL endpoints significantly less 'problems with choking when swallowing' and 'coughing' were found after gastrectomy. These differences were also clinically relevant. No significant differences were found in the occurrence and grade of postoperative complications. Furthermore, more lymph nodes were resected during esophagectomy with an equal number of positive lymph nodes and an equal R0 resection rate.

In the few studies on long-term HR-QoL in patients with GEJ carcinoma after esophagectomy or gastrectomy an overall decrease in HR-QoL was observed after esophago-gastric surgery, which restored within 6-12 months in disease-free patients [10, 23-25]. Generally, better global health and functional outcomes such as role and social functioning are found after a total gastrectomy compared to esophagectomy [8]. Also less fatigue, pneumonia and reflux related symptoms are found after gastrectomy compared to esophagectomy [8, 9]. Our results are different compared to these studies as no significant difference in global health

or functioning domains were found. Furthermore, no significant difference was found in reflux or fatigue scores. The former studies were heterogenous with respect to included patients (e.g. both distal esophageal, GEJ and cardia cancer) [8] and baseline characteristics (age, gender, co-morbidity, neoadjuvant therapy, open/minimally invasive approach) [7-10]. In three of these studies no correction for confounders was performed [7-9]. Furthermore, these studies had either a low response rate (34.5% and 52.5%) [9, 10] or a small sample size (N=27 and N=53) [7, 8]. In addition, except for the study by *Fuchs et al.*, follow-up was short, ranging from three to six months [7, 8, 10]. The current study describes a large patient cohort with a true GEJ/cardia carcinoma with a high response rate and long follow-up time. In addition, correction for confounders such as differences in baseline characteristics was performed. The long follow-up time decreased the influence of surgical approach (open versus minimally invasive) and neoadjuvant therapy (chemo- or chemoradiotherapy) on HR-QoL.

No significant difference was found in postoperative complications and Clavien-Dindo classification. More specifically, no differences were observed in anastomotic leakage rates between the groups, which corresponds with the findings of *Schumacher et al.* who compared a transthoracic esophagectomy (N=29) with a gastrectomy (N=67) in GEJ carcinoma [26]. They did find a significant difference in the occurrence of atrial fibrillation between the two groups, which can be explained by the transthoracic phase of the procedure in Ivor Lewis esophagectomy. This finding corresponds to those of other recent studies. The study of *Lohani et al.* found that the transthoracic approach (N=134) was an independent risk factor for the development of atrial fibrillation after surgery compared to transhiatal approach (N=58) [27]. In our study we did not observe such difference and the complication rate is comparable to that of other studies [14, 28, 29]. In the present study a minimally invasive approach was performed in 94.4% of the patients in the esophagectomy group. The open approach with right thoracotomy is well known to account for the majority of postoperative pulmonary complications (both pneumonia and pleural effusion) which drop significantly when adopting the minimally invasive approach [30]. The similar rate reported between the gastrectomy and the esophagectomy groups in postoperative pulmonary complications as well as the comparable results in symptoms such dyspnea could be explained by the reduced pulmonary surgical trauma.

There are limitations of this study that merit attention. Patients who did not participate in the study could have had a worse or better HR-QoL. However, a response rate of 80.2% was achieved, which is higher than the response rates published in recent studies [9, 10]. More importantly, baseline HR-QoL data is lacking. It remains unknown whether the treatment groups differed *a priori* with respect to HR-QoL and how HR-QoL may have changed over time. Two ongoing studies are relevant in this respect as they include a baseline. The RENAISSANCE trial in Germany investigates the effect of chemotherapy alone

versus chemotherapy followed by surgery on survival and HR-QoL in patients with limited-metastatic adenocarcinoma of the stomach or esophagogastric junction [31]. The POCOP cohort study in the Netherlands is set up to obtain clinical and HR-QoL data from patients with esophageal and gastric cancer at different points over time [32]. Furthermore, the two treatment groups differed with respect to sample size (30 vs 71) and baseline characteristics, with more patients having received chemoradiotherapy and significantly more minimally invasive procedures in the esophagectomy group. For most of these baseline characteristics statistical correction was performed. One should keep in mind that we could not adjust for all differences, in this naturally occurring sample. Conducting a randomized clinical trial with a sufficiently large number of patients with true GEJ carcinoma is a challenge that has yet to be taken up. Moreover, given the many outcomes the number of statistical tests relative to the sample size is large. However, a stringent P-value of <0.01 for significance was chosen to counteract this obstacle. Although we distinguished between primary and secondary outcomes, some of the results may have been found by chance. Moreover, the results of morbidity and pathology are biased by the inclusion criteria (alive and disease-free) and are therefore only applicable on the selected group of patients in this study with a long recurrence-free survival. Finally, the inclusion criterion 'alive and disease-free' precluded the investigation of a possible long-term survival difference between the two treatment groups. Conflicting results for HR-QoL and survival may be observed in such a study, and, additionally, individual patients may also value QoL and survival differently, making both endpoints essential subjects for future research projects. Yet, this study currently provides the most reliable long-term HR-QoL data.

In conclusion, after a follow-up of more than one year no significant difference was found in 'problems with eating', 'reflux' or 'nausea and vomiting'. Of the less clinically relevant HR-QoL domains 'choking when swallowing' and 'coughing' were found to be significantly less common in the gastrectomy group. No significant difference was found in postoperative complications or radicality of surgery. Based on this study it is difficult to determine a priori which procedure for GEJ cancer is to be preferred. However, the study provides important information on long-term HR-QoL following major Upper GI surgery. Patients may be informed about the HR-QoL domains that are likely to be affected by the different surgical procedures, which in turn may support shared decision making when a choice between the two treatment options is possible. A multicenter randomized trial examining long term HR-QoL, postoperative complications and pathology results in patients with GEJ or cardia carcinoma is the logical, much needed, next step.

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SUPPLEMENT

Table 5: Univariable and multivariable linear regression analysis of EORTC QLQ-C30 and EORTC QLQ-OG25 questionnaires' domains between total gastrectomy and Ivor Lewis esophagectomy.

	Univariable analysis						Multivariable analysis^			
	Total gastrectomy	Ivor Lewis	B	95% CI		P-value	B	95%CI		P-value
	n=30	n=71		Lower	Upper			Lower	Upper	
EORTC QLQ-C30										
Global health	71.4 (18.8)	76.1 (19.4)	-2.3	6.494	1.815	0.267				
Functioning										
Physical functioning	80.2 (17.9)	80.3 (21.3)	-0.03	-4.439	4.371	0.988				
Role functioning	75.5 (26.5)	70.2 (34.4)	2.7	-4.300	9.656	0.448				
Emotional functioning	82.8 (17.6)	74.5 (33.5)	4.1	-2.284	10.576	0.204				
Cognitive functioning	86.7 (18.3)	76.2 (33.7)	5.2	-1.247	11.731	0.112				
Social functioning	80.6 (23.2)	72.7 (33.7)	3.9	-2.752	10.649	0.245				
Symptom scores										
Fatigue	30.9 (24.4)	24.7 (23.4)	3.1	-1.989	8.237	0.228				
Nausea and vomiting	15.0 (22.5)	9.3 (17.9)	2.9	-1.313	7.032	0.177				
Pain	12.8 (19.4)	15.3 (19.4)	2.9	-1.270	-5.458	0.549				
Dyspnea	15.6 (22.7)	20.7 (23.4)	-2.6	-7.569	2.466	0.315				
Insomnia	11.1 (20.2)	20.7 (26.9)	-4.8	-10.210	0.659	0.084*	-6.5	-11.922	-0.981	0.021
Appetite loss	23.3 (32.9)	11.9 (23.0)	5.7	0.051	11.426	0.048*	4.4	-1.504	10.356	0.142
Constipation	8.9 (19.4)	5.0 (11.5)	1.9	-1.167	5.002	0.220				
Diarrhea	22.2 (30.7)	13.2 (21.3)	4.5	-0.738	9.812	0.091*	3.9	-1.505	9.401	0.154
Financial difficulties	10.0 (15.5)	8.6 (18.8)	0.7	-3.160	4.590	0.715				
EORTC QLQ-OG25										
Functioning										
Body image	85.1 (22.9)	78.2 (33.9)	3.4	-3.377	10.258	0.319				
Symptom scores										
Dysphagia	14.1 (18.0)	7.0 (11.5)	3.5	0.570	6.496	0.020*	3.0	-0.028	6.077	0.052
Eating	30.6 (22.0)	18.5 (21.5)	6.1	1.376	10.740	0.012*	5.4	0.595	10.137	0.028
Reflux	19.4 (21.9)	20.4 (28.7)	5.3	-0.491	-6.304	0.867				
Odynophagia	18.0 (24.2)	7.1 (12.9)	5.5	1.757	9.143	0.004*	4.8	1.010	8.611	0.014
Pain and discomfort	18.5 (25.5)	13.4 (17.9)	2.6	-1.975	7.101	0.265				
Anxiety	27.2 (26.1)	21.8 (21.9)	2.7	-2.293	7.739	0.284				
Eating with others	8.0 (14.5)	7.0 (17.4)	0.5	-3.136	4.136	0.786				
Dry mouth	23.3 (29.2)	14.0 (24.0)	4.7	-0.855	10.216	0.097*	2.9	-2.770	8.586	0.312
Trouble with taste	17.0 (27.2)	9.4	3.8	-0.937	8.543	0.115				
Trouble swallowing saliva	5.6 (15.4)	(19.358)	-0.3	-3.718	3.111	0.860				
Choked when swallowing	2.2 (8.5)	6.2 (15.9)	-6.0	-9.437	-2.466	0.001*	-6.0	-9.437	-2.466	**0.001**
Trouble with coughing	8.9 (15.0)	14.1 (18.4)	-11.8	-17.129	-6.472	0.000*	-13.1	-18.525	-7.643	**<0.001**
Trouble talking	6.7 (16.1)	32.5 (27.6)	-0.7	-4.071	2.646	0.675				
Weight loss	27.8 (27.8)	8.1 (15.2)	5.5	0.172	10.812	0.043*	4.1	-1.181	9.445	0.126
Hair loss	21.4 (33.6)	16.8 (23.0) 18.6 (22.7)	1.4	-6.889	9.757	0.730				

High mean values in Global health and functioning scores show better results, high mean values in symptom scores show worse results. Total gastrectomy and Ivor Lewis data are represented as mean (standard deviation). Regression coefficient (B) with 95% confidence interval (CI) are shown for univariable and multivariable analysis. Bold values represent significance. ^=Corrected for age, gender, ASA classification or neoadjuvant therapy. *=Health related quality of life (HR-QoL) domains with p<0.1 in univariate analysis were entered in multivariable analysis where they were corrected for age, gender, ASA classification and/or neoadjuvant therapy in case of confounding.

Chapter 3

Long-term health-related quality of life after McKeown and Ivor Lewis esophagectomy for esophageal carcinoma

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ABSTRACT

Introduction

Transthoracic esophagectomy with a cervical (McKeown) or an intrathoracic (Ivor Lewis) anastomosis are both surgical procedures that can be performed for distal esophageal or gastro-esophageal junction cancer. The purpose of this study was to investigate long-term health-related quality of life (HR-QoL) after McKeown and Ivor Lewis esophagectomy in a tertiary referral center.

Methods

Disease-free patients > 1 year following a McKeown or an Ivor Lewis esophagectomy with a 2-field lymphadenectomy for a distal or gastro-esophageal junction (GEJ) carcinoma visiting the outpatient clinic between 2014 and 2018 were asked to complete the EORTC QLQ-C30 and EORTC QLQ-OG25 questionnaires. HR-QoL was investigated in both groups.

Results

A total of 89 patients were included after McKeown and 115 after Ivor Lewis esophagectomy. Median follow-up was 2.4 years (IQR 1.7-3.6). Patients after McKeown esophagectomy reported more problems with 'eating with others' compared to patients after Ivor Lewis esophagectomy (mean scores: 49.9 vs 38.8). This difference was both clinically relevant and significant after correction for multiple testing (β=11.1, 95% CI 3.105 – 19.127, p=0.042). Patients in both groups reported a poorer HR-QoL (≥ 10 points) than the general population with respect to nausea and vomiting, dyspnea, appetite loss, financial difficulties, problems with eating, reflux, eating with others, choked when swallowing, trouble with coughing and weight loss.

Conclusion

Long-term HR-QoL of disease-free patients following a McKeown or Ivor Lewis esophagectomy for a distal or GEJ carcinoma is largely comparable. Irrespective of the surgical technique, patients' HR-QoL following esophagectomy is compromised. When given the choice, patients should be informed that after a McKeown esophagectomy more problems with eating with others can occur.

INTRODUCTION

Treatment of esophageal cancer usually consists of surgery with neoadjuvant or perioperative chemo(radio)therapy. In most cases a transthoracic esophagectomy with gastric tube reconstruction is performed with either an intrathoracic (Ivor Lewis) or cervical anastomosis (McKeown) [1]. Whether a cervical or intrathoracic anastomosis is performed mainly depends on the surgeon's experience, since in the Netherlands, both operations are still standard of care for patients with a distal esophageal or gastro-esophageal junction carcinoma. Both procedures are associated with considerable postoperative morbidity and an impairment in health-related quality of life (HR-QoL) with symptoms of reflux, dysphagia and fatigue [2-4]. Whether HR-QoL differs between a McKeown and Ivor Lewis esophagectomy is not well studied. A recent systematic review found significantly more anastomotic leakages following a McKeown esophagectomy, which may be due to the longer gastric tube with likely a more impaired perfusion at the tip of the gastric tube than in the shorter gastric tube after Ivor Lewis [5]. Such postoperative morbidity could have an adverse effect on long-term HR-QoL [6]. However, this meta-analysis included mainly small retrospective cohort studies that employed different definitions of outcome parameters. Moreover, during a McKeown esophagectomy the recurrent laryngeal nerve in the cervical region may be damaged, leading to hoarseness and swallowing problems [7]. The consequences of recurrent laryngeal nerve injury will likely negatively impact QoL, however, this has not yet been investigated. Studies comparing Ivor Lewis and McKeown with regard to HR-QoL did not find significant differences between the two procedures [4, 8], except for one study where significantly more pain and obstipation after Ivor Lewis esophagectomy was observed [9].

The aim of this study was to investigate long-term HR-QoL in disease-free patients having undergone either a transthoracic esophagectomy with gastric tube reconstruction with a cervical anastomosis (McKeown) or an intrathoracic anastomosis (Ivor Lewis) for a distal esophageal or gastro-esophageal junction (GEJ) carcinoma in a tertiary referral center.

METHODS

Study design, patient population, and clinical data

A prospective cohort study was performed in the Amsterdam UMC (location AMC). All patients attending the outpatient clinic > 1 year after a McKeown or an Ivor Lewis esophagectomy for a distal esophageal or GEJ carcinoma, in the period between 2014 and 2018, were eligible. After giving oral informed consent, patients were asked to complete quality of life questionnaires. Exclusion criteria were a mid or proximal esophageal tumor, cervical lymph node metastases, salvage esophagectomy, jejunal or colonic interposition or

recurrence or death during follow-up. In these patients with a distal or GEJ tumor technically both a McKeown and an Ivor Lewis esophagectomy are possible.

All clinical data (baseline patient, tumor, treatment characteristics and postoperative morbidity variables) for this study was obtained from a prospectively maintained database of all surgical patients with esophageal or gastric cancer from Amsterdam UMC (location AMC). Age, gender, tumor location, comorbidities (cardiovascular, pulmonal or metabolic), ASA classification, neoadjuvant therapy (chemotherapy/chemoradiotherapy), surgical approach (open/minimally invasive), cTNM stage, adjuvant therapy (chemotherapy/ chemoradiotherapy), histologic tumor type (adenocarcinoma, squamous cell carcinoma or other), (y)pTNM stage, radicality of surgery, (positive) lymph node yield and tumor response after neoadjuvant therapy were recorded. Anastomotic leakage, pneumonia, atrial fibrillation, recurrent nerve palsy, other complications and Clavien-Dindo grade were also recorded according to the ECCG criteria [10].

The need for ethical approval was waived by the Institutional Review Board of the Amsterdam UMC (location AMC) and therefore written informed consent was not needed. To strengthen the reporting of results and composition of this article the STROBE checklist was used [11].

Surgery and (neo)adjuvant therapy

All patients were discussed during the weekly Multi-Disciplinary Team meeting at the Gastrointestinal Oncology Centre Amsterdam (GIOCA). Operations were minimally invasive or open depending on tumor characteristics (open in case of close relation to trachea or bulky paratracheal lymph nodes), patient characteristics (open in case of previous open surgery or gastric surgery) and time period (before and after implementation of minimally invasive surgery in 2009). A 2-field lymphadenectomy (lymph node stations 2 on indication, 4, 7, 8, 9, 15-20 according to the 8th edition of the AJCC) was performed with a gastric tube reconstruction and a cervical or intrathoracic anastomosis. The location of the anastomosis mainly depended on the time period that patients were operated. Before 2013 a McKeown procedure was the preferred operation, also for distal esophageal and GEJ cancer. In 2013 the (minimally invasive) Ivor Lewis procedure was adopted and became the standard approach for distal and GEJ cancer. Chemoradiotherapy was administered according to the CROSS schedule if indicated (≥cT2N0-3M0 or cT1N+) [12]. If tumor involvement in the stomach was more than 2 cm, perioperative chemotherapy was generally administered.

Follow-up

All patients completed the questionnaires during postoperative out-patient clinic visits, varying from one to six years postoperatively. During these visits a medical history and physical examination were performed with additional imaging only in case of complaints or if disease recurrence was suspected (in accordance with the Dutch guideline [13]).

Endpoints: Health-related Quality of Life

For the evaluation of HR-QoL, the EORTC QLQ-C30 and EORTC QLQ-OG25 questionnaires were used [14]. The EORTC QLQ-C30 is validated for cancer patients. It consists of 28 questions employing response categories ranging from 1 (not at all) to 4 (very much) and two questions with response options ranging from 1 (very poor) to 7 (excellent). 15 HR-QoL domain scores are calculated from this questionnaire. The EORTC QLQ-OG25 is designed and validated for GEJ cancer patients and consists of 25 questions of which 16 HR-QoL domains are calculated.

The EORTC scoring system was used [15-17]. All answers were linearly transformed to scores ranging from 0 to 100. Mean values of HR-QoL domains were calculated for each surgical approach separately. A higher mean score in 'global health' and functioning domains represent better QoL and functioning. A higher mean symptom score represents higher level of symptoms.

Statistical analysis

Background (baseline and postoperative morbidity) characteristics were analyzed with Chi^2 or Fischer's exact tests when appropriate in case of categorical variables. In case of continues variables, Student's t test or Mann-Whitney U test were used for respectively normally distributed or not normally distributed variables.

The differences in QoL (sub)domains between McKeown and Ivor Lewis esophagectomies were analyzed using univariable and multivariable linear regression analysis. QoL (sub) domains with $p < 0.10$ in the univariable linear regression analysis were entered in multivariable linear regression analysis. Background variables showing a difference ($p < 0.10$) between the surgical groups were tested for confounding. If a variable caused a clinically relevant effect (>10% change in regression coefficient), this variable was considered a confounder and was added to the multivariable model. The Bonferroni method was used to correct for multiple testing after multivariable linear regression analysis by multiplying the p-value by the number of multivariable tests performed. The HR-QoL of both groups was compared to the HR-QoL of the general population using the EORTC reference values manual [18, 19]. Mean score differences of ≥ 10 points were considered meaningful. Also, a subgroup analysis was performed for patients with no or minor postoperative complications (Clavien-Dindo grade 0-2), to exclude the influence of severe postoperative complications on HR-QoL. 2-sided test was used and statistical significance was set at a p-value below 0.05. Again, a difference of ≥ 10 points in mean scores of the HR-QoL domains were considered clinically relevant according to EORTC guideline [20]. SPSS Statistics version 24 was used for all statistical analyses.

RESULTS

Patients

Baseline characteristics are displayed in table 1. A total of 204 of 335 patients were included (response rate 60.9%). Clinical information of patients who declined participation was not recorded due to data protection regulations. Eighty-nine patients were treated with a McKeown esophagectomy and 115 with an Ivor Lewis esophagectomy (figure 1). Median age was 65 years (IQR 58-71), the majority of patients were men (77.9%), had a distal esophageal adenocarcinoma (84.8%) and an ASA classification of 2 (48.5%). Median follow-up was 3.3 years (IQR 2.0-4.1) following McKeown and 2.1 (IQR 1.5-2.9) following Ivor Lewis ($p<0.001$). There was no significant difference in comorbidities between the two groups. Significantly more minimally invasive surgery was performed in the Ivor Lewis group compared to McKeown group (96.5% vs 84.3%, $p=0.002$). Chemoradiotherapy was the preferred neoadjuvant therapy in both groups ($p=0.649$). Significantly more anastomotic leakages (24.7% vs 8.7%; $p=0.002$) and recurrent nerve palsy (7.9% vs 1.7%, $p=0.043$) occurred after a McKeown esophagectomy. No significant difference was found in the incidence of atrial fibrillation, pneumonia or other complications, and Clavien-Dindo grade between the two groups (table 2).

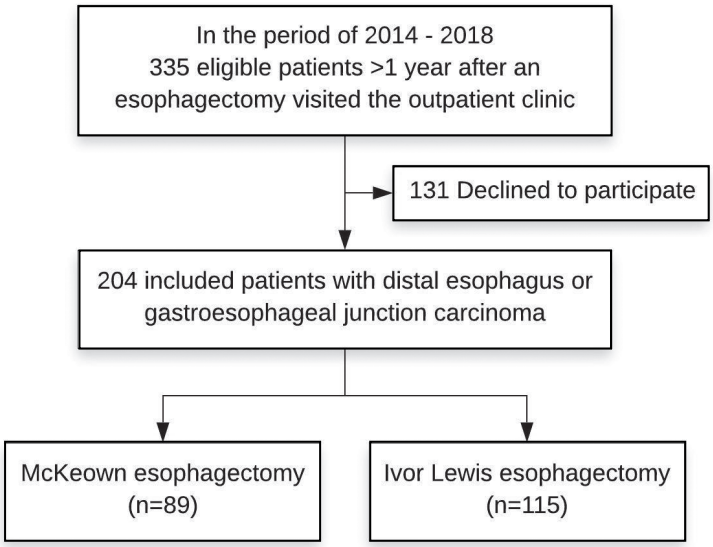

Figure 1: Study Flow Chart.

Table 1: Background baseline characteristics.

			Total		McKeown		Ivor Lewis		p-value
N			204		89		115		
Age (median (IQR), y)			65	(58-71)	64	(59.5-72)	67	(56-69)	**0.011**
Gender	**Male**		159	(77.9)	64	(71.9)	95	(82.6)	0.068
Tumor location	**Distal esophagus**		173	(84.8)	75	(84.3)	98	(85.2)	0.852
	GEJ		31	(15.2)	14	(15.7)	17	(14.8)	
Comorbidity	**No**		103	(50.5)	50	(47.2)	61	(53.0)	0.407
	Cardiovascular		86	(42.2)	39	(43.8)	47	(40.9)	0.672
	Pulmonal		14	(6.9)	8	(9.0)	6	(5.2)	0.291
	Metabolic		22	(10.8)	10	(11.2)	12	(10.4)	0.855
ASA classification	**1**		63	(30.9)	23	(25.8)	40	(34.8)	0.240
	2		99	(48.5)	49	(55.1)	50	(43.5)	
	3		42	(20.6)	17	(19.1)	25	(21.7)	
Neoadjuvant therapy	**No**		34	(16.7)	20	(22.5)	14	(12.2)	0.059
	Yes	**Chemotherapy**	5	(2.5)	1	(1.1)	4	(3.5)	0.649
		Chemoradiotherapy	165	(80.9)	68	(76.4)	97	(84.3)	
Approach	**Open**		18	(8.8)	14	(15.7)	4	(3.5)	**0.002**
	Minimally invasive		186	(91.2)	75	(84.3)	111	(96.5)	
cT	**T0**		6	(2.9)	5	(5.6)	1	(0.9)	0.298
	T1		29	(14.2)	14	(15.7)	15	(13.0)	
	T2		53	(26.0)	24	(27.0)	29	(25.2)	
	T3		114	(55.9)	44	(49.4)	70	(60.9)	
	T4		2	(1.0)	2	(2.2)	0	0	
cN	**N0**		90	(44.1)	38	(42.7)	52	(45.2)	0.680
	N1		76	(37.3)	32	(36.0)	44	(38.3)	
	N2		35	(17.2)	19	(21.3)	16	(13.9)	
	N3		3	(1.5)	0	0	3	(2.6)	
cM	**cM0**		204	(100)	89	(100)	115	(100)	1.000
Adjuvant therapy	**No**		179	(87.7)	86	(96.6)	93	(80.9)	**0.001**
	Yes	**Chemotherapy**	22	(10.8)	2	(2.2)	20	(17.4)	0.330
		Chemoradiotherapy	3	(1.5)	1	(1.1)	1	(1.7)	
Histologic type	**Adenocarcinoma**		164	(80.4)	60	(67.4)	103	(89.6)	**<0.001**
	Squamous cell carcinoma		33	(16.2)	24	(27.0)	9	(7.8)	
	Other		7	(3.4)	4	(4.5)	3	(2.6)	
pT	**T0**		55	(27.0)	23	(25.8)	32	(27.8)	0.491
	T1		55	(27.0)	28	(31.5)	27	(23.5)	
	T2		25	(12.3)	12	(13.5)	13	(11.3)	
	T3		69	(33.8)	26	(29.2)	43	(37.4)	
	T4		0	0	0	0	0	0	
pN	**N0**		140	(68.6)	64	(71.9)	76	(66.1)	0.487
	N1		45	(22.1)	19	(21.3)	26	(22.6)	
	N2		9	(4.4)	4	(4.5)	5	(4.3)	
	N3		10	(4.9)	2	(2.2)	8	(7.0)	
c/pM	**cM1**		2	(1.0)	1	(0.9)	1	(1.1)	1.000
Radicality	**R0**		202	(99.0)	89	(100)	113	(98.3)	1.000
	R1		2	(1.0)	0	0	2	(1.7)	

Table 1: Continued

		Total		McKeown		Ivor Lewis		p-value
Lymph nodes (median (IQR))		26	(20-37)	23	(17-31)	31	(22-39)	**<0.001**
Lymph node metastases (median (IQR))		0	(0-1)	0	(0-1)	0	(0-1)	0.378
Tumor	**1**	45	(26.5)	17	(24.6)	28	(27.7)	0.144
response	**2**	47	(27.6)	25	(36.2)	22	(21.8)	
after	**3**	42	(24,7)	14	(20.3)	28	(27.7)	
neoadjuvant	**4**	30	(17.6)	11	(15.9)	19	(18.8)	
therapy	**5**	6	(3.5)	2	(2.9)	4	(4.0)	

n (%) unless otherwise indicated. y = years. IQR = interquartile range. TNM staging classification (AJCC 8th edition). Bold values are significant.

Table 2: Background characteristics: postoperative morbidity.

		McKeown (N=89)		Ivor Lewis (N=115)		p-value
Postoperative complications	No	41	(46.1)	64	(55.7)	0.174
	Yes	48	(53.9)	51	(44.3)	
	Anastomotic leakage	22	(24.7)	10	(8.7)	**0.002**
	Treatment with antibiotics	3	(13.6)	0	0	
	Percutaneous drainage	11	(50.0)	1	(10.0)	
	Endoscopic management	3	(13.6)	3	(30.0)	
	Reoperation with preservation of anastomosis	4	(18.2)	6	(60.0)	
	Reoperation with resection of the anastomosis	1	(4.5)	0	0	
	Atrial fibrillation	17	(19.1)	24	(20.9)	0.731
	Pneumonia	12	(13.5)	13	(11.3)	0.638
	Recurrent nerve palsy	7	(7.9)	2	(1.7)	**0.043**
	Other	19	(21.3)	22	(19.1)	0.695
Clavien-Dindo classification	Grade 0	39	(43.8)	59	(51.3)	0.139
	Grade 1	4	(4.5)	9	(7.8)	
	Grade 2	24	(27.0)	13	(11.3)	
	Grade 3A	11	(12.4)	16	(13.9)	
	Grade 3B	0	0	1	(0.9)	
	Grade 4A	9	(10.1)	14	(12.2)	
	Grade 4B	2	(2.2)	3	(2.6)	

n (%) unless otherwise indicated. Bold values are significant.

Endpoints: HR-QoL domains

After univariable analysis of all HR-QoL functioning and symptom scores a P-value of < 0.10 was found in 'financial difficulties', 'dysphagia', 'eating', 'odynophagia', 'anxiety' and 'eating with others' domains. These HR-QoL domains were then entered in the multivariable analysis and were corrected for age, gender, neoadjuvant therapy (yes/no), surgical approach (open/minimally invasive), adjuvant therapy (yes/no), histologic tumor type (adenocarcinoma, squamous cell carcinoma or other), lymph node yield, anastomotic leakage, recurrent nerve palsy and/or follow-up (supplementary table 1). Patients after McKeown esophagectomy reported significantly more problems with eating with others compared to patients after Ivor Lewis esophagectomy (mean scores: 49.9 vs 38.8; p=0.042). This difference was clinically relevant as the difference between these two scores was 11.1 points. No other domains had significant mean score differences of more than 10 points (table 3 & supplementary table 1).

Table 3: Univariable and multivariable linear regression analysis of EORTC QLQ-C30 and EORTC QLQ-OG25 questionnaires' domains.

			Univariable analysis			
	McKeown n=89	Ivor Lewis n=115	B	95%CI		p-value
				Lower	Upper	
EORTC QLQ-C30						
Global Health	72.3 (19.5)	74.3 (19.5)	2.0	-3.452	7.437	0.471
Functioning						
Physical functioning	79.3 (18.7)	83 (19.3)	3.6	-1.680	8.932	0.179
Role functioning	74.5 (27.6)	76.7 (27.6)	2.1	-5.576	9.855	0.585
Emotional functioning	80.8 (21.8)	81.4 (23)	0.5	-5.739	6.816	0.866
Cognitive functioning	83.2 (20.1)	84.9 (21.5)	1.7	-4.149	7.527	0.569
Social functioning	79.3 (25.9)	81.1 (25.3)	1.7	-5.398	8.837	0.634
Symptom scores						
Fatigue	30.5 (24.6)	32.9 (26.7)	-2.4	-9.538	4.674	0.501
Nausea and vomiting	15.4 (21.7)	13.3 (20.3)	-2.1	-7.888	3.784	0.489
Pain	12.5 (21.3)	16.9 (22.9)	4.4	-1.858	10.567	0.168
Dyspnea	30.3 (32.4)	24.1 (26.7)	-6.3	-14.658	2.098	0.141
Insomnia	23.6 (29.8)	24.7 (30.6)	1.1	-7.304	9.533	0.794
Appetite loss	18.9 (28.3)	15.7 (26)	-3.2	-10.748	4.353	0.405
Constipation	11.1 (19.5)	8.4 (17.6)	-2.7	-7.864	2.454	0.302
Diarrhea	18.6 (24.7)	15.1 (23.5)	-3.5	-10.191	3.215	0.306
Financial difficulties	31.4 (31.1)	23.7 (26.9)	-7.7	-15.753	0.402	0.062*
EORTC QLQ-OG25						
Functioning						
Body image	84.6 (27.1)	81.5 (30)	-3.1	-11.138	4.944	0.449
Symptom scores						
Dysphagia	12.9 (17.7)	8.9 (15.6)	-4.0	-8.589	0.679	0.094*
Eating	29.5 (26.4)	22.5 (23.7)	-7.0	-13.960	0.005	0.050*
Reflux	24.6 (29.2)	20.8 (28.1)	-3.9	-11.908	4.171	0.344
Odynophagia	12.4 (20.3)	7.8 (17.3)	-4.6	-9.957	0.813	0.096*
Pain and discomfort	16.7 (25.9)	15.9 (26.1)	-0.8	-8.063	6.547	0.838
Anxiety	31.8 (30.8)	24.8 (25.9)	-7.0	-14.861	0.907	0.083*
Eating with others	18.2 (28.5)	7.6 (19.0)	-10.6	-17.604	-3.608	0.003*
Dry mouth	19.9 (27.4)	17.7 (25.9)	-2.1	-9.601	5.374	0.578
Trouble with taste	11 (22.4)	11.3 (20.8)	0.3	-5.774	6.380	0.922
Trouble swallowing saliva	10.2 (22.8)	10.2 (21.4)	-0.03	-6.216	6.148	0.991
Choked when swallowing	14.8 (25.2)	14.1 (22.3)	-0.7	-7.341	5.976	0.840
Trouble with coughing	29.2 (29.8)	31.8 (30.6)	2.7	-5.855	11.183	0.538
Trouble talking	9.4 (20.7)	6 (13.7)	-3.4	-8.431	1.674	0.188
Weight loss	20.5 (30.3)	17.6 (26.5)	-3.0	-10.897	5.095	0.475
Hair loss	19.8 (27.7)	10.8 (23.4)	-9.1	-22.377	4.223	0.177

Better Global health and functioning scores but worse symptom scores have high mean values. McKeown and Ivor Lewis data are represented as mean (standard deviation). Regression coefficient (B) with 95% confidence interval (CI). *=HR-QoL domains with p<0.1 in univariable analysis were entered in multivariable analysis and corrected for confounders (supplementary table 1). †=Mean value of HR-QoL domain after multivariable analysis ‡=Corrected for multiple testing. Bold values represent significance.

	Multivariable analysis						
	McKeown† n=89	Ivor Lewis† n=115	B	95%CI		p-value	p-value corrected‡
				Lower	Upper		
	60.4	59.1	1.3	-7.697	10.276	0.777	4.662
	7.5	4.7	2.8	-2.507	8.046	0.302	1.812
	45.4	38.9	6.5	-1.947	15.021	0.130	0.780
	20.0	15.0	5.0	-1.454	11.441	0.128	0.768
	66.3	58.0	8.3	-0.903	17.467	0.077	0.462
	49.9	38.8	11.1	3.105	19.127	**0.007**	**0.042**

When compared to the general population [50, 51], patients following McKeown or Ivor Lewis esophagectomies reported a poorer HR-QoL with respect to nausea and vomiting (mean difference is 10.5), dyspnea (mean difference is 15.0), appetite loss (mean difference is 10.4), financial difficulties (mean difference is 17.6), problems with eating (mean difference is 22.7), reflux (mean difference is 15.8), eating with others (mean difference is 11.0), choked when swallowing (mean difference is 10.7), trouble with coughing (mean difference is 17.0) and weight loss (mean difference is 17.1).

A subgroup analysis was performed for patients with no or minor postoperative complications (Clavien-Dindo grade 0-2) (supplementary table 2 & 3). A total of 148 patients were included: 67 after McKeown and 81 after Ivor Lewis esophagectomy. After univariable analysis of all HR-QoL functioning and symptom scores a p-value of < 0.10 was found in 'global health', 'nausea and vomiting', 'appetite loss', 'financial difficulties', 'dysphagia', 'eating', 'reflux', 'odynophagia', 'anxiety' and 'eating with others' domains. After multivariable analysis and correction for multiple testing patients with no or minor complications following a McKeown esophagectomy reported significantly more problems with eating with others compared to patients after an Ivor Lewis esophagectomy (mean scores: 47.1 vs 32.4; p=0.030). This difference was also clinically relevant with a mean score difference of 14.7 points.

DISCUSSION

This study investigated long-term HR-QoL in disease-free patients after a McKeown or Ivor Lewis esophagectomy with a 2-field lymphadenectomy for tumors where both procedures were technically possible (distal esophageal or GEJ carcinoma without the presence of cervical lymph node metastases). The results show that after prolonged follow-up, both surgical patient groups reported a highly comparable HR-QoL. However, after a McKeown esophagectomy, patients reported more problems with eating with others compared to patients after an Ivor Lewis esophagectomy. This difference remained after exclusion of the influence of severe postoperative complications. A subgroup of patients with no or minor postoperative complications also indicated to have trouble with eating with others following a McKeown esophagectomy, a finding that was not affected by major complications. Whereas the results of this study on long-term HR-QoL will not be decisive in choosing the type of surgery, they are useful when informing patients about the possible long-term consequences of these two surgical techniques.

There are only a few studies that investigated the difference in long-term HR-QoL between McKeown and Ivor Lewis esophagectomy in patients with esophageal carcinoma [4, 8, 9]. Overall, our findings are different compared to the literature as we only found one impaired HR-QoL domain after McKeown compared to Ivor Lewis esophagectomy, even in patients with no or minor postoperative complications. In the study of *Barbour et al.*

differences in HR-QoL results were observed after propensity score matching such as more pain and constipation 24 months after open Ivor Lewis esophagectomy compared to thoracoscopically assisted McKeown esophagectomy [9]. Two other studies found no significant difference in long-term HR-QoL between open Ivor Lewis and open McKeown. Because the previous studies mainly investigated HR-QoL after open procedures, they do not reflect current practice in most countries. Increasingly, most esophagectomies are performed minimally invasively, since the results of the TIME trial became available showing reduced postoperative morbidity, less pain and better HR-QoL following a minimally invasive esophagectomy [21]. In the current study a high rate of patients (91.2%) was operated by a minimally invasive approach, thereby reflecting current practice.

Postoperative complications occur in 59-65% of the patients after esophagectomy and the most common complications are anastomotic leakage (11.4-21%), pneumonia (14.6-21%) and atrial dysrhythmia (14.5-15%) [22, 23]. It has recently been shown that complications have a negative impact not only on HR-QoL but also on long-term survival [24]. Identifying the surgical approach with the least perioperative morbidity is therefore of great importance, as it may lead to better survival and HR-QoL [6]. A recent systematic review with a comprehensive meta-analysis found similar cardiac arrhythmia incidence but a higher incidence of pulmonary complications, anastomotic leakage and vocal cord injury after minimally invasive McKeown compared to minimally invasive Ivor Lewis esophagectomy [5]. This systematic review included patients with esophageal and GEJ carcinoma following minimally invasive McKeown and minimally invasive Ivor Lewis esophagectomies. Likewise, in this current study, all patients had distal esophageal or GEJ carcinoma and the majority of patients were operated minimally invasively (91.2%). However, this systematic review did not investigate long-term HR-QoL.

A number of limitations should be addressed. Since this was an observational, non-randomized study, some of the preoperative characteristics and postoperative morbidity between the two groups were different, including follow-up, age, gender, (neo)adjuvant therapy, surgical approach, histologic tumor type, lymph node yield, occurrence of anastomotic leakage and occurrence of recurrent nerve palsy. A statistical correction for all of the possible confounders was performed during multivariable linear regression. The majority of the patients (86.4%) following Ivor Lewis esophagectomy received adjuvant chemotherapy because of their participation in the SOX trial (NCT 02347904). Furthermore, this study investigates HR-QoL only in disease-free patients, as patients who did not survive could not have completed the questionnaires. The results of this study are not applicable to patients with cervical lymph node metastases, a more extended radiation field and a more proximal tumor as in these patients an Ivor Lewis esophagectomy could not have been performed, and these patients were excluded from this study. This study applies only to patients in whom both procedures were possible. In addition, station 2 (according to

the AJCC 8th edition [25]) was not part of the standard lymphadenectomy and was only performed on indication. Unfortunately it is not possible to exclude selection bias as the reason for patients to decline participation in this study and clinical information of these patients (such as the performed operation) was not recorded, following good clinical practice guidelines, General Data Protection Regulation and the Medical Contract Bill [26-28]. Furthermore, because of the high number of tested outcomes the chance of finding a significant result by coincidence is high. Therefore, a Bonferroni correction for multiple testing was performed. Moreover, clinical relevance of the results was tested. Strengths of the current study are that it has one of the largest sample sizes and one of the longest follow-up compared to other studies.

In conclusion, the present study investigating HR-QoL after Ivor Lewis and McKeown esophagectomy shows a highly comparable HR-QoL in patients with a distal esophageal or GEJ carcinoma. Only one HR-QoL domain – more problems in eating with others – was found to be significantly poorer in the McKeown compared to the Ivor Lewis group, even in patients with no or minor postoperative complications. These results apply to disease-free patients in whom both procedures are possible from an oncologic viewpoint. Additionally, irrespective of the surgical technique, patients' HR-QoL following esophagectomy is compromised. Future studies should not only investigate perioperative morbidity, pathology results and survival, but also long-term HR-QoL in these two procedures in a randomized controlled setting. Currently, such a study is being executed [29].

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SUPPLEMENT

Supplementary table 1: Multivariable linear regression analysis of long-term health-related quality of life.

	Covariates	B	95%CI		P-value
			Lower	Upper	
Financial difficulties	McKeown	1.3	-7.697	10.276	0.777
	Gender	-	-	-	-
	Age	-0.7	-1.124	-0.223	**0.004**
	Neoadjuvant therapy	-5.3	-15.717	5.194	0.322
	Surgical approach	-	-	-	-
	Adjuvant therapy	-8.3	-20.979	4.299	0.195
	Histologic type	2.4	0.156	4.590	**0.036**
	Lymph node yield	-	-	-	-
	Anastomotic leakage	-	-	-	-
	Recurrent nerve palsy	-	-	-	-
	Follow-up	0.4	0.071	0.639	**0.015**
Dysphagia	McKeown	2.8	-2.507	8.046	0.302
	Gender	-4.3	-10.263	1.747	0.164
	Age	-	-	-	-
	Neoadjuvant therapy	5.3	-1.176	11.798	0.108
	Surgical approach	-	-	-	-
	Adjuvant therapy	-	-	-	-
	Histologic type	0.3	-1.100	1.602	0.715
	Lymph node yield	-	-	-	-
	Anastomotic leakage	-	-	-	-
	Recurrent nerve palsy	-	-	-	-
	Follow-up	0.1	-0.069	0.264	0.248
Eating	McKeown	6.5	-1.947	15.021	0.130
	Gender	-7.8	-16.896	1.388	0.096
	Age	-0.2	-0.568	0.243	0.429
	Neoadjuvant therapy	5.2	-4.717	15.153	0.301
	Surgical approach	-	-	-	-
	Adjuvant therapy	3.7	-7.505	14.906	0.516
	Histologic type	-0.9	-3.013	1.258	0.419
	Lymph node yield	-0.1	-0.429	0.165	0.382
	Anastomotic leakage	10.7	0.477	20.882	**0.040**
	Recurrent nerve palsy	-8.8	-25.977	8.391	0.314
	Follow-up	-0.01	-0.274	0.248	0.924
Odynophagia	McKeown	5.0	-1.454	11.441	0.128
	Gender	-	-	-	-
	Age	-0.2	-0.560	0.063	0.117
	Neoadjuvant therapy	3.7	-0.643	11.068	0.321
	Surgical approach	-	-	-	-
	Adjuvant therapy	-2.5	-11.142	6.102	0.565
	Histologic type	0.2	-1.302	1.745	0.774
	Lymph node yield	-	-	-	-
	Anastomotic leakage	-	-	-	-
	Recurrent nerve palsy	-	-	-	-
	Follow-up	0.1	-0.115	0.273	0.422
Anxiety	McKeown	8.3	-0.903	17.467	0.077
	Gender	-5.0	-15.243	5.156	0.331
	Age	-0.5	-0.959	-0.051	0.029
	Neoadjuvant therapy	3.4	-7.718	14.435	0.551
	Surgical approach	4.4	-10.118	18.940	0.550
	Adjuvant therapy	-8.8	-21.368	3.749	0.168
	Histologic type	-2.5	-4.801	-0.167	0.036
	Lymph node yield	-	-	-	-
	Anastomotic leakage	-	-	-	-
	Recurrent nerve palsy	4.3	-15.460	24.000	0.670
	Follow-up	0.01	-0.278	0.302	0.077

Supplementary table 1: Continued

	Covariates	B	95%CI		P-value
			Lower	Upper	
Eating with others	McKeown	11.1	3.105	19.127	**0.007**
	Gender	-10.7	-19.444	-2.022	0.016
	Age	-0.5	-0.870	-0.097	0.015
	Neoadjuvant therapy	6.6	-2.841	15.966	0.170
	Surgical approach	1.2	-11.515	13.946	0.851
	Adjuvant therapy	-	-	-	-
	Histologic type	-0.6	-2.543	1.374	0.557
	Lymph node yield	-0.02	-0.301	0.268	0.908
	Anastomotic leakage	-	-	-	-
	Recurrent nerve palsy	-5.7	-22.306	10.923	0.500
	Follow-up	0.1	-0.152	0.330	0.467

B = regression coefficient. CI = confidence interval. Bold values represent significance.

Supplementary table 2: Univariable and multivariable linear regression analysis of EORTC QLQ-C30 and EORTC QLQ-OG25 questionnaires' domains of patients with no or minor postoperative complications (Clavien Dindo grade 0-2).

	Univariable analysis					
	McKeown n=67	Ivor Lewis n=81	B	95%CI		p-value
				Lower	Upper	
EORTC QLQ-C30						
Global Health	70.3 (20.7)	76.9 (17.8)	6.5	0.275	12.822	**0.041***
Functioning						
Physical functioning	79.2 (18.1)	84.3 (19.6)	5.1	-1.074	11.314	0.104
Role functioning	73.2 (28.8)	77.4 (27.2)	4.1	-5.011	13.278	0.373
Emotional functioning	78.4 (22.9)	80.2 (24.3)	1.8	-5.949	9.583	0.644
Cognitive functioning	80.9 (20.9)	82.9 (23.3)	2.0	-5.296	9.271	0.591
Social functioning	78.3 (27.6)	81.1 (25.4)	2.9	-5.769	11.481	0.514
Symptom scores						
Fatigue	35.0 (28.6)	30.1 (24.7)	-4.8	-13.482	3.838	0.273
Nausea and vomiting	17.5 (23.3)	11.7 (18.3)	-5.8	-12.569	0.951	0.092*
Pain	13.4 (21.7)	15.2 (21.8)	1.8	-5.331	8.932	0.619
Dyspnea	28.9 (32.8)	22.6 (24.6)	-6.2	-15.823	3.378	0.202
Insomnia	24.9 (29.2)	25.2 (30.4)	0.3	-9.427	10.087	0.947
Appetite loss	21.1 (28.8)	12.5 (22.6)	-8.7	-17.253	-0.139	**0.046***
Constipation	12.3 (20.9)	8.2 (18.7)	-4.1	-10.555	2.401	0.216
Diarrhea	18.7 (24.9)	15.6 (25.3)	-3.0	-11.286	5.188	0.466
Financial difficulties	33.3 (33.3)	23.4 (25.7)	-9.9	-19.608	-0.226	**0.045***
EORTC QLQ-OG25						
Functioning						
Body image	81.1 (29.1)	83.8 (29.4)	2.8	-6.865	12.409	0.571
Symptom scores						
Dysphagia	14.3 (18.9)	9.1 (16.6)	-5.2	-11.011	0.648	0.081*
Eating	32.4 (27.8)	20.5 (22.6)	-11.9	-20.157	-3.618	**0.005***
Reflux	28.1 (31.3)	20.0 (26.7)	-8.2	-17.739	1.432	0.095*
Odynophagia	14.2 (22.3)	8.0 (18.7)	-6.2	-13.091	0.722	0.079*
Pain and discomfort	18.2 (27.0)	17.1 (27.2)	-1.1	-10.040	7.931	0.817
Anxiety	35.8 (32.6)	23.4 (26.1)	-12.4	-22.007	-2.741	**0.012***
Eating with others	19.7 (29.8)	7.0 (18.3)	-12.7	-21.061	-4.298	**0.003***
Dry mouth	22.9 (28.6)	18.9 (26.9)	-4.0	-13.190	5.138	0.387
Trouble with taste	11.1 (23.6)	11.5 (20.7)	0.4	-6.957	7.761	0.914
Trouble swallowing saliva	13.1 (25.4)	12.8 (24.0)	-0.4	-8.495	7.760	0.929
Choked when swallowing	16.7 (27.6)	13.2 (22.4)	-3.5	-11.721	4.792	0.408
Trouble with coughing	31.8 (30.6)	34.2 (30.2)	2.4	-7.658	12.373	0.642
Trouble talking	7.0 (15.9)	6.8 (14.5)	-0.1	-5.158	4.863	0.954
Weight loss	22.4 (31.5)	16.6 (25.6)	-5.8	-15.297	3.623	0.225
Hair loss	20.7 (28.2)	14.5 (26.3)	-6.2	-22.348	10.023	0.447

Better Global health and functioning scores but worse symptom scores have high mean values. McKeown and Ivor Lewis data are represented as mean (standard deviation). Regression coefficient (B) with 95% confidence interval (CI). *=HR-QoL domains with p<0.1 in univariable analysis were entered in multivariable analysis and corrected for confounders (supplementary table 3). †=Mean value of HR-QoL domain after multivariable analysis ‡=Corrected for multiple testing. Bold values represent significance.

	Multivariable analysis						
	McKeown† n=67	Ivor Lewis† n=81	B	95%CI		p-value	p-value corrected‡
				Lower	Upper		
	35.3	40.2	-4.9	-12.211	2.495	0.194	1.940
	-2.9	-4.2	1.4	-6.203	8.939	0.721	7.210
	8.0	0.5	7.5	-2.545	17.505	0.142	1.420
	89.4	87.3	2.1	-8.546	12.721	0.698	6.980
	-1.6	-5.9	4.3	-2.648	11.232	0.223	2.230
	34.5	22.3	12.2	2.130	22.226	**0.018**	0.180
	15.2	8.6	6.5	-4.882	17.977	0.259	2.590
	19.6	13.2	6.4	-1.770	14.555	0.124	1.240
	68.6	56.6	12.0	0.321	23.772	**0.044**	0.440
	47.1	32.4	14.7	5.111	24.199	**0.003**	**0.030**

Supplementary table 3: Multivariable linear regression analysis of long-term health-related quality of life results of patients with no or minor postoperative complications (Clavien-Dindo grade 0-2).

	Covariates	B	95%CI		P-value
			Lower	Upper	
Global Health	McKeown	-4.9	-12.211	2.495	0.194
	Gender	-	-	-	-
	Age	0.5	0.150	0.842	**0.005**
	Neoadjuvant therapy	1.0	-7.673	9.681	0.819
	Surgical approach	-	-	-	-
	Adjuvant therapy	-	-	-	-
	Histologic type	1.1	-0.720	3.007	0.227
	Lymph node yield	0.1	-0.128	0.412	0.299
	Anastomotic leakage	-16.0	-29.340	-2.566	0.020
	Recurrent nerve palsy	14.6	-12.294	41.400	0.286
	Follow-up	-0.1	-0.285	0.163	0.590
Nausea and vomiting	McKeown	1.4	-6.203	8.939	0.721
	Gender	-6.7	-15.188	1.743	0.119
	Age	-	-	-	-
	Neoadjuvant therapy	-	-	-	-
	Surgical approach	7.2	-5.151	19.607	0.250
	Adjuvant therapy	-	-	-	-
	Histologic type	-1.5	-3.540	0.497	0.139
	Lymph node yield	0.3	-0.013	0.562	0.061
	Anastomotic leakage	18.2	3.725	32.755	**0.014**
	Recurrent nerve palsy	-	-	-	-
	Follow-up	0.3	0.046	0.522	**0.020**
Appetite loss	McKeown	7.5	-2.545	17.505	0.142
	Gender	-11.2	-22.649	0.211	0.054
	Age	0.3	-0.206	0.749	0.263
	Neoadjuvant therapy	6.2	-6.283	18.738	0.327
	Surgical approach	-	-	-	-
	Adjuvant therapy	9.6	-3.807	22.952	0.159
	Histologic type	-0.8	-3.527	1.831	0.532
	Lymph node yield	-0.1	-0.439	0.313	0.742
	Anastomotic leakage	7.3	-11.483	26.036	0.444
	Recurrent nerve palsy	-	-	-	-
	Follow-up	0.01	-0.306	0.320	0.966
Financial difficulties	McKeown	2.1	-8.546	12.721	0.698
	Gender	-6.0	-18.258	6.197	0.331
	Age	-0.9	-1.370	-0.338	**0.001**
	Neoadjuvant therapy	-6.9	-20.280	6.475	0.309
	Surgical approach	-12.0	-29.157	5.064	0.166
	Adjuvant therapy	-10.6	-25.342	4.146	0.157
	Histologic type	2.9	0.089	5.611	**0.043**
	Lymph node yield	-0.04	-0.438	0.368	0.864
	Anastomotic leakage	-	-	-	-
	Recurrent nerve palsy	-	-	-	-
	Follow-up	0.5	0.134	0.817	**0.007**
Dysphagia	McKeown	4.3	-2.648	11.232	0.223
	Gender	-	-	-	-
	Age	-	-	-	-
	Neoadjuvant therapy	7.3	-1.164	15.676	0.091
	Surgical approach	-	-	-	-
	Adjuvant therapy	-	-	-	-
	Histologic type	0.5	-1.229	2.303	0.549
	Lymph node yield	0.1	-0.120	0.400	0.289
	Anastomotic leakage	8.3	-4.424	20.957	0.200
	Recurrent nerve palsy	-	-	-	-
	Follow-up	0.1	-0.097	0.323	0.290

Eating	McKeown	12.2	2.130	22.226	**0.018**
	Gender	-3.7	-14.941	7.622	0.522
	Age	-0.2	-0.630	0.308	0.499
	Neoadjuvant therapy	12.3	-0.107	24.719	0.052
	Surgical approach	-	-	-	-
	Adjuvant therapy	-	-	-	-
	Histologic type	-0.8	-3.380	1.788	0.543
	Lymph node yield	0.04	-0.333	0.412	0.835
	Anastomotic leakage	17.8	-0.557	36.215	0.057
	Recurrent nerve palsy	-28.6	-64.788	7.639	0.121
	Follow-up	0.01	-0.296	0.309	0.967
Reflux	McKeown	6.5	-4.882	17.977	0.259
	Gender	-	-	-	-
	Age	-0.2	-0.722	0.367	0.521
	Neoadjuvant therapy	7.5	-6.591	21.585	0.294
	Surgical approach	-	-	-	-
	Adjuvant therapy	-12.5	-27.411	2.345	0.098
	Histologic type	-1.8	-4.674	1.127	0.229
	Lymph node yield	0.4	-0.021	0.827	0.062
	Anastomotic leakage	20.4	-0.021	40.833	0.050
	Recurrent nerve palsy	-39.5	-80.366	1.460	0.059
	Follow-up	0.3	-0.053	0.649	0.095
Odynophagia	McKeown	6.4	-1.770	14.555	0.124
	Gender	5.6	-3.589	14.858	0.229
	Age	-0.4	-0.792	-0.019	**0.040**
	Neoadjuvant therapy	7.3	-2.896	17.557	0.159
	Surgical approach	1.4	-11.400	14.221	0.828
	Adjuvant therapy	-4.0	-14.717	6.705	0.461
	Histologic type	-	-	-	-
	Lymph node yield	0.1	-0.151	0.447	0.329
	Anastomotic leakage	15.0	0.525	29.566	**0.042**
	Recurrent nerve palsy	-	-	-	-
	Follow-up	0.1	-0.141	0.357	0.392
Anxiety	McKeown	12.0	0.321	23.772	**0.044**
	Gender	-6.0	-19.123	7.216	0.373
	Age	-0.5	-1.032	0.065	0.083
	Neoadjuvant therapy	6.1	-8.500	20.700	0.410
	Surgical approach	-	-	-	-
	Adjuvant therapy	-13.3	-28.599	2.063	0.089
	Histologic type	-3.3	-6.408	-0.280	**0.033**
	Lymph node yield	0.1	-0.305	0.569	0.551
	Anastomotic leakage	14.9	-6.578	36.367	0.172
	Recurrent nerve palsy	9.4	-32.869	51.590	0.662
	Follow-up	0.01	-0.351	0.372	0.956
Eating with others	McKeown	14.7	5.111	24.199	**0.003**
	Gender	-14.0	-24.814	-3.135	**0.012**
	Age	-0.5	-0.987	-0.065	**0.026**
	Neoadjuvant therapy	13.7	1.463	26.034	**0.029**
	Surgical approach	0.3	-15.237	15.875	0.968
	Adjuvant therapy	-1.6	-14.170	11.023	0.805
	Histologic type	-0.9	-3.362	1.523	0.458
	Lymph node yield	0.2	-0.144	0.577	0.237
	Anastomotic leakage	-	-	-	-
	Recurrent nerve palsy	-	-	-	-
	Follow-up	0.1	-0.238	0.360	0.686

B = regression coefficient. CI = confidence interval. Bold values represent significance.

Chapter 4

Long-term quality of life following transthoracic and transhiatal esophagectomy for esophageal cancer

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ABSTRACT

Background

The impact of transthoracic (TTE) and transhiatal (THE) esophagectomy on long-term health-related quality of life (HR-QoL) in patients with distal esophageal or gastro-esophageal junction (GEJ) cancer has been studied with variable results. This study investigates long-term HR-QoL in patients having undergone TTE or THE.

Methods

Disease-free patients after TTE or THE for distal esophageal or GEJ cancer with a follow-up >2 years were included. Patients who visited the outpatient clinic of a tertiary referral center between 2014-2018 were asked to complete EORTC-QLQ-C30 and EORTC-QLQ-OG25 questionnaires. Uni- and multivariable linear regression analysis of HR-QoL was performed in all patients and in subgroups of minimally invasive esophagectomy and neoadjuvant therapy.

Results

A total of 132 patients after TTE and 56 after THE were included. When compared to the general population, all patients reported worse HR-QoL in 'role functioning' and 'social functioning', and in a range of disease- and/or treatment specific symptoms. The only significant difference between TTE and THE was a better HR-QoL score for 'hair loss' following TTE (ß=29.4,95%CI=-49.108 – -9.671, p=0.016). Subgroup analysis of minimally invasively operated patients showed better scores in ´physical functioning´ following TTE (ß=13.8,95%CI=2.755–24.933, p=0.030). No significant differences in HR-QoL were found between TTE and THE after neoadjuvant therapy.

Conclusion

Long-term HR-QoL is largely comparable in disease-free patients following TTE or THE for distal esophageal or GEJ cancer. If there were differences between the surgical groups, they were in favour of TTE. These findings may aid in preoperative counselling of patients with esophageal or GEJ cancer.

INTRODUCTION

Treatment of esophageal cancer usually consists of surgery in combination with (neo)adjuvant chemo(radio)therapy. Both a transhiatal (THE) and a transthoracic (TTE) esophagectomy may be feasible in distal esophageal and gastro-esophageal (GEJ) junction cancer. As survival of patients with esophageal cancer improves, the long-term health-related quality of life (HR-QoL) is becoming increasingly more important. In a randomized controlled trial (RCT), no significant survival differences were found between TTE and THE, although more lymph nodes were resected and more pulmonary complications were documented in the TTE group [1, 2].

A number of studies have assessed HR-QoL following TTE and THE and show diverse results [2-6]. Some studies, including the previously mentioned RCT, did not find differences in HR-QoL [3, 5, 6], whereas one study showed worse long-term HR-QoL following TTE in comparison to THE [4]. The results of these studies do not completely apply to current practice, as most were performed before the implementation of minimally invasive surgery and neoadjuvant therapy. For example, minimally invasive TTE results in fewer pulmonary complications and is associated with less postoperative pain, which in turn was found to positively affect HR-QoL [7, 8]. Furthermore, HR-QoL was found to decline during neoadjuvant chemoradiotherapy in patients with esophageal cancer [9], but no negative impact of neoadjuvant therapy has been found on postoperative HR-QoL after a follow-up of 12 months [10-14]. However, these findings are based on RCT's with pre-selected patients. The rationale for this study is to investigate long-term HR-QoL in esophageal cancer patients following esophagectomy from a naturally occurring sample in the era where minimally invasive surgery and neoadjuvant therapy have become standard treatment.

The aim of this study is to investigate long-term HR-QoL in disease-free patients after TTE and THE for distal esophageal and GEJ cancer in a tertiary referral center. Secondary aim is to compare long-term HR-QoL between TTE and THE in the 'minimally invasive' and 'neoadjuvant therapy' subgroups.

METHODS

Study design, patients and follow-up

In this prospective cohort study, patients were enrolled between October 2014 and October 2018 in Amsterdam UMC, location Academic Medical Center (AMC). Patients were asked to participate if they had undergone a THE or a TTE for a distal esophageal or GEJ cancer between 2006 and 2016. Included patients completed the European Organization for Research and Treatment of Cancer (EORTC) quality of life questionnaires during outpatient clinic visits. Essentially, all included patients with a distal esophageal or GEJ cancer could

technically have undergone both a TTE or a THE. Patients with a recurrence during follow-up, having undergone salvage esophagectomy and/or jejunal or colonic interposition, and patients who died were excluded from this study. Also, patients with mediastinal lymph node metastases above the level of the pulmonary vein were excluded, as in these patients only a TTE can be performed. Clinical information and reason for rejection of patients who declined participation were not registered, due to data protection regulations [15-17].

Patients were seen at regular intervals at the outpatient clinic until five years after surgery or longer if indicated. Imaging was only performed if a recurrence was clinically suspected, which is in accordance with the Dutch guideline [18].

The Institutional Review Board of Amsterdam UMC waived ethical approval. Patients gave oral informed consent. This article ensured accurate reporting by adhering to the STROBE checklist [19].

Neoadjuvant chemoradiotherapy or perioperative chemotherapy and surgery

In the AMC, individual patient treatment is decided upon during a weekly multi-disciplinary team meeting at the Gastrointestinal Oncology Center Amsterdam (GIOCA). Neoadjuvant therapy regimens for ≥cT2N0-3M0 or cT1N+ cancers in the period under study consisted of neoadjuvant chemoradiotherapy according to the CROSS scheme or, if there is more than 2 cm tumor involvement of the stomach, perioperative chemotherapy according to the MAGIC scheme [20]. A THE with a gastric tube reconstruction used to be the preferred approach for distal esophageal and GEJ cancer, but was gradually replaced by the transthoracic approach during the study period, because of the more radical lymphadenectomy by TTE. In the studied period both procedures were still carried out regularly. THE and TTE were either performed open or minimally invasively, depending on patient and tumor characteristics and time period (minimally invasive surgery was introduced in 2010). In THE, a 1-field lymphadenectomy was performed with extension of the field to the lower mediastinum (lymph node stations according to the 8th edition of the AJCC: 8Lo, 9, 15-20). During TTE, a 2-field lymphadenectomy was performed, including the paratracheal lymph node stations (lymph node stations 4, 5, 7, 8M, 8Lo, 9, 15-20 and 2 and 8Up on indication). During TTE either a cervical or intrathoracic anastomosis was performed, depending on either tumor characteristics or time period (the intrathoracic anastomosis was introduced in 2013).

Background, clinical, and postoperative morbidity variables

Clinical data were retrieved from a prospectively maintained upper gastrointestinal surgery database at the Amsterdam UMC, location AMC. The included background and clinical variables were: age, gender, follow-up (months), tumor location (distal esophagus or GEJ), comorbidities (cardiovascular, pulmonary or metabolic), ASA classification, (neo)adjuvant therapy (chemotherapy or chemoradiotherapy), surgical approach (open or minimally

invasive), cTNM stage, histologic tumor type (adenocarcinoma, squamous cell carcinoma or other), (y)pTNM stage, R0 resection rate, number of retrieved (positive) lymph nodes and tumor response after neoadjuvant therapy according to tumor regression grading (TRG) [21]. Postoperative morbidity variables included Clavien-Dindo classification (grade 5 was excluded from this study), and the following complications: atrial fibrillation, anastomotic leakage, pneumonia (these are the complications with the highest prevalence [22]) and other complications (wound infection, intra-abdominal abscess, sepsis, recurrent nerve injury, intrathoracic hernia, empyema, pulmonary embolus, pneumothorax) according to the Esophagectomy Complications Consensus Group (ECCG) [23].

Health-related Quality of Life

The cancer specific (EORTC QLQ-C30) and gastro-esophageal site-specific (EORTC QLQ-OG25) questionnaires were used, which are validated for cancer patients and gastro-esophageal cancer patients, respectively [24-26]. The EORTC QLQ-C30 contains 30 questions, out of which 15 multi- and single scale domains are generated: one ´global health´ domain, five functional domains (´physical´, ´role´, ´social´, ´cognitive´ and ´emotional functioning´) and nine symptom domains (´fatigue´, ´nausea and vomiting´, ´pain´, ´dyspnea´, ´insomnia´, ´appetite loss´, ´constipation´, ´diarrhea´ and ´financial difficulties´). The EORTC QLQ-OG25 contains 25 questions of which 16 multi- and single scale domains are generated: one functional domain (´body image´) and 15 symptom domains (´dysphagia´, ´reflux´, ´odynophagia´ and ´problems with eating with others´, ´pain and discomfort´, ´anxiety´, ´problems with eating´, ´dry mouth´, ´trouble with taste´, ´trouble swallowing saliva´, ´choking when swallowing´, ´trouble with coughing´, ´trouble talking´, ´weight loss´ and ´hair loss´).

Both questionnaires use a Likert scale of four points with answers ranging from 1 ‘not at all’ to 4 ‘very much’, except for the two questions about global HR-QoL, which employ a response scale ranging from 1 ‘very poor’ to 7 ‘excellent’. Following the scoring manual of EORTC QoL Group, all answers were linearly transformed into domain scores ranging from 0 to 100 [27]. A high score in ´global health´ and functional domains represents better HR-QoL and functioning, in contrast to symptom domains where a low score represents a low level of symptomatology and hence better HR-QoL.

Statistical analysis

First, the mean HR-QoL domain scores of the total study group (TTE and THE combined) with those of the general population were compared, based on the EORTC reference values manual [28, 29]. A mean score difference of more than 10 points was considered meaningful. Categorical variables (i.e. postoperative morbidity, patient and tumor characteristics) were subsequently analyzed using Chi^2 or Fisher’s exact tests. In case of continuous variables, Student’s t test (for normally distributed variables) or Mann-Whitney U test (for not normally distributed variables) were used.

For the analysis of the difference in HR-QoL domain scores between TTE and THE, univariable and multivariable linear regression analysis was used. HR-QoL domain scores were entered in the multivariable analysis if a p-value of <0.10 was reached in univariable analysis. In multivariable analysis, HR-QoL domain scores were standardly corrected for the possible confounders age and gender. Also, all background variables with a p-value difference of <0.10 between TTE and THE groups were considered candidate confounders. A variable was added to the multivariable analysis as a confounder if it caused clinically relevant effect (a change of >10% in regression coefficient). Furthermore, two additional subgroup univariable and multivariable linear regression analyses of HR-QoL domain scores were performed for patients operated minimally invasively (TTE versus THE) and for patients treated with neoadjuvant therapy (TTE versus THE). In addition, to investigate whether the level of the anastomosis in the TTE group influenced results, an additional subgroup analysis of HR-QoL domain scores was performed for patients in the TTE group with either a cervical or an intrathoracic anastomosis. Two-sided testing was performed. A p-value <0.05 was considered as statistically significant. A Bonferroni correction for multiple testing was performed for all HR-QoL domains that were entered in the multivariable analysis by multiplying the p-value by the number of tests performed in the multivariable analysis. Furthermore, mean difference (ß) in HR-QoL domain scores between two groups of 10 points or more was considered clinically relevant according to the EORTC guideline [30]. Statistical analyses were performed in SPSS Statistics version 24.

RESULTS

Demographics and cohort features

There were 238 eligible patients who visited the outpatient clinic during the inclusion period. Of these 238 patients, 188 completed the questionnaires (response rate 78.9%): 132 patients after TTE and 56 after THE (Figure 1). Median follow-up was significantly different between the two groups: 3.2 years [IQR 2.3-4.3] in the TTE group and 4.7 years [IQR 3.4-6.2] in the THE group (p<0.001). Median age was significantly higher in THE group (66 years [IQR 61-72] compared to TTE group (64 years [IQR 58-68], p=0.024). The majority of patients had ASA classification of 2 and there was no significant difference in comorbidities (cardiovascular, pulmonary or metabolic). Neoadjuvant chemoradiotherapy was administered more often in the TTE group (87.9% versus 50%; p=0.001). Also, TTE was performed significantly more often minimally invasively compared to THE (84.8% versus 39.3%; p<0.001). In the TTE group, a cervical anastomosis was performed in 59 (44.7%) patients, in the other 73 (55.3%) an intrathoracic anastomosis was performed. The majority of patients had an adenocarcinoma (87.8%). A significantly higher number of resected lymph nodes was found after TTE (median 26 [IQR 20-34]) compared to THE (median 18

[IQR 14-24], p<0.001), but the number of positive lymph nodes and tumor-free resection margins were not significantly different between groups (Table 1).

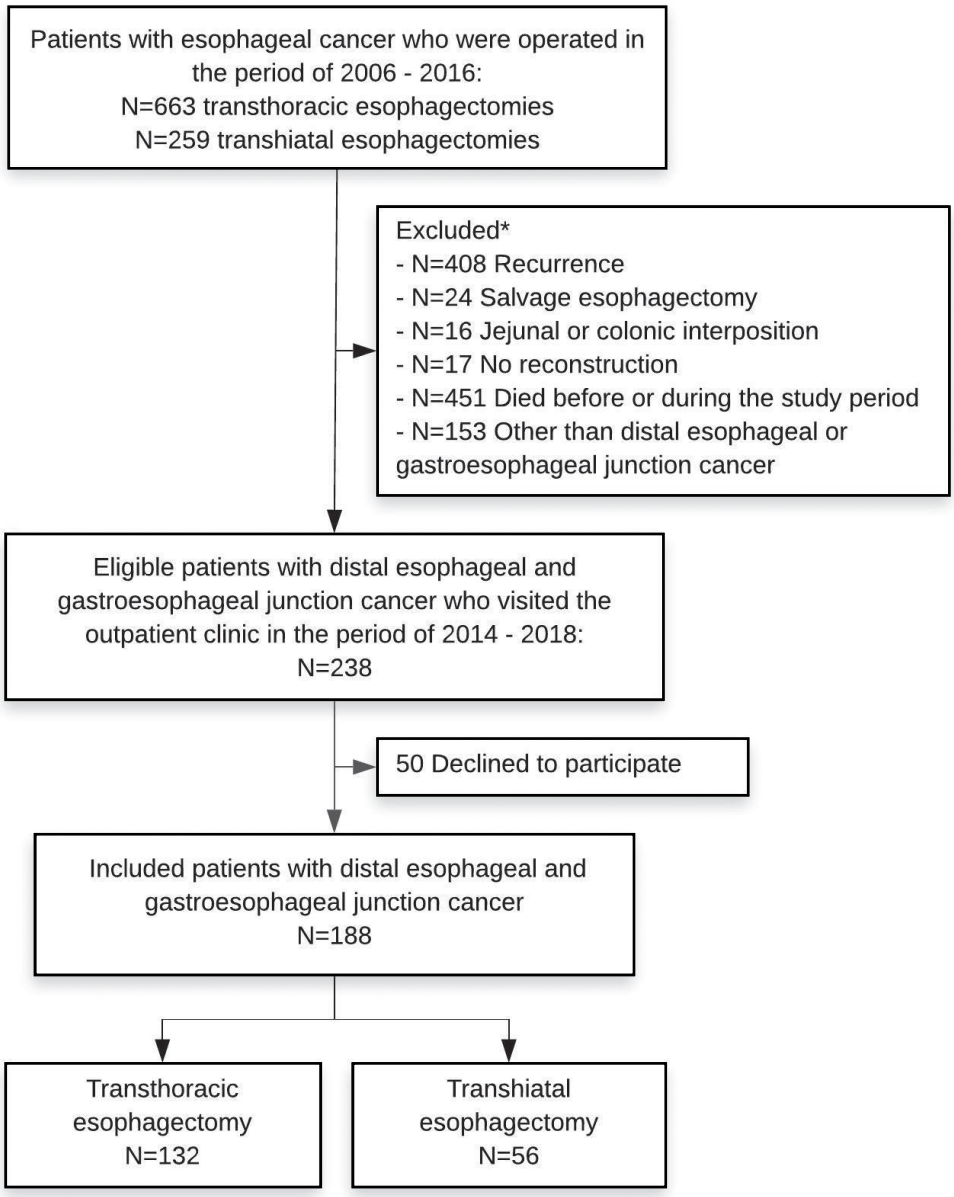

Figure 1: Study Flow Chart.

Table 1: Baseline characteristics of patients with distal esophageal or junctional cancer operated with transthoracic or transhiatal esophagectomy between 2006 – 2016.

N		TTE		THE		p-value
		132		56		
Age (median (IQR), y)		64	(58-68)	66	(61-72)	**0.024**
Gender	**Male**	110	(83.3)	41	(73.2)	0.111
Tumor location	**Distal esophagus**	121	(91.7)	31	(55.4)	0.088
	Gastro-esophageal junction	11	(8.3)	25	(44.6)	
Comorbidity	**No**	70	(53.0)	27	(48.2)	0.546
	Cardiovascular	52	(39.4)	22	(39.3)	0.989
	Pulmonary	9	(6.8)	6	(10.7)	0.385
	Metabolic	14	(10.6)	4	(7.1)	0.460
ASA classification	**1**	41	(31.1)	11	(19.6)	0.269
	2	67	(50.8)	34	(60.7)	
	3	24	(18.2)	11	(19.6)	
Neo-adjuvant therapy	**No**	16	(12.1)	22	(39.3)	**<0.001**
	Yes Chemotherapy	1	(0.8)	6	(10.7)	**0.001**
	Chemoradiotherapy	115	(87.9)	28	(50.0)	
Approach	**Open**	20	(15.2)	34	(60.7)	**<0.001**
	Minimally invasive	112	(84.8)	22	(39.3)	
Location of the anastomosis	**Cervical**	59	(44.7)	56	(100)	N/A
	Intrathoracic	73	(55.3)	N/A	N/A	
cT	**T0**	4	(3.0)	1	(1.8)	0.139
	T1	12	(9.1)	11	(19.6)	
	T2	35	(26.5)	8	(14.3)	
	T3	79	(59.8)	35	(62.5)	
	T4	2	(1.5)	1	(1.8)	
cN	**N0**	50	(37.9)	29	(51.8)	0.191
	N1	63	(47.7)	24	(42.9)	
	N2	16	(12.1)	3	(5.4)	
	N3	3	(2.3)	0	-	
Adjuvant therapy	**No**	115	(87.1)	47	(83.9)	0.562
	Yes Chemotherapy	13	(86.7)	8	(88.9)	1.000
	Chemoradiotherapy	4	(13.3)	1	(1.8)	
Histologic type	**Adenocarcinoma**	114	(86.4)	51	(91.1)	0.737
	Squamous cell carcinoma	13	(9.8)	4	(7.1)	
	Other	5	(3.8)	1	(1.8)	
(y)pT	**T0**	41	(31.1)	9	(16.1)	**0.026**
	T1	33	(25.0)	10	(17.9)	
	T2	18	(13.6)	8	(14.3)	
	T3	40	(30.3)	29	(51.8)	
(y)pN	**N0**	95	(72.0)	37	(66.1)	0.486
	N1	27	(20.5)	17	(30.4)	
	N2	6	(4.5)	1	(1.8)	
	N3	4	(3.0)	1	(1.8)	
pM	**M1**	1	(0.8)	0	-	1.000
Radicality	**R0**	132	(100)	56	(100)	N/A
Lymph nodes (median (IQR))		26	(20-34)	18	(14-24)	**<0.001**
Lymph node metastases (median (IQR))		0	(0-1)	0	(0-1)	0.179
Tumor response after neoadjuvant therapy according to TRG	**No response**	5	(4.3)	2	(6.5)	0.215
	Intermediate response	71	(61.7)	25	(80.6)	
	Complete response	39	(33.9)	4	(12.9)	

Data are presented as n (%) unless otherwise indicated. IQR = interquartile range. y = year. American Society of Anesthesiologists (ASA) classification. c/pTNM tumor staging classification. N/A = not applicable. TRG = tumor response grading. Bald values represent.

Anastomotic leakage, pneumonia, atrial fibrillation and other postoperative complications did not occur significantly differently between the two groups. Furthermore, no significant difference was found in Clavien-Dindo grade between TTE and THE (Table 2).

Table 2: Postoperative morbidity of patients with a distal esophageal or gastro-esophageal junction cancer operated with either transthoracic or transhiatal esophagectomy.

		TTE (N=132)		THE (N=56)		p-value
Postoperative complications	**No**	71	(53.8)	26	(46.4)	0.356
	Yes	61	(46.2)	30	(53.6)	
	Anastomotic leakage	18	(13.7)	13	(23.2)	0.111
	Pneumonia	19	(14.4)	7	(12.5)	0.731
	Atrial fibrillation	27	(20.6)	6	(10.9)	0.114
	Other	51	(38.6)	20	(35.7)	0.705
Clavien-Dindo classification	**Grade 0**	65	(49.2)	26	(46.4)	0.178
	Grade 1	7	(5.3)	6	(10.7)	
	Grade 2	25	(18.9)	15	(26.8)	
	Grade 3A	14	(10.6)	4	(7.1)	
	Grade 3B	0	0	2	(3.6)	
	Grade 4A	18	(13.6)	3	(5.4)	
	Grade 4B	3	(2.3)	0	0	

Data are presented as n (%) unless otherwise indicated.

Long-term HR-QoL following TTE or THE

All patients reported worse HR-QoL compared to the general population in 'role functioning' (mean difference 10.4), 'social functioning' (mean difference 11.6), 'nausea and vomiting' (mean difference 10.3), 'dyspnea' (mean difference 16.6), 'appetite loss' (mean difference 11.5), 'financial difficulties' (mean difference 20.5), 'dysphagia' (mean difference 11.4), 'eating difficulties' (mean difference 23.0), 'eating with others difficulties' (mean difference 13.5), 'reflux' (mean difference 15.8), 'choking when swallowing' (mean difference 13.6), 'trouble with coughing' (mean difference 16.4) and 'weight loss' (mean difference 19.9) [28, 29].

After univariable linear regression analysis of all HR-QoL domains between TTE and THE, a p-value of <0.10 was found in 'emotional functioning', 'social functioning', 'constipation' and 'hair loss'. Background variables age, gender, tumor location, neoadjuvant treatment, type of neoadjuvant therapy, surgical approach, (y)pT stage, lymph node yield and follow-up were selected as confounders for multivariable analysis. After multivariable analysis and Bonferroni correction, significantly fewer 'problems with hair loss' (mean score difference=29.4, 95%CI=-49.108 – -9.671, p=0.016) were found after TTE compared to THE. This difference in mean scores was clinically relevant with 29.4 points difference. Also, a clinically relevant difference in mean scores of 15.0 points was found in 'social functioning' domain. However, this difference was not statistically significant (Table 3 and supplementary table 1).

Table 3: Univariable and multivariable linear regression analysis of HR-QoL comparing transthoracic and transhiatal esophagectomy.

	Transthoracic esophagectomy Mean (SD) n=132	**Transhiatal esophagectomy** Mean (SD) n=56
EORTC QLQ-C30		
Global Health	72.7 (19.1)	76.71 (23.8)
Functioning		
Physical functioning	81.7 (19.6)	77.9 (21.2)
Role functioning	74.3 (27.1)	74.4 (31.8)
Emotional functioning	78.0 (23.6)	85.9 (20.8)
Cognitive functioning	82.9 (23.1)	86.4 (13.8)
Social functioning	78.8 (25.8)	69.0 (35.5)
Symptom scores		
Fatigue	32.6 (27.0)	30.2 (29.1)
Nausea and vomiting	14.6 (22.8)	12.7 (19.6)
Pain	18.1 (24.7)	14.3 (23.9)
Dyspnea	29.8 (28.9)	25 (30.7)
Insomnia	26.3 (31.3)	20.8 (26.6)
Appetite loss	19.9 (30.6)	13.9 (27.7)
Constipation	7.7 (15.8)	14.8 (25.6)
Diarrhea	15.4 (21.2)	18.5 (26.4)
Financial difficulties	29.8 (29.7)	30.3 (40.7)
EORTC QLQ-OG25		
Functioning		
Body image	77.3 (33.2)	69.3 (37.7)
Symptom scores		
Dysphagia	10.9 (16.5)	15.3 (18.4)
Eating	26.3 (24.7)	25.1 (28.6)
Reflux	22.1 (27.9)	23.4 (28.1)
Odynophagia	10.0 (20.4)	10.4 (16.7)
Pain and discomfort	15.9 (26.6)	17.3 (22.2)
Anxiety	31.4 (29.1)	26.3 (31.6)
Eating with others	14.2 (25.0)	16.4 (27.9)
Dry mouth	18.7 (26.6)	18.5 (25.4)
Trouble with taste	13.0 (23.1)	8.9 (19.6)
Trouble swallowing saliva	10.5 (22.2)	10.7 (20.2)
Choked when swallowing	15.8 (24.4)	20.8 (28.1)
Trouble with coughing	31.8 (31.7)	26.2 (32.2)
Trouble talking	8.5 (18.5)	7.1 (16.5)
Weight loss	23.7 (31.1)	16.3 (29.4)
Hair loss	15.9 (28.9)	31.3 (34.9)

Regression coefficient (B) with 95% confidence interval (CI) are shown for univariable and multivariable analysis. †=Corrected for confounders (Supplementary table 1). *=Health related quality of life (HR-QoL) domains with p<0.1 in univariable analysis were entered in multivariable analysis. ‡ = p-value corrected for multiple testing according to Bonferroni method.

	Univariable analysis				Multivariable analysis†				
	B	95%CI		p-value	B	95%CI		p-value	Corrected p-value‡
		Lower	Upper			Lower	Upper		
	4.0	-3.259	11.230	0.277					
	-3.9	-10.255	2.377	0.220					
	0.1	-9.009	9.164	0.987					
	8.0	0.702	15.226	0.032*	-3.0	-13.683	7.761	0.586	2.344
	3.5	-1.896	8.952	0.201					
	-10.0	-20.333	0.570	0.064*	15.0	2.724	27.230	**0.017**	0.068
	-2.4	-11.138	6.262	0.581					
	-2.0	-8.871	4.906	0.571					
	-3.8	-11.475	3.914	0.334					
	-4.8	-14.058	4.462	0.308					
	-5.5	-14.937	3.952	0.253					
	-6.0	-15.423	3.480	0.214					
	7.1	-0.363	14.608	0.062*	-3.1	-11.794	5.502	0.473	1.892
	3.1	-4.154	10.383	0.399					
	0.5	-11.595	12.585	0.935					
	-8.0	-18.990	2.924	0.150					
	4.4	-1.010	9.774	0.111					
	-1.2	-9.389	6.982	0.772					
	1.3	-7.604	10.104	0.781					
	0.4	-5.728	6.534	0.897					
	1.4	-6.650	9.415	0.735					
	-5.1	-14.525	4.345	0.289					
	2.2	-6.063	10.444	0.601					
	-0.2	-8.530	8.101	0.960					
	-4.0	-11.029	2.961	0.257					
	0.2	-6.567	7.065	0.943					
	5.1	-3.018	13.189	0.217					
	-5.6	-15.646	4.510	0.277					
	-1.3	-6.980	4.336	0.645					
	-7.4	-17.705	2.954	0.161					
	15.4	-0.636	31.431	0.060*	-29.4	-49.108	-9.671	**0.004**	**0.016**

Long-term HR-QoL following minimally invasive surgery

A total of 134 patients were operated minimally invasively: 112 received a minimally invasive TTE and 22 received a minimally invasive THE. After univariable analysis of all HR-QoL domains a p-value of <0.10 was found in 'physical functioning' and 'trouble talking' domains. Background variables age, gender, neoadjuvant treatment (yes/no), type of neoadjuvant therapy, cN stage and lymph node yield were selected as confounders (p-value < 0.10 in univariable analyses) for multivariable analysis. After multivariable analysis and Bonferroni correction only 'physical functioning' was found to be significantly better after minimally invasive TTE compared to minimally invasive THE (mean score difference=13.8, 95%CI=2.755 – 24.933, p=0.030) with a clinically relevant difference in mean scores of 13.8 points (Supplementary table 2 and 3).

Long-term HR-QoL following neoadjuvant therapy

A total of 116 patients in TTE group and 34 patients in THE group received neoadjuvant treatment. Background variables age, gender, ASA classification, surgical approach, pT stage, lymph node yield and follow-up were selected as confounders for the multivariable linear regression analysis. 'Social functioning', 'insomnia', 'constipation' and 'choked when swallowing' domains were entered in the multivariable linear regression analysis as these domains had a p-value <0.10 in univariable analysis. A clinically relevant difference in mean scores of 13.4 points was found in 'social functioning' domain between patients after neoadjuvant therapy and TTE compared to patients after neoadjuvant therapy and THE. However, this difference was not statistically significant (Supplementary table 2 and 4).

Long-term HR-QoL following a cervical or intrathoracic anastomosis after TTE

A total of 59 patients with a cervical anastomosis and 73 patients with an intrathoracic anastomosis were included in the TTE group. Background variables age, gender, follow-up, diabetes, tumor location, surgical approach, cN stage, histology, (positive) lymph node yield and adjuvant therapy were selected as confounders for the multivariable linear regression analysis. After univariable analysis only in 'fatigue' score a p<0.1 was found. After multivariable analysis no significant or clinically relevant differences were found in patients with either a cervical or intrathoracic anastomosis after TTE (data not shown).

DISCUSSION

This study investigated long-term HR-QoL in disease-free patients following either a TTE or a THE for distal esophageal and GEJ cancer. All patients reported impaired quality of life compared to the general population in 'role functioning' and 'social functioning' and as expected, in a range of disease- and/or treatment specific symptoms. The long-term HR-QoL was, in general, not significantly different between patients who had undergone TTE or THE. Patients following TTE reported fewer problems with hair loss compared to THE. Subgroup

analysis of minimally invasively operated patients showed better physical functioning in patients following TTE than THE. Subgroup analysis of patients following neoadjuvant therapy showed no differences in HR-QoL between TTE and THE. These few differences in HR-QoL do not have a decisive effect when choosing between the two surgical approaches. However, hair loss and physical functioning can impact daily social and physical activities adversely and may have a major impact on patients' well-being. Therefore, patients should be informed of these possible long-term effects on HR-QoL before surgery.

Earlier studies reported that the inevitable postoperative decrease in HR-QoL is restored within one year after esophagectomy in disease-free patients [31, 32]. This is also seen in patients following TTE and THE, as overall, no significant differences in HR-QoL have been reported that last up to one [6] or three years postoperatively [3, 5]. Only one study reported more 'nausea and vomiting', 'dyspnea' and 'constipation' 12 months after open TTE compared to open THE [4]. However, the results of these studies may not be completely applicable to current clinical practice as they were performed before the implementation of neoadjuvant therapy and minimally invasive esophagectomy in the treatment of esophageal cancer [7, 20]. In our study, patients reported less problems with hair loss after TTE compared to THE. This difference could be due to the administration of less chemotherapy in the TTE group. Similarly, a recent meta-analysis showed that patients reported more hair loss after chemotherapy and esophagectomy compared to patients after chemoradiotherapy and esophagectomy [33].

When minimally invasive esophagectomy is compared with open esophagectomy, better HR-QoL is found in 'global QoL', 'physical functioning', 'fatigue' and 'pain' domains at three months following a minimally invasive esophagectomy [34]. However, no difference in HR-QoL was observed after a follow-up of 12 months. In our study no subgroup analysis of HR-QoL could be performed between minimally invasive esophagectomy and open esophagectomy due to the small number of patients following open esophagectomy (N=20 in TTE group and N=34 in THE group). However, a subgroup analysis was performed for all minimally invasively operated patients and only one HR-QoL domain – 'physical functioning' - was found to be better following TTE compared to THE. Patients in the minimally invasive TTE group were significantly younger than patients in the minimally invasive THE group (median 64 years [IQR 57-69] versus median 68 years [IQR 62-74], p=0.043). We therefore corrected for age during multivariable analysis. As only a small number of patients were included in this subgroup, further investigation of HR-QoL is required employing larger sample sizes.

During neoadjuvant therapy patients in previous studies have reported worse HR-QoL, which restores to baseline levels after completion of neoadjuvant therapy [9, 12, 14, 35]. Postoperative HR-QoL does not seem to be influenced by neoadjuvant treatment in patients with esophageal cancer [10-14]. In both chemoradiotherapy and esophagectomy compared

to esophagectomy alone groups, a decline in HR-QoL is seen at three months postoperatively [10, 13]. Only one study reported less dysphagia, nausea and vomiting problems at three months follow-up in patients who received neoadjuvant treatment compared to surgery alone group [12]. Overall, a gradual improvement of HR-QoL to baseline level is seen at 12 months follow-up [10, 35], which remains stable the subsequent six years [11]. Our results are comparable to previous studies, as no difference in HR-QoL after a follow-up of two years was found in subgroup analysis of patients following neoadjuvant therapy between TTE and THE.

This study has some limitations. The study is prone to selection bias because of the nature of the inclusion process. Only patients who were still actively followed up at the outpatient clinic were eligible for inclusion. Patients who died, had recurrent disease, were lost to follow-up, or who were unwilling to participate, did not participate in this study, which may have led to a general bias towards the inclusion of patients who fare reasonably well. Furthermore, the results can be affected by the differences in baseline patient, treatment and tumor characteristics between TTE and THE groups. Patients after TTE were younger, received more often neoadjuvant chemoradiotherapy and were more often operated minimally invasively compared to patients after THE. This is mainly attributable to the time period in which patients were operated, where TTE gradually has replaced THE. This also explains the difference in follow-up. Apart from being operated upon in different time periods, the procedure of choice may have been dependent on localization and stage of disease. This may have led to additional selection bias. Also, in the TTE group both cervical and intrathoracic anastomoses were included, what could contribute to some heterogeneity, although a recent study showed largely comparable results in HR-QoL following a transthoracic esophagectomy with either a cervical or intrathoracic anastomosis [36]. Also in this study, subgroup analysis in patients with either a cervical or intrathoracic anastomosis following TTE did not show any significant or clinically relevant results. Furthermore, (y)pT stage and lymph node count were different between the two groups. We tried to minimize the effect of selection bias by correcting for these confounders in multivariable linear regression analysis. In addition, since this study did not employ a baseline HR-QoL measurement, we cannot exclude the possibility that QoL differed *a priori* between the two groups. An ongoing prospective observational cohort study of esophageal and gastric cancer patients collecting clinical data and HR-QoL prior to and following TTE and THE, will shed light on possible *a priori* HR-QoL differences (POCOP trial, NCT 02070146) [37]. Furthermore, no formal sample size calculation was performed and the number of statistical tests is high in relation to the sample size. We therefore used a Bonferroni correction for multiple testing. Moreover, the EORTC defined a mean difference of at least 10 points as clinically relevant. Nonetheless, we believe that the results of this study are valuable, since they provide a good insight in the wellbeing of disease-free patients after TTE and THE. Furthermore, this study employs a naturally occurring sample, has a relatively large sample size, a high response

rate and a long follow-up. Also, this study was the first to investigate long-term HR-QoL of patients who were operated minimally invasively and patients who received neoadjuvant therapy separately.

CONCLUSION

Long-term HR-QoL results are in general not different between disease-free patients following either TTE or THE for distal esophageal or GEJ cancer. The small differences that were found, were in the advantage of a TTE. These findings may aid in providing information to esophageal or GEJ cancer patients on what to expect regarding postoperative QoL. Future studies should include baseline measurements of HR-QoL. Because of the small differences in HR-QoL between THE and TTE, the oncological preference should be leading in the choice of procedure.

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SUPPLEMENT

Supplementary table 1: Multivariable linear regression analysis of patients after transthoracic or transhiatal esophagectomy.

	Covariates	B	95%CI		p-value
			Lower	Upper	
Emotional functioning	TTE	-3.0	-13.683	7.761	0.586
	Age	0.3	-0.175	0.748	0.222
	Gender	4.2	-6.384	14.835	0.432
	Tumor location				
	Neoadjuvant treatment (yes/no)				
	Neoadjuvant therapy (CH/CRT)	-3.7	-21.474	14.026	0.679
	Surgical approach	5.5	-5.818	16.800	0.339
	pT stage				
	Lymph node yield				
	Follow-up	0.3	0.089	0.602	**0.009**
Social functioning	TTE	15.0	2.724	27.230	**0.017**
	Age	0.7	0.118	1.191	**0.017**
	Gender	8.0	-4.276	20.219	0.200
	Tumor location				
	Neoadjuvant treatment (yes/no)				
	Neoadjuvant therapy (CH/CRT)	-9.7	-30.339	10.939	0.354
	Surgical approach	6.4	-4.841	17.713	0.261
	pT stage				
	Lymph node yield				
	Follow-up				
Constipation	TTE	-3.1	-11.794	5.502	0.473
	Age	0.2	-0.123	0.591	0.196
	Gender	-7.2	-15.666	1.215	0.093
	Tumor location				
	Neoadjuvant treatment (yes/no)				
	Neoadjuvant therapy (CH/CRT)	-7.6	-21.475	6.353	0.284
	Surgical approach	-4.8	-12.672	3.029	0.227
	pT stage	1.3	-1.153	3.745	0.297
	Lymph node yield	0.1	-0.226	0.412	0.564
	Follow-up				
Hair loss	TTE	-29.4	-49.108	-9.671	**0.004**
	Age	-1.5	-2.647	-0.281	**0.016**
	Gender	-27.3	-48.143	-6.403	**0.012**
	Tumor location				
	Neoadjuvant treatment (yes/no)				
	Neoadjuvant therapy (CH/CRT)	22.0	-14.115	58.202	0.226
	Surgical approach				
	pT stage				
	Lymph node yield				
	Follow-up				

Bold values represent significance. B=regression coefficient, CI=confidence interval. TTE is the reference to which THE is compared. CH = chemotherapy, CRT = chemoradiotherapy.

Supplementary table 2: Subgroup univariable and multivariable linear regression analysis of HR-QoL after transthoracic and transhiatal esophagectomy in patients who received neoadjuvant treatment and who were operated minimally invasively.

		Transthoracic esophagectomy Mean (SD) N(neo)=116 N(MI)=112	**Transhiatal esophagectomy** Mean (SD) N(neo)=34 N(MI)=22
EORTC QLQ-C30			
Global Health	NT	73.1 (19.7)	75.3 (24.2)
	MI	72.9 (19.8)	67.5 (24.7)
Functioning			
Physical functioning	NT	82.9 (19.6)	76.6 (21.9)
	MI	82.5 (18.7)	74.7 (21.1)
Role functioning	NT	75.7 (26.5)	72.2 (31.6)
	MI	74.5 (27.2)	73.9 (31.7)
Emotional functioning	NT	78.4 (23.9)	84.1 (23.3)
	MI	78.3 (23.7)	80.8 (23.4)
Cognitive functioning	NT	83.4 (23.4)	83.3 (14.4)
	MI	83.6 (23.3)	84.1 (14.4)
Social functioning	NT	79.7 (25.4)	66.5 (35.2)
	MI	79.0 (25.8)	73.5 (32.8)
Symptom scores			
Fatigue	NT	31.0 (27.1)	32.7 (31.6)
	MI	32.0 (26.2)	38.1 (29.8)
Nausea and vomiting	NT	14.6 (23.0)	10.1 (14.2)
	MI	14.9 (23.0)	13.3 (19.7)
Pain	NT	18.0 (24.8)	14.7 (25.5)
	MI	17.3 (23.5)	9.9 (17.6)
Dyspnea	NT	28.2 (29.0)	28.4 (31.9)
	MI	29.8 (29.1)	22.7 (34.7)
Insomnia	NT	26.8 (32.0)	16.7 (26.3)
	MI	26.3 (31.1)	15.2 (22.4)
Appetite loss	NT	19.6 (30.0)	15.7 (28.7)
	MI	19.3 (30.4)	13.6 (26.5)
Constipation	NT	7.9 (16.2)	16.2 (23.7)
	MI	7.2 (15.2)	15.9 (27.1)
Diarrhea	NT	13.5 (20.1)	16.2 (22.2)
	MI	16.1 (21.5)	15.9 (25.0)
Financial difficulties	NT	27.9 (29.3)	34.3 (42.1)
	MI	28.3 (28.2)	28.6 (39.8)

	Univariable analysis				Multivariable analysis†			
B	95%CI		p-value	B	95%CI		p-value	Corrected p-value‡
	Lower	Upper			Lower	Upper		
2.2	-5.933	10.418	0.589					
-5.4	-15.113	4.280	0.271					
-6.3	-14.115	1.419	0.108					
-7.8	-16.679	0.984	0.081*	13.8	2.755	24.933	**0.015**	**0.030**
-3.4	-14.229	7.380	0.532					
-0.6	-13.536	12.305	0.925					
5.7	-3.589	14.934	0.228					
2.5	-8.634	13.594	0.660					
-0.1	-8.567	8.424	0.987					
0.6	-9.845	10.986	0.914					
-13.1	-26.203	-0.081	**0.049***	13.4	1.623	25.187	**0.026**	0.104
-5.5	-17.963	6.947	0.383					
1.7	-9.148	12.583	0.755					
6.1	-6.272	18.497	0.331					
-4.5	-10.955	1.923	0.167					
-1.6	-11.990	8.776	0.760					
-3.3	-12.903	6.373	0.504					
-7.4	-17.870	3.032	0.163					
0.3	-11.174	11.715	0.963					
-7.0	-20.910	6.841	0.318					
-10.1	-22.010	1.752	0.094*	6.3	-7.221	19.748	0.360	1.440
-11.1	-24.891	2.665	0.113					
-4.0	-15.417	7.515	0.497					
-5.7	-19.415	8.099	0.417					
8.3	-0.625	17.159	0.068*	-4.6	-12.819	3.662	0.274	1.096
8.7	-3.952	21.283	0.169					
2.7	-5.380	10.692	0.515					
-0.2	-10.560	10.163	0.973					
6.5	-9.298	22.284	0.411					
0.3	-18.469	19.097	0.973					

Supplementary table 2: Continued

		Transthoracic esophagectomy Mean (SD) N(neo)=116 N(MI)=112	Transhiatal esophagectomy Mean (SD) N(neo)=34 N(MI)=22
EORTC QLQ-OG25			
Functioning			
Body image	NT	77.4 (32.9)	67.7 (39.4)
	MI	76.5 (33.9)	83.3 (26.7)
Symptom scores			
Dysphagia	NT	11.2 (16.9)	16.3 (18.8)
	MI	11.1 (16.7)	14.1 (19.8)
Eating	NT	26.0 (24.7)	29.2 (31.6)
	MI	26.3 (25.1)	30.6 (35.1)
Reflux	NT	22.6 (28.3)	20.3 (23.0)
	MI	22.5 (28.7)	23.1 (24.7)
Odynophagia	NT	10.2 (20.9)	9.8 (18.4)
	MI	10.8 (21.1)	9.9 (19.0)
Pain and discomfort	NT	17.1 (27.7)	14.7 (19.6)
	MI	16.0 (27.2)	13.6 (16.8)
Anxiety	NT	31.4 (29.7)	26.0 (32.4)
	MI	30.9 (28.6)	25.8 (29.9)
Eating with others	NT	14.5 (25.1)	19.6 (28.6)
	MI	13.4 (24.2)	18.2 (30.4)
Dry mouth	NT	19.1 (27.1)	13.7 (20.3)
	MI	18.2 (25.7)	24.2 (29.4)
Trouble with taste	NT	12.5 (22.4)	8.8 (22.2)
	MI	13.2 (23.8)	7.6 (22.8)
Trouble swallowing saliva	NT	9.8 (21.0)	9.9 (21.4)
	MI	10.6 (22.5)	16.7 (26.7)
Choked when swallowing	NT	15.8 (24.9)	19.6 (29.7)
	MI	17.3 (25.2)	19.7 (30.3)
Trouble with coughing	NT	32.1 (31.9)	23.5 (32.3)
	MI	34.9 (31.4)	27.3 (36.6)
Trouble talking	NT	8.1 (17.1)	8.8 (17.0)
	MI	7.8 (17.0)	1.5 (7.1)
Weight loss	NT	24.5 (30.6)	20.0 (33.4)
	MI	23.2 (30.6)	18.3 (33.3)
Hair loss	NT	15.7 (30.0)	29.2 (32.2)
	MI	15.7 (27.6)	26.7 (36.5)

NT = neoadjuvant therapy. MI = minimally invasive esophagectomy. N (neo) = number of patients after neoadjuvant therapy. N(MI) = number of patients after minimally invasive surgery. Regression coefficient (B) with 95% confidence interval (CI) are shown for univariable and multivariable analysis. †=Corrected for confounders (Supplementary table 3 and 4). *=Health-related quality of life (HR-QoL) domains with p<0.1 in univariable analysis were entered in multivariable analysis. ‡= p-value corrected for multiple testing according to Bonferroni method.

	Univariable analysis				Multivariable analysis[†]				
	B	95%CI		p-value	B	95%CI		p-value	Corrected p-value[‡]
		Lower	Upper			Lower	Upper		
	-9.7	-23.059	3.633	0.152					
	6.9	-6.449	20.184	0.303					
	5.2	-1.508	11.868	0.128					
	3.1	-4.879	11.041	0.445					
	3.2	-8.668	15.076	0.590					
	4.3	-11.873	20.461	0.589					
	-2.2	-12.715	8.268	0.676					
	0.6	-12.402	13.598	0.928					
	-0.4	-8.324	7.477	0.916					
	-1.0	-10.621	8.683	0.843					
	-2.4	-12.477	7.671	0.638					
	-2.4	-14.335	9.520	0.690					
	-5.4	-17.133	6.286	0.362					
	-5.1	-18.412	8.214	0.450					
	5.2	-4.885	15.192	0.312					
	4.8	-6.935	16.507	0.421					
	-5.3	-15.272	4.628	0.292					
	6.0	-6.205	18.212	0.332					
	-3.7	-12.335	4.982	0.403					
	-5.6	-16.579	-16.579	0.311					
	-0.1	-8.325	8.168	0.985					
	6.1	-4.692	16.813	0.267					
	3.8	-6.260	13.928	0.096*	-9.0	-20.272	2.227	0.115	0.460
	2.4	-9.652	14.478	0.693					
	-8.6	-21.008	3.781	0.172					
	-7.6	-22.544	7.337	0.316					
	0.7	-5.896	7.323	0.831					
	-6.3	-10.721	-1.836	**0.006***	7.3	-2.504	17.171	0.142	0.284
	-4.5	-17.158	8.199	0.486					
	-4.9	-19.850	10.066	0.519					
	13.5	-5.327	32.349	0.156					
	11.0	-16.964	38.987	0.430					

Supplementary table 3: Multivariable linear regression analysis of patients after minimally invasive transthoracic and transhiatal esophagectomy.

	Covariates	B	95%CI		p-value
			Lower	Upper	
Physical functioning	TTE	13.8	2.755	24.933	**0.015**
	Age	0.1	-0.307	0.552	0.572
	Gender	3.0	-7.756	13.844	0.578
	Neoadjuvant treatment (yes/no)				
	Neoadjuvant therapy (CH/CRT)	-8.4	-28.280	11.473	0.404
	cN stage				
	Lymph node yield				
Trouble talking	TTE	7.3	-2.504	17.171	0.142
	Age	0.1	-0.248	0.533	0.471
	Gender	-2.6	-12.162	7.015	0.596
	Neoadjuvant treatment (yes/no)				
	Neoadjuvant therapy (CH/CRT)	-4.8	-22.426	12.865	0.592
	cN stage				
	Lymph node yield				

Bold values represent significance. B = regression coefficient. CI = confidence interval. CH = chemotherapy. CRT = chemoradiotherapy

Supplementary table 4: Multivariable linear regression analysis of patients after transthoracic and transhiatal esophagectomy who received neoadjuvant treatment.

	Covariates	B	95%CI		p-value
			Lower	Upper	
Social functioning	TTE	13.4	1.623	25.187	0.026
	Age	0.6	0.103	1.174	0.020
	Gender	8.3	-3.951	20.497	0.183
	Follow-up				
	ASA classification				
	Surgical approach	6.3	-5.009	17.520	0.274
	pT stage				
	Lymph node yield				
Insomnia	TTE	6.3	-7.221	19.748	0.360
	Age	-0.5	-1.137	0.064	0.080
	Gender	-4.0	-17.913	9.937	0.572
	Follow-up				
	ASA classification				
	Surgical approach	-5.0	-18.080	8.018	0.447
	pT stage				
	Lymph node yield	0.4	-0.126	0.921	0.135
Constipation	TTE	-4.6	-12.819	3.662	0.274
	Age	0.2	-0.134	0.579	0.219
	Gender	-7.2	-15.634	1.255	0.095
	Follow-up				
	ASA classification				
	Surgical approach	-5.1	-12.957	2.712	0.198
	pT stage	1.4	-1.061	3.829	0.265
	Lymph node yield	0.1	-0.183	0.441	0.415
Choked when swallowing	TTE	-9.0	-20.272	2.227	0.115
	Age	-0.2	-0.696	0.334	0.488
	Gender	-12.3	-23.816	-0.699	0.038
	Follow-up				
	ASA classification				
	Surgical approach	9.0	-1.798	19.852	0.101
	pT stage	-2.0	-5.557	1.464	0.251
	Lymph node yield				

Bold values represent significance. B = regression coefficient, CI = confidence interval. CH = chemotherapy. CRT = chemoradiotherapy.

Chapter 5

Information needs in patients with potentially curable gastro-esophageal cancer

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ABSTRACT

Purpose

To examine (i) information needs of patients with and without postoperative complications, (ii) information needs of male and female patients and (iii) association between information needs and health-related quality of life (HR-QoL) following gastro-esophageal cancer surgery.

Methods

Patients were asked to complete EORTC QLQ-INFO25, EORTC QLQ-C30 & EORTC QLQ-OG25 questionnaires before and following curative surgery for gastro-esophageal cancer at the outpatient clinic between 2014-2018. Five information needs domains were investigated: information about the disease, about treatments, about medical tests, about things patients can do to help themselves and overall helpfulness. HR-QoL domains global health status, eating restrictions and anxiety were also investigated.

Results

A total of 132 patients completed the questionnaires at baseline, 216 at 6-12 months, 184 at 18-24 months and 163 at 3-5 years postoperatively. No significant differences in information needs were observed between patients with or without complications and between male and female patients. Of all patients at the different time points, 18.1%-23.5% reported that they did not receive any information about the things that they could do to help themselves. Information was reported to be more helpful by patients with higher global health status at 6-12 months ($p<0.001$), 18-24 months ($p<0.001$) and 3-5 years ($p=0.001$), and by patients with more anxiety at 18-24months ($p=0.009$) and 3-5years ($p<0.001$).

Conclusion

No differences in information needs in curatively treated gastro-esophageal cancer patients were observed between male and female patients and between patients with and without postoperative complications. However, information was reported to be more helpful in patients with higher global health status and more anxiety at different time points. These results partially support a personalized approach.

Implications for Cancer Survivors

This study demonstrates that gender and postoperative complications have no impact on information needs of curatively treated gastro-esophageal cancer patients, and shows that information is perceived to be more helpful in certain patient groups

INTRODUCTION

A fluent information exchange is the basis of a good relationship between a doctor and a patient. Receiving adequate information can help patients to feel more in control, to better understand the course of their treatment and to support the decision-making process [1]. Patients require information over a long period of time, starting at the time of the first doctor's visit. Cancer patients report a need for information about their treatment and recovery during diagnosis, treatment and post-treatment period [2]. Overall, patients with cancer report to be well-informed before surgery. Nevertheless, up to 51.6% of these patients indicate they wish that they had received more information [3]. Various factors have been found to be associated with more information needs in patients with cancer, such as the occurrence of postoperative complications, female gender, impaired health-related quality of life (HR-QoL) after surgery, younger age, having a partner and a lower education level [2, 4-7]. However, knowledge regarding information needs of patients with gastro-esophageal cancer is scarce. These patients may have different information needs as these patients often undergo major, complex surgical procedures that are frequently accompanied by postoperative complications and decreased quality of life (42-65%) [8-10]. In addition, the majority of gastro-esophageal cancer patients is male [11]. Four studies investigated information needs of esophageal cancer patients. Two studies promoted information provision to patients with esophageal cancer by developing a web-based question prompt sheet and by establishing a minimum set of information items [12, 13]. In addition to these studies that assist information provision, only two studies investigated the difference in information needs between different groups of patients with esophageal cancer. A small cohort study identified cultural differences in information needs between Italian (N=72) and Dutch (N=72) esophageal cancer patients [14]. Overall, Dutch patients were found to be more satisfied with the information received at diagnosis, and Italian patients reported more satisfaction with the information about the disease during neoadjuvant therapy. Lastly, in a recent study, the information needs of patients treated with curative (N=90) or palliative (N=22) intent were compared [15], and relation with HR-QoL was investigated. Patients who received palliative treatment reported to be less informed and less satisfied with the provided information. Some information items were associated with global health status and anxiety. The difference in information needs between gastro-esophageal cancer patients with and without postoperative complications and between male and female patients has not yet been investigated.

The aim of this study was to investigate the information needs of curatively treated gastroesophageal cancer patients and investigate possible differences between males and females and between patients with and without postoperative complications. Furthermore, we aimed to examine the association between information needs and HR-

QoL. We expected to find more information needs in gastro-esophageal cancer patients with postoperative complications, in female patients and in patients with impaired HR-QoL.

METHODS

Study design and patient population

This prospective comparative cohort study was performed in a tertiary referral center from October 2014 until October 2018. All consecutive patients who underwent an esophagectomy or a (sub)total gastrectomy for esophageal, gastroesophageal junction (GEJ) or gastric cancer between 2003 and 2018 were included. Patients following resection for a gastrointestinal stromal tumor, salvage procedures, and patients with a colonic interposition or no reconstruction were excluded from this study. Patients were asked to complete the questionnaires during the outpatient clinic visits at baseline (before surgery), at 6-12 months, at 18-24 months and at 3-5 years follow-up. Each patient completed the questionnaires at one or multiple time points, therefore the cohorts at baseline, at 6-12 months, at 18-24 months and at 3-5 years follow-up are not independent of each other.

The ethical approval of this study was waived by the Institutional Review Board of Amsterdam UMC (location AMC). Written informed consent was provided by all participants. The STROBE guidelines were followed for the structure of this article [16].

Treatment

Patients with esophageal or gastro-esophageal junction cancer were usually treated with neoadjuvant chemoradiotherapy [17]. Patients with gastric cancer usually received perioperative chemotherapy (Epirubicin, Oxaliplatin and Capecitabine) [18] or, if included in the CRITICS trial, were randomized to perioperative chemotherapy or preoperative chemotherapy and adjuvant chemoradiotherapy [19].

The type of esophageal or gastric cancer surgery depended on patient and tumor characteristics and included a transthoracic esophagectomy with gastric tube reconstruction with a cervical or intrathoracic anastomosis, a transhiatal esophagectomy with gastric tube reconstruction, a total gastrectomy with or without distal esophagectomy with a Roux-Y reconstruction and a subtotal gastrectomy with a Roux-Y reconstruction. Operations were either performed minimally invasively, open or hybrid.

Patient, tumor and treatment characteristics, and postoperative complications

The prospectively maintained database of Amsterdam UMC was used to obtain clinical data of patient, tumor and treatment characteristics. Recorded characteristics included age, gender, tumor location (mid esophagus, distal esophagus, GEJ and gastric), comorbidities (cardiovascular, pulmonary, diabetic or other), American Society of Anaesthesiologists (ASA)

classification, type of surgery (transthoracic or transhiatal esophagectomy, esophagectomy with an intrathoracic anastomosis [Ivor Lewis], esophagectomy with a cervical anastomosis [McKeown], total gastrectomy, subtotal gastrectomy, total gastrectomy with distal esophagectomy), surgical approach (minimally invasive, hybrid, open), neoadjuvant therapy (no, chemotherapy, chemoradiotherapy), adjuvant therapy (no, chemotherapy, chemoradiotherapy), recurrence (yes/no). Recorded postoperative complications, defined according to the Esophagectomy Complications Consensus Group (ECCG) criteria [20], included anastomotic leakage, supraventricular fibrillation, pneumonia, intra-abdominal abscess, wound infection, recurrent nerve palsy, re-operation, pulmonary embolism, chyle leakage, admission to the Intensive Care Unit and sepsis. The severity of complications was scored according to the Clavien-Dindo classification [21, 22].

Information needs

The validated European Organization for Research and Treatment of Cancer (EORTC) information needs of cancer patients questionnaire (EORTC QLQ-INFO25) contains 25 items from which scores for 13 domains can be calculated [23, 24]. We selected five of these domains (15 items) that are most applicable to daily clinical practice: information about the disease, information about treatments, information about medical tests, information about things patients can do to help themselves and whether the information was helpful.

We further selected topics from the EORTC QLQ-INFO25 questionnaire that patients need to be minimally informed about. These concerned the following seven items: How much information did you receive during your current illness or treatment about 1. The diagnosis of your disease?, 2. Whether the disease is under control?, 3. The results of the medical tests you have already received?, 4. The medical treatment (chemotherapy, radiotherapy, surgery or other treatment modality)?, 5. The expected benefit of the treatment?, 6. Things that you can do to help yourself get well (e.g. rest, contact with others)? and 7. Overall has the information you have received been helpful?. For these items, we examined the percentages of patients who indicated not to have received information at all. The aim was to find out on which topics the patients experienced a lack of information and to be able to select specific topics that doctors and other medical practitioners should focus on more when informing the patients during daily (out-patient) clinical practice.

The 15 questions of the five selected information needs domains employ four response options: (1) not at all, (2) a little, (3) quite a bit and (4) very much. The responses of the five selected information needs domains were linearly transformed into 0-100 scores. A higher score was indicative of more information received. The responses of the seven selected items were dichotomized into not at all versus a little to very much.

Health-related quality of life

The cancer-specific EORTC-QLQ-C30 and GEJ cancer specific EORTC-QLQ-OG25 questionnaires were used [25, 26]. EORTC-QLQ-C30 and EORTC-QLQ-OG25 contain 15 and 16 domains, respectively. Three HR-QoL domains, global health status (EORTC-QLQ-C30), eating restrictions (EORTC-QLQ-OG25) and anxiety (EORTC-QLQ-OG25), were selected for analysis in this study because they have previously been shown to be associated with various information needs domains in esophageal and other cancer patients. [3, 4, 14, 15, 27-29].

The global health status domain consisted of the scores of two questions with answers ranging from (1) very poor to (7) excellent. The eating restrictions and anxiety domains consisted of questions with answers ranging from (1) not at all to (4) very much. The responses of these domains were linearly transformed into 0-100 scores [30]. A higher score in global health status represents better global health status and a higher score in eating restrictions and anxiety represents more eating restrictions and more anxiety, respectively.

Statistical analysis

Differences in continuous patient, tumor and treatment variables were analyzed using Student t-test in case of normal distributions (shown as means with standard deviations [SD]) and Mann-Whitney U test in case of non-normal distributions (shown as medians with interquartile ranges [IQR]). Categorical baseline variables were analyzed using $\chi 2$ test and Fisher's exact test.

Univariable linear regression analysis was used to evaluate the differences in information needs between patients with and without postoperative complications at three time points: at 6-12 months, at 18-24 months and at 3-5 years follow-up. The percentage of patients who reported not to have received any information at all was calculated for all seven information needs items and compared with the percentage of patients who reported to have received at least a little bit of information at baseline, at 6-12 months, at 18-24 months and at 3-5 years follow-up. The difference in information needs between male and female patients, and the association between information needs and global health status, eating restrictions and anxiety HR-QoL domains, were investigated at baseline, at 6-12 months, at 18-24 months and at 3-5 years follow-up, using univariable linear regression analysis. All p-values were corrected for multiple testing by multiplication by the total number of tests performed, according to the Bonferroni correction. Although clinically relevant difference in mean scores varies between information needs domains [23], a mean score difference of more than 10 points was considered clinically relevant for this study as is it most likely the upper bound for most information needs domains. A p value of <0.01 was considered statistically significant. SPSS 26.0 software (SPSS, Inc., Chicago, IL, USA) was used for statistical analysis.

RESULTS

Patients, tumor and treatment characteristics

A total of 132 patients completed the questionnaires at baseline, 216 at 6-12 months, 184 at 18-24 months and 163 at 3-5 years follow-up (Table 1). The majority of patients at all time points had not had postoperative complications (52.8%-59.1%) and the majority was male (73.5%-78.8%). At baseline, most patients had GEJ/cardia cancer (43.9%) and at 6-12 months (54.6%), 18-24 months (63.0%) and at 3-5 years (71.2%) follow-up, most patients had distal esophageal cancer. The majority of patients at all time points received neo-adjuvant chemoradiotherapy (77.2%-80.9%) and were operated minimally invasively (73.6%-95.8%). Only the minority of patients received adjuvant treatment (19.0%-38.4%).

Table 1: Background characteristics of all patients after esophageal or gastric cancer surgery between 2003 – 2018.

		Baseline		6-12 months follow-up		18-24 months follow-up		3-5 years follow-up	
N		**132**		**216**		**184**		**163**	
Age (median [IQR]. yrs)		67	[60-71]	64	[58-70]	65	[58-71]	64	[58-69]
Gender	**Male**	97	(73.5)	163	(75.5)	145	(78.8)	123	(75.5)
Tumor location	**Distal esophagus**	51	(38.6)	118	(54.6)	116	(63.0)	116	(71.2)
	Mid esophagus	11	(8.3)	7	(3.2)	2	(1.1)	0	(0)
	GEJ/cardia	58	(43.9)	71	(32.9)	49	(26.6)	38	(23.3)
	Gastric	12	(9.1)	20	(9.3)	17	(9.2)	9	(5.5)
Comorbidity	**No**	60	(45.5)	112	(51.9)	92	(50.0)	91	(55.8)
	Cardiovascular	57	(43.2)	79	(36.6)	79	(42.9)	57	(35.0)
	Pulmonary	15	(11.4)	22	(10.2)	15	(8.2)	17	(10.4)
	Diabetic	14	(10.6)	23	(10.6)	21	(11.4)	17	(10.4)
ASA classification	**1**	18	(13.6)	58	(26.9)	53	(28.8)	44	(27.0)
	2	77	(58.3)	110	(50.9)	91	(49.5)	91	(55.8)
	3	37	(28.0)	48	(22.2)	40	(21.7)	28	(17.2)
Neo-adjuvant therapy	**No**	18	(13.6)	35	(16.2)	30	(16.3)	22	(13.5)
	Yes	114	(86.4)	181	(83.8)	154	(83.7)	141	(86.5)
	CTx	26	(22.8)	47	(26.0)	39	(25.3)	27	(19.1)
	CRTx	88	(77.2)	134	(74.0)	115	(74.7)	114	(80.9)
Operation	**Ivor Lewis esophagectomy**	79	(59.8)	124	(57.4)	84	(45.7)	48	(29.4)
	McKeown esophagectomy	25	(18.9)	47	(21.8)	58	(31.5)	91	(55.8)
	Total gastrectomy	11	(8.3)	20	(9.3)	28	(15.2)	17	(10.4)
	Subtotal gastrectomy	15	(11.4)	24	(11.1)	14	(7.6)	7	(4.3)
	Total gastrectomy with distal esophagectomy	2	(1.5)	1	(0.5)	0	(0)	0	(0)
Approach	**Minimally invasive**	118	(89.4)	207	(95.8)	171	(92.9)	120	(73.6)
	Open	14	(10.6)	9	(4.2)	13	(7.1)	43	(26.4)
Adjuvant therapy	**No**	82	(62.1)	133	(61.6)	132	(71.7)	132	(81.0)
	Yes	50	(37.9)	83	(38.4)	52	(28.3)	31	(19.0)
	CTx	50	(100)	81	(97.6)	50	(96.2)	26	(83.9)
	CRTx	0	(0)	2	(2.4)	2	(3.8)	5	(16.1)
Recurrance	**Yes**	22	(16.7)	19	(8.8)	7	(3.8)	2	(1.2)
Complications according to Clavien-Dindo grade	**Grade 0**	78	(59.1)	123	(56.9)	98	(53.3)	86	(52.8)
	Grade 1	8	(6.1)	16	(7.4)	8	(4.3)	8	(4.9)
	Grade 2	17	(12.9)	28	(13.0)	26	(14.1)	33	(20.2)
	Grade 3A	11	(8.3)	22	(10.2)	26	(14.1)	11	(6.7)
	Grade 3B	2	(1.5)	3	(1.4)	0	(0)	0	(0)
	Grade 4A	13	(9.8)	22	(10.2)	23	(12.5)	21	(12.9)
	Grade 4B	1	(0.8)	2	(0.9)	3	(1.6)	4	(2.5)
	Grade 5	2	(1.5)	0	(0)	0	(0)	0	(0)
Specific postoperative complications	**Atrial fibrillation**	22	(40.7)	28	(30.1)	33	(38.8)	28	(36.8)
	Anastomotic leakage	16	(29.6)	26	(28.0)	32	(37.6)	27	(35.5)
	Pneumonia	8	(14.8)	12	(12.9)	21	(24.7)	23	(30.3)
	Other	28	(51.9)	54	(58.1)	37	(43.5)	27	(35.5)

N = number of patients. Data are presented as n (%) unless otherwise indicated. ASA = American Society of Anesthesiologists Classification. Ivor Lewis = esophagectomy with an intrathoracic anastomosis. McKeown = esophagectomy with a cervical anastomosis. GEJ = gastroesophageal junction. CTx = chemotherapy. CRTx = chemoradiotherapy.

Information needs of all patients following esophageal and gastric cancer surgery

The highest percentage of patients who reported not to have received information at all was in the domain 'things they can do to help themselves get well' (18.1% to 23.5%) (Table 2). The percentage of patients who did not find the received information helpful at all ranged from 0% to 1.4%.

Table 2: The reported information received by patients following esophageal and gastric cancer surgery at baseline (N=132), at 6-12 months (N=216), at 18-24 months (N=184) and at 3-5 years (N=163) follow-up cohorts.

EORTC QLQ-INFO25 questions	The amount of information received	Baseline		6-12 months		18-24 months		3-5 years	
		N	%	N	%	N	%	N	%
1. The diagnosis of your disease?	(1) no at all	1	0.8	4	1.9	8	4.3	3	1.8
	(2) a little, (3) quite a bit or (4) very much	131	99.2	212	98.1	176	95.7	160	98.2
2. Whether the disease is under control?	(1) no at all	22	16.7	17	7.9	16	8.7	12	7.4
	(2) a little, (3) quite a bit or (4) very much	110	83.3	199	92.1	168	91.3	151	92.6
3. The results of the medical tests you have already received?	(1) no at all	2	1.5	10	4.6	12	6.5	8	4.9
	(2) a little, (3) quite a bit or (4) very much	130	98.5	206	95.4	172	93.5	155	95.1
4. The medical treatment (chemotherapy. radiotherapy. surgery or other treatment modality)?	(1) no at all	6	4.5	8	3.7	12	6.5	12	7.4
	(2) a little, (3) quite a bit or (4) very much	126	95.5	208	96.3	172	93.5	151	92.6
5. The expected benefit of the treatment?	(1) no at all	9	4.5	10	4.6	9	4.9	7	4.3
	(2) a little, (3) quite a bit or (4) very much	126	95.5	206	95.4	175	95.1	156	95.7
6. Things that you can do to help yourself get well (e.g. rest. contact with others)?	(1) no at all	31	23.5	39	18.1	36	19.6	38	23.3
	(2) a little, (3) quite a bit or (4) very much	101	76.5	177	81.9	148	80.4	125	76.7
7. Overall has the information you have received been helpful?	(1) not at all	0	-	3	1.4	1	0.5	1	0.6
	(2) a little, (3) quite a bit or (4) very much	132	100	213	98.6	183	99.5	162	99.4

N = number of patients.

Background characteristics and information needs of patients with and without postoperative complications

Comparing the group with postoperative complications to the group without complications, a significantly higher rate of pulmonary comorbidity was observed at 3-5 years of follow-up (15.6% vs 5.8%, p=0.042) in the group with postoperative complications (Supplementary Table 1). Furthermore, at 6-12 months and at 18-24 months, a higher rate of patients with postoperative complications had undergone an Ivor Lewis esophagectomy compared to patients without complications (58.1% vs 56.9%, p=0.025 and 46.5% vs 44.9%, p=0.005). At 3-5 years follow-up, the majority of patients with postoperative complications had undergone a McKeown esophagectomy compared to patients without complications (59.7% vs 52.3%, p=0.021).

Univariable linear regression analysis of information needs between patients with and without postoperative complications showed that none of the information needs domains were found to be either significantly or clinically different between the two groups at 6-12 months, at 18-24 months and at 3-5 years follow-up (Table 3 and Supplementary Table 2 for more detailed information).

Table 3: Univariable linear regression analysis of information needs between patients with and without postoperative complications following esophageal or gastric cancer surgery at 6-12 months, at 18-24 months and at 3-5 years follow-up.

		Univariable linear regression					
		6-12 months		18-24 months		3-5 years	
EORTC QLQ-INFO25 domains	**N range** **Complications**	116-122 No	87-90 Yes	94-98 No	83-86 Yes	80-84 No	71-75 Yes
Information about the disease	**Mean**	55.9	60.1	56.8	59.0	60.7	61.5
	SD	22.9	19.0	23.7	23.4	23.0	24.0
	p value	0.160		0.531		0.840	
	Corrected p value	0.800		2.655		4.200	
Information about medical tests	**Mean**	63.1	65.0	60.9	59.3	63.1	62.2
	SD	26.3	24.5	27.1	25.9	27.8	26.9
	p value	0.596		0.685		0.838	
	Corrected p value	2.980		3.425		4.190	
Information about treatments	**Mean**	56.3	56.1	56.4	53.0	59.2	55.9
	SD	23.8	22.0	24.6	23.9	25.9	25.9
	p value	0.960		0.358		0.425	
	Corrected p value	4.800		1.790		2.125	
Information about things you can do to help yourself	**Mean**	44.5	41.7	40.7	43.8	37.5	42.0
	SD	30.3	29.2	31.6	29.9	27.7	34.1
	p value	0.497		0.507		0.377	
	Corrected p value	2.485		2.535		1.885	
Overall the information was helpful	**Mean**	69.2	70.6	68.3	68.8	73.3	69.0
	SD	23.7	20.6	22.0	21.9	21.4	23.9
	p value	0.669		0.859		0.246	
	Corrected p value	3.345		4.295		1.230	

N = number of patients. SD = standard deviation. Corrected p value = corrected according to the Bonferroni correction.

Background characteristics and information needs of male and female patients

Comparing the group of male patients to the group of female patients, a significantly higher rate of male patients had undergone an Ivor Lewis esophagectomy at baseline and at 6-12 months (66.0% vs 42.9%, p=0.033 and 63.2% vs 39.6%, p=0.002) (Supplementary Table 3). Neo-adjuvant therapy was significantly more often administered to male patients compared to female patients in the 18-24 months follow-up group (86.9% vs 71.8%, p=0.023). Moreover, a significantly lower rate of female patients received adjuvant therapy compared to male patients in the baseline group (22.9% vs 43.3%, p=0.033).

Univariable linear regression analysis of information needs scores at baseline, showed that male patients reported to have received more information about the things they can do to help themselves than female patients, with a clinically relevant difference in mean scores of 10.3 points. However, this difference was not statistically significant. No statistically significant or clinically relevant differences in information needs between male and female patients were found at 6-12 months, at 18-24 months and at 3-5 years follow-up (Table 4 and Supplementary table 4 for more detailed information).

Table 4: Univariable linear regression analysis of information needs between male and female patients following esophageal or gastric cancer surgery at baseline, at 6-12 months, at 18-24 months and at 3-5 years follow-up.

		Univariable linear regression							
		Baseline		6-12 months		18-24 months		3-5 years	
EORTC QLQ-INFO25 domains	N range Complications	32-35 Female	92-96 Male	49-52 Female	154-160 Male	37-39 Female	141-145 Male	38-39 Female	113-120 Male
Information about the disease	Mean	58.4	53.8	59.3	57.1	62.1	56.7	66.1	59.5
	SD	24.7	23.5	22.7	20.9	25.6	22.8	26.7	22.1
	p value	0.326		0.529		0.201		0.168	
	Corrected p value	1.630		2.645		1.005		0.840	
Information about medical tests	Mean	65.8	60.3	67.6	62.7	60.7	60.1	69.4	60.5
	SD	24.8	24.6	23.0	26.2	25.2	26.9	27.3	27.1
	p value	0.266		0.232		0.896		0.083	
	Corrected p value	1.330		1.160		4.480		0.415	
Information about treatments	Mean	49.4	51.7	57.7	55.8	56.1	54.5	59.4	57.1
	SD	23.0	24.7	23.4	22.9	26.3	23.8	30.4	24.4
	p value	0.645		0.608		0.710		0.672	
	Corrected p value	3.225		3.040		3.550		3.360	
Information about things you can do to help yourself	Mean	28.4	38.8	41.5	43.9	38.7	43.0	34.2	41.4
	SD	24.8	30.6	32.3	29.0	30.9	30.7	34.2	29.6
	p value	0.080		0.620		0.452		0.213	
	Corrected p value	0.400		3.100		2.260		1.065	
Overall the information was helpful	Mean	71.6	68.2	68.3	70.3	72.5	67.5	73.5	70.5
	SD	20.3	23.6	21.7	22.6	23.6	21.4	24.4	22.1
	p value	0.467		0.585		0.215		0.472	
	Corrected p value	2.335		2.925		1.075		2.360	

N = number of patients. SD = standard deviation. Corrected p value = corrected according to the Bonferroni correction.

Information needs and health-related quality of life

After univariable linear regression analysis, patients with higher global health status indicated they had received more information about medical tests (p=0.001) and more information about treatments (p=0.008) at 18-24 months follow-up (Table 5). Also, they more often reported that overall, the information was helpful at 6-12 months (p<0.001), at 18-24 months (p<0.001) and at 3-5 years (p=0.001) follow-up. Patients with more eating restrictions reported they had received less information about things that they could do to help themselves at 18-24 months (p=0.005) and at 3-5 years (p=0.007) follow-up. Patients with more anxiety reported that the information was more helpful at 18-24 months (p=0.009) and at 3-5 years (p<0.001) follow-up. However, none of these results were clinically relevant as the mean score differences were less than 10 points.

Table 5: The association between information needs and global health status domain (EORTC QLQ-C30), eating restrictions domain (EORTC QLQ-OG25) and anxiety domain (EORTC QLQ-OG25) following esophageal or gastric cancer surgery at baseline, at 6-12 months, at 18-24 months and at 3-5 years follow-up.

EORTC QLQ-INFO25 domains		Global health status				Eating restrictions				Anxiety			
		Baseline	6-12 months	18-24 months	3-5 years	Baseline	6-12 months	18-24 months	3-5 years	Baseline	6-12 months	18-24 months	3-5 years
Information about the disease	**B**	0.2	0.2	0.2	0.1	-0.04	0.02	-0.1	-0.1	-0.1	-0.1	-0.1	-0.1
	p value	0.110	0.018	0.012	0.179	0.617	0.819	0.091	0.523	0.275	0.107	0.085	0.250
	Corrected p value	0.550	0.090	0.062	0.897	3.086	4.095	0.453	2.613	1.374	0.533	0.426	1.251
Information about medical tests	**B**	0.2	0.3	0.4	0.1	-0.03	0.03	-0.1	-0.04	0.01	-0.04	-0.2	-0.1
	p value	0.069	0.006*	<0.001*	0.421	0.713	0.708	0.235	0.631	0.950	0.564	0.009*	0.061
	Corrected p value	0.343	0.030	0.001*	2.106	3.564	3.539	1.177	3.157	4.748	2.820	0.044	0.307
Information about treat-ments	**B**	0.2	0.2	0.3	0.1	-0.1	0.01	-0.1	-0.01	-0.1	-0.1	-0.2	-0.1
	p value	0.084	0.005*	0.002*	0.336	0.527	0.884	0.245	0.918	0.045	0.198	0.009*	0.429
	Corrected p value	0.420	0.025	0.008*	1.682	2.634	4.418	1.225	4.592	0.225	0.988	0.047	2.145
Information about things you can do to help yourself	**B**	0.1	0.2	0.3	0.1	-0.1	-0.1	-0.3	-0.3	0.004	-0.05	-0.2	-0.1
	p value	0.565	0.034	0.052	0.290	0.311	0.617	0.001*	0.001*	0.965	0.573	0.112	0.093
	Corrected p value	2.826	0.172	0.258	1.449	1.555	3.085	0.005*	0.007*	4.826	2.867	0.558	0.463
Overall the information was helpful	**B**	0.1	0.4	0.4	0.3	0.1	-0.1	-0.1	-0.2	-0.1	-0.1	-0.2	-0.2
	p value	0.173	<0.001*	<0.001*	<0.001*	0.468	0.235	0.057	0.004*	0.245	0.178	0.002*	<0.001*
	Corrected p value	0.863	<0.001*	<0.001*	0.001*	2.338	1.173	0.283	0.020	1.226	0.892	0.009*	<0.001*

B = regression coefficient. *= significant p value. Corrected p value = corrected according to the Bonferroni correction for multiple testing.

DISCUSSION

This study investigated the information needs in potentially curable gastro-esophageal cancer patients in a tertiary referral center. These results show that patients with and without complications did not report different information needs at 6-12 months, at 18-24 months and at 3-5 years follow-up. At baseline, male patients reported they had received more information about the things they could do to help themselves compared to female patients. This difference, however, was not statistically significant. Furthermore, a higher global health status and more anxiety were positively associated, whereas having more eating restrictions was negatively associated with various information needs domains. Overall, most patients reported they found the received information at least a little bit helpful, but almost a quarter of all patients reported they did not receive any information about the things that they could do to help themselves. It was recently found that in order to improve information transmission, certain methods of information provision may be recommended, such as considering the effect of positive and negative framing, using visual forms of explanation during decision making and the use of explicit and affective communication [31, 32]. Whether medical practitioners who treat gastro-esophageal cancer patients need to be instructed on how to provide better information is currently being researched (NCT04232735) [33].

Very few studies investigated information needs of gastro-esophageal cancer patients, and, additionally, information needs between patients with and without complications has not previously been studied [12-15]. The results of the current study are not directly comparable with the results of previous studies on information needs because of different inclusion criteria and endpoints. Possible explanations for the absence of any observed differences in information needs between patients with and without complications in our study could be because of the relatively small sample size or the limited number of patients with major complications. In contrast to our study, previous studies that investigated information needs in patients with other cancers did not specify the severity of postoperative complications according to the Clavien-Dindo classification [18, 34]. Therefore, future studies should include such classifications and employ larger sample sizes to be able to test the hypothesis that major postoperative complications have a greater impact on information needs than minor or no complications.

This is the first study investigating the difference in information needs between male and female gastro-esophageal cancer patients. The association between information needs and gender has been investigated in patients with various other cancers. In a multicenter study with a total of 4020 cancer patients, small differences in information needs between male and female patients were found [4]. This study assessed information needs using six items including information needs concerning diagnosis of cancer, recovery chance, the course of

the disease, treatment options, complications and psychosocial support. Men reported that they were less informed about psychosocial support; however, women were more likely to inquire after information about this topic. The fact that we did not find any differences could be because fewer female patients (21.2%-26.5% compared to 51% in the multicenter study) were included in this study.

In a recent study an association was found between various information needs domains and two HR-QoL domains (global QoL and anxiety) in patients with esophageal cancer [15]. A higher global QoL score was found to be associated with more satisfaction with the received information and with receiving more information about things patients can do to help themselves. Patients who reported more anxiety indicated they had received more information about the disease, however, more anxiety was also associated with receiving less information about things that you can do to help yourself. In our study we also found a significant association between information needs and global health status and anxiety, but only with certain information needs domains (information about medical tests, information about treatments, overall the information was helpful and information about things that they can do to help themselves). In addition, we found that patients with more eating restrictions reported they had received less information about things that they could do to help themselves. However, the results may not be comparable because the inclusion criteria of our study included patients treated with curative intent, whereas in the previous study also patients treated with palliative intent were included.

This study has some limitations. This prospective comparative cohort study is prone to selection bias as some of the esophageal and gastric cancer patients did not complete the questionnaires. Clinical information of non-respondents is unknown; therefore, a non-respondent analysis could not be performed. Furthermore, the included patients were operated between 2003 - 2018 and in this long time period some changes were implemented in the treatment of patients with esophageal or gastric cancer including the introduction of minimally invasive surgery, (neo)adjuvant treatment and Enhanced Recovery After Surgery programs. Furthermore, all cohorts partly overlap, as all patients completed the questionnaires at one or multiple time point. Similarly, no longitudinal analysis could be performed because most patients did not complete questionnaires at every time point. Furthermore, the number of patients with major postoperative complications was small. Therefore, no subgroup analysis of the difference in information needs between patients with minor and major postoperative complications could be performed as the results may have been subject to low statistical power. Additionally, no multivariable analysis was executed as the aim was to investigate the information needs of a naturally occurring sample of patients with esophageal and gastric cancer. Subsequently, no correction for differences between the cohorts was performed.

This study has also a number of strengths. It is the first study to investigate the association between information needs and postoperative complications and gender in gastro-esophageal cancer patients. To counteract the chance of finding a significant association by chance, a more stringent p value was chosen as statistically significant and the Bonferroni correction for multiple testing was performed. In addition, to prevent over-interpretation of the results, we evaluated the clinical relevance as a mean difference of more than 10 points for all information needs domains. Another important strength of this study is also that it includes different cohorts of heterogeneous groups of gastro-esophageal cancer patients chosen at clinically relevant time points in the disease- and treatment trajectory, i.e., at baseline (prior to surgery), after primary treatment (6-12 months), at mid-term follow-up (18-24 months) and at long-term follow-up (3-5 years).

CONCLUSION

Overall, the results of this study suggest that patients with gastro-esophageal cancer, with or without postoperative complications and male or female patients, do not report different information needs. However, an association was found between information needs and HR-QoL, as patients with high global health status or with more anxiety reported that the received information was more helpful and patients with more eating restrictions reported to have received less information about things that they can do to help themselves. This study provides insight in which information patients report to have received and which information patients would like to receive more. The next step is to provide sufficient information in a way that patients can comprehend and accept. Future studies should focus on how to further improve such information provision to gastro-esophageal cancer patients.

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SUPPLEMENT

Supplementary table 1: Background characteristics of patients with and without postoperative complications after esophageal or gastric cancer surgery between 2003 – 2018.

		Baseline					6-12 months follow-up				
		With complications		Without complications		p value	With complications		Without complications		p value
N		54		78			93		123		
Age (median [IQR]. yrs)		66	[61-70]	67	[59-71]	0.765	64	[60-71]	63	[57-70]	0.285
Gender	Male	40	74.1	57	73.1	0.898	67	72.0	96	78.0	0.310
Tumor location	Distal esophagus	23	42.6	28	35.9	0.212	54	58.1	64	52.0	0.072
	Mid esophagus	3	5.6	8	10.3		5	5.4	2	1.6	
	GEJ/cardia	26	48.2	32	41.0		30	32.3	41	33.3	
	Gastric cancer	2	3.8	10	12.8		4	4.4	16	12.9	
Comorbidity	No	25	46.3	35	44.9	0.872	52	55.9	60	48.8	0.299
	Cardiovascular	25	46.3	32	41.0	0.548	29	31.2	50	40.7	0.153
	Pulmonary	6	11.1	9	11.5	0.939	12	12.9	10	8.1	0.251
	Diabetic	6	11.1	8	10.3	0.875	10	10.8	13	10.6	0.965
ASA classification	1	6	11.1	12	15.4	0.270	22	23.7	36	29.3	0.647
	2	36	66.7	41	52.6		49	52.7	61	49.6	
	3	12	22.2	25	32.1		22	23.7	26	21.1	
Neo-adjuvant therapy	No	8	14.8	10	12.8	0.743	19	20.4	16	13.0	0.143
	Yes	46	85.2	68	87.2		74	79.6	107	87.0	
	CTx	10	18.5	16	20.5	0.823	15	16.1	32	26.0	0.146
	CRTx	36	66.7	52	66.7		59	63.4	75	61.0	
Operation	Ivor Lewis esophagectomy	26	48.1	53	67.9	**0.001***	54	58.1	70	56.9	**0.025***
	McKeown esophagectomy	17	31.5	8	10.3		26	28.0	21	17.1	
	Total gastrectomy	7	13.0	4	5.1		8	8.6	12	9.8	
	Subtotal gastrectomy	2	3.7	13	16.7		4	4.3	20	16.3	
	Total gastrectomy with distal esophagectomy	2	3.7	0			1	1.1			
Approach	Minimally invasive	48	88.9	70	89.7	0.875	88	94.6	119	96.7	0.439
	Open	6	11.1	8	10.3		5	5.4	4	3.3	
Adjuvant therapy	No	36	66.7	46	59.0	0.370	64	68.8	69	56.1	0.057
	Yes	18	33.3	32	41.0		29	31.2	54	43.9	
	CTx	18	33.3	32	41.0	na	29	31.2	52	42.3	0.540
	CRTx	0		0			0		2	1.6	
Recurrence	Yes	8	14.8	14	17.9	0.635	8	8.6	11	8.9	0.930
Complications according to Clavien-Dindo grade	Grade 0	0		78	100	na	0		123	100	na
	Grade 1	8	14.8				16	17.2			
	Grade 2	17	31.5				28	30.1			
	Grade 3A	11	20.4				22	23.7			
	Grade 3B	2	3.7				3	3.2			
	Grade 4A	13	24.1				22	23.7			
	Grade 4B	1	1.9				2	2.2			
	Grade 5	2	3.7				0				
Specific postoperative complications	Atrial fibrillation	22	40.7			na	28	30.1			na
	Anastomotic leakage	16	29.6			na	26	28.0			na
	Pneumonia	8	14.8			na	12	12.9			na
	Other	28	51.9			na	54	58.1			na

N = number of patients. Data are presented as n (%) unless otherwise indicated. ASA = American Society of Anesthesiologists Classification. Ivor Lewis = esophagectomy with an intrathoracic anastomosis. McKeown = esophagectomy with a cervical anastomosis. GEJ = gastroesophageal junction. CTx = chemotherapy. CRTx = chemoradiotherapy. na=not applicable. * = represents significant p values

	18-24 months follow-up				3-5 years follow-up				
	With complications		Without complications		p value	With complications		Without complications		p value
	86		98			77		86		
	65	[60-71]	65	[58-71]	0.550	64	[58-70]	64	[58-70]	0.525
	64	74.4	81	82.7	0.173	59	76.6	64	74.4	0.744
	62	72.1	54	55.1		61	79.2	55	64.0	
	2	2.3	0		**0.004***	0		0		**0.032***
	20	23.3	29	29.6		16	20.8	22	25.6	
	2	2.3	15	15.3		0		9	10.5	
	44	51.2	48	49.0	0.768	36	46.8	55	64.0	**0.027***
	35	40.7	44	44.9	0.566	32	41.6	25	29.1	0.095
	7	8.1	8	8.2	0.995	12	15.6	5	5.8	**0.042***
	10	11.6	11	11.2	0.932	7	9.1	10	11.6	0.597
	22	25.6	31	31.6		17	22.1	27	31.4	
	44	51.2	47	48.0	0.654	41	53.2	50	58.1	**0.044***
	20	23.3	20	20.4		19	24.7	9	10.5	
	17	19.8	13	13.3	0.234	10	13.0	12	14.0	0.857
	69	80.2	85	86.7		67	87.0	74	86.0	
	12	14.0	27	27.6	**0.041***	8	10.4	19	22.1	**0.038***
	57	66.3	58	59.2		59	76.6	55	64.0	
	40	46.5	44	44.9		26	33.8	22	25.6	
	34	39.5	24	24.5		46	59.7	45	52.3	
	1	1.2	13	13.3	**0.005***	5	6.5	12	14.0	**0.021***
	11	12.8	17	17.3		0		7	8.1	
	0		0			0		0		
	77	89.5	94	95.9	0.092	56	72.7	64	74.4	0.807
	9	10.5	4	4.1		21	27.3	22	25.6	
	67	77.9	65	66.3	0.082	64	83.1	68	79.1	0.511
	19	22.1	33	33.7		13	16.9	18	20.9	
	19	22.1	31	31.6	0.527	10	13.0	16	18.6	0.625
	0		2	2.0		3	3.9	2	2.3	
	2	2.3	5	5.1	0.451	0		2	2.3	0.498
	0		98	100		0		86	100	
	7	8.2				7	9.2			
	26	30.6				33	43.4			
	26	30.6			na	11	14.5			na
	0					0				
	23	27.1				21	27.6			
	3	3.5				4	5.3			
	0					0				
	33	38.8			na	28	36.8			na
	32	37.6			na	27	35.5			na
	21	24.7			na	23	30.3			na
	37	43.5			na	27	35.5			na

Supplementary table 2: Complete univariable linear regression analysis of information needs between patients with and without postoperative complications following esophageal or gastric cancer surgery at 6-12 months, at 18-24 months and at 3-5 years follow-up.

						Univariable linear regression				
						B	95% CI		p value	Corrected p value
		Complications	N	Mean	SD		Lower	Upper		
6-12 months	Information about the disease	No	120	55.9	22.9	-4.2	-10.066	1.674	0.160	0.801
		Yes	89	60.1	19.0					
	Information about medical tests	No	120	63.1	26.3	-1.9	-8.940	5.149	0.596	2.982
		Yes	89	65.0	24.5					
	Information about treatments	No	116	56.3	23.8	0.2	-6.283	6.612	0.960	4.800
		Yes	87	56.1	22.0					
	Information about things you can do to help yourself	No	122	44.5	30.3	2.8	-5.398	11.098	0.497	2.483
		Yes	87	41.7	29.2					
	Overall the information was helpful	No	119	69.2	23.7	-1.3	-7.512	4.832	0.669	3.345
		Yes	90	70.6	20.6					
18-24 months	Information about the disease	No	98	56.8	23.7	-2.2	-9.042	4.677	0.531	2.655
		Yes	86	59.0	23.4					
	Information about medical tests	No	97	60.9	27.1	1.6	-6.161	9.357	0.685	3.424
		Yes	86	59.3	25.9					
	Information about treatments	No	97	56.4	24.6	3.3	-3.814	10.489	0.358	1.791
		Yes	84	53.0	23.9					
	Information about things you can do to help yourself	No	95	40.7	31.6	-3.1	-12.205	6.058	0.507	2.537
		Yes	83	43.8	29.9					
	Overall the information was helpful	No	94	68.3	22.0	-0.6	-7.095	5.922	0.859	4.295
		Yes	84	68.8	21.9					
3-5 years	Information about the disease	No	84	60.7	23.0	-0.8	-8.119	6.614	0.840	4.202
		Yes	75	61.5	24.0					
	Information about medical tests	No	81	63.1	27.8	0.9	-7.795	9.603	0.838	4.188
		Yes	74	62.2	26.9					
	Information about treatments	No	81	59.2	25.9	3.3	-4.880	11.523	0.425	2.125
		Yes	75	55.9	25.9					
	Information about things you can do to help yourself	No	80	37.5	27.7	-4.5	-14.611	5.574	0.377	1.887
		Yes	71	42.0	34.1					
	Overall the information was helpful	No	81	73.3	21.4	4.3	-2.967	11.506	0.246	1.228
		Yes	72	69.0	23.9					

N = number of patients. SD = standard deviation. B = regression coefficient. CI = confidence interval. Corrected p value = corrected according to the Bonferroni correction.

Supplementary table 4: Complete univariable linear regression analysis of information needs between male and female patients following esophageal or gastric cancer surgery at baseline, at 6-12 months, at 18-24 months and at 3-5 years follow-up.

						Univariable linear regression				
						B	95% CI		p value	Corrected p value
		Gender	N	Mean	SD		Lower	Upper		
Baseline	Information about the disease	Female Male	35 96	58.4 53.8	24.7 23.5	4.6	-4.670	13.960	0.326	1.628
	Information about medical tests	Female Male	34 97	65.8 60.3	24.8 24.6	5.5	-4.226	15.199	0.266	1.329
	Information about treatments	Female Male	32 96	49.4 51.7	23.0 24.7	-2.3	-12.116	7.533	0.645	3.226
	Information about things you can do to help yourself	Female Male	34 92	28.4 38.8	24.8 30.6	-10.3	-21.916	1.242	0.080	0.399
	Overall the information was helpful	Female Male	34 93	71.6 68.2	20.3 23.6	3.3	-5.698	12.348	0.467	2.336
6-12 months	Information about the disease	Female Male	52 157	59.3 57.1	22.7 20.9	2.2	-4.586	8.893	0.529	2.647
	Information about medical tests	Female Male	52 157	67.6 62.7	23.0 26.2	4.9	-3.146	12.925	0.232	1.158
	Information about treatments	Female Male	49 154	57.7 55.8	23.4 22.9	1.9	-5.510	9.393	0.608	3.040
	Information about things you can do to help yourself	Female Male	49 160	41.5 43.9	32.3 29.0	-2.4	-12.022	7.182	0.620	3.099
	Overall the information was helpful	Female Male	51 158	68.3 70.3	21.7 22.6	-2.0	-9.087	5.140	0.585	2.925
18-24 months	Information about the disease	Female Male	39 145	62.1 56.7	25.6 22.8	5.4	-2.916	13.775	0.201	1.004
	Information about medical tests	Female Male	39 144	60.7 60.1	25.2 26.9	0.6	-8.830	10.090	0.896	4.478
	Information about treatments	No Yes	38 143	56.1 54.5	26.3 23.8	1.7	-7.117	10.432	0.710	3.549
	Information about things you can do to help yourself	No Yes	37 141	38.7 43.0	30.9 30.7	-4.3	-15.509	6.935	0.452	2.259
	Overall the information was helpful	No Yes	37 141	72.5 67.5	23.6 21.4	5.0	-2.945	13.001	0.215	1.075
3-5 years	Information about the disease	Female Male	39 120	66.1 59.5	26.7 22.1	6.6	-2.863	16.099	0.168	0.838
	Information about medical tests	Female Male	38 117	69.4 60.5	27.3 27.1	8.8	-1.158	18.847	0.083	0.413
	Information about treatments	No Yes	38 118	59.4 57.1	30.4 24.4	2.3	-8.560	13.169	0.672	3.361
	Information about things you can do to help yourself	No Yes	38 113	34.2 41.4	34.2 29.6	-7.2	-18.662	4.192	0.213	1.064
	Overall the information was helpful	No Yes	39 114	73.5 70.5	24.4 22.1	3.0	-5.275	11.348	0.472	2.358

N = number of patients. SD = standard deviation. B = regression coefficient. CI = confidence interval. Corrected p value = corrected according to the Bonferroni correction.

Supplementary table 3: Background characteristics of male and female patients after esophageal or gastric cancer surgery between 2003 – 2018.

		Baseline					6-12 months follow-up				
		Male		Female		p value	Male		Female		p value
N		97		35			163		53		
Age (median [IQR]. yrs)		66	[60-70]	67	[60-73]	0.211	63	[59-70]	65	[58-71]	0.995
Tumor location	Distal esophagus	39	40.2	12	34.3	**0.004***	93	57.1	25	47.2	**0.001***
	Mid esophagus	5	5.2	6	17.1		2	1.2	5	9.4	
	GEJ/cardia	48	49.5	10	28.6		58	35.6	13	24.5	
	Gastric cancer	5	5.2	7	20.0		10	6.1	10	18.9	
Comorbidity	No	43	44.3	17	48.6	0.666	80	49.1	32	60.4	0.153
	Cardiovascular	42	43.3	15	42.9	0.964	61	37.4	18	34.0	0.650
	Pulmonary	11	11.3	4	11.4	0.989	19	11.7	3	5.7	0.210
	Diabetic	11	11.3	3	8.6	0.648	19	11.7	4	7.5	0.399
ASA classification	1	13	13.4	5	14.3	0.938	45	27.6	13	24.5	0.906
	2	56	57.7	21	60.0		82	50.3	28	52.8	
	3	28	28.9	9	25.7		36	22.1	12	22.6	
Neo-adjuvant therapy	No	11	11.3	7	20.0	0.201	23	14.1	12	22.6	0.143
	Yes	86	88.7	28	80.0		140	85.9	41	77.4	
	CTx	20	23.3	6	21.4	0.841	32	22.9	15	36.6	0.078
	CRTx	66	76.7	22	78.6		108	77.1	26	63.4	
Operation	Ivor Lewis esophagectomy	64	66.0	15	42.9	**0.033***	103	63.2	21	39.6	**0.002***
	McKeown esophagectomy	14	14.4	11	31.4		30	18.4	17	32.1	
	Total gastrectomy	9	9.3	2	5.7		17	10.4	3	5.7	
	Subtotal gastrectomy	8	8.2	7	20.0		12	7.4	12	22.6	
	Total gastrectomy with distal esophagectomy	2	2.1	0	0		1	0.6	0	0	
Approach	Minimally invasive	85	87.6	33	94.3	0.273	158	96.9	49	92.5	0.156
	Open	12	12.4	2	5.7		5	3.1	4	7.5	
Adjuvant therapy	No	55	56.7	27	77.1	**0.033***	100	61.3	33	62.3	0.905
	Yes	42	43.3	8	22.9		63	38.7	20	37.7	
	CTx	42	100	8	100	na	62	98.4	19	95.0	0.426
	CRTx	0	0	0	0		1	1.6	1	5.0	
Recurrence	Yes	12	12.4	10	28.6	0.027*	11	6.7	8	15.1	0.062
Complications according to Clavien-Dindo grade	Grade 0	57	58.8	21	60.0	0.164	96	58.9	27	50.9	0.430
	Grade 1	6	6.2	2	5.7		12	7.4	4	7.5	
	Grade 2	9	9.3	8	22.9		18	11	10	18.9	
	Grade 3A	10	10.3	1	2.9		17	10.4	5	9.4	
	Grade 3B	2	2.1	0	0		1	0.6	2	3.8	
	Grade 4A	11	11.3	2	5.7		17	10.4	5	9.4	
	Grade 4B	0	0.0	1	2.9		2	1.2	0	0	
	Grade 5	2	2.1	0	0		0	0	0	0	
Specific postoperative complications	Atrial fibrillation	17	17.5	5	14.3	0.659	19	11.7	9	17.0	0.316
	Anastomotic leakage	12	12.4	4	11.4	0.884	19	11.7	7	13.2	0.763
	Pneumonia	7	7.2	1	2.9	0.354	12	7.4	0	0	**0.041***
	Other	21	21.6	7	20.0	0.838	37	22.7	17	32.1	0.171

N = number of patients. Data are presented as n (%) unless otherwise indicated. ASA = American Society of Anesthesiologists Classification. Ivor Lewis = esophagectomy with an intrathoracic anastomosis. McKeown = esophagectomy with a cervical anastomosis. GEJ = gastroesophageal junction. CTx = chemotherapy. CRTx = chemoradiotherapy. na=not applicable. * = represents significant p values

18-24 months follow-up					3-5 years follow-up				
Male		Female		p value	Male		Female		p value
145		39			123		40		
64	[59-71]	66	[58-73]	0.536	64	[58-70]	65	[57-69]	0.708
91	62.8	25	64.1		86	69.9	30	75.0	
1	0.7	1	2.6	0.219	0	0	0	0	0.534
42	29.0	7	17.9		31	25.2	7	17.5	
11	7.6	6	15.4		6	4.9	3	7.5	
71	49.0	21	53.8	0.588	68	55.3	23	57.5	0.806
64	44.1	15	38.5	0.525	44	35.8	13	32.5	0.706
13	9.0	2	5.1	0.437	12	9.8	5	12.5	0.622
16	11.0	5	12.8	0.756	16	13.0	1	2.5	0.059
40	27.6	13	33.3		33	26.8	11	27.5	
72	49.7	19	48.7	0.710	67	54.5	24	60.0	0.655
33	22.8	7	17.9		23	18.7	5	12.5	
19	13.1	11	28.2	**0.023***	14	11.4	8	20.0	0.166
126	86.9	28	71.8		109	88.6	32	80.0	
28	22.2	11	39.3	0.060	21	19.3	6	18.8	0.948
98	77.8	17	60.7		88	80.7	26	81.3	
73	50.3	11	28.2		39	31.7	9	22.5	
41	28.3	17	43.6		66	53.7	25	62.5	
23	15.9	5	12.8		13	10.6	4	10.0	
8	5.5	6	15.4	**0.021***	5	4.1	2	5.0	0.714
0	0	0	0		0	0	0	0	
136	93.8	35	89.7	0.381	93	75.6	27	67.5	0.312
9	6.2	4	10.3		30	24.4	13	32.5	
106	73.1	26	66.7	0.428	99	80.5	33	82.5	0.778
39	26.9	13	33.3		24	19.5	7	17.5	
38	97.4	12	92.3	0.441	21	87.5	5	71.4	0.562
1	2.6	1	7.7		3	12.5	2	28.6	
5	3.4	2	5.1	0.641	1	0.8	1	2.5	0.432
81	55.9	17	43.6		64	52.0	22	55.0	
8	5.5	0	0		7	5.7	1	2.5	
15	10.3	11	28.2		23	18.7	10	25.0	
17	11.7	9	23.1	0.373	9	7.3	2	5.0	0.869
0	0	0	0		0	0	0	0	
21	14.5	2	5.1		17	13.8	4	10.0	
3	2.1	0	0		3	2.4	1	2.5	
0	0	0	0		0	0	0	0	
24	16.6	9	23.1	0.346	18	14.6	10	25.0	0.137
20	13.8	12	30.8	**0.013***	20	16.3	7	17.5	0.855
19	13.1	2	5.1	0.164	18	14.6	5	12.5	0.736
27	18.6	10	25.6	0.332	21	17.1	6	15.0	0.759

Chapter 6

Postoperative complications and long-term quality of life after esophagectomy: an analysis of the *Prospective Observational Cohort Study of Esophageal-gastric cancer Patients (POCOP)*

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ABSTRACT

Background

Esophagectomy has major effects on health-related quality of life (HR-QOL). Postoperative complications might contribute to a decreased HR-QOL. The aim was to investigate the difference in HR-QOL in patients with and without complications following esophagectomy for cancer in population-based study.

Methods

A prospective comparative cohort study was performed with the Netherlands Cancer Registry (NCR) and Prospective Observational Cohort Study of Esophageal-gastric cancer Patients (POCOP) data. All patients with esophageal and gastro-esophageal junction (GEJ) cancer after esophagectomy in the period 2015-2018 were included. HR-QoL was investigated at baseline, 3-, 6-, 9-, 12-, 18- and 24-months postoperatively and was compared between patients with and without complications and with and without anastomotic leakage.

Results

A total of 486 patients were included: 270 with and 216 without complications. Significantly more patients with complications had comorbidities (69.6%vs57.3%,p=0.001). No significant difference was found in HR-QoL over time between patients with and without complications. In both groups, a significant decline in short-term HR-QoL was found in various HR-QoL domains, that restored to baseline level at 12-months follow-up. No significant difference was found in HR-QoL between patients with and without anastomotic leakage. Patients with grade 2-3 anastomotic leakage reported significantly more 'choking-when-swallowing' at 6-months (ß=14.5,95% CI -24.833 – -4.202, p=0.049), 9-months (ß=22.4, 95% CI -34.259 – -10.591, p=0.007) and 24-months (ß=24.6, 95% CI -39.494 – -9.727, p=0.007) than patients with grade 1 or no anastomotic leakage.

Conclusion

In general, postoperative complications were not associated with decreased short-and long-term HR-QoL in patients following esophagectomy for esophageal or GEJ cancer. The temporary decrease in HR-QoL is likely related to the nature of esophagectomy and reconstruction itself.

INTRODUCTION

Curative treatment for patients with esophageal cancer usually consists of (neo)adjuvant chemo(radio) therapy and surgery. These treatments are often accompanied by side effects and complications [1, 2]. Surgeons strive to improve postoperative results by prehabilitation, Enhanced Recovery After Surgery (ERAS) programs and minimally invasive surgery [3-5]. However, still over 60% of esophagectomy patients experience postoperative complications [1, 6]. A complicated postoperative course is often accompanied by an increase in anxiety and depression, impeding patients' recovery from surgery [7, 8]. Complications are also related to a decreased survival [9].

Several studies have investigated the impact of postoperative complications on HR-QoL in cancer patients [10, 11]. Overall, cancer patients were found to report worse long-term HR-QoL following postoperative complications. A systematic review and meta-analysis have been performed encompassing 50 studies concerning the impact of complications on long term HR-QoL following cardiac, thoracic, gastrointestinal and vascular surgery. A negative effect of postoperative complications on patients' HR-QoL at 12-months post-operation was found [11]. Few studies investigated long-term HR-QoL in patients with and without complications following an esophagectomy [12-15]. Overall, an impaired short- and long-term HR-QoL is reported by patients with postoperative complications compared to patients without postoperative complications. Also, the occurrence of anastomotic leakage was associated with worse short-term HR-QoL [15]. However, these studies either did not include a baseline measurement, were performed before the implementation of minimally invasive surgery, did not include information on (neo)adjuvant treatment or the study was conducted in a single center with a limited number of patients [12-15].

The aim of this study was to investigate the difference in short and long-term HR-QoL in patients with and without a complicated postoperative course following multimodality treatment for esophageal and GEJ cancer in a nationwide cohort. We hypothesized that postoperative complications negatively influence short- and long-term HR-QoL.

METHODS

Study design

A population-based prospective comparative cohort study was performed with data from the Prospective Observational Cohort Study of Esophageal-gastric cancer Patients (POCOP) study and the Netherlands Cancer Registry (NCR).

Prospective Observational Cohort Study of Esophageal-gastric cancer Patients-database
POCOP is a nationwide Dutch, population-based, and observational cohort study of patient-reported outcome measures data from cancer patients, including those with esophageal or gastric cancer. The aim of POCOP is to gain insight in the quality of life course of cancer patients [16]. The inclusion of patients started in December 2015 in AMC and in the period of 2016 and 2019 an additional 53 medical centers joined the POCOP study. All patients with esophageal or gastric cancer in the 54 participating medical centers are asked to participate in the POCOP study, irrespective of whether they receive curative treatment or palliative treatment. Included patients complete, among others, the validated European Organization for Research and Treatment of Cancer (EORTC) quality of life questionnaires at baseline before initiation of treatment and at 3-, 6-, 9-, 12-, 18-, 24-months and subsequently annually after treatment [17]. A total of 261 patients were included in the POCOP study in 2016, 741 patients in 2017, 1423 patients in 2018 and 2065 patients in 2019. The rationale and design of the POCOP study have been described elsewhere [16].

Inclusion criteria for POCOP were patients diagnosed with esophageal or gastric cancer. Inclusion criteria for the current study were patients with esophageal and gastroesophageal junction (GEJ) cancer, who underwent an esophagectomy in the period of 2015 to 2018. Exclusion criteria were patients who underwent surgery for recurrent disease, patients who underwent salvage or palliative surgery, patients with a recurrence, patients undergoing a colon or jejunal interposition, and patients in whom no reconstruction was performed or who required emergency surgery. Informed consent was collected by POCOP and the Privacy Review Board of NCR approved this study. The POCOP study adheres to the required rules and regulations [16]. Ethical approval for this study was not required under the Dutch law. This manuscript was composed using the STROBE checklist [18].

The Netherlands Cancer Registry
The NCR manages data from all cancer patients in the Netherlands. This database stores patient, tumor and treatment information such as gender, age at diagnosis, tumor type and stage, diagnostic data, information on (neo)adjuvant treatment and surgery, postoperative morbidity and mortality and the hospital in which the patient was treated. All hospitals are required by Dutch law to provide this information to the NCR. The NCR does not register the severity of postoperative complications (Clavien-Dindo grade), nor does it subdivide pulmonary morbidity into separate pulmonary complications. The NCR cancer patients' clinical outcome data were combined with the POCOP patient-reported outcome measures for research purposes.

Multimodality treatment including esophagectomy with curative intent

Patients with an advanced (≥ cT2N0 or cT1N+) esophageal or GEJ carcinoma were usually treated with chemoradiotherapy according to the CROSS scheme [19]. In selected cases (e.g., > 2 cm involvement of the stomach), perioperative chemotherapy was administered (previously the MAGIC and increasingly during this study period the FLOT scheme) [20, 21]. After neoadjuvant therapy a transthoracic or transhiatal esophagectomy with a 1- or 2-field lymphadenectomy and gastric conduit reconstruction with a cervical or intrathoracic anastomosis was performed by an open, minimally invasive or hybrid approach.

Postoperative complications

The following postoperative complications are included in the NCR database: pulmonary complications, anastomotic leakage, cardiovascular complications, chyle leakage, wound abscess or infection, recurrent laryngeal nerve palsy, thromboembolic complication and other neurologic complications. Pneumonia was defined as a new or progressive lung infiltration confirmed by radiology imaging, in combination with at least two of the following clinical manifestations: leukocytosis or leukopenia, fever (>38 degrees Celsius) and purulent secretion [22]. Anastomotic leakage is divided into grade 1-3 according to the Esophageal Complications Consensus Group (ECCG) [23]. Grade 1 pertains to a leakage without the need of therapy change except for dietary changes, grade 2 is scored as a local leakage requiring an intervention other than surgery and grade 3 is scored in case of a leakage requiring surgery. The severity of other complications, such as the Clavien-Dindo classification [24, 25] is not registered in the NCR database. The definitions of postoperative complications used in the NCR can be found in the supplementary material (Supplementary table 1).

Outcomes: Quality of life according to EORTC questionnaires

The validated cancer-specific EORTC QLQ-C30 and tumour-specific EORTC QLQ-OG25 questionnaires were used for this study [26, 27]. The EORTC QLQ-C30 HR-QoL domains were: 'global health' (calculated from two questions with response categories ranging from very poor (1) to excellent (7)), five functioning scales including 'physical', 'role', 'social', 'cognitive' and 'emotional functioning' (calculated from 15 questions with response categories ranging from not at all (1) to very much (4)), and nine symptom scores of 'fatigue', 'nausea and vomiting', 'pain', 'dyspnea', 'insomnia', 'appetite loss', 'constipation', 'diarrhea', 'financial difficulties' (calculated from 13 questions with response categories ranging from not at all (1) to very much (4)) [26]. The EORTC QLQ-OG25 questionnaire contains 25 questions assessing 16 HR-QoL domains of 'body image', 'reflux', 'dysphagia', 'pain and discomfort', 'odynophagia', 'anxiety', 'problems with eating', 'problems with eating with others', 'trouble with swallowing of saliva', 'dry mouth', 'trouble with taste', 'choking when swallowing', 'trouble with talking', 'trouble with coughing', 'worrying about weight loss' and 'problems with hair loss'. All questions of the EORTC QLQ-OG25 questionnaire had response categories ranging from not at all (1) to very much (4) [27]. The 31 HR-QoL domain scores were linearly

transformed into scores ranging from 0 to 100. Missing data was managed according to the EORTC scoring manual [26, 27]. A higher score in global health and functioning domains represents better global health and functioning and a higher score in symptom domains represents more symptomatology.

Statistical analysis

The χ2 test and Fisher's exact test were used for categorical variables to compare baseline characteristics between the groups. Shapiro-Wilk's test was used to check the distribution pattern in continuous variables. For continuous variables a Mann-Whitney U test was used if the variable was not normally distributed (median with an interquartile range [IQR]) and Student's *t* test if the variable was normally distributed (mean with a standard deviation (SD)).

To examine the difference in HR-QoL over time between patients with and without postoperative complications following an esophagectomy, linear mixed models analysis was performed. To correct for multiple testing, a Bonferroni correction was performed by multiplying the p value by the number of tests performed. If a p value of < 0.05 was reached after linear mixed models analysis and correction for multiple testing, univariable linear regression analysis was performed for each follow-up time separately, to investigate at which follow-up point the difference in HR-QoL between patients with and without postoperative complications was significant. We did not perform multivariable analyses to adjust for possible *a priori* differences, as our goal was to investigate the difference in HR-QoL in a naturally occurring population.

Univariable linear regression analysis and Bonferroni correction for multiple testing were performed to examine the change in HR-QoL between baseline and short-term (3-, 6- and 9-months) and long-term (12-, 18- and 24-months) follow-up, for patients with postoperative complications and patients without postoperative complications separately.

A subgroup analysis was performed to compare the HR-QoL between patients with and without anastomotic leakage, and between patients with grade 2-3 anastomotic leakage and grade 1 or no anastomotic leakage over time using linear mixed models analyses. In addition, a separate analysis was performed investigating HR-QoL in patients with either a cervical or an intrathoracic anastomosis. Given the small number of patients with anastomotic leakage (N=83) and with grade 2-3 anastomotic leakage (N=54), a stringent p value of < 0.001 was chosen as statistically significant in linear mixed models analysis. A p value <0.05 was chosen as statistically significant in all other analyses.

Whereas the minimally important change in mean scores that represents clinical relevance varies between HR-QoL domains [26, 28], a cut-off point of 10 points is most likely the upper

bound for most HR-QoL domains. Therefore, in this current study, a mean HR-QoL score difference or change of more than 10 points was considered clinically relevant.

RESULTS

Patient and tumor characteristics

A total of 486 patients following an esophagectomy were included (Table 1). The response rate of the POCOP study was 69.6% at baseline and decreased to 12.5% at 24 months. However, these percentages are based on all included patients (i.e., patients undergoing palliative treatment, definitive chemoradiotherapy, primary surgery, and neoadjuvant treatment and surgery). The decrease in response rate is partially attributable to the death of part of this patient population. The exact response rate at baseline of the current study population could not be calculated as such detailed information was not registered separately. However, compared to baseline, the response rates of the current study population were 81.9%, 77.7%, 68.1%, 60.9%, 42.0% and 23.3% at 3-, 6-, 9-, 12-, 18- and 24-months follow-up respectively. The majority of the included patients in this study were male (79.8%) and the median age was 66 years [IQR 60-70]. Most patients were treated with neoadjuvant therapy (90.9%). Postoperative complications occurred in 55.6% (270) of all patients (Table 2). Among the most frequent complications were pulmonary complications (22.6%), anastomotic leakage (17.1%) and cardiac complications (11.3%). Of patients with anastomotic leakage 27.7% had grade 1, 41% had grade 2, 24.1% had grade 3 and 7.2% had an unknown grade anastomotic leakage. Patients with complications had significantly more comorbidities in general (69.6% vs 57.3%, p=0.001) and pulmonary comorbidities in particular (14.8% vs 5.6%, p=0.004). Significantly more minimally invasive esophagectomies (86.7% versus 71.3%, p=0.008) and more cervical anastomoses (37.8% versus 20.8%, p=0.002) were performed in the group with postoperative complications. The patient, treatment and tumor characteristics can be found in Table 1.

Table 1: Baseline patient, treatment and tumor characteristics.

		Total		No postoperative complications		Postoperative complications		p value
		N=486		N=216		N=270		
Age (median [IQR], y)		66	(60-70)	66	(60-70)	66	(60-71)	0.297
Gender	**Male**	388	(79.8)	172	(79.6)	216	(80.0)	0.919
Comorbidities	**No**	158	(35.5)	79	(42.7)	79	(30.4)	0.001
	Yes	287	(64.5)	106	(57.3)	181	(69.6)	
	1 or 2 comorbidities	135	(30.3)	60	(32.4)	75	(28.8)	
	> 2 comorbidities	152	(34.2)	46	(24.9)	106	(40.8)	
	Missing	41	-	31	-	10	-	
	Cancer	47	(9.7)	16	(7.4)	31	(11.5)	0.268
	Cardiovascular	112	(23.0)	39	(18.1)	73	(27.0)	0.094
	Pulmonal	52	(10.7)	12	(5.6)	40	(14.8)	0.004
	Hypertension	159	(32.7)	59	(27.3)	100	(37.0)	0.154
	Cerebrovascular accident	15	(3.1)	6	(2.8)	9	(3.3)	0.900
	Mental	8	(1.6)	2	(0.9)	6	(2.2)	0.478
	Gastrointestinal	20	(4.1)	7	(3.2)	13	(4.8)	0.542
	Liver	4	(0.8)	0	-	4	(1.5)	0.145
	Kidney	9	(1.9)	4	(1.9)	5	(1.9)	1.000
	Rheumatism	10	(2.1)	2	(0.9)	8	(3.0)	0.206
	Infectious disease	3	(0.6)	0	-	3	(1.1)	0.270
	Diabetes	61	(12.6)	19	(8.8)	42	(15.6)	0.075
ASA classification	**1**	32	(6.6)	13	(6.0)	19	(7.0)	0.108
	2	302	(62.1)	139	(64.4)	163	(60.4)	
	3	118	(24.3)	40	(18.5)	78	(28.9)	
	4	2	(0.4)	1	(0.5)	1	(0.4)	
	missing	32	(6.6)	23	(10.6)	9	(3.3)	
Systemic chemotherapy	**No**	15	(3.3)	6	(2.8)	10	(3.7)	0.519
	Preoperative	442	(90.9)	195	(90.3)	247	(91.5)	
	Pre- & postoperative	28	(5.8)	15	(6.9)	13	(4.8)	
Radiotherapy	**No**	38	(7.8)	13	(6.0)	25	(9.3)	0.174
	Preoperative	447	(92.0)	202	(93.5)	245	(90.7)	
	Postoperative	1	(0.2)	1	(0.5)	0	0	
Surgical technique	**Open**	40	(8.2)	26	(12.0)	14	(5.2)	**0.008**
	Minimally invasive abdomen	20	(4.1)	9	(4.2)	11	(4.1)	
	Minimally invasive thorax	13	(2.7)	6	(2.8)	7	(2.6)	
	Minimally invasive total	388	(79.8)	154	(71.3)	234	(86.7)	
	Missing	25	(5.1)	21	(9.7)	4	(1.5)	
Surgical approach	**Transthoracic**	426	(87.7)	176	(81.5)	250	(92.6)	**<0.001**
	Transhiatal	60	(12.3)	40	(18.5)	20	(7.4)	
Location anastomosis	**Cervical**	147	(30.2)	45	(20.8)	102	(37.8)	**0.002**
	Intrathoracic	308	(63.4)	142	(65.7)	166	(61.5)	
	Unknown	31	(6.4)	29	(13.4)	2	(0.7)	
cT	**Tx**	26	(5.3)	14	(6.5)	12	(4.4)	0.155
	Tis	1	(0.2)	-	-	1	(0.4)	
	T1	10	(2.0)	4	(1.8)	4	(1.5)	
	T2	160	(32.9)	79	(26.6)	81	(30.0)	
	T3	283	(58.2)	118	(54.6)	165	(61.1)	
	T4	6	(1.2)	1	(0.5)	5	(1.9)	
cN	**N0**	226	(46.5)	110	(50.9)	116	(43.0)	0.074
	N1	173	(35.6)	68	(31.5)	105	(38.9)	
	N2	80	(16.5)	38	(17.6)	42	(15.6)	
	N3	4	(0.8)	0	-	4	(1.5)	
cM	**cM1**	9	(1.9)	3	(1.4)	6	(2.2)	0.737
Histologic type	**Adenocarcinoma**	330	(67.9)	152	(70.4)	178	(65.9)	0.554
	Squamous cell carcinoma	110	(22.6)	46	(21.3)	64	(23.7)	
	Other	46	(9.5)	18	(8.3)	28	(10.4)	

Table 1: Continued

		Total		No postoperative complications		Postoperative complications		p value
		N=486		N=216		N=270		
(y)pT	**T0**	122	(25.1)	52	(24.1)	70	(25.9)	0.446
	Tx	4	(0.8)	3	(1.4)	1	(0.4)	
	T1	84	(17.3)	44	(20.3)	40	(14.8)	
	T2	89	(18.3)	38	(17.6)	51	(18.9)	
	T3	183	(37.7)	79	(36.6)	104	(38.5)	
	T4	4	(1.0)	-	-	4	(1.5)	
(y)pN	**N0**	293	(60.3)	124	(57.4)	169	(62.6)	0.535
	N1	113	(23.3)	57	(26.4)	56	(20.7)	
	N2	63	(13.0)	28	(13.0)	35	(13.0)	
	N3	16	(3.3)	7	(3.2)	9	(3.3)	
c/(y)pM	**M1**	14	(2.9)	7	(3.2)	7	(2.6)	1.000
Radicality	**R0**	449	(92.4)	197	(91.2)	252	(93.3)	0.310
	R1	24	(4.9)	8	(3.7)	16	(5.9)	
	Unknown	13	(2.7)	11	(5.1)	2	(0.7)	
Lymph nodes (median [IQR])		23.5	(19-32.3)	23	(17.3-32)	24	(20-33)	0.099
Lymph node metastases (median [IQR])		0	(0-1.3)	0	(0-2)	0	(0-1)	0.360
Tumor response after neoadjuvant therapy	**Complete regression**	120	(24.7)	49	(22.7)	71	(26.3)	0.608
	Subtotal pathologic response	94	(19.3)	44	(20.4)	50	(18.5)	
	Partial pathologic response	198	(40.7)	85	(39.4)	113	(41.9)	
	No pathologic response	35	(7.2)	12	(5.6)	23	(8.5)	
	Missing	39	(8.0)	26	(12.0)	13	(4.8)	

Bold p values represent significance (p<0.05). IQR = interquartile range. y = years. ASA = American Society of Anaesthesiologists Classification. cTNM = clinical TNM stage. pTNM = pathological TNM stage.

Table 2: Postoperative complications of 486 patients with esophageal and gastroesophageal junction cancer after an esophagectomy in the period 2015 to 2018.

	Number of patients (%)	
All postoperative complications	270	(55.6)
Pulmonary complication	110	(22.5)
Anastomotic leakage	83	(17.1)
Grade 1	23	(27.7)
Grade 2	34	(41.0)
Grade 3	20	(24.1)
Grade unknown	6	(7.2)
Cardiovascular complication	55	(11.3)
Chyle leakage	43	(8.8)
Wound abscess /infection	22	(4.5)
Recurrent laryngeal nerve palsy	13	(2.7)
Thromboembolic complication	4	(0.8)
Other neurologic complication	4	(0.8)

Anastomotic leakage grade 1: treatment involving observation, medical therapy or dietary modification, grade 2: treatment involving non-surgical intervention, grade 3: treatment requiring surgical intervention.

Comparison of health-related quality of life between patients with and without postoperative complications

After linear mixed models analyses and Bonferroni correction for multiple testing none of the HR-QoL domains were found to be significantly different at baseline and 3-, 6-, 9-, 12-, 18- and 24-months post-operation between patients with and without postoperative complications (Table 3).

Table 3: Linear mixed models analysis of health-related quality of life scores at baseline and at 3, 6, 9, 12, 18 and 24 months follow-up in patients with and without postoperative complications following esophagectomy.

		Mean HR-QoL score							p value	Corrected p value
		Baseline N(+)=270 N(-)=216	3 months N(+)=212 N(-)=187	6 months N(+)=196 N(-)=182	9 months N(+)=171 N(-)=162	12 months N(+)=152 N(-)=145	18 months N(+)=105 N(-)=99	24 months N(+)=50 N(-)=63		
EORTC QLQ-C30										
Global Health	**With complications**	74.5	71.4	68.3	72.6	72.0	71.9	73.5	0.343	10.633
	Without complications	74.3	70.2	69.2	73.1	74.6	74.7	76.6		
Functioning scores										
Physical functioning	**With complications**	88.2	77.6	74.4	78.3	79.4	79.7	80.6	0.073	2.263
	Without complications	88.7	79.1	77.9	82.3	81.9	83.4	82.7		
Role functioning	**With complications**	80.5	67.3	61.4	69.2	74.0	76.1	73.7	0.344	10.664
	Without complications	81.9	66.9	65.1	74.2	75.8	76.6	74.8		
Emotional functioning	**With complications**	78.7	81.4	83.0	82.8	82.7	81.3	82.8	0.193	5.983
	Without complications	78.0	82.1	84.7	84.4	85.5	85.1	86.3		
Cognitive functioning	**With complications**	89.3	85.7	84.5	85.9	84.7	84.4	83.5	0.687	21.297
	Without complications	89.0	86.1	86.2	83.5	86.5	85.9	85.2		
Social functioning	**With complications**	86.1	77.1	73.0	76.7	83.2	80.5	85.3	0.664	20.584
	Without complications	83.3	75.8	75.2	80.7	84.3	83.4	84.4		
Symptom scores										
Fatigue	**With complications**	26.2	34.1	39.4	35.1	32.6	31.9	31.0	0.333	10.323
	Without complications	25.5	36.8	36.1	31.7	29.6	29.8	29.3		
Nausea and vomiting	**With complications**	11.0	10.3	17.6	16.1	12.5	9.9	9.6	0.599	18.569
	Without complications	11.2	13.1	17.2	12.9	8.8	9.8	9.7		
Pain	**With complications**	16.4	20.5	19.7	17.8	17.1	16.1	18.0	0.174	5.394
	Without complications	14.7	20.4	17.4	15.8	15.4	13.2	13.7		
Dyspnea	**With complications**	16.4	20.5	19.7	17.8	17.1	16.1	18.0	**0.021**	0.651
	Without complications	14.7	20.4	17.4	15.8	15.4	13.2	13.7		
Insomnia	**With complications**	22.8	25.7	23.6	19.1	20.6	21.3	24.9	0.820	25.420
	Without complications	24.3	29.1	23.1	20.4	23.5	22.5	18.2		
Appetite loss	**With complications**	18.0	22.8	34.6	22.8	19.7	15.7	12.4	0.135	4.185
	Without complications	18.7	27.0	36.0	24.9	19.8	20.7	18.6		
Constipation	**With complications**	14.1	14.3	12.0	9.4	10.2	9.3	11.9	0.756	23.436
	Without complications	13.5	13.6	10.7	12.3	8.9	8.6	10.7		
Diarrhea	**With complications**	8.2	12.2	21.5	17.4	15.4	14.7	12.7	0.753	23.343
	Without complications	4.9	11.4	22.2	17.7	16.2	14.6	18.3		
Financial difficulties	**With complications**	5.8	7.6	8.2	8.1	7.9	8.3	6.8	0.436	13.516
	Without complications	6.3	8.2	6.2	7.4	7.3	6.1	4.1		
EORTC QLQ-OG25										
Functioning scores										
Body image	**With complications**	90.5	85.1	85.7	86.8	84.8	84.2	88.3	0.499	15.469
	Without complications	91.2	87.2	83.1	87.6	86.7	87.7	89.6		
Symptom scores										
Dysphagia	**With complications**	21.5	17.5	23.7	17.2	15.4	14.7	8.9	0.109	3.379
	Without complications	21.5	19.8	18.4	13.9	12.9	8.7	9.3		
Eating	**With complications**	30.8	28.4	40.6	32.9	31.4	28.1	23.4	0.712	22.072
	Without complications	32.2	31.2	38.5	31.0	27.2	25.2	25.8		

Table 3: Continued

		Mean HR-QoL score							p value	Corrected p value
		Baseline N(+)=270 N(-)=216	3 months N(+)=212 N(-)=187	6 months N(+)=196 N(-)=182	9 months N(+)=171 N(-)=162	12 months N(+)=152 N(-)=145	18 months N(+)=105 N(-)=99	24 months N(+)=50 N(-)=63		
Reflux	**With complications**	7.2	6.4	12.8	14.6	14.8	16.1	13.4	0.259	8.029
	Without complications	6.0	8.6	14.9	16.0	16.5	19.0	15.7		
Odynophagia	**With complications**	24.4	14.3	16.2	12.8	11.2	12.8	8.3	0.310	9.610
	Without complications	23.9	16.8	15.1	12.2	10.6	6.8	6.8		
Pain and discomfort	**With complications**	17.4	9.5	15.0	16.1	15.3	13.7	14.0	0.778	24.118
	Without complications	16.4	14.1	15.3	16.2	15.9	14.3	11.5		
Anxiety	**With complications**	48.8	41.2	32.5	30.0	31.4	29.1	28.3	0.395	12.245
	Without complications	50.9	40.4	31.7	29.2	26.5	26.0	24.7		
Eating with others	**With complications**	14.0	10.4	16.9	12.5	10.8	11.1	10.7	0.612	18.972
	Without complications	15.0	11.3	13.3	12.7	11.7	9.9	6.8		
Dry mouth	**With complications**	13.9	20.5	26.1	21.7	20.7	21.0	18.8	0.663	20.553
	Without complications	12.3	18.9	25.0	19.8	18.7	18.2	23.8		
Trouble with taste	**With complications**	12.4	22.2	26.0	18.6	15.3	13.8	17.4	0.223	6.913
	Without complications	9.4	19.6	22.4	15.7	16.9	13.6	12.8		
Trouble swallowing saliva	**With complications**	9.5	14.9	14.3	13.2	15.2	15.8	11.7	0.499	15.469
	Without complications	8.8	12.8	16.9	12.4	13.3	12.3	10.4		
Choked when swallowing	**With complications**	7.7	8.0	14.3	12.8	11.6	12.9	12.1	**0.024**	0.744
	Without complications	6.8	8.6	11.5	8.1	7.1	8.4	8.8		
Trouble with coughing	**With complications**	21.9	27.5	44.1	36.0	27.7	30.3	27.6	0.133	4.123
	Without complications	19.2	29.5	41.3	31.5	27.1	26.1	21.7		
Trouble talking	**With complications**	4.8	9.7	15.5	10.9	9.4	8.8	4.9	**0.045**	1.395
	Without complications	4.3	10.4	12.6	6.1	6.7	5.9	2.3		
Weight loss	**With complications**	17.6	17.7	22.7	24.7	20.6	16.6	19.9	0.679	21.049
	Without complications	18.7	19.6	24.2	20.6	19.9	16.2	15.4		
Problems with hair loss	**With complications**	81.7	46.6	54.9	61.0	62.3	54.8	69.9	0.528	16.368
	Without complications	73.3	47.4	57.1	49.7	57.5	62.4	59.3		

N(+) = number of patients with postoperative complications, N(-) = number of patients without postoperative complications. Values are represented as mean HR-QoL scores unless otherwise indicated. Bold p value represents significance (p<0.05). Corrected p value = corrected for multiple testing according to Bonferroni method.

Change in health-related quality of life in patients with no postoperative complications

A univariable linear regression analysis of the HR-QoL domains was performed between baseline and 3-, 6-, 9-, 12-, 18- and 24-months follow-up in patients without postoperative complications (Supplementary table 2). In eight HR-QoL domains a significant and clinically relevant decline in short-term HR-QoL scores compared to baseline was found, that recovered to baseline level at 12-months follow-up: 'trouble with coughing' (6- and 9-months), 'role functioning', 'fatigue' and 'trouble with taste' (3- and 6-months), 'physical functioning', 'dyspnea', 'appetite loss' and 'dry mouth' (6-months) (Figure 1).

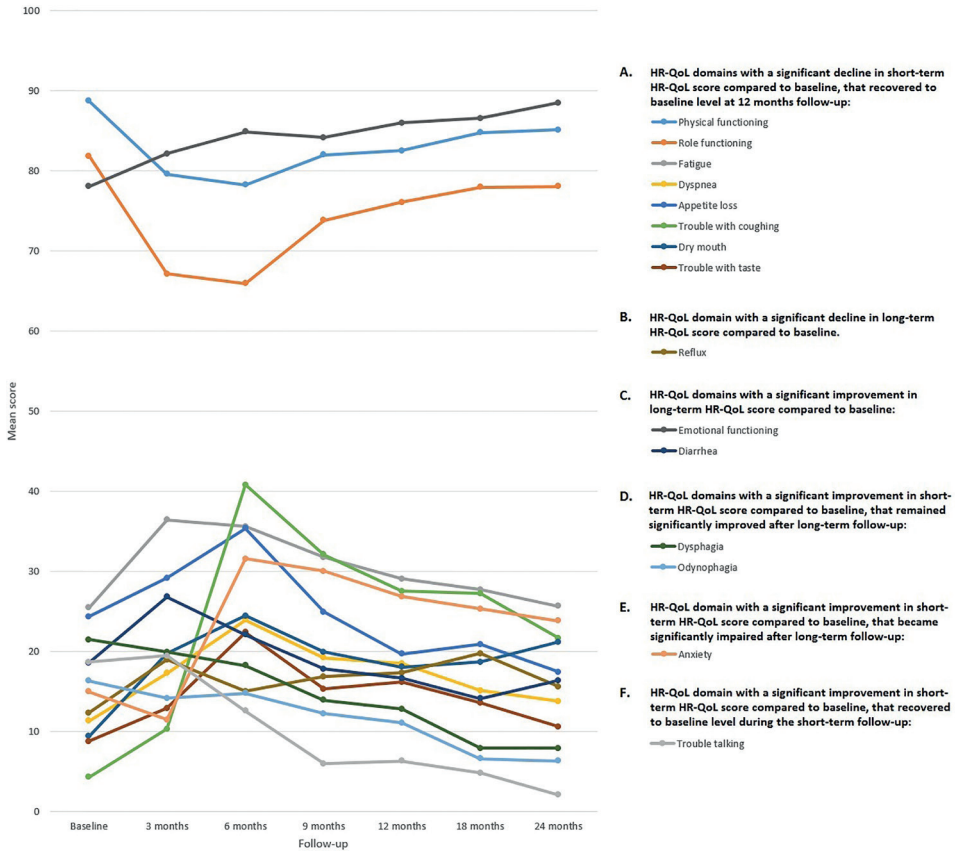

Figure 1: Change in health-related quality of life in patients without postoperative complications.

A. A significant decline in short-term health-related quality of life (HR-QoL) score compared to baseline was found in eight HR-QoL domains, that recovered to baseline level at 12-months follow-up: 'physical functioning' (3-, 6- and 9-months, p<0.001), 'role functioning' (3- and 6-months, p<0.001), 'fatigue' (3- and 6-months, p=0.002), 'trouble with coughing' (3-months, p=0.047; 6- and 9-months, p≤0.001), 'dyspnea' (6-months, p<0.001), 'appetite loss' (6-months, p<0.001), 'dry mouth' (6-months, p=0.004), 'trouble with taste' (3-months, p=0.005; 6-months, p<0.001). **B. & C.** In three HR-QoL domains HR-QoL score was found that either remained significantly impaired ('reflux', p=0.001) or improved significantly ('emotional functioning', p=0.003; 'diarrhea', p<0.001) after long-term follow-up compared to baseline. **D., E. & F.** In four HR-QoL domains an improved short-term HR-QoL score was found compared to baseline, that remained significantly improved ('dysphagia' and 'odynophagia', p≤0.001) or became significantly impaired ('anxiety', p<0.001) after long-term follow-up, or recovered to baseline level during the short-term follow-up ('trouble talking', p=0.001).

Change in health-related quality of life in patients with postoperative complications

A univariable linear regression analysis of the HR-QoL domains was performed between baseline and 3-, 6-, 9-, 12-, 18- and 24-months follow-up in patients with postoperative complications (Supplementary table 3). Clinically relevant and significantly more impaired short-term HR-QoL scores compared to baseline were found in 10 HR-QoL domains, that recovered to baseline level at 12-months follow-up: 'role functioning' and 'dyspnea' (3-, 6- and 9-months), 'trouble with coughing' (6- and 9-months), 'social functioning', 'fatigue', 'appetite loss', 'dry mouth', 'trouble with taste', 'diarrhea' and 'trouble talking' (6-months) (Figure 2).

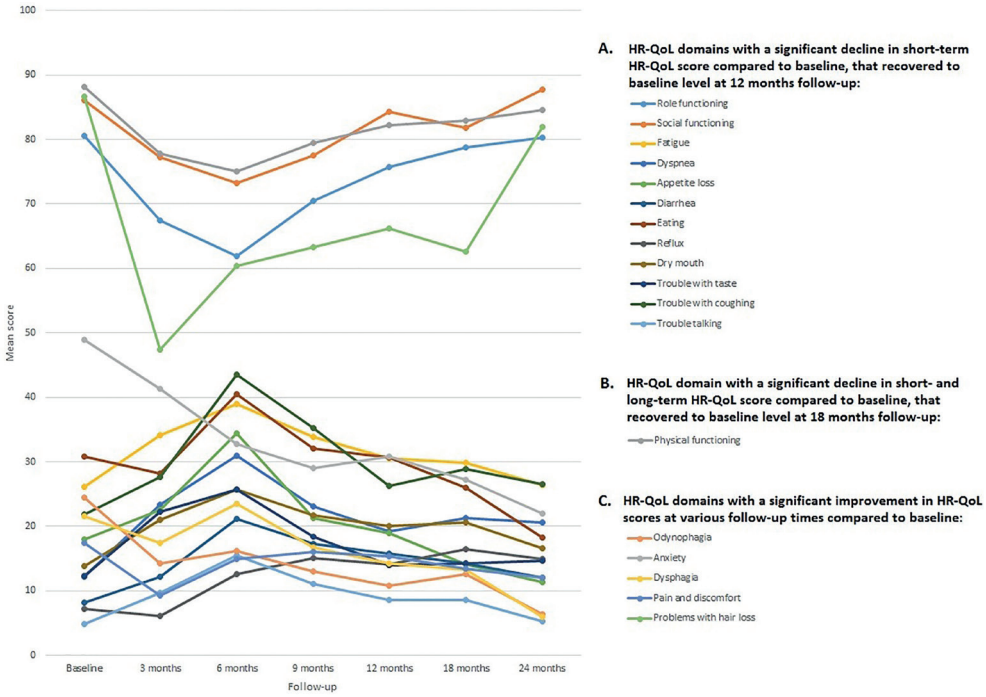

Figure 2: Change in health-related quality of life in patients with postoperative complications.

A. A significant decline in short-term health-related quality of life (HR-QoL) score compared to baseline was found in 12 HR-QoL domains, that recovered to baseline level at 12-months follow-up: 'role functioning (3- and 6-months, p<0.001; 9-months, p=0.027), 'social functioning' (3-months, p=0.010; 6-months, p<0.001; 9-months, p=0.035), 'fatigue' (6-months, p<0.001), 'dyspnea' (3- and 6-months, p<0.001; 9-months, p=0.006), 'appetite loss' (6-months, p<0.001), 'diarrhea' (6-months, p<0.001; 9-months, p=0.007), 'eating' (6-months, p=0.021), 'reflux' (9-months, p=0.013), 'dry mouth' (6-months, p<0.001), 'trouble with taste' (6-months, p<0.001), 'trouble with coughing' (6- and 9-months, p<0.001), 'trouble talking' (6-months, p<0.001). **B.** A significant decline in 'physical functioning' score was found at 3-, 6- and 9-months (p<0.001) and 12-months (p=0.045) follow-up that recovered to baseline level at 18-months follow-up. **C.** In five HR-QoL domains an improved HR-QoL score compared to baseline was found at all follow-up times ('odynophagia'; 3-months, p=0.001; 6-months, p=0.029; 9-, 12-, 18- and 24-months, p<0.001), at 6-, 9-, 12-, 18- and 24-months ('anxiety', p<0.001), at 3-months ('pain and discomfort', p=0.006; 'problems with hair loss', p<0.001) and at 24-months ('dysphagia', p<0.001).

Health-related quality of life after anastomotic leakage

HR-QoL scores were compared between patients with anastomotic leakage (N=83) and patients without anastomotic leakage (N=360) over time. After linear mixed models analysis and Bonferroni correction no p value was found below 0.001 in any of the domains (data not shown). HR-QoL scores were also compared between patients with severe (grade 2-3) anastomotic leakage (N=54) and patients with grade 1 or no anastomotic leakage (N=432) over time. After linear mixed models analysis and Bonferroni correction a significant difference in HR-QoL over time was found in the 'choked when swallowing' domain (p<0.001) (Table 4). After univariable linear regression analysis and correction for multiple testing, patients with grade 2-3 anastomotic leakage reported significantly more problems with 'choking when swallowing' compared to patients with grade 1 or no anastomotic leakage at 6- months (mean difference: 14.5, 95% CI -24.833 – -4.202, p=0.049), 9-months (mean difference: 22.4, 95% CI -34.259 – -10.591, p=0.007) and at 24-months follow-up (mean difference: 24.6, 95% CI -39.494 - -9.727, p=0.007) (Table 5). Mean scores differed more than 10 points and were therefore clinically relevant.

Table : Univariable linear regression analysis of health-related quality of life domain 'choked when swallowing' over time in patients with grade 1 or no anastomotic leakage and patients with grade 2 or 3 anastomotic leakage following esophagectomy.

		Univariable linear regression								
		Grade 1 or no anastomotic leakage		Grade 2 or 3 anastomotic leakage		B	95% CI		P value	Corrected p value
		Mean	SD	Mean	SD		Lower	Upper		
Choked when swallowing	**Baseline**	7.0	17.7	9.9	20.1	-2.9	-7.993	2.226	0.268	1.876
	3 months	7.9	16.2	12.3	26.2	-4.4	-13.176	4.345	0.315	2.205
	6 months	11.4	19.1	25.9	29.9	-14.5	-24.833	-4.202	**0.007**	**0.049**
	9 months	8.6	16.3	31.0	30.8	-22.4	-34.259	-10.591	**0.001**	**0.007**
	12 months	7.8	16.1	20.8	21.6	-13.0	-22.308	-3.746	**0.008**	0.056
	18 months	10.2	17.9	20.0	21.1	-9.8	-19.402	-0.168	0.046	0.322
	24 months	8.7	16.1	33.3	23.6	-24.6	-39.494	-9.727	**0.001**	**0.007**

SD = standard deviation. B = regression coefficient. 95% CI = confidence interval. Bold p values represent significance (p<0.05). Corrected p value = corrected for multiple testing according to Bonferroni correction.

Health-related quality of life after cervical and intrathoracic anastomosis

The HR-QoL scores of patients following esophagectomy with a cervical anastomosis (N=147) were compared over time with the HR-QoL scores of patients following esophagectomy with an intrathoracic anastomosis (N=308). After linear mixed models analysis and Bonferroni correction no significant difference was found in any of the domains (data not shown).

DISCUSSION

This study investigated the difference in short and long-term HR-QoL in patients with and without postoperative complications following multimodality treatment including an esophagectomy with curative intent for esophageal or GEJ cancer in a nationwide cohort. The results of this study show that, in general, the short and long-term HR-QoL does not differ between patients with and without postoperative complications following esophagectomy. However, anastomotic leakage grade 2-3 was found to affect 'choking when swallowing' in comparison to patients with anastomotic leakage grade 1 or no anastomotic leakage. The absence of differences in HR-QoL between patients with and without postoperative complications is in contrast to our hypothesis. When investigated separately, in both groups a decline in various short-term HR-QoL domain scores was found that restored to baseline level with time. The observed impairment in HR-QoL is therefore more likely to be attributable to functional complaints related to the reconstruction following esophagectomy, and remarkably, complications do not seem to influence this. A recent prospective multicentre study showed that the majority of patients have functional complaints that last up to more than one year following an esophagectomy [29]. The authors found a relation between the absence of 30-day complications and HR-QoL, with an increased physical, social and role functioning, and global health status in the group without complications.

Few other studies have investigated the influence of postoperative complications on HR-QoL following an esophagectomy [12-15]. Overall, an impaired HR-QoL was found at 6-months follow-up in patients with postoperative complications compared to patients without postoperative complications [13-15]. Anastomotic leakage, one of the most severe postoperative complications that is associated with development of strictures [30], was found to be associated with odynophagia and eating difficulties at 6-months following an esophagectomy with an intrathoracic anastomosis [15]. Only one study investigated the impact of major postoperative complications on long-term HR-QoL and found that patients reported more dyspnea, fatigue and eating restrictions at 6-months, 3-years and 5-years following the operation in comparison to patients with no postoperative complications [13]. The negative impact of postoperative complications on HR-QoL was found to last up to 10-years postoperatively [12]. The majority of these studies reported only major postoperative complications, although no complication grading system was used to define the severity of complications [12-14]. In 2016 the national audit for upper GI cancer (DUCA) started with the registration of the Clavien-Dindo classification for postoperative complications. Between 2016 and 2017, results showed that 1046 of 1617 patients (65%) had a complication following the esophagectomy with pneumonia as the most common complication (29%). In addition, pneumonia accounted for 47% of all pulmonary complications. A total of 29% of the patients with a complication had a Clavien-Dindo grade 3 or higher [1]. Perhaps, the majority of the included patients in the present study may have had a complication

grade Clavien-Dindo below 3, which may explain the absence of differences found in HR-QoL between patients with and without postoperative complications. In addition, patients with more severe anastomotic leakage (grade 2-3), reported more problems with 'choking when swallowing' at 6-, 9- and 24-months follow-up. This is in accordance with a previous study that found significantly more odynophagia and problems with eating in patients with anastomotic leakage compared to patients without an anastomotic leak at 6-months following an esophagectomy with an intrathoracic anastomosis [15]. In addition, as problems with eating are also known to be dependent on the anastomotic site [31], we performed an analysis comparing HR-QoL between patients with cervical and intrathoracic anastomosis and found no significant difference in HR-QoL between these two groups. However, as the number of patients in the grade 2-3 anastomotic leakage group was limited, this finding may be due to chance, despite the use of a Bonferroni procedure.

A number of study limitations should be addressed. Selection bias could have occurred as it is unknown how many patients were eligible and how many have died during the follow-up period. In addition, the reasons for declining participation were not recorded. The results could also be influenced by the decline in the response rate at long-term follow-up. Moreover, this was a population-based, non-randomized cohort study of patients who differed in the number of post-operative complications. Hence, the two groups differed with respect to a number of baseline variables, including: occurrence of (pulmonary) comorbidities, surgical technique (open/minimally invasive/hybrid), surgical approach (transthoracic/transhiatal) and the location of anastomosis (cervical/intrathoracic). No correction for confounders was performed, because we aimed to investigate the difference in HR-QoL in a naturally occurring population, considering age, gender, comorbidities and surgical technique. Furthermore, recurrent laryngeal nerve palsy is also likely independently related to HR-QoL. However, only a small number of patients in this study (N=13) had a recurrent laryngeal nerve palsy, therefore, no subgroup analysis could be performed. Also, it was not possible to investigate the influence of severity of complications according to Clavien-Dindo grade, nor to investigate the influence of separate pulmonary complications on HR-QoL, since the NCR does not register these data.

The strengths of this study are that this is a population-based prospective cohort study which counteracts the selection bias seen in randomized clinical trials that employ strict inclusion criteria. Also, this study includes a large sample of post-esophagectomy patients treated after implementation of improvements in esophageal cancer treatment, including minimally invasive surgery and neoadjuvant/perioperative therapy. To counteract the bias of multiple testing a Bonferroni correction was performed. As the number of patients with anastomotic leakage grade 2-3 was relatively small, a more stringent p value ($P<0.001$) was chosen for this subgroup analysis. Also, to prevent over-interpretation of the clinical relevance of the

results, a mean HR-QoL score change of more than 10 points was considered clinically relevant for all HR-QoL domains.

CONCLUSION

Patients with and without complications following esophagectomy report, in general, comparable short- and long-term HR-QoL up to 24-months post-surgery. In both groups of patients, a decline in short-term HR-QoL was seen in various domains that restored to baseline levels with time. Patients with anastomotic leakage grade 2-3 reported worse HR-QoL in a single HR-QoL domain – 'choking when swallowing' – compared to patients with grade 1 or no anastomotic leakage. The temporary decrease in HR-QoL is likely related to the nature of the esophagectomy and reconstruction itself and future research should focus on how to minimize these functional complaints.

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SUPPLEMENT

Supplementary table 1: definitions of postoperative complications in The Netherlands Cancer Registry.

Anastomotic leakage: full thickness defect of the esophagus, anastomosis, staple line or tube of the stomach regardless of the method of identification. Register anastomotic leakage regardless of grade.	**Grading:** I: Leakage for which conservative policy is used such as: expectant, medicinal or nutritional measure. II: Leakage requiring non-surgical intervention such as drain, stent or neck wound opening in ward. III: Leakage requiring surgical intervention. **Anastomotic leakage coding:** 0 none 1 anastomotic leak, grade I. 2 anastomotic leakage, grade II 3 anastomotic leakage, grade III 6 anastomotic leakage, grade unknown 8 not applicable 9 unknown
Pulmonary complication, which includes:	• Pneumonia • Pleural effusion (accumulation of an abnormal amount of fluid in the pleural space) requiring drainage • Pneumothorax (collapsed lung) that requires treatment • Atelectasis (loss of lung volume) requiring bronchoscopy • Respiratory failure requiring re-intubation and ventilation • Acute aspiration • Tracheobronchial injury (TBI) = broncho-esophageal fistula • ARDS (Acute Respiratory Distress Syndrome) fluid accumulation in the lungs (pulmonary edema) and low oxygen levels in the blood. • Prolonged chest drainage due to air leakage> 10 days
Cardiac complication, which includes:	• Cardiac arrest requiring resuscitation • (Acute) Myocardial infarction = heart infarction. AMI = acute myocardial infarction. • Atrial fibrillation, atrial dysrhythmia, atrial flutter, requiring treatment • Ventricular dysrhythmia (chamber / ventricular fibrillation (VF)) requiring treatment • Cardiac decompensation = Congestive heart failure (CHF), requiring treatment • Pericardial fluid requiring treatment
Thromboembolic complications, including:	• Deep vein thrombosis (DVT) • Pulmonary embolism • Thrombophlebitis / superficial venous thrombosis (thrombotic process in a superficial vein with signs of inflammation).
Chyle leakage: Chyle leakage may develop postoperatively as a result of damage to the lymph vessels during surgery. Record chyle leakage regardless of grade.	**Grading:** I: Chyle leakage requiring MCT diet (low fat diet) II: Chyle leakage for which TPV (total parenteral nutrition) is required III: Chyle leakage requiring intervention
Recurrent nerve injury = inferior laryngic nerve = recurrent laryngeal nerve = laryngeal nerve. Register recurrent nerve injuries regardless of grade.	**Grading:** I: Temporary outage for which no treatment II: Permanent failure requiring elective surgical intervention III: Permanent failure requiring acute surgical intervention

Supplementary table 1: Continued

Neurological complication other than recurrent nerve injury, including:	• TIA (Transient Ischaemic Attack), transient stroke. • CVA = Cerebro Vascular Accident (stroke / seizure). Could be cerebral infarction or cerebral haemorrhage. • Acute delirium = acute delirium = acute hallucinatory confusion with altered consciousness • Delirium tremens (DTs) • Other neurological injuries
Wound abscess / infection, which includes:	• Wound infection requiring wound opening or antibiotics • Central line infection requiring removal or antibiotics • Abscess (intrathoracic or intra-abdominal) • Sepsis • Other infections requiring antibiotics.

General information:
Register postoperative complications within 30 days of primary tumor resection.
Register one complication per group if multiple complications occur per main group.

Record anastomotic leakage within 30 days of primary tumor resection.
Register anastomotic leakage regardless of which anastomosis is leaking. So a leaking anastomosis that attaches part of the small intestine to another part of the small intestine in a Roux-Y reconstruction is also an anastomotic leakage. Places where anastomotic leakage may occur: gastroenterostomy (GE) anastomosis, duodenal stump, jejuno-jejunostomy, or entero-enterostomy.

Supplementary table 2: Univariable linear regression analysis of health-related quality of life scores of patients without postoperative complications following esophagectomy.

				Univariable analysis				
					95% CI		p value	Corrected p value
		Mean score	Standard deviation	B	Lower	Upper		
EORTC QLQ-C30								
Global Health	**Baseline**	74.3	17.8					
	3 months	70.4	19.3	4.0	0.313	7.604	**0.033**	6.138
	6 months	69.4	15.8	5.0	1.637	8.285	**0.004**	0.744
	9 months	72.9	17.3	1.4	-2.188	5.017	0.441	82.026
	12 months	74.9	17.4	-0.6	-4.343	3.148	0.754	140.244
	18 months	76.3	14.9	-1.9	-5.715	1.878	0.32	9.920
	24 months	77.9	15.5	-3.6	-8.455	1.323	0.152	28.272
Functioning scores								
Physical functioning	**Baseline**	88.7	14.6					
	3 months	79.6	18.7	9.1	5.804	12.472	**<0.001**	**<0.001**
	6 months	78.2	16.7	10.5	7.365	13.618	**<0.001**	**<0.001**
	9 months	82.0	16.9	6.7	3.506	9.922	**<0.001**	**0.009**
	12 months	82.5	17.6	6.2	2.691	9.673	**0.001**	0.186
	18 months	84.8	16.9	3.9	0.259	7.590	**0.036**	6.696
	24 months	85.1	15.9	3.6	-0.601	7.800	0.093	17.298
Role functioning	**Baseline**	81.9	25.4					
	3 months	67.1	32.9	14.7	8.890	20.597	**<0.001**	**<0.001**
	6 months	65.9	28.1	15.9	10.646	21.215	**<0.001**	**<0.001**
	9 months	73.8	27.1	8.1	2.698	13.434	**0.003**	0.558
	12 months	76.0	26.6	5.8	0.338	11.299	0.038	7.068
	18 months	77.9	24.4	3.9	-2.073	9.902	0.199	37.014
	24 months	78.0	24.8	3.8	-3.300	10.936	0.292	54.312
Emotional functioning	**Baseline**	78.0	19.6					
	3 months	82.1	17.7	-4.1	-7.773	-0.404	**0.030**	5.530
	6 months	84.9	18.9	-6.8	-10.632	-3.004	**<0.001**	0.092
	9 months	84.1	18.4	-6.1	-10.015	-2.204	**0.002**	0.372
	12 months	85.9	18.1	-7.9	-11.919	-3.886	**<0.001**	**0.024**
	18 months	86.5	18.0	-8.5	-13.053	-3.941	**<0.001**	0.053
	24 months	88.5	15.0	-10.5	-15.030	-5.884	**<0.001**	**0.003**

Supplementary table 2: Continued

		Univariable analysis						
		Mean score	Standard deviation	B	95% CI		p value	Corrected p value
					Lower	Upper		
Cognitive functioning	**Baseline**	89.0	18.5					
	3 months	86.5	18.3	2.5	-1.119	6.112	0.175	32.623
	6 months	86.4	17.8	2.6	-1.005	6.193	0.157	29.202
	9 months	83.3	20.6	5.6	1.660	9.605	**0.006**	1.116
	12 months	86.0	18.8	3.0	-0.964	6.905	0.138	25.668
	18 months	86.4	16.7	2.6	-1.684	6.889	0.233	43.338
	24 months	87.6	18.9	1.4	-3.837	6.637	0.599	111.414
Social functioning	**Baseline**	83.3	23.6					
	3 months	76.0	25.8	7.3	2.503	12.192	**0.003**	0.566
	6 months	75.9	23.4	7.5	2.799	12.118	**0.002**	0.372
	9 months	81.4	23.7	2.0	-2.874	6.808	0.425	79.05
	12 months	85.0	21.5	-1.6	-6.447	3.206	0.510	94.86
	18 months	85.2	21.8	-1.9	-7.361	3.658	0.509	94.674
	24 months	87.0	19.5	-3.7	-10.121	2.714	0.257	47.802
Symptom scores								
Fatigue	**Baseline**	25.5	23.4					
	3 months	36.4	25.3	-11.0	-15.726	-6.181	**<0.001**	**0.002**
	6 months	35.6	21.6	-10.1	-14.596	-5.671	**<0.001**	**0.002**
	9 months	31.7	21.8	-6.3	-10.904	-1.606	**0.008**	1.488
	12 months	29.1	22.7	-3.6	-8.487	1.291	0.149	27.714
	18 months	27.7	22.4	-2.2	-7.738	3.270	0.425	79.05
	24 months	25.6	20.2	-0.2	-6.566	6.226	0.958	178.188
Nausea and vomiting	**Baseline**	11.2	19.1					
	3 months	13.2	19.7	-2.0	-5.828	1.822	0.304	56.530
	6 months	17.1	20.8	-5.9	-9.835	-1.939	**0.004**	0.744
	9 months	12.9	18.8	-1.7	-5.559	2.253	0.406	75.516
	12 months	9.3	13.5	2.0	-1.402	5.364	0.250	46.500
	18 months	10.3	15.2	1.0	-3.323	5.265	0.657	122.202
	24 months	10.1	15.4	1.2	-3.986	6.360	0.652	121.272
Pain	**Baseline**	14.7	19.6					
	3 months	20.3	27.1	-5.5	-10.219	-0.808	**0.022**	4.054
	6 months	16.8	20.8	-2.1	-6.117	1.893	0.300	55.800
	9 months	15.2	22.9	-0.5	-4.895	3.936	0.831	154.566
	12 months	14.7	20.0	0.0	-4.133	4.210	0.986	183.396
	18 months	12.1	17.3	2.6	-1.893	7.126	0.254	47.244
	24 months	12.4	19.4	2.3	-3.199	7.807	0.411	76.446
Dyspnea	**Baseline**	11.3	19.4					
	3 months	17.3	25.6	-6.0	-10.497	-1.462	**0.010**	1.860
	6 months	23.9	25.7	-12.6	-17.186	-8.060	**<0.001**	**<0.001**
	9 months	19.2	25.6	-7.9	-12.658	-3.103	**0.001**	0.186
	12 months	18.5	24.9	-7.2	-12.039	-2.362	**0.004**	0.744
	18 months	15.2	20.4	-3.8	-8.537	0.870	0.110	20.46
	24 months	13.8	20.4	-2.4	-7.968	3.091	0.386	71.796
Insomnia	**Baseline**	13.5	22.3					
	3 months	13.2	23.8	-4.8	-10.837	1.140	0.112	20.832
	6 months	23.0	27.7	1.3	-4.322	6.963	0.646	120.156
	9 months	20.3	27.0	4.0	-1.794	9.805	0.175	32.550
	12 months	22.5	28.7	1.9	-4.229	8.004	0.544	101.184
	18 months	20.5	27.6	3.8	-3.034	10.638	0.275	51.150
	24 months	15.9	22.3	8.5	1.671	15.265	**0.015**	2.790
Appetite loss	**Baseline**	24.3	29.0					
	3 months	29.2	31.9	-8.2	-13.973	-2.441	**0.005**	0.930
	6 months	35.4	33.1	-16.8	-22.700	-10.832	**<0.001**	**<0.001**
	9 months	24.9	29.3	-6.3	-12.050	-0.636	**0.029**	5.394
	12 months	19.7	26.9	-1.1	-6.586	4.443	0.7030	130.758
	18 months	20.9	30.3	-2.3	-9.200	4.658	0.518	96.348
	24 months	17.5	26.7	1.1	-6.119	8.407	0.757	140.802
Constipation	**Baseline**	4.9	14.2					
	3 months	11.5	22.2	0.3	-4.205	4.876	0.885	164.61
	6 months	10.7	19.8	2.8	-1.352	6.966	0.185	34.410
	9 months	12.4	23.3	1.1	-3.555	5.793	0.638	118.668
	12 months	8.1	18.2	5.4	1.165	9.608	**0.013**	2.418
	18 months	7.4	18.2	6.1	1.399	10.763	**0.011**	2.046
	24 months	10.1	19.5	3.4	-2.687	9.558	0.270	50.22

Supplementary table 2: Continued

		Univariable analysis						
		Mean score	Standard deviation	B	95% CI		p value	Corrected p value
					Lower	Upper		
Diarrhea	**Baseline**	18.6	25.5					
	3 months	26.8	32.0	-6.5	-10.258	-2.805	**0.001**	0.186
	6 months	22.1	25.1	-17.2	-21.306	-13.016	**<0.001**	**<0.001**
	9 months	17.8	23.9	-12.9	-17.036	-8.698	**<0.001**	**<0.001**
	12 months	16.7	23.3	-11.7	-16.009	-7.448	**<0.001**	**<0.001**
	18 months	14.1	21.9	-9.2	-13.953	-4.453	**<0.001**	**<0.001**
	24 months	16.4	23.9	-11.5	-17.753	-5.174	**0.001**	0.186
Financial difficulties	**Baseline**	6.3	17.2					
	3 months	7.9	20.5	-1.6	-5.301	2.099	0.396	73.656
	6 months	5.2	16.4	1.2	-2.167	4.508	0.491	91.326
	9 months	6.2	17.2	0.1	-3.402	3.633	0.948	176.328
	12 months	6.7	17.9	-0.4	-4.083	3.311	0.838	155.868
	18 months	6.5	16.3	-0.1	-4.194	3.923	0.948	176.328
	24 months	3.7	12.1	2.6	-1.183	6.430	0.175	32.550
EORTC QLQ-OG25								
Functioning scores								
Body image	**Baseline**	91.2	19.8					
	3 months	87.1	22.7	4.1	-0.110	8.324	0.056	10.416
	6 months	83.3	26.7	7.9	3.139	12.601	**0.001**	0.186
	9 months	88.4	21.8	2.8	-1.500	7.096	0.201	37.386
	12 months	87.3	22.3	3.9	-0.584	8.454	0.088	16.368
	18 months	87.8	22.1	3.4	-1.705	8.603	0.188	34.968
	24 months	91.0	18.2	0.2	-5.286	5.683	0.943	175.398
Symptom scores								
Dysphagia	**Baseline**	21.5	21.8					
	3 months	19.9	25.4	1.6	-3.129	6.237	0.514	95.604
	6 months	18.2	18.9	3.2	-0.841	7.312	0.119	22.134
	9 months	13.9	17.1	7.5	3.594	11.478	**<0.001**	**0.037**
	12 months	12.8	17.0	8.7	4.633	12.702	**<0.001**	**0.006**
	18 months	7.9	12.6	13.5	9.696	17.384	**<0.001**	**<0.001**
	24 months	7.9	14.0	13.5	8.980	18.099	**<0.001**	**<0.001**
Eating	**Baseline**	32.2	26.9					
	3 months	31.1	30.5	1.1	-4.647	6.749	0.717	133.362
	6 months	38.6	24.9	-6.5	-11.631	-1.288	**0.014**	2.604
	9 months	31.5	24.4	0.7	-4.612	5.972	0.801	148.986
	12 months	26.8	23.2	5.4	-0.014	10.765	0.051	9.486
	18 months	24.4	21.7	7.8	1.683	13.864	**0.013**	2.418
	24 months	22.2	21.9	9.9	2.637	17.219	**0.008**	1.488
Reflux	**Baseline**	12.3	22.5					
	3 months	19.0	28.5	-2.6	-5.826	0.565	0.106	19.716
	6 months	15.0	22.3	-9.0	-12.751	-5.212	**<0.001**	**0.001**
	9 months	16.9	24.2	-10.9	-15.048	-6.662	**<0.001**	**<0.001**
	12 months	17.4	24.2	-11.3	-15.742	-6.944	**<0.001**	**<0.001**
	18 months	19.7	26.0	-13.7	-19.246	-8.172	**<0.001**	**0.001**
	24 months	15.6	23.5	-9.6	-15.797	-3.383	**0.003**	0.558
Odynophagia	**Baseline**	16.4	22.4					
	3 months	14.1	22.4	7.2	2.313	12.012	**0.004**	0.744
	6 months	14.8	18.3	9.1	4.872	13.358	**<0.001**	**0.006**
	9 months	12.2	19.0	11.7	7.294	16.115	**<0.001**	**<0.001**
	12 months	11.1	15.6	12.8	8.640	16.978	**<0.001**	**<0.001**
	18 months	6.6	10.6	17.3	13.378	21.196	**<0.001**	**<0.001**
	24 months	6.3	11.4	17.6	13.233	21.908	**<0.001**	**<0.001**
Pain and discomfort	**Baseline**	50.9	26.0					
	3 months	40.1	25.7	2.2	-2.200	6.628	0.325	60.45
	6 months	15.3	22.6	1.1	-3.383	5.543	0.634	117.924
	9 months	15.9	22.8	0.4	-4.208	5.040	0.86	159.96
	12 months	15.7	22.0	0.6	-4.088	5.323	0.797	148.242
	18 months	13.6	20.4	2.8	-2.466	7.971	0.3	55.8
	24 months	10.6	17.8	5.8	0.414	11.138	**0.035**	6.51

Supplementary table 2: Continued

		Univariable analysis						
		Mean score	Standard deviation	B	95% CI		p value	Corrected p value
					Lower	Upper		
Anxiety	**Baseline**	15.0	26.5					
	3 months	11.5	23.4	10.9	5.794	15.950	**<0.001**	**0.006**
	6 months	31.6	25.4	19.4	14.254	24.450	**<0.001**	**<0.001**
	9 months	30.0	26.1	20.9	15.575	26.235	**<0.001**	**<0.001**
	12 months	26.9	24.8	24.1	18.681	29.468	**<0.001**	**<0.001**
	18 months	25.3	23.1	25.6	19.570	31.602	**<0.001**	**<0.001**
	24 months	23.8	22.7	27.1	19.994	34.239	**<0.001**	**<0.001**
Eating with others	**Baseline**	6.0	14.0					
	3 months	8.6	17.9	3.5	-1.409	8.397	0.162	30.132
	6 months	12.8	23.8	2.1	-2.901	7.141	0.407	75.702
	9 months	12.1	21.3	2.9	-1.962	7.734	0.243	45.198
	12 months	11.7	23.2	3.3	-1.887	8.515	0.211	39.246
	18 months	9.2	19.0	5.8	0.601	10.970	**0.029**	5.394
	24 months	5.8	15.3	9.1	3.943	14.356	**0.001**	0.186
Dry mouth	**Baseline**	9.4	18.7					
	3 months	19.7	28.0	-6.7	-11.754	-1.548	**0.011**	2.046
	6 months	24.4	31.2	-12.1	-17.585	-6.613	**<0.001**	**0.004**
	9 months	19.9	27.1	-7.6	-12.763	-2.378	**0.004**	0.744
	12 months	18.1	25.8	-5.7	-10.911	-0.509	**0.032**	5.952
	18 months	18.7	27.1	-6.4	-12.560	-0.164	**0.044**	8.184
	24 months	21.2	27.0	-8.8	-16.228	-1.409	**0.001**	0.186
Trouble with taste	**Baseline**	8.8	19.8					
	3 months	12.9	22.7	-10.3	-15.058	-5.541	**<0.001**	**0.005**
	6 months	22.4	29.2	-13.0	-17.961	-8.027	**<0.001**	**<0.001**
	9 months	15.3	24.7	-5.9	-10.488	-1.326	**0.012**	2.232
	12 months	16.2	25.8	-6.8	-11.719	-1.861	**0.007**	1.302
	18 months	13.6	21.8	-4.2	-9.223	0.839	0.102	18.972
	24 months	10.6	18.8	-1.2	-6.447	4.110	0.663	123.318
Trouble swallowing saliva	**Baseline**	6.8	18.1					
	3 months	8.6	16.6	-4.1	-8.324	0.110	0.056	10.416
	6 months	16.7	26.7	-7.9	-12.601	-3.139	**0.001**	0.186
	9 months	11.6	21.8	-2.8	-7.096	1.500	0.201	37.386
	12 months	12.7	22.3	-3.9	-8.454	0.584	0.088	16.368
	18 months	12.2	22.1	-3.4	-8.603	1.706	0.188	34.968
	24 months	9.0	18.2	-0.2	-5.683	5.286	0.943	175.398
Choked when swallowing	**Baseline**	19.2	21.7					
	3 months	28.8	29.1	-1.8	-5.259	1.605	0.296	55.056
	6 months	11.3	18.0	-4.5	-8.060	-0.889	**0.015**	2.790
	9 months	8.1	14.8	-1.3	-4.688	2.182	0.474	88.164
	12 months	7.4	15.0	-0.6	-4.167	2.996	0.748	139.128
	18 months	8.9	15.6	-2.1	-6.290	2.064	0.320	59.520
	24 months	7.9	14.3	-1.1	-5.996	3.767	0.653	121.458
Trouble with coughing	**Baseline**	4.3	14.1					
	3 months	10.3	20.5	-9.6	-14.778	-4.513	**<0.001**	**0.047**
	6 months	40.8	30.5	-21.6	-26.975	-16.271	**<0.001**	**<0.001**
	9 months	32.1	28.0	-12.9	-17.981	-7.852	**<0.001**	**<0.001**
	12 months	27.5	24.7	-8.4	-13.255	-3.520	**0.001**	0.186
	18 months	27.2	24.6	-8.1	-13.485	-2.619	**0.0040**	0.744
	24 months	21.7	24.8	-2.5	-8.866	3.798	0.431	80.166
Trouble talking	**Baseline**	18.7	25.6					
	3 months	19.5	26.8	-6.0	-9.528	-2.482	**0.001**	0.186
	6 months	12.6	22.6	-8.3	-12.086	-4.457	**<0.001**	**0.005**
	9 months	6.0	14.4	-1.7	-4.602	1.236	0.258	47.988
	12 months	6.3	15.3	-2.0	-5.176	1.142	0.210	39.060
	18 months	4.8	13.6	-0.5	-3.841	2.861	0.774	143.964
	24 months	2.1	8.2	2.2	-0.575	4.984	0.119	22.134
Weight loss	**Baseline**	76.9	65.6					
	3 months	48.7	54.2	-0.8	-5.943	4.370	0.764	142.104
	6 months	23.7	27.6	-5.0	-10.301	0.239	0.061	11.346
	9 months	20.1	25.6	-1.4	-6.658	3.838	0.598	111.228
	12 months	18.6	25.5	0.0	-5.402	5.451	0.993	184.698
	18 months	15.3	26.3	3.4	-2.827	9.560	0.286	53.196
	24 months	13.2	20.3	5.4	-0.690	11.580	0.081	15.066

Supplementary table 2: Continued

		Univariable analysis						
		Mean score	Standard deviation	B	95% CI		p value	Corrected p value
					Lower	Upper		
Problems with hair loss	**Baseline**	23.9	24.6					
	3 months	16.8	24.6	28.2	11.500	44.814	**0.001**	0.186
	6 months	58.2	58.2	18.7	1.322	36.082	**0.035**	6.510
	9 months	60.0	60.6	16.9	-2.047	35.834	0.08	14.880
	12 months	64.1	62.4	12.8	-6.859	32.376	0.201	37.386
	18 months	70.6	63.5	6.3	-16.251	28.862	0.581	108.066
	24 months	66.7	64.5	10.2	-16.463	36.917	0.449	83.514

B = regression coefficient. 95% CI = confidence interval. Bold p values represent significance (p<0.05). Corrected p value = corrected according to the Bonferroni correction for multiple testing.

Supplementary table 3: Univariable linear regression analysis of health-related quality of life scores of patients with postoperative complications following esophagectomy.

		Univariable analysis						
		Mean score	Standard deviation	B	95% CI		p value	Corrected p value
					Lower	Upper		
EORTC QLQ-C30								
Global Health	**Baseline**	74.4	17.3					
	3 months	71.8	19.3	2.6	-0.667	5.940	0.117	21.762
	6 months	68.7	17.4	5.7	2.504	8.939	**0.001**	0.186
	9 months	73.5	17.7	0.9	-2.490	4.245	0.609	113.274
	12 months	73.8	16.3	0.6	-2.824	3.940	0.746	138.756
	18 months	73.6	17.0	0.8	-3.066	4.737	0.674	125.364
	24 months	77.2	16.9	-2.8	-7.985	2.465	0.300	55.800
Functioning scores								
Physical functioning	**Baseline**	88.2	15.3					
	3 months	77.8	22.5	10.4	6.860	13.957	**<0.001**	**<0.001**
	6 months	75.0	20.4	13.2	9.796	16.586	**<0.001**	**<0.001**
	9 months	79.4	19.5	8.8	5.296	12.224	**<0.001**	**<0.001**
	12 months	82.2	17.3	6.0	2.824	9.217	**<0.001**	**0.045**
	18 months	82.9	16.1	5.3	1.744	8.765	**0.003**	0.558
	24 months	84.6	15.9	3.6	-1.069	8.252	0.131	24.366
Role functioning	**Baseline**	80.5	25.7					
	3 months	67.5	33.1	13.0	7.612	18.470	**<0.001**	**<0.001**
	6 months	61.9	29.9	18.6	13.512	23.666	**<0.001**	**<0.001**
	9 months	70.5	28.0	10.0	4.879	15.128	**<0.001**	**0.027**
	12 months	75.7	26.4	4.8	-0.341	10.013	0.067	12.462
	18 months	78.7	23.3	1.8	-3.903	7.431	0.541	100.626
	24 months	80.3	23.5	0.2	-7.528	7.849	0.967	179.862
Emotional functioning	**Baseline**	78.7	20.1					
	3 months	81.1	20.3	-2.5	-6.117	1.180	0.185	34.41
	6 months	83.1	19.4	-4.4	-8.083	-0.757	**0.018**	3.348
	9 months	83.3	20.2	-4.6	-8.472	-0.720	**0.020**	3.720
	12 months	83.7	18.9	-5.1	-8.982	-1.141	**0.012**	2.232
	18 months	82.9	19.7	-4.3	-8.800	0.238	0.063	11.718
	24 months	87.3	17.4	-8.7	-14.642	-2.713	**0.004**	0.744
Cognitive functioning	**Baseline**	89.2	17.6					
	3 months	85.5	21.3	3.7	0.164	7.323	**0.040**	7.440
	6 months	84.5	20.4	4.8	1.286	8.252	**0.007**	1.302
	9 months	86.0	17.4	3.2	-0.139	6.617	0.060	11.160
	12 months	85.5	20.2	3.7	-0.013	7.399	0.051	9.486
	18 months	85.7	18.8	3.5	-0.560	7.570	0.091	16.926
	24 months	87.3	18.9	1.9	-3.515	7.287	0.493	91.698

Supplementary table 3: Continued

		Univariable analysis						
		Mean score	Standard deviation	B	95% CI		p value	Corrected p value
					Lower	Upper		
Social functioning	**Baseline**	86.1	19.8					
	3 months	77.3	25.7	8.8	4.534	12.982	**<0.001**	**0.010**
	6 months	73.2	24.9	12.9	8.615	17.112	**<0.001**	**<0.001**
	9 months	77.5	24.7	8.5	4.083	12.938	**<0.001**	**0.035**
	12 months	84.3	21.4	1.7	-2.328	5.807	0.401	74.586
	18 months	81.7	24.5	4.3	-0.980	9.607	0.110	20.460
	24 months	87.7	18.7	-1.6	-7.560	4.345	0.596	110.856
Symptom scores								
Fatigue	**Baseline**	26.2	21.6					
	3 months	34.1	26.8	-7.9	-12.325	-3.441	**0.001**	0.186
	6 months	39.0	23.1	-12.8	-16.922	-8.717	**<0.001**	**<0.001**
	9 months	33.8	22.4	-7.6	-11.827	-3.393	**<0.001**	0.080
	12 months	30.5	22.5	-4.3	-8.709	0.027	0.051	9.486
	18 months	29.9	21.3	-3.7	-8.540	1.179	0.137	25.482
	24 months	26.4	22.7	-0.2	-6.823	6.353	0.944	175.584
Nausea and vomiting	**Baseline**	11.0	18.1					
	3 months	10.2	18.5	0.8	-2.497	4.119	0.630	117.18
	6 months	17.4	20.2	-6.3	-9.811	-2.791	**<0.001**	0.086
	9 months	15.5	20.6	-4.4	-8.117	-0.765	**0.018**	3.348
	12 months	12.0	18.3	-0.9	-4.531	2.726	0.625	116.250
	18 months	9.2	12.9	1.8	-1.448	5.134	0.271	50.406
	24 months	8.3	14.4	2.7	-2.617	8.049	0.317	58.962
Pain	**Baseline**	16.4	20.7					
	3 months	20.8	25.2	-4.4	-8.605	-0.188	**0.041**	7.626
	6 months	19.5	22.9	-3.1	-7.175	0.945	0.132	24.607
	9 months	17.0	20.7	-0.6	-4.593	3.387	0.767	142.662
	12 months	15.7	22.7	0.7	-3.602	4.959	0.756	140.616
	18 months	14.3	20.7	2.1	-2.619	6.763	0.271	50.406
	24 months	13.7	19.0	2.7	-3.513	8.896	0.394	73.284
Dyspnea	**Baseline**	12.2	20.2					
	3 months	23.4	27.8	-11.2	-15.632	-6.685	**<0.001**	**<0.001**
	6 months	31.0	27.7	-18.7	-23.316	-14.145	**<0.001**	**<0.001**
	9 months	23.1	29.5	-10.9	-15.980	-5.850	**<0.001**	**0.006**
	12 months	19.3	27.3	-7.1	-12.060	-2.092	**0.006**	1.116
	18 months	21.3	24.1	-9.0	-14.283	-3.812	**0.001**	0.186
	24 months	20.7	27.7	-8.4	-16.653	-0.236	**0.044**	8.184
Insomnia	**Baseline**	22.8	27.3					
	3 months	25.9	31.8	-3.1	-8.511	2.295	0.259	48.174
	6 months	24.3	29.3	-1.5	-6.719	3.681	0.566	105.276
	9 months	19.0	25.3	3.8	-1.337	8.899	0.147	27.342
	12 months	20.4	26.6	2.4	-2.993	7.804	0.382	71.052
	18 months	21.3	26.2	1.5	-4.583	7.644	0.623	115.878
	24 months	22.7	29.7	0.1	-8.261	8.529	0.975	181.350
Appetite loss	**Baseline**	18.0	26.6					
	3 months	22.6	30.7	-4.6	-9.825	0.683	0.088	16.368
	6 months	34.4	31.7	-16.3	-21.663	-11.006	**<0.001**	**<0.001**
	9 months	21.4	27.3	-3.3	-8.514	1.819	0.203	37.758
	12 months	19.0	26.5	-1.0	-6.266	4.346	0.722	134.292
	18 months	14.1	21.6	3.9	-1.334	9.179	0.143	26.598
	24 months	11.3	18.6	6.7	0.563	12.820	**0.033**	6.138
Constipation	**Baseline**	14.1	24.2					
	3 months	14.4	25.0	-0.4	-4.810	4.069	0.870	161.82
	6 months	12.0	21.8	2.1	-2.181	6.397	0.335	62.310
	9 months	9.0	18.4	5.1	1.043	9.065	**0.014**	2.604
	12 months	9.6	19.4	4.4	0.184	8.666	**0.041**	7.626
	18 months	8.9	17.5	5.2	0.750	9.620	**0.022**	4.092
	24 months	10.0	20.5	4.1	-2.397	10.545	0.214	39.804
Diarrhea	**Baseline**	8.2	18.0					
	3 months	12.2	23.6	-4.0	-7.903	-0.185	**0.040**	7.440
	6 months	21.1	25.3	-13.0	-17.126	-8.785	**<0.001**	**<0.001**
	9 months	17.3	24.4	-9.1	-13.342	-4.810	**<0.001**	**0.007**
	12 months	15.8	23.3	-7.6	-11.915	-3.307	**0.001**	0.186
	18 months	14.3	23.0	-6.1	-11.049	-1.166	**0.016**	2.976
	24 months	12.0	23.1	-3.8	-10.711	3.068	0.272	50.592

Supplementary table 3: Continued

		Univariable analysis						
		Mean score	Standard deviation	B	95% CI		p value	Corrected p value
					Lower	Upper		
Financial difficulties	**Baseline**	5.8	16.6					
	3 months	7.3	16.9	-1.5	-4.512	1.557	0.339	63.054
	6 months	8.6	19.7	-2.8	-6.185	0.651	0.112	20.832
	9 months	8.6	19.6	-2.8	-6.375	0.769	0.124	23.064
	12 months	7.5	17.2	-1.6	-4.995	1.731	0.341	63.426
	18 months	8.3	19.5	-2.4	-6.686	1.826	0.261	48.546
	24 months	6.0	12.9	-0.2	-5.061	4.709	0.944	175.584
EORTC QLQ-OG25								
Functioning scores								
Body image	**Baseline**	90.5	19.9					
	3 months	85.3	24.0	5.2	1.145	9.225	**0.012**	2.232
	6 months	86.1	23.4	4.4	0.351	8.507	**0.033**	6.138
	9 months	87.5	22.0	3.1	-1.035	7.156	0.142	26.412
	12 months	85.8	26.0	4.7	-0.084	9.553	0.054	10.044
	18 months	87.0	24.7	3.5	-1.799	8.855	0.193	35.898
	24 months	90.0	18.1	0.5	-5.429	6.453	0.866	161.076
Symptom scores								
Dysphagia	**Baseline**	21.5	22.4					
	3 months	17.4	24.5	4.1	-0.104	8.368	**0.056**	10.416
	6 months	23.5	24.7	-2.0	-6.338	2.313	0.361	67.146
	9 months	16.7	20.8	4.8	0.620	9.021	**0.025**	4.65
	12 months	14.2	18.2	7.3	3.122	11.515	**0.001**	0.186
	18 months	13.3	19.7	8.2	3.334	13.145	**0.001**	0.186
	24 months	6.0	11.5	15.5	11.320	19.720	**<0.001**	**<0.001**
Eating	**Baseline**	30.8	27.3					
	3 months	28.2	30.6	2.5	-2.811	7.878	0.352	65.472
	6 months	40.6	25.5	-9.8	-14.719	-4.850	**<0.001**	**0.021**
	9 months	32.0	24.9	-1.3	-6.346	3.842	0.629	116.994
	12 months	30.7	24.7	0.1	-5.057	5.236	0.973	180.978
	18 months	26.1	23.2	4.7	-1.257	10.668	0.122	22.692
	24 months	18.2	20.7	12.6	5.857	19.246	**<0.001**	0.065
Reflux	**Baseline**	7.2	17.6					
	3 months	6.1	16.1	1.1	-1.953	4.201	**0.4730**	87.978
	6 months	12.5	19.9	-5.3	-8.849	-1.809	**0.003**	0.558
	9 months	15.1	21.2	-7.9	-11.725	-4.043	**<0.001**	**0.013**
	12 months	14.1	20.6	-6.9	-10.837	-2.991	**0.001**	0.186
	18 months	16.5	23.1	-9.3	-14.220	-4.368	**<0.001**	0.051
	24 months	15.0	18.5	-7.8	-13.438	-2.134	**0.008**	1.488
Odynophagia	**Baseline**	24.5	25.7					
	3 months	14.3	22.5	10.2	5.792	14.529	**<0.001**	**0.001**
	6 months	16.2	20.6	8.2	3.992	12.477	**<0.001**	**0.029**
	9 months	13.0	17.0	11.5	7.456	15.490	**<0.001**	**<0.001**
	12 months	10.8	17.2	13.7	9.514	17.792	**<0.001**	**<0.001**
	18 months	12.7	18.4	11.8	7.105	16.513	**<0.001**	**<0.001**
	24 months	6.3	12.1	18.1	13.549	22.724	**<0.001**	**<0.001**
Pain and discomfort	**Baseline**	17.4	23.9					
	3 months	9.3	18.0	8.1	4.301	11.851	**<0.001**	**0.006**
	6 months	14.9	19.5	2.5	-1.502	6.454	0.222	41.292
	9 months	16.1	19.4	1.3	-2.765	5.446	0.521	96.906
	12 months	15.3	20.8	2.1	-2.490	6.637	0.372	69.192
	18 months	13.5	17.5	4.0	-0.490	8.399	0.081	15.066
	24 months	12.0	15.1	5.4	0.290	10.541	**0.039**	7.254
Anxiety	**Baseline**	48.9	25.3					
	3 months	41.3	27.2	7.6	2.868	12.353	**0.002**	0.372
	6 months	32.7	25.2	16.1	11.467	20.830	**<0.001**	**<0.001**
	9 months	29.0	26.8	19.9	14.869	24.853	**<0.001**	**<0.001**
	12 months	30.8	26.6	18.1	12.933	23.273	**<0.001**	**<0.001**
	18 months	27.2	27.3	21.6	15.755	27.519	**<0.001**	**<0.001**
	24 months	22.0	21.4	26.9	19.375	34.387	**<0.001**	**<0.001**

Supplementary table 3: Continued

		Univariable analysis						
		Mean score	Standard deviation	B	95% CI		p value	Corrected p value
					Lower	Upper		
Eating with others	**Baseline**	14.0	26.6					
	3 months	10.8	23.0	3.3	-1.254	7.755	0.157	29.202
	6 months	16.6	25.3	-2.5	-7.406	2.317	0.304	56.544
	9 months	12.4	24.1	1.6	-3.350	6.568	0.524	97.464
	12 months	10.0	21.1	4.0	-0.626	8.697	0.090	16.740
	18 months	9.5	19.5	4.5	-0.418	9.441	0.073	13.578
	24 months	9.3	19.1	4.7	-1.567	10.971	0.140	26.040
Dry mouth	**Baseline**	13.8	21.5					
	3 months	21.1	28.4	-7.2	-11.889	-2.604	**0.002**	0.372
	6 months	25.7	29.7	-11.9	-16.858	-6.998	**<0.001**	**<0.001**
	9 months	21.8	27.0	-8.0	-12.778	-3.139	**0.001**	0.186
	12 months	20.0	25.9	-6.2	-11.096	-1.292	**0.013**	2.418
	18 months	20.6	26.3	-6.8	-12.523	-1.135	**0.019**	3.534
	24 months	16.7	20.5	-2.9	-9.329	3.608	0.385	71.610
Trouble with taste	**Baseline**	12.4	24.2					
	3 months	22.3	29.2	-10.0	-14.921	-5.020	**<0.001**	0.070
	6 months	25.7	31.4	-13.3	-18.665	-8.005	**<0.001**	**<0.001**
	9 months	18.3	24.4	-6.0	-10.673	-1.294	**0.013**	2.418
	12 months	14.0	22.9	-1.6	-6.406	3.125	0.499	92.814
	18 months	14.3	26.1	-1.9	-7.533	3.680	0.500	93.000
	24 months	14.7	23.5	-2.3	-9.613	4.999	0.535	99.51
Trouble swallowing saliva	**Baseline**	9.5	19.9					
	3 months	14.7	24.0	-5.2	-9.225	-1.145	**0.012**	2.232
	6 months	13.9	23.4	-4.4	-8.507	-0.351	**0.033**	6.138
	9 months	12.5	22.0	-3.1	-7.156	1.035	0.142	26.412
	12 months	14.2	26.0	-4.7	-9.553	0.084	0.054	10.044
	18 months	13.0	24.7	-3.5	-8.855	1.799	0.193	35.898
	24 months	10.0	18.1	-0.5	-6.453	5.429	0.866	161.076
Choked when swallowing	**Baseline**	7.7	18.0					
	3 months	8.0	18.2	-0.3	-3.541	3.015	0.875	162.750
	6 months	14.2	23.0	-6.5	-10.440	-2.610	**0.001**	0.186
	9 months	12.9	22.1	-5.2	-9.205	-1.254	**0.010**	1.860
	12 months	10.3	18.5	-2.6	-6.268	1.109	0.170	31.620
	18 months	12.8	20.4	-5.1	-9.616	-0.602	**0.027**	5.022
	24 months	12.2	20.1	-4.5	-10.667	1.600	0.145	26.970
Trouble with coughing	**Baseline**	21.8	23.0					
	3 months	27.7	29.9	-5.9	-10.807	-0.946	**0.020**	3.720
	6 months	43.5	30.1	-21.7	-26.772	-16.551	**<0.001**	**<0.001**
	9 months	35.3	26.5	-13.5	-18.189	-8.750	**<0.001**	**<0.001**
	12 months	26.2	23.4	-4.4	-9.010	0.261	0.064	11.904
	18 months	28.9	23.6	-7.0	-12.285	-1.798	**0.009**	1.674
	24 months	26.5	21.5	-4.7	-11.639	2.274	0.186	34.596
Trouble talking	**Baseline**	4.8	14.3					
	3 months	9.7	23.0	-4.9	-8.468	-1.325	**0.007**	1.302
	6 months	15.5	27.3	-10.6	-14.856	-6.382	**<0.001**	**<0.001**
	9 months	11.0	23.8	-6.2	-10.203	-2.222	**0.002**	0.372
	12 months	8.7	19.9	-3.8	-7.460	-0.208	**0.038**	7.068
	18 months	8.6	20.7	-3.7	-8.085	0.608	0.091	16.926
	24 months	5.3	12.3	-0.5	-4.748	3.747	0.817	151.962
Weight loss	**Baseline**	17.5	25.1					
	3 months	17.3	24.9	0.2	-4.311	4.770	0.921	171.306
	6 months	22.6	26.0	-5.0	-9.759	-0.305	**0.037**	6.882
	9 months	23.6	27.9	-6.1	-11.265	-0.882	**0.022**	4.092
	12 months	20.0	26.8	-2.5	-7.609	2.684	0.347	64.542
	18 months	14.3	25.3	3.3	-2.433	8.936	0.261	48.546
	24 months	15.0	26.4	2.6	-5.151	10.294	0.513	95.418
Problems with hair loss	**Baseline**	86.6	62.3					
	3 months	47.3	54.6	39.3	24.272	54.251	**<0.001**	**<0.001**
	6 months	60.4	59.8	26.2	9.733	42.721	**0.002**	0.372
	9 months	63.2	60.9	23.4	5.234	41.479	**0.012**	2.232
	12 months	66.2	62.6	20.4	1.491	39.337	**0.035**	6.510
	18 months	62.7	64.1	23.9	2.670	45.205	**0.028**	5.208
	24 months	81.9	62.9	4.7	-23.213	32.533	0.741	137.826

B = regression coefficient. 95% CI = confidence interval. Bold p values represent significance (p<0.05). Corrected p value = corrected according to the Bonferroni correction for multiple testing.

Chapter 7

Gastrectomy versus esophagectomy for gastroesophageal junction tumors: short- and long-term outcomes from the Dutch Upper GI Cancer Audit

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ABSTRACT

Objective

Investigate long-term survival, morbidity, mortality and pathology results in patients following esophagectomy or total gastrectomy for GEJ cancer.

Background

Both a total gastrectomy and an esophagectomy may be valid treatment options in patients with gastroesophageal junction (GEJ) cancer. Which procedure results in the most optimal patient outcome is not well studied. The aim of this study was to investigate the long-term survival, morbidity, mortality and pathology results in patients following esophagectomy or total gastrectomy for GEJ cancer.

Methods

A retrospective comparative cohort study of prospectively collected data from the Dutch Upper GI Cancer Audit combined with survival data of the Dutch medical insurance database was performed. Patients with GEJ cancer in whom a total gastrectomy or an esophagectomy was performed between 2011-2016 were compared. The primary outcome was 3-year overall survival. Postoperative morbidity, mortality, 3-year conditional survival, radicality of resection and lymph node yield were secondary endpoints.

Results

A total of 871 patients were included: 790 following esophagectomy and 81 following gastrectomy. The 3-year overall survival was 35.8% after esophagectomy and 28.4% after gastrectomy (HR 1.2, 95%CI 0.721-1.836, p=0.557). Postoperative morbidity, mortality, radicality of resection, lymph node yield and 3-year conditional survival did not differ significantly between groups.

Conclusion

A total gastrectomy and an esophagectomy for GEJ cancer show largely comparable results with regard to long-term survival, postoperative morbidity, mortality and pathology results. If both procedures are feasible other parameters such as surgeon's experience and quality of life should be considered when planning for surgery.

INTRODUCTION

Cancer of the gastroesophageal junction (GEJ) has a rapidly increasing incidence [1]. Treatment usually consists of (neo)adjuvant chemo(radio)therapy and surgery [2]. Both a total gastrectomy and an esophagectomy may be technically possible and selecting the most suitable surgical procedure poses a challenge to surgeons treating GEJ cancer. There is no conclusive evidence which procedure yields the best outcome regarding postoperative morbidity and mortality, pathology results (radicality of surgery and lymph node yield) and long-term survival.

As esophagectomy usually includes a thoracic part, which induces more surgical trauma and, especially if an open esophagectomy is performed, is associated with an increased incidence of pulmonary complications [3, 4]. However, a more extensive lymphadenectomy can be performed during a thoracoabdominal approach, compared to an abdominal approach [5]. Furthermore, a lower rate of R1 resections may be found following a transthoracic approach (esophagectomy) compared to a transhiatal approach (gastrectomy) [6, 7]. Two recent systematic reviews reported no difference in 5-year survival, 30-day mortality and pathology results between esophagectomy and gastrectomy [8, 9] although one of those systematic review [8] reported a higher rate of postoperative morbidity after an esophagectomy compared to a gastrectomy. Even though the 30-day mortality is described in most studies included in these systematic reviews, the long-term survival rate is poorly investigated. Also, heterogeneity exists in and between the included studies, as some included not only GEJ but also distal esophageal and gastric cardia cancer, and some excluded patients following neoadjuvant therapy, making results difficult to interpret for patients with true GEJ cancer in the era of neoadjuvant therapy.

The aim of this study was to investigate the difference in long-term survival, postoperative morbidity, mortality and pathology results in GEJ cancer patients following an esophagectomy or a total gastrectomy at a population level. We hypothesized to find a higher 3-year overall and conditional survival in the esophagectomy group, because a more extended lymphadenectomy can be performed with a lower chance of a proximal non-radical resection, however, at the cost of increased postoperative morbidity.

METHODS

Study design and patient population

The data for this population-based comparative cohort study was obtained from the Dutch Upper Gastrointestinal Cancer Audit (DUCA) [10]. The DUCA is a mandatory national audit, containing prospective data on the diagnostic process and surgical results of all patients with esophageal or gastric cancer operated in the Netherlands. The purpose of this registration is

to gain insight into the quality of care and to accelerate its improvement. This system points to potential areas for improvement as hospitals receive feedback on their own results, compared to the national average. Patients in the DUCA are operated by gastro-intestinal surgeons, who perform both the thoracic as well as the abdominal part of an esophagectomy. The same surgeons usually also perform the gastrectomies (although in few centers only esophagectomies or only gastrectomies are being performed). Survival data was obtained from VEKTIS, a database of medical insurance organizations of the Netherlands, containing the date of death and information on medical treatments of almost all Dutch people (99%) [11]. Survival data from the VEKTIS database was merged with the DUCA database on the 1st of September, 2017 and the validation of accuracy and completeness has been previously described in a separate article by *van der Werf et al.* [12].

Surgeons who registered patients in the DUCA database, could choose from ten input options for tumor location: cervical, intrathoracic (proximal part), intrathoracic (middle part), intrathoracic (distal part), esophagus-stomach transition point (GEJ), fundus, corpus, antrum, pylorus and diffuse gastric cancer. Choice for location was made by the responsible surgeon. Patients with an adenocarcinoma of the GEJ were included in this study. Patients who underwent a total gastrectomy or an esophagectomy (transthoracic and transhiatal) with curative intent in the period between January 2011 and December 2016 were compared. Patients in whom no anastomosis was performed or who underwent no resection, patients operated for recurrent disease, or patients with a colonic or jejunal interposition, patients undergoing salvage, palliative or emergency surgery, and patients with a squamous cell carcinoma were excluded from this study. In addition, all patients who underwent a subtotal gastrectomy were excluded. In the Netherlands, a subtotal gastrectomy is a distal gastrectomy, hence cannot be performed for a GEJ cancer. Ethical approval for this study was not required under Dutch law. The STROBE checklist was used for guidance during the composition of this paper [13].

(Neo)adjuvant therapy

(Neo)adjuvant therapy was administered according to the Dutch guidelines for gastric and esophageal cancer [14, 15]. In case of a true GEJ cancer, patients usually received neoadjuvant chemoradiotherapy according to the CROSS regimen [16]. Patients with cardia or GEJ cancers extending >2cm in to the stomach were usually treated with perioperative chemotherapy (EOX: Epirubicin, Oxaliplatin and Capecitabine) according to MAGIC study protocol [17]. Patients who participated in the CRITICS study received adjuvant chemoradiotherapy following neoadjuvant chemotherapy and gastrectomy [18]. Patients with World Health Organization functional Classification (WHO) grade ≥ 3 or early stage cancer (≤cT2N0) received no neoadjuvant or perioperative therapy [19].

Surgical techniques

Surgery was performed according to the Dutch guidelines for gastric and esophageal cancer [14, 15]. In total gastrectomy, the entire stomach was removed by a minimally invasive or an open approach with a modified D2 lymphadenectomy, after which an esophagojejunostomy was created with Roux-Y reconstruction. An esophagectomy was either performed open or minimally invasively by a transthoracic (TTE) or transhiatal (THE) approach, with an extended 1-field (THE) or 2-field (TTE) lymphadenectomy, with a cervical or intrathoracic esophagogastric anastomosis.

Endpoints

The primary endpoint was 3-year overall survival. Long-term disease specific survival could not be analyzed as the cause of death was not registered in either the VEKTIS or DUCA database. Secondary endpoints were postoperative morbidity (anastomotic dehiscence, pulmonary complications, chyle leakage, cardiac complications, supraventricular arrhythmia, re-interventions, length of Intensive Care Unit (ICU) stay, length of hospital stay, readmissions), short-term mortality (30-day and 90-day), 3-year conditional survival (survival calculated after exclusion of combined 30-day/in-hospital mortality) and pathology results (R0-resection rate, circumferential resection margin (CRM), (positive) lymph node count). Accurate information on location of resected lymph nodes in the DUCA database is lacking. Since 2016, a division into five regions ('intrathoracic high' (paratracheal, laryngeal nerve, aorto-pulmonal), 'intrathoracic low' (subcarinal, paraesophageal), 'N1 gastric lymph node stations' (at least 3 out of 6), 'N2 gastric lymph node stations' (at least 3 out of 6) and distant lymph node stations) has been added to the registry. As the inclusion period of this study was January 2011 and December 2016, we cannot analyze location of resected lymph nodes in this complete cohort.

Statistical analysis

Statistical analysis was performed with SPSS 26.0 software (SPSS, Inc., Chicago, IL, USA). The distribution of continuous variables was assessed using Shapiro-Wilk's test. For normally distributed continuous variables mean values with standard deviation (SD) were reported. In the case of not normally distributed continuous variables, median values with interquartile ranges (IQR) were reported. Binary and categorical variables were reported as proportions. For the analysis of baseline patient and tumor characteristics, Mann-Whitney U test, student's t test, χ2-test or Fisher's exact test were used where applicable. TTE and THE were analyzed separately because results may differ regarding morbidity and lymph node yield. The 3-year overall and conditional survival was displayed using Kaplan Meier survival curves and analyzed using Cox regression analysis. Baseline patient and tumor characteristics with a p value <0.1 were added to the multivariable regression analysis as possible confounders using backwards stepwise method. The 3-year overall and conditional survival of patients after TTE, THE and total gastrectomy was compared to exclude the effect of heterogeneity

in the esophagectomy group. Subgroup analyses was performed in patients following perioperative chemotherapy, in patients following neoadjuvant chemoradiotherapy and in (y)pN+ patients. For the analysis of secondary outcomes (postoperative mortality, morbidity and pathology results) Mann-Whitney U test, student's t test, $\chi 2$-test or Fisher's exact test were used where applicable and a Bonferroni correction for multiple testing was performed. If a $p < 0.1$ was found, postoperative morbidity, mortality and/or pathology results were entered in the multivariable analysis. Multivariable logistic regression was planned for dichotomous variables (postoperative morbidity, re-interventions, mortality, readmissions and R0 resection rate) and multivariable linear regression was planned for linear variables (length of ICU stay, length of hospital stay, CRM and (positive) lymph node count). A two-sided alpha of 0.05 was considered statistically significant.

RESULTS

Demographics and cohort features

A total of 871 patients with GEJ cancer, out of 7214 registered upper gastrointestinal (Upper GI) cancer patients, were included in the analysis. 790 patients underwent an esophagectomy (365 TTE and 425 THE) and 81 patients underwent a total gastrectomy (Table 1). The reasons for patient exclusion can be found in the flowchart in figure 1. Most patients were male: 84.4% in the esophagectomy and 82.7% in the gastrectomy group. Patients following an esophagectomy were significantly younger than patients following a gastrectomy (median 65 years [IQR 58-70] vs median 68 years [IQR 60-74], p=0.004). Patients in the esophagectomy group received significantly more neoadjuvant treatment than patients in the gastrectomy group (92.5% vs 85.1%, p<0.001). The majority of patients receiving neoadjuvant treatment in the gastrectomy group received perioperative chemotherapy (83.8%) and the majority of patients in the esophagectomy group received neoadjuvant chemoradiotherapy (80.1%, p<0.001). An open approach was significantly less common in the esophagectomy group compared to the gastrectomy group (48.2% vs 60.5%, p<0.001).

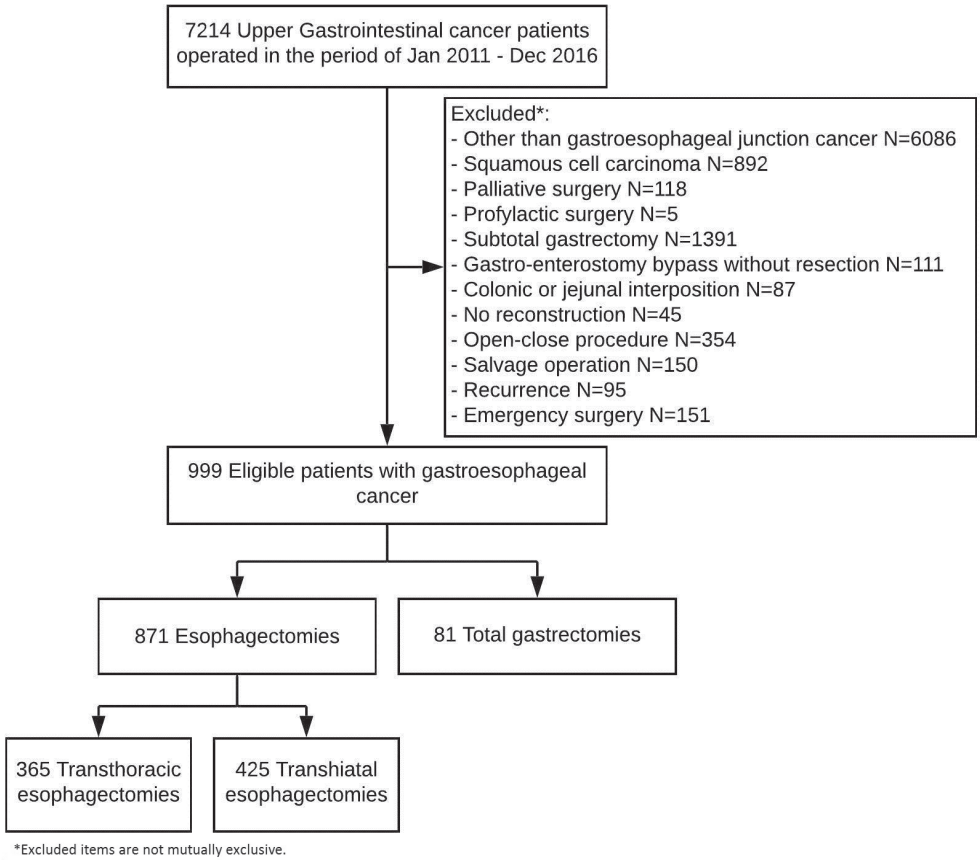


Figure 1: Study Flow Chart.

Table 1: Baseline patient and tumor characteristics of patients after transthoracic or transhiatal esophagectomy and total gastrectomy (N=871) in the period of 2011-2016.

		Transthoracic esophagectomies		Transhiatal esophagectomies		All esophagectomies		Gastrectomies		p value*
		N=365		N=425		N=790		N=81		
Gender (men)		312	(85.5)	355	(83.5)	667	(84.4)	67	(82.7)	0.687
Age (median (IQR), y)		64	[57-69]	66	[59-72]	65	[58-70]	68	[60-74]	**0.004**
Body Mass Index (median [IQR], kg/m²)		25.0	[23.0-28.0]	25.7	[23.3-29.0]	25.5	[23.1-28.4]	25.2	[22.7-27.7]	0.238
Comorbidity	**No**	124	(34.0)	83	(19.5)	207	(26.2)	19	(23.5)	0.591
	Yes	241	(66.0)	342	(80.5)	583	(73.8)	62	(76.5)	
	Cardiac	73	(20.0)	116	(27.3)	189	(23.9)	28	(34.6)	**0.035**
	Vascular	116	(31.8)	194	(45.6)	310	(39.2)	37	(45.7)	0.260
	Diabetic	48	(13.2)	71	(16.7)	119	(15.1)	19	(23.5)	**0.049**
	Pulmonary	47	(12.9)	76	(17.9)	123	(15.6)	18	(22.2)	0.122
	Thrombotic	13	(3.6)	21	(4.9)	34	(4.3)	12	(14.8)	0.001
ASA	**1**	82	(22.5)	61	(14.5)	143	(18.2)	10	(12.5)	**0.012**
	2	216	(59.2)	249	(59.0)	465	(59.1)	39	(48.8)	
	3	67	(18.4)	109	(25.8)	176	(22.4)	30	(37.5)	
	4	0	0	3	(0.7)	3	(0.4)	1	(1.3)	
Neoadjuvant therapy	**No**	20	(5.5)	39	(9.2)	59	(7.5)	12	(15.0)	**<0.001**
	Yes	344	(94.5)	385	(90.8)	729	(92.5)	68	(85.1)	
	Chemotherapy	57	(15.6)	88	(20.7)	145	(19.9)	57	(83.8)	**<0.001**
	Chemoradiotherapy	287	(78.6)	297	(69.9)	584	(80.1)	11	(16.2)	
cT	**T0**	0	0	0	0	0	0	0	0	0.581
	T1	13	(3.7)	18	(4.4)	31	(4.1)	3	(4.0)	
	T2	50	(14.4)	67	(16.5)	117	(15.5)	16	(21.3)	
	T3	275	(79.0)	310	(76.2)	585	(77.5)	55	(73.3)	
	T4	10	(2.9)	12	(2.9)	22	(2.9)	1	(1.3)	
cN	**N0**	125	(35.8)	154	(38.2)	279	(37.1)	28	(36.8)	0.634
	N1	137	(39.3)	168	(41.7)	305	(40.6)	28	(36.8)	
	N2	77	(22.1)	70	(17.4)	147	(19.5)	16	(21.1)	
	N3	10	(2.9)	11	(2.7)	21	(2.8)	4	(5.3)	
cM	**M0**	351	(99.2)	410	(99.5)	761	(99.3)	80	(98.8)	0.454
	M1	3	(0.8)	2	(0.5)	5	(0.7)	1	(1.2)	
Approach	**Open**	76	(20.8)	305	(71.8)	381	(48.2)	49	(60.5)	**<0.001**
	Hybrid	16	(4.4)	115	(27.0)	131	(16.6)	29	(35.8)	
	Minimal invasive	273	(74.8)	5	(1.2)	278	(35.2)	3	(3.7)	
Adjuvant therapy	**No**	329	(90.6)	363	(86.6)	692	(88.5)	39	(49.4)	**<0.001**
	Yes	34	(9.3)	56	(13.2)	90	(11.5)	40	(50.6)	
	Chemotherapy	28	(82.4)	51	(91.1)	79	(87.8)	34	(85.0)	0.409
	Chemoradiotherapy	6	(17.6)	5	(8.9)	11	(12.2)	5	(12.5)	
	Radiotherapy	0	0	0	0	0	0	1	(2.5)	
Histology	**Adenocarcinoma**	365	(100)	425	(100)	790	(100)	81	(100)	na
(y)pT	**T0**	43	(12.3)	47	(12.1)	90	(12.2)	4	(12.5)	**<0.001**
	T1	47	(13.4)	59	(15.1)	106	(14.3)	3	(9.4)	
	T2	71	(20.3)	82	(21.0)	153	(20.7)	7	(21.9)	
	T3	185	(52.9)	200	(51.3)	385	(52.0)	13	(40.6)	
	T4	4	(1.1)	2	(0.5)	6	(0.8)	5	(15.6)	
(y)pN	**N0**	182	(51.6)	203	(51.9)	385	(51.7)	15	(46.9)	0.305
	N1	80	(22.7)	84	(21.5)	164	(22.0)	6	(18.8)	
	N2	55	(15.6)	62	(15.9)	117	(15.7)	4	(12.5)	
	N3	36	(10.2)	41	(10.5)	77	(10.3)	7	(21.9)	
(y)pM	**M0**	348	(98.9)	405	(98.3)	753	(98.6)	76	(93.8)	**0.013**
	M1	4	(1.1)	7	(1.7)	11	(1.4)	5	(6.2)	

Data are presented as n (%) unless otherwise indicated. ASA = American Society of Anesthesiologists Classification. cTNM = clinical TNM staging classification before the treatment (AJCC 8th edition). IQR = interquartile range. *All esophagectomies vs gastrectomies. Bold p values represent significance. na = not applicable.

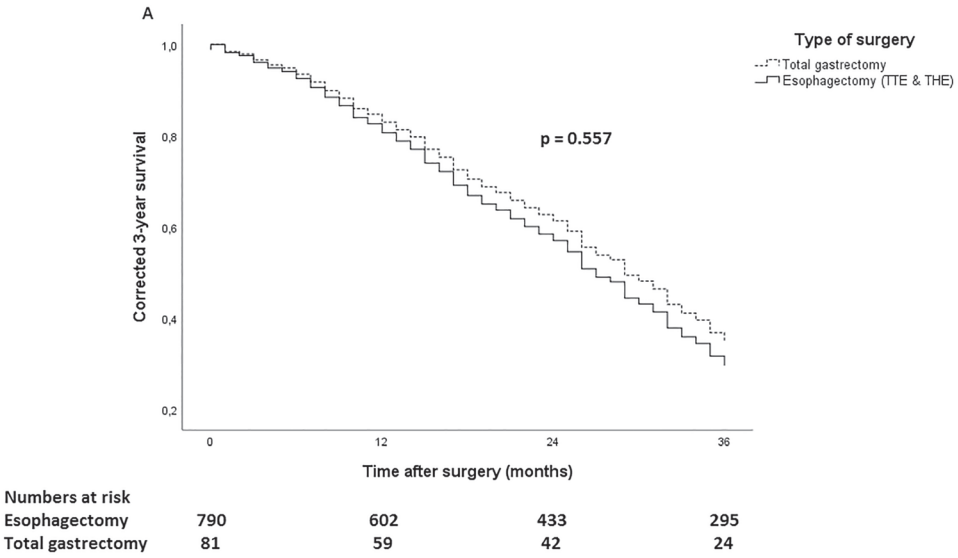
Primary endpoint: The 3-year overall survival

The Cox proportional hazards assumption was not violated, and Cox regression revealed that the 3-year overall survival was not significantly different between patients undergoing an esophagectomy or a gastrectomy (35.8% vs 28.4%, p=0.557) after correction for the possible confounders age, operation date, comorbidities (cardiac, diabetic, thrombotic), ASA classification, neoadjuvant therapy (yes/no and chemoradiotherapy or chemotherapy), surgical approach (open, hybrid or minimally invasive), adjuvant therapy (yes/no), (y)pT stage and (y)pM stage (Table 4 and Figure 2A). The 3-year overall survival did not differ between a TTE, a THE and a total gastrectomy (supplementary figure 1 A). Subgroup analyses in patients following perioperative chemotherapy, in patients following chemoradiotherapy and in (y)pN+ patients did not show differences in 3-year overall and conditional survival (supplementary figure 2-4). The number of gastrectomy patients in those subgroup analyses however, became so small, that strong conclusions cannot be drawn.

Table 4: Cox regression of the 3-year overall survival of patients with gastroesophageal cancer after an esophagectomy or a total gastrectomy.

		Hazard ratio	95% CI		p value
			Lower	Upper	
Esophagectomy		1.2	0.721	1.836	0.557
Age		1.0	0.986	1.007	0.491
Operation date					**<0.001**
	2011	1.1	0.735	1.636	0.652
	2012	1.4	0.965	2.157	0.074
	2013	2.0	1.410	2.929	**<0.001**
	2014	5.0	3.456	7.372	**<0.001**
	2015	10.0	6.703	15.029	**<0.001**
Cardiac comorbidity		1.0	0.768	1.220	0.782
Diabetes		1.2	0.915	1.520	0.203
Thrombotic comorbidity		1.2	0.786	1.820	0.404
ASA classification					0.372
	ASA 1	1.1	0.878	1.454	0.343
	ASA 2	1.3	0.962	1.831	0.085
	ASA 3	1.1	0.362	3.167	0.902
Neoadjuvant therapy		1.1	0.912	1.285	0.365
Surgical approach		1.0	0.955	1.106	0.468
Adjuvant therapy		0.9	0.655	1.251	0.546
(y)pT stage		1.1	1.068	1.169	**<0.001**
(y)pM stage		1.1	0.602	2.121	0.704

ASA classification = American Society of Anesthesiologists classification. Bold p values represent significance.



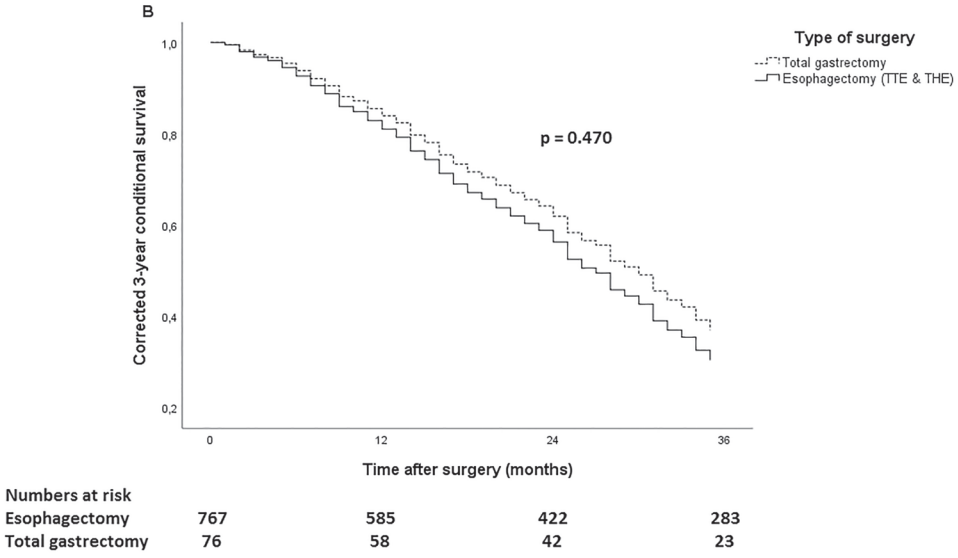


Figure 2: A: Corrected 3-year overall survival of patients with gastroesophageal junction cancer after an esophagectomy or a total gastrectomy. B: Corrected 3-year conditional survival of patients with gastroesophageal junction cancer after an esophagectomy or a total gastrectomy

Secondary endpoints: 3-year conditional survival, postoperative morbidity, mortality and pathology results

After univariable analysis and correction for multiple testing no significant difference was found in postoperative morbidity, 30-day and 90-day mortality, length of hospital stay, readmissions, re-interventions, positive lymph node count, R0 resection rate or median

CRM between the esophagectomy and gastrectomy groups (Table 2). However, after univariable analysis a difference with a p < 0.1 between esophagectomy and gastrectomy groups was found in length of ICU stay (median 2 days [IQR 1-4] vs median 1 day [IQR 0-2], p<0.001) and total lymph node count (median 17 [IQR 12-23] vs median 21 [IQR 16-31], p<0.001). A multivariable linear regression was performed including a correction for the possible confounders age, operation date, comorbidities (cardiac, diabetic, thrombotic), ASA classification, neoadjuvant therapy (yes/no and chemoradiotherapy or chemotherapy), surgical approach (open, hybrid or minimally invasive), adjuvant therapy (yes/no), (y) pT stage and/or (y)pM stage. However, no significant difference was found between esophagectomy and gastrectomy in length of ICU stay (ß=3.6, 95% CI -0.043 - 7.292, p = 0.053) or total lymph node count (ß=-3.1, 95% CI -6.446 - 0.165, p = 0.063) (Table 3). In addition, no significant difference was found in 3-year conditional survival between patients following an esophagectomy or a gastrectomy (36.9% vs 30.3%, p=0.470) (Table 5 and Figure 2B). The 3-year conditional survival was also not significantly different between a TTE, a THE and a total gastrectomy (supplementary figure 1 B).

Table 2: Secondary endpoints (postoperative morbidity, mortality and pathology results) of 871 patients with gastroesophageal cancer after esophagectomy or total gastrectomy.

		Transthoracic esophagectomies		Transhiatal esophagectomies		All esophagectomies		Gastrectomies		p value*	Corrected p value
		N=365		N=425		N=790		N=81			
Postoperative morbidity	**No**	157	(43.0)	194	(46.2)	351	(44.7)	41	(50.6)	0.309	6.180
	Yes	208	(57.0)	226	(53.8)	434	(55.3)	40	(49.4)		
	Anastomotic leakage	58	(17.6)	83	(20.1)	14	(18.2)	14	(18.2)	0.861	17.220
	Pulmonary complications	104	(28.5)	104	(24.8)	208	(26.5)	23	(28.4)	0.718	14.360
	Chyle leakage	37	(10.3)	4	(1.0)	41	(5.3)	3	(3.8)	0.790	15.800
	Cardiac complications	37	(10.1)	48	(11.5)	85	(10.8)	23	(28.4)	0.541	10.820
	Supraventricular arrhythmia	7	(4.2)	4	(2.0)	11	(3.0)	1	(2.3)	0.801	16.020
	Other	37	(10.1)	36	(8.6)	73	(9.3)	7	(8.6)	0.843	16.860
Re-interventions	**Yes**	94	(25.8)	71	(16.9)	165	(21.0)	25	(31.3)	**0.036**	0.720
	Radiologic	37	(39.8)	31	(45.6)	68	(42.2)	14	(56.0)	0.197	3.940
	Endoscopic	38	(40.9)	11	(16.4)	49	(30.6)	8	(32.0)	0.890	17.800
	Re-operation	55	(58.5)	48	(69.6)	103	(63.2)	14	(56.0)	0.490	9.800
Length of ICU stay (median [IQR]. days)		2	[1-4]	1	[1-3]	2	[1-4]	1	[0-2]	**<0.001**	**<0.001**
Length of hospital stay (median [IQR]. days)		12	[9-19]	11	[9-16]	12	[9-17]	10	[8-19]	0.094	1.880
Readmissions		58	(16.1)	48	(11.4)	106	(13.4)	12	(14.8)	0.687	13.740
30-day/in-hospital mortality		6	(1.6)	13	(3.1)	19	(2.4)	3	(3.7)	0.450	9.000
90-day mortality		6	(1.6)	10	(2.4)	16	(2.0)	2	(2.5)	0.680	13.600
Resection rate	**R0**	335	(92.3)	337	(90.0)	712	(91.0)	71	(87.7)		
	R1	28	(7.7)	39	(9.3)	67	(8.6)	10	(12.3)	0.316	6.320
	R2	0	0	3	(0.7)	3	(0.4)	0	0		
Circumferential resection margin (median [IQR]. mm)		4	[2-8]	3	[1-6.5]	3	[1-7]	3.5	[1-10]	0.956	19.120
Total lymph node count (median [IQR])		20	[15-27]	15	[10-20]	17	[12-23]	21	[16-31]	<0.001	<0.001
Positive lymph node count (median [IQR])		0	[0-3]	0	[0-3]	0	[0-3]	1	[0-5]	0.138	2.760

Data are presented as N (%) unless otherwise indicated. IQR = interquartile range. *All esophagectomies vs gastrectomies. Bold p values represent significance.

Table 3: Multivariable linear regression analysis of lymph node count and length of Intensive Care Unit stay of patients with gastroesophageal cancer after esophagectomy or total gastrectomy.

	Covariates	B	95%CI		P-value
			Lower	Upper	
Lymph node count	**Esophagectomy**	-3.1	-6.446	0.165	0.063
	Age	-0.1	-0.198	-0.062	**<0.001**
	Operation date	0.7	0.283	1.108	**0.001**
	Cardiac comorbidity	-	-	-	-
	Diabetes	-	-	-	-
	Thrombotic comorbidity	-	-	-	-
	ASA classification	-	-	-	-
	Neoadjuvant therapy	-1.9	-3.018	-0.857	**<0.001**
	Surgical approach	2.1	1.555	2.563	**<0.001**
	Adjuvant therapy	2.2	0.055	4.273	**0.044**
	(y)pT stage	0.3	0.041	0.611	**0.025**
	(y)pM stage	-6.4	-11.150	-1.661	0.008
Length of ICU stay	**Esophagectomy**	3.6	-0.043	7.292	0.053
	Age	-	-	-	-
	Operation date	-	-	-	-
	Cardiac comorbidity	-	-	-	-
	Diabetes	-	-	-	-
	Thrombotic comorbidity	-	-	-	-
	ASA classification	2.0	0.861	3.132	0.001
	Neoadjuvant therapy	-0.7	-1.982	0.494	0.239
	Surgical approach	0.3	-0.186	0.873	0.204
	Adjuvant therapy	-1.2	-3.579	1.248	0.343
	(y)pT stage	-0.2	-0.481	0.166	0.338
	(y)pM stage	-	-	-	-

B = regression coefficient, CI = confidence interval. ICU = Intensive Care Unit. ASA = American Society of Anesthesiologists Classification. *All esophagectomies vs gastrectomies. Bold p values represent significance.

Table 5: Cox regression of the 3-year conditional survival of patients with gastroesophageal cancer after an esophagectomy or a total gastrectomy.

		Hazard ratio	95% CI		p value
			Lower	Upper	
Esophagectomy		1.2	0.735	1.951	0.470
Age		1.0	0.985	1.006	0.366
Operation date					**<0.001**
	2011	1.1	0.697	1.590	0.806
	2012	1.4	0.914	2.092	0.125
	2013	2.1	1.439	3.031	**<0.001**
	2014	5.1	3.454	7.514	**<0.001**
	2015	10.9	7.189	16.468	**<0.001**
Cardiac comorbidity		0.9	0.726	1.174	0.517
Diabetes		1.1	0.881	1.494	0.309
Thrombotic comorbidity		1.2	0.793	1.870	0.369
ASA classification					0.569
	ASA 1	1.1	0.868	1.442	0.387
	ASA 2	1.3	0.913	1.761	0.157
	ASA 3	1.2	0.392	3.480	0.780
Neoadjuvant therapy		1.1	0.911	1.300	0.350
Surgical approach		1.0	0.966	1.122	0.290
Adjuvant therapy		1.0	0.694	1.332	0.813
(y)pT stage		1.1	1.072	1.177	**<0.001**
(y)pM stage		1.1	0.554	2.072	0.837

ASA classification = American Society of Anesthesiologists classification. Bold p values represent significance.

DISCUSSION

This study investigated the long-term survival, postoperative morbidity, mortality and pathology results in patients following an esophagectomy or a total gastrectomy for GEJ cancer. The results show that the 3-year overall and conditional survival of patients with GEJ cancer undergoing either an esophagectomy or a gastrectomy did not differ significantly. In addition, postoperative morbidity, short-term mortality and pathology results were not different between the two surgical approaches. Although not in line with our hypothesis, the study results contribute to clinical decision making by showing that both procedures can be performed with comparable short- and long-term results for patients with GEJ cancer. In addition, a recent study showed that the majority of patients have significant symptoms more than one year following an esophagectomy [20], however, largely comparable results were found between a gastrectomy and an esophagectomy regarding long-term quality of life [21]. Therefore, surgeons can base their decision with respect to the operative procedure for patients with GEJ cancer on personal and center experience.

A high heterogeneity was observed across previous studies investigating long-term survival, morbidity, mortality and pathology results in patients following an esophagectomy or a total gastrectomy [8, 9]. In some studies, administration of neoadjuvant therapy was either excluded or not reported and most studies also included distal esophageal or cardia/gastric cancers, rendering the comparison with our results difficult. Nonetheless, two systematic reviews, mostly comprised of retrospective mono-center studies, reported no significant difference in 5-year overall survival, 30-day mortality, lymph node yield or radicality of surgery, although a higher rate of postoperative morbidity was seen after esophagectomy in one. The most recent systematic review included one randomized controlled trial (RCT) [22]. This RCT compared patients after left thoracoabdominal approach (N=85) versus abdominal-transhiatal approach (N=82) and found no significant difference in 5-year overall survival but increased morbidity after left thoracoabdominal approach. In this RCT only patients with (sub)cardia cancer were included and all patients were operated by an open approach via a left thoracoabdominal incision, and therefore, the results of this RCT cannot be directly compared to the present study. Furthermore, a recent study with the national audit data (DUCA) compared the quality of the surgical resection, morbidity and mortality between a TTE and a THE esophagectomy in patients with a distal esophageal or GEJ cancer [23]. In this study, an increased morbidity and short-term mortality was found in the transthoracic group, but also a higher lymph node yield. However, long-term survival was not investigated. In the present study, a subgroup analysis of 3-year overall and conditional survival between TTE and THE was performed and showed no significant difference between the two groups. However, these results are only applicable to patients with GEJ cancer.

In the Netherlands, centralization of esophageal cancer surgery was initiated in 2011, whereas centralization of gastric cancer surgery was initiated two years later, in 2013. Since then, a minimum of 20 esophagectomies and 20 gastrectomies yearly is required to perform either gastrectomies or esophagectomies at a center. Mortality rates for gastrectomy have dropped from 7.7% in 2011 to 4.4% in 2018, while mortality rates following esophagectomy have dropped as well, but were already much lower compared to gastrectomy (4.1% in 2011 and 2.7% in 2018) [2, 24]. This delayed centralization for gastrectomies may partially explain why a higher morbidity following gastrectomy was observed in this population-based study. In addition, the pathology results, with a high R0 resection and similar (y)pN0 rate in both groups probably contribute to the comparable survival rates in both groups, even though a higher (y)pT4 rate was observed in the gastrectomy group.

Furthermore, minimally invasive esophagectomy is associated with less pulmonary complications compared to open esophagectomy [25]. Minimally invasive esophagectomy has become the preferred approach in the Netherlands, where 90.9% of all esophagectomies were performed minimally invasively in 2018 [2]. Also, in this study the majority of patients were operated minimally invasively, perhaps that is why less postoperative morbidity than expected was observed in the esophagectomy group. The comparable postoperative morbidity results may also contribute to similar long-term survival, as has been shown that survival may impair in patients with severe complications [12].

Various retrospective studies have been unable to determine the optimal extent of lymph node dissection for GEJ cancer [26-28]. A recent prospective study investigated the incidence of lymph node metastases in each lymph node station in patients with a GEJ tumor. They found a >10% rate of lymph node metastases in stations 1, 2, 3, 7, 9, and 11p, and at least 1 of the lower mediastinal lymph node stations. If esophageal involvement exceeded 4 cm, station 106recR (right recurrent laryngeal nerve) was also affected in more than 10% of the cases and other upper middle and lower mediastinal lymph node stations were regularly affected. Therefore, the authors propose to perform a right transthoracic approach in all patients with a GEJ tumor that invades the esophagus for more than 4 cm [29]. Unfortunately, such detailed information in the DUCA database is lacking. The registration of the location of resected lymph nodes in the DUCA database started in 2016 and the location of lymph node metastases is not recorded. Therefore, we could only provide information about whether a lymphadenectomy was performed. Due to a thoracic as well as an abdominal phase of the surgery we expected more lymph nodes to be resected in patients who underwent an esophagectomy. We found no significant difference in total lymph node count however, between patients who underwent an esophagectomy or a gastrectomy. Also, there was no significant difference in positive lymph node count or radicality of surgery. Our findings are in accordance with a recent systematic review where also no difference in total lymph

node count and R0-resection rate was found between esophagectomy and gastrectomy in patients with GEJ cancer [8].

A large difference in the number of patients with GEJ cancer treated with either an esophagectomy or a gastrectomy is seen in our data. Apparently, in the Netherlands, a preference for an esophagectomy exists for patients with GEJ cancer, although the reasons for this selection are unknown. This preference could be based on tumor characteristics (e.g. slightly more ingrowth in the distal esophagus), on surgeon's experience or expert opinion, there are however no data to support this.

The present study has several limitations. It is a retrospective comparative cohort study of prospectively collected data and no propensity score matching could be performed as it would have highly reduced the number of included patients with GEJ cancer who underwent a total gastrectomy. Furthermore, the DUCA-VEKTIS database was merged on the 1st of September 2017, and therefore no survival data after this date were available. Also, no disease specific survival could be analyzed as the cause of death is neither reported in the DUCA nor VEKTIS database. Since DUCA only recently added the Clavien-Dindo classification for postoperative complications to the audit, these data were unavailable for the vast majority of our cohort, and as such could not be analyzed. The anatomical location of the GEJ cancer could not be classified according to the Siewert-Stein classification [30], as it is not included in the DUCA database. However, extensive input options for esophageal tumor location are available in the DUCA database, including cervical, proximal intrathoracic, mid-thoracic, distal thoracic and esophagus-stomach transition point and this choice is made by the responsible surgeon. The number of statistical tests performed was high, therefore, a Bonferroni correction for multiple testing was performed, to counteract the possibility of finding a significant difference by chance. Furthermore, this study does not include any patient-reported outcome measures.

A strength of the current multicenter study in the Netherlands is that it includes one of the largest samples of patients with GEJ cancer with long-term survival data at a population level.

In conclusion, this study shows that an esophagectomy and a total gastrectomy in patients with GEJ cancer show largely comparable results with regard to postoperative morbidity and mortality, pathology results as well as long-term survival. Other parameters such as surgeon's experience should be considered when planning surgery if both procedures are technically feasible. However, these results need confirmation by randomized controlled trials.

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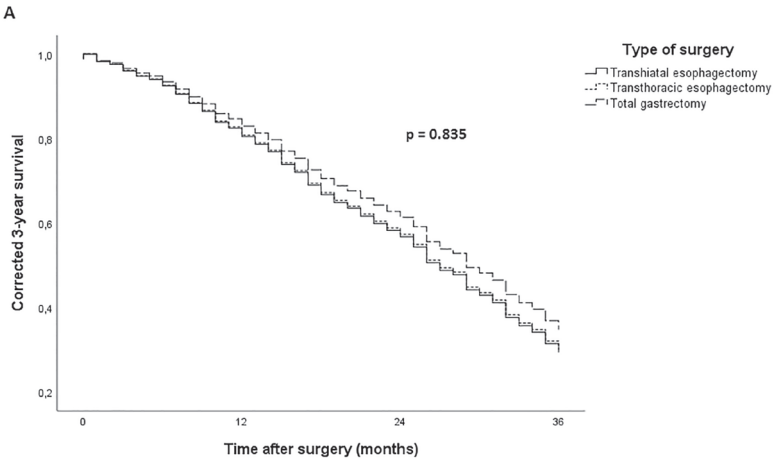
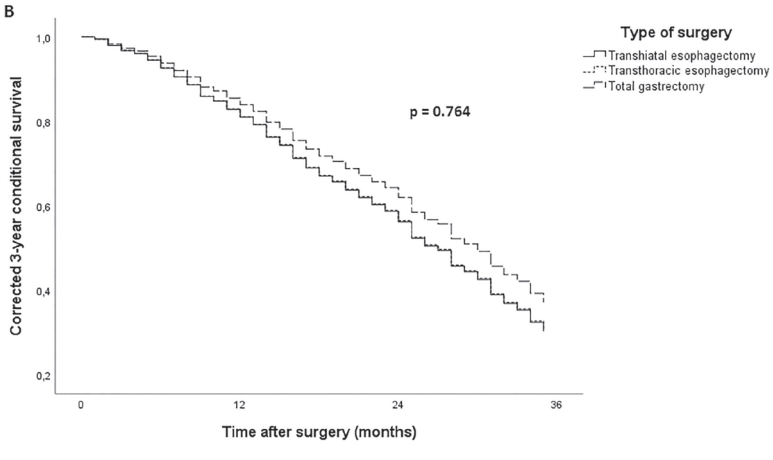
SUPPLEMENT



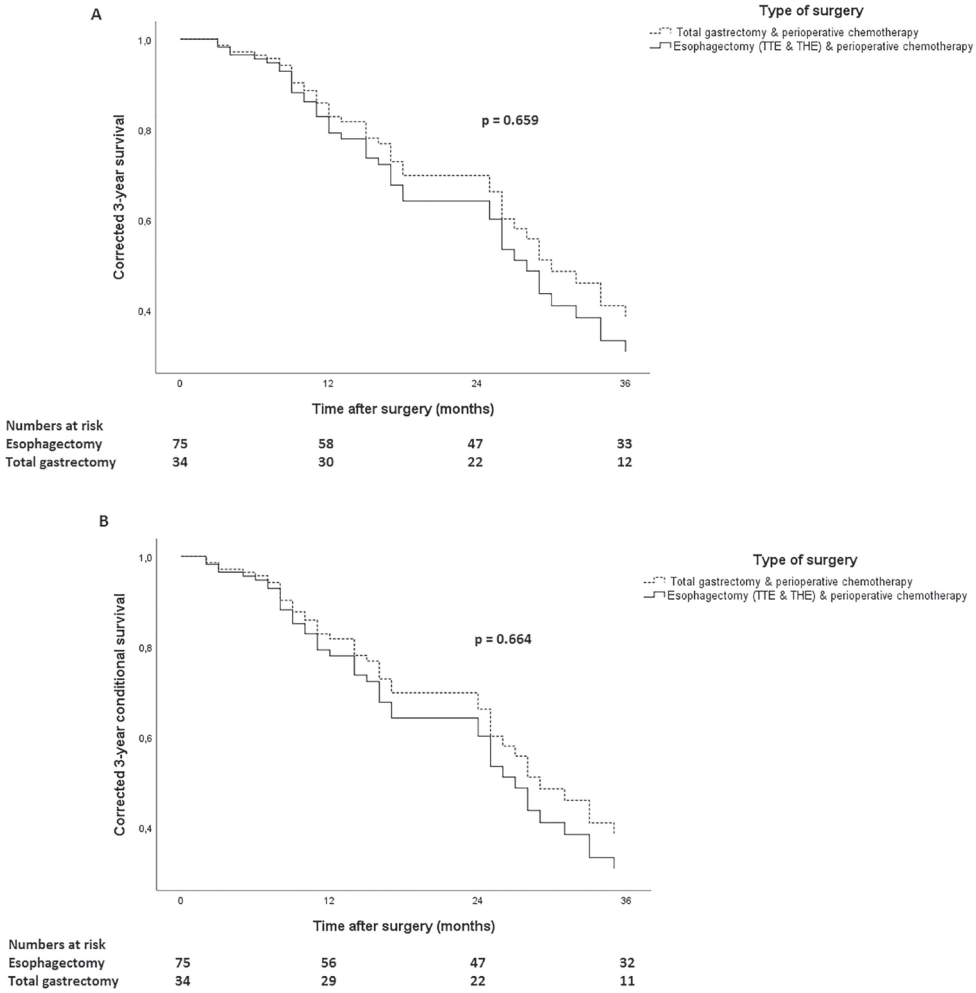
Numbers at risk				
Transhiatal esophagectomy	425	329	260	187
Transthoracic esophagectomy	365	273	173	108
Total gastrectomy	81	59	42	24



Numbers at risk				
Transhiatal esophagectomy	409	321	257	181
Transthoracic esophagectomy	358	264	165	102
Total gastrectomy	76	58	42	23

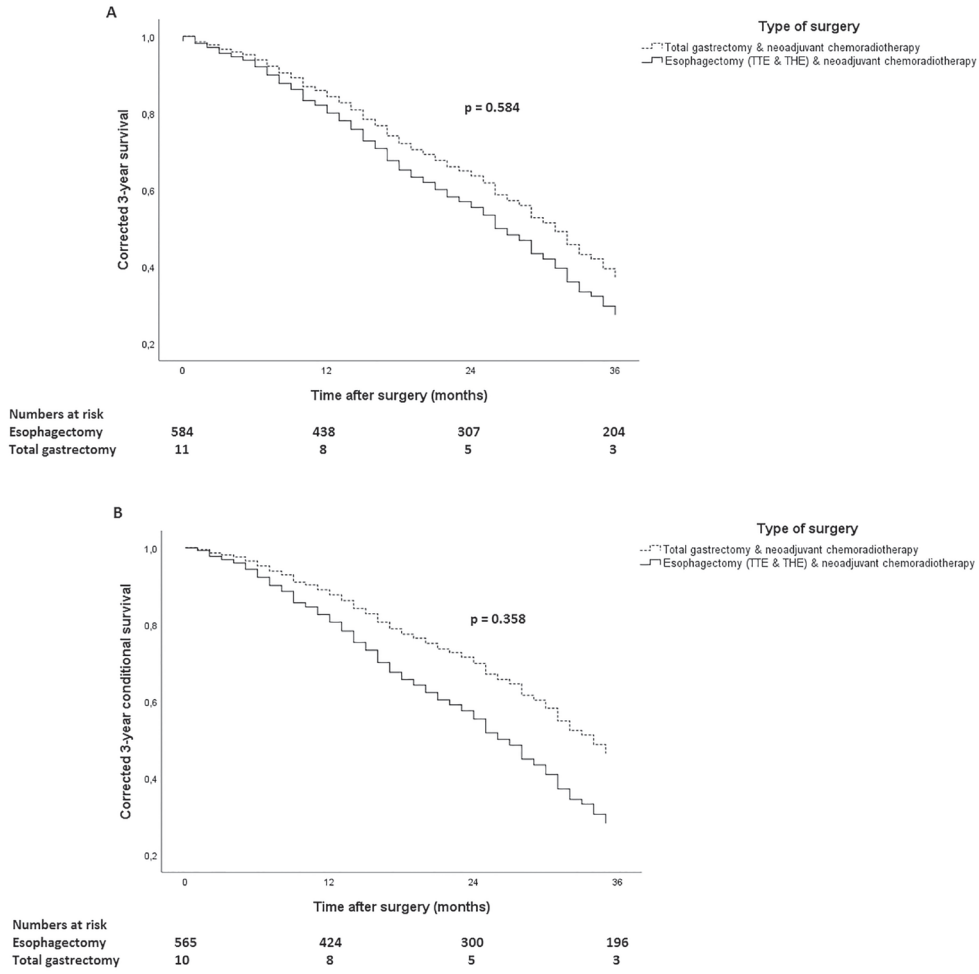
Supplementary figure 1 A & B:

A: corrected 3-year overall survival of patients with gastroesophageal junction cancer after transhiatal esophagectomy, transthoracic esophagectomy or total gastrectomy. B: corrected 3-year conditional survival of patients with gastroesophageal junction cancer after transhiatal esophagectomy, transthoracic esophagectomy or total gastrectomy.



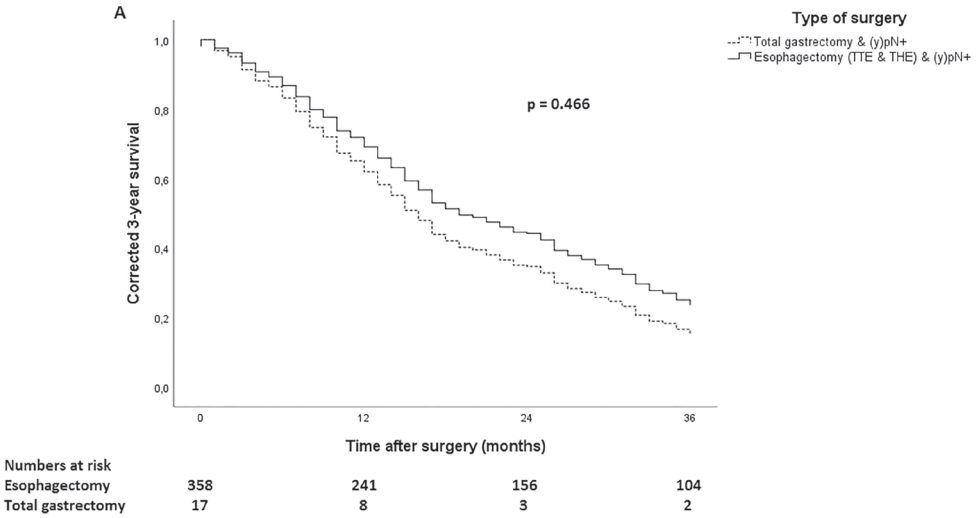
Supplementary figure 2 A & B:

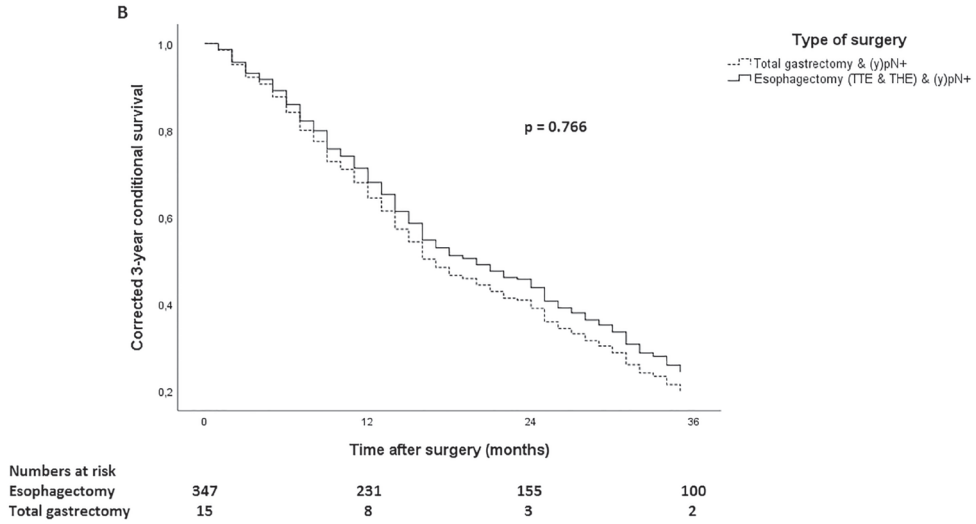
A: corrected 3-year overall survival of patients with gastroesophageal junction cancer after esophagectomy (THE=transhiatal, TTE=transthoracic) & perioperative chemotherapy or total gastrectomy & perioperative chemotherapy. B: corrected 3-year conditional survival of patients with gastroesophageal junction cancer after esophagectomy (THE=transhiatal, TTE=transthoracic) & perioperative chemotherapy or total gastrectomy & perioperative chemotherapy.



Supplementary figure 3 A & B:

A: corrected 3-year overall survival of patients with gastroesophageal junction cancer after esophagectomy (THE=transhiatal, TTE=transthoracic) & neoadjuvant chemoradiotherapy or total gastrectomy & neoadjuvant chemoradiotherapy. B: corrected 3-year conditional survival of patients with gastroesophageal junction cancer after esophagectomy (THE=transhiatal, TTE=transthoracic) & neoadjuvant chemoradiotherapy or total gastrectomy & neoadjuvant chemoradiotherapy.





Supplementary figure 4 A & B:

A: corrected 3-year overall survival of patients with gastroesophageal junction cancer after esophagectomy (THE=transhiatal, TTE=transthoracic) & (y)pN+ (positive lymph node burden) or total gastrectomy & (y)pN+. B: corrected 3-year conditional survival of patients with gastroesophageal junction cancer after esophagectomy (THE=transhiatal, TTE=transthoracic) & (y)pN+ (positive lymph node burden) or total gastrectomy & (y)pN+.

Chapter 8

Summary

The studies in this thesis focus on the differences in health-related quality of life (HR-QoL), information needs and other short- and long-term postoperative outcomes of esophageal and gastric cancer patients following various surgical approaches. In this chapter we present the main findings of the studies included in this thesis.

In the prospective cohort study in **chapter 2** we aimed to investigate the difference in HR-QoL in patients with gastroesophageal junction cancer following a total gastrectomy or an Ivor Lewis esophagectomy after a follow-up of more than one year. A total of 30 patients after total gastrectomy and 71 patients after Ivor Lewis esophagectomy were included. Patients after a total gastrectomy reported less choking when swallowing and less trouble with coughing than patients after an esophagectomy. This difference was also clinically relevant. We did not find significant differences in any of the other 29 HR-QoL outcomes. In addition, significantly more lymph nodes were resected in the esophagectomy group, however, no differences were found in the number of positive lymph nodes, postoperative complications and radicality of resection.

In **chapter 3** we investigated the difference in HR-QoL in patients with distal esophageal or gastroesophageal junction cancer following a McKeown or an Ivor Lewis esophagectomy after a follow-up of more than one year. In this study a total of 204 patients were included: 89 after McKeown esophagectomy and 115 after Ivor Lewis esophagectomy. Of the 31 HR-QoL outcomes compared, we found that patients after McKeown esophagectomy reported more problems with eating with others compared to patients after Ivor Lewis esophagectomy. This difference was also found to be clinically relevant. In this prospective cohort study, we also compared the combined HR-QoL results of all patients after McKeown and Ivor Lewis esophagectomy with the HR-QoL of the general population. As expected, a poorer HR-QoL was reported by the group of patients following surgery with regard to a variety of HR-QoL domains: nausea and vomiting, dyspnea, appetite loss, financial difficulties, problems with eating, reflux, eating with others, choked when swallowing, trouble with coughing and weight loss. A subgroup analysis was subsequently conducted comparing HR-QoL between patients having no or minor postoperative complications (Clavien-Dindo grade 0-2) following either McKeown or Ivor Lewis esophagectomy. Patients with no or minor postoperative complications after McKeown esophagectomy reported more problems with eating with others compared to patients with no or minor complications after Ivor Lewis esophagectomy. This difference was also clinically relevant.

Chapter 4 was a prospective cohort study comparing the HR-QoL of patients with distal esophageal and gastroesophageal junction cancer following either a transhiatal (n=56) or transthoracic esophagectomy (n=132) after a follow-up of more than two years. In general, comparable HR-QoL results were found between a transthoracic and transhiatal esophagectomy, except for significantly better HR-QoL regarding hair loss in patients after

transthoracic esophagectomy. This surprising difference could be due to significantly less chemotherapy administration in the transthoracic esophagectomy group compared to the transhiatal esophagectomy group. Compared with the general population, poorer HR-QoL was found in patients following transhiatal and transthoracic esophagectomy in the following HR-QoL domains: role functioning, social functioning, nausea and vomiting, dyspnea, appetite loss, financial difficulties, dysphagia, difficulties with eating, difficulties of eating with others, reflux, choking when swallowing, trouble with coughing and weight loss. Additional analyses were performed for two subgroups within the two main surgical groups: (i) patients operated minimally invasively and (ii) patients treated with neoadjuvant therapy. Patients after minimally invasive transthoracic esophagectomy reported clinically relevant and significantly better physical functioning compared to patients after minimally invasive transhiatal esophagectomy. In the subgroup of patients who were treated with neoadjuvant therapy no significant differences were found between patients after transhiatal esophagectomy and transthoracic esophagectomy. Furthermore, to investigate whether the level of anastomosis had an influence on the study results, the HR-QoL was compared between patients with a cervical and an intrathoracic anastomosis following a transthoracic esophagectomy and no significant differences in HR-QoL were found.

Overall, **chapters 2, 3** and **4** showed that small differences in HR-QoL can be found following different surgical approaches in patients with distal esophageal and gastroesophageal junction cancer. These results may aid in information provision to patients prior to surgery on what can be expected following treatment.

The prospective comparative cohort study in **chapter 5** aimed to investigate the information needs of patients following esophageal and gastric cancer in cohorts at baseline (n=132), at 6-12 months (n=216), at 18-24 months (n=184) and at 3-5 years (n=163) after surgery. The differences in information needs were compared between patients with and without postoperative complications, and male and female patients. Also, the association between information needs and HR-QoL was investigated. Patients with and without postoperative complications, as well as male and female patients did not report different information needs. However, a variety of information needs domains were found to be positively or negatively associated with HR-QoL. Receiving information about medical tests and receiving information about treatments were positively associated with global health status in the 18-24 months follow-up cohort. Receiving information about things that patients can do to help themselves was negatively associated with eating restrictions in the 18-24 months and 3-5 years follow-up cohorts. Indicating that the information was helpful was positively associated with global health status in the cohorts assessed at 6-12 months, 18-24 months and 3-5 years follow-up. Patients with more anxiety reported that the information was helpful in the 18-24 months and 3-5 years follow-up cohorts. In this study we also selected seven topics from the information needs questionnaire that patients need to be minimally informed

about. The percentages of patients who reported to not have received any information at all was compared to the percentages of patients who reported to have received at least a little bit of information. For all seven information topics, the majority of patients reported to find the received information at least a little bit helpful. However, still many reported to not have received any information on various topics and up to 23.5% of patients reported not to have received information at all about the things that they can do to help themselves. In conclusion, this study showed that no differences in information needs were found between patients with and without postoperative complications, and between male and female patients. However, as some HR-QoL domains were found to be associated with information needs, a personalized approach of providing information to patients with esophageal and gastric cancer should be preferred.

In **chapter 6** the difference in HR-QoL over time was investigated between patients with and without postoperative complications following treatment for esophageal or gastroesophageal junction cancer. This population-based prospective comparative cohort study included a total of 486 patients: 270 with and 216 without postoperative complications. The HR-QoL was investigated at baseline, 3-, 6-, 9-, 12-, 18- and 24-months after surgery in a naturally occurring sample. Results showed a significant decline in short-term HR-QoL that restored to baseline level at 12 months follow-up. However, patients with and without postoperative complications did not report significantly different HR-QoL over time. In a subgroup analysis the difference in HR-QoL over time was investigated between patients with and without anastomotic leakage, and between patients with no or mild (grade 1) versus severe (grade 2-3) anastomotic leakage. No significant difference was found in HR-QoL between patients with and without anastomotic leakage. Patients with severe (grade 2-3) anastomotic leakage reported significantly more problems with choking when swallowing compared to patients with grade 1 or no anastomotic leakage at 6-months, at 9-months and at 24-months follow-up. This difference was also clinically relevant. Furthermore, no significant or clinically relevant differences were found in HR-QoL of patients with cervical versus intrathoracic anastomosis. Overall, the study in **chapter 6** showed that the occurrence of postoperative complications did not significantly influence HR-QoL over time. The temporary decrease in HR-QoL that was seen in all patients is most likely related to the nature of the esophagectomy and to the reconstruction, which results in a broad spectrum of functional complaints that improve during the first postoperative year and that patients get accustomed to.

Chapter 7 included a population-based comparative cohort study that aimed to investigate the difference in 3-year overall survival, 3-year conditional survival, postoperative morbidity, mortality and pathology results in patients with gastroesophageal junction cancer following a total gastrectomy or an esophagectomy. In this study a total of 871 patients were included: 81 following total gastrectomy and 790 following esophagectomy. No significant differences were found between patients following total gastrectomy or esophagectomy

in terms of 3-year overall and conditional survival. Also, postoperative morbidity, 30-day and in-hospital mortality, 90-day mortality, radicality of resection and lymph node yield did not differ significantly between groups. In conclusion, this study showed that when both an esophagectomy and a total gastrectomy are technically feasible in patients with gastroesophageal cancer, other parameters such as quality of life and surgeon's experience can be considered when choosing surgical approach.

Chapter 9

General discussion and future perspectives

This thesis aims to advance knowledge on HR-QoL, information needs and clinical postoperative outcomes of esophageal and gastric cancer patients.

Survival of curatively treated esophageal and gastric cancer patients has increased in recent years to 40-50 per cent at 5 years after treatment [1-3]. Therefore, information about long-term HR-QoL has also gained more attention. Among others and of relevance to this thesis, type of surgical approach, occurrence of postoperative complications and information provision have been found to influence HR-QoL in cancer patients [4-11]. Differences in HR-QoL between different groups of patients with esophageal and gastric cancer can be expected as these patients endure a variety of major operations. In patients with distal esophageal cancer, different types of esophagectomies are possible, such as a transhiatal esophagectomy or a transthoracic esophagectomy with a cervical or an intrathoracic anastomosis. In case of a gastroesophageal junction cancer, also a total gastrectomy can be performed. These operations can either be performed open, hybrid or minimally invasively. In a recent multicenter study, three postoperative symptoms (low mood, pain due to scars on chest, and reduced activity tolerance and energy) were found to be associated with impaired HR-QoL in patients with esophageal cancer [12]. As patients with esophageal and gastric cancer may be confronted with a range of postoperative complications, differences in HR-QoL can be expected. In addition, the information needs concerning treatment and the post-treatment period may vary among patients. To date, the optimal surgical approach in patients with distal esophageal and gastroesophageal junction cancer is still debated.

Gastroesophageal junction cancer: total gastrectomy or esophagectomy

When planning the surgical approach in patients with gastroesophageal junction cancer, both a total gastrectomy and an esophagectomy can be possible. The main goal of curative treatment is to gain optimal oncologic outcome in terms of a radical resection and improvement of survival. In theory, during an esophagectomy, a more extended lymphadenectomy and a more radical resection (i.e. proximal and circumferential margin) are possible, which, however, could come at the cost of increased morbidity. In this specific group, no significant survival benefit has been found following either of the two operations in two systematic reviews [13, 14]. In addition, similar 30-day mortality and pathology results were identified between esophagectomy and total gastrectomy. Therefore, HR-QoL can be an important endpoint in the clinical decision-making process regarding which surgical procedure to choose. Each individual patient may have a unique, personal view on HR-QoL. Investigating the differences in HR-QoL after a total gastrectomy and an esophagectomy may help informing patients of what can be expected of HR-QoL following treatment. In previous research, patients with gastroesophageal junction cancer following a total gastrectomy reported better HR-QoL compared to patients following an esophagectomy, such as better global health status and physical functioning, and less fatigue and gastrointestinal symptoms [7, 8, 15]. However, these studies included a heterogeneous group of patients (e.g., with distal esophageal, gastroesophageal junction

and cardia cancers), had a short follow-up or a low response rate. Therefore, the study in **chapter 2** included only patients with true gastroesophageal junction and cardia cancer with a long follow-up and also had a high response rate. **Chapter 2** showed that patients with gastroesophageal junction cancer reported significantly less choking when swallowing and less trouble with coughing following a total gastrectomy compared to an esophagectomy, after a follow-up of more than one year. None of the other 29 HR-QoL outcomes were significantly different between the two groups. In addition, 3-year overall survival and 3-year conditional survival did not differ significantly between a total gastrectomy and an esophagectomy in patients with gastroesophageal junction cancer (**chapter 7**). Also, other postoperative outcomes, such as morbidity, mortality and pathology results, were found to be comparable between patients following a total gastrectomy and an esophagectomy. The results of the study in **chapter 7** are more representative of current medical practice of gastroesophageal junction cancer than the results of the previously mentioned systematic reviews [13, 14], as it included patients with only true gastroesophageal junction cancer. Additionally, patients who received neoadjuvant treatment were not excluded in contrast to the previous studies. In conclusion, the results of the studies included in **chapter 2** and **7** provide important information about the differences in long-term HR-QoL and other postoperative outcomes that may help inform patients of what can be expected following different surgical approaches. In some cases, HR-QoL may be the decisive factor when both a total gastrectomy and an esophagectomy are possible, although other parameters such as surgeons' and patients' preferences may also influence the clinical decision-making process. Future research should investigate the effects of both surgical procedures on morbidity, survival and HR-QoL in a randomized controlled setting. Currently, such a trial has been initiated, comparing a total gastrectomy with a transthoracic esophagectomy in patients with gastroesophageal junction cancer with regard to overall survival, disease-free survival, location and number of tumor positive lymph nodes, radical resection rate, postoperative complications, cost-effectiveness and HR-QoL. Results of this randomized controlled trial will provide level II evidence which surgical approach results in a more radical resection with improved overall and disease-free survival, and better HR-QoL [16].

McKeown or Ivor Lewis esophagectomy for distal esophageal and gastroesophageal junction cancer

In patients with distal esophageal and gastroesophageal junction cancer, both a McKeown and an Ivor Lewis esophagectomy are usually possible. The main difference between these two operations is the location of the anastomosis and the accompanied chance of the occurrence of anastomotic leakage. A systematic review found significantly more anastomotic leakages, vocal cord injuries and strictures after a McKeown esophagectomy compared to an Ivor Lewis esophagectomy [17]. Nonetheless, both operations were declared clinically safe, as no significant differences in severe anastomotic leakage, 30-day/ in-hospital and 90-day mortality were found. When HR-QoL of patients undergoing either

a McKeown or an Ivor Lewis esophagectomy was compared, no differences were found in two studies [18, 19], however, another study reported significantly less obstipation and pain after a McKeown esophagectomy [20]. Most of the operations in these previous studies were performed by an open approach. The results of the 'Traditional Invasive versus Minimally invasive Esophagectomy' (TIME) trial showed that minimally invasive surgery reduced postoperative pulmonary morbidity and pain, and resulted in a better HR-QoL compared to an open approach. Since then, esophagectomies are increasingly being performed minimally invasively [21]. **Chapter 3** therefore, represents current clinical practice in the Netherlands, as over 90% of all included operations in this study were minimally invasive esophagectomies. The study in this chapter investigated differences in HR-QoL between a McKeown and an Ivor Lewis esophagectomy and found that patients after a McKeown reported more problems with eating with others compared to patients following an Ivor Lewis after a follow-up of more than one year. None of the other 30 HR-QoL outcomes were significantly different between the two groups. In a previous study, major postoperative complications were found to negatively impact HR-QoL in patients with esophageal cancer [22]. Therefore, we performed a subgroup analysis of HR-QoL between patients with no or minor complications after a McKeown esophagectomy and an Ivor Lewis esophagectomy and found that the difference in problems with eating with others remained significant. In addition, when compared to the general population, patients after an esophagectomy reported more problems with eating, problems with eating with others, appetite loss, weight loss, reflux, nausea and vomiting, choking when swallowing, trouble with coughing, problems with dyspnea and financial difficulties. The results found in this study are important as they may help informing patients of the possible changes in HR-QoL following a McKeown and an Ivor Lewis esophagectomy after a long-term follow-up. Currently, the difference between a minimally invasive McKeown (control group) and a minimally invasive Ivor Lewis esophagectomy (intervention group) in patients with esophageal cancer is being investigated in a randomized controlled setting [23]. In this randomized controlled trial postoperative morbidity, anastomotic leakage incidence, mortality, cost-effectiveness and HR-QoL are compared between the two surgical procedures. Outcome of this study will hopefully provide the answers on whether either of the two operations results in less postoperative complications including a lower anastomotic leakage rate, shorter length of hospital stay, lower mortality, better cost-effectiveness, and HR-QoL.

Transthoracic or transhiatal approach for distal esophageal and gastroesophageal junction cancer

Both a transthoracic and a transhiatal esophagectomy may be possible in patients with distal esophageal or gastroesophageal junction cancer. In a randomized controlled trial similar overall and disease-free survival was found between a transthoracic and a transhiatal approach in patients with mid-esophageal, distal esophageal or gastric cardia cancer. However, significantly more pulmonary complications occurred after a transthoracic

esophagectomy besides a higher obtained lymph node yield [24]. Also differences in HR-QoL have been investigated following these two operations. One study reported worse HR-QoL at 12 months after a transthoracic esophagectomy compared to a transhiatal esophagectomy in terms of more dyspnea, constipation, vomiting and nausea [11] whereas other studies found no significant differences [10, 25, 26]. However, these studies were performed before the implementation of neoadjuvant treatment and minimally invasive surgery in esophageal cancer treatment. In **chapter 4** we performed a study after implementation of these treatments and the results showed that patients reported largely comparable HR-QoL following a transthoracic esophagectomy compared to transhiatal esophagectomy after a follow-up of more than two years. Also, patients after minimally invasive transthoracic esophagectomy reported better physical functioning compared to patients after minimally invasive transhiatal esophagectomy. In the subgroup of patients who received neoadjuvant therapy, no significant differences were found between transthoracic and transhiatal esophagectomies. This finding is consistent with previous research indicating no influence of neoadjuvant therapy on HR-QoL postoperatively [27-29]. In **chapter 4**, HR-QoL of all patients was also compared with that of the general population. As expected, worse HR-QoL was found in patients following surgery in role and social functioning, appetite loss, financial difficulties, nausea and vomiting, dyspnea, dysphagia, eating difficulties, reflux, choking when swallowing, weight loss, difficulties with eating with others, and trouble with coughing. In previous studies the location of the anastomosis was found to be associated with HR-QoL [19, 30]. Therefore, we checked for the possible influence of the anastomosis location in the transthoracic esophagectomy group on HR-QoL and found no significant differences in HR-QoL between patients with a cervical or intrathoracic anastomosis in the transthoracic esophagectomy group. As the transhiatal approach is significantly less often performed in recent years, a new randomized controlled trial that compares transhiatal esophagectomy with transthoracic esophagectomy is not to be expected. Future projects may want to investigate HR-QoL following different approaches in transthoracic esophagectomy in the era of neoadjuvant therapy and minimally invasive surgery.

Information needs of esophagogastric cancer patients

Information provision should ideally be tailored to the specific needs of a patient. As a first step, information needs of patients with esophageal and gastric cancer need to be investigated. Some differences in information needs between Dutch and Italian patients with esophageal cancer have been observed [31]. Overall, patients in the Netherlands reported to be more satisfied with the received information after diagnosis, and Italian patients reported to be more satisfied with the information during neo-adjuvant treatment. In another study among patients with esophageal cancer, information needs of patients who received palliative treatment were compared with the information needs of patients after curative treatment. Patients after palliative treatment reported to want more information, to be less informed about the disease and to be less satisfied with the received information than patients after

curative treatment [32]. The information needs of patients with esophagogastric cancer with and without postoperative complications, and male and female patients were not investigated yet. It was important to investigate this, as patients after major esophageal and gastric cancer surgeries often endure postoperative complication [33, 34] and because generally, male and female cancer patients report to have different information needs [6]. These were therefore the objectives of **chapter 5**. We did not find differences in information needs between patients with and without complications and between male and female patients. An additional objective was to examine whether there was an association between perceived information needs and HR-QoL domains global health status, anxiety and eating restrictions. We found that receiving information about medical tests and treatments, and finding the received information overall helpful was associated with better global health status. Surprisingly, patients with more anxiety also reported that the information was more helpful. Receiving a lot of information about things that you can do to help yourself was related to less eating restrictions. These findings are in accordance with a previous study, which also found significant positive associations between information needs and global health status and anxiety, as well as negative associations between information needs and anxiety [32].

Information provision requires good communication. Recently, several communication methods were found to improve information provision, such as a visual form of explanation, using explicit and affective communication and considering the effect of negative and positive framing [35, 36]. Currently, the 'Stimulating evidence based, personalized and tailored information provision to improve decision making after Oesophagogastic CancEr diagnosis' (SOURCE) study is being performed that aims to improve information provision and decision making after an esophageal or gastric cancer diagnosis [37]. A randomized trial is part of this study. The experimental arm includes a communication skills training for oncologists, both medical and surgical, in combination with a website containing empirically based prediction models for expected survival, postoperative complications and HR-QoL following a range of treatments, which they can use to help inform patients. In the other arm, oncologists inform their patients as they are used to. The primary outcome of this trial is the precision of information provision about post-treatment outcomes during consultation. Secondary outcomes include, among others, satisfaction with communication, patients' knowledge of the received information and HR-QoL. Understanding the information needs of esophagogastric cancer patients will help medical practitioners to better inform patients and tailor the information provision to their needs. Developing a nationwide database for information needs of esophageal and gastric cancer patients may be a helpful next step. Such a database already exists for the collection of HR-QoL data following esophageal cancer [38]. The collection of data on information needs could be added to this database.

HR-QoL after postoperative complications

Postoperative complications are common in patients with esophageal and gastric cancer [33, 34]. Postoperative complications have been found to be associated with impaired HR-QoL in previous studies [22, 39, 40]. However, these studies were performed before the implementation of neoadjuvant therapy and minimally invasive surgery and did not specify the severity of the complications or included a limited number of patients from a single center. In **chapter 6**, HR-QoL was investigated at baseline, 3-, 6-, 9-, 12-, 18- and 24-months after surgery in a multicenter study including a naturally occurring sample. As found in previous studies [41, 42], a significant decline in short-term HR-QoL was reported by all patients that restored to baseline level at around 12-months after surgery. Patients with and without postoperative complications following an esophagectomy did not report different HR-QoL over time. Unfortunately, we were unable to investigate the influence of severity of complications according to the Clavien-Dindo classification on HR-QoL, because such information was not available for the entire study period. However, during the study period 2016-2017, a total complication rate of 65% and a 36% complication rate of Clavien-Dindo grade < 3 was recorded in the national audit for upper GI cancer (DUCA) [33]. Therefore, one could speculate that the majority of the included patients with complications in the study described in **chapter 6** had a Clavien-Dindo grade < 3. The small number of major complications with a Clavien-Dindo grade 3 and higher in the group of patients with complications may explain why no significant differences between patients with and without complications were observed. Nonetheless, patients with anastomotic leakage grade 2 or 3 reported to have more problems with choking when swallowing at 6-, 9- and 24-months follow-up compared to patients with grade 1 or no anastomotic leakage. Future studies are needed that investigate the influence of major postoperative complications on HR-QoL in patients with esophageal and gastric cancer using the Clavien-Dindo classification.

Methodological limitations

A number of methodological limitations of the studies included in this thesis merit attention. All studies were non-randomized, cross-sectional cohort studies. Also, most of these studies included convenience samples of a relatively small magnitude. Therefore, various measures were taken to maximize adequate interpretation of the results. First, valid and widely used patient-reported questionnaires were used, i.e., the European Organization for Research and Treatment of Cancer (EORTC) questionnaires. Since randomization was not possible in real life settings, we corrected for a priori differences using multivariable linear and logistic analyses. Given the unfavorable ratio of number of tests to number of patients, we applied Bonferroni corrections to counteract multiple testing. Moreover, in some cases a more stringent p-value was adopted to indicate statistical significance. It is important to acknowledge whether results are clinically relevant. We therefore also adopted measures for determining clinical relevance. A threshold of 10 points difference in mean HR-QoL

scores was used to determine clinical relevance of the results, as this cut-off point is very likely indicative of clinical relevance for all HR-QoL domains included in our studies [43, 44].

The studies included in this thesis provide new information about HR-QoL, information needs and postoperative outcomes of esophageal and gastric cancer patients treated in a clinical setting.

Overall conclusion

According to the studies included in this thesis there are no major differences in HR-QoL between esophagogastric cancer patients following various surgical approaches. In addition, similar survival and postoperative outcomes were found in patients with gastroesophageal junction cancer following an esophagectomy or a total gastrectomy. Male and female patients with esophageal and gastric cancer, as well as patients with and without postoperative complications reported similar information needs. However, patients with higher global health status and more anxiety reported to find the information more helpful. Medical practitioners may be made more aware of the small differences in HR-QoL and the information needs of patients, which in turn may help them better inform esophageal and gastric cancer patients.

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Appendices

Summary in Dutch *(Nederlandse samenvatting)*
Authors and affiliations
List of publications
PhD portfolio
Acknowledgements *(Dankwoord)*
Curriculum Vitae Auctoris

SUMMARY IN DUTCH *(NEDERLANDSE SAMENVATTING)*

De studies in dit proefschrift richten zich op het verschil in gezondheidsgerelateerde kwaliteit van leven, informatiebehoefte, en andere korte- en lange termijn postoperatieve uitkomsten bij slokdarm- en maagkankerpatiënen die zijn behandeld met verschillende chirurgische technieken. Dit hoofdstuk geeft de belangrijkste resultaten weer van de studies die zijn opgenomen in dit proefschrift.

In de prospectieve cohortstudie van **hoofdstuk 2** namen patiënten met gastro-oesofageale overgangstumoren deel, die werden behandeld met een totale maagresectie (n = 30) of een Ivor Lewis oesofagusresectie (n = 71) na een follow-up periode van meer dan een jaar. We onderzochten het verschil in kwaliteit van leven tussen deze twee groepen patiënten. Na een totale maagresectie rapporteerden patiënten minder klachten met zich verslikken tijdens het eten en minder moeite met hoesten dan patiënten die een oesofagusresectie hadden ondergaan. Dit verschil was tevens klinisch relevant. Er werden geen significante verschillen gevonden in de overige 29 kwaliteit van leven uitkomsten. Verder werden er bij de groep die een oesofagusresectie hadden ondergaan, aanzienlijk meer lymfeklieren gereseceerd. Echter, er werden geen verschillen gevonden in het aantal positieve lymfeklieren, postoperatieve complicaties en de radicaliteit van de resecties tussen beide groepen patiënten.

In **hoofdstuk 3** werd de kwaliteit van leven vergeleken tussen patiënten met distaal gelegen slokdarmtumoren of tumoren op de gastro-oesofageale overgang na een McKeown (n = 89) of een Ivor Lewis (n = 115) oesofagusresectie na een follow-up duur van meer dan een jaar. Van de 31 kwaliteit van leven uitkomsten die werden vergeleken, rapporteerden patiënten die een McKeown oesofagusresectie ondergingen meer problemen met eten te hebben dan werd gerapporteerd door de groep die was behandeld met een Ivor Lewis oesofagusresectie. Dit verschil bleek tevens klinisch relevant te zijn. In deze prospectieve cohortstudie vergeleken we eveneens de gecombineerde kwaliteit van leven resultaten van alle patiënten na een McKeown en een Ivor Lewis oesofagusresectie met de kwaliteit van leven zoals gerapporteerd door de algehele populatie. Zoals verwacht, werd er een slechtere kwaliteit van leven gerapporteerd door de groep patiënten die chirurgisch was behandeld met betrekking tot een verscheidenheid aan kwaliteit van leven domeinen: kortademigheid, misselijkheid en braken, verlies van eetlust, problemen met eten, reflux, problemen met eten in gezelschap, verslikken tijdens het eten, moeite met hoesten, financiële problemen en gewichtsverlies. Hierna werd een subgroep analyse uitgevoerd, waarbij de kwaliteit van leven werd vergeleken tussen patiënten die geen of milde postoperatieve complicaties ondervonden (Clavien-Dindo graad 0-2) volgend op een McKeown dan wel een Ivor Lewis oesofagusresectie. Patiënten zonder of met milde postoperatieve complicaties na een McKeown oesofagusresectie rapporteerden meer problemen tijdens het eten met anderen

dan de patiënten waar eveneens geen of milde postoperatieve complicaties optraden, maar werden behandeld met een Ivor Lewis oesofagusresectie.

Hoofdstuk 4 behandelt een prospectieve cohortstudie die de kwaliteit van leven vergeleek tussen patiënten met distaal gelegen slokdarmtumoren en patiënten met gastro-oesofageale overgang tumoren, volgend op een transhiatale (n=56) of transthoracale oesofagusresectie (n=132) na een follow-up van meer dan twee jaar. Na transhiatale en transthoracale oesofagusresecties werden vergelijkbare kwaliteit van leven resultaten gevonden. Er was één uitzondering: patiënten die een transthoracale oesofagusresectie hadden ondergaan rapporteerden significant minder haarverlies. Dit verrassende verschil kan het gevolg zijn van het feit dat in de transthoracale oesofagusresectie groep minder perioperatieve chemotherapie werd toegediend dan in de transhiatale oesofagusresectie groep. Vergeleken met de algemene bevolking werd er een slechtere kwaliteit van leven gevonden bij patiënten na een transhiatale en transthoracale oesofagusresectie in de volgende kwaliteit van leven-domeinen: financiële problemen, sociaal en rol functioneren, misselijkheid en braken, kortademigheid, verlies van eetlust, dysfagie, eetproblemen, problemen met eten in gezelschap, reflux, verslikken tijdens het eten, problemen met hoesten en gewichtsverlies. Aanvullende analyses werden uitgevoerd voor de twee subgroepen binnen de twee belangrijkste chirurgische groepen: (i) patiënten die minimaal invasief werden geopereerd en (ii) patiënten die werden behandeld met neoadjuvante therapie. Patiënten die een minimaal invasieve transthoracale oesofagusresectie ondergingen, rapporteerden een statistisch significant en klinisch relevant beter fysiek functioneren in vergelijking met patiënten na een minimaal invasieve transhiatale oesofagusresectie. In de subgroep van patiënten die werden behandeld met neoadjuvante therapie werden geen significante verschillen gevonden tussen patiënten na transhiatale en transthoracale oesofagusresectie. Om te onderzoeken of de locatie van de anastomose van invloed was op de resultaten, werd de kwaliteit van leven vergeleken tussen patiënten met een cervicale anastomose en patiënten met een intrathoracale anastomose na een transthoracale oesofagusresectie. Er werden hierbij geen significante verschillen in kwaliteit van leven gevonden.

Over het algemeen laten de **hoofdstukken 2, 3 en 4** zien dat er kleine verschillen in kwaliteit van leven bestaan na verschillende chirurgische technieken bij patiënten met een maligne distale slokdarmtumor en gastro-oesofageale overgangstumor. Deze resultaten kunnen bijdragen aan het informeren van patiënten voorafgaand aan de operatie over wat er na de behandeling kan worden verwacht.

De prospectieve vergelijkende cohortstudie in **hoofdstuk 5** was gericht op het onderzoeken van de informatiebehoeften van patiënten die slokdarm- of maagtumor hadden doorgemaakt. Daaraan namen patiënten op verschillende momenten in hun ziektetraject deel: bij aanvang vóór de operatie (n = 132), na 6-12 maanden (n = 216), na 18-24 maanden (n = 184) en 3-5

jaar (n = 163) na de operatie. De verschillen in informatiebehoefte werden vergeleken tussen patiënten met en zonder postoperatieve complicaties, en tussen mannelijke en vrouwelijke patiënten. Ook werd de relatie tussen informatiebehoefte en kwaliteit van leven onderzocht. Patiënten met en zonder postoperatieve complicaties, evenals mannelijke en vrouwelijke patiënten rapporteerden geen verschillende informatiebehoeften. Een verscheidenheid aan domeinen van informatiebehoeften bleek positief of negatief geassocieerd te zijn met kwaliteit van leven. Het ontvangen van informatie over medische tests en over behandelingen was positief geassocieerd met algehele kwaliteit van leven in het follow-up cohort van 18-24 maanden. Het ontvangen van informatie over dingen die patiënten kunnen doen om zichzelf te helpen, was negatief geassocieerd met meer eetbeperkingen in de follow-up cohorten van 18-24 maanden en 3-5 jaar. Het aangeven dat de informatie nuttig was, was positief geassocieerd met algehele kwaliteit van leven in de cohorten van 6-12 maanden, 18-24 maanden en 3-5 jaar follow-up. Patiënten met meer angst rapporteerden dat de informatie nuttig was in de follow-up cohorten van 18-24 maanden en 3-5 jaar. In deze studie hebben we ook zeven onderwerpen geselecteerd uit de vragenlijst over informatiebehoeften waarover patiënten tenminste moeten worden geïnformeerd. De percentages patiënten die aangaven helemaal geen informatie te hebben ontvangen, werden vergeleken met de percentages patiënten die aangaven tenminste een klein beetje informatie te hebben ontvangen. Voor alle zeven informatiebehoefte onderwerpen gaf de meerderheid van de patiënten aan, de ontvangen informatie op zijn minst een beetje nuttig te vinden. Echter, tot 23,5% van de patiënten rapporteerde helemaal geen informatie te hebben ontvangen over de dingen die ze kunnen doen om zichzelf te helpen. Dit onderzoek liet al met al zien dat er geen verschillen in informatiebehoefte werden gevonden tussen patiënten met en zonder postoperatieve complicaties en tussen mannelijke en vrouwelijke patiënten. Aangezien sommige kwaliteit van leven domeinen geassocieerd bleken te zijn met informatiebehoeften, verdient een gepersonaliseerde benadering van het verstrekken van informatie aan patiënten met slokdarm- en maagtumoren de voorkeur.

Hoofdstuk 6 beschrijft het onderzoek naar het verschil in kwaliteit van leven in patiënten met en zonder complicaties op verschillende tijdsintervallen na behandeling van slokdarmtumoren of tumoren van de gastro-oesofageale overgang. Deze prospectieve vergelijkende cohortstudie in de Nederlandse slokdarm- en gastro-oesofageale overgangstumoren patiëntenpopulatie omvatte in totaal 486 patiënten: 270 met en 216 zonder postoperatieve complicaties. De kwaliteit van leven werd onderzocht op baseline, 3-, 6-, 9-, 12-, 18- en 24-maanden na de operatie in een natuurlijk voorkomend cohort. De resultaten toonden een significante afname van de kwaliteit van leven op korte termijn, welke na 12 maanden herstelde tot het baseline niveau. Patiënten met en zonder postoperatieve complicaties rapporteerden echter geen significant verschillende kwaliteit van leven in de loop van de tijd. In een subgroep analyse werd het verschil in kwaliteit van leven onderzocht tussen patiënten met en zonder naadlekkage, en tussen patiënten zonder

of mild verlopende naadlekkage (graad 1) versus ernstig verlopende naadlekkage (graad 2-3). Er werd geen significant verschil gevonden in kwaliteit van leven tussen patiënten met en zonder naadlekkage in de loop van de tijd. Echter, als we keken naar de ernst van de naadlekkage, vonden we dat patiënten met een ernstige naadlekkage (graad 2-3) significant meer verslikken tijdens het eten rapporteerden dan patiënten met een graad 1 of geen naadlekkage na 6 maanden, na 9 maanden en na 24 maanden follow-up. Dit verschil was ook klinisch relevant. Daarnaast werden geen significante of klinisch relevante verschillen gevonden in kwaliteit van leven van patiënten met een cervicale versus een intrathoracale anastomose. Deze studie toonde aan dat het optreden van postoperatieve complicaties de kwaliteit van leven in de loop van de tijd niet significant beïnvloedde. Een tijdelijke afname in kwaliteit van leven die bij alle patiënten werd waargenomen, houdt hoogstwaarschijnlijk verband met de aard van de oesofagusresectie en de reconstructie, welke resulteren in een breed scala aan functionele klachten, die gedurende het eerste postoperatieve jaar verbeteren en waar patiënten aan gewend raken.

Tenslotte wordt in **hoofdstuk 7** een op de populatie gebaseerde, vergelijkende cohortstudie beschreven, die tot doel had het verschil in postoperatieve morbiditeit, mortaliteit, 3-jaars totale overleving, 3-jaars conditionele overleving en pathologische resultaten te onderzoeken bij patiënten met een maligne gastro-oesofageale overgangstumor na een totale maagresectie of een oesofagusresectie. In deze studie werden in totaal 871 patiënten geïncludeerd: 81 na een totale maagresectie en 790 na een slokdarmresectie. Er werden geen significante verschillen gevonden in 3-jaars totale en conditionele overleving tussen patiënten na een totale maagresectie of oesofagusresectie. Postoperatieve morbiditeit, 30- en 90-dagen mortaliteit, radicaliteit van resectie en lymfeklieropbrengst verschilden niet significant tussen de groepen. Concluderend toonde deze studie aan dat wanneer zowel een oesofagusresectie als een totale maagresectie technisch haalbaar zijn bij patiënten met een maligne gastro-oesofageale overgangstumor, andere parameters zoals kwaliteit van leven en de ervaring van de chirurg kunnen worden meegewogen bij het kiezen van de chirurgische benadering.

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LIST OF PUBLICATIONS

E. Jezerskyte, MD, A.C. Mertens, MD, S. van Dieren, PhD, W.J. Eshuis, MD, PhD, M.A.G. Sprangers, MD, PhD, M.I. van Berge Henegouwen, MD, PhD, S.S. Gisbertz, MD, PhD on behalf of the Dutch Upper Gastrointestinal Cancer Audit (DUCA) group. Gastrectomy versus Esophagectomy For Gastroesophageal junction Tumors: Short- And Long-term Outcomes From the Dutch Upper GI Cancer Audit. Annals of surgery. 2020 Nov; in press. first published online 17 November 2020.

E. Jezerskyte, MD, L.M. Saadeh, MD, PhD, E.R.C. Hagens, MD, L. Noteboom, MSc, M.A.G. Sprangers, MD, PhD, H.W.M. van Laarhoven, MD, PhD, W.J. Eshuis, MD, PhD, M.I. van Berge Henegouwen, MD, PhD, S.S. Gisbertz, MD, PhD. Long-term quality of life following transthoracic and transhiatal esophagectomy for esophageal cancer. Journal of Gastrointestinal Surgery. 2020 Sep; in press. first published online 9 September 2020.

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PHD PORTFOLIO

Name PhD student: Eglė Jezerskytė
PhD period: 15 January 2019 – 15 January 2021
Promotores: prof. dr. M.I. van Berge Henegouwen & prof. dr. M.A.G. Sprangers
Copromotor: dr. S.S. Gisbertz

	Year	ECTS
General courses		
Specific courses		
PROM's summer school, Harvard medical school	2020	0.2
Seminars, workshops and master classes		
Weekly research seminars department of surgery	2019 – 2020	2.0
Weekly research meetings upper GI surgery	2019 – 2020	2.0
Biannual multidisciplinary research meeting upper GI oncology	2019 – 2020	0.5
Journal club	2019 – 2020	0.5
Master class "Medische Psychologie over de Amstel"	2019	0.5
Oral presentations		
Difference in long-term HR-QoL after 3-stage vs 2-stage esophagectomy for esophageal carcinoma, *Digestive Disease Days, Veldhoven*	2019	0.5
Long-term HR-QoL after transthoracic and transhiatal esophagectomy for esophageal cancer, *Digestive Disease Days, Veldhoven*	2019	0.5
Long-term quality of life after total gastrectomy versus Ivor Lewis esophagectomy, *Digestive Disease Days, Veldhoven*	2019	0.5
Long term quality of life in patients after McKeown versus Ivor Lewis esophagectomy, *Digestive Disease Days, Veldhoven*	2018	0.5
Long term quality of life in patients after total gastrectomy versus Ivor Lewis esophagectomy, *Digestive Disease Days, Veldhoven*	2017	0.5
Poster presentations		
Gastrectomy Versus Esophagectomy For Gastroesophageal-junction Tumors: Short- And Long-term Outcomes From The Dutch Upper GI Cancer Audit, *Cancer Center Amsterdam retreat, Noordwijkerhout*	2020	0.5
Long-term HR-QoL after McKeown and Ivor Lewis esophagectomy for esophageal carcinoma, *Congress of the European Society for Disease of the Esophagus, Athens*	2019	0.5
Long-term HR-QoL after transthoracic and transhiatal esophagectomy for esophageal cancer, *Congress of the European Society for Disease of the Esophagus, Athens*	2019	0.5
Long-term HR-QoL after total gastrectomy versus Ivor Lewis esophagectomy, *Congress of the European Society for Disease of the Esophagus, Athens*	2019	0.5
Long-term quality of life after total gastrectomy versus Ivor Lewis esophagectomy, *United European Gastroenterology Week, Barcelona*	2019	0.5
Long term quality of life in patients after McKeown versus Ivor Lewis esophagectomy, *World congress of the International Society for Diseases of the Esophagus, Vienna*	2018	0.5
Long term quality of life in patients after total gastrectomy versus Ivor Lewis esophagectomy, *Congress of the European Society for Diseases of the Esophagus, Utrecht*	2017	0.5
Long term quality of life in patients after total gastrectomy versus Ivor Lewis esophagectomy, *Second International Gastric Cancer congress, Beijing*	2017	0.5

	Year	ECTS
(Inter)national conferences attended		
Cancer Center Amsterdam Retreat, *Noordwijkerhout*	2020	0.5
Wetenschapsdag Chirurgie, *Amsterdam*	2019	0.5
Congress of the European Society for Diseases of the Esophagus, *Athens*	2019	0.75
Digestive Disease Days, *Veldhoven*	2019	0.25
Chirurgendagen, *Veldhoven*	2019	0.5
Digestive Disease Days, *Veldhoven*	2018	0.25
Congress of the European Society for Diseases of the Esophagus, *Utrecht*	2017	0.5
Digestive Disease Days, *Veldhoven*	2017	0.25
Teaching		
-		
Other		
Organising weekly research meetings upper GI surgery	2019-2021	1.0
Grants		
-		

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CURRICULUM VITAE AUCTORIS

Eglė Jezerskytė was born in Kaunas, Lithuania on June 9th 1990. She spent her childhood mostly in Kaunas and Vilnius, travelling all around in Lithuania during summer with her parents and two older sisters. Wild camping, hiking in forests, sleeping in a hay barn of a befriended farmer are some of her happiest Lithuanian memories. A few years after her father passed away, Eglė moved to Amsterdam to live with her oldest sister. Rūta, the first soloist at the National Ballet of the Netherlands at the time, took Eglė under her wing and Eglė often refers to that year as "the most fun year of her life".

Very quickly Eglė learned to speak Dutch and in 2009 she graduated from the Amsterdams Lyceum. One of her dreams has always been to become a medical doctor. Her first attempt to get into Medical School right after the graduation was unsuccessful. In order to follow her passion, she chose to study Biomedical sciences at the University of Amsterdam and Physiotherapy at the Hogeschool van Amsterdam for two years. Even though these studies were not her first choices, she enjoyed them very much. Eventually, in 2011, Eglė's dream came true and she started Medical School at the University of Amsterdam. During her Bachelor studies she followed an Honours program and participated in various extracurricular activities such as making head and neck anatomy dissections for an elective course at the Department of Anatomy.

To gain experience in research Eglė initiated multiple research projects during her Masters program under the supervision of prof. dr. M.I. van Berge Henegouwen and dr. S.S. Gisbertz at the Amsterdam UMC, location AMC. She collected questionnaires about the quality of life and information needs of patients with esophageal and gastric cancer and built a database concerning these topics. After graduating from Medical School Eglė worked as a surgical resident not in training at the Waterlandziekenhuis in Purmerend and afterwards at the Amsterdam UMC, location AMC. Eglė enjoyed the direct contribution to the well-being of her patients very much. From January 2019 to January 2021 she worked as a full-time researcher elaborating on the research projects that she started during her Masters program as well as initiating new research proposals. Currently, Eglė is working as a resident not in training at the Emergency Department at the OLVG.

Besides her work in the medical world, Eglė loves beekeeping, travelling and being with family and friends. In the future Eglė will continue to grow as a person and to become an experienced, professional and empathetic doctor.