Laparoscopic versus open gastrectomy for gastric cancer

Arjen van der Veen

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PhD thesis, Utrecht University, the Netherlands

Publication of this thesis van financially supported by Department of Surgery and department of Radiation Oncology, UMC Utrecht Cancer Center, Division of Imaging & Oncology, Nederlandse Vereniging voor Gastroenterologie, Chipsoft, KARL STORZ Endoscopie Nederland B.V., iMove Medical and GD Medical.

Cover & lay-out: Wendy Schoneveld ‖ www.wenziD.nl
Printed by: Gildeprint BV
ISBN: 978-94-6419-569-9

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Laparoscopische versus open maagresectie voor maagkanker
(met een samenvatting in het Nederlands)

Proefschrift

ter verkrijging van de graad van doctor aan de Universiteit Utrecht
op gezag van de rector magnificus, prof. dr. H.R.B.M. Kummeling,
ingevolge het besluit van het college voor promoties
in het openbaar te verdedigen op

donderdag 22 september 2022 des middags te 2.15 uur

door

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geboren op 1 augustus 1992
te Leeuwarden

Promotoren: Prof. dr. R. van Hillegersberg
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CONTENTS

CHAPTER 1

General introduction and thesis outline

GENERAL INTRODUCTION

Gastroesophageal cancer

Cancer of the gastroesophageal tract can be divided in three main anatomical locations: esophageal cancer, gastric cancer and gastroesophageal junction (GEJ) cancer located at the borderline of the esophagus and stomach(1,2).

Esophageal cancer is the seventh most prevalent cancer and the sixth most common cause of cancer-related death worldwide(3). In the Netherlands, 3000 new cases are diagnosed annually(4). Squamous cell carcinoma and adenocarcinoma are the 2 dominant subtypes worldwide, with adenocarcinoma nowadays comprising two-thirds of all esophageal carcinomas in Western populations(3). Gastric cancer is the fifth most prevalent cancer and the fourth most common cause of cancer-related death worldwide(3). In the Netherlands, 1000 new cases are diagnosed annually(4). Adenocarcinoma is the dominant histology worldwide(3).

The incidence rate of distal gastric cancers in Western populations is still declining and is markedly lower than in Eastern populations(3). This has been attributed to a decreased prevalence of H. pylori infections (associated with almost 90% of new cases of non-proximal gastric cancer) and improvements in hygienic circumstances and the preservation and storage of foods(3,5). Contrarily, the incidence rate of more proximal gastric and GEJ cancers is increasing, especially in high-income countries. Of GEJ cancer specifically, the incidence has risen by up to 350% in Western Europe since the 1970's(6). Likewise, in the Netherlands, the incidence of (mainly distal) oesophageal cancer nearly tripled in a period of 30 years(4). Key risk factors for esophageal and GEJ cancer are obesity and gastroesophageal reflux disease. Proximal gastric, GEJ and distal esophageal adenocarcinoma are thought to have similar epidemiological characteristics(3). Hence, the exact anatomical location of these tumors in relation to the top of the gastric folds appears to be important from a treatment perspective, but less so from an epidemiological perspective.

Traditionally, histological classifications divide gastric adenocarcinoma in an intestinal or diffuse type(2,7). The diffuse types can be further classified as signet ring cell type and non-signet ring cell type. In general, intestinal type occurs more distally in the stomach and more often in Eastern populations and has a better prognosis(8). Diffuse type is less often confined to the distal stomach, occurs more often in Western populations, has been suggested to be less responsive to chemotherapy (especially the signet ring cell subtype) and has a worse prognosis(9).

Recently, genomic classifications were introduced, based upon comprehensive molecular analysis such as whole-genome sequencing of fresh-frozen tumour samples(10,11). These genomic classifications reveal a clear distinction between esophageal squamous cell carcinoma and gastroesophageal adenocarcinoma. The latter can be further

classified in 4 subtypes. Importantly, it was demonstrated that distal esophageal adenocarcinoma and proximal gastric adenocarcinomas are, from a genomic perspective, often the same disease. This is in line with the previously mentioned epidemiological patterns(3).

Lastly, small cell or large cell neuroendocrine carcinoma (NEC) can be seen as a separate entity, next to squamous cell carcinoma and (the multiple subtypes of) adenocarcinoma(12). Gastroesophageal NEC is a rare and aggressive histology that bears histological similarities to the somewhat more common pulmonary NEC(13,14). In some cases, gastroesophageal NEC can occur as a mixed adenoneuroendocrine carcinoma (MANEC)(15).

Treatment of esophageal cancer

Unfortunately, 40% of patients with esophageal cancer in the Netherlands have incurable disease at diagnosis, mainly due to extra-regional lymph node metastases, distant organ metastases or local ingrowth in surrounding organs(4). Such patients are treated with best supportive care or palliative systematic therapy, resulting in a median survival of only 5 months(4).

The remaining 60% of patients have potentially curable disease stage at diagnosis. For the majority of these patients, the cornerstone of treatment is esophagectomy with gastric conduit reconstruction, combined with preoperative chemoradiotherapy or perioperative chemotherapy(16,17). The surgery can be performed open, conventional thoracolaparoscopically or robot-assisted thoracolaparoscopically(18–20). The latter approach was developed in 2003 at the UMC Utrecht and leads to reduced cardiopulmonary complications, compared to the open approach(19). Despite these and other improvements, postoperative complications still occur in >60% of patients, leading to major postoperative morbidity or even mortality(21,22). In addition, of these patients with potentially curable disease at diagnosis in the Netherlands, the 5-year survival is only 30%(4).

Treatment of gastric cancer

Unfortunately, 50% of patients with gastric cancer in the Netherlands have incurable disease at diagnosis, mainly due to peritoneal metastases, other distant organ metastases or extra-regional lymph node metastases(4). Such patients are treated with best supportive care or palliative systematic therapy, resulting in a median survival of only 4 months(4).

The remaining 50% of patients have potentially curable disease stage at diagnosis. For the majority of these patients, the cornerstone of treatment is gastrectomy, combined with perioperative chemotherapy(23,24). The goal of surgery is to perform a radical resection of the tumor and can consist of a distal or total gastrectomy. A distal gastrectomy is mainly performed for tumors located in the gastric antrum, distally of the watershed, whereas a

total resection is mainly performed for non-distal tumors and/or diffuse-type gastric cancer(25–27). The surgery can be performed open or laparoscopically(28,29). The laparoscopic approach is most often performed conventionally (i.e. without robot-assistance) and will be discussed in more detail below(30). In the Netherlands, postoperative complications occur in about 40% of patients, leading to major postoperative morbidity or even mortality(22,31). In addition, of these patients with potentially curable disease at diagnosis in the Netherlands, the 5-year survival is only 35%(4).

Treatment of gastric cancer: East versus West

Treatment of gastric cancer differs between Eastern and Western populations(8). For gastric cancer in the Western population, the incidence of the disease is lower, patients present with fewer distal gastric cancers, more advanced tumor stages (cT3-4N0-3 or cT1-2N1-3) and patients generally have higher age, higher body weight and more comorbidities, compared with Eastern populations(8). Consequently, some Eastern countries have nationwide screening programs for gastric cancer, whereas Western countries do not. Moreover, in Western populations, hospital case volumes are markedly lower, total gastrectomy is more frequently performed, perioperative chemotherapy is more frequently administered and prognosis is generally worse(8,23,24).

Laparoscopic gastrectomy for gastric cancer

Gastrectomy can be performed via an open or laparoscopic approach(28,29). Open gastrectomy has long been the gold standard worldwide. The abdominal cavity is accessed via an upper midline laparotomy(32). During laparoscopic gastrectomy, the abdominal cavity is generally accessed via 5 5-12mm ports for a camera and laparoscopic instruments and a muscle-sparing mini-laparotomy (≤5 cm) is performed to use the resection specimen(32,33). Laparoscopic distal gastrectomy was first performed in Japan in 1992, attempting to reduce surgical trauma(34). Consequently, the adaptation of laparoscopic gastrectomy started in Eastern populations and included mainly distal gastrectomy for early gastric cancer(35).

Several Eastern multicenter randomized controlled trials demonstrated the safety and efficacy of laparoscopic distal gastrectomy regarding hospital stay, postoperative complications and lymph node yield(36–39). However, these trials were mainly performed in patients with early gastric cancer and did not include patients undergoing total gastrectomy. In addition, quality of life data are largely lacking(36–40).

Recently, laparoscopic gastrectomy is rapidly being adopted in Western populations with locally advanced gastric cancer, as large population-based studies reported reduced hospital stay, equal or reduced postoperative complications and equal lymph node yield after laparoscopic gastrectomy(28,29,41,42). However, no multicenter randomized trials

had been performed in Western populations(40). As described previously, Eastern evidence cannot necessarily be extrapolated to the Western populations, due to important differences in treatment that may affect outcome(8). Due to the lack of level-1 evidence in Western populations, concerns of a reduced lymph node yield in patients with locally advanced gastric cancer still exist and Western guidelines do not generally consider laparoscopic gastrectomy a standard treatment option(26,27).

Furthermore, costs of the laparoscopic operation itself (the unit costs) are expected to be higher compared to open gastrectomy, as a result of longer operating times and surgical materials/disposables(40,41,43). If laparoscopic gastrectomy would lead to reduced hospital stay and reduced postoperative complications, it could nevertheless be cost-effective, compared to open gastrectomy(28,32,41–43). However, no results from are available worldwide from prospective cost-effectiveness analyses in randomized trials on laparoscopic versus open gastrectomy(43–46). Hence, even though laparoscopic gastrectomy is rapidly being adopted worldwide, solid data on its cost-effectiveness are lacking.

Personalized treatment of gastroesophageal cancer

The treatment for patients with potentially curable gastroesophageal cancer was described above(16,23,24). Currently, the fast majority of these patients are recommended the same optimal treatment: preoperative chemoradiotherapy followed by resection or perioperative chemotherapy combined with resection. Hence, the current treatment paradigm is a relatively "one size fits all" based upon the results of landmark clinical trials(16,23,24). Nevertheless, in some patients this treatment leads to cure, whereas in others it does not. Likewise, some patients undergo major postoperative complications and reductions in quality of life, whereas others do not(21,31,42,47). Of course, more effective treatments are required for gastroesophageal cancer patients in general, as postoperative survival is to low and postoperative morbidity to high across the majority of gastroesophageal cancer patients. In addition, the treatment should be more tailored to the individual patient. However, there are multiple challenges before a more personalized treatment is possible. Some of these challenges are described in the 2 following paragraphs.

For multiple subtypes of gastroesophageal cancer data on optimal treatment is lacking, which hampers treatment decisions at multidisciplinary tumor boards. For GEJ tumors with their midpoint between ≤1 cm proximal and ≤ 2 cm distal from the top of gastric folds (Siewert type II "true" cardia carcinoma), it is often not clear whether an esophagectomy or a transhiatally extended gastrectomy should be performed(48,49). For gastroesophageal cancer with lung or liver oligometastases, it is unclear whether a curative approach with local treatment of the tumor and metastases is feasible in selected patients(50–54). For gastroesophageal (MA)NEC, it is unclear whether the biopsy diagnosis is reliable and, due to the aggressive nature of NECs, whether curative treatment is feasible(13–15). For diffuse

type and SRCC type gastric cancer, due to these tumors being more resistant to chemotherapy, it is unclear whether treatment should consist of perioperative chemotherapy combined with surgery or primary surgery(9,55).

On another note, it is difficult to predict which patients will have high surgical associated morbidity, as the cause of postoperative complications is often multifactorial(56–58). Furthermore, if a patient is deemed to be at high risk for postoperative complications, ideally an alternative tailored surgical approach will be used that causes less morbidity for this specific patient, yet achieves comparable oncological outcome. Unfortunately, such approaches are currently limited and the treatment that can be chosen at multidisciplinary tumor boards are generally either the standard surgery with optimal chances of cure, definitive chemoradiotherapy for esophageal cancer with (especially for adenocarcinoma) inferior chances of cure or palliative treatment(4).

The examples above are relevant, yet small pieces of a larger puzzle. Ultimately, to improve outcomes, treatment should be further tailored to the individual patient, based upon the anatomical location of the tumor (and its metastases), the tumor genome and its unique susceptibility to specific treatments and the patient's genome and condition and its unique susceptibility to side effects of specific treatments.

THESIS OUTLINE

The first aim of this thesis was to compare the two most important approaches of curative surgery for the relatively common gastric adenocarcinoma: laparoscopic versus open gastrectomy (part I). The second aim of this thesis was to evaluate treatment for less common subtypes of gastroesophageal cancer and treatment in patients at high risk for postoperative complications, to work towards a more personalized treatment of gastroesophageal cancer (part II).

Research questions

Part I. Lazparoscopic versus open gastrectomy for gastric cancer (LOGICA-trial)

- Does laparoscopic gastrectomy lead to better postoperative recovery, less postoperative pain and equal oncological efficacy, compared to open gastrectomy in a multicenter randomized trial (chapter 2 and 3)?
- How does the cost-effectiveness compare between laparoscopic and open gastrectomy in a multicenter randomized trial (chapter 4)?
- Is body composition as measured on pre-operative CT-scan a predictor for postoperative complications after gastrectomy (chapter 5)?

Part II. Personalized treatment of gastroesophageal cancer

- Does preoperative chemotherapy combined with surgery improve outcomes in (signet ring cell) diffuse type gastric and gastroesophageal junction adenocarcinomas, compared to surgery alone (chapter 6)?
- What is the accuracy of biopsy diagnosis and what are the outcomes of multimodal or surgical treatment in gastroesophageal (mixed adeno)neuroendocrine carcinoma (chapter 7)?
- What are the outcomes of surgery for hepatic or pulmonary metastases from metastatic gastroesophageal cancer (chapter 8)?
- Is it safe and feasible to perform laparoscopic ischemic conditioning prior to esophagectomy in patients with esophageal cancer and arterial calcifications as measured on pre-operative CT-scan (ISCON-trial protocol) (chapter 9)?
- What are the outcomes of transthoracic esophagectomy versus transhiatal extended gastrectomy for gastroesophageal junction type II adenocarcinoma in a multinational randomized trial (CARDIA-trial protocol) (chapter 10)?

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Part one

Laparoscopic versus open gastrectomy for gastric cancer (LOGICA-trial)

CHAPTER 2

Laparoscopic versus open gastrectomy for gastric cancer (LOGICA): a multicenter randomized clinical trial

Journal of Clinical Oncology 2021

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ABSTRACT

Background

The oncologic efficacy and safety of laparoscopic gastrectomy are under debate for the Western population with predominantly advanced gastric cancer undergoing multimodality treatment.

Methods

In 10 experienced Upper GI centers in the Netherlands, patients with resectable (cT1-4aN0-3bM0) gastric adenocarcinoma were randomized to either laparoscopic or open gastrectomy. No masking was performed. The primary outcome was hospital stay. Analyses were performed by intention-to-treat. It was hypothesized that laparoscopic gastrectomy leads to shorter hospital stay, less postoperative complications and equal oncological outcomes.

Results

Between 2015 and 2018, 227 patients were randomized to laparoscopic (n=115) or open gastrectomy (n=112). Preoperative chemotherapy was administered in 77 patients (67%) in the laparoscopic group and 87 patients (78%) in the open group. Median hospital stay was 7 days [IQR 5-9] in both groups (p=0.34). Median blood loss was less in the laparoscopic group (150 versus 300 ml, p<0.001), whereas mean operating time was longer (216 versus 182 minutes, p<0.001). Both groups did not differ regarding postoperative complications (44% versus 42%, p=0.91), in-hospital mortality (4% versus 7%, p=0.40), 30-day readmission rate (9.6% versus 9.1%, p=1.00), R0 resection rate (95% versus 95%, p=1.00), median lymph node yield (29 versus 29 nodes, p=0.49), 1-year overall survival (76% versus 78%, p=0.74) and global health-related quality of life up to 1 year postoperatively (mean differences between +1.5 and +3.6 on a 1-100 scale; 95% confidence intervals include zero).

Conclusion

Laparoscopic gastrectomy did not lead to a shorter hospital stay in this Western multicenter randomized trial with predominantly advanced gastric cancer patients. Postoperative complications and oncological efficacy did not differ between laparoscopic and open gastrectomy.

CONTEXT SUMMARY

Key objective
Laparoscopic gastrectomy is generally not considered a standard treatment option for gastric cancer in Western guidelines. This is the first Western multicenter randomized trial comparing laparoscopic versus open gastrectomy.

Knowledge Generated
Laparoscopic versus open gastrectomy were comparable in terms of hospital stay (primary outcome), postoperative complications, R0 resection rate, lymph node yield, 1-year overall survival and quality of life.

Relevance
These results support the application of laparoscopic gastrectomy as a safe alternative to open gastrectomy in experienced centers.

INTRODUCTION

Gastric cancer is the sixth most prevalent cancer and the third most common cause of cancer related death worldwide(1). Surgical resection with lymphadenectomy is the cornerstone of multimodality curative treatment(2). Open gastrectomy has long been the gold standard worldwide, but laparoscopic gastrectomy is rapidly being adopted, as large population-based studies reported reduced hospital stay, equal or reduced postoperative complications and equal lymph node yield after laparoscopic gastrectomy(3–5).

Several Eastern multicenter randomized controlled trials demonstrated the safety and efficacy of laparoscopic distal gastrectomy regarding hospital stay, postoperative complications and lymph node yield(6–9). However, these trials were mainly performed in patients with early gastric cancer and did not include patients undergoing total gastrectomy. In addition, quality of life data are lacking(6–10).

There are no Western multicenter randomized controlled trials comparing laparoscopic with open distal gastrectomy or laparoscopic with open total gastrectomy(10). Eastern evidence cannot necessarily be extrapolated to the Western population, as important differences likely influence outcome of laparoscopic gastrectomy. The Western population has a lower incidence of gastric cancer, more comorbidities, higher BMI, higher age and presents with more advanced tumor stages(11). Moreover, hospital case volumes are markedly lower, total gastrectomy is more frequently performed and perioperative

chemotherapy more frequently administered (2,12). Due to the lack of level 1 evidence, concerns of a reduced lymph node yield in patients with advanced gastric cancer still exist and Western guidelines do not generally consider laparoscopic gastrectomy a standard treatment option(13,14). Therefore, the current randomized controlled trial included patients undergoing distal or total gastrectomy in a Western population with mainly advanced gastric cancer. Laparoscopic and open gastrectomy were compared under the hypothesis that laparoscopic gastrectomy leads to shorter hospital stay and less postoperative complications, with comparable postoperative mortality, lymph node yield and R0 resection rate.

METHODS

Trial design

This was a multicenter randomized controlled, open-label, superiority trial comparing laparoscopic with open gastrectomy in 10 Dutch centers. Patients with histologically proven, resectable (cT1-4aN0-3bM0) gastric adenocarcinoma and an Eastern Cooperative Oncology Group (ECOG) performance status of ≤2. were included. Exclusion criteria were gastroesophageal junction Siewert type I tumors, recurrent gastric cancer, previous (benign) gastric surgery, and non-elective surgery (surgery that could not be regularly planned, i.e. due to bleeding, perforation or outlet obstruction). Robotic assisted gastrectomies were not included(15). The study protocol was approved by the institutional review board at each participating center and published previously(16).

Randomization and masking

After written informed consent was obtained by the local study coordinator, patients were randomized to either laparoscopic or open gastrectomy. The randomization was performed in a 1:1 ratio by an online block tool with random block sizes of 2, 4, or 6 patients per block, stratifying for total/distal gastrectomy and hospital. No masking was performed.

Procedures

Clinical staging included gastro-esophagoscopy with biopsy and computed tomography (CT) of the thorax and abdomen. All patients were discussed in a multidisciplinary tumor board meeting prior to treatment. Perioperative chemotherapy was recommended in all eligible patients with advanced tumors (cT3-4N0 or cT1-2N+).

Surgical procedures included total or distal gastrectomy with total omentectomy and D2 lymphadenectomy, as previously described(16). Supplementary material 1 provides additional details.

Postoperative treatment was according to the guidelines for Enhanced Recovery After Surgery (ERAS)(17). The postoperative protocol was established at a meeting with all

participating centers, prior to start of the trial. Postoperative protocols did not differ between treatment groups, except for epidural analgesia, which could be initiated during open gastrectomy only(16). On postoperative day 1, liquid oral feeding could be initiated. Hospital discharge criteria included: started mobilization, oral or enteral intake according to nutritional demand, without supplementary intravenous fluids and adequate pain control with oral medication.

Quality control

Participating hospitals performed at least 20 gastrectomies annually (open and laparoscopic combined)(18). Prior to start of the trial, to standardize surgical technique, all surgeons had completed the European Society of Surgical Oncology (ESSO) laparoscopic gastrectomy training program(19). In addition, each surgical team had performed at least 20 laparoscopic gastrectomies and 2 procedural videos were approved by the trial principal investigators (RvH and JR).

During the trial, intraoperative photos were taken to demonstrate the completeness of the lymphadenectomy. To ensure pathological quality, lymph node stations were separately marked along the resection specimen or provided in separate containers. Supplementary material 1 provides additional details.

Outcomes

The primary outcome was hospital stay in number of postoperative days. Secondary outcomes included intraoperative blood loss, operating time, postoperative complications, postoperative day that discharge criteria were met, in-hospital mortality, readmission rate within 30 days after discharge, R0 resection rate, lymph node yield, overall survival and quality of life (EORTC-QLQ-C30 and EORTC-QLQ-STO22)(16). Complications were defined according to the Esophagectomy Complications Consensus Group (ECCG) definitions and scored according to the Clavien-Dindo Classification, as previously described(16,20,21). Complications were reported by each hospital in accordance to the requirements for the mandatory nationwide registry, the Dutch Upper GI Cancer Audit(18). Supplementary material 1 provides further secondary outcome definitions.

Statistical considerations

To detect a reduction in mean postoperative hospital stay of 4 days, i.e. from 18 to 14 days (standard deviation=10, α=0.05, power=0.80), 105 patients were estimated to be needed in each treatment group(16).

Intention-to-treat analyses were performed (Figure 1). In addition, prespecified subgroup and per-protocol analyses were performed(16). Univariable analyses were performed with the chi-squared test, Fisher's exact test, independent sample t-test or Mann-Whitney U test, depending on the type of data and distribution. Survival analyses were

performed using Kaplan-Meier curves and log-rank tests, with day of inclusion until death as the time period. Multivariable analyses were performed with linear regression, Poisson regression with robust error variances or multivariable Cox regression, adjusting for stratification factors only (total/distal gastrectomy and hospital) (22,23). Postoperative quality of life was assessed using linear mixed-effects models adjusting for baseline quality of life and stratification factors. Supplementary material 1 provides further statistical details.

RESULTS

Patient characteristics

From February 2015 - August 2018, 517 patients met the study inclusion criteria, and 227 patients (44%) were included. A total of 115 patients were randomly assigned to laparoscopic gastrectomy and 112 patients to open gastrectomy (Figure 1). Patient characteristics at baseline were well balanced between treatment groups (Table 1). Advanced cancer (cT3-4N0 or cT1-2N+) was clinically staged in 88 patients (77%) in the laparoscopic group and 84 patients (75%) in the open group. Preoperative chemotherapy was administered in 77 patients (67%) in the laparoscopic group and 87 patients (78%) in the open group. Details on the chemotherapy regimens are provided in Table 1.

Surgery and postoperative treatment

In the laparoscopic group, all 115 patients proceeded to surgery (Figure 1, Table 2). Diagnostic laparoscopy without resection was performed in 7 patients (6%) due to peritoneal carcinomatosis (n=5) or tumor invasion in adjacent structures (n=2). An esophagogastric resection with cervical esophagostomy was performed in 1 patient (1%) for a cardia tumor expanding in the gastric corpus and distal esophagus. A total gastrectomy was performed in 48 patients (42%) and a distal gastrectomy in 59 patients (51%). A distal gastrectomy with D1 lymphadenectomy was performed in 1 patient (1%) with a bleeding tumor and intraoperatively diagnosed peritoneal carcinomatosis. Laparoscopic gastrectomy was converted to open gastrectomy in 7 patients (6%) due to bleeding (n=2), adhesions (n=2), or insufficient exposure due to tumor invasion in adjacent structures (n=3).

In the open group, out of 112 patients, 110 proceeded to surgery. One patient did not receive surgery because metastatic disease was diagnosed during restaging and the other because of poor patient condition on reevaluation. Furthermore, diagnostic laparoscopy or laparotomy without resection was performed in 3 patients (3%) due to peritoneal carcinomatosis (n=1), tumor invasion in adjacent structures (n=1) or both (n=1). A total gastrectomy was performed in 43 patients (39%) and a distal gastrectomy in 64 patients (58%). Two patients (2%) assigned to open gastrectomy underwent a laparoscopic gastrectomy instead.

Table 1. Patient characteristics at baseline

n (%)	Laparoscopic gastrectomy 115	Open gastrectomy 112
Age, years (mean (SD))	67.9 (11.4)	66.9 (12.1)
Male sex	68 (59.1)	72 (64.3)
BMI, kg/m^2 (median [IQR])	25.5 [22.8, 28.9]	25.3 [22.3, 27.7]
ASA score		
1	7 (6.1)	14 (12.5)
2	83 (72.2)	65 (58.0)
3	25 (21.7)	33 (29.5)
Cardiovascular comorbidity	64 (55.7)	63 (56.2)
Pulmonary comorbidity	21 (18.3)	24 (21.4)
Previous abdominal surgery	30 (26.1)	36 (32.1)
Location of tumor		
Proximal stomach	15 (13.0)	15 (13.4)
Middle stomach	36 (31.3)	36 (32.1)
Distal stomach	64 (55.7)	61 (54.5)
cT-stage		
cT1	7 (6.1)	7 (6.2)
cT2	36 (31.3)	30 (26.8)
cT3	61 (53.0)	63 (56.2)
cT4	11 (9.6)	12 (10.7)
cN1-3	50 (43.5)	54 (48.2)
Preoperative chemotherapy[1]	77 (67.0)	87 (77.7)

IQR = interquartile range; SD = standard deviation; ASA = American Society of Anaesthesiologists.
[1]Preoperative chemotherapy regimens were: epirubicin + cisplatin + capecitabine (ECC) or equivalent (laparoscopic n=57, open n=68), fluorouracil + leucovorin + oxaliplatin + docetaxel (FLOT) (laparoscopic n=13, open n=13) or other (laparoscopic n=7, open n=7).

Postoperative chemotherapy was started in 41 patients (36%) in the laparoscopic group and 44 patients (40%) in the open group (p=0.59).

Primary outcome

Median hospital stay was 7 days [IQR 5-9] in both treatment groups (probability of shorter hospital stay after laparoscopic gastrectomy, 0.54; 95% CI, 0.46 to 0.61; p=0.34). Mean (±SD) hospital stay was 9.5 days (±10.8) in the laparoscopic group and 9.2 days (±8.2) in the open group (p=0.83).

Secondary outcomes

The secondary outcomes are presented in Table 2-4. Regression analyses with confidence intervals are presented in Supplementary material 3.

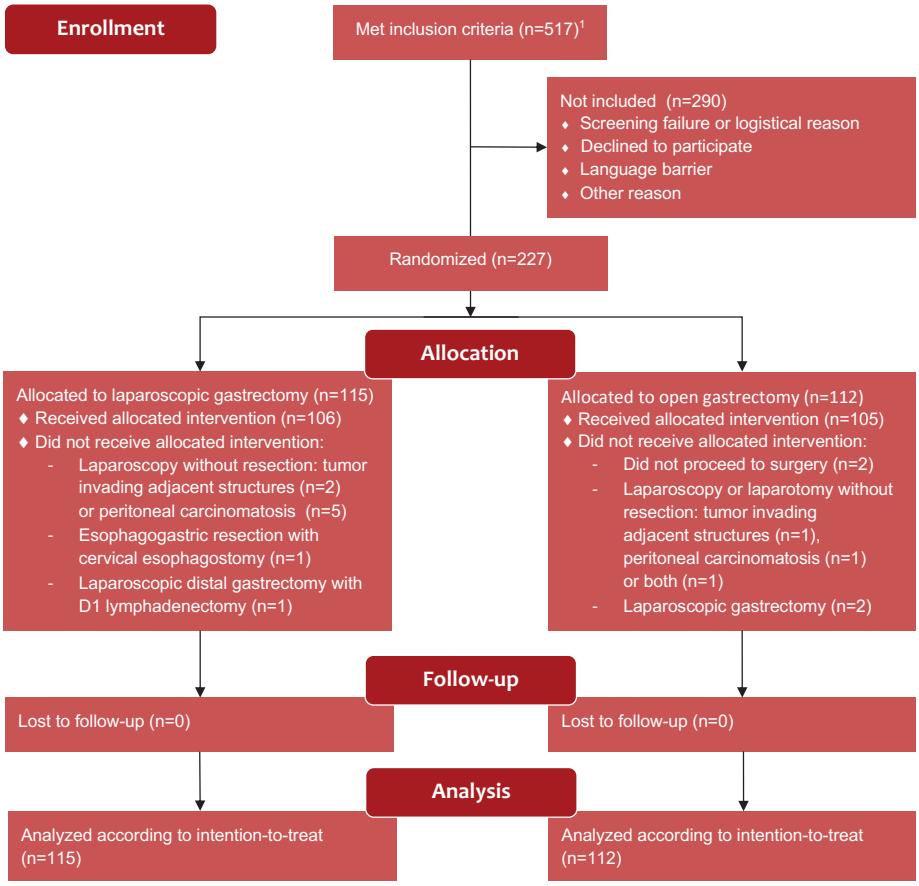


Figure 1. Trial flow
All 227 patients who underwent randomization were included in the intention-to-treat analysis: 115 in the laparoscopic gastrectomy group and 112 in the open gastrectomy group. A total of 211 patients underwent their allocated treatment according to protocol and were included in the per-protocol analyses: 106 in the laparoscopic gastrectomy group and 105 in the open gastrectomy group.
[1]The Dutch Upper GI Cancer Audit (DUCA) is a mandatory registration that contains every patient that underwent a gastrectomy for gastric cancer, including open-close procedures(18). DUCA data were used to calculate the total amount of patients that met the study inclusion criteria during the inclusion period of each trial center.

Table 2. Intraoperative and postoperative outcomes

n (%)	Laparoscopic gastrectomy 115	Open gastrectomy 110	p
Primary outcome			
Hospital stay, days (median [IQR])[1]	7.0 [5.00, 9.00]	7.0 [5.00, 9.00]	0.343 **
Secondary outcomes			
Type of operation			0.394 *
Total gastrectomy	48 (41.7)	43 (39.1)	
Distal gastrectomy	59 (51.3)	64 (58.2)	
Esophagogastric resection	1 (0.9)	0 (0.0)	
No resection	7 (6.1)	3 (2.7)	
Lymphadenectomy			1.000 *
D1	1 (0.9)	0 (0.0)	
D2	107 (99.1)	107 (100)	
Operating time, minutes (mean (SD))	216 (68.8)	182 (53.7)	<0.001
Unknown	2 (1.7)	0 (0.0)	
Blood loss, ml (median [IQR])	150 [50, 250]	300 [150, 508]	<0.001**
Unknown	4 (3.5)	4 (3.6)	
Conversion	7 (6.1)	0 (0.0)	
Intraoperative complications			0.442*
None	108 (93.9)	102 (92.7)	
Bleeding	4 (3.5)	5 (4.5)	
Pancreas injury	0 (0.0)	2 (1.8)	
Other	3 (2.6)	1 (0.9)	
Surgeon mental effort (mean (SD))[2]	58 (21.6)	55 (21.5)	0.328
Unknown	39 (33.9)	40 (36.4)	
Postoperative complications	50 (43.5)	46 (41.8)	0.907
CDC of most severe complication			0.335*
1	9 (7.8)	5 (4.5)	
2	22 (19.1)	16 (14.5)	
3a	5 (4.3)	6 (5.5)	
3b	3 (2.6)	8 (7.3)	
4a	6 (5.2)	2 (1.8)	
4b	0 (0.0)	1 (0.9)	
5	5 (4.3)	8 (7.3)	
Anastomotic leakage	10 (8.7)	11 (10.0)	0.915
Anastomotic leakage grade (ECCG)			0.682*
I	3 (2.6)	1 (0.9)	
II	1 (0.9)	1 (0.9)	
III	6 (5.2)	9 (8.2)	
Pneumonia	17 (14.8)	13 (11.8)	0.647

Table 2. Continued

n (%)	Laparoscopic gastrectomy 115	Open gastrectomy 110	p
Atrial fibrillation or flutter	10 (8.7)	6 (5.5)	0.493
Wound infection	6 (5.2)	3 (2.7)	0.500*
Fascia dehiscence	1 (0.9)	3 (2.7)	0.361*
Pancreatitis or pancreas leakage	3 (2.6)	2 (1.8)	1.000*
Feeding jejunostomy	21 (18.3)	19 (17.3)	0.985
Feeding nasojejunal tube	8 (7.0)	10 (9.1)	0.731
First oral intake, days (median [IQR])	1.0 [1.00, 1.00]	1.0 [1.00, 1.00]	0.653**
Unknown	5 (4.6)	3 (2.7)	
First defecation, days (median [IQR])	4.0 [3.00, 5.00]	4.0 [3.00, 5.00]	0.743**
Unknown	13 (11.3)	15 (13.6)	
Discharge criteira met, days (median [IQR])[3]	6.0 [5.00, 9.00]	6.5 [5.00, 9.00]	0.421**
Intensive care unit stay, days (median [IQR])	0 [0.00, 0.00]	0 [0.00, 0.00]	0.986**
In-hospital mortality	5 (4.3)	8 (7.3)	0.401*
30-day postoperative mortality	5 (4.3)	7 (6.4)	0.563
90-day postoperative mortality	12 (10.4)	10 (9.1)	0.909
Readmission within 30 days after discharge	11 (9.6)	10 (9.1)	1.000
Postoperative chemotherapy	41 (35.7)	44 (40.0)	0.495
Time to postoperative chemotherapy, days (median [IQR])[4]	45 [38.00, 60.75]	50 [41.00, 57.00]	0.415**

IQR = interquartile range; SD = standard deviation; CDC = Clavien-Dindo Classification; ECCG = Esophagectomy Complications Consensus Group. *Fisher's exact test. **Mann-Whitney U test.

[1] Hospital stay with exclusion of in-hospital mortality cases is shown. Analyses of hospital stay with inclusion of in-hospital mortality cases (day of death as day of discharge) yielded similar results: median 7.00 days [IQR 5.00-9.50] versus 7.00 days [IQR 5.00-9.75], p=0.485.

[2] Surgeon ergonomics were measured on a 1-150 scale by the Subjective Mental Effort Questionnaire (SMEQ), completed by the surgeons immediately after surgery. Higher scores indicate more mental effort.

[3] Postoperative days until the criteria for hospital discharge were fulfilled and there was no medical reason to keep the patient hospitalized. The discharge criteria are described in the method section.

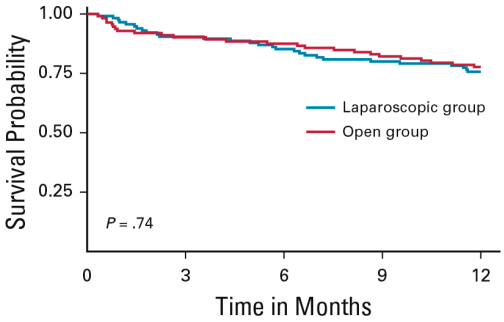
[4] From the day of surgery until the day that postoperative chemotherapy was started.

Blood loss and operating time

The laparoscopic group had less median blood loss (150 versus 300 ml, p<0.001) and a longer mean operating time (216 versus 182 minutes, p<0.001).

Postoperative course

Postoperative complications occurred in 50 patients (44%) in the laparoscopic group and 46 patients (42%) in the open group (p=0.91). The incidence of anastomotic leakage did not differ between treatment groups (9% versus 10%, p=0.92). Median days until the predefined discharge criteria were met did not differ between the laparoscopic and open group (6.0 versus 6.5 days, p=0.42). Supplementary material 4 provides additional details.



Number at risk					
Laparoscopic group	115	104	98	92	87
Open group	112	101	98	92	87

Figure 2. Overall 1-year survival. Kaplan-Meier plots are displayed. No subjects were censored, as no patients were lost to follow-up.

In-hospital mortality occurred in 5 patients (4%) in the laparoscopic group and 8 patients (7%) in the open group (p=0.40). The 30-day readmission rate did not differ between treatment groups (9.6% versus 9.1%, p=1.00).

Pathology and survival

R0 resection rate (95% versus 95%, p=1.00) and median lymph node yield (29 [IQR 21-37] versus 29 [IQR 22-39], p=0.49) did not differ between treatment groups (Table 3). The 1-year overall survival also did not differ between the laparoscopic and open group (76% versus 78%, p=0.74) (Figure 2). The hazard ratio for all-cause mortality within 1 year for the laparoscopic group was 1.14 (95% CI 0.65-1.99, adjusted for the stratification factors: total/distal gastrectomy and hospital).

Quality of life

Global health-related quality of life did not significantly differ between the laparoscopic and open group at 6 weeks, 3 months, 6 months, 9 months and 1 year postoperatively (mean differences between +1.5 and +3.6; 95% CIs include zero) (Table 4). No significant differences were observed between the laparoscopic and open group for all functional and symptom scales tested at all time points, except for a significant difference at 1 time point only for role-functioning, insomnia and appetite loss, and at 3 time points for financial difficulties.

Per-protocol and subgroup analyses

Per-protocol analyses and prespecified subgroup analyses for total/distal gastrectomy, early/advanced cancer and intestinal/diffuse Lauren subtypes were performed. These analyses yielded results similar to the main intention-to-treat analyses (Supplementary material 2,3,5).

Table 3. Pathological outcomes of the patients in whom a resection was performed

n (%)	Laparoscopic gastrectomy 108	Open gastrectomy 107	p
Lymph node yield, nodes (median [IQR])	29.0 [21.0, 37.0]	29.0 [22.0, 39.0]	0.487 **
R0 resection	103 (95.4)	102 (95.3)	1.000 *
Distance to proximal margin, mm (median [IQR])[1]	40.0 [10.0, 77.5]	41.0 [10.0, 70.0]	0.714 **
Unknown	8 (7.4)	5 (4.7)	
Not applicable	5 (4.6)	9 (8.3)	
Distance to distal margin, mm (median [IQR])[1]	25.0 [10.0, 60.0]	25.0 [10.0, 50.0]	0.748 **
Unknown	8 (7.4)	5 (4.7)	
Not applicable	5 (4.6)	9 (8.3)	
Tumor histology			1.000 *
Adenocarcinoma	107 (99.1)	106 (99.1)	
Neuroendocrine carcinoma grade 3	0 (0.0)	1 (0.9)	
Neuroendocrine tumor grade 1	1 (0.9)	0 (0.0)	
Lauren classification			0.154 *
Intestinal type	52 (48.2)	64 (59.8)	
Diffuse type	49 (45.4)	36 (33.6)	
Mixed type	3 (2.8)	5 (4.7)	
Unknown or not applicable	4 (3.7)	2 (1.9)	
(y)pT-stage			0.178 *
(y)pT0	5 (4.6)	9 (8.4)	
(y)pTis	2 (1.9)	0 (0.0)	
(y)pT1a	3 (2.8)	4 (3.7)	
(y)pT1b	12 (11.1)	10 (9.3)	
(y)pT2	13 (12.0)	13 (12.1)	
(y)pT3	39 (36.1)	50 (46.7)	
(y)pT4a	30 (27.8)	21 (19.6)	
(y)pT4b	4 (3.7)	0 (0.0)	
pN-stage			0.46
(y)pN0	44 (40.7)	50 (46.7)	
(y)pN1 (1-2)	18 (16.7)	17 (15.9)	
(y)pN2 (3-6)	18 (16.7)	21 (19.6)	
(y)pN3a (7-15)	22 (20.4)	12 (11.2)	
(y)pN3b (≥16)	6 (5.6)	7 (6.5)	
pM1[2]	5 (4.6)	3 (2.8)	0.721 *
Mandard tumor regression			0.363 *
Grade 1	5 (4.6)	9 (8.3)	
Grade 2	3 (2.8)	5 (4.6)	
Grade 3	18 (16.7)	30 (27.8)	
Grade 4	23 (21.3)	22 (20.4)	
Grade 5	23 (21.3)	18 (16.7)	
Unknown	0 (0.0)	3 (2.8)	
Not applicable	36 (33.3)	20 (18.5)	

IQR = interquartile range. *Fisher's exact test. **Mann-Whitney U test.

[1]In pathology reports where ">10mm" was used to describe the distance to the proximal margin (laparoscopic n=18, open n=21) and distal margin (laparoscopic n=23, open n=23), a distance of 10mm was used.

[2]pM1 because: tumor depositions in omentum (n=3), peritoneal carcinomatosis (n=2), positive lymph node retropancreatic (n=1), hepatic metastasis (n=1) and left adnex metastasis (n=1).

Table 4. Quality of life up to 1 year after surgery, between group differences

	Laparoscopic group at baseline		Laparoscopic versus open group at 6 weeks		Laparoscopic versus open group at 3 months		Laparoscopic versus open group at 6 months		Laparoscopic versus open group at 9 months		Laparoscopic versus open group at 1 year	
	Mean (±SD)[3]		Mean [95% CI][3]		Mean [95% CI][3]		Mean [95% CI][3]		Mean [95% CI][3]		Mean [95% CI][3]	
Quality of life questionnaire (QLQ)-C30												
Global health-related quality of life[1]	70	(22)	+2.5	[-3.3 to 8.4]	+1.6	[-4.3 to 7.5]	+3.6	[-2.4 to 9.6]	+1.5	[-4.7 to 7.7]	+2.5	[-3.9 to 8.9]
Functional scales[1]												
Physical functioning	81	(21)	-0.04	[-5.3 to 5.3]	+2.2	[-3.1 to 7.5]	+0.4	[-5.0 to 5.8]	-1.1	[-6.6 to 4.5]	-1.5	[-7.2 to 4.2]
Role functioning	70	(30)	+4.0	[-4.0 to 12]	**+9.4**	**[1.4 to 17.4]**	+1.2	[-6.9 to 9.4]	-0.8	[-9.3 to 7.7]	-2.4	[-11.1 to 6.3]
Emotional functioning	79	(24)	+0.5	[-5.2 to 6.1]	+0.9	[-4.8 to 6.5]	+2.2	[-3.6 to 8.0]	+1.8	[-4.2 to 7.9]	+0.5	[-5.7 to 6.7]
Cognitive functioning	87	(22)	+2.8	[-2.8 to 8.4]	+3.2	[-2.4 to 8.8]	+2.9	[-2.9 to 8.6]	+3.4	[-2.6 to 9.3]	+4.2	[-1.9 to 10.3]
Social functioning	79	(26)	-2.0	[-8.5 to 4.5]	+3.1	[-3.4 to 9.6]	+0.8	[-5.8 to 7.5]	-2.1	[-9.0 to 4.8]	+0.7	[-6.4 to 7.8]
Symptom scales[2]												
Fatigue	34	(27)	-0.8	[-7.7 to 6.1]	-2.7	[-9.6 to 4.3]	-1.2	[-8.3 to 5.8]	-0.4	[-7.8 to 6.9]	-4.4	[-11.9 to 3.2]
Nausea and vomiting	10	(21)	-1.3	[-7.7 to 5.2]	+1.5	[-5.0 to 7.9]	-0.6	[-7.2 to 6.1]	+2.1	[-4.8 to 9.0]	-1.4	[-8.5 to 5.6]
Pain	15	(25)	+0.9	[-6.3 to 8.2]	+0.5	[-6.8 to 7.8]	-2.8	[-10.3 to 4.6]	-1.9	[-9.6 to 5.9]	-2.0	[-9.9 to 6.0]
Dyspnoea	19	(27)	+3.7	[-3.0 to 10.4]	-1.3	[-8.1 to 5.4]	-1.3	[-8.1 to 5.5]	+2.1	[-5.0 to 9.2]	+0.3	[-7.0 to 7.6]
Insomnia	20	(34)	+2.4	[-7.1 to 11.9]	-1.8	[-11.3 to 7.7]	**+9.8**	**[0.1 to 19.5]**	+3.8	[-6.3 to 13.8]	-0.2	[-10.5 to 10.1]
Appetite loss	23	(34)	-1.2	[-10.7 to 8.3]	**+9.8**	**[0.2 to 19.3]**	+5.2	[-4.5 to 14.9]	+0.8	[-9.4 to 11.0]	-2.7	[-13.1 to 7.7]
Constipation	13	(24)	+1.4	[-5.1 to 7.9]	+2.3	[-4.2 to 8.7]	+1.7	[-5.0 to 8.3]	+2.6	[-4.3 to 9.4]	-1.4	[-8.4 to 5.7]
Diarrhea	11	(27)	-3.1	[-10.9 to 4.8]	+6.5	[-1.4 to 14.5]	+4.4	[-3.7 to 12.5]	+2.4	[-6.1 to 10.9]	+0.4	[-8.2 to 9.1]
Financial difficulties	8	(23)	-1.8	[-7.1 to 3.5]	**-6.0**	**[-11.3 to -0.7]**	-3.3	[-8.7 to 2.1]	**-7.0**	**[-12.6 to -1.3]**	**-6.9**	**[-12.7 to -1.2]**
QLQ-STO22												

Table 4. Continued

	Laparoscopic group at baseline		Laparoscopic versus open group at 6 weeks		Laparoscopic versus open group at 3 months		Laparoscopic versus open group at 6 months		Laparoscopic versus open group at 9 months		Laparoscopic versus open group at 1 year	
	Mean (±SD)[3]		**Mean [95% CI][3]**		**Mean [95% CI][3]**		**Mean [95% CI][3]**		**Mean [95% CI][3]**		**Mean [95% CI][3]**	
Functional scales[1]												
Body image	83	(32)	+6.5	[-1.5 to 14.4]	+3.7	[-4.2 to 11.7]	+4.8	[-3.3 to 12.9]	+1.7	[-6.7 to 10.2]	+5.0	[-3.7 to 13.7]
Symptom scales[2]												
Dysphagia	18	(23)	-0.4	[-6.7 to 5.9]	+0.5	[-5.8 to 6.8]	-0.3	[-6.7 to 6.2]	+0.6	[-6.1 to 7.3]	-3.0	[-9.8 to 3.9]
Pain	19	(22)	+1.1	[-4.7 to 7.0]	+3.4	[-2.5 to 9.2]	+1.8	[-4.1 to 7.8]	+0.4	[-5.8 to 6.6]	-0.4	[-6.7 to 6.0]
Reflux	14	(23)	+0.6	[-5.7 to 6.9]	+1.2	[-5.1 to 7.5]	-1.9	[-8.3 to 4.5]	-0.1	[-6.8 to 6.5]	+0.5	[-6.4 to 7.3]
Eating restrictions	23	(26)	-2.8	[-9.5 to 3.9]	+3.7	[-2.9 to 10.4]	-1.0	[-7.7 to 5.8]	-0.8	[-7.9 to 6.2]	+3.6	[-3.7 to 10.8]
Anxiety	35	(27)	-1.5	[-8.2 to 5.2]	+0.3	[-6.4 to 7.0]	-2.0	[-8.8 to 4.9]	-3.8	[-10.9 to 3.4]	-3.0	[-10.3 to 4.3]
Dry mouth	21	(34)	-0.6	[-9.7 to 8.5]	+5.5	[-3.6 to 14.6]	+2.1	[-7.2 to 11.4]	+1.6	[-8.1 to 11.3]	+0.1	[-9.8 to 10.1]
Taste	32	(35)	-1.5	[-11.1 to 8.0]	+8.4	[-1.1 to 17.9]	+2.5	[-7.2 to 12.2]	+0.2	[-9.9 to 10.3]	+2.3	[-8.2 to 12.7]
Hair loss	36	(40)	-3.4	[-13.2 to 6.4]	+0.3	[-9.8 to 10.4]	+3.7	[-6.6 to 14.0]	+1.5	[-9.3 to 12.3]	+6.2	[-4.9 to 17.3]

SD = standard deviation; CI = confidence interval. Linear mixed-effects models were performed, adjusting for the baseline quality of life and stratification factors (total/distal gastrectomy and hospital). Displayed differences are of the laparoscopic group compared to the open group (i.e. a "+" indicates a higher value in the laparoscopic group). Bold values indicate significant differences (95% CI does not include zero).

[1] Scores range 0-100: higher scores represent a better quality of life or functioning.
[2] Scores range 0-100: higher scores represent more severe symptoms.
[3] Baseline, 6 weeks, 3 months, 6 months, 9 months and 1 year questionnaires were available in the laparoscopic group for respectively 98, 84, 85, 79, 70 and 70 patients and for respectively 89, 84, 81, 80, 76 and 68 in the open group. The baseline characteristics of patients with available questionnaires were compared between the open and laparoscopic group. No differences were found (data not shown). The missing of questionnaires is regarded to be due to random chance.

DISCUSSION

In this multicenter randomized controlled trial on laparoscopic versus open gastrectomy in a Western population with mainly advanced gastric cancer, hospital stay, postoperative complications, R0 resection rate, lymph node yield, 1-year overall survival and global health-related quality of life did not differ between treatment groups. Laparoscopic gastrectomy resulted in less intraoperative blood loss and a longer operating time. This is the first multicenter trial to support the safety and efficacy of laparoscopic total and distal gastrectomy in a Western population(10). These results support the use of laparoscopic gastrectomy as an alternative to open gastrectomy, but superiority could not be demonstrated. Surgical teams trained in laparoscopic gastrectomy may offer laparoscopic gastrectomy as an alternative approach.

The current trial provides no evidence for a reduced hospital stay following laparoscopic gastrectomy, since the median hospital stay was 7 days [IQR 5-9] in both treatment groups. The trial was powered to detect an estimated population difference in hospital stay of 4 days between laparoscopic and open gastrectomy. This was based upon a meta-analysis, which was the best available evidence prior to start of the trial(3). The current hospital stay was markedly shorter than reported in this meta-analysis and was also shorter than the median hospital stay observed after distal gastrectomy in the Eastern CLASS trial (laparoscopic 9 days, open 10 days)(8). The short hospital stay after both open and laparoscopic surgery in the current trial was likely achieved by the implementation of the enhanced recovery after surgery (ERAS) program(17). A strength of the current trial is that the ERAS program was applied in both treatment groups, which was not the case in population-based studies and the meta-analysis on which the current trial was powered(3–5). Potential differences in ERAS programs between hospitals presumably did not influence the conclusions, since randomization was stratified by hospital and multivariable analyses correcting for hospital did not affect the results. Furthermore, median days until the predefined discharge criteria were met did not significantly differ between treatment groups. The current trial conclusions are presumably not influenced by lack of statistical power, since not even a small relevant difference in hospital stay was observed between treatment groups.

Postoperative complications and in-hospital mortality did not differ between laparoscopic and open gastrectomy in the current trial. The Gastrectomy Complications Consensus Group (GCCG) definitions were published after completion of the current trial(24). Hence, the current trial used the Esophagectomy Complications Consensus Group (ECCG) definitions, which bear great similarities to the GCCG definitions(20). Population data from the Dutch Upper GI Cancer Audit (DUCA) on laparoscopic versus open gastrectomy are also defined according to the ECCG. The DUCA reports similar patient

baseline characteristics and similar rates of complications (37% versus 40%, p=0.49), anastomotic leakage (8% versus 7%, p=0.53) and in-hospital mortality (6% versus 4%, p=0.21) as the current trial(5). Comparable 30-day mortality rates were reported in 9010 gastrectomies from European national cancer registries: the Netherlands (6.9%), Sweden (3.5%), Denmark (4.3%) and England (5.9%)(25).

The reported short-term mortality (3.5-6.9%), complication (37-40%) and anastomotic leakage (7-8%) rates in the Dutch population are relatively high compared to the short-term mortality (0.0-1.8%), complication (14-24%) and anastomotic leakage (2-6%) rates generally reported in the Eastern population(3,5–9,26). This is likely caused by differences in patient and tumor characteristics(11). In addition, the Western population has lower hospital case volumes resulting in less surgical routine and preoperative chemotherapy is more frequently administered. Lastly, these rates are higher after total gastrectomy than after distal gastrectomy(26,27). Despite these differences, it remains important to compare the results of the current trial to the Eastern trials on distal gastrectomy. Two large Eastern randomized trials on distal gastrectomy for early cancer were performed: the KLASS-01 trial reported a reduction in postoperative complications and hospital stay after laparoscopic gastrectomy, whereas the JCOG0912 trial reported comparable postoperative complication rates between laparoscopic and open gastrectomy(6,7). Five Eastern randomized trials on advanced gastric cancer were included in a meta analyses, which reported no significant difference in postoperative complication rates or hospital stay between laparoscopic and open gastrectomy(10). This is in line with the results of the current trial. Eastern multicenter trials on laparoscopic versus open total gastrectomy are not available(10). The Japanese nationwide registry reported increased postoperative complications after laparoscopic total gastrectomy(26,28). The current trial does not confirm this observation as no difference in postoperative complication rates was observed.

The oncological quality in the current trial was high with an R0 resection rate of 95%. This is higher than the previous CRITICS (90%) and FLOT4 trials (91%)(2,29). Furthermore, an adequate lymph node yield was obtained, which did not differ between the laparoscopic and open group (median 29 nodes). This clearly exceeds the quality standard of the American Joint Committee on Cancer and the National Comprehensive Cancer Network that recommend a minimum of 15 nodes to be retrieved and examined. These results show that the existing concerns for a lower lymph node yield after laparoscopic gastrectomy can be dismissed for surgeons that have completed their learning curve(13).

As quality control is essential in gastroesophageal surgery trials, the current trial design included several quality control measures(30). The current results show that laparoscopic gastrectomy is safe and effective in Dutch centers that completed a structured proctoring program. The required experience of 20 cases was based upon a large Dutch cohort study that analyzed the learning curve and was chosen to reflect a completed learning curve (4).

The 1-year overall survival did not differ between treatment groups in the current trial. The 5-year survival rates should be awaited. Nevertheless, the fact that no difference was observed in complications, R0 resection rate, lymph node yield and 1-year overall survival underlines the safety and efficacy of the laparoscopic procedure.

This is the first randomized controlled trial comparing quality of life after laparoscopic versus open gastrectomy. No significant or clinically relevant differences were observed between treatment groups for global health-related quality of life and nearly all functioning and symptom scales, up to 1 year postoperatively(31). The current trial had sufficient statistical power to detect a clinically relevant difference of 10 points on global health-related quality of life, since this would require 70 patients per group (standard deviation=21, α=0.05, power=0.80) (31,32). Indeed, none of the 95% confidence intervals for global health-related quality of life in the current trial include a 10 point difference (Table 4).

A limitation of the current trial is that it was impossible to mask the surgical team and undesirable to mask the ward nurses for the allocated treatment, as the patients' wounds had to be inspected prior to discharge. Patients were also not masked, since they were randomized preoperatively (instead of intraoperatively) and informed on their allocated procedure immediately after randomization, for practical and ethical reasons. Even though the same postoperative protocol and hospital discharge criteria were used in both treatment groups and 30 day readmission rate was equal, physician and patient related bias influencing the day of discharge cannot be completely ruled out. Another possible limitation is the inclusion of both early and advanced gastric cancer, and both total and distal gastrectomy. The main reason for this trial design was to reflect the daily practice of gastric cancer patients in the Western population. As is the case in the Western population, mainly advanced cancers (76%) were included and both distal gastrectomy (54%) and total gastrectomy (40%) were performed at a comparable proportion(4,5). The randomization was stratified and the prespecified subgroup analyses and per-protocol analyses were consistent with the main intention-to-treat analyses. Thus, this allows for increased generalizability of the current trial results to the general population.

In conclusion, laparoscopic gastrectomy did not lead to a reduced hospital stay in the current Western multicenter randomized controlled trial with predominantly advanced gastric cancer patients. Postoperative complications, R0 resection rate, lymph node yield, 1-year overall survival and quality of life did not differ between treatment groups.

ACKNOWLEDGMENTS

The authors would like to thank ZonMW (The Netherlands Organisation for Health Research and Development) for the funding of the current trial (project number 837002502). In addition, the authors would like to thank Johnson & Johnson for providing an unrestricted educational grant for the proctoring of laparoscopic gastrectomy in centers before entering the trial. Furthermore, the authors would like to thank the Prospective Observational Cohort study of Oesophageal-gastric cancer Patients (van den Braak et al. Acta Oncol 2018) for collecting and sharing quality of life questionnaires of 38 included patients. Lastly, the authors would like to thank everyone that contributed to the data collection and local coordination at the 10 participating hospitals, with special mentioning of Maaike van Dam, Helma van Berkum and Monique Heijmans (Catharina Hospital, Eindhoven); Antoinette van Groenestyn (University Medical Center Utrecht); Jerôme Profar, Stan Tummers and Kees de Mooij (Zuyderland Medical Center, Heerlen and Sittard-Geleen); Maureen de Vries and Edith Bouwmeester (Erasmus University Medical Center, Rotterdam); Graziella Kallenberg-Lantrua and Dorien Berends (Leiden University Medical Center); Ilse Masselink (ZGT Hospitals, Almelo); Damiana Beumer (Gelre Hospitals, Apeldoorn); Sander Mertens and Rob Tolboom (Meander Medical Center, Amersfoort); Marianne Kalff and Loes Noteboom (Amsterdam UMC, Location AMC) and Jennifer Straatman, Nicole van der Wielen and Nel de Vries (Amsterdam UMC, Location VUmc).

FUNDING

This trial was funded by ZonMW (The Netherlands Organisation for Health Research and Development), project number 837002502

TRIAL REGISTRATION NUMBER

NCT02248519

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SUPPLEMENTARY MATERIAL

Supplementary material 1
ADDITIONAL METHODOLOGICAL DETAILS

Surgical procedures

Surgical procedures were performed as previously described(1). Distal gastrectomy was performed for tumors located in the antrum, whereas total gastrectomy was performed for tumors located in the corpus or in case of diffuse-type gastric cancer. The resection included a total omentectomy. A D2 lymphadenectomy was performed, consisting of lymph node stations 1-3, 4sa, 4sb, 4d, 5-7, 8a, 9, 11p, 11d and 12a for total gastrectomy and 1, 3, 4sb, 4d, 5-7, 8a, 9, 11p and 12a for distal gastrectomy(1,2).

Quality control

All participating hospitals performed at least 20 gastrectomies annually (laparoscopic and open combined), which is the minimum hospital volume according to Dutch guidelines(3). All surgeons were board certified gastro-intestinal and/or oncological surgeons and had completed the European Society of Surgical Oncology (ESSO) laparoscopic gastrectomy training program, including participation in a hands-on cadaver course and on-site proctoring(4). In the Netherlands, operative procedures are not performed by individual surgeons but by a dedicated team per hospital. Each team had performed at least 20 laparoscopic gastrectomies, and had a positive review of at least 2 procedural video's by one of the principal investigators (RvH or JR), prior to start of the trial.

During the trial, all surgeons performed both laparoscopic and open gastrectomies. Intraoperative photos were taken after the lymphadenectomy to demonstrate the area of nodal dissection including (the remainder of) lymph node stations 8, 9, 11 and 12. These photos were centrally reviewed for adequacy of the lymphadenectomy by the principal investigators on a weekly basis and feedback was given when needed.

To ensure pathological quality, the lymph node stations were separately marked along the resected specimen. Lymph node stations 8, 9, 11 and 12 were dissected and provided in separate containers. Pathological evaluation was performed by experienced pathologists per center, according to a standardized protocol.

Secondary outcome definitions – additional details

R0 resection of the distal and proximal margin was defined according to the College of American Pathologists(5). Pathological outcomes are shown only for patients who underwent a resection. Discharge criteria met was defined as the postoperative day that the predefined criteria for hospital discharge were fulfilled and there was no medical reason

to keep the patient hospitalized. The criteria for hospital discharge were described under "methods – procedures" and included: started mobilization, oral or enteral intake according to nutritional demand, without supplementary intravenous fluids and adequate pain control with oral medication.

Statistical considerations – additional details

As prespecified, the primary analysis of hospital stay was performed by the Mann-Whitney U test, due to the non-Gaussian distribution. The confidence interval was calculated according to the methods by Fay and Malinovsky(6). Hospital stay was calculated twice: with and without in-hospital mortality casus (hospital stay without in-hospital mortality is reported throughout the manuscript, however Table 2 reports both). The Poisson regressions were performed with robust error variances for binary outcomes according to the methods by Zou et al (7,8). Primary outcome data did not contain missing values. Quality of life data of alive patients was available for 79-83% at each time point and missing values were accounted for in the mixed-effects model. Other secondary outcome data were missing for <1%, hence no data imputation was performed. As prespecified in the trial protocol, no correction was made for multiple testing. Statistical analysis was performed using IBM SPSS Statistics version 25.0.0.2 (IBM Corp. Armonk, New York, USA) and R statistical computing version 3.5.1 (R Foundation for Statistical Computing, Vienna, Austria). The study was controlled by an external data monitoring committee.

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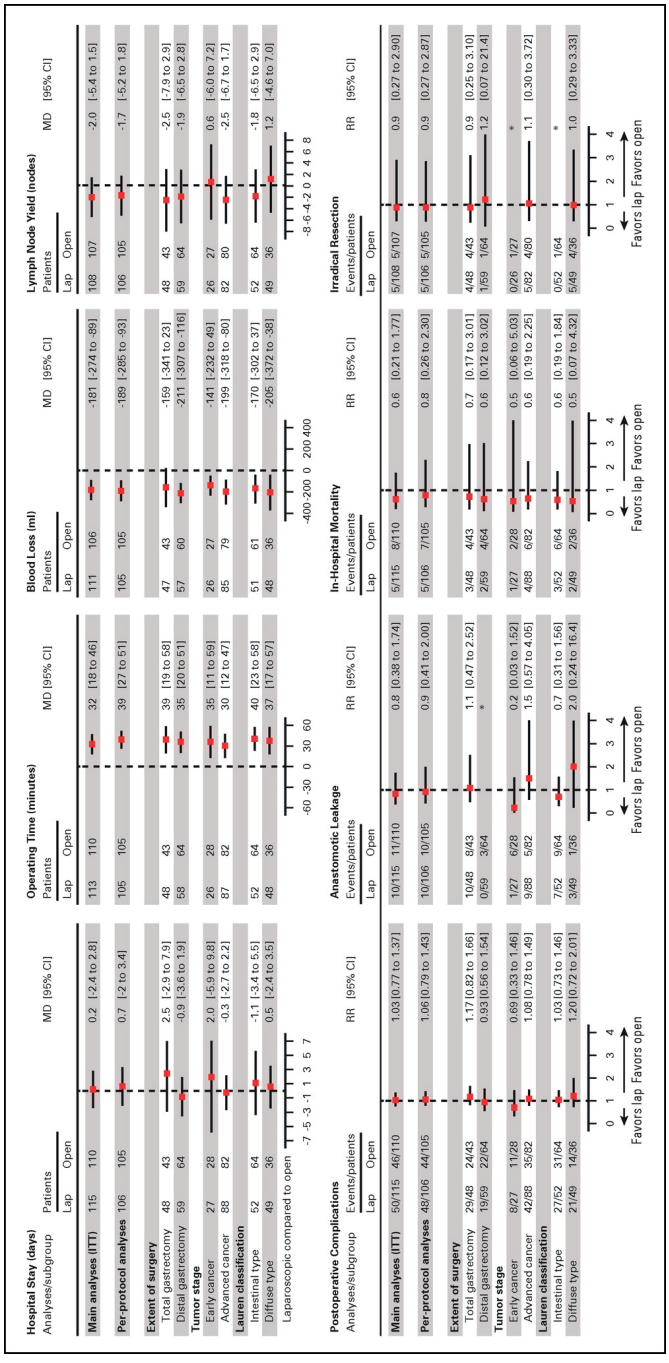
Supplementary material 2
RESULTS FROM PER-PROTOCOL AND SUBGROUP ANALYSES

After total gastrectomy, median hospital stay was 8 days [IQR 7-14] in the laparoscopic group and 8 days [IQR 7-11.5] in the open group (0.51; 95% CI, 0.39 to 0.63; p=0.82). After distal gastrectomy, median hospital stay was 6 days [IQR 5-7] in the laparoscopic group and 6 days [IQR 5-8] in the open group (0.53; 95% CI, 0.43 to 0.63; p=0.60).

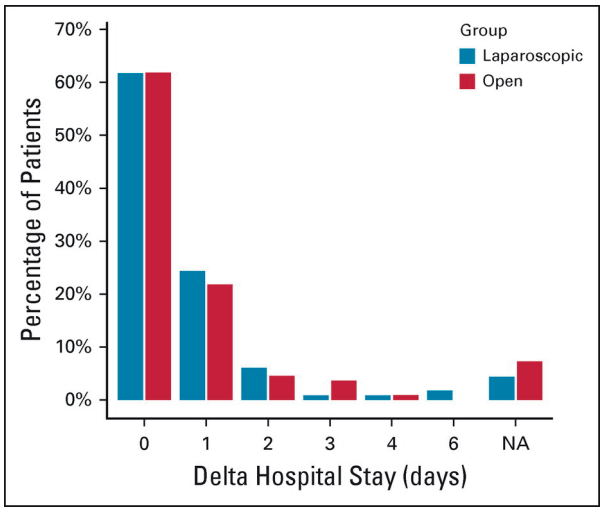
Per-protocol analyses and prespecified subgroup analyses for total/distal gastrectomy, early/advanced cancer and intestinal/diffuse Lauren subtypes yielded results similar to the main intention-to-treat analyses: no differences between the laparoscopic and open groups for hospital stay, postoperative complications, anastomotic leakage, in-hospital mortality, R0 resection rate, lymph node yield and 1-year overall survival. The laparoscopic groups had less blood loss and a longer operating time (Supplementary material 3,5).

Supplementary material 3



Subgroup analyses and per-protocol analyses for continuous outcomes (top 4 tables) and binary outcomes (bottom 4 tables). MD = mean difference; RR = relative risk; CI = confidence interval; ITT = intention-to-treat; lap = laparoscopic. Multivariable linear regression analyses (top 4 tables) and multivariable Poisson regression analyses with robust error variances (bottom 4 tables) were performed adjusting for the stratification factors: total/distal resection and hospital. The Poisson regressions were performed according to the methods of Zou et al., producing relative risks (Supplementary material 1). Logistic regressions, producing odds ratios, yielded similar results (data not shown). The results are displayed as mean differences of the laparoscopic group compared to the open group (top 4 tables) or relative risk for the laparoscopic group compared to the open group (bottom 4 tables). The per-protocol analyses included all patients that received allocated treatment (Figure 1). The subgroups were derived from the main intention-to-treat dataset. Patients that did not undergo a total or distal gastrectomy were excluded from the total/distal gastrectomy subgroup analyses (n=11). The following patients were excluded from the Lauren classification subgroup analyses: mixed type Lauren classification (n=8), no definitive Lauren classification available due to no resection performed (n=12) and unknown or not applicable Lauren classification (n=6). *Relative risk could not be calculated, as there were 0 events in one of the treatment groups.

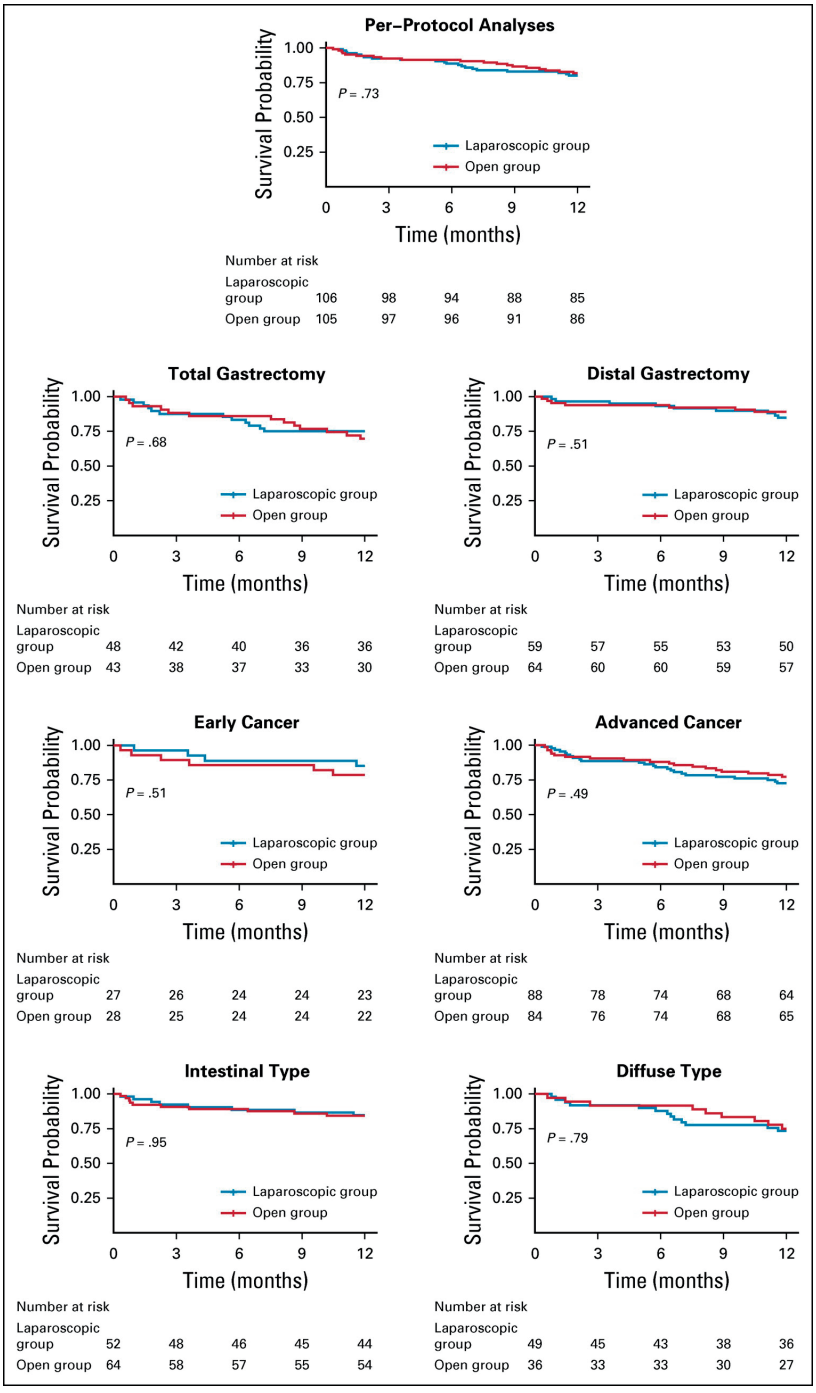
Supplementary material 4



The difference (delta) between day of discharge criteria met and day of actual discharge are displayed. The following deltas (Δ) were observed for the laparoscopic versus open group, respectively: Δ0 days in 71 (62%) versus 68 (62%) patients, Δ1 day in 28 (24%) versus 24 (22%) patients, Δ2 days in 7 (6%) versus 5 (5%) patients, Δ3 days in 1 (1%) versus 4 (4%) patients, Δ4 days in 1 (1%) versus 1 (1%) patients, Δ6 days in 2 (2%) versus 0 (0%) patients and not applicable (NA) in 5 (4%) versus 8 (7%) patients that died during admission.

Supplementary material 5

Overall 1-year survival subgroup analyses and per-protocol analyses. No subjects were censored, as no patients were lost to follow-up. The subgroups were derived from the main intention-to-treat dataset. Patients that did not undergo a total or distal gastrectomy were excluded from the total/distal gastrectomy subgroups (n=13). The following patients were excluded from the Lauren classification subgroups: mixed type Lauren classification (n=8), no definitive Lauren classification available due to no resection performed (n=12) and unknown or not applicable Lauren classification (n=6). ►


Per–Protocol Analyses
Survival Probability
1.00
0.75
0.50
0.25
P = .73
Laparoscopic group
Open group
0
3
6
9
12
Time (months)
Number at risk
Laparoscopic group 106 98 94 88 85
Open group 105 97 96 91 86
Total Gastrectomy
P = .68
Laparoscopic group 48 42 40 36 36
Open group 43 38 37 33 30
Distal Gastrectomy
P = .51
Laparoscopic group 59 57 55 53 50
Open group 64 60 60 59 57
Early Cancer
P = .51
Laparoscopic group 27 26 24 24 23
Open group 28 25 24 24 22
Advanced Cancer
P = .49
Laparoscopic group 88 78 74 68 64
Open group 84 76 74 68 65
Intestinal Type
P = .95
Laparoscopic group 52 48 46 45 44
Open group 64 58 57 55 54
Diffuse Type
P = .79
Laparoscopic group 49 45 43 38 36
Open group 36 33 33 30 27

CHAPTER 3

Pain and opioid consumption after laparoscopic versus open gastrectomy for gastric cancer (LOGICA): a secondary analysis of a multicenter randomized clinical trial

Submitted

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ABSTRACT

Importance
Laparoscopic surgery has the potential to reduce pain and thus postoperative opioid consumption. Yet, it remains unclear whether laparoscopic gastrectomy reduces pain and opioid consumption, compared to open gastrectomy.

Objective
To compare postoperative pain and opioid consumption after laparoscopic versus open gastrectomy for gastric cancer.

Design
This is a secondary analysis of a multicenter randomized trial (LOGICA-trial).

Participants
All patients with resectable gastric adenocarcinoma (cT1-4aN0-3bM0) included between 2015-2018 in the LOGICA-trial were included in the current study.

Interventions
Laparoscopic versus open gastrectomy.

Main Outcomes and Measures
Postoperative pain was analyzed by Numeric Rating Scales (NRS, 0-10) and WHO analgesic steps at postoperative day (POD) 1-10 and at discharge. In addition, opioid consumption in oral morphine equivalents (OME, mg/day) were analyzed at POD 1-5. Postoperative pain by NRS was a prespecified outcome measurement, whereas the others were not. Regression and mixed model analyses were performed, with and without correction for epidural analgesia. Main analyses were according to intention-to-treat.

Results
A total of 225 patients underwent surgery, of whom 115 were randomized to the laparoscopic group and 110 to the open group. Epidural analgesia was given in 16 patients (14%) in the laparoscopic group and 73 patients (66%) in the open group. Mean highest daily pain scores were between NRS 2-4 at all PODs and <2 at discharge and did not relevantly differ between treatment arms. At POD 1-3, mean opioid consumption was 131, 118 and 53mg OME lower in the laparoscopic group, compared to the open group, respectively (all $p<0.001$). After correcting for epidural analgesia, these differences remained significant at POD 1-2 (47mg OME, $p=0.002$ and 69mg OME, $p<0.001$, respectively). At discharge, 27% of patients in the laparoscopic group received opioids versus 43% of patients in the open group ($p=0.006$).

Conclusions and Relevance
In this multicenter randomized trial, postoperative NRS pain scores were comparable between laparoscopic and open gastrectomy. After laparoscopic gastrectomy, this was generally achieved without epidural analgesia and with significantly lower opioid consumption, compared to open gastrectomy.

Trial registration number *NCT02248519*

KEY POINTS

Question
What is the difference in postoperative pain and opioid consumption between laparoscopic and open gastrectomy for gastric cancer in a multicenter randomized trial?

Findings
Postoperative pain scores were acceptable in both treatment arms. After laparoscopic gastrectomy, this was generally achieved without epidural analgesia, with significantly lower opioid consumption at postoperative day 1-2 and with reduced opioid prescriptions at discharge (27% versus 43%, p=0.006).

Meaning
After laparoscopic gastrectomy, adequate pain control can be achieved without epidural analgesia. Together with reduced opioid prescriptions at discharge, these could be relevant advantages over open gastrectomy, especially in light of the current opioid epidemic.

INTRODUCTION

Gastric cancer is the sixth most prevalent cancer and the third most common cause of cancer related death worldwide(1). Gastrectomy with lymphadenectomy is the cornerstone of multimodality curative treatment(2). Open gastrectomy has long been the gold standard worldwide. However, laparoscopic gastrectomy for advanced gastric cancer is rapidly being adopted(3–5). Laparoscopic surgery has the potential to reduce pain and thus postoperative opioid consumption(6,7). This could be highly relevant since postoperative opioid usage is a potential important contributor to the current opioid epidemic(8–13).

The Dutch LOGICA-trial on laparoscopic versus open gastrectomy for gastric cancer has reported similar safety and oncological efficacy for laparoscopic and open gastrectomy, in concordance with previous trials from the East(14–18). However, detailed pain and analgesic results from randomized trials on laparoscopic versus open gastrectomy are limited. Three Eastern trials on distal gastrectomy indicated a reduction in pain and/or use of analgesics after laparoscopic compared to open gastrectomy(17,19,20). However, since analgesics were not the primary outcome of these trials, analgesic consumption was generally expressed as one composite endpoint (i.e. any analgesics given during POD 6-10[yes/no]). Hence, it is difficult to judge the clinical relevance of these results for the patient. Furthermore, these trials did not include total gastrectomy.

Postoperative pain was a prespecified outcome measurement during the LOGICA-trial, but not yet reported(21,22). The current study aims to provide a detailed secondary analysis, comparing postoperative pain and opioid consumption between laparoscopic and open gastrectomy in the multicenter randomized LOGICA-trial(14). It was hypothesized that laparoscopic gastrectomy would lead to reduced pain and/or reduced opioid consumption.

METHODS

LOGICA-trial design and previous results

All patients who participated in the LOGICA-trial were included in this secondary analysis. The LOGICA-trial was a multicenter randomized controlled, open-label, superiority trial comparing laparoscopic with open gastrectomy in 10 Dutch hospitals. The protocol and main results were published previously (clinicaltrials.gov NCT02248519)(14,21). Briefly, between 2015-2018, 227 patients with surgically resectable (cT1-4aN0-3bM0) gastric cancer were included and randomized to laparoscopic (n=115) or open gastrectomy (n=112). Both groups did not differ regarding median initial hospital stay (7 versus 7 days, p=0.34), postoperative complication rate (44% versus 42%, p=0.91) and all other postoperative outcome parameters.

Postoperative protocol

As previously described, multiple quality control measures were included in the trial and the treatment protocols were in accordance with the guidelines for Enhanced Recovery After Surgery (ERAS)(14,21,23).

Postoperative pain protocols were left to the discretion of each participating hospital and did not differ between treatment arms, except for epidural analgesia. For open gastrectomy, epidural analgesia was the standard unless there were (relative) contraindications. For laparoscopic gastrectomy, epidural analgesia was not allowed according to the trial protocol and pain control was achieved via intravenous opioids, oral opioids or paracetamol

only. Patients that received epidural analgesia anyway were regarded protocol-violations but analyzed according to the intention-to-treat principle nonetheless. Epidurals were placed between intervertebral levels T5-T10. Though all infusions contained local anesthetics (all hospitals used bupivacaine) and an opioid, type of opioid and infusion rates varied between hospitals. All hospitals administrated paracetamol 1,000mg/6 hours, but Nonsteroidal anti-inflammatory drug (NSAID) usage was limited. Between hospitals, different opioids were used orally and intravenously and intravenous opioids were administered in different ways (as single injections, continuous administration and/or patient-controlled boluses). Some hospitals added esketamine as part of a multimodal analgesic protocol in patients with insufficient pain control from opioids.

Postoperative evaluation and pain control

Standardly, pain scores (NRS) were assessed by the ward nurse once every 8 hours and after each intervention for pain. Additionally, a dedicated pain team evaluated pain control at POD 1 in all patients, and hereafter daily in patients receiving epidural analgesia, intravenous opioids or patients in whom pain control was difficult. This pain team evaluated pain scores in combination with opioid consumption, side effects, complications and in case of epidural analgesia, the epidural sensory block range was tested. An NRS <4 in rest and <6 while mobilizing was generally considered to be acceptable. In case of insufficient pain control with opioids, analgesics daily opioid dose was increased or non-opioids were added (for example NSAID's or esketamine). In case of epidural analgesia with an inadequate sensory block, an epidural top-up was performed and continuous infusion was increased if a top-up was successful. If a top-up was unsuccessful the epidural was removed and the patient switched to intravenous or oral opioids. Opioids were removed from the epidural mixture in patients who received opioids parallel to epidural analgesia. In case of sufficient pain control, intravenous opioids or epidural analgesia were gradually switched to oral opioids and then to paracetamol only.

Primary outcomes

The primary outcomes of the current study included daily postoperative pain scores, daily analgesic steps of the WHO pain ladder as an indicator of pain severity and daily opioid consumption(24–26).

Pain scores were assessed in admitted patients at POD 1-10 and at the morning of discharge. Pain was assessed on a 0-10 NRS(22). The mean of the highest collected NRS pain scores of the day were used for the main analyses.

Analgesic steps were assessed in admitted patients at POD 1-10 and at the day of discharge. Analgesic steps were based on the WHO analgesic ladder: I. no analgesics or paracetamol +/- NSAID, II. addition of weak opioids (i.e. tramadol), III. addition of strong opioids, IV. addition of epidural or esketamine(24–26). For illustrative purposes, step III

was split by route of administration: orally or intravenously.

Data on all administered analgetics, administration routes and dosages were collected for postoperative day (POD) 1-5. For optimal comparison, opioids were converted into daily oral morphine equivalents (OME)(27,28). For example, 1mg intravenous (IV) morphine = 3mg OME.

Secondary outcomes

Secondary outcomes included quality and efficacy of epidural analgesia: quality of sensory block, incidence of top-ups, replacements, need for additional analgesia, day of removal and occurrence of minor or major epidural related complications (Supplementary material 1).

Further secondary outcomes included addition of non-steroidal anti-inflammatory drugs (NSAIDs) or esketamine, opioid intoxications, use of an enema and mobilization milestones (first time sitting in a chair or walking in the hallway).

Data collection

Analgesic steps and pain severity scores at POD 1-5 were registered prospectively in the LOGICA electronic case report forms (eCRF). An additional retrospective data collection was performed in each participating hospital's patient files and medication dispense registries, to collect the data regarding opioid consumption (including dosages) at POD 1-5, analgesic steps and pain severity scores at POD 6-10 and at discharge and all secondary outcomes. Opioid consumption was not collected after POD 5, since this retrospective data collection was time consuming.

Statistical considerations

This was a secondary analysis of the LOGICA-trial. NRS pain scores were a prespecified outcome measurement, whereas opioid consumption was not(21). Analyses were according to intention-to-treat(14,21). Primary outcomes were displayed descriptively in bar and line charts. Additionally, comparative statistics were performed between treatment arms. Differences in pain scores and daily opioid consumption at POD 1-5 were analyzed with linear mixed-effects models, pain at discharge with linear regression and analgesic step at discharge with Poisson regression with robust error variances for binary outcomes(29,30). The study protocol caused an inherent difference between treatment arms in epidural analgesia and consequently analgesic steps at the first PODs(21). Hence, comparative statistics were performed only for the analgesic step at discharge and not at POD 1-10. For optimal transparency, all models were performed with and without correction for initiation of epidural analgesia. Secondary outcomes were compared with chi-squared tests, Fisher's exact tests or Mann-Whitney U tests(31), depending on the type of data and distribution. $P<0.05$ was considered statistically significant. Supplementary material 2 provides additional methodological details.

RESULTS

Primary outcomes

Between 2015-2018, 115 patients in the laparoscopic group and 110 in the open group underwent surgery (Table 1). Supplementary material 3 displays the study flowchart. Epidural analgesia was initiated in 16 patients (14%) in the laparoscopic group and 73 patients (66%) in the open group (Supplementary material 4).

Mean highest daily pain scores during admission at POD 1-10 and at discharge are displayed descriptively in Figure 1. At POD 1, the highest daily pain score was mean 0.8 point higher in the laparoscopic group, compared to the open group (95%CI [0.20-1.38], p=0.008). After correcting for epidural analgesia, the highest daily pain score at POD 1 did no longer differ between the laparoscopic versus the open group (mean difference 0.20 points, 95%CI [-0.50 to 0.90], p=0.576). At POD 2-10 and at discharge, there were no significant differences between treatment arms, regardless of correction for epidural analgesia (Table 2). Mean first daily pain scores and median pain scores were generally lower in both treatment arms but showed similar results between treatment arms as the mean highest daily pain scores (Supplementary material 5).

The analgesia use, as WHO pain ladder steps during admission at POD 1-10 and at discharge, is displayed descriptively in Figure 2. At POD 1-7, step 1 analgesics were more often administrated in the laparoscopic group, compared to the open group, who received more often step 3 analgesics. At POD 8-10, the majority of laparoscopic patients had been discharged and this difference was no longer present. Step 2 analgetics (weak opioids) were seldom prescribed. At discharge, step 2-3 analgesics were administered in 27% of patients in the laparoscopic group versus 43% of patients in the open group (RR 0.88, 95%CI [0.80-0.96], p=0.005) (Figure 2). This difference remained significant after correcting for previous epidural analgesia (RR 0.89, 95%CI [0.80-0.99], p=0.039).

Mean daily opioid consumption per administration route are displayed descriptively in Figure 3. At POD 1-3, mean daily total opioid consumptions were 131, 118 and 53 mg OME lower in the laparoscopic group, compared to the open group, respectively (95%CI [-158 to -105], p<0.001; 95%CI [-144 to -92], p<0.001 and 95%CI [-80 to -27], p<0.001, respectively) (Table 2). At POD 4-5, there were no significant differences between treatment arms (Table 2). After correcting for epidural analgesia, mixed model estimated mean total opioid consumption at POD 1 and 2 were 47 and 69 mg OME lower in the laparoscopic group, compared to the open group, respectively (95%CIs [-77 to -18] and [-98 to -40], p=0.01 and p<0.001, respectively), whereas POD 3-5 did not significantly differ between treatment arms (Table 2).

Table 1. type of surgery, analgesics and secondary outcomes.

n (%)	Laparoscopic gastrectomy n=115	Missing or NA	Open gastrectomy n=110	Missing or NA	P
Type of operation		0 (0)		0 (0)	0.397
Total gastrectomy	48 (41.7)		43 (39.1)		
Distal gastrectomy	59 (51.3)		64 (58.2)		
Esophagogastric resection	1 (0.9)		0 (0.0)		
No resection	7 (6.1)		3 (2.7)		
IV opioid POD 1-5[1]	62 (57.4)	7 (6.1)	49 (45.4)	2 (1.8)	[2]
IV opioid type		54 (47)		62 (56.4)	[2]
Piritramide	10 (16.4)		4 (8.3)		
Fentanyl	3 (4.9)		10 (20.8)		
Morphine	48 (78.7)		34 (70.8)		
IM / SC opioid POD 1-5[1]	24 (23.1)	11 (9.6)	17 (16.5)	7 (6.4)	[2]
IM / SC opioid type		92 (80)		94 (85.5)	[2]
Piritramide	5 (21.7)		10 (62.5)		
Fentanyl	2 (8.7)		0 (0.0)		
Morphine	16 (69.6)		6 (37.5)		
Oral opioid POD 1-5[1]	77 (74.0)	11 (9.6)	89 (81.7)	1 (0.9)	[2]
Oral opioid type		46 (40)		29 (26.4)	[2]
Oxycodone	67 (97.1)		79 (97.5)		
Tramadol	1 (1.4)		2 (2.5)		
Buprenorphine	1 (1.4)		0 (0.0)		
Esketamine POD 1-5[1]	14 (12.7)	5 (4.3)	15 (13.8)	1 (0.9)	0.979
NSAID POD 1-5[1]		4 (3.5)		1 (0.9)	0.611 [3]
Metamizole	4 (3.6)		6 (5.5)		
Diclofenac	2 (1.8)		1 (0.9)		
Naproxen	0 (0.0)		1 (0.9)		
No	105 (94.6)		101 (92.7)		
Enema POD 1-5[1]	43 (39.1)	5 (4.3)	41 (38.0)	2 (1.8)	0.975
Opioid intoxication	0 (0.0)	5 (4.3)	0 (0.0)	2 (1.8)	NA
POD of first sitting in chair (median [IQR])	1 [1.00, 1.00]	6 (5.2)	1 [1.00, 2.00]	2 (1.8)	0.048 [4]
POD of first walking in hallway (median [IQR])	2 [1.00, 3.00]	12 (10.4)	2 [2.00, 3.00]	7 (6.4)	0.004 [4]

NA = not applicable; IV = intravenous; IM = intramuscular; SC = subcutaneous; NSAID = Nonsteroidal anti-inflammatory drug; POD = postoperative day; IQR = interquartile range.

[1]This variable indicates whether the medication was given at least once during the first 5 postoperative days. If such a medication was given, then the type of medication was constant over de the different PODs (except for 1 patient who received IV Morphine on POD 1-2 and IV Piritramide on POD 4, registered here under IV Morphine).

[2]No statistical test performed.

[3]Fisher's exact test performed.

[4]Mann-Whitney U test performed.

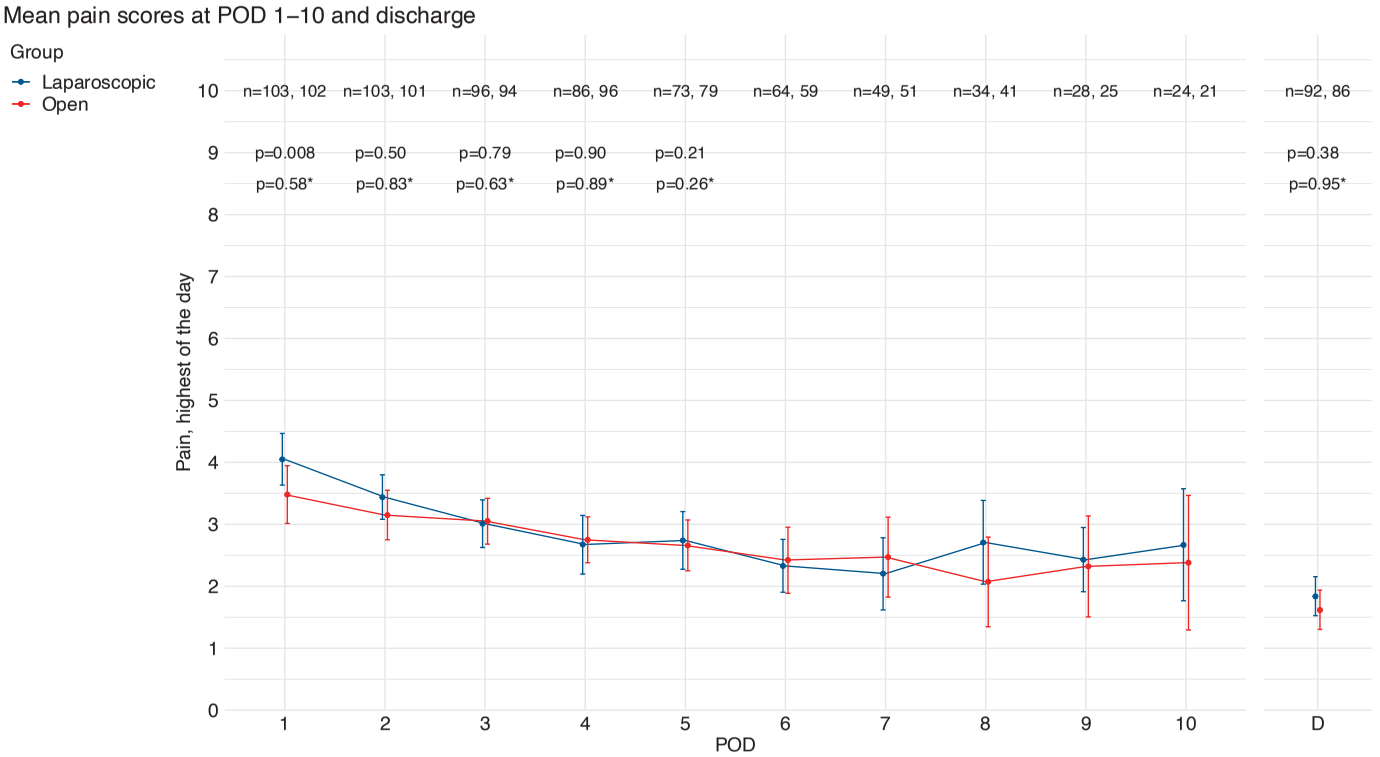

Figure 1. Mean pain scores (highest of the day) at POD 1-10 and discharge, with 95% confidence intervals. P-values from de mixed model between group comparison at POD 1-5 and linear regression at discharge (table 3) are displayed above the brackets. * = p-value corrected for epidural analgesia. POD = Postoperative Day, D = Day of discharge. n = number of patients. Of note, day of discharge is variable per patient and often not directly following POD 10.

Table 2. pain scores and opioid consumption: between group differences of mixed model and linear regression analyses.

	Mixed model – between group differences								
	POD 1			**POD 2**			**POD 3**		
	ΔMean [95% CI]		**p**	**ΔMean [95% CI]**		**p**	**ΔMean [95% CI]**		**p**
Uncorrected for epidural									
Pain score	0.79	[0.20 to 1.38]	0.008	0.20	[-0.39 to 0.79]	0.501	-0.08	[-0.70 to 0.54]	0.790
Total opioid, mg OME	-131	[-158 to -105]	<0.001	-118	[-144 to -92]	<0.001	-53	[-80 to -27]	<0.001
Corrected for epidural									
Pain score	0.20	[-0.50 to 0.90]	0.576	-0.08	[-0.79 to 0.63]	0.828	-0.18	[-0.92 to 0.56]	0.630
Total opioid, mg OME	-47	[-77 to -18]	0.002	-69	[-98 to -40]	<0.001	-23	[-52 to 6]	0.120

The highest pain score of the day was used. The between-group differences are displayed for laparoscopic gastrectomy, compared to open gastrectomy. Analyses are displayed with and without correction of pre-operative initiation of epidural analgesia. In addition, all analyses were corrected for the stratification factors (total/distal gastrectomy and hospital). Bold values indicate significant differences. The number of patients included in the mixed model for total opioids were 110 for the laparoscopic and 100 for the open group. For pain score, this was 106 in the laparoscopic and 109 in the open group. L = laparoscopic group, O = open group, CI = confidence interval, OME = oral morphine equivalent.

Secondary outcomes

Secondary outcomes regarding quality and efficacy of epidural analgesia are displayed in Table 1 and 2. Epidural analgesia resulted in an adequate sensible block in 78-100% of patients. However, this could be an overestimation, as patients with an inadequate block and subsequently removed epidural could have been reported as missing/not applicable (Supplementary material 4). Most epidurals were removed at POD 2 and 3. Of the patients that received epidural analgesia, intravenous opioids were given at least once during POD 1-5 in 21% of the laparoscopic group and 28% of the open group. In 6 out of 73 patients (8%) with an epidural in the open group, hypotension occurred as a (minor) complication. No other epidural related complications were reported.

The use of postoperative esketamine, NSAIDs, and postoperative enema did not differ between treatment arms (Table 1). No opioid intoxications occurred.

The probabilities of earlier first time sitting in a chair and walking in the hallway were higher in the laparoscopic group, compared to the open group (estimated probabilities 0.56, 95%CI 0.50-0.61, p=0.048 and 0.61, 95%CI 0.54-0.68, p=0.0041, respectively). However, median POD and interquartile ranges (IQR) were low in both arms for first time sitting in a chair (median 1 [IQR 1-1] versus 1 [IQR 1-2]) and walking in the hallway (median 2 [IQR 1-3] versus 2 [IQR 2-3]).

							Linear regression		
	POD 4			POD 5			Discharge		
	ΔMean [95% CI]		p	ΔMean [95% CI]		p	ΔMean [95% CI]		p
	-0.04	[-0.71 to 0.62]	0.898	-0.64	[-1.64 to 0.36]	0.207	0.20	[-0.25 to 0.65]	0.379
	-13	[-45 to 19]	0.422	-18	[-47 to 11]	0.223			
	0.05	[-0.72 to 0.83]	0.889	-0.63	[-1.72 to 0.47]	0.263	0.02	[-0.59 to 0.62]	0.949
	5	[-30 to 39]	0.782	-8	[-40 to 24]	0.625			

Per-protocol analyses

All analyses were repeated in the prespecified per-protocol dataset and no relevant differences were found compared to the main intention-to-treat dataset (Supplementary material 3).

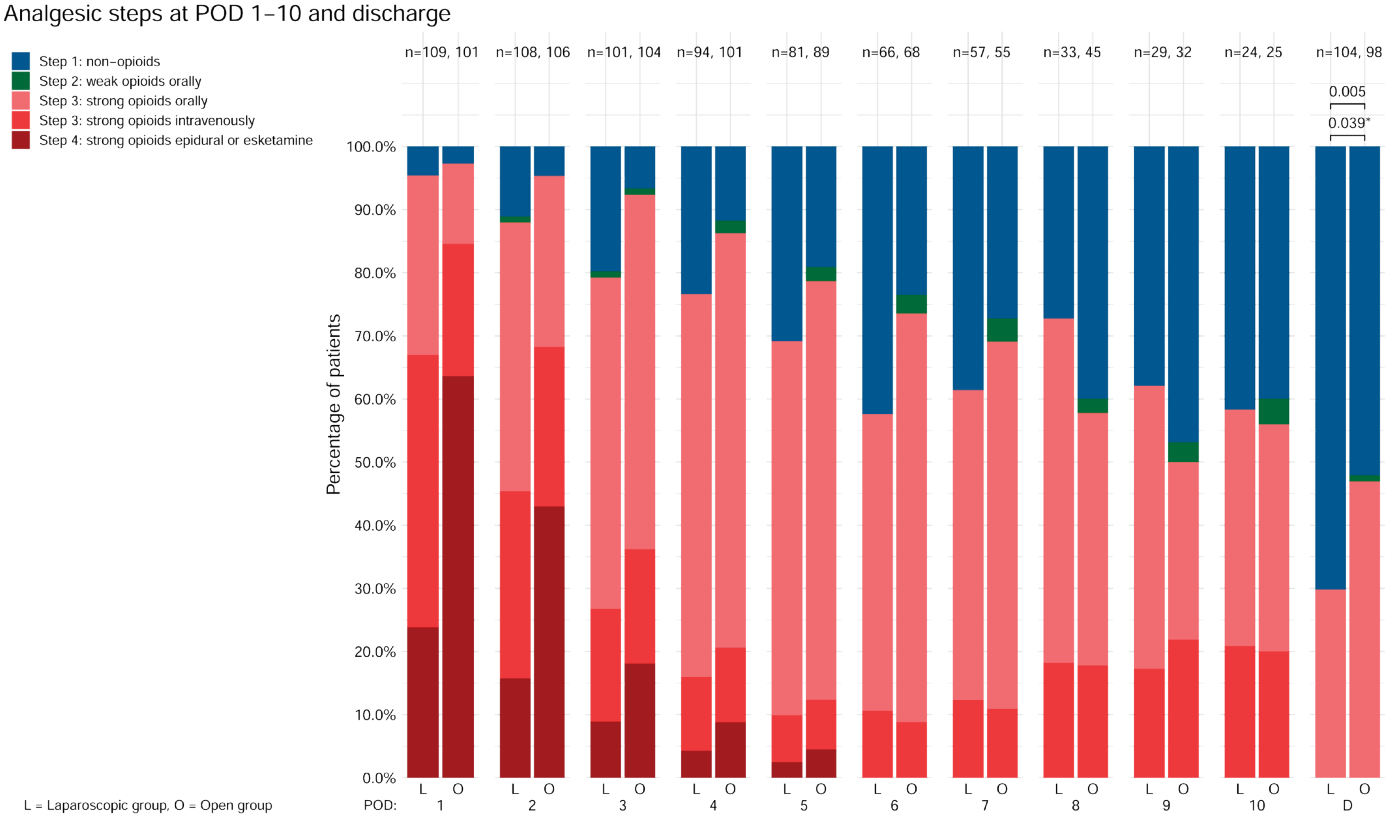

Figure 2. Analgesic steps at POD 1-10 during hospital admission and at discharge. Of note, day of discharge is variable per patient and often not directly following POD 10. P-values from the Poisson regressions (table 3) are displayed above the brackets. * = p-value corrected for epidural analgesia. L = laparoscopic group. O = open group, POD = Postoperative day, D = Day of discharge. n = number of patients.

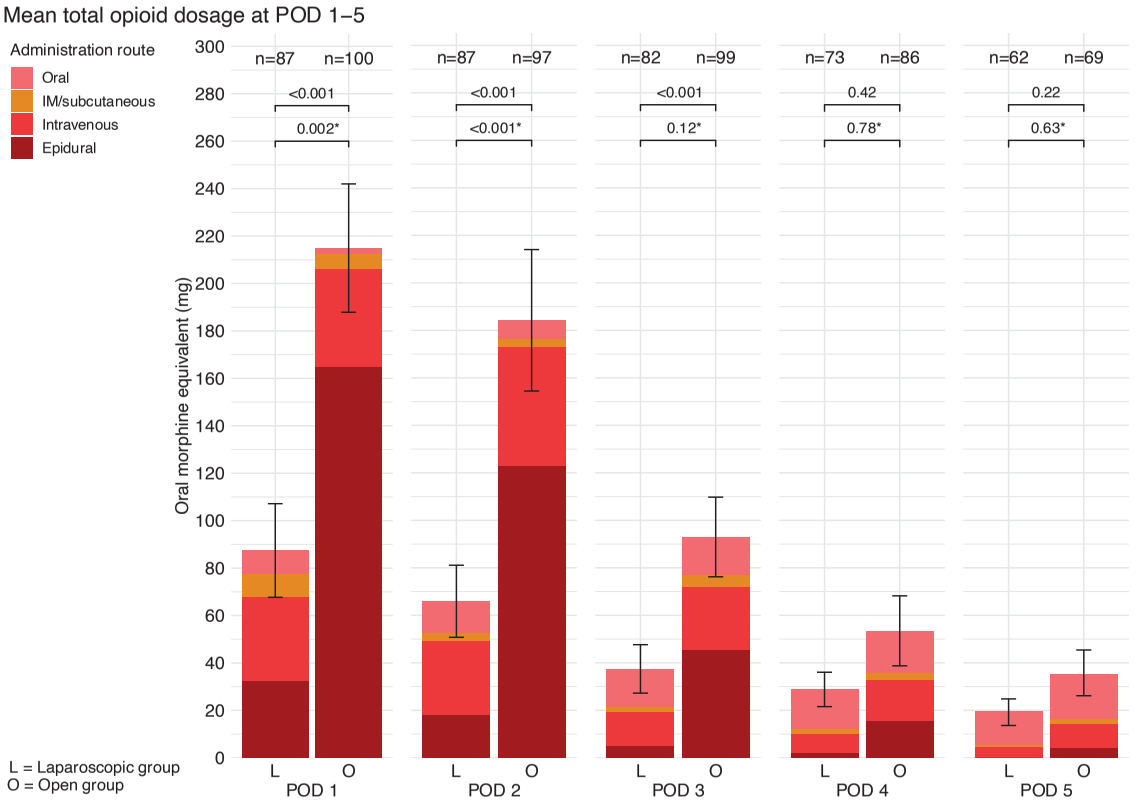

Figure 3. Mean total opioid dosages at POD 1-5. 95% confidence intervals are displayed for the mean total opioid dosages (the sum of the 4 administration routes). P-values from de mixed model between group comparison (table 3) are displayed above the brackets. * = p-value corrected for epidural analgesia. L = laparoscopic group. O = open group, POD = Postoperative Day, IM = intramuscular, n = number of patients.

DISCUSSION

In this multicenter randomized trial on laparoscopic versus open gastrectomy for gastric cancer, pain scores were comparable and adequate in both treatment arms during all PODs and at discharge (between 2-4 at all PODs and <2 at discharge). Mobilization milestones were quickly reached in both treatment arms and only modestly quicker in the laparoscopic group. In the laparoscopic group, mean daily opioid consumption was significantly lower and significantly fewer patients used oral opioids at discharge. Hence, laparoscopic gastrectomy led to adequate pain control, generally without epidural analgesia and with a clinically relevantly lower consumption of opioids, compared to open gastrectomy.

The higher opioid consumptions in the open group were partly due to the majority of this group receiving epidural analgesia, through which local anesthetics and opioids are administered. Epidural administered opioids also reach the systemic circulation and were therefore added to the daily opioid consumption(28). Nevertheless, even after correcting for epidural analgesia, mean daily opioid consumption at POD 1-2 was still up to 69mg OME lower in the laparoscopic group, which likely reflects lower analgesic requirements due to reduced pain from the smaller incisions of the laparoscopic surgery itself. Furthermore, usage of oral opioids at POD 1-7 and discharge (27% versus 43%) was lower in the laparoscopic group, compared to the open group.

These opioid reductions are deemed especially relevant in light of the current opioid epidemic(12,13,32). In the USA, approximately 76 million adults reported to have used prescribed opioid drugs in 2015-2016 and prescription opioid deaths have increased from 3442 deaths in 1999 to 17,029 in 2017(32). In Europe and more specifically the Netherlands, prescription opioid users nearly doubled from 4,109 per 100,000 inhabitants in 2008, to 7,489 in 2017(8). Oxycodone use almost quadrupled in this period and opioid prescribing after surgery, especially in the context of increasingly short hospital stays due to ERAS protocols, has been recognized as an important potential contributor to opioid misuse and related harm(8,10). Hence, the lower opioid consumption at discharge in the laparoscopic surgery group could be a relevant benefit.

It would be especially relevant if this would also result in reduced long-term opioid users after laparoscopic gastrectomy. Chronic opioid use often begins with treatment of acute pain and approximately 3,3% of patients exposed to chronic use become addicted(8,9). Indeed, 3 recent non-randomized studies evaluated laparoscopic versus open colectomy and 2 of these studies associated laparoscopic surgery with both reduced short-term and long-term opioid usage(6,7,33). Unfortunately, the current trial only had data up to 1-year postoperatively regarding patient-reported pain scores (showing no differences between treatment arms), but no data on opioid consumption up to 1-year postoperatively(14). Future research is required to examine how many short-term opioid users become long

term users after gastrectomy and whether this differs between laparoscopic and open gastrectomy.

Three trials on distal gastrectomy briefly reported on pain or analgesic consumption upon publishing the main trial results(17,19,20). However, since analgesics were not the primary outcome, none of these trials reported detailed descriptions of the postoperative pain protocols. Importantly, opioid dosages in morphine equivalents per postoperative day were not reported. Instead, one or two composite outcomes were included with limited details (i.e. any analgesics given during POD 6-10[yes/no]). Although this makes it hard to judge the clinical relevance of these outcomes for the patient, these composite outcomes did indicate reduced pain and/or analgesics after laparoscopic gastrectomy, which is in line with the current study results. An advantage of the current study is that the pain and analgesic related data were reported in a high level of detail and that total gastrectomy was also included.

Epidural analgesia is an invasive procedure and complications can occur, such as hypotension and not adequately functioning epidural catheters in up to one-third of patients(23,34). Fortunately, complications such as hypotension were only reported in a minority of patients in the current trial, though this might be an underrepresentation due to the retrospective data collection of epidural details(35). Importantly, 29% of patients in the open group with epidural analgesia also received intravenous opioids sometime during the first 5 PODs, indicating that the epidural analgesia itself often was insufficient. Nevertheless, adequate pain control was achieved in both treatment arms.

It is important to note that the trial protocol only allowed for epidural analgesia in the open group, since ERAS guidelines indicated that epidural analgesia provided superior pain control compared to intravenous analgesia in open abdominal surgery(23). Whether adequate pain control could have also been achieved without epidural analgesia in the open group was not investigated. In the laparoscopic group, it was expected that adequate pain control could be achieved without epidural analgesia. A limitation is that protocol violations occurred in 11% of the laparoscopic group that received epidural analgesia regardless. These were caused at random due to logistical errors, mainly the responsible anaesthesiologist not being aware of the trial protocol. Presumably this did not affect our conclusions, since analyses were performed according to intention-to-treat and were performed with and without correction for epidural analgesia. An additional limitation is that clinicians were not blinded for the randomization. Although pain scores at discharge were comparable between treatment arms, clinician bias could theoretically have contributed to a difference in opioids prescribed at discharge. Lastly, a limitation is that the postoperative pain management protocols differed between hospitals. However, aside from epidural analgesia, in each hospital the protocols did not differ between treatment arms and randomization was stratified by hospital. Hence, this presumably did not affect our conclusions and, as it

reflects daily practice, allows for increased generalizability of the current trial results to the general population.

Strengths of the current study are that it is the first randomized trial on this subject in a Western population and the first to also include total gastrectomy(18). A pain team was involved in each hospital and the primary outcomes were presented in a high level of detail. An ERAS protocol and multiple surgical quality control measures were in place, as described previously(14).

In conclusion, in the current multicenter randomized trial on laparoscopic versus open gastrectomy, adequate pain management was achieved in both treatment arms. After laparoscopic gastrectomy, this was generally achieved without epidural analgesia and with significantly lower consumption of opioids, compared to open gastrectomy. In light of the current opioid epidemic, this could be a relevant advantage of laparoscopic gastrectomy. Importantly, clinicians should try to reduce opioid prescriptions at discharge, after both laparoscopic and open gastrectomy.

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SUPPLEMENTARY MATERIAL

Supplementary material 1 - Epidural complication definitions

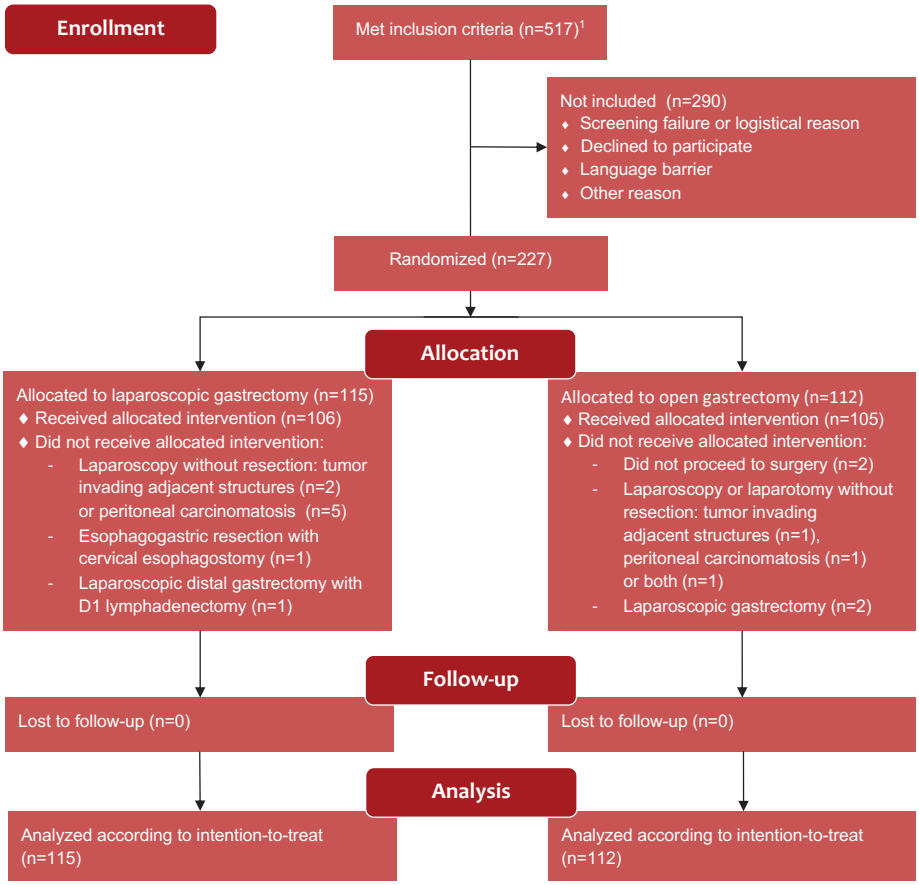
The patient charts were retrospectively reviewed for the epidural related complications. Minor complications were defined as: catheter problems, hypotension, bradypnea, transient tingling in the legs, hallucinations and other. Major complications were defined as: meningitis, epidural hematoma, epidural abscess and other.

Supplementary material 2 – Additional methodological details

The study protocol was approved by the institutional review board at each participating hospital (Haverkamp et al. BMC Cancer. 2015;15:556). This trial was funded by ZonMW (The Netherlands Organisation for Health Research and Development), project number 837002502.

Differences in analgesic step at discharge between treatment arms were analyzed with Poisson regression with robust error variances for binary outcomes, providing relative risks (RR) for having step II-III, instead of step I (Zou et al. Am J Epidemiol. 2004;159(7):702–6, Knol et al. Cmaj. 2012;184(8):895–9). All statistical models were corrected for the stratification factors (total/distal gastrectomy and hospital). For optimal transparency, all models were performed with and without correction for initiation of epidural analgesia for linear and Poisson regression and an interaction factor epidural analgesia*postoperative day for mixed-effects models. Modelling assumptions were examined and met. The amount of missing and non-applicable (NA) data was reported. In the linear mixed-effects models, only pain scores at POD 1-5 were included, since the score at POD 6-10 were often missing non-randomly due to discharged patients. Furthermore, missing data of patients who died or were discharged within 5 days postoperatively were regarded as non-random and this was corrected for by adding this missing pattern as an interaction variable (Son et al. "Application of pattern mixture models to address missing data in longitudinal data analysis using spss". Nurs Res. 2012;61(3):195–203.). Other missing data were regarded to be at random and were accounted for in the mixed-effects models (with a first-order autoregressive structure with homogenous variances) and excluded from the other analyses. Mixed model analyses were performed using IBM SPSS Statistics version 26.0.0.1 (IBM Corp., Armonk, NY) and all other analyses were using R statistical computing version 4.0.3 (R Foundation for Statistical Computing, Vienna, Austria.

Additional per-protocol analyses were performed with exclusion of patients that did not undergo allocated surgical treatment(van der Veen et al. J Clin Oncol. 2021;39(9):978–89). Furthermore, additional pain score analyses were performed, by using the mean of the first collected pain score of the day (generally collected during the morning rounds). In addition, pain scores were also analyzed by using the medians.



Supplementary material 3. Trial flow

A total of 225 patients who underwent randomization and surgery were included in the intention-to-treat analysis for postoperative outcomes: 115 in the laparoscopic gastrectomy group and 110 in the open gastrectomy group. A total of 211 patients underwent their allocated treatment according to protocol and were included in the per-protocol analyses: 106 in the laparoscopic gastrectomy group and 105 in the open gastrectomy group.

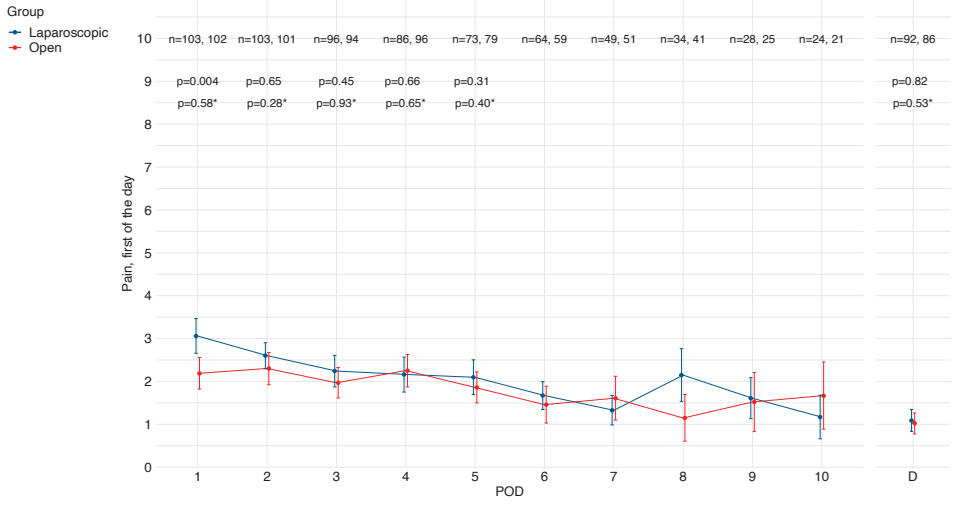
[1]The Dutch Upper GI Cancer Audit (DUCA) is a mandatory registration that contains every patient that underwent a gastrectomy for gastric cancer, including open-close procedures (Busweiler et al. Br J Surg. 2016;103(13):1855–63). DUCA data were used to calculate the total amount of patients that met the study inclusion criteria during the inclusion period of each trial center.

Supplementary material 4. Epidural details

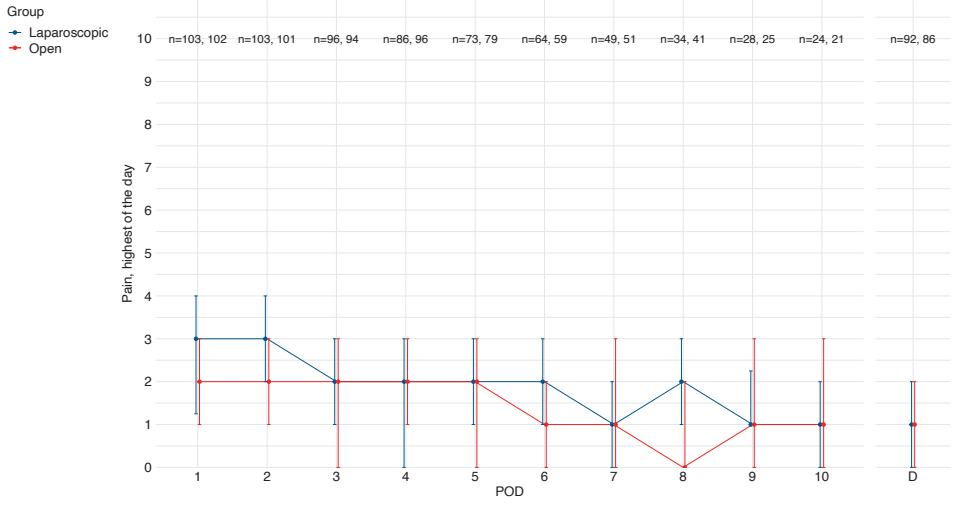
n (%)	Laparoscopic gastrectomy Epidural subgroup n=16		Missing or NA		Open gastrectomy Epidural subgroup n=73		Missing or NA	
Type of operation			0	(0)			0	(0)
Total gastrectomy	8	(50.0)			34	(46.6)		
Distal gastrectomy	4	(25.0)			37	(50.7)		
Esophagogastric resection	1	(6.2)			0	(0.0)		
No resection	3	(18.8)			2	(2.7)		
Epidural opioid type[1]			3	(18.8)			10	(13.7)
Sufentanyl	12	(92.3)			50	(68.5)		
Fentanyl	0	(0.0)			3	(4.1)		
Morphine	1	(7.7)			10	(13.7)		
Epidural switched to local anesthetic only[2]	2	(16.7)	4	(25)	9	(13.6)	7	(9.6)
Epidural day of removal			0	(0)			0	(0)
POD 0[3]	2	(12.5)			2	(2.7)		
POD 1	2	(12.5)			10	(13.7)		
POD 2	4	(25.0)			21	(28.8)		
POD 3	6	(37.5)			28	(38.4)		
POD 4	2	(12.5)			6	(8.2)		
POD 5	0	(0.0)			4	(5.5)		
POD 6	0	(0.0)			2	(2.7)		
Epidural replacement	0	(0.0)	0	(0)	1	(1.4)	0	(0)
Epidural adequate sensibel block POD 1	13	(100.0)	3	(18.8)	65	(97.0)	6	(8.2)
Epidural adequate sensibel block POD 2	11	(91.7)	4	(25)	59	(96.7)	12	(16.4)
Epidural adequate sensibel block POD 3	7	(77.8)	7	(43.8)	39	(95.1)	32	(43.8)
Epidural adequate sensibel block POD 4	2	(100.0)	14	(87.5)	11	(100.0)	62	(84.9)
Epidural adequate sensibel block POD 5	0	(NA)	16	(100)	5	(100.0)	68	(93.2)
Epidural top-up			4	(25)			11	(68.8)
Performed once, effective	1	(8.3)			3	(4.8)		
Performed once, not effective	0	(0.0)			3	(4.8)		
Performed twice, both effective	0	(0.0)			2	(3.2)		
Performed twice, once effective	0	(0.0)			1	(1.6)		
Not performed	11	(91.7)			53	(85.5)		
IV opioid POD 1-5[4]	3	(21.4)	2	(12.5)	20	(28.2)	2	(2.7)
Epidural related complication			1	(6.3)			0	(0)
Minor complication: hypotension	0	(0.0)			6	(8.2)		
Major complication	0	(0.0)			0	(0.0)		
None	15	(100.0)			67	(91.8)		

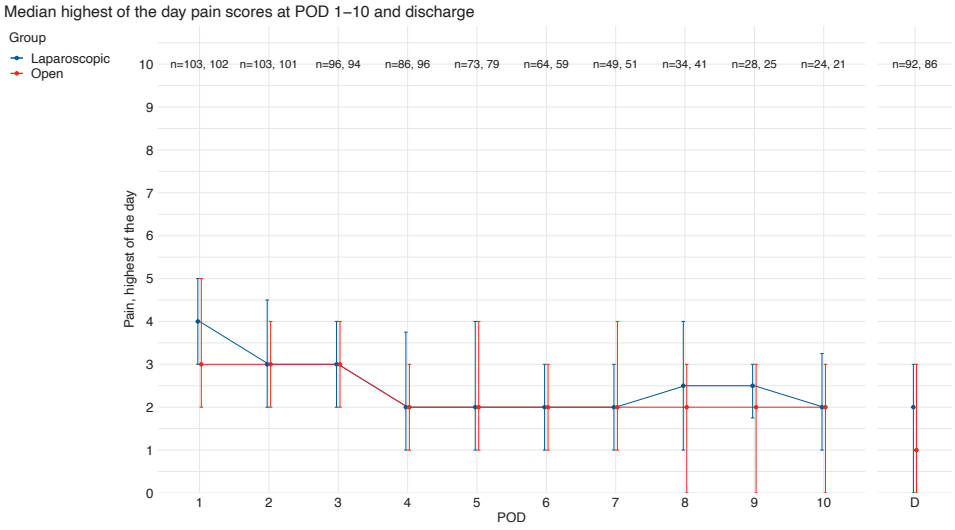
NA = not applicable; IV = intravenous; POD = postoperative day. [1]If epidural opioids were given, then the type of opioid was constant over de the different PODs. [2] This variable indicates whether at any time during POD 1-5 the opioid was removed from the epidural and thus only a local anesthetic was given over the epidural. [3]POD 0 = day of surgery. [4]This variable indicates whether IV opioids were given at least once during the first 5 PODs.

Mean first of the day pain scores at POD 1–10 and discharge



Median first of the day pain scores at POD 1–10 and discharge





Supplementary material 5. Pain scores: mean first of the day, median first of the day and median highest of the day at POD 1-10 and discharge, with 95% confidence intervals for means and interquartile ranges for medians. P-values from de mixed model between group comparison at POD 1-5 and linear regression at discharge (table 3) are displayed above the brackets. * = p-value corrected for epidural analgesia. POD = Postoperative Day, D = Day of discharge. Of note, day of discharge is variable per patient and often not directly following POD 10.

CHAPTER 4

Cost-effectiveness of laparoscopic versus open gastrectomy for gastric cancer (LOGICA): a multicenter randomized clinical trial

JAMA Surgery 2022 [in press]

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ABSTRACT

Importance

Laparoscopic gastrectomy is rapidly being adopted worldwide as an alternative to open gastrectomy to treat gastric cancer. However, laparoscopic gastrectomy might be more expensive as a result of longer operating times and more expensive surgical materials. Thus far, the cost-effectiveness of both procedures had not been prospectively evaluated in a randomized trial.

Objective

To compare the cost-effectiveness of laparoscopic compared to open gastrectomy

Design

Cost-effectiveness data were collected alongside a multicenter randomized trial on laparoscopic versus open gastrectomy for resectable gastric adenocarcinoma (cT1-4aN0-3bM0). A modified societal perspective and 1-year time horizon were used. Costs were calculated on individual patient level, by using hospital registry data and medical consumption and productivity loss questionnaires. The unit costs of laparoscopic and open gastrectomy were calculated bottom-up. Quality-adjusted life-years (QALYs) were calculated with the EQ-5D questionnaire. Missing questionnaire data were imputed with multiple imputation. Bootstrapping was performed to estimate the uncertainty surrounding the cost-effectiveness.

Setting

Multicenter randomized trial performed in 10 Dutch tertiary referral centers

Intervention

laparoscopic versus open gastrectomy

Main Outcome and Measure

total costs and QALYs

Results

Between 2015 and 2018, 227 patients were included. Unit costs for initial surgery were calculated to be €8,124 for laparoscopic total gastrectomy, €7,353 for laparoscopic distal gastrectomy, €6,584 for open total gastrectomy and €5,893 for open distal gastrectomy. Mean total costs after 1-year follow-up were €26,084 in the laparoscopic group and €25,332 in the open group (difference €752, 3.0%). Mean QALY contributions over 1 year were

0.665 in the laparoscopic group and 0.686 in the open group (difference -0.021). Bootstrapping showed that these differences between treatment arms were relatively small compared to the uncertainty of the analysis.

Conclusions and Relevance
Even though the laparoscopic gastrectomy itself was more expensive, after 1-year follow-up, differences in both total costs and effectiveness were limited between laparoscopic and open gastrectomy. These results supports centers to choose, based upon their own preference, whether or not to (de)implement laparoscopic gastrectomy as an alternative to open gastrectomy.

KEY POINTS

Question
What is the cost-effectiveness of laparoscopic compared to open gastrectomy in a multicentre prospectively randomized controlled trial?

Findings
Even though the laparoscopic gastrectomy itself was more expensive, after 1-year follow-up, differences in both total costs and effectiveness were limited between laparoscopic and open gastrectomy.

Meaning
These comparable costs and effectiveness supports centers to choose, based upon their own preference, whether or not to (de)implement laparoscopic gastrectomy as an alternative to open gastrectomy.

INTRODUCTION

Gastric cancer is the sixth most prevalent cancer and the third most common cause of cancer related death worldwide(1). Gastrectomy with lymphadenectomy is the cornerstone of multimodality curative treatment(2). Open gastrectomy has long been the gold standard worldwide. However, application of laparoscopic gastrectomy for advanced gastric cancer is estimated to have grown in the Netherlands from 5% in 2012 to 80% in 2019 and worldwide from 6-9% in 2014 to 33-39% in 2020(3–5).

The recent Western LOGICA-trial on laparoscopic versus open gastrectomy for predominantly advanced gastric cancer reported similar safety and oncological efficacy for both procedures, in concordance with previous trials from the East(6–10). Costs of the laparoscopic operation itself (the unit costs) are expected to be higher compared to open gastrectomy, due to longer operating times and surgical materials/disposables (6–9,11). Upon initiation of the LOGICA-trial, it was hypothesized that these higher unit costs would be compensated for by reduced hospital stay and reduced postoperative complications(3,11–14). However, these benefits were not demonstrated in the LOGICA-trial and the majority of other randomized trials on advanced gastric cancer(6–9). Hence, the clinical benefit of laparoscopic gastrectomy has not been proven so far, whereas its unit costs might be higher. This necessitates a dedicated randomized cost-effectiveness analysis between both procedures.

Thus far, costs and cost-effectiveness of laparoscopic gastrectomy has been analyzed in three observational cohort studies(11,15,16). Furthermore, a model based study was recently performed, using input from Eastern randomized trials and Western retrospective studies on laparoscopic distal gastrectomy only(17). Hence, it remains difficult to draw conclusions on costs and cost-effectiveness of laparoscopic total and distal gastrectomy, especially for the Western population(10).

Cost-effectiveness data were prospectively collected during the multicenter randomized LOGICA-trial on laparoscopic versus open gastrectomy(6,13). The cost-effectiveness results are reported here.

METHODS

In this prospective cost-effectiveness analysis, costs and quality-adjusted-life-years (QALYs) of patients undergoing total or distal gastrectomy were compared between the open and laparoscopic approach as part of the multicenter randomized LOGICA-trial(6). A modified societal perspective was used with a 1-year time horizon, starting on the day of surgery and corresponding to the LOGICA-trial follow-up period(18). Hence, results are not discounted.

LOGICA-trial

This was a multicenter randomized controlled, open-label, superiority trial comparing laparoscopic with open gastrectomy in 10 Dutch hospitals. The study protocol was approved by the institutional review board at each participating hospital, registered at clinicaltrials.gov (NCT02248519) and published at the start of the trial(13). Briefly, after obtaining informed consent, patients with surgically resectable (cT1-4aN0-3bM0) gastric cancer were

randomized between laparoscopic and open surgery (stratified by total/distal gastrectomy and hospital). Surgical procedures included total or distal gastrectomy with D2 lymphadenectomy. Multiple surgical and pathological quality control measures were in place(6). Alongside this trial, the EuroQol five-dimensional questionnaire (EQ-5D), iMedical Consumption (iMC) questionnaire and Short Form-Health and Labour (SF-HL) questionnaire were sent to the patients at baseline (only EQ-5D), 6-weeks, 3-months, 6-months, 9-months and 12-months(19–21).

The clinical results were published recently(6). Briefly, between 2015-2018, 227 patients were included and randomized to laparoscopic (n=115) or open gastrectomy (n=112) (Figure 1). In the laparoscopic group, mean operating time was longer (216 versus 182 minutes, p<0.001). Both groups did not differ regarding mean initial hospital stay (9.5 versus 9.2 days, p=0.83), R0 resection rate (95% versus 95%, p=1.00), median lymph node yield (29 versus 29 nodes, p=0.49), postoperative complications (44% versus 42%, p=0.91) and 1-year overall survival.

Resource use and costs

Unit costs of surgery

No standardized unit costs were available for laparoscopic and open gastrectomy and were therefore calculated bottom-up for laparoscopic total and distal gastrectomy and open total and distal gastrectomy. Costs for laparoscopy/laparotomy without resection and gastroesophageal resection without anastomosis were also calculated bottom-up for the intention-to-treat analysis, but not reported as unit costs. The unit cost included costs of the operation room (including the room itself, personnel and overhead), disposable materials, laparoscopic equipment and epidural. Furthermore, reoperation unit costs were calculated using a simple approach which included only the operation room costs.

Operation room costs were estimated by multiplying the operating time of each individual patient by a minute price of the operation room, which was recently calculated in one of the participating centers of the LOGICA-trial(22).

Of the disposable materials, vessel sealers, staplers, barbed sutures and wound protecting retractor ports were categorized as expensive and the remaining materials as inexpensive (Supplementary material 1). The amount of used expensive disposable materials were estimated per individual patient, based on the materials used during normal practice at each of the 10 participating hospitals (as supplied by a trial surgeon of each hospital) for each type of operation (laparoscopic versus open gastrectomy, distal versus total gastrectomy, or other) and type of anastomosis (circular stapled, linear stapled or hand sewn). Prices were obtained from the purchase department of one of the participating hospitals.

Other costs were calculated as a standard price per laparoscopic or open gastrectomy (not per individual patient). Inexpensive disposable materials costs were based on the

materials used during normal practice at one of the participating hospitals. Laparoscopic equipment costs per gastrectomy were calculated with depreciation and service costs at one of the participating hospitals (Supplementary material 2-3).

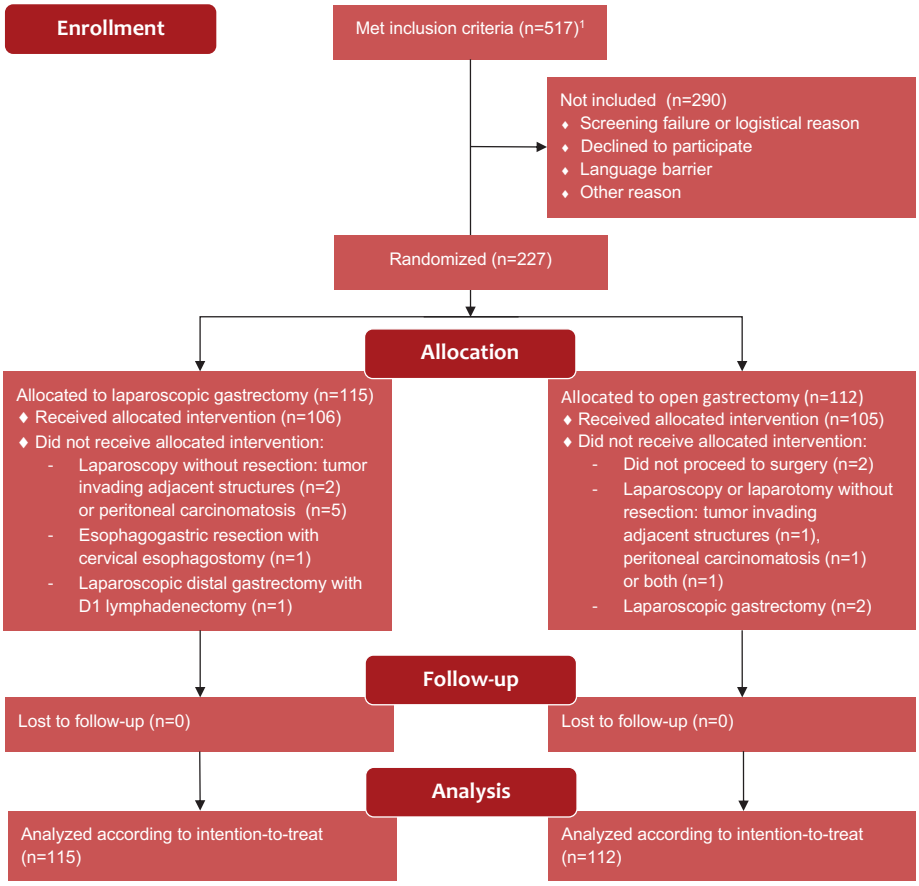

Figure 1. Trial flow chart. All 227 patients who underwent random assignment were included in the intention-to-treat analysis: 115 in the laparoscopic gastrectomy group and 112 in the open gastrectomy group. A total of 211 patients underwent their allocated treatment according to the protocol and were included in the per-protocol analyses: 106 in the laparoscopic gastrectomy group and 105 in the open gastrectomy group.
[1]The Dutch Upper GI Cancer Audit (DUCA) is a mandatory registration that contains every patient who underwent a gastrectomy for gastric cancer, including open-close procedures (Busweiler et al: Br J Surg 103:1855-1863, 2016). DUCA data were used to calculate the total number of patients who met the study inclusion criteria during the inclusion period of each trial center.

Other direct and indirect costs

All hospital procedures, registered for reimbursement purposes, were collected from each of the 10 participating hospital registries. In addition, data on extramural care, such as GP consultations, home care, family care was available from the iMC questionnaire(23). Costs were calculated per individual patient, by multiplying the number of procedures with the unit costs of every procedure. Unit costs were based on the Dutch guideline on costing research in healthcare and the Dutch Healthcare Authority (NZa)(18,24). Furthermore, indirect costs to society associated with productivity losses were estimated using the SF-HL questionnaires using the friction cost method(21).

Quality-adjusted life-years (QALYs)

QALYs were calculated with the EQ-5D in which a value of 0 represents death and 1 represents perfect health(19). The Dutch EQ-5D tariff was applied(25). The QALY contribution over one year was calculated for each patient using an area under the curve approach with linear interpolation between time points. From the day a patient died, their EQ-5D was assumed to be zero. The QALY contributions were corrected for baseline EQ-5D scores and stratification factors by linear regression.

Cost effectiveness and sensitivity analysis

Statistical analysis was performed using R statistical computing version 4.0.3. Missing values were imputed with multiple imputing using the R MICE package, using baseline characteristics, treatment outcomes, available questionnaires at other time points and hospital costs as predictors. Aside from 2 patients with missing operation durations, data on costs from all 10 participating hospitals were complete. The EQ-5D questionnaire values were available for 78-83% patients at each time point. Therefore, 20 imputed datasets were created.

Cost-effectiveness was then evaluated via standard health economics statistics(26). The total costs and the QALY contribution of the laparoscopic and open gastrectomy groups were estimated and compared with each other. To estimate the uncertainty of the costs and QALY outcomes, bootstrapping was used with 100 iterations for each of the 20 imputed datasets. Finally, a cost-effectiveness plane was constructed in which each dot represents the costs and QALY of laparoscopic gastrectomy compared to open gastrectomy of one iteration(26). As prespecified, analyses were performed according to intention-to-treat and subgroup analyses were performed for patients that underwent total or distal gastrectomy(13).

RESULTS

Unit costs of gastrectomy

Mean unit costs of the initial surgery were €8,124 for laparoscopic total gastrectomy, €7,353 for laparoscopic distal gastrectomy, €6,584 for open total gastrectomy and €5,893 for open distal gastrectomy (Table 1). The majority of costs were for the operation room itself, personnel and overhead (€5,236; €4,687; €4,274 and €3,938; respectively), followed by disposable material costs (€2,814; €2,592; €2,200 and €1,877; respectively), whereas epidural costs and laparoscopic equipment costs had a small contribution to total costs (Table 1 and 2). Additional details on the laparoscopic equipment cost calculation, anastomotic technique and expensive disposable material costs are provided in Supplementary material 2-5.

Costs in laparoscopic and open group

Costs of surgery

Mean initial surgery costs were €7,380 in the laparoscopic and €5,972 in the open group (Table 2). These costs were somewhat lower than the gastrectomy unit costs, since some patients did not undergo surgery or underwent surgery without resection. Mean total reoperation costs were €317 in the laparoscopic and €308 in the open group.

Admission costs

Mean total costs of admissions (including initial and readmissions) were €11,411 in the laparoscopic and €12,890 in the open group (Table 2). This includes mean costs for hospital stay (€8,518 versus €7,738), ICU stay (€1,775 versus €2,958) and rehabilitation center or nursing home stay (€1,118 versus €2,194). The violin plots show that the distribution of admission and home care costs for individual patients is similar in both treatment groups (Figure 2). Further details on length of admissions are given in Table 2.

Direct costs

Mean costs for home care or informal care were €1,697 in the laparoscopic and €1,188 in the open group. Mean total costs for diagnostics and consultations were €4,505 in the laparoscopic and €4,409 in the open group (Table 2). Furthermore, mean costs were €455 versus €249 for chemotherapy, and €151 versus €121 for other, for the laparoscopic versus open group, respectively (Table 2).

Indirect costs

Mean total costs for work productivity losses (absenteeism and presenteeism) were €169 in the laparoscopic and €195 in the open group (Table 2).

Table 1. Unit costs of gastrectomy

		TOTAL GASTRECTOMY				DISTAL GASTRECTOMY			
		Laparoscopic gastrectomy n = 48		Open gastrectomy n = 43		Laparoscopic gastrectomy n = 58[1]		Open gastrectomy n = 64	
	Cost per unit	Mean number of units	Mean costs	Mean number of units	Mean costs	Mean number of units	Mean costs	Mean number of units	Mean costs
Minute price of operation (including operation room, personnel and overhead)	€ 22,00	238	€ 5.236	194	€ 4.274	213	€ 4.687	179	€ 3.938
Expensive disposable materials (vessel sealer, staplers, barbed sutures and extraction ports)	variable	48	€ 2.432	43	€ 2.042	58	€ 2.210	64	€ 1.729
Inexpensive laparoscopic disposable materials	€ 234,09	48	€ 235	2	€ 11	58	€ 235	0	€ 0
Inexpensive other disposable materials	€ 147,46	48	€ 147	43	€ 147	58	€ 147	64	€ 147
Use of laparoscope	€ 51,00	48	€ 51	2	€ 2	58	€ 51	0	€ 0
Epidural	€ 136,00	8,00	€ 23	34,00	€ 108	4,00	€ 9	37,00	€ 79
Total surgery costs (without imputation)			€ 8.124		€ 6.584		€ 7,340*		€ 5.893

Unit costs of laparoscopic and open gastrectomy as calculated with a bottom-up approach including costs for the OR room, personnel, laparoscope, staplers, vessel sealer, other disposable materials and epidural.

[1]Operation duration was missing in one patient. With imputation of this patient, total surgery costs in the laparoscopic distal gastrectomy group were €7,353.

Total costs

Mean total costs up to 1 year postoperatively were €26,084 in the laparoscopic and €25,332 in the open group (difference €752, 3.0%)(Table 2). The violin plots show that the distribution of costs for individual patients is similar in both treatment groups (Figure 2).

Table 2. Number of procedures, costs and QALYs

		Laparascopic gastrectomy (n= 115)			**Open gastrectomy (n= 112)**		
		COSTS					
	Type of procedure	**Number of individuals with procedure**	**Mean number of procedures**	**Mean costs**	**Number of individuals with procedure**	**Mean number of procedures**	**Mean costs**
SURGERY	Initial surgery	115	1,0	€ 7.380	112	1,0	€ 5.972
	Reoperation	11	0,1	€ 317	17	0,2	€ 308
ADMISSIONS	Hospital stay	115	14,6	€ 8.518	112	13,3	€ 7.738
	ICU stay	16	0,7	€ 1.775	18	1,2	€ 2.958
	Rehabilition centre or nursing home	12	3,3	€ 1.118	14	7,3	€ 2.194
CARE	Home care / informal care	75	73,8	€ 1.697	64	51,7	€ 1.188
DIAGNOSTICS	Endoscopy	45	0,7	€ 128	30	0,6	€ 124
	Imaging	79	4,0	€ 552	76	3,9	€ 567
	Lab	45	191,4	€ 1.736	30	182,2	€ 1.756
	Other	49	2,0	€ 135	45	1,6	€ 91
CONSULTATIONS	Out patient visits	109	23,4	€ 1.737	110	24,2	€ 1.717
	General practitioner	104	6,6	€ 218	95	4,6	€ 153
CHEMOTHERAPY		32	-	€ 455	21	-	€ 249
WORK ABSENCE		34		€ 169	31		€ 195
OTHER		75	14,4	€ 151	64	10,4	€ 121
TOTAL				€ 26.084			€ 25.332
		QALYs					
	Baseline EQ5D	0,819			0,829		
	QALYs over 1 year*	0,665			0,686		

Number of procedures and costs of patients receiving either laparoscopic or open gastrectomy during one year follow-up, subdivided in surgery costs, admission costs, care costs, costs for diagnostics, consultations, work absence and other costs and the baseline EQ5D value and quality adjusted life years (QALYs) over one year. Of note, different procedures have different costs, hence the mean number of procedures is not linearly related to mean costs.
*QALYs over 1 year are adjusted for baseline QALYs and stratification factors (total/distal gastrectomy and hospital).

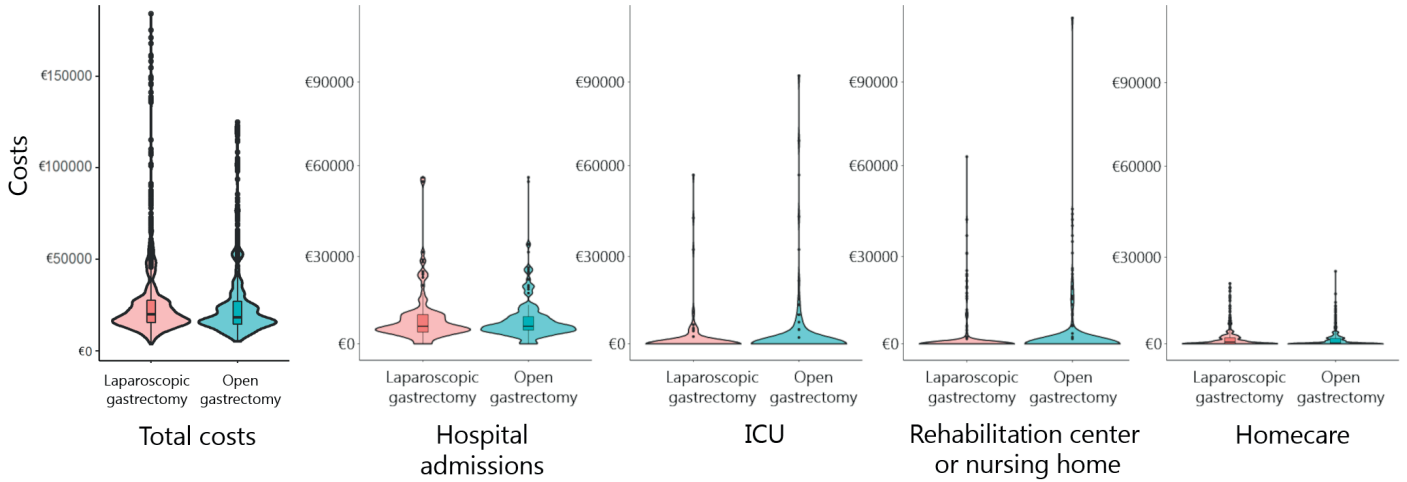

Figure 2a. Distribution of the per patient total costs during one year follow-up for patients receiving either laparoscopic or open gastrectomy.

Figure 2b. Distribution of the per patient costs during one year follow-up for patients receiving either laparoscopic or open gastrectomy for hospital admissions, ICU, rehabilitation center or nursing home and homecare. Of note, for hospital admissions and ICU, these were observed costs, since there were no missings. For rehabilitation center, nursing home and homecare costs, these also include imputations of missings. ICU = intensive care unit.

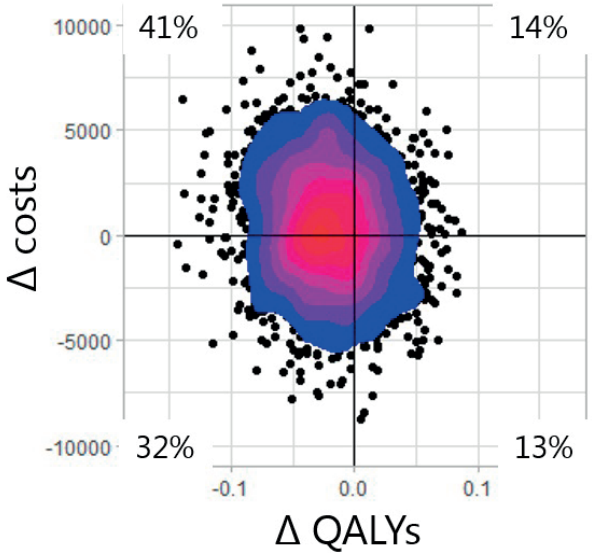

Figure 3. Costs and QALYs gained of the laparoscopic group, compared to open group for 2000 bootstrap iterations displayed in a cost-effectiveness plane. Of all bootstrap iterations, 13% were in the bottom right quadrant (lower costs and higher effectiveness for the laparoscopic group), 14% in the upper right quadrant (higher costs and higher effectiveness), 32% in the bottom left quadrant (lower costs and lower effectiveness) and 41% in the upper left quadrant (higher costs and lower effectiveness). QALY = quality-adjusted-life-year.

Quality-adjusted life-years (EQ-5D)

At baseline, mean EQ-5D values were 0.819 in the laparoscopic and 0.829 in the open group. Mean QALY contribution over 1 year postoperatively, adjusted for baseline QALYs and stratification factors, were 0.665 in the laparoscopic and 0.686 in the open group (difference -0.021, corresponding to 7.7 days in perfect health).

Sensitivity analysis

The 2000 bootstrap iterations are displayed in the cost-effectiveness plane, illustrating the uncertainty around the difference in costs and QALYs between treatment arms (Figure 3). Of all iterations, 13% represented lower costs and higher effectiveness for the laparoscopic group, 14% represented higher costs and higher effectiveness, 32% represented lower costs and lower effectiveness and 41% represented higher costs and lower effectiveness.

Total and distal subgroup analyses

For total gastrectomy (n=91), mean total costs and adjusted QALY contributions over 1 year were €32,297 and 0.617 in the laparoscopic group, compared to €30,787 and 0.626 in the open group, respectively (Supplementary material 6). For distal gastrectomy (n=123),

these outcomes were €21,999 and 0.750 in the laparoscopic group, compared €21,884 and 0.761 in the open group, respectively (Supplementary material 7). For total and distal gastrectomy, the bootstrap iterations were clearly divided over all 4 quadrants of the cost-effectiveness plane (Supplementary material 7 and 9).

DISCUSSION

To the best of our knowledge, this is the first time that cost-effectiveness of laparoscopic versus open gastrectomy for gastric cancer was prospectively evaluated in a multicenter randomized controlled trial. A detailed bottom-up calculation showed that the unit costs for the initial surgery were €8,124 (US$9603, exchange rate: 1.18) for laparoscopic total gastrectomy, €7,353 (US$8,691) for laparoscopic distal gastrectomy, €6,584 (US$7,783) for open total gastrectomy and €5,893 (US$6,966) for open distal gastrectomy. The difference in mean total costs after 1-year follow-up was smaller with €752 (3.0%), €26,084 (US$30,832) in the laparoscopic and €25,332 (US$29,943) in the open group. Uncertainty of this difference was estimated in the bootstrap analysis, in which 45% of the iterations indicated lower total costs for the laparoscopic group and 55% indicated higher total costs. Hence, the difference in total costs was limited between laparoscopic and open gastrectomy.

The mean QALY contributions up to 1 year postoperatively were 0.021 lower in the laparoscopic group, compared to the open group, corresponding to 7.7 days in perfect health. In the bootstrap analysis, 27% of iterations indicated higher and 73% lower QALY contributions for the laparoscopic group, showing that both laparoscopic or open gastrectomy could be effective. This is in line with the postoperative complications, 1-year survival and disease specific EORTC quality of life questionnaire outcomes, which did not differ between treatment arms in the current trial(6,27,28). Likewise, the recent Western STOMACH trial also showed no difference between laparoscopic and open gastrectomy regarding postoperative complications and 1-year survival(7).

The total €752 (3.0%) higher costs in the laparoscopic group were mainly due to higher unit costs of initial surgery due to longer operating time and higher disposable material costs. The disposable material costs were higher in the laparoscopic group, in spite of the fact that expensive laparoscopy compatible staplers were also used in two-thirds of the open group patients. These surgeons prefer the triple-row of staples and longer arm with increased maneuverability. The higher costs of initial surgery were only partly compensated by cost-savings in the laparoscopic group in admission costs. The mean total admission costs were lower in the laparoscopic group, due to shorter ICU stay and rehabilitation and nursing home stay, even though the hospital stay was longer. The longer hospital stay in the laparoscopic group was due to longer readmissions that occurred after 30 days

postoperatively, whereas the initial postoperative admission length and amount of readmissions with 30 days did not differ between treatment arms(6). The shorter mean ICU stay was mainly a result of a shorter ICU stay in the patients with anastomotic leakage in the laparoscopic group (n=10) compared to the patients with anastomotic leakage in the open group (n=11). The authors believe this is most likely due to random chance, since the anastomotic technique and leakage severity did not significantly differ between laparoscopic and open gastrectomy(6). Furthermore, rehabilitation center and nursing home costs were lower in the laparoscopic group (€1,118 versus €2,194), mainly due to one patient that stayed there for the entire 1-year follow-up period after open distal gastrectomy. Lastly, homecare and informal care costs were higher in the laparoscopic group (€1,697 versus €1,188). All other costs were similar between treatment arms.

In the prespecified total and distal laparoscopic gastrectomy subgroups, mean QALY contributions were only 0.009-0.011 lower, compared to the open subgroups (corresponding to 3-4 days in perfect health)(13). However, mean costs were €1,510 higher in the laparoscopic total subgroup and only €115 in the laparoscopic distal subgroup, compared to the open subgroups. This difference in costs is mainly due to the aforementioned patient in the open distal gastrectomy subgroup with high rehabilitation center and nursing home costs. Importantly, the bootstrapping also demonstrated in the total and distal subgroup that, compared to the uncertainty of the analysis, the differences between laparoscopic and open gastrectomy were relatively small.

Three non-randomized studies with observed patient data on costs for laparoscopic versus open gastrectomy are available, performed in the Japanese nationwide database (US$21,510 versus $21,024, p=0.002)(15), US academic medical centers database (US$40,633 versus $41,326, p=0.017)(16) and in a single Dutch center (€8,187 versus €7,673, p=0.729)(11). Unfortunately, data on QALYs were not included and details on costs were limited in the multicenter studies(15,16). Most importantly, due to the lack of randomization, these studies are likely subject to historical, hospital and selection bias.

Recently, a model-based cost-effectiveness study reported laparoscopic distal gastrectomy to be cost-effective, compared to open distal gastrectomy(17). Cost-effectiveness was contrived by combining costs from a retrospective Canadian dataset, QALYs from 2 clinical studies performed between 2000-2005 and complication probabilities from Eastern randomized trials and Western retrospective studies on laparoscopic versus open distal gastrectomy(17,29,30). Hence, it is likely more representative for early gastric cancer in the Eastern population, than for advanced cancer or the Western population(10,17). Moreover, the increased cost-effectiveness of laparoscopic distal gastrectomy in Western populations was based on a mean hospital stay reduction of 3.2 days from non-randomized retrospective studies, whereas the current trial and STOMACH trial were randomized and found no difference in hospital stay between laparoscopic and open gastrectomy(6,7).

Strengths and limitations of the clinical results of the current trial have been discussed previously(6). Further strengths of the cost-effectiveness analysis include the unprecedented level of detail in which surgical costs were calculated bottom-up and the inclusion of extramural costs such as nursing homes, home care, consultations to the GP and (work) productivity losses. An additional strength is the completeness of resource use derived from all 227 included patients in 10 hospital registries where the surgical follow-up was performed. Costs components that contributed most to total costs (surgery, hospital and ICU stay and diagnostics) were derived from these hospital registries and thus not influenced by imputed missing questionnaires. However, since surgical treatment of gastric cancer is centralized in the Netherlands, the 10 participating hospitals are tertiary referral centers and the main limitation of the current study is that costs were not available from the referring hospitals or other centers where the patients could have been treated(31). For instance, postoperative chemotherapy, follow-up by the medical oncologist and diagnostics and treatment of non-surgical complications are often performed at the referring hospital and thus not included in the current intramural costs. Thus, the current study is not able to provide a detailed comparison of postoperative chemotherapy costs. Therefore, the absolute costs of gastrectomy patients after 1-year follow-up could be an underestimation of the actual costs. Nevertheless, since the current trial was randomized, the comparison of laparoscopic versus open gastrectomy is expected to remain unaffected.

In the current study, total costs were €752 (3.0%) higher in the laparoscopic group, compared to the laparoscopic group. Bootstrapping showed that this difference was relatively small compared to the uncertainty of the analysis. The comparable cost-effectiveness between treatment arms in the current study support centers to choose, based upon their own preference, whether or not to (de)implement laparoscopic gastrectomy as an alternative to open gastrectomy.

In conclusion, this was the first cost-effectiveness analysis performed alongside a multicenter randomized trial on laparoscopic versus open gastrectomy for gastric cancer. Even though laparoscopic gastrectomy unit costs were higher, differences in both total costs and effectiveness up to 1-year postoperatively were limited between laparoscopic and open gastrectomy.

ACKNOWLEDGMENTS

The authors would like to thank each patient that participated in the current trial. In addition, the authors would like to thank ZonMW (The Netherlands Organisation for Health Research and Development) for the funding of the current trial (project number 837002502). Also, the authors would like to thank Johnson & Johnson for providing an unrestricted educational grant for the proctoring of laparoscopic gastrectomy in centers before entering the trial. ZonMW and Johnson & Johnson had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication. Furthermore, the authors would like to thank the Prospective Observational Cohort Study of Oesophageal-Gastric Cancer Patients for collecting and sharing quality of life questionnaires of 38 included patients. In addition, the authors would like to thank Roelof Oostlander and Jeroen Spruijt of University Medical Center Utrecht for their contributions to data collection. Finally, the authors would like to thank everyone who contributed to data collection and local coordination at the 10 participating hospitals, with special mentioning of Antoinette van Groenestyn (University Medical Center Utrecht); Maaike van Dam, Helma van Berkum, and Monique Heijmans (Catharina Hospital, Eindhoven); Jerôme Profar, Stan Tummers, and Kees de Mooij (Zuyderland Medical Center, Heerlen and Sittard-Geleen); Maureen de Vries and Edith Bouwmeester (Erasmus University Medical Center, Rotterdam); Graziella Kallenberg-Lantrua and Dorien Berends (Leiden University Medical Center); Ilse Masselink (ZGT Hospitals, Almelo); Damiana Beumer (Gelre Hospitals, Apeldoorn); Sander Mertens and Rob Tolboom (Meander Medical Center, Amersfoort); Marianne Kalff and Loes Noteboom (Amsterdam UMC, Location AMC); and Jennifer Straatman, Nicole van der Wielen, and Nel de Vries (Amsterdam UMC, Location VUmc).

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SUPPLEMENTARY MATERIAL

Supplementary material 1. Disposable materials

Item	Supplier
Expensive disposable	
Ligasure Maryland 5mm-37cm	Medtronic / Covidien
Ligasure Impact 36mm-18cm	Medtronic / Covidien
Harmonic ACE Laparoscopic Shears 5mm-36cm	Johnson & Johnson / Ethicon
Endo GIA Ultra Universal Stapler 12mm	Medtronic / Covidien
Endo GIA Reload 60mm*	Medtronic / Covidien
Echelon Flex Endopath Stapler 60mm	Johnson & Johnson / Ethicon
Echelon Endopath Reload 60mm*	Johnson & Johnson / Ethicon
Echelon Flex GST Powered Stapler 60mm	Johnson & Johnson / Ethicon
Echelon Endopath GST Reload 60mm*	Johnson & Johnson / Ethicon
GIA Stapler 100mm-3.8mm	Medtronic / Covidien
GIA Loading Unit 100x3.8mm	Medtronic / Covidien
Proximate Linear Cutter 55mm	Johnson & Johnson / Ethicon
Proximate Linear Cutter Reloads 55mm	Johnson & Johnson / Ethicon
EEA Circular Stapler 25mm-4.8mm XL	Medtronic / Covidien
EEA OrVil 25 mm	Medtronic / Covidien
Ethicon Circular Stapler	Johnson & Johnson / Ethicon
V-Loc Barbed Suture	Medtronic / Covidien
Stratafix Spiral PDS Plus Suture	Johnson & Johnson / Ethicon
Alexis Wound Protector/Retractor	Applied medical
Dextrus Seal Cap Assembly	Johnson & Johnson / Ethicon
Dextrus Fixed-Length Access Retractor Medium	Johnson & Johnson / Ethicon
Inexpensive laparoscopic disposable	
Versaport Optical Trocar 5mm	Medtronic / Covidien
Optical Cannula 5mm	Medtronic / Covidien
Versaport Optical Trocar 12mm	Medtronic / Covidien
Optical Cannula 12mm	Medtronic / Covidien
Trocar Blunt Tip 10mm	Medtronic / Covidien
Endo Paddle Retractor	Medtronic / Covidien
Inexpensive disposable	
Hem-o-lok Ligation Clip	Teleflex Medical
Electrosurgery Extension Blade Electrode	Medtronic / Covidien

Prices could not be made public since this information was considered confidential by the supplying companies.
*For endoscopic stapler reloads, there was limited to no difference in price between different colors and sizes.

Supplementary material 2 – laparoscopic equipment costs calculation

Laparoscopic equipment purchasing costs were €56,255.00 (Supplementary material 4), as obtained by the purchase department of one of the participating hospitals. By dividing these costs by the product lifespan, purchasing costs per year were calculated to be €6,745.50. Based upon standard hospital policy, yearly maintenance costs are 15% of purchasing costs for the laparoscope and camera head and 7% of purchasing costs for the other equipment, resulting in yearly maintenance costs of €5,521.58. Hence yearly costs to provide one operation room with laparoscopic equipment (including purchase costs, depreciation and maintenance) were €12,267. A year was assumed to contain 240 business days, of which the laparoscopic equipment was assumed to be used on 120 business days (either for laparoscopic gastrectomy or other laparoscopic surgery). Furthermore, a laparoscopic gastrectomy was assumed to take half a business day. Hence, costs per laparoscopic gastrectomy were estimated to be (€12,267 / 120 days) * 0.5 day = €51.11.

Supplementary material 3. Laparoscopic equipment costs per laparoscopic gastrectomy

Product	Purchase costs	Product lifespan, years	Purchasing costs per year (depreciation included)	Yearly costs for maintenance	Yearly costs (maintenance and depreciation included)	Costs per business day	Costs per gastrectomy
Laparoscope	€ 12,266.00	10	€ 1,226.60	€ 1,839.90	€ 3,066.50	€ 25.55	€ 12.78
Camera head	€ 5,100.00	10	€ 510.00	€ 765.00	€ 1,275.00	€ 10.63	€ 5.31
Light source	€ 6,460.00	10	€ 646.00	€ 484.50	€ 1,130.50	€ 9.42	€ 4.71
Video processor	€ 9,075.00	10	€ 907.50	€ 680.63	€ 1,588.13	€ 13.23	€ 6.62
Insufflator	€ 5,339.00	10	€ 533.90	€ 400.43	€ 934.33	€ 7.79	€ 3.89
Trolley	€ 2,532.00	10	€ 253.20	€ 189.90	€ 443.10	€ 3.69	€ 1.85
Two monitors	€ 11,200.00	5	€ 2,240.00	€ 840.00	€ 3,080.00	€ 25.67	€ 12.83
Monitor suspension system	€ 4,283.00	10	€ 428.30	€ 321.23	€ 749.53	€ 6.25	€ 3.12
	€ 56,255.00		€ 6,745.50	€ 5,521.58	€ 12,267.08	€ 102.23	€ 51.11

Supplementary material 4. Type of anastomosis

n (%)	Laparoscopic gastrectomy 115		Open gastrectomy 110		p	
Type of operation					0.394	*
Total gastrectomy	48	(41.7)	43	(39.1)		
Distal gastrectomy	59	(51.3)	64	(58.2)		
Esophagogastric resection	1	(0.9)	0	(0.0)		
No resection	7	(6.1)	3	(2.7)		
n (%)	**Laparoscopic total gastrectomy 48**		**Open total gastrectomy 43**		**p**	
Type of anastomosis[1]					1.000	*
Circular stapled	31	(27.0)	28	(25.5)		
Linear stapled	14	(12.2)	13	(11.8)		
Hand sewn	3	(2.6)	2	(1.8)		
Anastomotic leakage	10	(20.8)	8	(18.6)	0.998	
Circular stapled, expensive disposable material costs, mean €	2140		1676[2]			
Linear stapled, expensive disposable material costs, mean €	1195		1001			
n (%)	**Laparoscopic distal gastrectomy 59**		**Open distal gastrectomy 64**		**p**	
Type of anastomosis[1]					0.002	*
Circular stapled	1	(0.9)	1	(0.9)		
Linear stapled	57	(49.6)	51	(46.4)		
Hand sewn	1	(0.9)	12	(10.9)		
Anastomotic leakage	0	(0.0)	3	(4.7)	0.245	*
Linear stapled, expensive disposable material costs, mean €	1591		1284			
Hand sewn, expensive disposable material costs, mean €	-		-	667[3]		

Disposable material costs are calculated for groups with n>5 only. *Fisher's exact test. [1]The esophagojejunostomy or gastrojejunostomy. [2]Circular stapler costs for the esophagojejunostomy were similar between the laparoscopic and open group, but wound protecting retractor port costs for the resection specimen and linear stapler costs for the rest of the procedure were higher in the laparoscopic group. [3]Hand sewn anastomoses were performed in hospitals that used exclusively non-laparoscopic compatible staplers in open surgery (i.e. for cutting the stomach), which further reduced its costs.

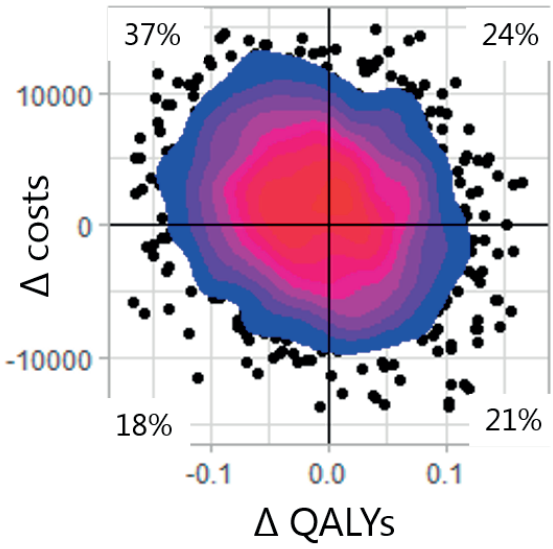
Supplementary material 5 – details on stapler usage

Of the patients in the open group in whom an anastomosis was performed (n=107), expensive laparoscopic compatible staplers were used almost exclusively in 67 patients (63%), scarcely in 22 patients (21%) and never in 18 patients (17%).

Supplementary material 6. Subgroup analyses on patients with total resection

		Laparascopic gastrectomy (n= 48)			Open gastrectomy (n= 43)		
		COSTS					
	Type of procedure	Number of individuals with procedure	Mean number of procedures	Mean costs	Number of individuals with procedure	Mean number of procedures	Mean costs
SURGERY	Initial surgery	48	1,0	€ 8.124	43	1,0	€ 6.584
	Reoperation	11	0,1	€ 380	17	0,2	€ 457
ADMISSIONS	Hospital stay	48	18,1	€ 10.702	43	15,5	€ 9.015
	ICU stay	11	1,5	€ 3.736	10	2,4	€ 5.633
	Rehabilition centre or nursing home	5	2,8	€ 1.081	2	2,1	€ 810
CARE	Home care / informal care	34	74,6	€ 1.716	23	53,2	€ 1.223
DIAGNOSTICS	Endoscopy	25	1,1	€ 209	16	1,0	€ 226
	Imaging	40	6,0	€ 847	37	6,6	€ 1.092
	Lab	25	292,4	€ 2.198	16	264,6	€ 2.203
	Other	27	3,4	€ 231	22	2,3	€ 134
CONSULTATIONS	Out patient visits	45	29,8	€ 2.106	41	34,6	€ 2.383
	General practitioner	45	8,4	€ 277	38	5,6	€ 183
CHEMOTHERAPY		0	-	€ 362	0	-	€ 491
WORK ABSENCE		13		€ 180	14		€ 145
OTHER		34	13,9	€ 148	23	14,0	€ 208
TOTAL				€ 32.297			€ 30.787
		QALYs					
	Baseline EQ5D	0,850			0,808		
	QALYs over 1 year*	0,617			0,626		

Number of procedures and costs of patients receiving either laparoscopic or open gastrectomy during one year follow-up, subdivided in surgery costs, admission costs, care
costs, costs for diagnostics, consultations, work absence and other costs and the baseline EQ5D value and quality adjusted life years (QALYs) over one year. Of note, different procedures have different costs, hence the mean number of procedures is not linearly related to mean costs.
*QALYs over 1 year are adjusted for baseline QALYs and hospital.

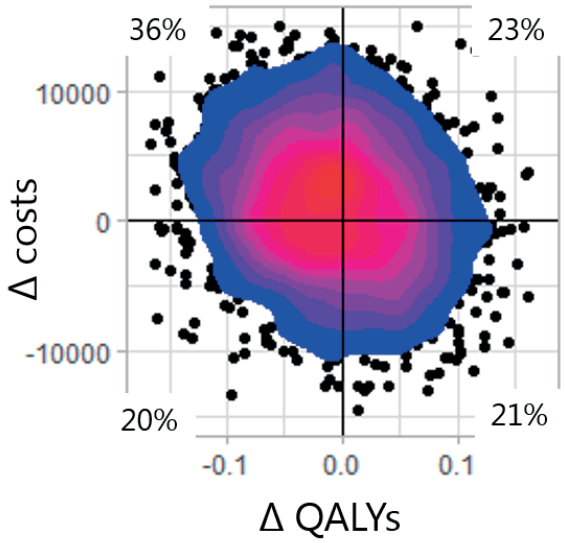


Supplementary material 7. Subgroup analyses on patients with total gastrectomy. Costs and QALYs gained of the laparoscopic total gastrectomy subgroup, compared to open total gastrectomy subgroup for 2000 bootstrap iterations displayed in a cost-effectiveness plane. Of all bootstrap iterations, 21% were in the bottom right quadrant (lower costs and higher effectiveness for the laparoscopic total subgroup), 24% in the upper right quadrant (higher costs and higher effectiveness), 18% in the bottom left quadrant (lower costs and lower effectiveness) and 37% in the upper left quadrant (higher costs and lower effectiveness). QALY = quality-adjusted-life-year.

Supplementary material 8. Subgroup analyses on patients with distal resection

		Laparascopic gastrectomy (n= 59)			Open gastrectomy (n= 64)		
		COSTS					
	Type of procedure	Number of individuals with procedure	Mean number of procedures	Mean costs	Number of individuals with procedure	Mean number of procedures	Mean costs
SURGERY	Initial surgery	59	1,0	€ 7.353	64	1,0	€ 5.893
	Reoperation		0,1	€ 309		0,2	€ 233
ADMISSIONS	Hospital stay	59	12,7	€ 7.306	64	12,1	€ 6.954
	ICU stay	5	0,2	€ 420	8	0,5	€ 1.306
	Rehabilition centre or nursing home	4	1,6	€ 439	10	9,8	€ 2.719
CARE	Home care / informal care	33	71,5	€ 1.645	37	47,7	€ 1.097
DIAGNOSTICS	Endoscopy	14	0,4	€ 67	10	0,2	€ 55
	Imaging	35	2,5	€ 327	36	2,3	€ 236
	Lab	14	126,1	€ 1.487	10	137,0	€ 1.519
	Other	20	1,1	€ 66	20	1,2	€ 67
CONSULTATIONS	Out patient visits	56	19,6	€ 1.531	64	17,6	€ 1.324
	General practitioner	52	5,3	€ 175	52	4,0	€ 131
CHEMOTHERAPY		0	-	€ 591	0	-	€ 81
WORK ABSENCE		14		€ 132	13		€ 211
OTHER		33	15,9	€ 150	37	8,0	€ 56
TOTAL				€ 21.999			€ 21.884
		QALYs					
	Baseline EQ5D	0,792			0,843		
	QALYs over 1 year*	0,750			0,761		

Number of procedures and costs of patients receiving either laparoscopic or open gastrectomy during one year follow-up, subdivided in surgery costs, admission costs, care costs, costs for diagnostics, consultations, work absence and other costs and the baseline EQ5D value and quality adjusted life years (QALYs) over one year. Of note, different procedures have different costs, hence the mean number of procedures is not linearly related to mean costs.
*QALYs over 1 year are adjusted for baseline QALYs and hospital.



Supplementary material 9. Subgroup analyses on patients with distal gastrectomy. Costs and QALYs gained of the laparoscopic distal gastrectomy subgroup, compared to the open distal gastrectomy subgroup for 2000 bootstrap iterations displayed in a cost-effectiveness plane. Of all bootstrap iterations, 21% were in the bottom right quadrant (lower costs and higher effectiveness for the laparoscopic distal gastrectomy subgroup), 23% in the upper right quadrant (higher costs and higher effectiveness), 20% in the bottom left quadrant (lower costs and lower effectiveness) and 36% in the upper left quadrant (higher costs and lower effectiveness). QALY = quality-adjusted-life-year.


Prospective

CHAPTER 5

Body composition is a predictor for postoperative complications after gastrectomy for gastric cancer; a prospective side-study of the LOGICA-trial

Journal of Gastrointestinal Surgery 2022

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ABSTRACT

Purpose

There is a lack of prospective studies evaluating the effects of body composition on postoperative complications after gastrectomy in a Western population with predominantly advanced gastric cancer.

Methods

This is a prospective side-study of the LOGICA-trial, a multicenter randomized trial on laparoscopic versus open gastrectomy for gastric cancer. Trial patients who received preoperative chemotherapy followed by gastrectomy with an available preoperative restaging abdominal CT-scan were included. The CT-scan was used to calculate the mass (M) and radiation attenuation (RA) of skeletal muscle (SM), visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT). These variables were expressed as Z-scores, depicting how many standard deviations each patient's CT-value differs from the sex-specific study sample mean. Primary outcome was the association of each Z-score with the occurrence of a major postoperative complication (Clavien-Dindo grade ≥3b).

Results

From 2015-2018, a total of 112 patients were included. A major postoperative complication occurred in 9 patients (8%). A high SM-M Z-score was associated with a lower risk of major postoperative complications (RR 0.47, 95% CI 0.28-0.78, p=0.004). Furthermore, high VAT-RA Z-scores and SAT-RA Z-scores were associated with a higher risk of major postoperative complications (RR 2.82, 95% CI 1.52-5.23, p=0.001 and RR 1.95, 95% CI 1.14-3.34, p=0.015, respectively). VAT-M, SAT-M and SM-RA Z-scores showed no significant associations.

Conclusion

Preoperative low skeletal muscle mass and high visceral and subcutaneous adipose tissue radiation attenuation (indicating fat depleted of triglycerides) were associated with a higher risk of developing a major postoperative complication in patients treated with preoperative chemotherapy followed by gastrectomy.

INTRODUCTION

Gastric cancer is the sixth most prevalent cancer and the third most common cause of cancer related death worldwide [1]. Perioperative chemotherapy followed by gastrectomy is the treatment of choice in the Western population [2]. Approximately 42% of all gastric cancer patients who undergo surgical resection develop a postoperative complication and 21% a major postoperative complication (Clavien-Dindo grade III or higher) [3, 4].

Clinically, accurate prediction of major postoperative complication may help in the choice to refrain from surgery in very fragile patients or to improve the patient's health status preoperatively. Several risk factors for a higher risk of postoperative complications and mortality have been identified (age, malnutrition, anemia, smoking, total gastrectomy). Yet, these factors do not fully explain the observed wide variation in postoperative complications after gastrectomy [5, 6].

Recently, sarcopenia and other body composition parameters such as myosteatosis (lipid infiltration in skeletal muscle) have been identified as independent risk factors for postoperative complications [7-9]. Sarcopenia is defined as a progressive loss of skeletal muscle strength in the presence of low skeletal muscle mass or skeletal muscle quality [10-15]. An example of reduced muscle quality is myosteatosis which is associated with reduced physical fitness [16]. For both lower- and upper gastrointestinal surgery, previous studies have demonstrated that sarcopenia, myosteatosis and other body composition parameters are associated with a worse postoperative outcome [13, 17-19]. For gastric cancer surgery, a recent meta-analysis including mostly Eastern studies showed that the odds of developing major postoperative complications and overall mortality were higher in patients with a low muscle mass [9]. However, most the studies included in this meta-analysis were retrospective and used a wide variety of sarcopenia cut-off points. Furthermore, Western and Eastern gastric cancer population have important differences, impeding generalizability of Eastern studies on the Western population [20]. Hence, there is a need for more prospective Western studies.

The aim of the current study was to evaluate body composition as predictor for postoperative complications in patients with gastric cancer treated with preoperative chemotherapy and gastrectomy.

MATERIALS & METHODS

Study design

This is a multicenter, prospective, observational cohort side-study of patients included in the Laparoscopic versus open gastrectomy for gastric cancer (LOGICA) trial [21]. The current side-study was initiated in 2015 together with the LOGICA-trial. The LOGICA-trial

evaluated surgical and oncological outcomes between laparoscopic and open gastric surgery for gastric cancer. The results of the main trial were previously published [21]. The current side-study was conducted in compliance with the Dutch law and in accordance with the principles of the declaration of Helsinki. Written informed consent was obtained from all participating patients for inclusion in the LOGICA-trial. The abdominal computed tomography (CT) scans of all LOGICA-trial participants were pseudonymised and used for body composition analysis, as was approved by the Dutch Ethical Committee of Utrecht (medisch-ethische toetsingscommissie).

Procedures

Clinical staging included gastroesophagoscopy with biopsy and a CT-scan of the thorax and abdomen. All patients were discussed in a multidisciplinary tumor board meeting prior to treatment. Perioperative chemotherapy was recommended in all eligible patients with advanced tumors (cT3-4N0-3 or cT1-2N1-3). For each individual patient who underwent preoperative chemotherapy, the multidisciplinary tumor board of each individual hospital determined whether a restaging CT-scan was made during the last courses of chemotherapy or after completion of chemotherapy. A restaging CT-scan was thus not obligatory, as is in line with standard of care in the Netherlands.

In the LOGICA-trial, patients were randomized in a 1:1 ratio between laparoscopic and open surgery [21]. Surgical procedures included total or distal gastrectomy with total omentectomy and D2 lymphadenectomy, as previously described [21]. Postoperative treatment protocols were in accordance with to the guidelines for Enhanced Recovery After Surgery (ERAS) [22]. Multiple quality control measures were included in the LOGICA-trial, as previously described [21].

Patients and data collection

Patients included in the LOGICA-trial were eligible for this study and therefore met the same inclusion criteria set for the trial [21]. Both study arms (laparoscopic- and open gastrectomy) were included. The primary analysis included the patients who underwent preoperative chemotherapy followed by a D2 gastrectomy. As this was a observational prospective side-study, a restaging CT-scan was not obligatory and only patients with a restaging CT-scan were included. Subgroup analyses were performed in patients who underwent primary surgery, by using he CT-scan closest to the operation date (but within 6 months prior to the operation data). The distinction between the primary surgery group and preoperative chemotherapy group was made, since the primary surgery group was expected to consist of a more heterogeneous cohort of patients in worse clinical condition and with different preoperative body composition, compared to the preoperative chemotherapy group.

For the purpose of the current prospective side-study, the patients included in the LOGICA-trial completed the Short Nutritional Assessment Questionnaire (SNAQ) [23] and Groningen Frailty Index (GFI) questionnaire [24] one week prior to gastrectomy. Higher questionnaire scores indicate more malnutrition or more frailty, respectively.

Body composition analysis

For each abdominal CT-scan a single transverse slice at the level of the third lumbar vertebra (L3) was extracted by a single researcher trained in body composition analysis (TT). Total cross-sectional surface area (cm^2) measurements of skeletal muscle tissue (SM), visceral adipose tissue (VAT), and subcutaneous adipose tissue (SAT) were performed using Slice-O-Matic 5.0® software using predefined Hounsfield unit (HU) ranges (-29 to 150 HU, -150 to -50 HU, and -190 to -30 HU respectively) [13, 25, 26]. Total cross-sectional surface area (cm^2) of SM, VAT and SAT was corrected for patient height to calculate the L3-index (cm^2/m^2). This parameter will be referred to as the mass (M) of these 3 tissues: SM-M, VAT-M and SAT-M (Table 2).

Additionally, these 3 tissues were assessed for radiation attenuation (RA). RA indicates how much radiation is absorbed in the body tissues (expressed in HU) during the diagnostic CT-scan. The remaining radiation passes through the body and produces a grayscale image on CT. The RA of fat lies between -190 to -30 HU; the RA of water is per definition 0 HU and the RA of muscle lies between -29 to 150 HU. Hence, a decreased RA in fat could be indicative of better nutritional status (higher triglyceride concentration, lower water concentration), whereas a decreased RA in muscle could be indicative of worse muscle quality due to myosteatosis (higher triglyceride concentration) or muscle edema (higher water concentration) [25, 27-31]. The RA of the 3 tissues will be referred to as: SM-RA, VAT-RA and SAT-RA (Table 2).

Z-score

In an effort to correct for the effects of sex and standardize the scores, SM-M, VAT-M, SAT-M, SM-RA, VAT-RA and SAT-RA were expressed as Z-scores. The Z-score depicts how each patient's standard deviation differs from the mean value of patients of the same sex [32]. It is calculated by taking the measured value of each patient and subtracting the sex-specific mean and thereafter dividing by the sex-specific standard deviation.

Outcome measurements

The primary outcome was the association of the 6 body composition Z-scores (SM-M, VAT-M, SAT-M, SM-RA, VAT-RA and SAT-RA) with the occurrence of a major postoperative complication. Secondary outcomes were the association of the SNAQ score [23] and GFI [24] with the occurrence of a major postoperative complication. Postoperative

complications were defined according to the Esophagectomy Complications Consensus Group (ECCG) definitions and scored according to the Clavien-Dindo Classification, as previously described [21, 33, 34]. A major postoperative complication was defined as a Clavien-Dindo grade ≥ 3b complication.

Statistical analysis

Statistical analysis was performed using R statistical computing version 3.6.1 (R Foundation for Statistical Computing, Vienna, Austria). As previously described, the primary analysis included patients who underwent preoperative chemotherapy followed by gastrectomy. Subgroup analyses included patients who underwent primary surgery. The Z-scores of the body composition parameters were used, as previously described. Gaussian distributed continuous data are presented as means with standard deviations and non-Gaussian distributed continuous data as medians with interquartile ranges. Univariable and multivariable Poisson regression with robust error variances were performed for the binary outcome major postoperative complication yes/no, producing relative risks according to the methods by Zou et al [35, 36]. The 6 body composition Z-scores (SM-M, VAT-M, SAT-M, SM-RA, VAT-RA and SAT-RA), SNAQ score and GFI were each tested in a separate multivariable model without correction from the other 6 body composition Z-scores, SNAQ score and GFI. Relevant baseline and treatment characteristics were first tested univariably and added to the multivariable models only if the *p*-value was 0.200 or smaller. This was done to prevent over-fitting of the models.

RESULTS

Patient characteristics

From February 2015 to August 2018, 227 patients were included in the LOGICA-trial in the 10 participating hospitals. A total of 164 patients received preoperative chemotherapy and 63 patients received primary surgery (Figure 1).

Of the 164 patients in the preoperative chemotherapy group, 6 patients received a laparoscopy without resection and 1 patient received an esophagogastric resection with cervical esophagostomy [21]. The remaining 157 patients were potentially eligible for inclusion in the primary analysis. A total of 6 patients (4%) were excluded because one hospital chose not to partake in the current side-study and 39 patients (25%) were excluded because no restaging CT-scan was available. The remaining 112 patients (71%) were included in the primary analysis.

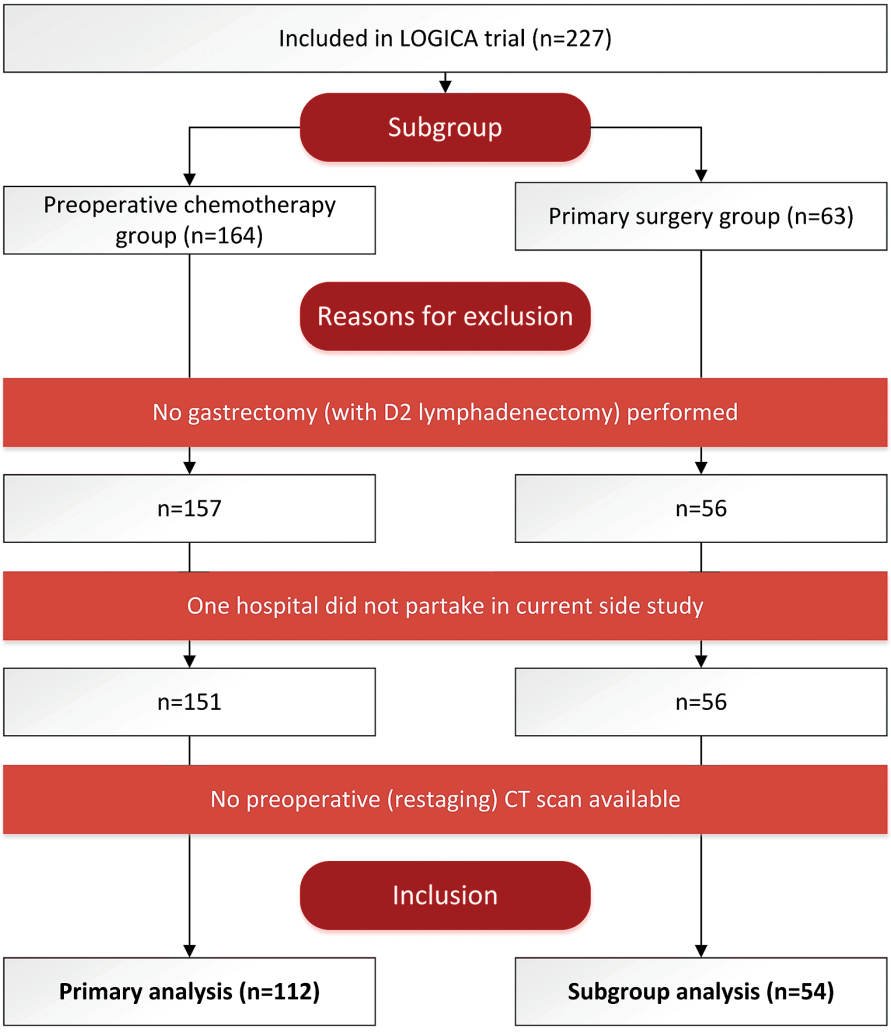

Figure 1. Study flow

Of the 63 patients in the primary surgery group, 4 patients received a laparoscopy or laparotomy without resection, 1 patient received a distal gastrectomy with D1 lymphadenectomy and 2 patients did not proceed to surgery [21]. The remaining 56 were potentially eligible for inclusion in the subgroup analysis. After exclusion of 2 patients (4%) without available CT-scans, the remaining 54 patients were included in the subgroup analysis.

Patient characteristics at baseline, body composition parameters, treatment characteristics and outcomes are described in Table 1. In the preoperative chemotherapy group, preoperative chemotherapy was completed in 89 patients (79%), stopped prematurely in 21 patients (19%) and data on completion were missing in two patients (2%). Total gastrectomy was performed in 50 patients (45%) and distal gastrectomy in 62 patients (55%). A grade ≥3b postoperative complication occurred in 9 patients (8%). The excluded 33 patients without a restaging CT-scan had similar patient characteristics, treatment and outcome as the included 112 patients (Supplementary material 1).

Table 1. Patient characteristics, treatment and outcomes

n (%)	**Preoperative chemotherapy 112**		**Primary surgery 54**	
Male sex	73	(65.2)	32	(59.3)
Age, years (mean (SD))	65.6	(9.6)	74.7	(8.3)
BMI, kg/m^2 (median [IQR])	25.7	[23.2, 29.0]	25.4	[22.1, 28.1]
ASA score				
1	14	(12.5)	3	(5.6)
2	73	(65.2)	36	(66.7)
3	25	(22.3)	15	(27.8)
Cardiovascular comorbidity	55	(49.1)	38	(70.4)
Pulmonary comorbidity	23	(20.5)	12	(22.2)
Location of tumor				
Proximal stomach	14	(12.5)	3	(5.6)
Middle stomach	31	(27.7)	20	(37.0)
Distal stomach	67	(59.8)	31	(57.4)
cT-stage				
cT1	5	(4.5)	8	(14.8)
cT2	29	(25.9)	20	(37.0)
cT3	67	(59.8)	23	(42.6)
cT4	11	(9.8)	3	(5.6)
cN1-3	51	(45.5)	22	(40.7)
Advanced cancer[1]	88	(78.6)	32	(59.3)
SNAQ score (mean (SD))	2	(2.1)	2.3	(2.5)
Missing	38	(34.9)	15	(27.8)
GFI (mean (SD))	2.9	(2.3)	2.9	(2.3)
Missing	26	(23.2)	11	(20.4)
SM, cm^2/m^2 (mean (SD))	44.8	(8.1)	42.8	(8.0)
VAT, cm^2/m^2 (mean (SD))	51.9	(32.3)	57.5	(36.8)
SAT, cm^2/m^2 (mean (SD))	63.8	(33.4)	58.6	(31.1)
SM-RA, HU (mean (SD))	36.7	(10.7)	32.0	(8.0)
VAT-RA, HU (mean (SD))	-90.5	(7.8)	-89.9	(8.8)
SAT-RA, HU (mean (SD))	-96.1	(8.9)	-92.5	(9.7)

Table 1. Continued

n (%)	Preoperative chemotherapy 112		Primary surgery 54	
Preoperative chemotherapy				
ECC or equivalent	84	(75.0)	n/a	
FLOT	19	(17.0)	n/a	
Other	9	(8.0)	n/a	
Preoperative chemotherapy completed (>80% of courses)				
Yes	89	(79.5)	n/a	
No	21	(18.8)	n/a	
Missing	2	(1.8)	n/a	
Type of operation				
Total gastrectomy	50	(44.6)	18	(33.3)
Distal gastrectomy	62	(55.4)	36	(66.7)
Laparoscopic gastrectomy	53	(47.3)	34	(63.0)
Complication	38	(33.9)	31	(57.4)
CDC of most severe complication				
1	8	(7.1)	2	(3.7)
2	16	(14.3)	12	(22.2)
3a	5	(4.5)	3	(5.6)
3b	2	(1.8)	3	(5.6)
4a	4	(3.6)	2	(3.7)
4b	0	(0.0)	1	(1.9)
5	3	(2.7)	8	(14.8)
Anastomotic leakage	8	(7.1)	8	(14.8)
Anastomotic leakage grade (ECCG)				
I	2	(1.8)	1	(1.9)
II	1	(0.9)	0	(0.0)
III	5	(4.5)	7	(13.0)
Adjuvant chemotherapy started	59	(52.7)	1	(1.9)
1-year all-cause mortality	20	(17.9)	16	(29.6)

IQR = interquartile range; SD = standard deviation; ASA = American Society of Anaesthesiologists; SM = skeletal muscle; SAT = subcutaneous adipose tissue; VAT = visceral adipose tissue; RA = radiation attenuation; HU = Hounsfield units; SNAQ = Short Nutritional Assessment Questionnaire; GFI = Groningen Frailty Index. ECC = Epirubicin + Cisplatin + Capecitabine; FLOT = Fluorouracil + Leucovorin + Oxaliplatin + Docetaxel; CDC = Clavien-Dindo Classification; ECCG = Esophagectomy Complications Consensus Group. [1]Defined as cT3-4N0 or cT1-2N+.

In the primary surgery group, total gastrectomy was performed in 18 patients (33%) and distal gastrectomy in 36 patients (67%). A grade ≥3b postoperative complication occurred in 14 patients (26%).

Table 2. Variables and abbreviations

Variable	Abbreviation
Skeletal muscle	SM
Visceral adipose tissue	VAT
Subcutaneous adipose tissue	SAT
Mass	-M
Mass indicates the amount of the assessed tissue, corrected for the patient's height. Higher scores indicate a higher volume of tissue.	
Radiation attenuation	-RA
Radiation attenuation indicates how much radiation is absorbed in tissues upon making a CT-scan (expressed in Hounsfield units). Higher values indicate lower triglyceride concentration. For muscle, this indicates worse tissue quality. For fat, this indicates better nutritional reserves.	
Short Nutritional Assessment Questionnaire	SNAQ
Higher scores indicate more malnutrition	
Groningen Frailty Index	GFI
Higher scores indicate more frailty	

CT-scan timing

The CT-scan timing is displayed in Figure 2. For the preoperative chemotherapy group, median time from start of preoperative chemotherapy to restaging CT-scan was 56 days [IQR 42-63]. Median time from restaging CT-scan to surgery was 37 days [IQR 31-55]. For the primary surgery group, median time from CT-scan to surgery was 39 days [IQR 28-56].

Primary analyses – preoperative chemotherapy group

Tissue mass

In the preoperative chemotherapy group, a high SM-M Z-score (more muscle) was significantly associated with a lower risk of a grade ≥3b postoperative complication in univariable (RR 0.48, 95% CI 0.30-0.77, p=0.002) and multivariable analyses (RR 0.47, 95% CI 0.28-0.78, p=0.004) (Table 3a, Figure 3).

A high VAT-M Z-score (more visceral fat) showed a trend towards being associated with a lower risk of a grade ≥3b postoperative complication in univariable (RR 0.47, 95% CI 0.16-1.36, p=0.164) and multivariable analyses (RR 0.44, 95% CI 0.14-1.40, p=0.166), but did not reach statistical significance (Table 3a).

Likewise, a high SAT-M Z-score (more subcutaneous fat) showed a trend towards being associated with a lower risk of a grade ≥3b postoperative complication in univariable (RR 0.64, 95% CI 0.37-1.10, p=0.105) and multivariable analyses (RR 0.61, 95% CI 0.35-1.08, p=0.088), but did not reach statistical significance (Table 3a).

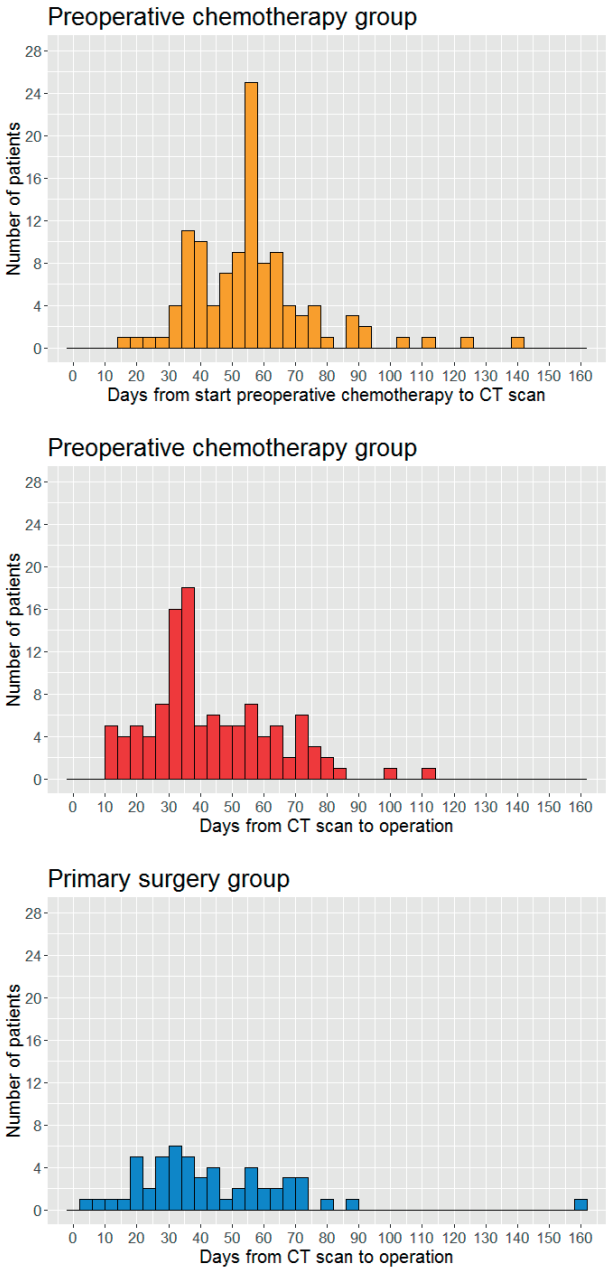

Figure 2. Histograms showing the timing of the CT scans.
*The primary surgery group has one outlier at 160 days. This patient underwent a staging CT scan, followed by an endoscopic submucosal dissection for early stage gastric cancer. Pathological analysis showed dubious radicality and angioinvasion, which prompted extensive cardiac screening of the patient due to comorbidity, followed by distal gastrectomy. This patient did not suffer a severe postoperative complication and was discharged in good clinical condition 10 days after surgery.

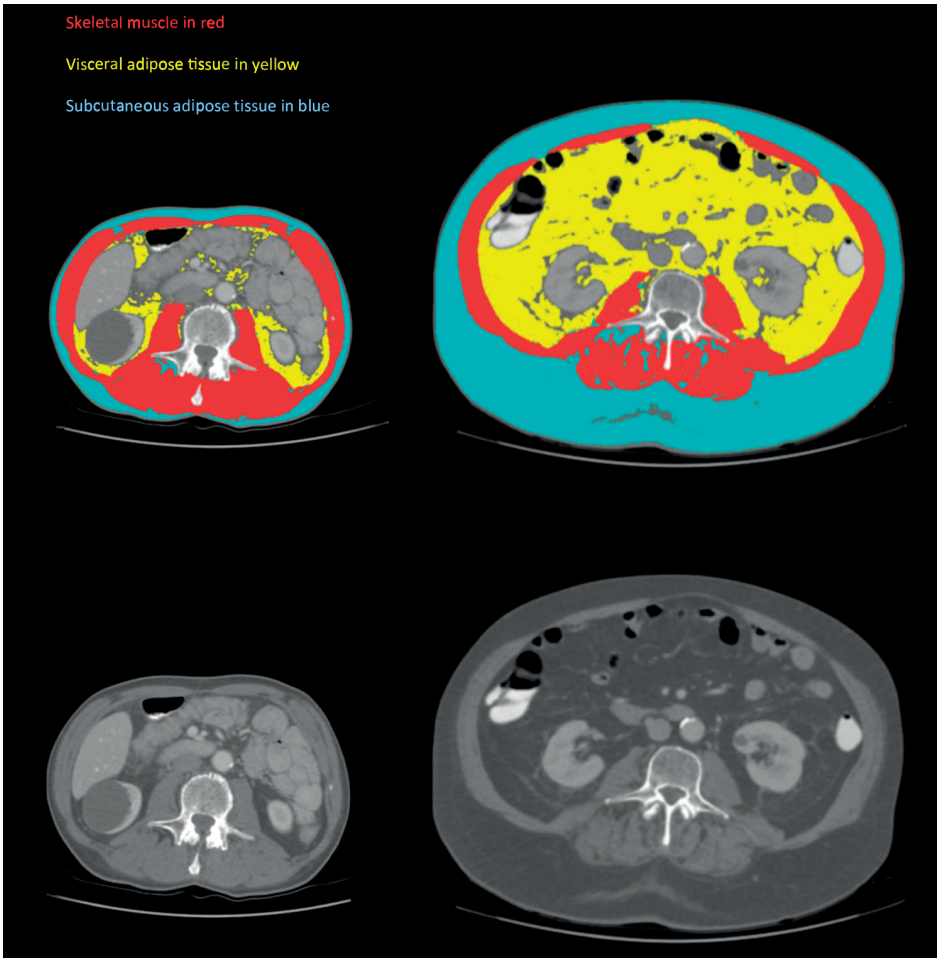

Figure 3. Example CT scans. In the top 2 scans SM, VAT and SAT are delineated in red, yellow and blue, respectively. The bottom 2 scans are the same scans without delineations. On the left a patient is displayed with low Z-scores for VAT-M/SAT-M (low amount of fat) and high Z-scores for VAT-RA/SAT-RA (lighter shade of grey, indicative of low triglyceride concentration) On the right a patient is displayed with high Z-scores for VAT-M/SAT-M (high amount of fat) and low Z-scores for VAT-RA/SAT-RA (darker shade of grey, indicative of high triglyceride concentration). The body composition of the patient on the left is associated with a higher rate of severe postoperative complications.

Radiation attenuation

In the preoperative chemotherapy group, a high SM-RA Z-score (good muscle quality) was not associated with a lower risk of a grade ≥3b postoperative complication in univariable (RR 0.95, 95% CI 0.61-1.48, p=0.821) and multivariable analyses (RR 0.95, 95% CI 0.58-1.55, p=0.825) (Table 3a).

In contrast, a high VAT-RA Z-score (visceral fat depleted of triglycerides) was associated with a higher risk of a grade ≥3b postoperative complication in both univariable (RR 2.62, 95% CI 1.39-4.94, *p*=0.003) and multivariable analyses (RR 2.82, 95% CI 1.52-5.23, *p*=0.001) (Table 3a).

Likewise, a high SAT-RA Z-score (subcutaneous fat depleted of triglycerides) was associated with a higher risk of a grade ≥3b postoperative complication in both univariable (RR 2.00, 95% CI 1.13-3.53, *p*=0.017) and multivariable analyses (RR 1.95, 95% CI 1.14-3.34, *p*=0.015) (Table 3a).

SNAQ and GFI

In the preoperative chemotherapy group, a high SNAQ score (more malnutrition) was not associated with an increased risk of a grade ≥3b postoperative complication in both univariable (RR 0.99, 95% CI 0.70-1.42, *p*=0.971*)* and multivariable analyses (RR 1.07, 95% CI 0.79-1.44, *p*=0.684*)* (Table 3a). Likewise, a high GFI (more frailty) showed a trend towards being associated with a lower risk of a grade ≥3b postoperative complication in univariable (RR 0.76, 95% CI 0.52-1.11, *p*=0.157*)* and multivariable analyses (RR 0.78, 95% CI 0.56-1.10, *p*=0.156*)*, but did not reach statistical significance (Table 3a).

Total versus distal gastrectomy

In the preoperative chemotherapy group, distal gastrectomy showed a trend towards being associated with a lower risk of a grade ≥3b postoperative complication in univariable analysis (RR 0.40, 95% CI 0.11-1.53, *p*=0.182). Hence, in multivariable analyses, each CT body composition parameter, the SNAQ score and GFI were adjusted for whether a total or distal gastrectomy was performed (table 3a).

Subgroup analysis - primary surgery group

Tissue mass

In the primary surgery group, a high SM-M Z-score (more muscle) was significantly associated with an increased risk of a grade ≥3b postoperative complication in univariable (RR 1.47, 95% CI 1.22-1.77, *p*<0.001) and multivariable analyses (RR 1.58, 95% CI 1.28-1.94, *p*<0.001) (Table 3b).

VAT-M and SAT-M (amount of fat) were not significantly associated with the occurrence of a grade ≥3b postoperative complication (Table 3b).

Radiation attenuation

In the primary surgery group, SM-RA, VAT-RA and SAT-RA (quality of muscle or fat) were not significantly associated with the occurrence of a grade ≥3b postoperative complication (Table 3b).

Table 3a. Preoperative chemotherapy group

Relative risks of having a postoperative grade ≥3b complication						
	Preoperative chemotherapy group					
	Univariable			**Multivariable**		
	RR	**[95% CI]**	*p*	**RR**	**[95% CI]**	*p*
SM-M Z-score	0.48	[0.30-0.77]	**0.002**	0.47	[0.28-0.78]	**0.004** *
VAT-M Z-score	0.47	[0.16-1.36]	0.164	0.44	[0.14-1.40]	0.166 *
SAT-M Z-score	0.64	[0.37-1.10]	0.105	0.61	[0.35-1.08]	0.088 *
SM-RA Z-score	0.95	[0.61-1.48]	0.821	0.95	[0.58-1.55]	0.825 *
VAT-RA Z-score	2.62	[1.39-4.94]	**0.003**	2.82	[1.52-5.23]	**0.001** *
SAT-RA Z-score	2.00	[1.13-3.53]	**0.017**	1.95	[1.14-3.34]	**0.015** *
SNAQ score	0.99	[0.70-1.42]	0.971	1.07	[0.79-1.44]	0.684 *
GFI	0.76	[0.52-1.11]	0.157	0.78	[0.56-1.10]	0.156 *
Additional year of age	1.00	[0.95-1.05]	0.980			
ASA score						
1 or 2	Ref	-	-			
3	0.99	[0.22-4.5]	0.994			
cT stage						
T1-2	Ref	-	-			
T3-4	1.53	[0.33-7.0]	0.586			
cN stage						
cN0	Ref	-	-			
cN1-3	0.96	[0.27-3.38]	0.945			
Distal gastrectomy	0.40	[0.11-1.53]	0.182	0.40	[0.10-1.58]	0.191 **
Laparoscopic surgery	0.89	[0.25-3.14]	0.857			

Poisson regressions with robust error variances were performed, producing a relative risk of having a postoperative grade ≥3b complication (yes/no) for each of the CT body composition parameters. Bold values indicate significance ($p < 0.05$). RR = relative risk; CI = confidence interval and ref = reference; SM = skeletal muscle; VAT = visceral adipose tissue; SAT = subcutaneous adipose tissue; M = mass; RA = radiation attenuation; SNAQ = Short Nutritional Assessment Questionnaire; GFI = Groningen Frailty Index. *In multivariable analyses, each CT body composition parameter, the SNAQ score and GFI were adjusted only for whether a total or distal gastrectomy was performed. ** The displayed values for the variable distal gastrectomy are from the multivariable analysis in which SM-M Z-score and distal gastrectomy were included only. The values for the variable distal gastrectomy in the multivariable analyses of the remaining 5 CT body composition parameters, SNAQ score and GFI were comparable (data not shown).

SNAQ and GFI

In the primary surgery group, a high SNAQ score (more malnutrition) was not associated with an increased risk of a grade ≥3b postoperative complication in univariable and multivariable analyses (Table 3b). However, a high GFI (more frailty) was significantly associated with an increased risk of a grade ≥3b postoperative complication in univariable (RR per extra point 1.30, 95% CI 1.17-1.45, $p<0.001$) and multivariable analyses (RR per extra point 1.30, 95% CI 1.16-1.45, $p<0.001$) (Table 3b).

Table 3b. Primary surgery group

Relative risks of having a postoperative grade ≥3b complication							
	Primary surgery group						
	Univariable			**Multivariable**			
	RR	**[95% CI]**	**p**	**RR**	**[95% CI]**	**p**	
SM-M Z-score	1.47	[1.22-1.77]	**<0.001**	1.58	[1.28-1.94]	**<0.001**	*
VAT-M Z-score	1.06	[0.69-1.61]	0.798	1.17	[0.76-1.80]	0.466	*
SAT-M Z-score	0.96	[0.57-1.63]	0.883	1.04	[0.61-1.79]	0.875	*
SM-RA Z-score	1.50	[0.91-2.48]	0.109	0.59	[0.23-1.52]	0.277	*
VAT-RA Z-score	1.30	[0.91-1.85]	0.145	1.25	[0.85-1.83]	0.251	*
SAT-RA Z-score	1.23	[0.88-1.72]	0.221	1.25	[0.90-1.74]	0.178	*
SNAQ score	1.03	[0.86-1.24]	0.711	1.01	[0.85-1.20]	0.937	*
GFI	1.30	[1.17-1.45]	**<0.001**	1.30	[1.16-1.45]	**<0.001**	*
Additional year of age	0.99	[0.95-1.04]	0.810				
ASA score							
1 or 2	Ref	-	-				
3	1.44	[0.58-3.6]	0.432				
cT stage							
T1-2	Ref	-	-				
T3-4	1.44	[0.58-3.6]	0.438				
cN stage							
cN0	Ref	-	-				
cN1-3	0.81	[0.31-2.09]	0.660				
Distal gastrectomy	0.50	[0.21-1.21]	0.123	0.44	[0.18-1.06]	0.069	**
Laparoscopic surgery	0.59	[0.24-1.43]	0.243				

Poisson regressions with robust error variances were performed, producing a relative risk of having a postoperative grade ≥3b complication (yes/no) for each of the CT body composition parameters. Bold values indicate significance ($p < 0.05$). RR = relative risk; CI = confidence interval and ref = reference; SM = skeletal muscle; VAT = visceral adipose tissue; SAT = subcutaneous adipose tissue; M = mass; RA = radiation attenuation; SNAQ = Short Nutritional Assessment Questionnaire; GFI = Groningen Frailty Index. *In multivariable analyses, each CT body composition parameter, the SNAQ score and GFI were adjusted only for whether a total or distal gastrectomy was performed. ** The displayed values for the variable distal gastrectomy are from the multivariable analysis in which SM-M Z-score and distal gastrectomy were included only. The values for the variable distal gastrectomy in the multivariable analyses of the remaining 5 CT body composition parameters, SNAQ score and GFI were comparable (data not shown).

Total versus distal gastrectomy

In the primary surgery group, distal gastrectomy showed a trend towards being associated with a lower risk of a grade ≥3b postoperative complication in univariable analysis (RR 0.50, 95% CI 0.21-1.21, p=0.123). Hence, in multivariable analyses, each CT body composition parameter, the SNAQ score and GFI were adjusted for whether a total or distal gastrectomy was performed (table 3b).

DISCUSSION

This prospective multicenter study found that patients with a low skeletal muscle mass on preoperative restaging CT-scan had a significantly higher risk of developing a major postoperative complication after preoperative chemotherapy followed by gastrectomy. Furthermore, patients with higher visceral or subcutaneous adipose tissue radiation attenuation (fat depleted of triglycerides) also had a significantly higher risk of developing a major postoperative complication. This is the first prospective multicenter study on the effects of body composition on postoperative complications in a Western population with predominantly advanced gastric cancer. These findings may help in better preoperative identification of high-risk patients.

A recent meta-analysis of Borggreve et al [9] concluded that patients with low skeletal muscle mass had an increased chance of developing (major) postoperative complications. However, only four retrospective studies from a Western population were included in this meta-analysis [7, 8, 37, 38]. Three studies (n=36, n=56 and n=138) found a statistically significant association between sarcopenia and an increased risk of postoperative complications [7, 37, 38], whereas the study by Tegels et al. (n=152) did not [8]. The Tegels et al. study results might be explained due to the retrospective single-center design, introducing possible selection and historical bias. In addition, patients were likely in a poor condition since only 46.3% received preoperative chemotherapy, which is recommended for all eligible patients in the Western advanced gastric cancer population since 2006 [8]. Lastly, binary cut-off values for sarcopenia were used from the Prado et al. study, which were based on obese Canadian patients and were not externally validated [12, 13]. The current study does not have these limitations, due to the prospective design and the fact that all body composition parameters were expressed as continuous Z-scores.

Low skeletal muscle radiation attenuation (SM-RA) indicates a greater accumulation of lipids/fat in and around myocytes, this is called myosteatosis [39]. The current study found no association between low skeletal muscle radiation attenuation (SM-RA) and postoperative complications after preoperative chemotherapy and gastrectomy. Literature on SM-RA in other abdominal cancers is ambiguous, with some studies demonstrating an association between low SM-RA and poor prognoses (possibly due to poor physical fitness) [11, 16, 31, 40], whereas other studies do not [17, 41-43].

Lower visceral adipose tissue radiation attenuation (VAT-RA) and subcutaneous adipose tissue radiation attenuation (SAT-RA) indicate a higher concentration of lipids/fat in the adipose tissue [30].

This is a fairly new but very relevant outcome, which has been shown to be associated with worse outcomes in other abdominal cancers [17, 44]. In the current study on gastric cancer, low VAT-RA and SAT-RA (fat with high triglyceride concentration) were associated

with a lower risk of developing a major postoperative complication after preoperative chemotherapy followed by gastrectomy. This effect might be due to the better nutritional status of these patients and increased lipid reserves. Whether this finding of low VAT-RA and SAT-RA on CT-scan can also be seen intraoperatively, for example as fat that easily tears, was not investigated in the current study, but might be of interest for further research (Figure 3). Of note, VAT-M and SAT-M (quantity of fat) were previously reported to be associated with VAT-RA and SAT-RA, indicating that all these variables are indicators of the patients' lipid reserves. Indeed, VAT-M and SAT-M also showed a trend towards an association with major postoperative complications in the current study. Surprisingly, age and American Society of Anaesthesiologists (ASA) score were not significantly associated with the risk of developing a major postoperative complication in the current trial cohort, underlining the added value of the CT body composition parameters in predicting postoperative complications. Furthermore, the main LOGICA paper from which this manuscript is a side study of, showed no difference between laparoscopic and open gastrectomy with respect to postoperative complications (44% vs 42%, p = 0.91) [21]. Moreover, both the laparoscopic and open study arm had comparable amount of patients who received total- and distal gastrectomy, as the randomization was stratified for total/distal gastrectomy.

Importantly, since postoperative complications are associated with lower survival rates after gastroesophageal surgery, reducing postoperative complications is key [45]. Nevertheless, it lies beyond the scope of the current study to determine whether the effect of body composition is prognostic and can't be influenced (i.e. patients with a poor prognosis have poor preoperative body composition) or whether this effect can be influenced with therapeutic interventions (i.e. patients have poor postoperative outcomes due to poor preoperative body composition, improving body composition would improve outcomes). Hence, based upon the current study data, the authors are not able to recommend whether additional nutritional replacement based on preoperative body composition is of additive value or not.

For patients undergoing primary surgery in the current study (n=54), a lower skeletal muscle (SM) Z-score was associated with a significantly lower risk of developing a major postoperative complication. Strikingly, an opposite effect was found in the preoperative chemotherapy followed by gastrectomy group (n=112). The primary surgery group result is presumably due to (selection) bias, though an actual effect cannot be excluded based upon the current study data. The authors believe results from the primary surgery group should be regarded with caution, since the primary surgery group is deemed to be representative of a more heterogeneous cohort of patients, who are in worse clinical condition and have a worse prognosis, compared to the more homogenous preoperative chemotherapy group. Indeed, the primary surgery group has a higher mean age (75 versus

66 years), higher prevalence of cardiovascular comorbidity (70% versus 49%), higher number of distal gastrectomies performed (67% versus 55%), higher occurrence of a grade ≥3b postoperative complication (26% versus 8%) and higher occurrence of 1-year mortality (30% versus 18%). The majority of patients in the primary surgery group were older, had advanced cancer and, according to Dutch guidelines, should receive perioperative chemotherapy if eligible [2, 46]. Hence, a proportion of the primary surgery group was likely in poor clinical condition, deeming them not eligible for preoperative chemotherapy. The current study results underline that future research should analyze patients undergoing preoperative chemotherapy follow by surgery and patients undergoing primary surgery as separate groups.

A higher frailty, indicated by the Groningen frailty index, showed a trend but no statistically significant association for the development of a major postoperative complication in the preoperative chemotherapy group [47]. In the primary surgery group, a higher GFI (more frailty) was significantly associated with reduced occurrence of a major postoperative complication. As mentioned in the previous paragraph, results from the primary surgery group should be regarded with caution due to possible (selection) bias. Furthermore, a higher SNAQ score was not predictive for the development of a major postoperative complication in both the preoperative chemotherapy- and the primary surgery group. The SNAQ was originally designed as a hospital screening tool for malnutrition.

Current literature highlights the effects of gastric cancer in relations to malnutrition and the development of cancer cachexia. Malnutrition could occur through physical obstruction of the gastrointestinal tract or systemic inflammation due to cancer [43, 48]. In the current trial, malnourished patients' nutrition was preoperatively optimized according to standard care, based upon the national guidelines and the guidelines of Enhanced Recovery After Surgery (ERAS) [22, 49]. Perhaps no association was found between the SNAQ score and major postoperative complications, due to the SNAQ being a subjective patient reported outcome, which was not specifically designed for scientific purposes in a trial cohort. The authors believe CT body composition measures are more objective and thus more reliable.

In the preoperative chemotherapy group, the restaging CT-scans, and not the initial staging CT-scans, were used to determine the patients' body composition. The restaging CT-scans were expected to give the best uniform representation of the patients' condition during surgery, since body composition often changes during preoperative chemotherapy [19, 50-52].

A limitation of the current study is the exclusion of 39 patients, due to the unavailability of a restaging CT-scan. Since the current study was an observational prospective side-study of the LOGICA-trial, the restaging CT-scan was not obligatory but made according to

standard of care. Even though the multidisciplinary tumor board decided when a restaging CT-scan did not have to be made, these missing's appear to have occurred at random, since patient characteristics, treatment and outcome did not change upon including these 39 patients (Online Resource 1). Thus, selection bias is presumably limited. It is considered a strength of the current study that the timing of the CT-scans was reported in detail, which is not the case in the majority of studies in the recent Borggreve et al. meta-analysis [9].

In addition, the average BMI of our cohort was relatively low (~ 25) when compared to that of the American-, Canadian- or South American population. This is representative for the typical West-European population with gastric cancer. Considering this, one could argue that the findings of this study cannot necessarily be extrapolated to populations with a higher BMI [3]. The occurrence of any postoperative complication is used as an outcome in some body composition studies in literature, whereas other studies use only postoperative complications of a certain Clavien-Dindo grade [9]. In the current study, a grade ≥3b complication was used, since predicting this grade preoperatively is deemed to be the most useful to guide clinical decision making. In the preoperative chemotherapy group, the point estimated relative risks for the SM-M, VAT-RA and SAT-RA Z-scores were 0.47, 2.82 and 1.95, respectively. Hence, a patient with a VAT-RA of 1 standard deviation above the study population mean (belonging to the 16% highest VAT-RA values in the study population) would have almost 3 times the estimated chance of developing a grade ≥3b postoperative complication, compared to the patient with an average VAT-RA (Figure 3).

Based upon the current study results, routine assessment and collection of CT body composition could be implemented in standard oncological care of gastric cancer patients. Once large prospectively collected datasets with continuous variables for CT body composition, known predictors such as age, ASA grade and type of resection and postoperative complication rates are available to serve as population reference values, body composition can be used to guide clinical decision making for the individual patient [53]. Body composition analysis could then be used during preoperative multidisciplinary tumor board discussions to objectively and reproducibly predict the relative risk of a major postoperative complication.

In conclusion, this prospective multicenter study demonstrated that low skeletal muscle mass and a high visceral or subcutaneous adipose tissue radiation attenuation (fat depleted of triglycerides) are strong predictors of developing a major postoperative complication in gastric cancer patients treated with preoperative chemotherapy followed by gastrectomy. Incorporating body composition analysis could lead to a better selection of at-risk patients for major postoperative complications and aid in treatment decision making.

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SUPPLEMENTARY MATERIAL

Supplementary material 1. Patient characteristics, treatment and outcome of the preoperative chemotherapy group with and without exclusion of patients with no available restaging CT-scan

	Preoperative chemotherapy, main study population		**Preoperative chemotherapy, patients without restaging CT-scan not excluded**	
n (%)	112		112	
Male sex	73	(65.2)	98	(64.9)
Age, years (mean (SD))	65.6	(9.6)	65.1	(10.1)
BMI, kg/m^2 (median [IQR])	25.7	[23.2, 29.0]	25.2	[22.7, 28.6]
ASA score				
1	14	(12.5)	17	(11.3)
2	73	(65.2)	99	(65.6)
3	25	(22.3)	35	(23.2)
Cardiovascular comorbidity	55	(49.1)	77	(51.0)
Pulmonary comorbidity	23	(20.5)	31	(20.5)
Location of tumor				
Proximal stomach	14	(12.5)	22	(14.6)
Middle stomach	31	(27.7)	44	(29.1)
Distal stomach	67	(59.8)	85	(56.3)
cT-stage				
cT1	5	(4.5)	6	(4.0)
cT2	29	(25.9)	41	(27.2)
cT3	67	(59.8)	91	(60.3)
cT4	11	(9.8)	13	(8.6)
cN1-3	51	(45.5)	70	(46.4)
Advanced cancer[1]	88	(78.6)	121	(80.1)
SNAQ score, (mean (SD))	2	(2.05)	2.18	(2.09)
Missing	38	(34.9)	48	(31.8)
GFI, (mean (SD))	2.9	(2.3)	3.08	(2.34)
Missing	26	(23.2)	37	(24.5)
Preoperative chemotherapy				
ECC or equivalent	84	(75.0)	114	(75.5)
FLOT	19	(17.0)	26	(17.2)
Other	9	(8.0)	11	(7.3)
Preoperative chemotherapy completed (>80% of courses)				
Yes	89	(79.5)	120	(79.5)
No	21	(18.8)	29	(19.2)
Missing	2	(1.8)	2	(1.3)
Type of operation				
Total gastrectomy	50	(44.6)	69	(45.7)
Distal gastrectomy	62	(55.4)	82	(54.3)

Supplementary material 1. Continued

n (%)	Preoperative chemotherapy, main study population 112		Preoperative chemotherapy, patients without restaging CT-scan not excluded 112	
Laparoscopic gastrectomy	53	(47.3)	69	(45.7)
Complication	38	(33.9)	58	(38.4)
CDC of most severe complication				
1	8	(7.1)	10	(6.6)
2	16	(14.3)	24	(15.9)
3a	5	(4.5)	6	(4.0)
3b	2	(1.8)	7	(4.6)
4a	4	(3.6)	6	(4.0)
4b	0	(0.0)	0	(0.0)
5	3	(2.7)	5	(3.3)
Anastomotic leakage	8	(7.1)	12	(7.9)
Anastomotic leakage grade (ECCG)				
I	2	(1.8)	2	(1.3)
II	1	(0.9)	2	(1.3)
III	5	(4.5)	8	(5.3)
Adjuvant chemotherapy started	59	(52.7)	79	(52.3)
1-year all-cause mortality	20	(17.9)	24	(15.9)

IQR = interquartile range; SD = standard deviation; ASA = American Society of Anaesthesiologists; SM = skeletal muscle; SAT = subcutaneous adipose tissue; VAT = visceral adipose tissue; RA = radiation attenuation; HU = Hounsfield units; SNAQ = Short Nutritional Assessment Questionnaire; GFI = Groningen Frailty Index. ECC = epirubicin + cisplatin + capecitabine, FLOT = fluorouracil + leucovorin + oxaliplatin + docetaxel , CDC = Clavien-Dindo Classification; ECCG = Esophagectomy Complications Consensus Group. [1]Defined as cT3-4N0 or cT1-2N+.

Part two

Personalized treatment of gastroesophageal cancer


Retrospective

CHAPTER 6

Multimodal therapy versus primary surgery for gastric and gastroesophageal junction diffuse type carcinoma, with a focus on signet ring cell carcinoma: a nationwide study

Submitted

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ABSTRACT

Background

Diffuse type adenocarcinoma and, more specifically, signet ring cell carcinoma (SRCC) of the stomach and gastroesophageal junction (GEJ) have a poor prognosis and the value of neoadjuvant chemo(radio)therapy (nCRT) is unclear.

Methods

All patients who underwent surgery for diffuse type gastric and GEJ carcinoma between 2004 and 2015 were retrospectively included from the Netherlands Cancer Registry. The primary outcome was overall survival after surgery. Kaplan Meier curves were plotted. Furthermore, multivariable Poisson and Cox regressions were performed, correcting for confounders. To comply with the Cox regression proportional hazard assumption, gastric cancer survival was split in <90 days and >90 days postoperative by adding an interaction variable.

Results

Analyses included 2046 patients with diffuse type cancer: 1728 gastric (50% SRCC) and 318 GEJ cancer (39% SRCC). In the gastric cancer group, 49% received nCT and 51% primary surgery (PS). All-cause mortality within 90 days postoperatively was lower after nCT (HR=0.29; 95%CI [0.20-0.44], p<0.001). Also after 90 days, mortality was lower in the nCT group (HR for the interaction variable 2.84; 95%CI [1.87-4.30], p<0.001; Total HR=0.29*2.84=0.84). In the GEJ group, 38% received nCT, 22% nCRT and 39% PS. All-cause mortality was lower after nCT (HR=0.63 [95%CI 0.43-0.93], p=0.020), compared to PS. The nCRT group was removed from the Cox regression analysis, since the Kaplan Meier curves of nCRT and PS intersected. The results for gastric and GEJ were similar between the SRCC and non-SRCC subgroups.

Conclusion

For gastric and GEJ diffuse type cancer, including SRCC, nCT was associated with increased survival.

MINI-ABSTRACT

The value of neoadjuvant treatment for patients with diffuse type gastric or gastroesophageal junction adenocarcinomas, including signet ring cell carcinomas, remains unclear. This study shows that neoadjuvant chemotherapy was associated with better survival when compared to primary surgery. Hence, neoadjuvant chemotherapy should remain standard of care in these patients.

INTRODUCTION

The Laurén classification system categorizes gastric adenocarcinomas into intestinal type, diffuse type and mixed type. Intestinal type carcinomas form glands, whereas diffuse type carcinomas consist of poorly cohesive cells[1]. In diffuse type adenocarcinomas often signet ring cells are found, and if the tumor predominantly consists of signet ring cells (>50%), the tumor is defined as a signet ring cell carcinoma (SRCC) according to the World Health Organization[2]. Generally, gastric adenocarcinomas are known for a poor prognosis, with a 5-year survival in stage I-III disease less than 40%[3–5]. Survival in diffuse types is suggested to be worse when compared to other types[6–8], with reported survival rates as low as 15%[9].

Curative treatment for gastric adenocarcinoma in general consists of surgical resection with lymphadenectomy, if possible combined with perioperative chemotherapy[5,10]. The poor prognosis of diffuse type gastric cancer is caused by unfavorable characteristics, such as deeper infiltrating tumors causing a higher rate of incomplete resections, a higher prevalence of lymph node and peritoneal metastases, resulting in a reduced disease-free survival[6,11]. Moreover, it is suggested that diffuse type adenocarcinomas exhibit a lower response to neoadjuvant chemo(radio)therapy compared to intestinal type adenocarcinomas[12]. A large French population-based study reported a significantly worse survival for diffuse types with perioperative chemotherapy compared to surgery alone, specifically for SRCC. In that study, perioperative chemotherapy did not result in tumor or nodal down-staging, and thus lacked cytostatic effect[13]. It was therefore suggested to consider primary surgery as standard of care for these tumors. Since other large studies are lacking, several national and international guidelines still state that it is too early to omit (neo)adjuvant chemo(radio)therapy in diffuse type adenocarcinoma[14,15]. In the Netherlands, neoadjuvant chemotherapy is started with the intent to also give adjuvant chemotherapy (perioperative therapy)[5,10]. In the current study, it was decided to only

analyze neoadjuvant treatment, to reduce selection and immortal time bias. The aim of the current study was to compare neoadjuvant treatment combined with surgery to primary surgery for diffuse type gastric and gastroesophageal junction (GEJ) adenocarcinomas.

METHODS

Study design

This population-based retrospective study retrieved anonymous data from the Netherlands Cancer Registry (NCR). Each newly diagnosed cancer patient in the Netherlands is reported to the NCR by the National Automated Pathology Archive (PALGA). The NCR subsequently registers patient, tumor and treatment-related characteristics of each patient. The patient's vital status is annually updated through a linkage with the municipal personal records database. Data collection from hospital records is performed by trained data managers using the NCR's manual for registration and coding. The Privacy Review Board of the NCR and the scientific committee of the Dutch Upper-GI Cancer Group (DUCG) approved this study.

Study population and study outcomes

All patients who underwent a surgical resection for diffuse type gastric adenocarcinoma or a SRCC of the stomach or GEJ between 2004 and 2015 in the Netherlands were included. The definition of SRCCs varied over the years, according to the World Health Organization (WHO), depending on the percentage of signet ring cells in the tumor (varying from >50% to 90%)[16–18]. Patients with metastatic disease (cM1) and non-resectable disease (cT4b) were excluded. Based on tumor location, patients were subdivided into: gastric or GEJ, with GEJ mostly consisting of Siewert type II and III tumors, as type I was usually registered as distal esophageal cancer. The following treatment groups were distinguished: i. primary surgery group (PS; defined as surgery without (neo)adjuvant chemo(radio)therapy, ii. neoadjuvant chemotherapy group (nCT; defined as patients treated with neoadjuvant chemotherapy and surgery, with the intention to also administer adjuvant chemotherapy according to national guidelines) and iii. neoadjuvant chemoradiotherapy group (nCRT; only for GEJ cancer, defined as patients with GEJ cancer treated with nCRT and surgery).

The primary outcome was overall survival. Furthermore, patient, tumor and treatment-related characteristics and short-term oncological outcomes were described, including the frequency of missing values per variable. Finally, resection radicality was evaluated and defined according to the College of American Pathologists[19].

Diagnosis and treatment

Diagnosis, staging and treatment of gastric cancer in the Netherlands are advised to be performed according to the national guidelines and the at that time applicable edition of the Union for International Cancer Control TNM staging system[20–22]. The recommended staging process consists of endoscopy with biopsies and computed tomography (CT) scan of thorax and abdomen. If indicated, an endoscopic ultrasound (EUS), fluorodeoxyglucose positron emission tomography with CT (FDG-PET/CT) and/or staging laparoscopy with peritoneal lavage are performed [22]. Following publication of the MAGIC trial in 2006, the recommended curative treatment for gastric adenocarcinoma consists of perioperative chemotherapy (epirubicin, cisplatin, and capecitabin according to the MAGIC regimen, or similar) combined with (sub)total gastrectomy and lymphadenectomy[5]. Since 2006, the recommended curative treatment for GEJ tumors consisted of perioperative chemotherapy similar to the MAGIC regimen combined with surgery. As of 2010, this was changed to either perioperative chemotherapy or nCRT according to the CROSS regimen [23](based on the advice of the local multidisciplinary tumor board), combined with surgery. Surgery consists of total gastrectomy, transhiatal esophagectomy or transthoracic esophagectomy and, regardless of the procedure, combined with lymphadenectomy[23]. Annual hospital volume of surgery for patients with gastric or GEJ cancer undergoing gastrectomy was based on the hospital gastrectomy volume and for patients with GEJ cancer undergoing esophagectomy it was based on esophagectomy volume. Low volume was defined as performing <20 procedures annually, mid as 20-40 and high as >40.

Statistical analysis

The chi-squared test or Fisher's exact test was used to compare categorical data between groups. The Mann-Whitney-Wilcoxon test with interquartile ranges (IQR) was used to compare non-Gaussian distributed continuous data between groups. Overall survival (OS) analyses were performed separately for the gastric cancer diffuse type group (regardless whether signet ring cells were present), the gastric cancer SRCC subgroup, the GEJ cancer diffuse type group, and the GEJ SRCC subgroup. The 90-day mortality was compared between treatment groups and Kaplan Meier curves were plotted for each treatment group, displaying overall survival up to 5 years, or in case of sufficient numbers at risk, up to 10 years. Survival time was calculated from date of surgery until death or end of follow-up. Differences in survival between treatment groups were compared by log-rank tests and univariable and multivariable Cox regression. Hazard ratios (HRs) were provided for all-cause mortality with 95% confidence intervals (CIs). The proportional hazard assumption was assessed by visually checking the Kaplan Meier curves and performing Schoenfeld's global test (see Supplementary material 1-2 for additional details). To comply with the proportional hazard assumption, for gastric cancer, additional regression analyses with an

interaction variable "nCT[yes/no]*>90 days postoperatively[yes/no]" were performed[24,25]. It was decided to split the HR at 90 days postoperatively, since this allows for easy interpretation of the HRs by clinicians reading the current paper and since 90 day mortality is commonly regarded a parameter for surgery-related mortality[26–28]. For the GEJ nCRT group, a split was not possible due to low numbers, hence the GEJ nCRT group was removed from the Cox regression analyses (Supplementary material 1-2). The multivariable Cox regression were adjusted for relevant patient, tumor and treatment-related characteristics that could influence clinical decision making (i.e. characteristics that are known preoperatively): age, sex, previous malignancy, cTNM stage, year of diagnosis, hospital annual volume and surgical treatment. Due to the small sample size of the GEJ SRCC subgroup to prevent over-fitting, only patient, tumor and treatment-related characteristics with $p<0.200$ in univariable Cox regression analysis were added to the multivariable analysis[29,30]. Furthermore, in the GEJ SRCC subgroup, the variable "year of surgery" was further aggregated (2004-2009/2010-2015) due to limited numbers in the categories. Possible collinearity was assessed between the variables neoadjuvant therapy, year of surgery and hospital volume. Lastly, additional analyses were performed to assess the association between annual hospital volume with R+ resection rate. The binary outcome R+ resection rate was analyzed by multivariable Poisson regression with robust error variances according to the methods by Zou et al., providing relative risks (RR)[31,32]. All statistical analyses were performed using SPSS version 25.0 (IBM Corp., Armonk, NY) and R statistical computing version 3.6.1 (R Foundation for Statistical Computing, Vienna, Austria). $P<0.05$ was considered statistically significant.

RESULTS

Study population

In the Netherlands, 2233 patients underwent a surgical resection with curative intent for diffuse type gastric or GEJ adenocarcinoma between 2004 – 2015. Patients with gastric cancer who underwent neoadjuvant radiotherapy (n=1) or nCRT (n=10) were excluded, as this was not standard of care. Likewise, patients who underwent surgery within 7 days after diagnosis were regarded as emergency surgery and were also excluded (n=26). A total of 123 patients were excluded due to metastatic (cM1) disease and 27 due to non-resectable disease (cT4b) (Figure 1). Baseline characteristics are presented in Table 1.

Treatment and histopathological outcomes

In the diffuse type gastric cancer group, 49% of patients were treated with nCT, and 51% underwent primary surgery. In the diffuse type GEJ group, 38% were treated with nCT, 22% with nCRT, whereas 39% underwent primary surgery (Table 2). For the gastric and

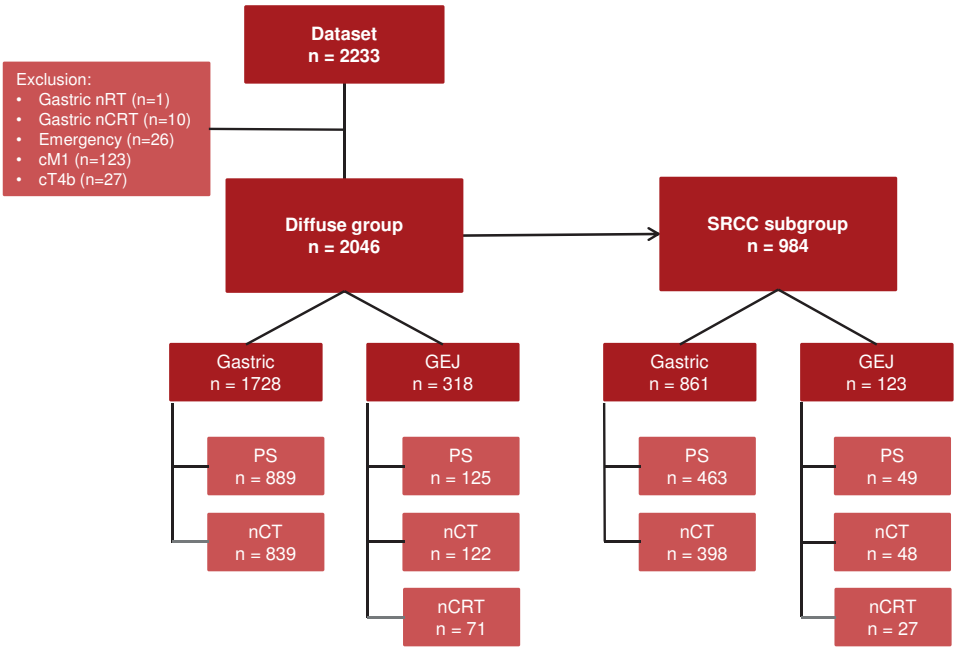

Figure 1. Flow chart
GEJ: gastroesophageal junction tumor; nCRT: neoadjuvant chemoradiotherapy; nCT: neoadjuvant chemotherapy; nRT: neoadjuvant radiotherapy; PS: primary surgery; SRCC: signet ring cell carcinoma.

GEJ SRCC subgroups, these percentages largely corresponded to the diffuse type group (Supplementary material 3).

Histopathological parameters for diffuse type tumors are presented in Table 3

Survival

Follow-up and proportional hazards

Median follow-up time of survivors in the entire cohort was 72 months [range: 11-156 months, interquartile range: 34-144 months]. The assessment of the proportional hazard assumptions is described in the method section and Supplementary material 1-2.

Gastric diffuse type cancer

For gastric diffuse type cancer, 90-day postoperative mortality in the PS and nCT groups was 13.2% and 3.7%, respectively (p<0.001). Median survival was 21.2 months and 34.1 months, respectively (p<0.001, Figure 2). In multivariable Cox regression, a total of 1190 events (deaths) were observed. The HR for "nCT[yes/no]" was 0.29 (95%CI [0.20-0.44], p<0.001) and the HR for the interaction variable "nCT[yes/no]*>90 days postoperatively[yes/

no]" was 2.84 (95%CI [1.87-4.30], p<0.001). Thus, patients treated with nCT had a significantly reduced all-cause mortality within 90 days postoperatively (HR=0.29) and after 90 days (HR=0.29*2.84=0.84), compared to patients treated with PS (Table 4a).

Table 1. Baseline characteristics of 2046 patients who were diagnosed with a diffuse type gastroesophageal adenocarcinoma and underwent surgical resection

	Gastric (n=1728)		GEJ (n=318)	
	No. (%)	**Missing values (%)**	**No. (%)**	**Missing values (%)**
Patient characteristics				
Age, years (mean ± SD)	65.5 ± 12.6	0 (0)	63.3 ± 11.0	0 (0)
Gender (male, %)	953 (55)	0 (0)	252 (79)	0 (0)
Malignancy[1]	193 (11)	0 (0)	32 (10)	0 (0)
Tumor characteristics				
cT-stage		918 (52)		79 (25)
T1	74 (9)		2 (1)	
T2	428 (53)		83 (35)	
T3	230 (28)		142 (59)	
T4	78 (10)		12 (5)	
cN-stage		293 (17)		28 (9)
N0	1020 (71)		125 (43)	
N1	337 (24)		133 (46)	
N2	72 (5)		30 (10)	
N3	6 (<1)		2 (1)	
cM-stage (M0)	1640 (100)	88 (5)	303 (100)	15 (5)
Tumor location[2]		52 (3)		59 (10)
Proximal	51 (3)		318 (100)	
Mid	461 (28)		n.a.	
Distal	776 (46)		n.a.	
Overlapping	388 (23)		n.a.	
Tumor differentiation		539 (31)		91 (29)
Well/moderate	67 (6)		25 (11)	
Poorly/undifferentiated	1122 (94)		202 (89)	
Signet ring cell carcinoma (%)	861 (50)		123 (39)	
Hospital volume		0 (0)		0 (0)
<20 resections	1356 (79)		158 (50)	
20-40 resections	300 (17)		93 (29)	
>40 resections	72 (4)		67 (21)	
Year of surgery		0 (0)		0 (0)
2004 – 2008	451 (26)		101 (32)	
2008 – 2012	643 (37)		125 (39)	
2012 – 2015	634 (37)		92 (29)	

Percentages may not add up to 100% due to rounding. BMI: Body Mass Index. [1]Currently or previously treated malignancy other than gastroesophageal carcinoma. [2]Gastric: proximal included fundus (n=51); mid included corpus (n=356), lesser (n=81) and greater (n=24) curvature; distal included antrum (n=624) and pylorus (n=152).

Table 2. Treatment characteristics of 2046 patients who were diagnosed with a diffuse type carcinoma, divided per location

	Gastric (n=1728)		GEJ (n=318)	
	No. (%)	**Missing values (%)**	**No. (%)**	**Missing values (%)**
Neoadjuvant treatment		0 (0)		0 (0)
Chemotherapy	839 (49)		122 (38)[3]	
Chemoradiotherapy	0 (0)		71 (22)[3]	
Radiotherapy only	0 (0)		0 (0)	
None	889 (51)		125 (39)[3]	
Surgical treatment		0 (0)		0 (0)
Subtotal gastrectomy	969 (61)		n.a.	
Total gastrectomy	621 (39)		69 (20)	
Transthoracic esophagectomy	n.a.		56 (18)	
Transhiatal esophagectomy	n.a.		59 (18)	
Esophagectomy, unknown type	n.a.		124 (39)	
Unknown type of resection	138 (8)		10 (3)	
Adjuvant treatment		0 (0)		0 (0)
Chemotherapy[1]	459 (27)		556 (18)	
Chemoradiotherapy[2]	72 (4)		5 (2)	
Radiotherapy only	3 (<1)		0 (0)	
None	1194 (69)		257 (81)	

Percentages may not add up to 100% due to rounding. [1]442 patients in the gastric and 55 patients in the GEJ group underwent aCT in the context of nCT. Of these patients, 72 in the gastric and 10 in the GEJ group underwent additional radiotherapy. 17 patients in the gastric and 1 patient in the GEJ group did not undergo nCT. [2]53 patients in the gastric and 3 patients in the GEJ group underwent nCT followed by aCRT (instead of perioperative chemotherapy) within the context of the CRITICS trial (Cats et al., 2018). [3]For GEJ, the treatment combinations were: gastrectomy as PS (n=22), gastrectomy + nCT (n=45), gastrectomy + nCRT (n=2), esophagectomy as PS (n=96), esophagectomy + nCT (n=74), esophagectomy + nCRT (n=69), unknown resection as PS (n=6), unknown resection + nCT (n=4).

Gastric SRCC subgroup

In the gastric SRCC subgroup, 90-day postoperative mortality in the PS and nCT groups was 11.2% and 3.5%, respectively (p<0.001). Median survival was 22.8 months and 34.0 months, respectively (p=0.002, Figure 2). In multivariable Cox regression, the HR for "nCT[yes/no]" was 0.33 (95%CI [0.18-0.61], p<0.001) and the HR for the interaction variable "nCT[yes/no]*>90 days postoperatively[yes/no]" was 2.61 (95%CI [1.41-4.83], p<0.001). Thus, patients treated with nCT had a significantly reduced all-cause mortality within 90 days (HR=0.33) and after 90 days (HR=0.33*2.61=0.87), compared to patients treated with PS (Table 4a).

Table 3. Histopathological outcomes of 2046 patients who were diagnosed with a diffuse type carcinoma, divided per location

	Gastric (n=1728)		GEJ (n=318)	
	No. (%)	**Missing values (%)**	**No. (%)**	**Missing values (%)**
Tumor stage				
pT-stage		10 (1)		5 (2)
T0	45 (3)		20 (6)	
T1	270 (16)		19 (6)	
T2	450 (26)		112 (36)	
T3	660 (38)		148 (47)	
T4	293 (17)		14 (5)	
pN-stage		33 (2)		3 (1)
N0	684 (40)		113 (36)	
N1	447 (26)		100 (32)	
N2	291 (17)		64 (20)	
N3	273 (16)		38 (12)	
pM-stage		77 (5)		13 (4)
M0	1571 (91)		298 (98)	
M1	80 (5)		7 (2)	
Radicality of the resection (R0, %)	1285 (74)	88 (5)	236 (74)	14 (4)
Lymph node yield (median, IQR)	15 [9-23]	3 (<1)	16 [10-22]	0 (0)
Total positive lymph nodes (median, IQR)	1 [0-6]	34 (2)	2 [0-7]	1 (<1)

Percentages may not add up to 100% due to rounding.

GEJ diffuse type cancer

For GEJ diffuse type cancer, 90-day postoperative mortality in the PS, nCT and nCRT groups was 9.6%, 3.3% and 7.0%, respectively (p=0.133). Median survival was 19.3 months, 31.5 months and 20.6 months, respectively (p=0.01, Figure 3). Due to non-compliance with the proportional hazard assumption, the nCRT group was excluded from the multivariable Cox regression and a total of 189 events (deaths) were observed. Patients treated with nCT had a significantly reduced all-cause mortality (HR 0.63 [95%CI 0.43-0.93], p=0.020), compared to patients treated with PS (Table 4b).

GEJ SRCC subgroup

In the GEJ SRCC subgroup, 90-day postoperative mortality in the PS, nCT and nCRT groups was 12.2%, 6.4% and 3.7%, respectively (p=0.366). Median survival was 17.3 months, 32.8 months and 15.6 months, respectively (p=0.08, Figure 3). Due to non-compliance with the proportional hazard assumption, the nCRT group was excluded from the multivariable Cox regression. Patients treated with nCT had a significantly reduced all-cause mortality (HR 0.53 [95%CI 0.31-0.92], p=0.024), compared to patients treated with PS (Table 4b).

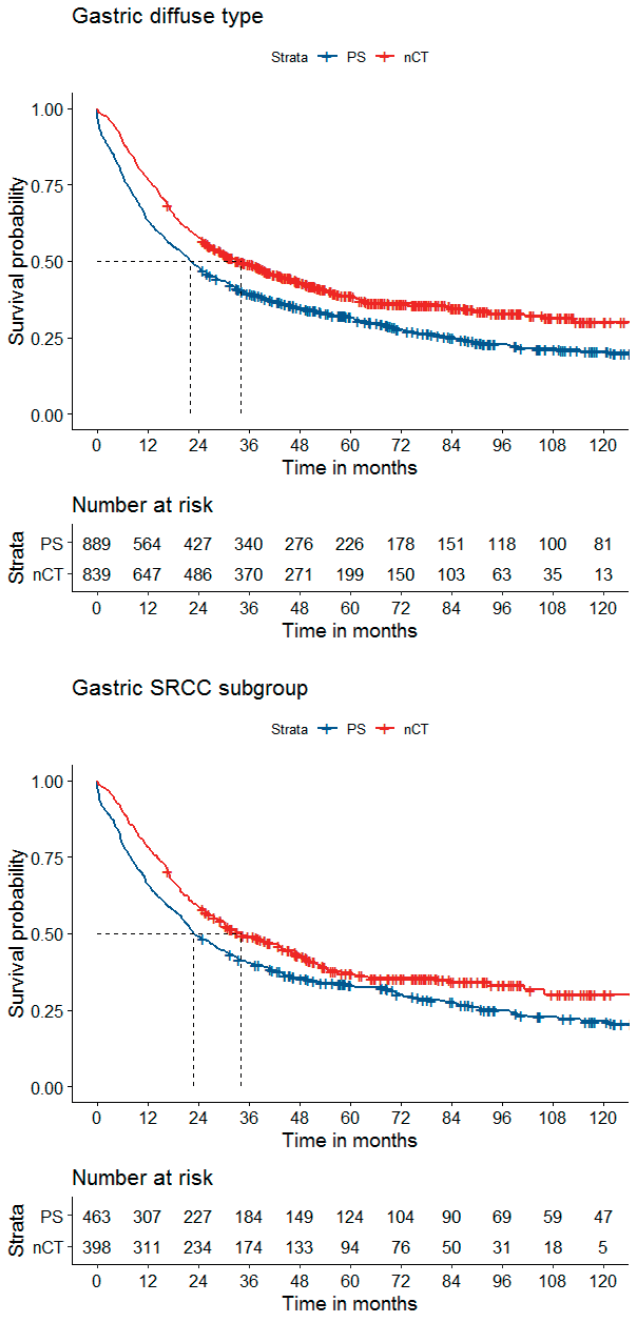

Figure 2. Overall 10-year survival for gastric diffuse type carcinoma (top) and the gastric SRCC subgroup (bottom). Kaplan-Meier plots and number of patients at risk are displayed. Median survival times are shown by interrupted lines. Censoring of patients is shown by a "+" on the plotted graphs.

Table 4a. Univariable and multivariable Cox regression analyses on the influence of nCT on all-cause mortality for diffuse and SRCC type gastric cancer

	Gastric - diffuse type					
	Univariable			**Multivariable**		
	HR	**[95% CI]**	**p**	**HR**	**[95% CI]**	**p**
nCT	0.27	[0.18-0.40]	**<0.001**	0.29	[0.20-0.44]	**<0.001**
nCT*>90 days postoperatively[1]	3.08	[2.03-4.66]	**<0.001**	2.84	[1.87-4.30]	**<0.001**
Additional year of age	1.02	[1.02-1.03]	**<0.001**	1.02	[1.01-1.02]	**<0.001**
Female sex	0.95	[0.84-1.06]	0.356	1.03	[0.92-1.15]	0.636
Previous malignancy	1.29	[1.08-1.53]	**0.005**	1.19	[0.99-1.42]	0.058
cT-stage						
T1	Ref	-	-	Ref	-	-
T2	3.58	[2.32-5.52]	**<0.001**	3.32	[2.14-5.16]	**<0.001**
T3	4.40	[2.82-6.86]	**<0.001**	3.79	[2.41-5.97]	**<0.001**
T4	7.49	[4.63-12.1]	**<0.001**	5.61	[3.43-9.2]	**<0.001**
Tx	3.18	[2.08-4.9]	**<0.001**	2.84	[1.85-4.4]	**<0.001**
cN-stage						
N0	Ref	-	-	Ref	-	-
N+	1.73	[1.51-2.0]	**<0.001**	1.57	[1.36-1.8]	**<0.001**
Nx	1.33	[1.14-1.5]	**<0.001**	1.27	[1.08-1.5]	**0.003**
cMx	1.52	[1.20-1.9]	**<0.001**	1.34	[1.05-1.7]	**0.021**
Year of surgery						
2004 – 2005	Ref	-	-	Ref	-	-
2006 – 2007	1.06	[0.84-1.3]	0.598	1.11	[0.87-1.4]	0.405
2008 – 2009	1.01	[0.80-1.3]	0.910	1.12	[0.88-1.4]	0.364
2010 – 2011	0.87	[0.69-1.1]	0.268	1.11	[0.85-1.4]	0.457
2012 – 2013	0.89	[0.70-1.1]	0.321	1.06	[0.81-1.4]	0.674
2014 – 2015	0.92	[0.72-1.2]	0.496	1.02	[0.76-1.4]	0.908
Hospital volume						
<20 gastrectomies	Ref	-	-	Ref	-	-
20-40 gastrectomies	0.91	[0.78-1.1]	0.271	1.00	[0.83-1.2]	0.989
>40 gastrectomies	0.87	[0.64-1.2]	0.397	1.06	[0.76-1.5]	0.728
Surgical treatment						
Total gastrectomy	Ref	-	-	Ref	-	-
Subtotal gastrectomy	0.71	[0.63-0.8]	**<0.001**	0.63	[0.56-0.7]	**<0.001**
Unknown type of procedure	1.08	[0.88-1.3]	0.478	0.94	[0.75-1.2]	0.565

Bold values indicate significance ($p < 0.05$). HR = hazard ratio, CI = confidence interval and ref = reference.
[1]For diffuse type gastric cancer, in multivariable analysis, patients receiving nCT had a significantly reduced all-cause mortality within 90 days postoperatively (HR = 0.29) and after 90 days (HR = 0.29 * 2.84 = 0.84). For the gastric SRCC subgroup, in multivariable analysis, patients receiving nCT had a significantly reduced all-cause mortality within 90 days postoperatively (HR = 0.33) and after 90 days (HR = 0.33 * 2.61 = 0.87).

	Gastric - SRCC subgroup					
	Univariable			Multivariable		
	HR	[95% CI]	p	HR	[95% CI]	p
	0.30	[0.17-0.54]	**<0.001**	0.33	[0.18-0.61]	**<0.001**
	2.86	[1.54-5.28]	**<0.001**	2.61	[1.41-4.83]	**<0.001**
	1.02	[1.02-1.03]	**<0.001**	1.02	[1.02-1.03]	**<0.001**
	0.88	[0.75-1.04]	0.124	0.98	[0.83-1.15]	0.791
	1.23	[0.94-1.61]	0.128	1.07	[0.81-1.42]	0.613
	Ref	-	-	Ref	-	-
	3.44	[1.98-5.99]	**<0.001**	3.07	[1.75-5.41]	**<0.001**
	5.19	[2.94-9.17]	**<0.001**	4.32	[2.40-7.75]	**<0.001**
	9.59	[5.09-18.0]	**<0.001**	7.36	[3.87-14.0]	**<0.001**
	3.00	[1.76-5.13]	**<0.001**	2.59	[1.50-4.46]	**<0.001**
	Ref	-	-	Ref	-	-
	1.90	[1.56-2.31]	**<0.001**	1.74	[1.41-2.14]	**<0.001**
	1.39	[1.13-1.71]	**0.002**	1.30	[1.04-1.61]	**0.020**
	1.61	[1.17-2.22]	**0.004**	1.44	[1.03-2.03]	**0.034**
	Ref	-	-	Ref	-	-
	1.32	[0.97-1.80]	0.076	1.35	[0.98-1.85]	0.063
	1.13	[0.83-1.56]	0.439	1.23	[0.88-1.72]	0.222
	1.02	[0.74-1.40]	0.897	1.27	[0.89-1.82]	0.184
	0.99	[0.71-1.38]	0.950	1.15	[0.79-1.67]	0.463
	1.01	[0.71-1.43]	0.977	1.11	[0.73-1.70]	0.619
	Ref	-	-	Ref	-	-
	1.02	[0.74-1.40]	0.897	1.27	[0.89-1.82]	0.184
	0.99	[0.71-1.38]	0.950	1.15	[0.79-1.67]	0.463
	Ref	-	-	Ref	-	-
	1.01	[0.71-1.43]	**<0.001**	1.11	[0.73-1.70]	**<0.001**
	0.90	[0.72-1.13]	0.368	1.00	[0.78-1.29]	0.969

Table 4b. Univariable and multivariable Cox regression analyses on the influence of nCT and nCRT on all-cause mortality for SRCC and diffuse type GEJ cancer.

	GEJ - diffuse type					
	Univariable			**Multivariable**		
	HR	**[95% CI]**	**p**	**HR**	**[95% CI]**	**p**
Neoadjuvant treatment						
PS	Ref	-	-	Ref	-	-
nCT	0.64	[0.48-0.86]	**0.003**	0.63	[0.43-0.93]	**0.020**
Additional year of age	1.01	[0.99-1.02]	0.303	1.00	[0.99-1.02]	0.537
Female sex	1.35	[0.97-1.88]	0.071	1.57	[1.11-2.24]	**0.011**
Previous malignancy	1.15	[0.73-1.81]	0.545	1.10	[0.68-1.78]	0.710
cT-stage						
T1-2	Ref	-	-	Ref	-	-
T3-4	1.00	[0.71-1.41]	0.994	1.00	[0.69-1.45]	0.993
Tx	0.85	[0.58-1.24]	0.392	0.76	[0.51-1.14]	0.184
cN-stage						
N0	Ref	-	-	Ref	-	-
N+	1.57	[1.15-2.15]	**0.005**	1.49	[1.06-2.11]	**0.023**
Nx	1.76	[1.10-2.81]	**0.017**	1.71	[1.05-2.79]	**0.030**
cMx	1.36	[0.79-2.36]	0.265	1.33	[0.73-2.42]	0.346
Year of surgery						
2004 – 2005	Ref	-	-	Ref	-	-
2006 – 2007	0.96	[0.60-1.53]	0.853	1.04	[0.64-1.68]	0.889
2008 – 2009	0.71	[0.44-1.15]	0.165	0.79	[0.46-1.36]	0.389
2010 – 2011	0.81	[0.46-1.44]	0.475	1.16	[0.58-2.33]	0.678
2012 – 2013	0.52	[0.29-0.94]	**0.030**	0.76	[0.38-1.52]	0.440
2014 – 2015	0.55	[0.28-1.06]	0.074	0.82	[0.39-1.71]	0.592
Year of surgery simplified (SRCC only)						
2004 – 2009						
2010 – 2015						
Hospital volume						
<20 resections	Ref	-	-	Ref	-	-
20-40 resections	0.60	[0.41-0.88]	**0.008**	0.71	[0.46-1.10]	0.130
>40 resections	0.74	[0.50-1.09]	0.128	0.59	[0.38-0.92]	**0.019**
Surgical treatment						
Total gastrectomy	Ref	-	-	Ref	-	-
Esophagectomy	1.00	[0.72-1.38]	1.000	1.09	[0.75-1.60]	0.640
Procedure unknown	1.09	[0.52-2.31]	0.811	0.88	[0.40-1.94]	0.752

Bold values indicate significance ($p < 0.05$). HR = hazard ratio, CI = confidence interval and ref = reference.

	GEJ - SRCC subgroup					
	Univariable			Multivariable		
	HR	[95% CI]	p	HR	[95% CI]	p
	Ref	-	-	Ref	-	-
	0.61	[0.39-0.96]	**0.032**	0.53	[0.31-0.92]	**0.024**
	1.01	[0.99-1.03]	0.404			
	1.55	[0.94-2.55]	0.086	1.61	[0.96-2.71]	0.070
	0.88	[0.44-1.77]	0.720			
	Ref	-	-			
	1.00	[0.60-1.66]	0.998			
	0.74	[0.39-1.41]	0.362			
	Ref	-	-	Ref	-	-
	1.90	[1.16-3.11]	**0.011**	1.75	[1.05-2.93]	**0.032**
	2.51	[1.24-5.10]	**0.011**	2.56	[1.20-5.45]	**0.015**
	2.01	[0.96-4.24]	0.066	1.54	[0.71-3.33]	0.271
	Ref	-	-			
	1.70	[0.73-3.96]	0.219			
	1.52	[0.66-3.52]	0.329			
	1.27	[0.51-3.18]	0.611			
	0.76	[0.26-2.27]	0.625			
	1.07	[0.22-5.18]	0.930			
	Ref	-	-	Ref	-	-
	0.71	[0.43-1.17]	0.177	1.24	[0.67-2.31]	0.489
	Ref	-	-			
	0.75	[0.41-1.39]	0.368			
	0.87	[0.50-1.51]	0.610			
	Ref	-	-			
	0.97	[0.58-1.63]	0.919			
	1.06	[0.36-3.12]	0.909			

Annual hospital volume

For patients with gastric diffuse type cancer, surgery in a mid or high volume hospital was not associated with R+ resection rate or reduced all-cause mortality in multivariable analyses, as compared to surgery in a low volume hospital (Table 4a, Supplementary material 4 and 6).

For patients with GEJ diffuse type cancer, to analyze the effect of hospital volume, the nCRT group was not excluded. Surgery in a mid or high volume hospital was associated with a lower R+ resection rate compared to a low volume hospital in multivariable analyses (20-40 resections: RR 0.67 [95%CI 0.38-1.18], p=0.167; >40 resections: RR 0.47 [95%CI 0.25-0.91], p=0.025)(Supplementary material 5). In addition, surgery in a mid of high volume hospital was associated with lower all-cause mortality compared to a low volume hospital (20-40 resections, HR 0.69 [95%CI 0.47-1.02], p=0.060; >40 resections, HR 0.60 [95%CI 0.41-0.89], p=0.010)(Supplementary material 6 and 7).

Assessment of collinearity

For gastric diffuse type cancer, both PS and nCT patients were included in most years of surgery as well as in low, mid and high hospital volumes (Supplementary material 8 table A). Hence collinearity presumably did not affect the comparison of PS versus nCT.

For GEJ diffuse type cancer, there was a partial overlap between hospital volume, neoadjuvant therapy and year of surgery, indicating possible collinearity (Supplementary material 8 tables B and D). Nevertheless, upon removal of the variable hospital volume from the Cox Regression and Poisson regression analyses, the neoadjuvant treatment and year of surgery HRs and RRs remained largely unchanged (Supplementary material 5 and 7). Hence, collinearity was not an issue.

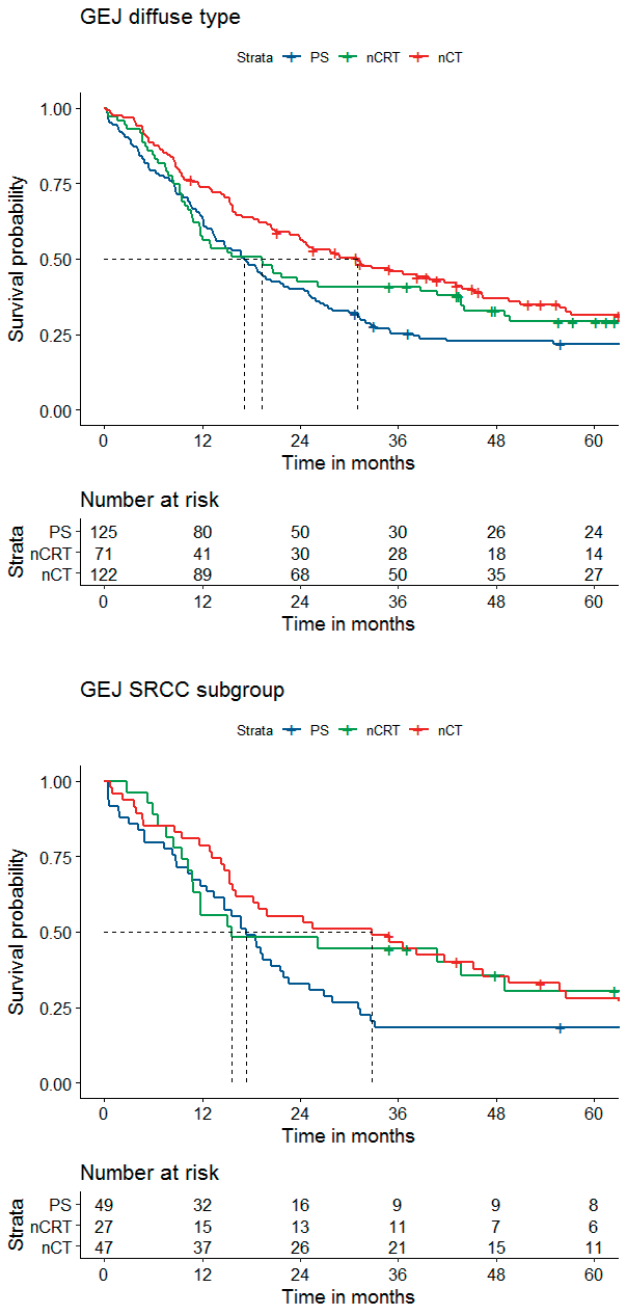

Figure 3. Overall 5-year survival for GEJ diffuse type carcinoma (top) and the GEJ SRCC subgroup (bottom). Kaplan-Meier plots and number of patients at risk are displayed. Median survival times are shown by interrupted lines. Censoring of patients is shown by a "+" on the plotted graphs.

DISCUSSION

In this large population-based study, nCT for patients with gastric and GEJ diffuse adenocarcinoma, including SRCC type, was associated with increased overall survival, compared to PS. This indicates that nCT should remain standard of care.

Messager et al. reported that PS should be considered as standard of care for gastric SRCC, because perioperative chemotherapy was not found to provide survival benefit in their cohort[13]. To evaluate this further, a French randomized controlled trial was initiated in 2012 (NCT01717924) aiming to evaluate survival of patients with SRCC after PS and adjuvant chemotherapy versus nCT, surgery and adjuvant chemotherapy[14,33], but inclusion has not yet been completed.

The current study found an association with longer survival in patients treated with nCT, both for diffuse type gastric and GEJ adenocarcinomas, including the SRCC subgroups, after multivariable analyses correcting for relevant baseline and treatment factors. For the gastric group, this reduction in all-cause mortality was strongest within 90 days postoperatively (HR=0.29), although a long-term reduction in mortality was also observed (HR=0.84). The associated increased short-term survival (lower 90-day postoperative mortality rates) may be caused by a better physical condition of patients in the nCT group due to selection bias. We believe a physiological effect of nCT causing a reduction in 90-day mortality is highly unlikely.

The associated increased long-term survival in the gastric and GEJ nCT group is likely a combination of a biological effect of nCT and selection bias. This biological effect of chemotherapy has been clearly demonstrated for gastric cancer overall in several prospective trials[5,10]. However, these populations mostly consisted of intestinal type tumors, with only a small proportion of diffuse types, which makes the evidence less convincing for the latter group. Regarding selection bias, the patients who are in good condition and without comorbidities and thus are expected to have a longer survival, are also expected to be the patients selected to undergo neoadjuvant chemotherapy. Unfortunately, comorbidities, WHO performance status and postoperative complications were not registered in the NCR during this period and could not be corrected for in the current study. Nevertheless, retrospective studies that do correct for these factors will still contain residual selection bias and improvements in survival should always be interpreted with caution. Importantly, this limitation is present in all currently available studies since all studies are retrospective. Despite these limitations, the authors believe that based on the current results and all currently available literature there are insufficient arguments to omit nCT from standard of care.

A further argument in favour of nCT is that MAGIC(-like) regimens were administered during the period of the current study, whereas the more effective FLOT regimen was only

implemented as standard of care since 2019. Indeed, although the FLOT4 trial was not powered for this subgroup analysis, the FLOT regimen showed a trend towards reduced mortality compared with the MAGIC regimen for diffuse type cancer (HR 0.85) and SRCC (HR 0.74)[10]. Hopefully, prospective trials, such as the ongoing French trial (NCT01717924) will provide a definitive answer on the added value of nCT in case of gastric SRCC[33].

For GEJ tumors, the PS and nCRT Kaplan Meier curves intersected in the current study. Hence, the proportional hazard assumption was not met. Since the nCRT group was small, splitting the HR was impossible and comparing PS with nCRT in a multivariable Cox regression was, unfortunately, impossible. Thus, results from the randomized Neo-AEGIS and ESOPEC trials comparing FLOT versus CROSS in esophageal and GEJ adenocarcinoma should be awaited[34,35].

For gastric diffuse type cancer, no significant difference in survival or R+ resection rate were found in low versus mid and high volume hospitals. However, for GEJ diffuse type cancer, undergoing surgery in hospitals with a high annual case volume was associated with markedly increased survival, compared to hospitals with a low annual case volume. Presumably, this difference is due to a difference in technical difficulty and the fact that initiation of centralization of gastric cancer started later. Indeed, centralization of gastroesophageal cancer care was initiated in 2006 in the Netherlands, based on earlier findings that centralization decreases postoperative morbidity and improves survival[36–38]. Hospitals performing esophagectomy were required to perform a minimum of 10 resections annually since 2006 and 20 resections annually since 2011. For gastrectomy, 10 resections were required annually since 2012 and 20 resections annually since 2013. Strikingly, for GEJ diffuse type adenocarcinomas resected in a low-volume hospital, overall survival was significantly worse when compared to higher volume hospitals. In addition, multivariable analyses showed that R+ resection rates were twice as high in low-volume hospitals, which likely will have contributed to the difference in survival. Both selecting the optimal procedure and the technical performance of the procedure are challenging for GEJ tumors in general. For diffuse type tumors specifically, this is likely further complicated due to the more infiltrative character of the tumor[6,11,39]. For GEJ diffuse type adenocarcinomas especially, it is thus essential that the surgical team has a broad experience in operating these tumors, which supports centralization.

Because of the aforementioned centralization, collinearity was assessed between hospital volume, neoadjuvant therapy and year of surgery and was shown to be of limited influence on the current study results. Furthermore, aside from the previously discussed selection bias, we believe we were effectively able to deal with most, if not all, forms of bias in our analyses. To prevent immortal time bias in the comparison between PS and nCT, survival duration was calculated from the date of surgery. As a further measure to prevent immortal time bias and reduce selection bias, the groups were selected based upon

neoadjuvant therapy only, despite the fact that in the Netherlands, neoadjuvant chemotherapy is always given with the intention to also give adjuvant therapy (perioperative therapy). Historical bias was prevented by correction for the year of resection. Lastly, hospital bias was minimized since it was a population-based study which included all hospitals in the Netherlands and a correction was made for hospital annual case volume.

A limitation of the SRCC subgroup analyses is that the definition of SRCC differed over the years and was dependent on the interpretation of the evaluating pathologist. As this is a worldwide issue, a recent consensus on the pathological definition was published, with only SRCC cancers with at least 90% poorly cohesive cells having signet ring cell morphology classified as SRCC[18]. Unfortunately, such agreements were not available during the study period and therefore the SRCC definition and coding is variable in our cohort. However, all currently available retrospective studies, including the study by Messager et al., have also been struggling with the uniformity of the SRCC definition and selection bias[13]. Despite these limitations, the current study is the largest nationwide population-based study in the field and may aid policy making and clinical decision making.

Our results may have the following implications: i. although these results and the results from the only other large population study by Messager et al. are retrospective and thus subject to bias, the conjunction of all currently available literature provides insufficient arguments to omit nCT in the standard curative treatment of gastric and GEJ diffuse type carcinoma, including SRCC[13,14,40]. Our results show that administering nCT in patients with diffuse type gastric and GEJ cancer is actually associated with a better survival compared to surgery alone and should therefore remain standard of care. ii. For GEJ diffuse type carcinoma, treatment should be centralized and resections should not be performed in hospitals with low annual volumes since this was associated with more R+ resections and reduced survival in the current population study.

In conclusion, this population-based study shows that, in patients with gastric or GEJ diffuse type adenocarcinoma, including SRCC, nCT was associated with better survival when compared to PS. Hence, nCT should remain standard of care in these patients. Moreover, in patients with GEJ adenocarcinoma, surgery in hospitals with low annual case volumes was associated with more R+ resections and a lower survival. Thus, centralization of care is advised for these patients.

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SUPPLEMENTARY MATERIAL

Supplementary material 1 - Proportional hazard assumption, statistical details

A key assumption of the Cox regression is proportional hazards, which means that the HR assigned to a variable is constant over time (Therneau et al: "Modeling Survival Data: Extending the Cox Model", 2000). For example, 100 patients receiving "treatment A" are compared with 100 patients receiving "treatment B" and the results yield a hazard ratio of 0.5. The difference between treatment A and B could for example be mortality at 1 year of 10 versus 20 patients, at 3 years of 20 versus 40 patients and at 5 years of 30 versus 60 patients. Hence, the relative difference (not the absolute difference) between treatment groups remains roughly constant over time.

In the current study, the proportional hazard assumptions were assessed in two ways. Kaplan Meier curves were plotted and visually checked for converging or even intersecting lines and for insufficiently diverging lines (i.e. lines showing the same absolute difference over time, but not the same relative difference), all of which indicate that the proportional hazard assumption is not met. In addition, the proportional hazard assumption was directly tested on the outcome variables in the definitive multivariable cox regression models via Schoenfeld's global test, which rejects the proportional hazard assumption (H_0) if $p<0.05$ (Abeysekera et al: J Natl Sci Found Sri Lanka 37:41-51, 2009).

Results of the proportional hazard assumption assessments per subgroup are described in the table in Supplementary material 2. In the gastric groups, an interaction variable "nCT[yes/no]*>90 days[yes/no]" was added to the Cox regression with the "survSplit" function from the "survival" package in R (https://www.rdocumentation.org/packages/survival/versions/3.2-3/topics/survSplit). Hence, a HR for mortality within 90 days and after 90 days was provided (Borucka: "Extensions of Cox Model for Non-Proportional Hazards Purpose", Paper SP07, PhUSE annu. Conf. 2013). After addition of this interaction variable, the proportional hazard assumption was no longer rejected.

It was decided to split the HR at 90 days postoperatively, since this allows for easy interpretation of the HRs by clinicians reading the current paper and since 90 day mortality is commonly regarded a parameter for surgery-related mortality (Walters et al: Ann Thorac Surg 98:506–12, 2014; Low et al: Ann Surg 262:286-94, 2015).

In the GEJ groups, the Kaplan Meier nCRT curve clearly intersects with the PS curve (Figure 3), hence the proportional hazard assumption (H_0) was rejected, even though Schoenfeld's tests p values were 0.100 and 0.120. Due to the small numbers of the nCRT group, it wouldn't be possible to split the HR. Hence the nCRT group was removed from the Cox regression (Table 4b). Furthermore, the Kaplan Meier <20 annual resection curve sufficiently diverges from the 20-40 annual resection curve (Supplementary material 7), hence the proportional hazard assumption (H_0) was accepted, even though Schoenfeld's tests p value was 0.028.

Supplementary material 2. Proportional hazard assumptions, assessment and corrections

Primary analysis		
	Gastric - diffuse type nCT versus PS	**Gastric - SRCC subgroup nCT versus PS**
Without correction:		
Kaplan Meier curves	Insufficiently diverging	Insufficiently diverging
Schoenfeld's test	X^2 statistic=7.31, p=0.0069	X^2 statistic=4.70, p=0.030
Proportional hazard assumption (H_0)	Rejected	Rejected
Presumed cause of rejection	Difference in 90 day mortality (= surgery related mortality)	Difference in 90 day mortality (= surgery related mortality)**
Correction	Interaction variable "nCT[yes/no]*>90 days[yes/no]" added	Interaction variable "nCT[yes/no]*>90 days[yes/no]" added
After correction:		
Schoenfeld's test	nCT[yes/no]: X^2 statistic=0.024, p=0.877; nCT[yes/no]*>90 days[yes/no]: X^2 statistic=0.050, p=0.824	nCT[yes/no]: X^2 statistic=0.325, p=0.569; nCT[yes/no]*>90 days[yes/no]: X^2 statistic=0.287, p=0.592
Proportional hazard assumption (H_0)	Accepted	Accepted

Post hoc analyses		
	Gastric - diffuse type Annual resections <20 versus 20-40	**Annual resections <20 versus >40**
Without correction:		
Kaplan Meier curves	Overlapping	Overlapping
Schoenfeld's test	X^2 statistic=0.0187, p=0.89	X^2 statistic=1.566, p=0.21
Proportional hazard assumption (H_0)	Accepted	Accepted

	GEJ - diffuse type nCRT versus PS	nCT versus PS	GEJ - SRCC subgroup nCRT versus PS	nCT versus PS
	Intersecting	Sufficiently diverging	Intersecting	Sufficiently diverging
	X^2 statistic=2.712, p=0.100	X^2 statistic=0.0333, p=0.855	X^2 statistic=2.47, p=0.120	X^2 statistic=0.0312, p=0.860
	Rejected	Accepted	Rejected	Accepted
	Small sample size of nCRT group		Small sample size of nCRT group	
	Exclusion of nCRT group from Cox regression		Exclusion of nCRT group from Cox regression	
	Not applicable		Not applicable	
	Not applicable		Not applicable	

	GEJ - diffuse type Annual resections <20 versus 20-40	Annual resections <20 versus >40
	Sufficiently diverging	Sufficiently diverging
	X^2 statistic=4.810, p=0.028	X^2 statistic=0.0294, p=0.864
	Accepted	Accepted

Supplementary material 3. Treatment characteristics of 984 patients who were diagnosed with a signet ring cell carcinoma, divided per location

	Gastric (n=861)		GEJ (n=123)	
	No. (%)	**Missing values (%)**	**No. (%)**	**Missing values (%)**
Neoadjuvant treatment		0 (0)		0 (0)
Chemotherapy[1]	398 (46)		47 (38)	
Chemoradiotherapy	0 (0)		27 (22)	
Radiotherapy only	0 (0)		0 (0)	
None	463 (54)		49 (40)	
Surgical treatment		0 (0)		0 (0)
Subtotal gastrectomy	503 (58)		n.a.	
Total gastrectomy	287 (33)		23 (19)	
Transthoracic esophagectomy	n.a.		16 (13)	
Transhiatal esophagectomy	n.a.		21 (17)	
Unknown type of resection	71 (8)		63 (51)	
Adjuvant treatment		0 (0)		0 (0)
Chemotherapy[1]	219 (25)		20 (17)	
Chemoradiotherapy[2]	36 (4)		2 (2)	
Radiotherapy only	0 (0)		0 (0)	
None	606 (70)		101 (82)	

Percentages may not add up to 100% due to rounding. [1]214 patients in de gastric and 20 patients in the GEJ group underwent aCT in the context of perioperative chemotherapy. Of these patients, 38 in the gastric group and 3 in the GEJ underwent additional radiotherapy. 5 patients in the gastric group did not undergo nCT. [2]24 patients in the gastric and 1 patient in the GEJ group underwent nCT.

Supplementary material 4. Multivariable Poisson regression on treatment factors associated with the occurrence of an R+ resection for diffuse type gastric cancer, corrected by patient and tumor characteristics

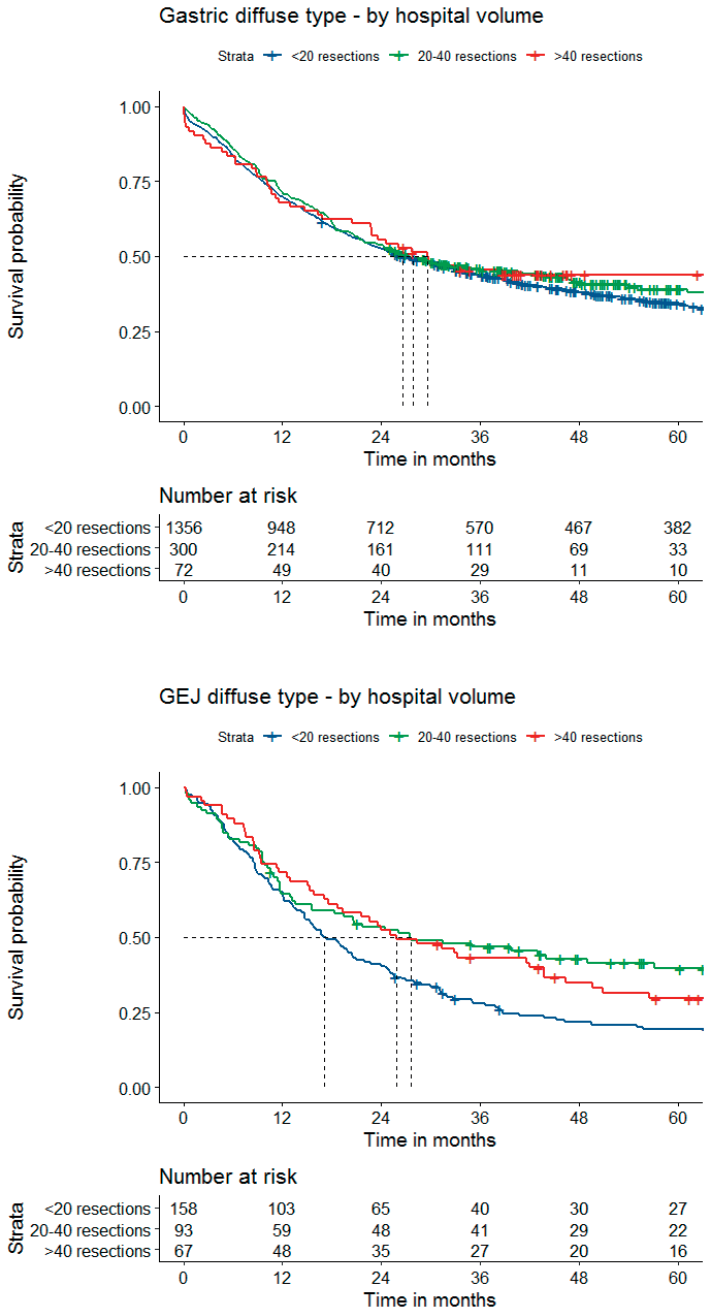
	Gastric - diffuse type					
	Univariable			**Multivariable**		
	RR	**[95% CI]**	**p**	**RR**	**[95% CI]**	**p**
Hospital volume						
<20 resections	Ref	-	-	Ref	-	-
20-40 resections	0.73	[0.56-0.97]	0.028	0.81	[0.60-1.09]	0.159
>40 resections	0.69	[0.40-1.20]	0.189	0.92	[0.52-1.62]	0.767
nCT	0.85	[0.71-1.02]	0.085	0.81	[0.65-1.02]	0.079
Additional year of age	1.01	[1.00-1.01]	0.065	1.01	[1.00-1.01]	0.176
Female sex	1.01	[0.84-1.22]	0.885	1.09	[0.91-1.31]	0.339
Previous malignancy	1.01	[0.75-1.35]	0.954	1.02	[0.76-1.37]	0.886
cT-stage						
T1	Ref	-	-	Ref	-	-
T2	5.35	[1.74-16.44]	0.003	5.34	[1.73-16.42]	0.004
T3	6.81	[2.20-21.04]	0.001	5.88	[1.88-18.34]	0.002
T4	12.17	[3.92-37.76]	<0.001	9.16	[2.93-28.60]	<0.001
Tx	4.67	[1.53-14.27]	0.007	4.20	[1.38-12.78]	0.012
cN-stage						
N0	Ref	-	-	Ref	-	-
N+	1.74	[1.42-2.13]	<0.001	1.49	[1.20-1.84]	<0.001
Nx	1.38	[1.08-1.78]	0.012	1.25	[0.97-1.61]	0.080
cMx	1.83	[1.35-2.47]	<0.001	1.38	[0.99-1.92]	0.056
Year of surgery						
2004 – 2005	Ref	-	-	Ref	-	-
2006 – 2007	0.96	[0.65-1.42]	0.849	1.00	[0.70-1.43]	0.987
2008 – 2009	1.20	[0.83-1.74]	0.330	1.33	[0.93-1.91]	0.121
2010 – 2011	0.88	[0.60-1.30]	0.515	1.15	[0.76-1.73]	0.512
2012 – 2013	0.74	[0.50-1.10]	0.142	0.92	[0.61-1.39]	0.693
2014 – 2015	0.74	[0.50-1.11]	0.149	0.89	[0.57-1.39]	0.610
Surgical treatment						
Total gastrectomy	Ref	-	-	Ref	-	-
Subtotal gastrectomy	0.67	[0.55-0.81]	<0.001	0.63	[0.52-0.77]	<0.001
Unknown type of procedure	1.26	[0.95-1.67]	0.108	1.00	[0.73-1.35]	0.981

Bold values indicate significance ($p < 0.05$). RR= relative risk, CI = confidence interval and ref = reference.

Supplementary material 5. Multivariable Poisson regression on treatment factors associated with the occurrence of an R+ resection for diffuse GEJ cancer, corrected by patient and tumor characteristics

	GEJ - diffuse type								
	Univariable			**Multivariable**			**Multivariable without annual hospital volume**		
	RR	**[95% CI]**	**p**	**RR**	**[95% CI]**	**p**	**RR**	**[95% CI]**	**p**
Neoadjuvant treatment									
PS	Ref	-	-	Ref	-	-			
nCT	0.83	[0.53-1.28]	0.391	0,70	[0.41-1.19]	0.188	0.67	[0.39-1.98]	0.142
nCRT	0.40	[0.20-0.82]	0.012	0,38	[0.17-0.84]	0.017	0.33	[0.15-2.21]	0.006
Additional year of age	0.99	[0.98-1.01]	0.404	0.99	[0.97-1.01]	0.245	0.99	[0.97-1.31]	0.250
Female sex	1.56	[1.00-2.43]	0.048	1.67	[1.03-2.71]	0.037	1.58	[0.99-1.69]	0.056
Previous malignancy	1.30	[0.71-2.36]	0.395	1.16	[0.65-2.05]	0.619	1.18	[0.68-3.03]	0.556
cT-stage									
T1-2	Ref	-	-	Ref	-	-	Ref	-	-
T3-4	0.95	[0.58-1.53]	0.825	1,04	[0.66-1.65]	0.864	1.01	[0.63-4.28]	0.980
Tx	0.81	[0.44-1.48]	0.488	0,69	[0.38-1.26]	0.224	0.69	[0.38-2.31]	0.236
cN-stage									
N0	Ref	-	-	Ref	-	-	Ref	-	-
N+	1.61	[0.98-2.63]	0.058	1,49	[0.91-2.45]	0.116	1.50	[0.91-1.85]	0.114
Nx	2.11	[1.07-4.13]	0.030	1,71	[0.83-3.53]	0.146	1.83	[0.90-2.24]	0.096
cMx-stage	1.93	[0.95-3.91]	0.067	1.75	[0.85-3.60]	0.129	1.70	[0.81-2.47]	0.162
Year of surgery									
2004 – 2005	Ref	-	-	Ref	-	-	Ref	-	-
2006 – 2007	0.76	[0.38-1.53]	0.445	0,84	[0.44-1.60]	0.592	0.88	[0.45-3.96]	0.710
2008 – 2009	0.58	[0.28-1.22]	0.155	0,71	[0.34-1.50]	0.369	0.71	[0.34-3.11]	0.380
2010 – 2011	0.72	[0.35-1.49]	0.376	1,33	[0.55-3.22]	0.522	1.33	[0.55-4.12]	0.533
2012 – 2013	0.65	[0.31-1.38]	0.261	1,42	[0.61-3.30]	0.414	1.26	[0.55-4.13]	0.589
2014 – 2015	0.30	[0.11-0.81]	0.018	0,69	[0.25-1.87]	0.461	0.63	[0.23-3.94]	0.363
Hospital volume									
<20 resections	Ref	-	-	Ref	-	-			
20-40 resections	0.57	[0.34-0.96]	0.036	0,67	[0.39-1.18]	0.167			
>40 resections	0.51	[0.27-0.95]	0.035	0,47	[0.25-0.91]	0.025			
Surgical treatment									
Total gastrectomy	Ref	-	-	Ref	-	-	Ref	-	-
Esophagectomy	0.94	[0.56-1.56]	0.804	1,38	[0.80-2.36]	0.247	1.06	[0.64-3.77]	0.813
Type of procedure unknown	1.63	[0.60-4.41]	0.341	1,62	[0.61-4.33]	0.333	1.63	[0.61-3.75]	0.331

Bold values indicate significance ($p < 0.05$). RR= relative risk, CI = confidence interval and ref = reference.



Supplementary material 6. Overall 5-year survival for diffuse type gastric carcinoma (top) and GEJ diffuse type carcinoma (bottom), stratified by hospital volume. Kaplan-Meier plots and number of patients at risk are displayed. Median survival times are shown by interrupted lines. Censoring of patients is shown by a "+" on the plotted graphs.

Supplementary material 7. Univariable and multivariable Cox regression analyses on all-cause mortality for diffuse type GEJ cancer, without exclusion of the nCRT group

	GEJ - diffuse type								
	Univariable			Multivariable			Multivariable without annual hospital volume		
	RR	[95% CI]	p	RR	[95% CI]	p	RR	[95% CI]	p
Neoadjuvant treatment									
PS	Ref	-	-	Ref	-	-			
nCT	0.65	[0.48-0.86]	0.003	0.64	[0.44-0.92]	0.017	0.62	[0.43-0.90]	0.013
nCRT[1]	0.77	[0.55-1.08]	0.131	0.89	[0.56-1.42]	0.632	0.82	[0.51-1.30]	0.387
Additional year of age	1.00	[0.99-1.02]	0.458	1.00	[0.99-1.02]	0.488	1.00	[0.99-1.02]	0.467
Female sex	1.24	[0.91-1.68]	0.168	1.45	[1.05-2.00]	0.025	1.41	[1.03-1.95]	0.034
Previous malignancy	1.03	[0.68-1.58]	0.878	1.02	[0.65-1.60]	0.927	1.00	[0.64-1.56]	0.996
cT-stage									
T1-2	Ref	-	-	Ref	-	-	Ref	-	-
T3-4	1.08	[0.80-1.47]	0.604	1.03	[0.74-1.42]	0.880	1.06	[0.77-1.47]	0.714
Tx	0.95	[0.66-1.36]	0.781	0.85	[0.58-1.24]	0.408	0.90	[0.62-1.31]	0.570
cN-stage									
N0	Ref	-	-	Ref	-	-	Ref	-	-
N+	1.66	[1.25-2.19]	<0.001	1.66	[1.22-2.25]	<0.001	1.62	[1.20-2.18]	0.002
Nx	1.89	[1.20-2.96]	0.006	1.83	[1.14-2.93]	0.012	1.84	[1.15-2.94]	0.011
cMx-stage	1.36	[0.79-2.33]	0.270	1.28	[0.71-2.31]	0.416	1.21	[0.67-2.16]	0.530
Year of surgery									
2004 – 2005	Ref	-	-	Ref	-	-	Ref	-	-
2006 – 2007	1.05	[0.65-1.68]	0.852	1.13	[0.70-1.82]	0.630	1.16	[0.71-1.87]	0.556
2008 – 2009	0.80	[0.50-1.29]	0.369	0.91	[0.54-1.55]	0.740	0.90	[0.53-1.52]	0.696
2010 – 2011	0.88	[0.53-1.46]	0.614	1.16	[0.62-2.16]	0.636	1.11	[0.59-2.08]	0.744
2012 – 2013	0.55	[0.32-0.93]	0.024	0.77	[0.41-1.44]	0.410	0.68	[0.36-1.28]	0.231
2014 – 2015	0.79	[0.46-1.34]	0.373	1.16	[0.62-2.18]	0.647	1.04	[0.56-1.94]	0.897
Hospital volume									
<20 resections	Ref	-	-	Ref	-	-			
20-40 resections	0.64	[0.47-0.87]	0.005	0.69	[0.47-1.02]	0.060			
>40 resections	0.74	[0.53-1.03]	0.073	0.60	[0.41-0.89]	0.010			
Surgical treatment									
Total gastrectomy	Ref	-	-	Ref	-	-	Ref	-	-
Esophagectomy	0.97	[0.72-1.32]	0.867	1.11	[0.77-1.59]	0.593	0.89	[0.64-1.25]	0.508
Type of procedure unknown	1.09	[0.52-2.28]	0.829	0.90	[0.42-1.97]	0.801	0.93	[0.43-2.03]	0.863

Bold values indicate significance ($p < 0.05$). HR = hazard ratio, CI = confidence interval and ref = reference. [1]nCRT does not comply with the proportional hazard assumption, hence nCRT can be used as a correction for the remaining variables (i.e. hospital volume), but no conclusions should be drawn from the specific nCRT HR, 95% CI and p value.

Supplementary material 8. Associations between Neoadjuvant treatment, year of surgery and hospital volume

A	Gastric - diffuse type				
	Neoadjuvant treatment				
	PS		nCT		
n (%)	889		839		p
Year of surgery					<0.001
2004 – 2005	128	(14)	0	(0)	
2006 – 2007	241	(27)	62	(7)	
2008 – 2009	152	(17)	156	(19)	
2010 – 2011	124	(14)	194	(23)	
2012 – 2013	142	(16)	206	(25)	
2014 – 2015	102	(11)	221	(26)	
Hospital volume					<0.001
<20 resections	755	(85)	601	(72)	
20-40 resections	107	(12)	193	(23)	
>40 resections	27	(3)	45	(5)	

B	GEJ - diffuse type						
	Neoadjuvant treatment						
	PS		nCT		nCRT		
n (%)	125		122		71		p
Year of surgery							<0.001
2004 – 2005	26	(21)	2	(2)	1	(1)	
2006 – 2007	51	(41)	13	(11)	1	(1)	
2008 – 2009	27	(22)	36	(30)	3	(4)	
2010 – 2011	7	(6)	24	(20)	22	(31)	
2012 – 2013	9	(7)	24	(20)	21	(30)	
2014 – 2015	5	(4)	23	(19)	23	(32)	
Hospital volume							<0.001
<20 resections	84	(67)	64	(52)	10	(14)	
20-40 resections	22	(18)	37	(30)	34	(48)	
>40 resections	19	(15)	21	(17)	27	(38)	

C	Hospital volume, annual resections						
	<20		20-40		>40		
n (%)	1356		300		72		p
Year of surgery							<0.001
2004 – 2005	127	(9)	0	(0)	1	(1)	
2006 – 2007	290	(21)	10	(3)	3	(4)	
2008 – 2009	285	(21)	21	(7)	2	(3)	
2010 – 2011	276	(20)	42	(14)	0	(0)	
2012 – 2013	253	(19)	75	(25)	20	(28)	
2014 – 2015	125	(9)	152	(51)	46	(64)	

D	Hospital volume, annual resections						
	<20		20-40		>40		
n (%)	158		93		67		p
Year of surgery							<0.001
2004 – 2005	24	(15)	1	(1)	4	(6)	
2006 – 2007	46	(29)	8	(9)	11	(16)	
2008 – 2009	39	(25)	18	(19)	9	(13)	
2010 – 2011	25	(16)	13	(14)	15	(22)	
2012 – 2013	13	(8)	25	(27)	16	(24)	
2014 – 2015	11	(7)	28	(30)	12	(18)	

Percentages may not add up to 100% due to rounding. Table A displays the influence of year of surgery and hospital volume on the comparison of PS with nCT in the gastric diffuse type group. Table B displays this influence in the GEJ diffuse type group. Table C displays the influence of year of surgery on the comparison of low, mid and high volume centers in the gastric diffuse type group. Table D displays this influence in the GEJ diffuse type group.


Retrospective

CHAPTER 7

Management of resectable esophageal and gastric (mixed adeno)neuroendocrine carcinoma: a nationwide cohort study

European Journal of Surgical Oncology 2018

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ABSTRACT

Introduction

The aim of this study is to provide insight in accuracy of diagnosing, current treatment and survival in patients with resectable esophageal and gastric neuroendocrine- and mixed adenoneuroendocrine carcinomas (NEC, MANEC).

Methods

All patients with esophageal or gastric (MA)NEC, who underwent surgical resection between 2006-2016, were identified from the Dutch national registry for histo- and cytopathology (PALGA). Patients with a neuroendocrine tumor lower than grade 3 were excluded. Data on patients, treatment and outcomes were retrieved from the patient records. Diagnosis by endoscopic biopsy was compared with diagnosis by resection specimen. Kaplan Meier survival analysis was performed.

Results

A total of 49 patients were identified in 25 hospitals, including 21 patients with esophageal (MA)NEC and 26 patients with gastric (MA)NEC on resection specimen. Biopsy diagnosis of (MA)NEC was correct in 23/27 patients. However, 20/47 patients with definitive diagnosis of (MA)NEC, were misdiagnosed on biopsy. Neoadjuvant therapy was administered in 13 (62%) esophageal (MA)NECs and 12 (46%) gastric (MA)NECs. Survival curves were similar with and without neoadjuvant therapy. One (4.8%) esophageal (MA) NEC and 4 (15%) gastric (MA)NECs died within 90 days postoperatively. For esophageal (MA)NEC the median overall survival (OS) after surgery was 37 months and 1-, 3- and 5-year OS were 71%, 50% and 35%, respectively. For gastric (MA)NEC, the median OS was 23 months and 1-, 3- and 5-year OS were 62%, 50% and 39%, respectively.

Conclusion

Localized esophageal and gastric (MA)NEC are often misdiagnosed on endoscopic biopsies. After resection, long-term survival was achieved in respectively 35% and 39% of patients.

INTRODUCTION

Neuroendocrine neoplasms of the esophagus and stomach are very rare and can be divided into low-grade (grade 1 and 2) or high-grade (grade 3) neoplasms (1, 2). Low-grade neuroendocrine neoplasms, with a Ki-index of <20% or <20 mitoses per 10 high power fields, are classified as neuroendocrine tumors (NET) whereas high-grade neuroendocrine neoplasms, with a Ki-index of >20% or >20 mitoses per 10 high power fields, are classified as neuroendocrine carcinomas (NEC). Non-neuroendocrine components, usually adenocarcinoma and more rarely squamous cell carcinoma (SCC), can be present in NEC. When both the neuroendocrine and the non-neuroendocrine components represent at least 30% of such a tumor, they are called mixed adenoneuroendocrine carcinoma (MANEC)(1). For NEC and MANEC pooled, we use the term (MA)NEC.

Little is known about the optimal treatment strategy for esophageal and gastric MANEC (3). One may suggest to focus treatment on the more aggressive component. This could be the high-grade NEC component, though data is lacking. Based on our experience, we hypothesize that MANEC can be missed due to sampling error. However, there is no data on this matter. The nomenclature for (MA)NEC has changed frequently in the past decades(1, 4, 5), leading to inconsistent terminology in the literature and considerable confusion among clinicians and pathologists(3). Most studies on NEC do not clearly define MANEC as a separate subgroup. However, in the WHO 2010 classifications MANEC and NEC are considered distinct entities (1).

Small retrospective cohort studies on the treatment and outcome of patients with NEC are mostly from Asian populations, all In patients who did not undergo neoadjuvant treatment prior to surgery (6-12). Studies show a poor prognosis for both esophageal and gastric NEC and the role of surgery for esophageal NEC remains undefined (8, 11-13). Other studies show favorable survival rates after surgical resection for NEC (7, 9, 10, 14).

The aim of this study is to provide insight in accuracy of diagnosing, current treatment and survival in patients with resectable esophageal and gastric (MA)NEC in a Western cohort.

METHODS

Patients and data

All patients with esophageal or gastric (MA)NEC, who underwent surgical resection of the primary tumor between January 2006 and May 2016 in the Netherlands were included. Patients were identified by searching the nationwide registry of histo- and cytopathology in the Netherlands (PALGA) for “stomach” or “esophagus” and “neuroendocrine tumor”

(and all synonyms). The PALGA database collects every pathological report generated by all pathology departments in the Netherlands since 1971 (15). Patients that did not undergo resection of the primary tumor and patients with a low-grade (grade 1 or 2) neuroendocrine component were excluded.

All patients with a definitive diagnosis of (MA)NEC on the resection specimen were included in the study and in all statistical analyses. As this is the gold standard, the current study contains all cases of resected (MA)NEC with no missed cases.

In addition, patients with a false positive diagnosis of (MA)NEC on biopsy (i.e. a biopsy diagnosis of (MA)NEC, but a definitive diagnosis on resection specimen of non-(MA)NEC), were included in the analysis of accuracy of biopsy diagnosis, but excluded from analyses of baseline characteristics, (neo)adjuvant therapy and survival.

Clinical data was retrieved from each patient by review of the hospital's medical record. Every hospital was visited to retrieve these data. These data included demographic data, comorbidities and ASA physical status score(16), details on (neoadjuvant) treatment, pathology reports of pre-operative biopsies and post-operative resection specimens and data on follow-up including recurrence of disease. Due to the retrospective nature of the current study, informed consent was not required by the Committee on Research Involving Human Subjects of the University Medical Center Utrecht.

Pathology diagnosis of (MA)NEC

All pathology reports were reviewed by a dedicated upper gastrointestinal pathologist in the University Medical Center of Utrecht (LB). The histological specimen were not reviewed. The review determined whether or not the WHO 2010 classification was used. If this was not the case, the diagnoses was adjusted according to the 2010 WHO classifications(1). MANEC was thus defined as a tumor consisting for >30% of a NEC component (with Ki-index of >20%) and for >30% of an adenocarcinoma component. Tumors consisting of a low-grade (grade 1 or 2) neuroendocrine component and an adenocarcinoma were not considered a MANEC. The WHO 2010 diagnosis of (MA)NEC on the resection specimen was considered the definitive diagnosis. Biopsy diagnosis was based upon all pre-operative biopsies (reviews of these biopsies that were performed post operatively after diagnosis on the resection specimen, were not taken into account).

Treatment, outcome and survival analyses

Gastroesophageal junction (GEJ) tumors in patients who underwent esophagectomy were classified as esophageal and GEJ tumors from patients who underwent a gastrectomy were classified as gastric. Post-operative complications were scored according to the Clavien-Dindo Classification of Surgical Complications (CD)(17).

Radicality of resection was defined according to the Union for International Cancer Control (UICC) (18). Tumor regression grades were scored according to the Mandard score (19). Often, no clear distinction could be made between Mandard 4 or Mandard 5 and these scores were therefore combined. Unless noted otherwise, mixed tumors received one Mandard score for the entire tumor.

Progression free survival (PFS) was defined as the interval between date of surgery and date of first recurrence or progression of (residual) disease regardless of organ or tissue or death from any cause. OS was defined as the interval between date of surgery and date of last follow-up or death. As part of standardized clinical follow-up in the Netherlands, abdominal and thoracic CT scans were made only when there was suspicion of recurrent disease.

Statistical analysis

Differences between two groups were compared by chi-squared tests for nominal data and by Mann-Whitney U tests for ordinal data. Kaplan-Meier survival analysis was conducted for determination of PFS and OS and the generation of survival curves. Potential follow-up time was calculated with Kaplan-Meier estimate of potential follow-up ("reverse Kaplan-Meier"). Actual follow-up to recurrence was the time between surgery and recurrence on follow-up. Differences between nonintersecting survival curves were analyzed by the log-rank test. All p-values are shown as 2-sided p-values. P-value < 0.05 were considered statistically significant. SPSS IBM Statistics 21 (IBM corp., Armonk, New York) was used for management and statistical analyses of the data.

RESULTS

Patient demographics

See table 1 for a flowchart of patient inclusion. A total of 49 patients from 25 hospitals were identified. All patients underwent a surgical resection of the primary tumor between January 2006 and May 2016. Two patients had a biopsy diagnosis of NEC, but a definitive diagnosis of adenocarcinoma and NET grade 2, respectively. The remaining 47 patients did have a diagnosis of (MA)NEC on the resection specimen.

Patient demographics are presented in table 1. No statistically significant differences were observed in patient demographics between the NEC and MANEC groups and the groups receiving neoadjuvant therapy or not (Supplementary material 1-4).

Out of 18 patients with a gastric NEC, 3 had a synchronous adenocarcinoma (2 located in the stomach, one in the distal esophagus). These adenocarcinomas were also removed by the primary resection.

Table 1. Patients demographics

n(%)	Esophageal 21[1]	Gastric 26[3]
Definitive diagnosis		
MANEC	9 (43)[2]	8 (31)[4]
NEC	12 (57)	18 (69)
Gender		
Male	16 (76)	21 (81)
Female	5 (24)	5 (19)
Mean age (±SD) at diagnosis, years	62.9 (9.5)	67.8 (10)
Mean BMI (±SD), kg/m2[5]	25.3 (4.9)	23.2 (3.9)
ASA score		
1	3 (14)	5 (29)
2	14 (67)	15 (58)
3	4 (19)	6 (23)
Comorbidities[6]		
Cardiac	6 (29)	6 (23)
Vascular	11 (52)	12 (46)
Diabetes	2 (9.5)	3 (12)
Pulmonary	5 (24)	5 (19)

[1]Includes 4 patients with GEJ cancer. [2]Includes 8 NEC + adenocarcinoma and 1 NEC + adenosquamous carcinoma [3]Includes 8 patients with GEJ cancer. [4]All NEC + adenocarcinoma. [5]BMI was missing in 7 patients. [6]Two patients with esophageal NEC were treated with curative intent for malignancies in the past 5 years (one patient with carcinoma of sigmoid colon, one patient with acute myeloid leukemia). Two patients with gastric NEC were treated for prostate cancer in the past 5 years.

Neoadjuvant and adjuvant therapy

Details on (neo)adjuvant therapy are presented in table 3. A total of 13 (62%) of esophageal (MA)NECs received neoadjuvant therapy (10 chemoradiotherapy, 3 chemotherapy). From a total of 10 patients with biopsy diagnosis of esophageal NEC, only 2 patients received neoadjuvant cis- or carboplatin/etiposide (in combination with radiotherapy in 1 patient). A total of 12 (46%) gastric (MA)NECs received neoadjuvant chemotherapy. From a total of 14 patients with biopsy diagnosis of gastric NEC, only 1 patients received neoadjuvant cisplatin/etoposide.

A good response (MANDARD score 1 or 2) to neoadjuvant treatment was seen in 3/13 esophageal (MA)NECs and in 1/12 gastric (MA)NEC. One patient with esophageal MANEC (NEC + adenosquamous carcinoma) did not show response in the NEC component but showed a complete response (Mandard 1) in the adenosquamous carcinoma component. One patient with NEC in the gastric antrum and a synchronous adenocarcinoma in the gastric corpus had no response in the NEC and a complete response of the adenocarcinoma. Both patients were scored as Mandard 4-5. The grouped MANDARD

Figure 1. Flowchart of patient inclusion. [1]See table 4 for more information.

scores (1-2, 3 or 4-5) were compared between the 5 patients that received cis- or carboplatin/etiposide and the 15 patients that received a standard regimen. No significant result was found (p = 0.275) (Supplementary material 5).

None of the patients with an esophageal MANEC and 4/12 patients with an esophageal NEC started adjuvant chemotherapy. None of the gastric MANEC patients and 4/18 of the gastric NEC patients started adjuvant chemotherapy.

Surgery and pathology

Surgical and pathological results are presented in table 2. The surgical margins were negative in all patients with esophageal (MA)NEC and 23 (88%) of the patients with gastric (MA) NEC. Preoperative biopsy diagnosis was compared to the definitive diagnosis of the resection specimen (table 4). In 20/24 patients with biopsy diagnoses of esophageal or gastric NEC, a concordant definitive diagnosis of the resection was found. In 2 patients, the definitive diagnosis of the resection specimen was MANEC, in 1 patient adenocarcinoma, and in 1 patient NET grade 2. All 3 patients with biopsy diagnosis of MANEC had a concordant definitive diagnosis of MANEC in the resection specimen. However, 13/16 patients with MANEC were misdiagnosed on biopsy and 9/29 patients with NEC were misdiagnosed on biopsy.

Concerning the 13 misdiagnosed MANECs, in 2/13 cases it was unknown whether immunohistochemical stainings for neuroendocrine markers (NE stainings) were performed. In 4/13 patients, NE stainings were performed and biopsy diagnoses were 2 times NEC, 1 adenocarcinoma and 1 SSC, respectively. Most likely these cases represent sampling errors. Importantly, NE stainings were not performed in 7/13 cases. For the 9 misdiagnosed NECs, in 1/9 patient it was unknown whether NE stainings were performed. In 2/9 patients, NE stainings were performed and the biopsy diagnoses were GIST + focal NEC and NET grade 2, respectively. In 6/9 patients no NE stainings were initially performed on the biopsy and the preoperatative diagnosis was adenocarcinoma in all 6 cases. Indeed, in 3 of these patients a post-operative review of the biopsy with additional NE stainings was performed and in retrospect the diagnosis was NEC in all three cases.

Survival outcomes esophageal (MA)NEC

One (4.8%) patient with esophageal MANEC died within 90 days postoperatively due to hepatic metastasis. Median potential follow-up of esophageal (MA)NEC was 57 months (IQR 45-68). The median PFS time was 12 months (range 1-131). The 1-, 3- and 5- year PFS were 52%, 42% and 27%, respectively. The median OS time was 37 months (range 2-131). The 1-, 3- and 5- year OS were 71%, 50% and 35%, respectively (figure 2). No difference in OS was observed between both the group of patients that received neoadjuvant therapy and the group that did not (figure 2B) and the group of patients with esophageal MANEC and esophageal NEC (figure 2C), as the survival curves overlapped.

Survival outcomes gastric (MA)NEC

A total of 4 (15%) patients with gastric (MA)NEC died within 90 days postoperatively. One patient had an R0 resection and died postoperatively due to sepsis. One patient had an R2 resection and died postoperatively due to anastomotic leakage and sepsis. One patient had an R2 resection and gradually declined in health after surgery. Lastly, one patient had an

Table 2. Surgical and pathological results

n (%)	Esophageal 21	Gastric 26
Type of surgery		
Transthoracic esophagectomy	12 (57)	N/A
Transhiatal esophagectomy	9 (43)	N/A
Total gastrectomy	N/A	16 (62)
Distal gastrectomy	N/A	7 (27)
Other	0 (0)	3 (12) [1]
pT		
T0	2 (10)	1 (3.9)
T1	3 (14)	1 (3.9)
T2	6 (29)	7 (27)
T3	10 (48)	14 (54)
T4	0 (0)	3 (12)
pN		
Nx	0 (0)	1 (3.9)
N0	7 (14)	9 (35)
N1	10 (48)	6 (23)
N2	3 (14)	5 (19)
N3	1 (5)	5 (19)
pM		
M0	21 (100)	26 (100)
M1	0 (0)	0 (0)
Pathological stage grouping		
IA	2 (10)	1 (4)
IB	3 (14)	3 (12)
IIA	2 (10)	6 (23)
IIB	5 (24)	5 (15)
IIIA	6 (29)	6 23)
IIIB	2 (10)	4 (15)
IIIC	1 (5)	0 (0)
Missing	0 (0)	1 (4)
Resection margins		
Complete resection (R0)	21 (100)	23 (88)
R1-R2	0 (0)	3 (12)
Lymph nodes		
Median lymph node yield (range)[2]	17.0 (4-42)	13.5 (2-60)
Median positive lymph nodes (range)[2]	1.0 (0-10)	2.0 (0-14)
Number of complications post-op (CD)		
1	1 (4.8)	1 (3.8)
2	8 (38)	6 (23)
3	3 (14)	4 (15)
4	0 (0)	1 (3.9)
5	0 (0)	2 (7.7)
90-day mortality	1 (4.8)	4 (15)

[1]Other operations were: 1 gastric wedge resection, 1 GEJ resection with intra-abdominal gastric conduit and 1 distal gastrectomy in combination with classic Whipple procedure. [2]Lymph node yield was missing in 2 patients. In one of these 2 patients, the amount of positive lymph nodes was also missing.

R0 resection and locoregional and intrahepatic reoccurrence 2 months after surgery. Median potential follow-up of gastric (MA)NEC was 59 months (IQR 27-88). The median PFS time was 15 months (range 0-131). The 1-, 3- and 5- year PFS were 58%, 45% and 40% respectively. The median OS time was 23 months (range 0-131) (figure 3). The 1-, 3- and 5- year OS were 62%, 50% and 39% respectively. There was no difference in OS observed

Table 3. (Neo)adjuvant therapy

n (%)	**Esophageal MANEC** 9	**Esophageal NEC** 12	**Gastric MANEC** 8	**Gastric NEC** 18
Neoadjuvant therapy				
Chemotherapy completed	1 (11)	2 (17)	2 (25)	6 (33)
Chemotherapy started but not completed	0 (0)	0 (0)	2 (25)	2 (11)
Chemoradiotherapy completed	4 (44)	6 (50)	0 (0)	0 (0)
No neoadjuvant therapy	4 (44)	4 (33)	4 (50)	10 (56)
Type of neoadjuvant regimen				
ECC or EOC[1]	1 (11)	1 (8)	4 (50)	5 (28)
Chemotherapy, details missing	0 (0)	0 (0)	0 (0)	2 (11)
Chemoradiotherapy, details missing	1 (11)	2 (17)	0 (0)	0 (0)
RT + carboplatin + paclitaxel[2]	2 (22)	2 (17)	0 (0)	0 (0)
RT + cisplatin + etoposide[3]	1 (11)	2 (17)	0 (0)	0 (0)
Carboplatin + etoposide	0 (0)	1 (8)	0 (0)	0 (0)
Cisplatin + etoposide	0 (0)	0 (0)	0 (0)	1 (6)
None	4 (44)	4 (33)	4 (50)	10 (56)
Mandard				
1	0 (0)	2 (17)	0 (0)	1 (6)
2	1 (11)	0 (0)	0 (0)	0 (0)
3	3 (33)	2 (17)	0 (0)	2 (11)
4 or 5	1 (11)	4 (33)	4 (50)	5 (28)
No neoadjuvant therapy	4 (44)	4 (33)	4 (50)	10 (56)
Adjuvant therapy				
Chemotherapy completed	0 (0)	4 (33)	0 (0)	2 (11)
Chemotherapy started but not completed	0 (0)	0 (0)	0 (0)	2 (11)
No	9 (100)	8 (67)	8 (100)	14 (78)
Type of adjuvant regimen				
ECC	0 (0)	1 (8)	0 (0)	3 (17)
Cisplatin + etoposide	0 (0)	2 (16)	0 (0)	1 (6)
Oxaliplatin + capecitabine	0 (0)	1 (8)	0 (0)	0 (0)
None	9 (100)	8 (67)	8 (100)	14 (78)

ECC: epirubicin, cisplatin and capecitabine. EOC: epirubicin, oxaliplatin and capecitabine. RT: radiotherapy. [1]Consisted of 6 patients receiving ECC and 5 patients receiving EOC. [2]All 4 patients received 41.4 Gy. [3]Two patients received 50 Gy, 1 patient received 50.4 Gy.

between both the group of patients that received neoadjuvant therapy and the group of patients that did not do not, as the survival curves overlapped (figure 3B). There was no statistically significant difference in OS between gastric MANEC and gastric NEC patients ($p = 0.403$) (figure 3C).

Pathology of recurrence

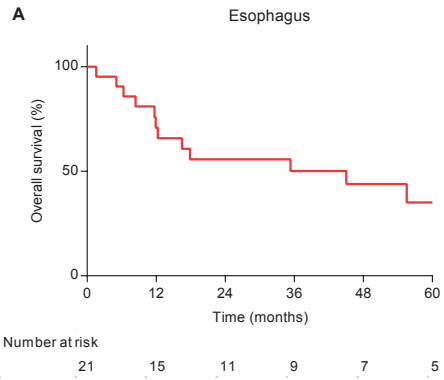
In patients with esophageal or gastric (MA)NEC, recurrence disease was seen in 25/47 patients. The location of recurrence was variable: locoregional in 5 patients, systemic in 14 patients and a combination of locoregional and systemic in 6 patients (Supplementary material 6).

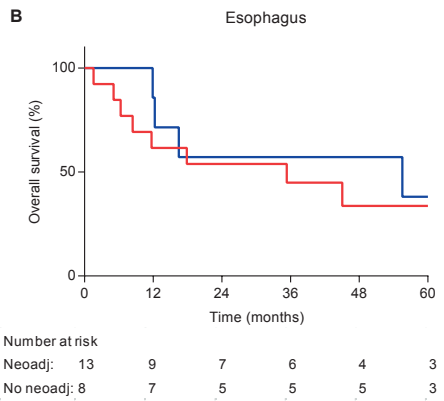
For esophageal and gastric MANEC, recurrence (either locoregional, distant or both) was diagnosed in 12/17 patients (8 esophageal, 4 gastric) after a median actual follow-up of 10 months (IQR 5-20). In 8 patients (6 esophageal, 2 gastric) recurrence was diagnosed by biopsy (often in combination with CT scans) and in the other 4 cases on CT scan without biopsy. In 5 (63%) patients (4 esophageal, 1 gastric) an isolated NEC component was seen on biopsy, in 3 (38%) patients (2 esophageal, 1 gastric) a MANEC was seen on biopsy and in none of the patients an isolated adenocarcinoma component was seen on biopsy. All 5 patients with an isolated NEC component on biopsy had received a form of neoadjuvant treatment, whereas all patients with a MANEC on biopsy had not.

Table 4. Accuracy of biopsy diagnosis

Preoperative biopsy	n	PA resection	n (%)
NEC	24	NEC	20 (83)
		MANEC	2 (8)
		Adenocarcinoma	1 (4)
		NET grade 2	1 (4)
MANEC	3	MANEC	3 (100)
Adenocarcinoma	17	MANEC	11 (55)
SCC	1	NEC	9 (45)
NET grade 2	1		
GIST + focal NEC	1		
N/A[1]	2	MANEC	1 (50)
		NEC	1 (50)
Total	49		49

[1]Pathology of biopsy and resection were both re-evaluated in these two hospitals after surgery. A definitive diagnosis was provided, but this was based upon the conjunction of information from both biopsy and resection. It was thus impossible to make a reliable comparison of biopsy diagnosis and diagnosis of the resection specimen.





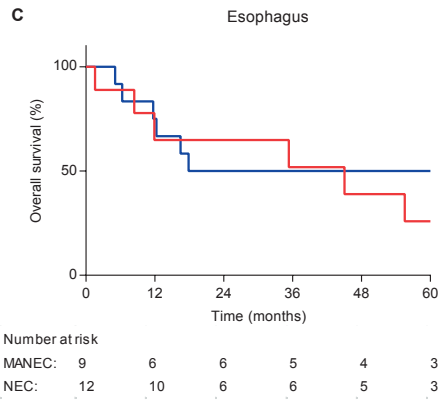
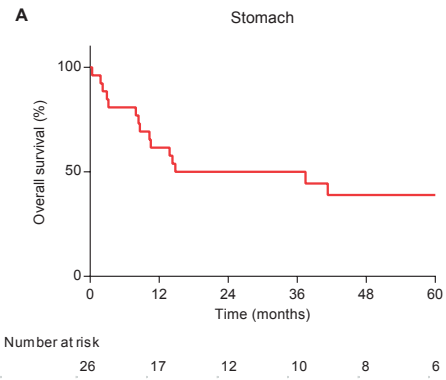
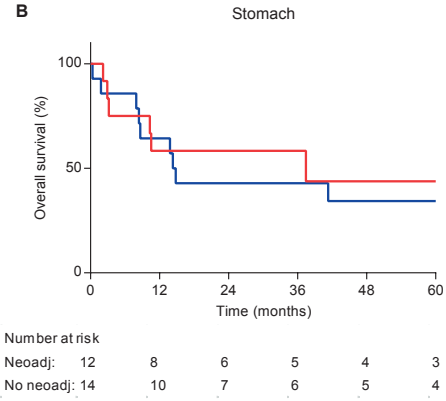


Figure 2. A: Overall survival (OS) for patients with esophageal (MA)NEC, B: OS for patients with esophageal (MA)NEC, neoadjuvant therapy versus no neoadjuvant therapy. C: OS for patients with esophageal (MA)NEC, MANEC versus NEC.





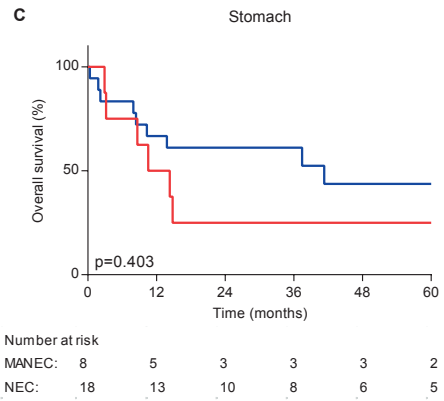


Figure 3. A: Overall survival (OS) for patients with gastric (MA) NEC, B: OS for patients with gastric (MA)NEC, neoadjuvant therapy versus no neoadjuvant therapy. C: OS for patients with gastric (MA)NEC, MANEC versus NEC.

DISCUSSION

This study shows that, if (MA)NEC is recognized on biopsy diagnosis, this diagnosis is reliable and can thus be used to determine treatment strategies. Unfortunately the majority of MANECs (11/16) and many of the NECs (9/29), appear to be missed on biopsy diagnosis (most often diagnosed as adenocarcinoma). Therefore, many patients with (MA)NEC will receive neoadjuvant treatment as is established for adenocarcinoma(20, 21). Of note, in the majority of missed (MA)NEC cases immunohistochemistry for neuroendocrine markers was not performed, underscoring the importance of a low threshold for additional stainings.

The current study shows that between 2006-2016 a total of 21 esophageal and 26 gastric (MA)NECs were resected in the Netherlands. Korse et al.(2) demonstrated that between 2001-2010, so a comparable timespan as the current study, a total of 204 esophageal and 115 gastric (MA)NECs were diagnosed in the Netherlands. The comparison of these data suggests that only a small proportion of patients with esophageal or gastric (MA)NEC on biopsy diagnosis received a surgical resection. Most likely, metastatic disease at the time of presentation is an important reason that most (MA)NEC patients did not undergo surgical resection(2).

One patient with esophageal MANEC (4.8%) and 4 patients with gastric (MA)NECs (15%) died within 90 days postoperatively. A relatively good long-term survival for esophageal and gastric (MA)NEC was observed, comparable with survival data of esophageal and gastric adenocarcinoma and SCC treated with curative intent (20, 21). Curative treatment of localized esophageal and gastric (MA)NEC is thus feasible. For localized esophageal (MA)NEC, promising survival was also observed in the two largest recent cohort studies (7, 10). However, older literature reported dismal survival rates (8, 11, 12). With regard to localized gastric (MA)NEC, a relatively good survival was observed in the two most recent large Asian studies (9, 14). In contrast, the latest and largest Western study reported very poor survival rates (11).

In the current study, no (statistically significant) differences were observed in the survival curves between patients with esophageal/gastric NEC and MANEC. However, numbers are small. Three other studies compared survival between patients with esophageal/gastric NEC and MANEC and showed conflicting results(3, 10, 14). In some of these studies, patients with localized and metastatic disease or patients with NET (grade 1 or 2) and NEC were pooled. This makes it difficult to compare their results with our results. In the current study, for esophageal and gastric (MA)NEC, survival curves overlapped for the groups that received neoadjuvant therapy and the groups that did not. The overlapping survival curves could be due to the small effect of the types of neoadjuvant regimens administered in the current study, as is indicated by the few good responders (Mandard 1 or 2). However, due to the small numbers of the study it is difficult to draw conclusions. Most patients with

NEC treated with neoadjuvant chemotherapy received a chemotherapy regimen other than the recommended cis/carboplatin in combination with etoposide or irinotecan. (8, 22-25). Strikingly, the vast majority of patients with a preoperative biopsy diagnosis of NEC also did not receive this recommended regimen. Possibly more effect of neoadjuvant therapy is seen if patients are treated with a cis/carboplatin + etoposide or irinotecan regimen. Some data on this regimen in the adjuvant setting is available (see below), but further data on neoadjuvant chemotherapy is lacking.

Only three retrospective studies of reasonable size analyzed the survival benefit of adjuvant chemotherapy in localized esophageal NEC(6, 7, 12). Two of these studies also briefly mention patients with MANEC as a subgroup. Though retrospective in nature, improved survival was demonstrated for patients receiving adjuvant chemotherapy after surgery as opposed to surgery alone (median survival of 20 months versus 5 months, 17.0 months versus 6.5 months and >28.2 months versus 14.6 months). In the current study, few esophageal or gastric patients with NEC (26.7%) and none of the patients with MANEC received adjuvant chemotherapy, suggesting that this can be improved.

Recurrences of patients with upper gastrointestinal MANEC showed pathology of MANEC (none of these patients received neoadjuvant treatment) or isolated NEC (all of these patients received neoadjuvant therapy) and never of adenocarcinoma. Although the numbers are very small, this might suggest that the adenocarcinoma component is more sensitive to the administered neoadjuvant therapy regimens than the NEC component. The administration of a chemotherapy regimen that is more effective against the NEC component, but still effective against the adenocarcinoma component, might thus improve the outcome of patients with upper gastrointestinal MANEC. However, further research is warranted on this matter.

The current study has certain limitations. Only patients with localized disease who underwent surgical resection were included, therefore no comparison was made with a control group that did not undergo surgery. The study is retrospective, hence selection bias and other unknown biases are unavoidable. Although this is one of the larger cohorts in literature, the absolute numbers are still low which made it impossible to perform regression analyses with correction for confounding factors. As these tumors are exceedingly rare, large prospective studies are not likely to be performed in the near future and clinical decisions will thus have to be based on retrospective data. Further studies (i.e. retrospective multicenter studies in large countries, with optimal neoadjuvant regimens and analysis of Mandard scores and survival) are required to analyze the benefit of neoadjuvant therapy and to determine whether MANECs should be treated as NECs, adenocarcinomas or as a separate entity.

In conclusion, this cohort study demonstrates that localized esophageal and gastric (MA)NEC are often misdiagnosed on endoscopic biopsies. However, if recognized, biopsy

diagnosis is reliable. After resection, long-term survival was achieved in 35% of patients with esophageal (MA)NEC and 39% of patients with gastric (MA)NEC. Extensive evaluation of the treatment strategy for each patient in a dedicated multidisciplinary tumor board is mandatory.

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SUPPLEMENTARY MATERIAL

Supplementary material 1. Patients demographics, stratified by neoadjuvant treatment

n (%)	Esophageal neoadj 13	Esophageal no neoadj 8	P	Gastric neoadj 12	Gastric no neoadj 14	P
Definitive diagnosis			0.604			0.793
MANEC	5 (39)	4 (50)		4 (33)	4 (29)	
NEC	8 (62)	4 (50)		8 (67)	10 (71)	
Gender			0.920			0.759
Male	10 (77)	6 (75)		10 (83)	11 (79)	
Female	3 (23)	2 (25)		2 (17)	3 (21)	
Mean age (±SD) at diagnosis, years	62.1 (9.1)	64.1 (11)	0.595	64.5 (10)	70.6 (9.7)	0.231
Mean BMI (±SD), kg/m^2	26.1 (5.5)	23.8 (3.6)	0.432	22.3 (3.4)	24.2 (4.2)	0.152
ASA score			0.301			0.193
1	2 (15)	1 (13)		3 (25)	2 (14)	
2	10 (77)	4 (50)		8 (67)	7 (50)	
3	1 (8)	3 (38)		1 (8.3)	5 (36)	
Comorbidities						
Cardiac	4 (31)	2 (25)	0.776	1 (8.3)	5 (36)	0.099
Vascular	7 (54)	4 (50)	0.864	4 (33.3)	8 (57)	0.225
Diabetes	1 (8)	1 (13)	0.716	2 (16.7)	1 (7)	0.449
Pulmonary	2 (15)	3 (38)	0.248	3 (25)	2 (14)	0.490

Supplementary material 2. Surgical and pathological results, stratified by neoadjuvant therapy

n (%)	**Esophageal neoadj** 13	**Esophageal no neoadj** 8	**P**	**Gastric neoadj** 12	**Gastric no neoadj** 14	**P**
Type of surgery			0.154			0.557
Transthoracic esophagectomy	9 (69)	3 (38)		N/A	N/A	
Transhiatal esophagectomy	4 (31)	5 (63)		N/A	N/A	
Total gastrectomy	N/A	N/A		8 (67)	8 (57)	
Distal gastrectomy	N/A	N/A		3 (25)	4 (29)	
Other	0 (0)	0 (0)		1 (8.3)	2 (14)	
pT			0.268			0.160
T0	2 (15)	0 (0)		1 (8.3)	0 (0)	
T1	2 (15)	1 (13)		1 (8.3)	0 (0)	
T2	4 (31)	2 (25)		4 (33.3)	3 (21)	
T3	5 (39)	5 (63)		5 (41.7)	9 (64)	
T4	0 (0)	0 (0)		1 (8.3)	2 (14)	
pN			0.500			0.186
Nx	0 (0)	0 (0)		0 (0)	1 (7)	
N0	6 (46)	1 (13)		3 (25)	6 (43)	
N1	4 (31)	6 (75)		3 (25)	3 (21)	
N2	2 15)	1 (13)		2 (17)	3 (21)	
N3	1 (8)	0 (0)		4 (33)	1 (7)	
pM			1.00			1.000
M0	13 (100)	8 (100)		14 (100)	12 (100)	
M1	0 (0)	0 (0)		0 (0)	0 (0)	
Resection margins			1.00			0.449
Complete resection (R0)	8 (100)	13 (100)		10 (83)	13 (93)	
R1-R2	0 (0)	0 (0)		2 (17)	1 (7)	
Lymph nodes						
Median lymph node yield (range)	18 (4-28)	16 (10-42)	0.697	14 (2-24)	13 (3-60)	0.910
Median positive lymph nodes (range)	1 (0-10)	1 (0-5)	0.500	3.5 (0-14)	2 (0-10)	0.205
Complications post-op (CD)			0.414			0.106
1	5 (39)	5 (63)		9 (75)	4 (29)	
2	6 (46)	2 (25)		0 (0)	6 (43)	
3	2 (15)	1 (13)		2 (17)	2 (14)	
4	0 (0)	0 (0)		1 (8.3)	0 (0)	
5	0 (0)	0 (0)		0 (0)	2 (14)	
90-day mortality	1 (8)	0 (0)	0.421	2 (17)	2 (14)	0.867

Supplementary material 3. Patients demographics, stratified by histology (MANEC or NEC)

n (%)	Esophageal MANEC 9	Esophageal NEC 12	P	Gastric MANEC 8	Gastric NEC 18	P
Gender			0.338			0.115
Male	8 (90)	8 (67)		5 (63)	16 (89)	
Female	1 (11)	4 (33)		3 (38)	2 (11)	
Mean age (±SD) at diagnosis, years	64.2 (7.3)	61.8 (11.0)	0.862	64.3 (12)	69.4 (9.5)	0.429
Mean BMI (±SD), kg/m2	24.3 (3.5)	26.0 (5.8)	0.545	24.4 (6)	22.7 (3.1)	0.569
ASA score			0.345			0.849
1	0 (0)	3 (25)		1 (13)	4 (22)	
2	7 (78)	7 (58)		6 (75)	9 (50)	
3	2 (22)	2 (17)		1 (13)	5 (28)	
Comorbidities						
Cardiac	3 (33)	3(25)	0.676	1 (13)	5 (28)	0.393
Vascular	4 (44)	7(58)	0.528	3 (38)	9 (50)	0.555
Diabetes	2 (22)	0 (0)	0.086	2 (25)	1 (6)	0.152
Pulmonary	2 (22)	3(25)	0.882	0 (0)	5 (28)	0.097

Supplementary material 4. Surgical and pathological results, stratified by histology (MANEC or NEC)

n (%)	Esophageal MANEC 9	Esophageal NEC 12	P	Gastric MANEC 8	Gastric NEC 18	P
Type of surgery			0.889			0.793
Transthoracic esophagectomy	5 (56)	7 (58)		N/A	N/A	
Transhiatal esophagectomy	4 (44)	5 (42)		N/A	N/A	
Total gastrectomy	N/A	N/A		6 (75)	10 (56)	
Distal gastrectomy	N/A	N/A		2 (25)	5 (28)	
Other	0 (0)	0 (0)		0 (0)	3 (17)	
pT			0.972			0.683
T0	0 (0)	2 (17)		0 (0)	1 (6)	
T1	2 (22)	1 (8)		1 (13)	0 (0)	
T2	3 (33)	3 (25)		1 (13)	6 (33)	
T3	4 (44)	6 (50)		5 (63)	9 (50)	
T4	0 (0)	0 (0)		1 (13)	2 (11)	
pN			0.972			0.357
Nx	0 (0)	0 (0)		1 (13)	0 (0)	
N0	4 (44)	3 (25)		1 (13)	8 (44)	
N1	2 (22)	8 (67)		2 (25)	4 (22)	
N2	2 (22)	1 (8)		3 (38)	2 (11)	
N3	1 (11)	0 (0)		1 (13)	4 (22)	
pM			1.00			1.00
M0	9 (100)	12 (100)		8 (100)	18 (100)	
M1	0 (0)	0 (0)		0 (0)	0 (0)	
Resection margins			1.00			0.220
Complete resection (R0)	9 (100)	12 (100)		8 (100)	15 (83)	
R1-R2	0 (0)	0 (0)		0 (0)	3 (17)	
Lymph nodes						
Median lymph node yield (range)	18.0 (6-42)	15.0 (4-28)	0.277	20.0 (2-44)	13.0 (3-60)	0.418
Median positive lymph nodes (range)	1.0 (0-10)	1.0 (0-3)	1.00	3.0 (0-10)	1.5 (0-14)	0.220
Complications post-op (CD)			0.972			0.849
1	4 (44)	6 (50)		4 (50)	9 (50)	
2	4 (44)	4 (33)		1 (13)	5 (28)	
3	1 (11)	2 (17)		2 (25)	2 (11)	
4	0 (0)	0 (0)		1 (13)	0 (0)	
5	0 (0)	0 (0)		0 (0)	2 (11)	
90-day mortality	1 (8)	0 (0)	0.237	1 (13)	3 (17)	0.786

Supplementary material 5. MANDARD score per chemotherapy regimen

n (%)	MANDARD 1-2 4	MANDARD 3 7	MANDARD 4-5 14
Cis- or carboplatin/etiposide	1 (25)	3 (43)	1 (7)
Standard regimen	2 (50)	4 (57)	9 (64)
Chemotherapy details missing	1 25)	0 (0)	4 (29)

Grouped MANDARD scores (1-2, 3 or 4-5) for the patients that received cis- or carboplatin/etiposide compared to the patients that received a standard regimen. Details on chemotherapy were missing in 5 patients. P = 0.275.

Supplementary material 6. Location of recurrence

Location of recurrence n (%)	Esophageal MANEC 9	Esophageal NEC 12	Gastric MANEC 8	Gastric NEC 18
Locoregional	1 (11)	1 (8)	-	3 (17)
Systemic single site				
Liver	2 (22)	1 (8)	2 (25)	2 (11)
Lung	1 (11)	-	-	1 (6)
Brain	-	2 (17)	-	-
Axilla	1 (11)	-	-	-
Systemic multiple sites				
Liver, lung	-	-	-	1 (6)
Skin, bone	1 (11)	-	-	-
Locoregional and systemic single site				
Locoregional, liver	1 (11)	-	2 (25)	-
Locoregional, lung	1 (11)	-	-	-
Locoregional and systemic multiple sites				
Locoregional, liver, lung	-	1 (8)	-	-
Locoregional, liver, lung, peritoneum	-	1 (8)	-	-
No recurrence/ death without recurrence	1 (11)	6 (50)	4 (100)	11 (61)


Retrospective

CHAPTER 8

Resection of hepatic and pulmonary metastasis from metastatic esophageal and gastric cancer: a nationwide study

Diseases of the Esophagus 2019

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ABSTRACT

Introduction

The standard of care for gastroesophageal cancer patients with hepatic or pulmonary metastases is best supportive care or palliative chemotherapy. Occasionally, patients can be selected for curative treatment instead. The current study aimed to evaluate patients who underwent a resection of hepatic or pulmonary metastasis with curative intent.

Methods

The Dutch National Registry for Histo- and Cytopathology was used to identify these patients. Data were retrieved from the individual patient files. Kaplan-Meier survival analysis was performed.

Results

Between 1991–2016, 32,057 patients received a gastrectomy or esophagectomy for gastroesophageal cancer in the Netherlands. Of these patients, 34 selected patients received a resection of hepatic metastasis (n=19) or pulmonary metastasis (n=15) in 21 different hospitals. Only 4 patients received neoadjuvant therapy before metastasectomy. The majority of patients had solitary, metachronous metastases. After metastasectomy, grade 3 (Clavien-Dindo) complications occurred in 7 patients and mortality in 1 patient. After resection of hepatic metastases, the median potential follow-up time was 54 months. Median overall survival (OS) was 28 months and the 1-, 3- and 5- year OS were 84%, 41% and 31% respectively. After pulmonary metastases resection, the median potential follow-up time was 80 months. The median OS was not reached and the 1-, 3- and 5- year OS were 67%, 53% and 53% respectively.

Conclusion

In selected patients with gastroesophageal cancer with hepatic or pulmonary metastases, metastasectomy was performed with limited morbidity and mortality and offered a 5-year OS of 31-53%. Further prospective studies are required.

INTRODUCTION

Gastric and esophageal cancer are the third (723,000 deaths annually) and sixth (400,000 deaths annually) most common cause of cancer-related deaths worldwide(1). Neoadjuvant chemo(radio)therapy or perioperative chemotherapy followed by surgical resection is the cornerstone of curative care for gastroesophageal cancer(2–4). However, up to 40% of patients with gastroesophageal cancer present with synchronous metastatic disease and are regarded incurable(5,6). Approximately another 50% will develop metachronous metastases during follow-up after surgery(7–11). The most common sites of metastases are the lung, liver, peritoneum and bone(12,13). Currently, the standard treatment for patients with hepatic or pulmonary metastases from gastroesophageal cancer consists of best supportive care or palliative chemotherapy. This leads to a median survival of 4-5 months for esophageal and 4-11 months for patients with gastric cancer (14,15). Resection of hepatic or pulmonary metastases has been established as a treatment option for other tumors, such as endocrine and colorectal cancer(16–22). Several small retrospective studies suggest that resection of hepatic and pulmonary metastases from gastroesophageal cancer is also feasible and may increase survival in a selected group of patients(23–27). Unfortunately large series on metastasectomy are scarce for metastatic gastric cancer and even scarcer for esophageal cancer. According to a meta-analysis published in 2018 (28), no Western series exist that report on the resection of metachronous pulmonary metastasis.

The aim of the current study was to identify and evaluate all patients in the Netherlands who underwent a resection of hepatic or pulmonary metastases from gastroesophageal cancer with curative intent. Primary outcomes were progression free survival (PFS) and overall survival (OS). Secondary outcomes included surgical complications. Lastly, we wanted to describe the factors that may influence long-term survival.

METHODS

Patients and Data

All patients who underwent a resection of hepatic or pulmonary metastases from gastroesophageal cancer between January 1991 and March 2016, were identified from the Dutch national registry for Histo- and Cytopathology (PALGA). The PALGA database collects every pathological report generated by pathology departments in the Netherlands since 1975(29). The PALGA database was searched for "(stomach OR esophagus) AND (liver OR lung) AND metastases AND resection" and synonyms. Summaries of the pathology reports were supplied by PALGA and used for further patient selection. Patients treated with curative intent, and of whom patient records were available, were included.

Patient and treatment-related characteristics, as well as surgical outcome and histopathological data were retrospectively collected from the individual patient files. The Netherlands Comprehensive Cancer Organisation (IKNL) supplied the total number of gastrectomies and esophagectomies performed for gastroesophageal cancer in the Netherlands between January 1991 and March 2016.

The primary tumor was staged according to the tumor node metastasis (TNM) classification system of the International Union Against Cancer (UICC). Radicality was defined according to the UICC standards; R0: complete microscopic resection, R1: microscopic residual disease or R2: macroscopic residual disease, either at location of metastasis or elsewhere in the body. Curative intent was defined as patients for whom the intention of the surgery was to perform an R0 resection. Metastases were considered synchronous when they were diagnosed within 6 months after diagnosis of the primary tumor. Location of hepatic metastases were defined according to Couinaud's liver segments(30). Location of pulmonary metastases were defined according to definition of The Thoracic Society(31). Hepatic resections were divided into major and minor resections. Minor resections were defined as a resection of less than four segments, every other resection was defined as a major resection. This study received ethical approval (Institutional Review Board number 16-312/C) from the Medical Ethics Review Committee of the UMCU, and the need to obtain informed consent was waived.

OUTCOMES

The primary outcomes were PFS and OS. PFS was defined as the interval between metastasectomy and recurrence or progression of (residual) disease regardless of organ or tissue, or death from any cause. OS was defined as the interval between metastasectomy and date of last follow-up or death.

Secondary outcome in the current study was the safety of metastasectomy, expressed in terms of postoperative morbidity and 30 day mortality and in hospital mortality. Postoperative complications were classified according to the Clavien Dindo classification. Follow-up was not standardized.

Statistical considerations

Data were analyzed using SPSS for windows, version 22.0 (IBM corp., Armonk, New York). All continuous data were presented as median (range) or mean (± standard deviation (SD)) based on their distribution; all categorical data were presented as a number (percentage). Patient and treatment-related characteristics in relation to surgical procedure were studied using descriptive statistics. Potential follow-up time was calculated with Kaplan-Meier

estimate of potential follow-up ("reverse Kaplan-Meier")(32). Kaplan-Meier curves were used to assess PFS and OS. Non-overlapping curves were compared with the Log-rank test.

RESULTS

Patients

Between January 1991 and March 2016, a total of 32,057 patients received a gastrectomy or esophagectomy for gastroesophageal cancer in the Netherlands. The 14.984 patients with esophageal or cardia cancer had an adenocarcinoma in 77,74% of cases, a squamous cell carcinoma in 20,64% and a histology of "other/unspecified" in 1,62%. The 17.073 patients with gastric cancer had an adenocarcinoma in 98.93% of cases, squamous cell carcinoma in 0,02% and a histology of "other/unspecified" in 1,05%.

Our initial PALGA search yielded summaries of 309 patients that could potentially be included in the current study. A total of 138 of these patients were excluded, because based upon the summaries of the pathology reports, it was clear that a biopsy was performed instead of a metastasectomy with curative intent. For the remaining 171 patients, the patient files (if available) were reviewed. Patients were excluded who did not receive a resection of gastroesophageal metastasis with curative intent (primary tumor was never resected, biopsy instead of resection, multiple other metastases left in situ or metastasis not of gastroesophageal origin on definitive pathology) or who had unavailable patient files. The remaining 34 patients from 21 different hospitals were included. These patients were thus treated with a resection of hepatic or pulmonary metastasis from gastroesophageal origin with curative intent.

Hepatic resection for metastases from gastroesophageal cancer

A resection of hepatic metastases was performed in 19 patients (Table 1). The (neo)adjuvant treatments are described in table 1 and 2. Extrahepatic metastasis prior to hepatic resection was present in 1 patient. This patient had a retrosternal metastasis that was treated with resection and radiotherapy. Metachronous metastases were diagnosed in 13 patients and synchronous metastases in 6 patients. The metastases were solitary in 16 patients and non-solitary (2 metastases) in 3 patients.

The operative characteristics of the hepatic resections are displayed in Table 2a. Metastases were unilobar in 17 patients and confined to 1 liver segment in 12 patients. An R0 resection was achieved in 17 patients. After hepatic resection, complications were encountered in 6 patients. This led to a re-intervention in 4 patients and death within 30 days in 1 patient. This patient had extensive cardiovascular comorbidities. He was re-admitted after a post-operative hemorrhage. After a total intensive care unit stay of 26 days, this patient died due to ventricular fibrillation.

Table 1. Gastroesophageal cancer: patient and treatment-related characteristics in relation to surgical procedure

Characteristic		Hepatic resection (n=19)		Pulmonary resection (n=15)	
Gender	Female	4	21.1%	5	33.3%
	Male	15	78.9%	10	66.7%
Mean age (years)		59.7	±12.2	63.5	±8.79
Mean BMI (kg/m^2)		20.6	±3.49	24.5	±2.85
	Missing	7	36.8%	3	20.0%
ASA score	I	3	15.8%	1	6.67%
	II	10	52.6%	6	40.0%
	III	2	10.5%	4	26.7%
	Missing	4	21.1%	4	26.7%
Organ of primary tumor	Stomach	8	42.1%	4	26.7%
	Esophagus	11	57.9%	11	73.3%
Location primary tumor	Middel	0		2	13.3%
	Distal	7	36.8%	8	53.3%
	Cardia (esophagectomy)	3	15.8%	1	6.67%
	Cardia (gastrectomy)	1	5.26%	4	26.7%
	Corpus	2	10.5%	0	
	Antrum	4	21.1%	0	
	Pars pylori	1	5.26%	0	
	Missing	1	5.26%	0	
Stage of primary tumor	0	1	5.26%	0	
	IA	3	15.8%	3	20.0%
	IB	1	5.26%	0	
	IIA	4	21.1%	6	40.0%
	IIB	2	10.5%	1	6.67%
	IIIA	5	26.3%	5	33.3%
	IIIB	1	5.26%	0	
	IV	2	10.5%	0	
Histology of primary tumor	Adenocarcinoma	17	89.5%	9	60.0%
	Squamous cell carcinoma	1	5.26%	4	26.7%
	Neuroendocrine carcinoma[1]	1	5.26%	1	6.67%
	Undifferentiated	0		1	6.67%
Differentiation of primary tumor	Moderately	8	42.1%	5	33.3%
	Poorly	4	21.1%	4	26.7%
	Undifferentiated	0		1	6.67%
	Missing	7	36.8%	5	33.3%
(Neo)adjuvant therapy of primary tumor	Neoadjuvant CRT	6	31.6%	4	26.7%
	Neoadjuvant CT	0		1	6.67%
	Neoadjuvant and adjuvant CT	2	10.5%	3	20.0%
	None	11	57.9%	7	46.7%

Table 1. Continued

Characteristic		Hepatic resection (n=19)		Pulmonary resection (n=15)	
History of extrahepatic or extrapulmonary metastasis prior to metastasectomy	Yes	1	5.26%	0	
	No	18	94.7%	15	100.0%
Interval diagnoses primary tumor and metastases	Synchronous	6	31.6%	1	6.7%
	Metachronous	13	68.4%	14	93.3%
Median interval (months) between diagnosis of primary tumor and diagnosis of metastases[2]		20	11-27	30	18-39
	Missing	2	10.5%	1	6.67%
Number of metastases	1	16	84.2%	13	86.7%
	2	3	15.8%	2	13.3%

Data are n (%), mean (±SD) and median (IQR). Abbreviations. BMI = Body Mass Index , ASA = american society of anesthesiologists, CRT = chemoradiotherapy, CT = chemotherapy. [1] Both patients had a high-grade neuroendocrine neoplasm with a Ki-index of >20% or >20 mitoses per 10 high power fields, which were thus classified as neuroendocrine carcinoma(40).[2]For the metachronous tumors.

Survival after hepatic resection

The median potential follow-up time was 54 months. Kaplan-Meier survival curves after hepatic resection for gastroesophageal cancer metastases are displayed in Figure 1. The median progression free survival (PFS) was 16 months and the 1-, 3- and 5- year PFS were 58%, 21% and 21% respectively. The median overall survival (OS) was 28 months and the 1-, 3- and 5- year OS were 84%, 41% and 31% respectively.

A subgroup analysis of the 8 patients with gastric cancer hepatic metastasis a median OS of 23 months and the 1-, 3- and 5- year OS were 75%, 25% and 25% respectively. The 11 patients with esophageal cancer hepatic metastasis had a median OS of 52 months and the 1-, 3- and 5- year OS were 91%, 55% and 27% respectively.

Pulmonary resection for metastases from gastroesophageal cancer

A resection of pulmonary metastases was performed in 15 patients (Table 1). The (neo) adjuvant treatments are described in table 1 and 2. None of the patients had extrapulmonary metastases. Metachronous metastases were diagnosed in 14 patients and synchronous metastases in 1 patient. The metastases were solitary in 13 patients and non-solitary (2 metastases) in 2 patients.

The operative characteristics of the pulmonary resections are displayed in Table 2b. An R0 resection was achieved in 12 patients, an R1-2 resection in 2 patients and data on the radicality was missing in 1 patient. After pulmonary resection, complications were encountered in 6 patients, though data on complications was missing in 2 patients. The complication led to a reintervention in 4 patients and there was no 30 day mortality or in hospital mortality. The median hospital stay was 7 days.

Table 2a. Hepatic resecton: perioperative and histological outcomes

Outcomes		**n=19**	
(Neo)adjuvant therapy prior to hepatic resection	Neoadjuvant CRT[1]	2	10.5%
	Neoadjuvant CT[2]	1	5.3%
	Neoadjuvant CRT, followed by neoadjuvant CIT [3]	1	5.3%
	Adjuvant CRT	1	5.3%
	None	13	68.4%
	Missing	1	5.3%
Timing of hepatic resection	Before primary resection	2	10.5%
	Combined resection (of primary and metastasis)	3	15.8%
	After primary resection	14	73.7%
Median interval (months, IQR) that metastasectomy was performed after primary resection [4]		18	(12-28)
Year of hepatic resection	1995-2000	3	15.8%
	2001-2005	2	10.5%
	2006-2010	4	21.1%
	2011-2014	10	52.6%
Distribution	Unilobar	17	89.5%
	Bilobar	2	10.5%
Segments	1	12	63.2%
	>2	7	36.8%
Mean diameter (in mm) of metastasis[5]		34.5	±37.5
	Missing	2	10.5%
Type of hepatic resection	Minor	14	73.7%
	Major	5	26.3%
Radicality	R0	17	89.5%
	R1-2	2	10.5%
Complications	Total	6	31.6%
	CD1	0	0.0%
	CD2	2	10.5%
	CD3	3	15.8%
	CD4	0	0.0%
	CD5	1	5.3%
Reintervention		4	21.1%
30-day postoperative mortality		1	5.3%
Median hospital stay (days, range)		7	1-76
	Missing	3	15.8%

Data are n (%), mean (±SD) or median. Abbreviations. CD = Clavien-Dindo classification. CRT = chemoradiotherapy, CT = chemotherapy. CIT = chemo-immunotherapy. [1]Combined resection of primary tumor and metastasis, neoadjuvant therapy was aimed at the primary tumor. [2]Metastasis was inititally too large for resection, however after induction chemotherapy, resection could be performed. [3]Metastasectomy was performed before resection of primary tumor. [4]Only the 14 patients who received their metastasectomy after their primary resection are included. [5]metastasis with largest diameter, as based upon pathology in 11 cases and CT-scan in 2 cases.

Table 2b. Pulmonary resection: perioperative and histological outcomes

Outcomes		**n=15**	
(Neo)adjuvant therapy prior to pulmonary resection	Adjuvant radiotherapy	1	6.7%
	None	14	93.3%
Timing of pulmonary resection	Before primary resection	0	
	Combined resection (of primary and metastasis)	0	
	After primary resection	15	100.0%
Median interval (months, IQR) that metastasectomy was performed after primary resection		15	(16-35)
Year of pulmonary resection	1991-1995	2	13.3%
	1996-2000	0	
	2001-2005	1	6.7%
	2006-2010	6	40.0%
	2011-2015	6	40.0%
Distribution	Left, superior lobe	2	13.3%
	Left, inferior lobe	4	26.7%
	Right, superior lobe	8	53.3%
	Right, inferior lobe	0	
	Middle lobe	0	
	Missing	1	6.7%
Mean diameter (in mm) of metastasis[1]		17.3	±12.6
	Missing	2	13.3%
Operative methods	Wedge resection	11	73.3%
	Segmentectomy	0	
	Lobectomy	4	26.7%
Radicality	R0	12	80.0%
	R1-2	2	13.3%
	Missing	1	6.7%
Complications	Total	6	40.0%
	CD1	2	13.3%
	CD2	0	
	CD3	4	26.7%
	CD4	0	
	CD5	0	
	Missing	2	13.3%
Reintervention		4	26.7%
30-day postoperative mortality		0	
Median hospital stay (days, range)		12	3-41
	Missing	1	6.67%

Data are n (%), mean (±SD) or median. Abbreviations. CD = Clavien-Dindo classification. [1]metastasis with largest diameter, as based upon pathology in 11 cases and CT-scan in 2 cases.

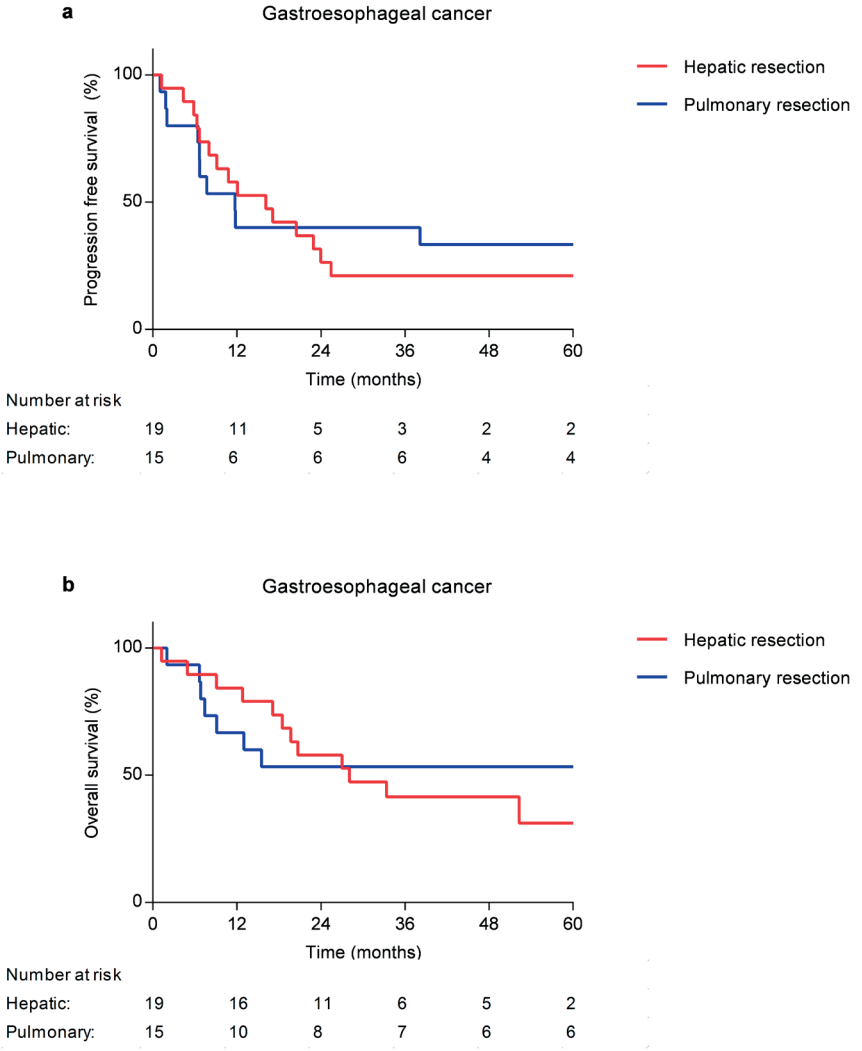

Figure 1. Kaplan-Meier survival curves after hepatic or pulmonary resection, displaying progression free survival (a) and overall survival (b).

Survival after pulmonary resection

The median potential follow-up time was 80 months. Kaplan-Meier survival curves after pulmonary resection for gastroesophageal cancer metastases are displayed in Figure 1. The median PFS was 12 months and the 1-, 3- and 5- year PFS were 40%, 40% and 33% respectively. The median OS was not reached and the 1-, 3- and 5- year OS were 67%, 53% and 53% respectively.

A subgroup analysis of the 4 patients with gastric cancer pulmonary metastasis showed a median OS of 7 months. The 1-, 3- and 5- year OS was 25%. The 11 patients with esophageal cancer did not reach the median OS and the 1-, 3- and 5- year OS were 82%, 64% and 64% respectively.

Disease free interval subgroup analysis

Two further subgroup analyses were performed comparing OS for patients with a disease free interval (DFI) of <24 months vs >24 months and comparing OS for patients with synchronous vs metachronous metastasis. These analyses are displayed in Supplementary material 1.

DISCUSSION

The current study reports on patients who underwent a resection of hepatic and pulmonary metastases from gastroesophageal cancer. According to a meta-analysis published in 2018(28), this is the first Western series on the resection of predominantly metachronous pulmonary metastasis from esophageal cancer. Metastasectomy was performed in selected patients with low postoperative morbidity and mortality rates, leading to a 5-year OS of 31-53%. The median OS was 28 months in the hepatic resection group and the median OS was not reached in the pulmonary resection group. The survival rates in these selected patients are favorable compared to the current standard treatment of best supportive care or palliative chemotherapy, which leads to a median survival of 4-11 months(14,15).

Previous retrospective studies on patients with hepatic metastases from gastric cancer demonstrated a favorable survival after a hepatic resection (23,24). Only 2 series with over 5 patients exist on hepatic metachronous metastases from esophageal cancer that were treated with esophagectomy and hepatic resection(28). Liu et al. reported a 2-year OS of 21.2% in 26 patients and Adam et al. reported a 3-year OS of 12-32% (33,34). The current study demonstrates a 3-year and 5-year OS of 55% and 27% respectively, in 11 patients after hepatic resection.

Data on pulmonary resections for gastroesophageal pulmonary metastasis are also scarce. A recent systematic review on pulmonary resections for gastric cancer pulmonary metastasis found only 44 patients reported in literature thus far and reported a median survival of 45 months (25). In 3 small retrospective cohort series, all Japanese with predominantly squamous cell carcinoma, pulmonary resections for esophageal cancer pulmonary metastasis were found to be feasible and leading to a 5-year OS of 30-44%. They conclude that pulmonary resection could be considered in selected patients(27,35,36). The current study, which included 15 Western patients with mostly gastroesophageal adenocarcinoma, also supports this conclusion.

Although hepatic and pulmonary metastasectomies may be performed rather safely, they do carry a certain risk. This is illustrated by 1 postoperative death and 7 postoperatieve re-interventions in 34 patients in the current study. In the selected patient group in the current study, the risk for postoperative complications and death seems acceptable as relatively favorable OS rates were achieved. In patients with metastatic gastroesophageal cancer, quality of life must be taken into account as well. Unfortunately, data on quality of life after resection of gastroesophageal metastases are lacking.

Metastasectomy of gastroesophageal hepatic or pulmonary metastases is not the standard of care in the Netherlands. The patients described in the current study are highly selected. Most patients had metachronous metastasis with long intervals between diagnosis of the primary tumor and the metastasis. The metachronous presentation could be indicative of a more favorable cancer biology, as is the case for metachronous hepatic metastases from colorectal cancer(37). Furthermore, except for one patient, all patients had oligometastatic disease. The majority of metastasis were solitary and radically resected and a slight majority of the primary tumors were moderately differentiated. Comparable characteristics were also reported as favorable prognostic factors in the study by Kobayashi et al. on patients who underwent pulmonary metastasectomy of esophageal cancer metastases (27). It is possible that these factors contributed to the favorable survival in the current study and these factors could be used as a means of selecting physically fit patients for curative therapy, ideally within the context of a prospective study.

Only 7 patients in the current study had synchronous oligometastasis and it is thus difficult to use the data in the current study to discuss a procedure to select these patients for curative therapy. For these patients, a tailored approach is required which could include any combination of systemic therapy, resection of the primary tumor and local treatment of the metastasis by resection or (stereotactic body) radiotherapy. Recently, the AIO-FLOT3 trial also demonstrated favorable results: a median OS of 31 months with perioperative chemotherapy and combined resection of the primary tumor and oligometastasis in patients with limited synchronous metastatic diseases(38). The AIO-FLOT5 trial is currently investigating this approach in a randomized setting (39).

A strength of the current study is the use of the Dutch national registry for histo- and cytopathology, which guaranteed the inclusion of all patients who underwent a hepatic or pulmonary resection with curative intent for metastatic gastroesophageal cancer (with available patient files) in the Netherlands within a time frame of 25 years. A limitation of the current study is its retrospective nature. Especially in old patient files, some variables were missing and the reason why a resection was or was not performed was not always explicitly mentioned. The main limitation of the current study is selection bias. Nevertheless, one could speculate that the favorable survival is unlikely to be the result of selection alone, but rather of selection in combination with metastasectomy.

In conclusion, in selected patients with gastroesophageal cancer with hepatic or pulmonary metastasis, metastasectomy was performed with limited morbidity and mortality and offered a 5-year OS of 31-53%. These results justify the conduction of prospective studies with strict inclusion criteria, which can evaluate whether or not more patients can be selected for a metastasectomy and if an improvement in survival and quality of life is observed in a randomized setting.

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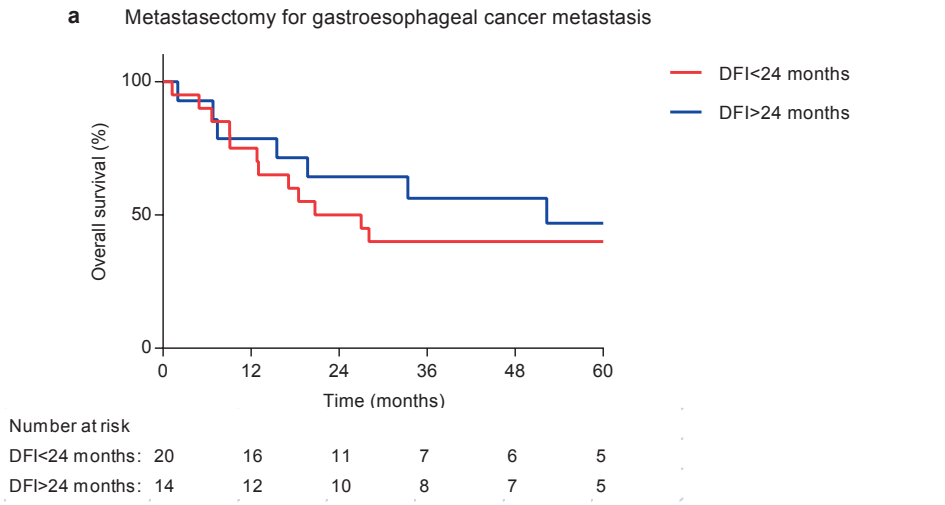
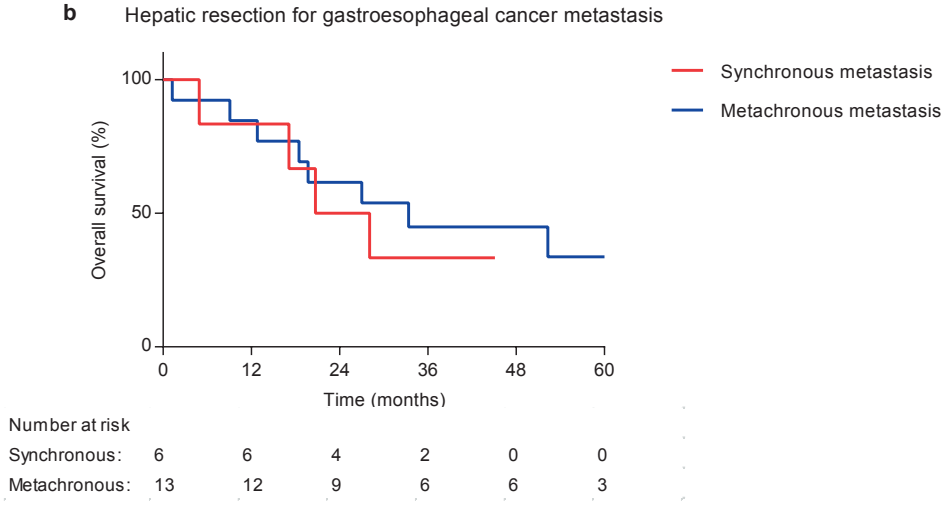
SUPPLEMENTARY MATERIAL

Supplementary Results: Disease free interval subgroup analysis

A subgroup analysis was performed comparing the OS of the 20 patients with a disease free interval (DFI) <24 months versus the 14 patients with a DFI >24 months. The hepatic and pulmonary resection groups were combined for this purpose. The median OS (after metastasectomy) of the DFI < 24 months group was 24 months and the median OS of the DFI > 24 months group was 52 months ($p = 0.47$) (Supplementary material 1a).

Another subgroup analysis was performed comparing the OS of the 13 patients with metachronous hepatic metastasis versus the 6 patients with synchronous hepatic metastasis. The median OS of the metachronous group was 33 months and the median OS of the synchronous group was 24 months. No difference in OS was observed between these groups, as the Kaplan-Meier curves overlapped (Supplementary material 1b). As only 1 of the patients in the pulmonary resection group had synchronous metastasis, no further subgroup analysis was performed in this group.





Supplementary material 1. Kaplan-Meier survival curves in patients who underwent a resection of hepatic metastasis from gastroesophageal cancer, stratified by a disease free interval (DFI) <24 months and DFI >24 months for the hepatic and pulmonary resection groups combined(a) and synchronous and metachronous metastasis for the hepatic resection group (b).


Prospective

CHAPTER 9

The ISCON-trial protocol: laparoscopic ischemic conditioning prior to esophagectomy in patients with esophageal cancer and arterial calcifications

BMC Cancer 2022

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ABSTRACT

Background

Anastomotic leakage is the most important surgical complication following esophagectomy. A major cause of leakage is ischemia of the gastric tube that is used for reconstruction of the gastrointestinal tract. Generalized cardiovascular disease, expressed by calcifications of the aorta and celiac axis stenosis on a pre-operative CT scan, is associated with an increased risk of anastomotic leakage. Laparoscopic ischemic conditioning (ISCON) aims to redistribute blood flow and increase perfusion at the anastomotic site by occluding the left gastric, left gastroepiploic and short gastric arteries prior to esophagectomy. This study aims to assess the safety and feasibility of laparoscopic ISCON in selected patients with esophageal cancer and concomitant arterial calcifications.

Methods

In this prospective single-arm safety and feasibility trial based upon the IDEAL recommendations for surgical innovation, a total of 20 patients will be included recruited in 2 European high-volume centers for esophageal cancer surgery. Patients with resectable esophageal carcinoma (cT1-4a, N0-3, M0) with "major calcifications" of the thoracic aorta accordingly to the Uniform Calcification Score (UCS) or a stenosis of the celiac axis accordingly to the modified North American Symptomatic Carotid Endarterectomy Trial (NASCET) score on preoperative CT scan, who are planned to undergo esophagectomy are eligible for inclusion. The primary outcome variables are complications grade 2 and higher (Clavien-Dindo classification) occurring during or after laparoscopic ISCON and before esophagectomy. Secondary outcomes include intra- and postoperative complications of esophagectomy and the induction of angiogenesis by biomarkers of microcirculation and redistribution of blood flow by measurement of indocyanine green (ICG) fluorescence angiography.

Discussion

We hypothesize that in selected patients with impaired vascularization of the gastric tube, laparoscopic ISCON is feasible and can be safely performed 12-18 days prior to esophagectomy. Depending on the results, a randomized controlled trial will be needed to investigate whether ISCON leads to a lower percentage and less severe course of anastomotic leakage in selected patients.

Trial registration

Clinicaltrials.gov, NCT03896399. Registered 4 January 2019, https://www.clinicaltrials.gov/ct2/show/NCT03896399?term=ISCON&draw=2&rank=1

BACKGROUND

Transthoracic esophagectomy with 2-field lymphadenectomy is the standard of surgical care for patients with esophageal cancer [1]. The reconstruction of choice is a gastric tube with intrathoracic (Ivor-Lewis) or cervical esophagogastrostomy (McKeown). This gastric tube is perfused only by the right gastroepiploic artery, as all other gastric arteries are ligated during gastric mobilization. This is associated with severe change of microcirculation in the gastric tube, reducing gastric perfusion up to 50% [2]–[5]. Reduced blood flow may lead to impaired healing of the anastomosis and could result in anastomotic leakage. Anastomotic leakage occurs in 15% - 30% of patients after esophagectomy [6]. It is considered the most important complication after esophagectomy, increasing postoperative morbidity and mortality. Anastomotic leakage has a multifactorial etiology. Some risk factors have been identified, such as severe comorbidity, diabetes mellitus, smoking status, radiation field and cervical anastomosis [7], [8].

Another important risk factor is the vascular status which can be inferred from calcification in the thoracic aorta, defined by the uniform calcification score (UCS). The UCS is calculated on diagnostic CT scans by scoring the presence of arterial calcification in the thoracic aorta based on a visual grading system. In addition, the presence of a local stenosis of the celiac trunk is also associated with an increased risk of anastomotic leakage [12]. This stenosis is defined by the modified North American Symptomatic Carotid Endarterectomy Trial score (modified NASCET score). Higher percentages of anastomotic leakage (33-37%) were observed in patients with calcifications compared to patients without calcifications, who had lower incidences of leakage (9-19%) [9]–[11].

The higher prevalence of anastomotic leakage in these patients are hypothesized to be the result of a reduced micro or macro perfusion of the gastric tube [2]–[4], [13]. Anastomotic leakage percentages might be reduced by ischemic conditioning (ISCON) of the gastric tube. ISCON aims to increase perfusion at the anastomotic site by redistribution of the gastric blood flow [14]. This is achieved by occluding all of the gastric arteries except the right gastric and right gastroepiploic artery during a separate intervention, days or weeks prior to esophagectomy.

To date, several studies reported ISCON to be safe in esophageal surgery and its possible efficacy in decreasing anastomotic leakage [15], [16]. However, all studies were retrospective and performed in unselected patients. Therefore, the current prospective safety and feasibility trial aims to investigate the feasibility and safety of performing laparoscopic ISCON for esophageal cancer in patients at high-risk for anastomotic leakage, as based upon their vascular status on pre-operative CT scans (defined by the UCS of the thoracic aorta and modified NASCET score of the celiac axis). The hypothesis of this study is that in these selected patients with an increased risk of vascular impairment of the gastric tube, laparoscopic ISCON is feasible and can be safely performed prior to esophagectomy.

METHODS/DESIGN

Design

This study is designed as a prospective single-arm safety and feasibility trial performed at the University Medical Center Utrecht and the University Hospital of Cologne.

Ethical consideration

The study protocol was approved by the Medical Ethical Committees of the University Medical Center Utrecht (reference number NL67819.041.18) and the University of Cologne (reference number 18-299). The trial was prospectively registered at clinicaltrials.gov.

Patient population

All patients with a resectable esophageal carcinoma (cT1-4aN0-3M0) scheduled for an esophagectomy are eligible for screening for inclusion in the study. Accordingly to policies in the Netherlands and Germany, included patients undergo neoadjuvant chemo(radio) therapy followed by laparoscopic ISCON and subsequent esophagectomy. An exception will be made for patients with early esophageal cancer (cT1-2N0M0) and patients who are not fit enough for neoadjuvant treatment, they will bypass neoadjuvant treatment and undergo primary ISCON followed by esophagectomy. Detailed inclusion and exclusion criteria are listed below.

Inclusion criteria:

- Histologically proven adenocarcinoma or squamous cell carcinoma of the esophagus or gastroesophageal junction
- Planned to undergo transthoracic esophagectomy or transhiatal esophagectomy
- Preoperative CT-scan
- Arterial calcifications: "major calcifications" of the thoracic aorta according to the (UCS) or a stenosis of the celiac axis according to the modified NASCET score
- ASA classification I-III
- European Clinical Oncology Group (ECOG) performance status of 0-2
- Age > 17
- Written informed consent

Exclusion criteria:

- Not able to undergo study treatment
- Presence of metastatic disease

UCS and NASCET score

Preoperative staging examinations of all patients are routinely performed on CT scanners with 64 detector rows or more. A slice thickness of maximum 3.0 mm is used. Two clinicians (of whom at least one is a radiologist) will independently score the calcifications on the preoperative CT scans of the thoracic aorta (UCS score) and the celiac axis (modified NASCET score). Any disagreements will be solved based on discussion. The UCS will be used in order to consistently score CT images on arterial calcification at the thoracic aorta (heart – celiac axis). Scores of 0, 1 or 2 will be assigned, corresponding with absent, minor or major calcifications, respectively (see table 1). Stenosis of the celiac axis will be evaluated by using multiplane reconstructions. Accordingly to the NASCET score, the diameters of the normal (a) and narrowest (b) lumen of the celiac axis will be measured. The percent stenosis (s) will be calculated using the following formula: $s = (a-b)/a \times 100$

Table 1. Uniform Calcification Score: Definitions used to visually grade arterial calcification on preoperative CT images. MCSD: maximum cross-sectional diameter

Anatomical location	Calcification scores		
	0	1	2
Coronary arteries[1]	Absent	Multiple foci or calcification extending over ≥slices	Calcified arteries covering a large segment of a coronary branch
Supra-aortic arteries[1]	Absent	Calcification in 1 supra-aortic artery	Calcification in >1 supra-aortic artery
Thoracic-aorta	Absent	≤9 foci or ≤3 calcifications extending over ≥3 slices	>9 foci or >3 calcifications over ≥3 slices
Celiac axis[1]	Absent	Single focus with MCSD ≤10 mm or extending over ≤3 slices	MCSD >10mm or extending over ≥3 slices or involving proximal (aortoceliac) and distal (hepatosplenic) parts

[1]the Uniform Calcification Score of these anatomical locations are secondary outcome measures.

Laparoscopic ISCON

The first operation aims to partially devascularize the stomach by laparoscopic clipping of the left gastric artery, reached through the hepatogastric ligament at the lesser curvature. Furthermore, transection (with the harmonic scalpel or comparable instrument) of the short gastric vessels including the left gastroepiploic artery is performed. This operation will be kept as minimalistic as possible. Vascularization of the right gastric artery and the right gastroepiploic artery along the greater curvature will remain preserved. No lymph node dissection or gastric tube formation will be performed.

Postoperative management ISCON

Patients are allowed to drink liquids, soup and supplemental nutrition drinks (high energy, high protein oral nutritional supplements) on postoperative day 0. All patients will have a form of liquid or solid enteral nutrition between ISCON and esophagectomy. Patients will be eligible for discharge on postoperative day 3, depending on the clinical course. A dietician will be consulted to ensure that the patient is optimized in terms of nutrition between ISCON and esophagectomy. All patients will receive a mandatory outpatient clinic standard follow-up appointment on postoperative day 6-8, unless they are still admitted at the hospital. Patients will be re-admitted 0-1 day before esophagectomy.

Esophagectomy

Esophagectomy will be performed after an interval of 12-18 days after ISCON. If a gastroparesis is suspected, a nasogastric tube will be placed before anaesthesia to avoid aspiration. Esophagectomy will consist of a transthoracic esophagectomy with intrathoracic or cervical anastomosis or a transhiatal esophagectomy with cervical anastomosis. In the University Hospital of Cologne, an intrathoracic anastomosis will be created in all patients except for those with a tumor localized in the cervical compartment. In the University Medical Center Utrecht, a cervical anastomosis will be created for proximal and mid esophageal tumors while an intrathoracic anastomosis will be created for distal esophageal tumors. Alternatively, instead of a transthoracic esophagectomy, a transhiatal esophagectomy can be performed in patients with increased comorbidity.

The esophagectomy includes laparoscopic gastric mobilization, abdominal lymph node dissection, intrathoracic lymph node dissection (for transthoracic esophagectomies), esophagectomy and intrathoracic or cervical anastomosis. The abdominal phase will be performed as a minimally invasive procedure, the thoracic procedure can be performed by an open or a (robot assisted) thoracoscopic approach.

If, for any reason, it is not possible to perform the second operation within 12-18 days, it will be attempted to perform the second operation as soon as possible (i.e. within 30 days) based on the discretion of the surgeon who performed the first operation.

Translational program

To assess the effect of laparoscopic ISCON on macro- and microcirculation, a translational program is included in the study. This program consists of two parts: measurements of macro- and microcirculation. This will be investigated by means of blood samples (cytokine profile), biopsies (vascularity) and ICG fluorescence angiography. Blood samples will be collected before ISCON and esophagectomy and will be screened on biomarkers. The presence and the level of biomarkers will be compared in the blood samples before and after ISCON to detect potential changes. Biopsies will be taken via gastroscopy preoperatively

to ISCON as well as esophagectomy, either within 24 hours before surgery or immediately after anesthesia. Three biopsies will be taken from the gastric fundus since the anastomosis will likely be located somewhere in the fundus. In order to identify the fundus, the endoscopy will be performed right after the laparoscopic camera is inserted so that the table surgeon is able to point out the fundus. Finally, if a stapler is used for performance of the anastomosis, the gastric anastomotic donut will be collected and if the anastomosis is hand-sewn, the tip of the gastric tube will be collected to for further pathological analysis and to detect morphological changes of the microvasculature. ICG will be performed during ISCON, before and after the occlusion of the gastric arteries and during esophagectomy, before the creation of the gastric conduit and optionally before the creation of the intrathoracic anastomosis. The ICG procedure is standardized and included in the protocol as described in Supplementary material 1. The goal is to quantify the effect of laparoscopic ISCON on gastric perfusion which is described in Supplementary material 2. During ICG, the camera keeps the gastric fundus in view. If ICG is also performed for the anastomosis, the camera keeps the gastric conduit in view. The different time points of the translational program are summarized in Table 2.

Table 2. Summary of time points of the translational program. h=hour

	ICG fluorescence	Biomarkers
<24 h to start of ISCON		Biopsies of anastomotic site + peripheral blood (10ml EDTA)
ISCON: before occlusion of arteries	X	
ISCON: 10 minutes after occlusion of arteries	X	
<24 h to start of esophagectomy		Biopsies of anastomotic site + peripheral blood (10ml EDTA)
Esophagectomy: before formation of gastric tube	X	
Optional: esophagectomy : before formation of intrathoracic anastomosis	(X)	
Esophagectomy: after completion of anastomosis		Gastric anastomotic donut or tip of gastric tube

Primary outcome

Complications are defined according to the Esophageal Complications Consensus Group (ECCG) and graded according to the Clavien Dindo Classification [17] [18]. The primary outcome measure is the percentage of complications grade ≥2 occurring during or after ISCON and before esophagectomy.

Secondary outcomes

The main secondary outcome measures include all grade 1 complications occurring during or after ISCON and before esophagectomy according to the Clavien Dindo Classification. Intraoperative outcomes will be scored during both surgeries including the presence of adhesions, intraoperative complications and the vascularisation of the stomach (based on the color of the tissue). Furthermore, for ISCON, the duration of the procedure, blood loss, oral intake, weight and day of discharge will be collected. Lastly, 30 day mortality, anastomotic leakage of any grade and all other postoperative complications grade ≥ 3b will be collected after esophagectomy.

Translational outcomes

Secondary outcomes regarding the translational program are induction of angiogenesis by biomarkers of microcirculation, redistribution of blood flow by measurement of indocyanine green (ICG) fluorescence angiography. Serum levels of several proangiogenic cytokines (VEGF, IL-8, IL-6, TNF-α and Ang-2) will be determined in peripheral blood samples by ELISA [19]. The obtained biopsies and gastric donut samples/tip of the gastric conduit will be collected from the endoscopy unit or the operation theatre and will be fixed in formaldehyde. Paraffin embedded sections (10μm) will be stained by immunohistochemistry against CD31 (vessel density) or smooth-muscle-actin positive pericytes to detect morphological changes of the microvasculature. The strength of the ICG will be scored on videos that are recorded during the operation in 2 fashions, subjectively and objectively.

Data collection

All data will be collected and stored in an electronic Clinical Research Form application called OpenClinica. The coordinating investigators will oversee the overall data collection process. OpenClinica generates a subject number for each patient and securely stores all entered research data in a pseudonymized fashion. A code file that links subjects numbers to individual patients will be securely stored in each center, and will only be accessible to the local study coordinators. Collected baseline data (age, gender, body mass index, comorbidities) and treatment details (neoadjuvant therapy, surgical techniques, postoperative complications, mortality) will be prospectively entered in a case report form with built-in validation checks. Patient-reported outcome measures (PROMs) will be collected prior to both surgeries by asking patients to complete the questionnaires (EORTC QLQ-C30 and QLQ-OG25).

Sample size

This is a prospective single arm safety and feasibility trial, classified as a "stage 2a Development" study according to the IDEAL recommendations for surgical innovation[20].

Based upon these recommendations, a total of 20 subjects will be included and no formal sample size calculations are performed (10 patients per centre).

Statistical analyses

Statistical analyses in this study are primarily based on descriptive means. Categorical data will be summarized as frequencies. Normally distributed continuous data will be summarized as means with corresponding standard deviations. Non-normally distributed continuous data will be summarized as medians with corresponding interquartile ranges. Analysis will be performed with SPSS software (IBM).

Data Safety Monitoring Board & Monitoring

This study is classified as a medium risk study. Monitoring will be performed in both centers by an external independent Contract Research Organization according to the Study Monitoring Plan. Based upon advice of the Data Safety Monitoring Board (DSMB) of the UMC Utrecht, a DSMB will not be assigned. Instead of a DSMB, an independent Medical Safety Officer -a Professor in Gastroenterology- was assigned to perform ongoing safety surveillance together with the researchers. After the first 5 patients underwent esophagectomy, all serious adverse events (SAEs) will be evaluated with the Medical Safety Officer. After the first 10 patients underwent both surgeries, an interim analysis will be performed which is described in detail below. All SAEs will be reported by the sponsor to the ethical committee and to the Medical Safety Officer.

Interim analysis

An interim analysis will be performed after hospital discharge (after esophagectomy) of the first 10 patients included in the study. The stopping rules are the occurrence of one of the following:

- > 40% postoperative complication of gastric perforation requiring re-intervention, during or after laparoscopic ISCON and before esophagectomy.
- > 40% patients having an aspiration pneumonia after laparoscopic ISCON, resulting in a prolonged hospital stay.
- > 40% patients not able to undergo the planned esophagectomy within 30 days after laparoscopic ISCON, due to complications specifically attributed to laparoscopic ISCON.

DISCUSSION

Anastomotic leakage is the predominant surgical complication after esophagectomy [18]. The cause of an anastomotic leakage is multifactorial[7], [8]. One of these factors includes hypovascularization of the gastric conduit which opposes healing of the anastomosis and consequently contributes to leakages. In retrospective analyses of both participating centres of the current study, major calcifications of the aorta and celiac axis have been shown to be an independent risk factor for anastomotic leakage [21], [22]. The preoperative identification of patients at risk for anastomotic leakage allows for personalized treatment programs. The ISCON-trial is a safety and feasibility study aiming to stimulate the vascularisation of the gastric conduit prior to the esophagectomy in selected patients. Patients at high risk for anastomotic leakage are selected via calcification scores on preoperative CT-scans.

Efficacy ISCON

Several studies have investigated the efficacy of ISCON. A recent meta-analyses published in 2020 showed that ISCON seems to reduce the incidence and severity of anastomotic leakage [23]. Yet ISCON failed to demonstrate a significant reduction of leakage precentages in other meta-analyses and systematic reviews of clinical studies [16], [24], [25]. One explanation for this controversy could be the fact that multiple factors contribute to the development of anastomotic leakage ensuing that ISCON alone might not have enough impact to significantly decrease anastomotic leakage numbers. However, this discrepancy could also be explained by the heterogeneity and retrospective nature of the studies. The heterogeneity is caused by several factors including the selection of patients, the time interval between ISCON and esophagectomy, which arteries are occluded and the technique that is used for ISCON (radiological versus laparoscopic). These factors could have influenced the efficacy and are discussed separately in the consecutive paragraphs.

Selection of patients

The majority of the studies reporting on ISCON did not select patients [25]. In the current study, the UCS for major calcifications of the thoracic aorta was used as an indicator of poor generalized cardia vascular status. The location of thoracic aorta was internally and externally validated as a predictor for anastomotic leakage after esophagectomy in 3 studies [13], [21], [26].

Interval

Another discussion point is the interval between ISCON and esophagectomy which has been widely discussed in the literature [25]. On the one hand, the interval should be long

enough to redistribute the blood flow of the stomach. On the other hand, the interval should be short enough to avoid hindering the esophagectomy due to potential adhesions or causing a delay in the treatment. In the literature, intervals range between 4 and over a 100 days. Increasing evidence is available arguing for an interval of 2 weeks. Animal studies have demonstrated that immediately after ISCON, the gastric perfusion drops to 20-30%. After 1 week, the gastric perfusion around 60% and 2 weeks after ISCON, the gastric perfusion is over 90% [27], [28]. In addition, a recent meta-analysis compared the studies with an interval of >2 weeks versus <2 weeks and showed a trend towards lower leakage percentages for >2 weeks, whereas no reduction in leakages was seen for <2 weeks [23]. In addition, an interval of 2 weeks is likely to be short enough to prevent the development of adhesions. In order to minimalize adhesions, ISCON procedure is kept as lean as possible and no further preparations for the esophagectomy will be performed during the first operation. The presence of adhesions during esophagectomy will be scored accordingly to the Peritoneal adhesion index [29].To take into account for logistics, as scheduling surgeries and weekends, an interval of 12 till 18 days between ISCON and esophagectomy is used in the current trial.

Radiological versus surgical ISCON

In the current study, ISCON is performed by occluding the left gastric, left gastroepiploic and short gastric arteries in an attempt to achieve a maximum ischemic effect. In contrast, some of the retrospective studies occluded only the left gastric artery [25]. Furthermore, ISCON could be performed radiologically as well as surgically. Superiority of one technique over the other has not yet be demonstrated. In the current study, ISCON will be performed laparoscopically since our study team already has experience with this procedure. In addition, a potential benefit of surgical ISCON is the precise and certain occlusion of the target arteries. Radiologically, it could be more difficult to selectively occlude the short gastric arteries. Instead of the short gastrics, the splenic artery could be partly embolized with a risk of splenic ischemia [30]. Furthermore, surgical ISCON allows for a translational arm with ICG measurements. Advantages of radiological ISCON are that it can be performed under local anesthesia and it does not cause adhesions.

Safety ISCON

A meta-analysis on ISCON was published in 2017 including 11 retrospective studies and a combined total of 1152 patients. None of the included studies reported any major complications associated with the ISCON procedure itself [16]. This indicates that this procedure can be safely performed in unselected patients. Furthermore, since major calcifications of the thoracic aorta according to the UCS score have a relatively high prevalence (30%), we postulated that this meta-analysis likely also include a proportion of

patients with major aortic calcification, and that ISCON could thus also be safe in these selected patients [13]. None of the retrospective studies reported perforation due to ischemia after ISCON. Hence, we will remain vigilant for this complication, but deem the chance of it occurring slim. Based upon prior clinical experience in the University Hospital of Cologne, we expect gastroparesis to occur in up to 25% of patients. Since patients with gastroparesis could be at an increased risk of acquiring an aspiration pneumonia, patients' intake and complaints as nausea and vomiting will be closely monitored and gastroparesis will be treated by emptying the stomach via nasogastric tube placement. None of the retrospective studies report on gastroparesis and nutritional intake after ISCON. This could be explained due to the retrospective data collection. In the current study we use a clear definition of gastroparesis and will prospectively collect nutritional intake data which strengthen the study. Importantly, as mentioned, the meta-analysis included only retrospective studies and had a high degree of heterogeneity with regards to selection of patients, the time interval between ISCON, which arteries are occluded and the technique that is used for ISCON (radiological versus laparoscopic)[23]. The safety and feasibility of ISCON in selected patients have not yet been demonstrated in a prospective trial.

CONCLUSION

In summary, the ISCON-trial is a single-arm prospective study investigating the safety and feasibility of laparoscopic ISCON 12-18 days prior esophagectomy in a highly selected group of patients at risk to develop an anastomotic leakage. In addition, a translational program is set up to assess the postulated effect of laparoscopic ISCON. The ISCON-trial is unique with respect to its prospective study design and the careful selection of eligible patients by means of atrial calcifications. If the hypothesis is confirmed that ISCON is safe and feasible, a randomized controlled, multicentre trial will be set up to determine whether esophagectomy preceded by ISCON is superior over esophagectomy without ISCON in terms of anastomotic leakage.

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SUPPLEMENTARY MATERIAL

Supplementary material 1: ICG – intraoperative protocol

Anesthesiology:

- Check for contra-indications: allergy for Jodium/ICG, hyperthyroidism or thyroid adenoma.
- Start of the operation: Verdye ICG vial contains 50mg of injection powder. This is dissolved by adding 20ml of sterile water (=2,5mg/ml). 2 syringes are prepared, each with 3ml solution (containing 7.5mg ICG). The syringes and vial are kept in a dark space.
- During an ICG angiography: the mean arterial pressure is kept at >70mm Hg and is kept at a constant level. ICG 3ml (7.5mg) rapid bolus is given over a peripheral venous catheter and flushed with 10ml NaCl

Surgery, laparoscopic ischemic conditioning:

ICG angiography 1: Laparoscopy with ischemic conditioning, ICG **prior to** *occlusion of arteries*

- Video of the operation is being recorded
- Position the camera activate near-infrared filter and set-up gain/background light according to the figure 1.
- Surgeon asks anesthesiologists to inject ICG (after camera has been properly positioned).
- Camera does not move for 90 seconds (even the slightest movement disrupts measuring ICG influx speed)
- Camera is free to move: close-up inspection of entire stomach (to prevent misleading non-existent demarcations due to a difference in depth of the camera to the relevant structures, giving a weaker signal)

ICG angiography 2: Laparoscopy with ischemic conditioning, ICG **10 minutes after** *occlusion of arteries*

This ICG angiography is performed in similar fashion as the first ICG angiographies. The camera is set-up to visualize the exact same anatomic structures and with the exact same gain/background light.

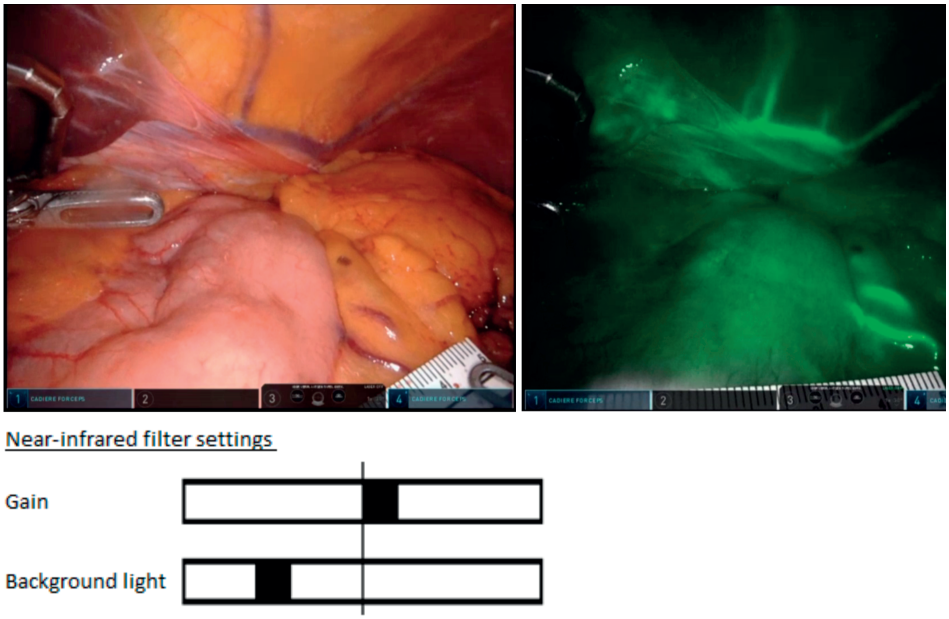

Figure 1. The gastric fundus is visualized, together with the diaphragm as reference. *Of note, these filter settings are from the Da Vinci Firefly system, other systems might require different settings for good visualization.*

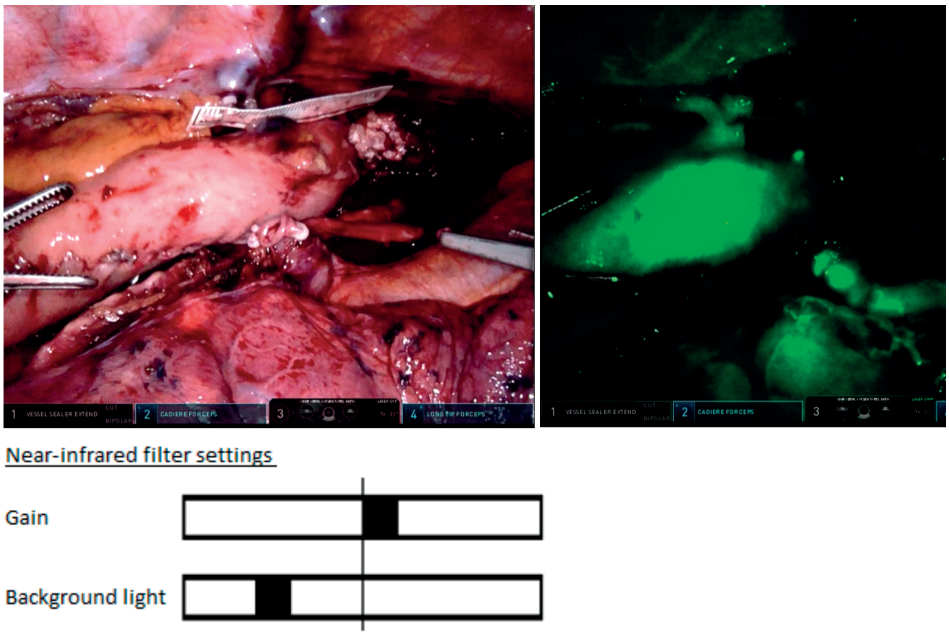

Figure 2. Tip of the gastric tube and planned location of anastomosis are visualized, together with the intercostal vessels and right lung as references. *Of note, these filter settings are from the Da Vinci Firefly system, other systems might require different settings for good visualization.*

Surgery, esophagectomy:

ICG angiography 3: esophagectomy, ICG before formation of the gastric tube

This ICG angiography is performed in similar fashion as the first 2 ICG angiographies. An attempt is made to set-up the camera to visualize the exact same anatomic structures and with the exact same gain/background light as during the first 2 ICG angiographies.

Optional: ICG angiography 4: esophagectomy, ICG before formation of intrathoracic anastomosis

- Video of the operation is being recorded
- Position the camera, activate near-infrared filter and set-up gain/background light according to figure 2.
- Surgeon asks anesthesiologists to inject ICG (after camera has been properly positioned).
- Camera does not move for 90 seconds (even the slightest movement disrupts measuring ICG influx speed)
- Camera is free to move: close-up inspection of gastric tube up to the tip (to prevent misleading non-existent demarcations due to a difference in depth of the camera to the relevant structures, giving a weaker signal)

Supplementary material 2: ISCON ICG – postoperative quantification

The camera is positioned to visualize the area of interest (i.e. gastric fundus in abdomen measurement and proximal part of the gastric conduit where the surgeon intents to create the anastomosis in the thoracic measurement). A challenge of standardizing fluorescence measurements are factors influencing intraoperative perfusion such as differences in patient physiology, co-morbidity and intraoperative hypotension. Therefore the patient itself is used as a reference for his own physiology by visualizing controls (1 control in the abdominal measurement: the diaphragm, 2 controls in the thoracic measurement: the lung below the gastric tube and the thoracic wall above the gastric tube). Next, ICG is administrated in a peripheral venous line (figure 1A). The control measurements should show green fluorescence first, followed by the gastric tube, indicating good perfusion of the gastric tube (as can be seen in figure 1A-E). If only the controls show green fluorescence, but the gastric tube does not, this would indicate poor perfusion of the gastric tube.

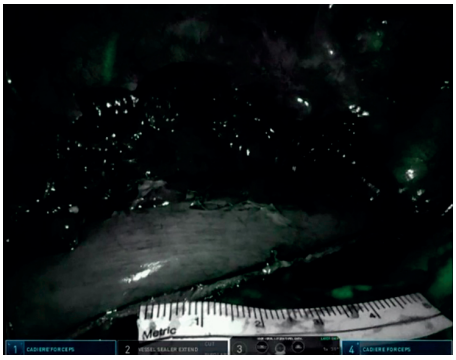

Figure 1A. 34 seconds after ICG injection. The grey gastric tube is centrally in the screen. The control measurement of the lung (partially blocked by the ruler) first shows green fluorescence, the thoracic wall is not yet strongly green fluorescent.

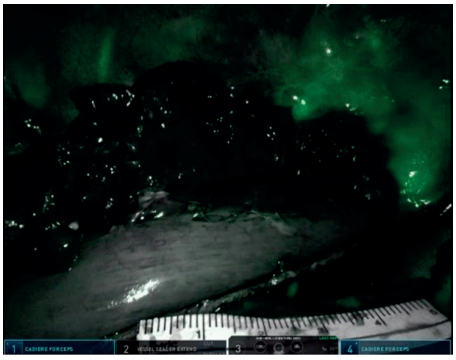

Figure 1B. 38 seconds after ICG injection. The control measurement of the thoracic wall also shows green fluorescence.

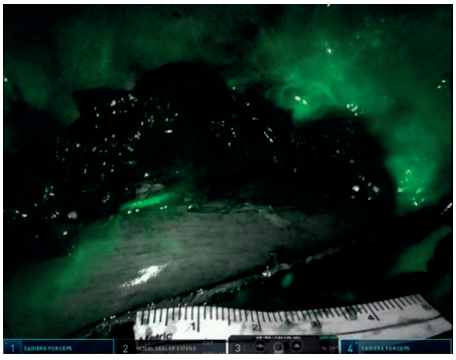

Figure 1C. 42 seconds after ICG injection. The more distal part of the gastric tube (left in the picture) starts to show green fluorescence.

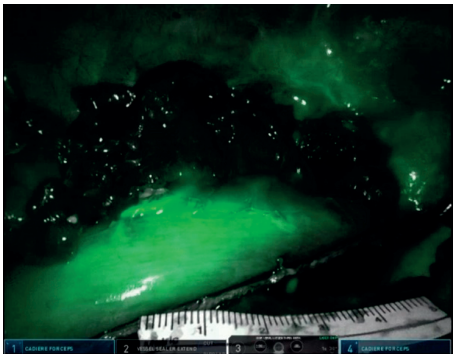

Figure 1D. 50 seconds after ICG injection. Both the distal and proximal part of the gastric tube show green fluorescence.

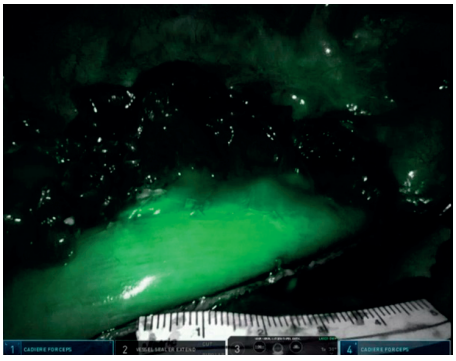

Figure 1E. 80 seconds after ICG injection. Green fluorescence in most proximal part of the gastric tube (right part of screen) is slightly improved compared to the image at 50 seconds.

To quantify the fluorescence, pre-defined regions of the gastric tube are selected (figure 2). The intensity of the green fluorescence is stronger in the central vision of the camera than in the periphery. Therefore, the camera was not moved during the entire measurement. As mentioned, a challenge of standardizing fluorescence measurements are factors influencing intraoperative perfusion. To correct for the above 2 challenges, the selected regions of interest use themselves as a reference for measuring the intensity of the fluorescence. The intensity of the fluorescence (the greenness of the pixels) is measured in arbitrary units at each selected region of interest. The maximum arbitrary units is set at 100%. Next, graphs are plotted with the intensity on the Y-axis and the time on the X-axis (Figure 3). The time until reaching the maximum intensity will be calculated as the mean slope to maximum intensity (the "steepness of the graph"). In case the maximum intensity of 100% is reached quickly, the mean slope to maximum intensity is large, indicating good perfusion. If the maximum intensity of 100% is reached slowly, the mean slope to maximum intensity is small, indicating poor perfusion.

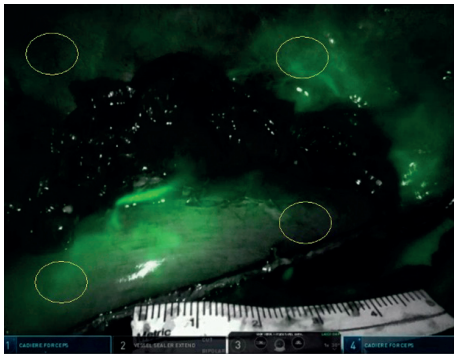

Figure 2. Pre-defined regions of the gastric tube are selected to quantify the fluorescence. In this case: the proximal gastric tube at 1 cm from the proximal tip and the distal gastric tube at 6 cm from the proximal tip. In addition, 2 control measurements at the thoracic wall were selected. The lung (below the gastric tube, directly above the ruler), though not used as a control in this example, is also a good site to use as a control.

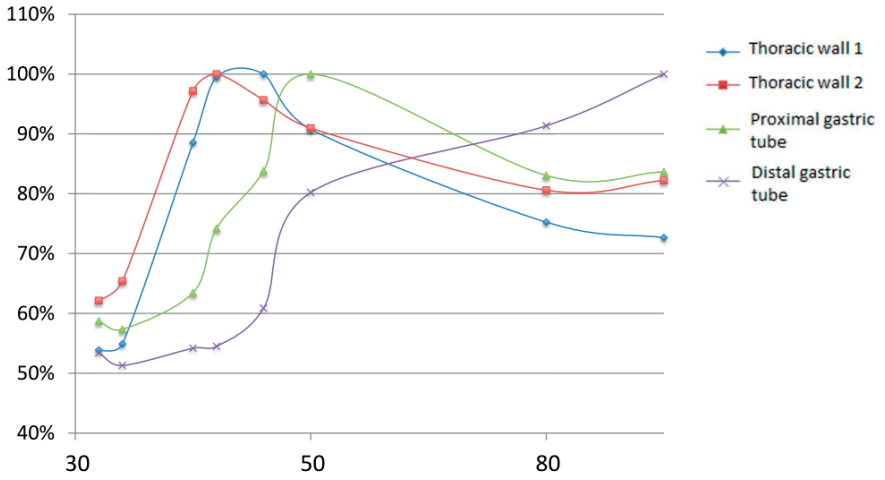

Figure 3. Intensity of fluorescence in % on the y-axis, time after injection of ICG in seconds on the x-axis. The graph shows how the control measurements (in this case the intrathoracic wall) show a quick rise in fluorescence (high mean slope to maximum intensity), followed by the proximal gastric tube and lastly the distal gastric tube (lower mean slope to maximum intensity). This is in accordance to normal physiology, as the gastric tube is perfused from distally by the right gastroepiploic artery.

9

CHAPTER 10

The CARDIA-trial protocol: a multinational, prospective, randomized, clinical trial comparing transthoracic esophagectomy with transhiatal extended gastrectomy in adenocarcinoma of the gastroesophageal junction (GEJ) type II

BMC cancer 2020

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**Both authors contributed equally*

ABSTRACT

Background

Adenocarcinoma of the gastroesophageal junction (GEJ) Siewert type II can be resected by transthoracic esophagectomy or transhiatal extended gastrectomy. Both allow for a complete tumor resection, yet there is an ongoing controversy about which surgical approach is superior with regards to quality of life, oncological outcomes and survival. While some studies suggest a better oncological outcome after transthoracic esophagectomy, others favor transhiatal extended gastrectomy for a better postoperative quality of life. To date, only retrospective studies are available, showing ambiguous results.

Methods

This study is a multinational, multicenter, randomized, clinical superiority trial. Patients (n = 262) with a GEJ type II tumor resectable by both transthoracic esophagectomy and transhiatal extended gastrectomy will be enrolled in the trial. Type II tumors are defined as tumors with their midpoint between ≤1 cm proximal and ≤2 cm distal of the top of gastric folds on preoperative endoscopy. Patients will be included in one of the participating European sites and are randomized to either transthoracic esophagectomy or transhiatal extended gastrectomy. The trial is powered to show superiority for esophagectomy with regards to the primary efficacy endpoint overall survival. Key secondary endpoints are complete resection (R0), number and localization of tumor infiltrated lymph nodes at dissection, post-operative complications, disease-free survival, quality of life and cost-effectiveness. Postoperative survival and quality of life will be followed-up for 24 months after discharge. Further survival follow-up will be conducted as quarterly phone calls up to 60 months.

Discussion

To date, as level 1 evidence is lacking, there is no consensus on which surgery is superior and both surgeries are used to treat GEJ type II carcinoma worldwide. The CARDIA trial is the first randomized trial to compare transthoracic esophagectomy versus transhiatal extended gastrectomy in patients with GEJ type II tumors. Several quality control measures were implemented in the protocol to ensure data reliability and increase the trial´s significance. It is hypothesized that esophagectomy allows for a higher rate of radical resections and a more complete mediastinal lymph node dissection, resulting in a longer overall survival, while still providing an acceptable quality of life and cost-effectiveness.

Trial registration the trial was registered on August 2nd 2019 at the German Clinical Trials Register under the trial-ID DRKS00016923.

Background

Adenocarcinomas of the gastroesophageal junction (GEJ) are located at the borderline of the stomach and esophagus. GEJ tumors show an increase in incidence in the Western world. In the Netherlands for example, the incidence of esophageal cancer more than doubled in a period of less than 20 years [1]. Approximately 27% of patients with a GEJ tumor, suffer from a GEJ Siewert type II 'true' cardia carcinoma, meaning that the midpoint of the tumor is between ≤ 1 cm proximal and ≤ 2 cm distal from the GEJ (see figure 1) [2]. Earlier studies suggested that these tumors can have two distinct etiologies (esophageal and gastric) [3], whereas more recent genetic analysis showed that the origin may be similar [4]. Regardless of the hypothesized origin, given that the incidence of GEJ cancer has risen by up to 350% in Western Europe since the 1970's, determination of optimal treatment is imperative to improve patient outcomes [5].

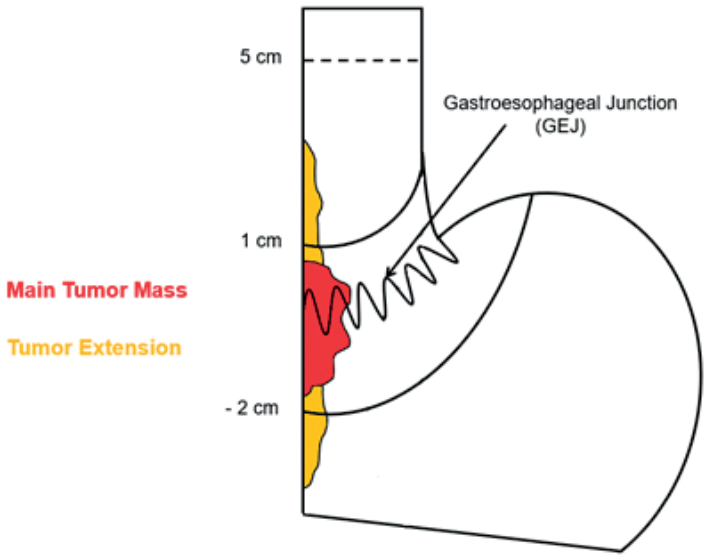

Figure 1. Endoscopic classification of GEJ type II tumors according to the Siewert classification of GEJ cancer. Type II tumors have their midpoint 1 cm above to 2 cm below the cardia.

Successful surgery is the cornerstone of multimodal treatment leading to a 5-year survival rate of 40-50% [6, 7]. There is an ongoing controversy about the optimal surgical approach for Siewert type II tumors. In order to provide the best, intentionally curative, treatment in patients with GEJ tumors, a radical resection of the tumor needs to be combined with removal of adjacent lymph nodes. This can be achieved by two surgical approaches: a transthoracic esophagectomy or a transhiatal extended gastrectomy. Two recent international surveys on this topic show that the worldwide preferred surgical

approach for Siewert type II tumors was extended gastrectomy in 66% of respondents, followed by esophagectomy in 27% [8]. Although extended gastrectomy was found in some studies to be associated with a higher quality of life [9, 10], oncological outcome may be compromised with a higher rate of microscopic neoplastic invasion of the circumferential resection margin and less lymph node metastases resected [11]. To date, the superior surgical approach concerning survival, oncological outcome and quality of life remains unclear, as only retrospective studies are available, showing ambiguous results. This lack of level 1 evidence translates to the lack of consensus in current clinical practice worldwide.

METHODS

Objective

The objective of this study is to compare transthoracic esophagectomy versus transhiatal extended gastrectomy in patients with resectable Siewert type II GEJ adenocarcinoma. The primary efficacy endpoint is overall survival and key secondary endpoints are complete resection (R0), post-operative complications, number and localization of tumor infiltrated lymph nodes at dissection, disease-free survival, quality of life and cost-effectiveness. It is hypothesized that esophagectomy allows for a higher rate of radical resections and a more complete mediastinal lymph node dissection resulting in a longer overall survival, while providing an acceptable quality of life and cost-effectiveness.

Study Design

This study is a multinational randomized clinical trial comparing the two surgical procedures. High-volume academic and non-academic hospitals in Germany, the Netherlands, Sweden, Ireland, Switzerland and France will participate in the trial. It is conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice Guidelines. The protocol has so far been approved by the independent ethics committee of the University Hospital of Cologne, University of Leipzig Medical Center, University Hospital rechts der Isar, University Medical Center of the Johannes Gutenberg University Mainz and the Medical Center – University of Freiburg. Any modifications to the protocol which may impact the trial will be communicated with the participating institutions and approved by the ethics committee again. The surgeon, patient and coordinating researcher will not be blinded for the allocated treatment.

Study population

The study will evaluate patients with GEJ type II carcinoma whose tumor can be safely resected by both transthoracic esophagectomy and transhiatal extended gastrectomy. In detail, the inclusion criteria are:

- Histologically proven adenocarcinoma of the GEJ type II
- Resectable by both transthoracic esophagectomy and transhiatal extended gastrectomy according to the local surgical investigator
- Pre-treatment stage cT1-4a, N0-3, M0
- In case of stage cT4a, curative resectability must be explicitly verified by the local surgical investigator prior to randomization
- Completion of all four cycles of chemotherapy (FLOT) preoperatively, in case of locally advanced tumors (cT3-T4 or N+)
- Age ≥ 18
- ECOG Eastern Cooperative Oncology Group (ECOG) performance status 0–2
- ASA < 4.
- Adequate bone marrow function (white blood cells > 3x10^9 /l; hemoglobin > 9 g/dl; platelets > 100x10^9 /l), renal function (glomerular filtration rate >60 ml/min), and liver function (total bilirubin < 1.5x upper level of normal (ULN), aspartate transaminase (AST) < 2.5x ULN and alanine transaminase (ALT) < 3x ULN)
- Written informed consent

The exclusion criteria are:

- Histologically proven adenocarcinoma of the GEJ type I and III
- Tumor resectable only by transthoracic esophagectomy or only by transhiatal extended gastrectomy, according to the local surgical investigator
- Tumor expanding more than 5 cm proximal of the GEJ
- Positive lymph nodes only resectable by transthoracic esophagectomy (i.e. in the mid-upper mediastinum) or only resectable by transhiatal extended gastrectomy according to the local surgical investigator.
- Clinically significant (active) cardiac disease (i.e. symptomatic coronary artery disease or myocardial infarction within last 12 months), resulting in a left ventricular ejection fraction < 50% (determined by echocardiography)
- Clinically significant lung disease (forced expiratory volume in one second (FEV1) < 1.5 l/s)
- Pregnant women and nursing mothers

Patient screening and chemotherapy

Figure 2 displays the trial flow. All patients will undergo evaluation in a multidisciplinary tumor board and standard tumor staging before inclusion. The staging examinations will include an endoscopy with a detailed description of the tumor localization, the classification according to Siewert and biopsy extraction for histology. To standardize endoscopic definition of Siewert type II tumors, a separate Standard Operating Procedure (SOP) for

staging endoscopies has been developed. Type II tumors are defined as all tumors in which the center of the main tumor mass (half the distance between the proximal and distal edges of the main tumor mass) is 1 cm above to 2 cm below the cardia. The GEJ (or cardia) is defined as the top of gastric folds after desufflation. Tumors that expand more than 5 cm above the GEJ will also be excluded from the trial, as these are not potentially resectable by a transhiatal extended gastrectomy. In the case of severe tumor stenosis, which prevents passage of the (normal and ultra slim) endoscope and therefore an endoscopic tumor classification according to Siewert, the patient can't be included in the trial.

A computed tomography of the thorax and abdomen will be performed to identify metastatic disease and the extension of the disease. In addition, endoscopic ultrasound to

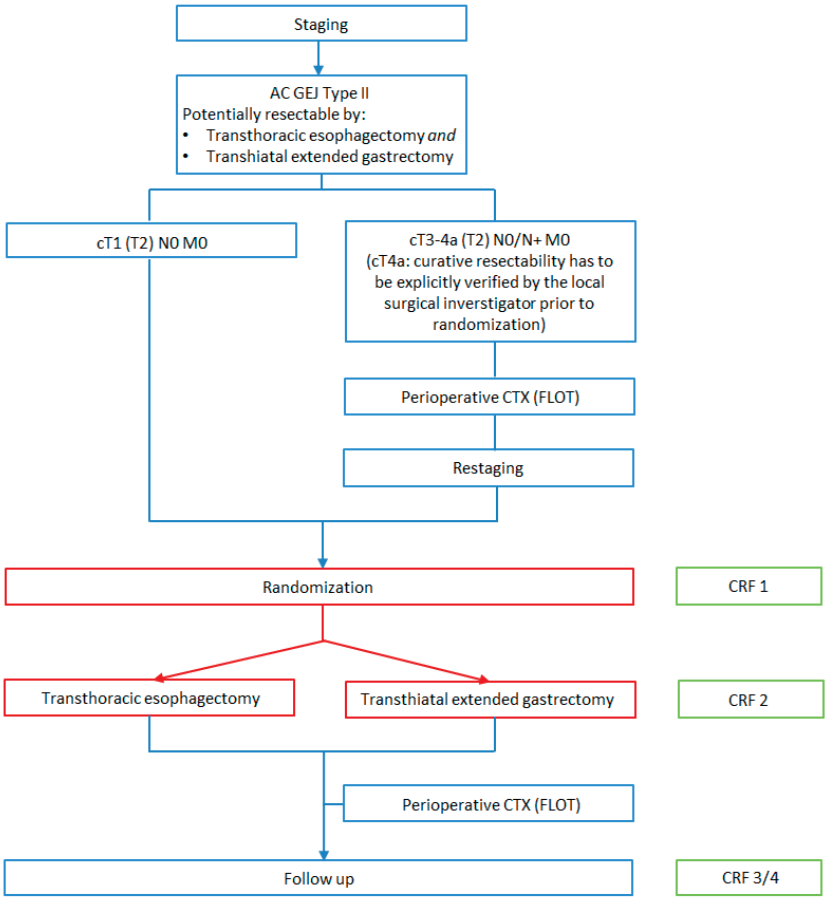

Figure 2. Trial flow chart.

determine the tumor infiltration depth and fluorodeoxyglucose positron emission tomography with CT (FDG-PET/CT or PET) to identify distant metastases are recommended in staging, yet not mandatory. The complete preoperative work-up will further include a physical examination, medical history, demography, vital signs and laboratory tests. In patients with a history or symptoms of cardiac and/or pulmonary disease, additional cardiology consultation, echocardiography (ejection fraction >50 %) and pulmonary function tests (FEV1 > 1.5 l) will be mandatory.

For patients with locally advanced adenocarcinomas (T2 or higher, N+) multimodal treatment is the standard care according to international guidelines [12]. For T3-T4 or N+ staged patients, perioperative chemotherapy according to the FLOT protocol [13] will be obligatory for patients in the CARDIA trial. For T2 N0 staged patients, perioperative FLOT chemotherapy will be recommended, but will not be compulsory for inclusion in the CARDIA trial. It can be administered based upon the individual decision per patient. T1 N0 M0 staged patients will receive a primary resection. Perioperative chemotherapy is not part of the investigated treatment and thus does not have to be performed at the designated trial sites. If patients with locally advanced adenocarcinoma GEJ type II were fully diagnosed as described above by long-term reliable external gastroenterological collaborators of high-volume centers and secondly referred to the respective surgical department after finishing multimodal treatment with the FLOT regimen, they can also be included in the CARDIA trial.

For patients undergoing chemotherapy, restaging after four preoperative cycles will be mandatory and screening examinations will take place during restaging. Patients who do not undergo chemotherapy will receive all screening examinations during their primary staging.

Patient inclusion and randomization

When baseline assessments and staging or restaging are completed, inclusion and exclusion criteria for the trial will be validated. Written informed consent will be obtained from all trial participants. Immediately after the patient has given his written consent to participate in the trial, randomization to one of the therapeutic arms will be performed by means of a 24/7 internet service based on permuted blocks of varying length, stratified by trial site and/or surgeon and tumor stage.

Patient follow-up

The follow-up will include seven regular visits for check-up every three to six months with a total of 24 month after discharge. Further follow-up will be conducted as quarterly phone calls to determine survival up to 60 months after discharge. For a detailed listing of the procedures and items recorded in the eCRF for each trial visit, see table 1. If a tumor

recurrence is clinically suspected during the follow-up period, a CT of the thorax and abdomen as well as an endoscopy will be performed on indication to further document the disease-free survival. Loss-to-follow-up will be minimised by commissioning a person at the trial site to manage and encourage follow-up and providing of excellent and free medical care. We therefore assume a small attrition rate of 0.05 per year and study arm.

Table 1. Visit schedule

	V0	V1	V2	V3	V4	V5	V6	V7	V8	V9	Survival-Follow-up
Demography	X										
Medical history	X										
Oncological history	X										
Tumor classification	X										
Pregnancy test[1]		X									
Inclusion / Exclusion		X									
Laboratory	X										
Biopsy	X										
Randomisation		X									
Physical examination	X		X	X	X	X	X	X	X	X	
Anamnesis	X			X	X	X	X	X	X	X	
Endoscopy	X				X[2]	X[2]	X[2]	X[2]	X[2]	X[2]	
CT/MRI	X				X[2]	X[2]	X[2]	X[2]	X[2]	X[2]	
Concomitant Medication	X		X	X	X	X	X	X	X	X	
EORTC QLQ-C30, -STO22, -OG 25-		X	X		X	X	X	X	X	X	
OP – Description			X								
Post-OP Complication			X								
Pathology			X								
Reference pathology			X								
AE/SAE			X	X	X						
Survival				X	X	X	X	X	X	X	X
EOS											or earlier for premature withdrawal

V0 Screening, V1 Baseline/Randomization, V2 Discharge, V3 +1 month, V4 +3 months, V5 +6 months, V6 +9 months, V7 +12 months, V8 +18 months, V9 +24 months, Survival Follow-up up to 60 months – quarterly by phone. [1]Negative serum pregnancy test during screening period for women of child-bearing age. [2]Only in case of a clinically suspected tumor recurrence.

Surgery

Patients will either receive a transthoracic esophagectomy or transhiatal extended gastrectomy depending on randomization outcome. However, the surgeon should change his/her surgical strategy if tumor-free resection margins can't be achieved, as described below. In general, technical details of both surgical procedures are left to the individual surgeon's preference as long as the primary goal of a complete tumor resection is achieved.

This also includes all established minimally invasive surgical techniques as well as the application or support of robotic surgery devices.

Transthoracic esophagectomy

The esophagectomy will be performed by means of a right transthoracic approach combined with resection of the proximal stomach (GEJ). Transhiatal access or access by thoraco-phreno-laparotomy is not allowed. A gastric conduit is constructed, and continuity is re-established by intrathoracic anastomosis (Ivor-Lewis). Cervical anastomosis (McKeown) is not allowed. The procedure includes a 2-field lymphadenectomy, resection of lymph node stations 1-3, 4sa, 7, 8a, 9, 11p, 11d, 12, 107, 108 and 110 according to JGCA/JES [14, 15] is mandatory. Resection of lymph node station 106 is recommended, yet not mandatory. Resection of stations 106recL and 106recR are optional (see figure 3). A detailed table with anatomical descriptions of the lymph node stations and the corresponding JGCA/JES and AJCC classification can be found in the Supplementary material 1. A total of at least 25 lymph nodes should be examined per resection according to the German S3 guidelines for gastric cancer [16]. In addition to the lymph node stations, the thoracic duct compartment also has to be resected [17].

Transhiatal extended gastrectomy

Transhiatal extended gastrectomy will be performed according to common practice at the specific hospitals. Reconstruction will be achieved by esophagojejunostomy and Jejunojejunostomy (Roux-en-Y reconstruction). For all patients randomized for transhiatal extended gastrectomy an intraoperative endoscopy is mandatory prior to transection of the tubular esophagus to ensure a tumor-free upper resection margin. In addition, an intraoperative frozen section of the oral resection margin should be performed to confirm a complete resection of the primary tumor. If a complete resection cannot be achieved, strategy must be changed and a transthoracic esophagectomy must be performed. Again, a 2-field lymphadenectomy is performed harvesting at least 25 lymph nodes, including lymph node stations 1-1-7, 8a, 9, 11p, 11d, 12a and the lower paraesophageal lymph node station 110 (see figure 3).

Surgical quality control

The participating sites will be expert high-volume hospitals with a caseload of at least 15 esophagectomies and 10 transhiatal extended gastrectomies per year over the last 3 years. Only surgeons that are experienced to perform both types of surgery will be eligible to participate in this randomized trial. Surgeons who wish to use a total minimally invasive or robotic assisted approach for the esophagectomy or transhiatal gastrectomy must demonstrate that they have performed this surgical technique at least twenty times in a

designated surgical team. This is to ensure quality of surgery and standardized perioperative management and to ensure a substantial allocation of patients to the trial within the designated recruitment period.

As an ongoing surgical quality assurance throughout the trial, photographs of the operating area will be taken during each surgery, showing the completeness of the lymphadenectomy. These images will be used for ongoing feedback during the course of the trial on the surgical technique. Additionally, they will be analyzed in depth if the half-yearly safety analysis by the Data Monitoring Committee (DMC) shows a reduced number of resected lymph nodes or high number of R1 resections, which could indicate insufficient surgical quality at the respective trial site.

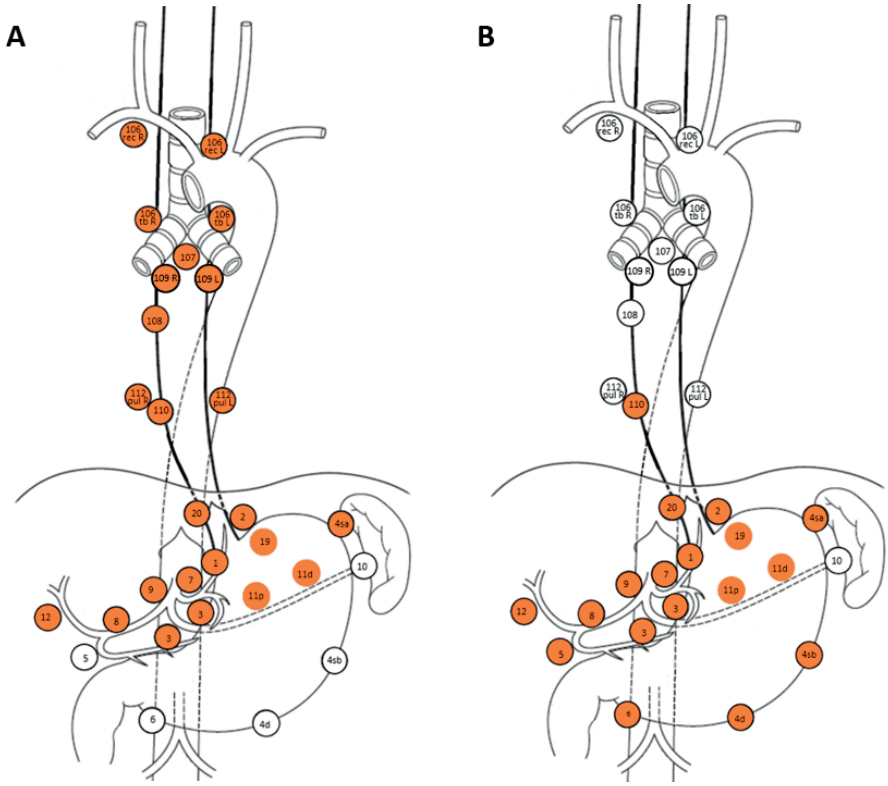

Figure 3. Obligatory and optional lymph node stations for lymph node dissection during transthoracic esophagectomy (A) and transhiatal extended gastrectomy (B). Lymph node stations which should be resected are marked in orange [15]., altered.

Pathological quality control

To ensure quality of the pathological examination, the lymph node dissection will be divided by the surgeon in single packages for each lymph node station so that the pathologist can individually analyze the different lymph node packages. However, the peritumoral stations will be marked en-bloc by the surgeon, instead of being resected in single packages, so analysis of the circumferential resection margin is not compromised. The pathological analysis of the entire surgical specimen will be carried out at each site according to a standard CARDIA trial pathology protocol. To ensure the quality of the pathological assessment of the circumferential resection margin, the resection margin samples of the respective surgical specimen will be re-analyzed by one of two reference pathologies which are located at the University Hospital of Cologne and the University Medical Center Utrecht.

Postoperative treatment

The postoperative treatment will not differ between both treatment arms. Epidural analgesia will be performed, and other analgesia can be given according to each centers standard practice. Mobilization under supervision of a physiotherapist will start as soon as the patient is stable. Enteral feeding via a jejunostomy catheter for patients will be allowed. Patients will be discharged according to standard practice of each surgical center.

Outcome measures

The primary endpoint is overall survival, which will be followed up until 60 months after discharge of surgery. The key secondary endpoints are complete resection (R0), post-operative complications according to the Esophageal Complications Consensus Group (ECCG) definitions [18] and scored on severity by the the Clavien-Dindo classification [19], number and localization of tumor infiltrated lymph nodes at dissection, disease-free survival, quality of life (EORTC QLQ-C30, QLQ-STO22, and QLQ-OG25 after 3, 6, 9, 12, 18, 24 months) and cost-effectiveness.

After consolidation of the EORTC questionnaires data during the course of the trail, a cost effectiveness analysis of both procedures based on direct costs and resulting QALYs will be performed and the incremental cost-effectiveness ratio will be calculated. For simplification of the process, only German sites classified as excellence centers will be included into the analysis, so that consistent national costs (e.g. DRG based, medical supply, labor costs based on tariffs) can be comparable.

Data management and safety

The trial database will be developed and validated before data entry based on standard operating procedures at the Clinical Trial Centre Cologne (CTCC). All changes made to the data will be documented in an audit trail. The database will be integrated into a general

IT infrastructure and safety concept with a firewall and backup system. Plausibility checks will be run during data entry. The CTCC Data Management will conduct further checks for completeness and plausibility and will clarify any questions with the trial sites electronically via the trial software.

The trial sites will be monitored closely to ensure patient´s safety and the quality of the data collected. Postoperative complications classified as Dindo-Clavien grade IIIb and higher (requiring surgical, endoscopic or radiological intervention under general anesthesia) or anastomosis incufficiency will be considered adverse events. A serious adverse event is defined as the death of a patient. AEs and SAEs will only be reported until three months after discharge (V4).

Sample size calculation

The primary endpoint is overall survival. We assume a cumulative survival after 2.5 years of 45% for transthoracic esophagectomy and 30% for transhiatal extended gastrectomy [20, figure 1c]. This corresponds to a hazard ratio of 0.663. A total of 188 events need to be observed to detect this difference with the stratified log-rank test (two-sided type I error 5%, power 80%, accounting for the interim analysis according to two-sided symmetric O'Brien-Fleming type alpha-spending at 94 events). Thus, 262 patients need to be enrolled and followed up (assuming 2,5 years of accrural, 5 years of follow-up and 5% censoring per year) [21]. For the key secondary outcome R0 resection Parry et al. report percentages of 87% and 71%, respectively [20]. This corresponds to an odds ratio of 2.73. Thus, 262 enrolled patients are also sufficient to give the stratified Mantel-Hanszel test at least 80% power (two-sided type I error 5%). Before participating in the trial, each center reported possible recruitment figures based on the number of patients with GEJ type II tumors in recent years. Screening will continue until the target sample size is achieved.

Statistical analysis

The primary analysis will be performed on the full analysis set (intention-to-treat) and comprises all patients with written informed consent and who were operated. The analysis is as assigned by stratified randomization (i.e. site or surgeon and tumor stage). The primary outcome of overall survival will be evaluated by the stratified log-rank test and is event-driven (i.e. following observation of 188 events). The hazard ratio with 95% confidence interval (CI) is estimated by stratified Cox regression. The assumption of non-informative censoring is examined using standard approaches (i.e. Kaplan-Meier curves, examining patterns of censoring across covariates and association between censoring and covariates). The key secondary outcome R0 resection rate is analyzed by comparing the corresponding odds between treatment groups with the stratified Mantel-Haenszel test. A missing assessment is counted as failure. Contingency tables of strata with "empty rows or columns"

are pooled. The combined Mantel-Haenszel odds ratio with 95% CI is calculated. The potential impact of clustering associated with both interventions is addressed in a sensitivity analysis [22, 23]. The secondary outcome quality of life is averaged over 36 months (area under curve, AUC) and tested for non-inferiority of the esophagectomy arm regarding a margin of 80%. Missing values are linearly interpolated. The key outcomes overall survival, R0 resection and quality of life are tested in a fixed sequence, thus no alpha-correction is required for strong type I error control (5%, two-sided).

Subgroup analyses are done by sex, tumor stage and (essential) compliance with the protocol (i.e. per protocol analysis). Adverse events are summarized and listed by seriousness, severity and relatedness to treatment. Cumulative survival 30, 36 and 60 months following surgery is estimated by Kaplan-Meier method (with 95% CI according to Greenwood's formula). Methods for rates and proportions are used to describe hospital mortality and the incidence of post-operative complications. A linear mixed model is fit to health related quality of life data from EORTC questionnaires QLQ-C30, QLQ-STO22, and QLQ-OG25. Cost-effectiveness is determined as the ratio $\Delta C/\Delta E$ where ΔC is the difference in resource use (costs) and ΔE the gain in months of life or in quality of life. The cost-effectiveness (cost per life-month gained or cost per quality-of-life-unit) will be calculated from a societal perspective.

Interim analysis

When half the events (94 deaths) have occurred, an interim analysis will be performed (O'Brien-Fleming type alpha-spending). The outcomes will be evaluated by the DMC. Premature termination of the trial will be considered if the interim analysis or other research show a significant difference in survival between both treatment groups. In addition, the stop-criteria are: < 70 % complete resection without tumor residual (R0) in one or both arms as well as > 50 % less than 10 lymph nodes harvested in one or both arms. These criteria will be continuously evaluated by the DMC.

DISCUSSION

In the year 2000, a study on Siewert type I-III GEJ tumors was conducted that compared both surgical approaches. No difference was found between esophagectomy and extended gastrectomy regarding 30-day mortality and 5-year survival [24]. Two years later a retrospective study was conducted in which no statistically significant survival benefit for either one of the surgical approaches was found [11]. Post-operative mortality turned out to be independent of surgical procedure. However, extended gastrectomy was associated with higher microscopic neoplastic invasion of the resection margin than esophagectomy

(R0 resection rate: 23.7% and 6.6%, respectively). No differentiation between Type I, II or III was made. Another retrospective research on GEJ type I-III tumors showed that there was no significant difference found in R0 resection, lymph node removal, or post-operative mortality rates with respect to operative approaches. However, gastrectomy was demonstrated to have a significantly worse 5-year survival than esophagectomy, 27% and 37% respectively [25]. In 2014, the Haverkamp et al systematically reviewed manuscripts published between 1995-2013 on surgical strategies of adenocarcinomas of the GEJ and found no clear oncological benefit of either esophagectomy or gastrectomy [10]. More recently, Dutch data suggested that in patients with a type II GEJ adenocarcinoma, a positive circumferential resection margin was more common with gastrectomy. Furthermore, the high prevalence of mediastinal nodal involvement indicates that a full lymphadenectomy of these lymph node positions should be considered. However, no significant difference in 5-year survival was found [10, 20, 26].

The systematic review from Haverkamp et al. included 2 retrospective studies on quality of life, these studies suggested a better quality of life after gastrectomy [10]. The Cologne group recently published a retrospective monocentric analysis of own data on long-term quality of life after surgery for adenocarcinoma of the esophagogastric junction type II and detected that health related quality of life after extended gastrectomy with Roux-en-Y reconstruction was indeed superior to that after esophagectomy and gastric tube reconstruction. Patients with cancer-free survival of at least 24 months after esophagectomy or extended gastrectomy for GEJ type II were identified from a prospectively maintained database and EORTC questionnaires were send to these patients. Improved HRQL after gastrectomy was mainly due to less pulmonary symptoms perioperatively and reflux-related symptoms in the long-term follow-up [9].

To date, only retrospective studies are available on surgical therapy of GEJ type II carcinoma, leading to a great controversy about the superior surgical procedure [25]. The CARDIA-trial will be the first randomized, clinical trial to determine the surgery of choice for this disease An essential prerequisite for a realistic statement on the therapy of GEJ II tumors is the exact definition of these tumors according to the Siewert classification, which has been described as challenging by other studies [26, 27]. Therefore, all sites will use the endoscopic SOPs in which this is defined in detail. Not only the spread of the main tumor mass but also the tumor extension are considered to ensure resectability of the tumors preoperatively. As perioperative chemotherapy is standard care for all T3-4 or N+ stage patients according to international guidelines [12], chemotherapy is also obligatory for these patients in the current trial. By including patients after chemotherapy, the patient cohort represents the actual group of patients with GEJ II tumors, of which up to 60% are already in an advanced tumor stage at initial diagnosis that requires neoadjuvant therapy [28]. The stratification of randomization is intended to reduce the regional influence of the

site or the surgeon on the one hand, and the influence of the tumor stage on the primary outcome on the other.

Several quality control measures were implemented through every step of the protocol to improve data reliability and therefore the significance of this trial, as the quality of surgery has often been the subject of discussion in clinical gastroesophageal cancer trials. Therefore, only expert high-volume hospitals with a caseload of at least 15 esophagectomies and 10 transhiatal extended gastrectomies per year over the last 3 years are eligible to participate in the trial. Training materials will be provided to all sites before the start of the trial. During the course of the trial, photographs will be taken by the surgeons during each operation, to show the completeness of the lymphadenectomy. They are evaluated by the medical coordinators of the trial and used for continuous feedback to the individual sites. In addition, the DMC can also view the images if there are indications for insufficient surgical quality at an individual site. To ensure not only the surgical but also the pathological quality of the trial, all obligatory lymph node stations are clearly defined and will be sent to the pathology department in separate packages. In addition, a reference pathology was established for the assessment of the resection margins at the UCC and UMCU.

In conclusion, the incidence of GEJ cancer markedly increases. All studies that investigated both surgical procedures only consisted of retrospective series showing ambiguous results on survival and postoperative morbidity. The CARDIA-trial is the first randomized, clinical trial that compares transthoracic esophagectomy versus transhiatal extended gastrectomy in patients with GEJ type II tumors. To ensure the data reliability and trial quality, several control measures were implemented in the trial protocol. We hypothesize that transthoracic esophagectomy will allow for a higher rate of radical resections and a more complete mediastinal lymph node dissection, resulting in a longer overall survival, while providing an acceptable quality of life and cost-effectiveness.

TRIAL STATUS

Pre-selection visits were conducted at sixteen potential study centers of which twelve were selected for inclusion. The trial centers in Cologne, Leipzig and Munich have been initiated. In addition, the study protocol was approved by two further ethics committees. Recruitment has already started at the University Clinic Cologne, where four patients have been enrolled so far (status May 09th 2020).

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SUPPLEMENTARY MATERIAL

Supplementary material 1. Definitions of lymph node stations

TTE	THG	Name of station	Definition [14, 15]	JGCA 3rd /JES 11th [15]	AJCC/ UICC 8th [29]
		Abdominal			
M	M	Right paracardial	Right paracardial LNs, including those along the first branch of the ascending limb of the left gastric artery	1	-
M	M	Left paracardial	Left paracardial LNs including those along the esophagocardiac branch of the left subphrenic artery	2	-
M	M	Lesser curvature	Lesser curvature LNs along the branches of the left gastric artery and along the 2nd branch and distal part of the right gastric artery	3	-
M	M	Short gastric vessels	Left greater curvature LNs along the short gastric arteries (perigastric area)	4sa	-
	M	Left gastroepiploic artery	Left greater curvature LNs along the left gastroepiploic artery (perigastric area)	4sb	-
	M	Right gastroepiploic artery	Right greater curvature LNs along the 2nd branch and distal part of the right gastroepiploic artery	4d	-
	M	Suprapyloric	Suprapyloric LNs along the 1st branch and proximal part of the right gastric artery	5	-
	M	Infrapyloric	Infrapyloric LNs along the first branch and proximal part of the right gastroepiploic artery down to the confluence of the right gastroepiploic vein and the anterior superior pancreatoduodenal vein	6	-
M	M	Left gastric artery	LNs along the trunk of left gastric artery between its root and the origin of its ascending branch	7	-
M	M	Common hepatic artery (anterosuperior)	Anterosuperior LNs along the common hepatic artery	8a	-
M	M	Celiac artery	Celiac artery LNs	9	-
M	M	Proximal splenic artery	Proximal splenic artery LNs from its origin to halfway between its origin and the pancreatic tail end	11p	-
M	M	Distal splenic artery	Distal splenic artery LNs from halfway between its origin and the pancreatic tail end to the end of pancreatic tail	11d	-
M	M	Hepatoduodenal ligament	Hepatoduodenal ligament LNs along the proper hepatic artery, in the caudal half between the confluence of the right and left hepatic ducts and the upper border of the pancreas	12a	-
		Thoracic			
M		Thoracic duct compartment	The thoracic duct is located within the posterior mediastinum, in the paraaortic compartment. This compartment is bounded by the aortoesophageal and aortopulmonary ligament anteriorly and by the spine posteriorly [17]	-	-
M		Pulmonary ligament	Lymph nodes located in the pulmonary ligament(s), including lymph nodes adjacent to the pericardium and the inferior pulmonary vein. A distinction between left and right must be included	112pul	9

TTE	THG	Name of station	Definition [14, 15]	JGCA 3rd /JES 11th [15]	AJCC/ UICC 8th [29]
M	O	Lower paraesophageal	Lymph nodes located around the lower thoracic esophagus	110	8L/8R
M		Middle paraoesophageal	Lymph nodes located around the middle thoracic esophagus	108	8M
M		Subcarnial	Lymph nodes located caudal to the carina of the trachea. The lateral boundaries are the extended line of both lateral margins of the trachea	107	7
O[1]		Left tracheobronchial	Left tracheobronchial lymph nodes: The superior border is the inferior wall of the aortic arch, and the lymph nodes are located in the area surrounded by the medial wall of the aortic arch	106tbL	4L
O[1]		Right tracheobronchial	Right tracheobronchial lymph nodes: The superior border is the inferior wall of the azygos vein	106tbR	4R
O		Left recurrent nerve	Lymph nodes located along the left recurrent laryngeal nerve	106recL	2L
O		Right recurrent nerve	Lymph nodes located along the right recurrent laryngeal nerve	106recR	2R

TTE = transthoracic esophagectomy, THG = transhiatal extended gastrectomy, M = mandatory to resect, O = optional to resect, O[1] = recommended to resect (yet not mandatory), JGCA Japanese Gastric Cancer Association, JES Japan Esophageal Society, AJCC American Joint Committee of Cancer, UICC Union for International Cancer Control.

Part three

Summary and general discussion

CHAPTER 11

Summary

Chapter 1. General introduction and thesis outline
Gastric and esophageal cancer are the third and sixth more common causes of cancer-related death worldwide. In addition, the incidence of adenocarcinoma of the proximal stomach, gastroesophageal junction (GEJ) and distal esophagus is increasing, especially in Western populations. Unfortunately, only slightly over 50% of patients are diagnosed with potentially curable disease. Treatment with curative intent generally consists of surgical resection and chemo(radio)therapy. However, this treatment can lead to major morbidity and less than 40% of patients undergoing this treatment are cured. In addition, for the majority of patients, the current optimal treatment is relatively similar. Ultimately, to improve outcomes, treatment should be further tailored to the individual patient. The first aim of this thesis was to compare the two most important approaches of curative surgery for the relatively common gastric adenocarcinoma: laparoscopic versus open gastrectomy (part I). The second aim of this thesis was to evaluate treatment for less common subtypes of gastroesophageal cancer and treatment in patients at high risk for postoperative complications, to work towards a more personalized treatment of gastroesophageal cancer (part II).

Part I. Laparoscopic versus open gastrectomy for gastric cancer (LOGICA-trial)
Chapter 2. Postoperative recovery and oncological efficacy
A multicenter randomized controlled trial was performed on laparoscopic versus open gastrectomy in a Western population with mainly locally advanced gastric cancer. Hospital stay, postoperative complications, R0 resection rate, lymph node yield, 1-year overall survival and global health-related quality of life did not differ between treatment groups. In addition, laparoscopic gastrectomy resulted in less intraoperative blood loss and longer operating time. These results support trained surgical teams to use of laparoscopic gastrectomy as an alternative, yet not superior, approach to open gastrectomy.

Chapter 3. Pain and opioid consumption
A secondary analysis of the multicenter randomized LOGICA-trial was performed on postoperative pain and opioid consumption. Mean pain scores were comparable and acceptable in both treatment arms during all postoperative days and at discharge. In the laparoscopic group, this was generally achieved without epidural analgesia. Furthermore, in the laparoscopic group, mean daily opioid consumption at postoperative days 1-2 was significantly lower and at discharge significantly fewer patients used oral opioids, compared to the open group. These could be relevant advantages of laparoscopic gastrectomy, especially in light of the current opioid epidemic.

Chapter 4. Cost-effectiveness
A prospective cost-effectiveness analysis was performed in the multicenter randomized

LOGICA-trial. The laparoscopic gastrectomy itself was more expensive than open gastrectomy, due to longer operating times and more expensive disposable materials (€7,380 versus €5,972). After 1-year follow-up, total costs of laparoscopic gastrectomy were €26,084, compared to €25,332 for open gastrectomy. Differences in quality-adjusted-life-years were 0.665 versus 0.686, respectively. As these were relative small difference compared to the uncertainty of the analysis, differences in both total costs and effectiveness were deemed limited between laparoscopic and open gastrectomy. This comparable cost-effectiveness supports centers to choose, based upon their own preference, whether or not to (de) implement laparoscopic gastrectomy as an alternative to open gastrectomy.

Chapter 5. Body composition as a predictor for complications
A prospectively side-study of the LOGICA-trial was performed on the effect of preoperative CT-scan body composition on postoperative complications after gastrectomy. Patients with a low skeletal muscle mass on preoperative restaging CT-scan had a significantly higher risk of developing a major postoperative complication after treatment with preoperative chemotherapy and gastrectomy. Furthermore, patients with higher visceral or subcutaneous adipose tissue radiation attenuation (fat depleted of triglycerides) also had a significantly higher risk of developing a major postoperative complication. These findings may contribute to better preoperative identification of high-risk patients.

Part II. Personalized treatment of gastroesophageal cancer
Chapter 6. Diffuse type carcinoma of the stomach and gastroesophageal junction
A nationwide retrospective cohort study was performed on patients with gastric or gastroesophageal junction diffuse type adenocarcinoma, including signet ring cell carcinoma. This type is generally regarded to be more aggressive and less responsive to chemotherapy than intestinal type adenocarcinoma. Nevertheless, our study demonstrated that neoadjuvant chemotherapy prior to surgery was associated with better survival, compared to surgery alone. Hence, neoadjuvant chemotherapy should remain standard of care in these patients. Moreover, in patients with gastroesophageal junction adenocarcinoma, surgery in hospitals with low annual case volumes was associated with more irradical resections and lower survival. Thus, centralization of care is advised for these patients.

Chapter 7. (Mixed adeno)neuroendocrine carcinoma of the stomach and esophagus
A nationwide retrospective cohort study was performed on patients with gastric or esophageal (mixed adeno)neuroendocrine carcinoma ((MA)NEC). This is an exceedingly rare subtype that is regarded to be very aggressive and especially older literature reports dismal survival rates. Our study demonstrated that (MA)NECs are often misdiagnosed as adenocarcinoma on endoscopic biopsies. However, if (MA)NECs are recognized, biopsy

diagnosis is reliable and can be used to determine treatment strategies. Even though the majority of patients are presumed to present with metastastic disease at diagnosis, this study demonstrated that patients with localized gastroesophageal (MA)NEC that underwent resection had a 5-year survival of 35-39%. Hence, treatment with curative intent can be considered a valid treatment option at multidisciplinary tumor board discussions.

Chapter 8. Hepatic and pulmonary oligometastases from gastroesophageal cancer
A nationwide retrospective cohort study was performed on patients who underwent a resection with curative intent of hepatic or pulmonary metastases from gastroesophageal cancer. Standard of care for these patients during the study period was best supportive care or palliative chemotherapy, leading to a median survival of 4-5 months. Our study included highly selected patients only, presumably in clinically good condition and generally with favorable tumor biology such as metachronous oligometastatic disease. The resection of hepatic or pulmonary metastases was performed with relatively low postoperative morbidity and mortality rates and the 5-year overall survival of included patients was 31–53%. These results justify the conduction of future prospective studies with strict inclusion criteria, to evaluate whether local treatment of gastroesophageal oligometastases in highly selected patients can be of added value regarding survival and quality of life.

Chapter 9. ISCON-trial
A prospective single-arm safety and feasibility trial was initiated in 2 European centers on the performance of laparoscopic ischemic conditioning (ISCON) 12-18 days prior to esophagectomy, in patients with esophageal cancer and arterial calcifications on preoperative CT-scan. Poor generalized cardiovascular status of these patients presumably results in poor vascularization of the gastric tube reconstruction after esophagectomy, leading to increased risk of anastomotic leakage and associated morbidity and mortality. ISCON could potentially increase gastric tube perfusion due to redistribution of blood flow and consequently reduce anastomotic leakage. We hypothesize that the aforementioned approach is safe and feasible. Depending on the results of the current single-arm trial, a randomized controlled trial will be designed to investigate whether ISCON leads to a lower percentage and less severe course of anastomotic leakage in selected patients.

Chapter 10. CARDIA-trial
A multinational, multicenter, randomized controlled trial was initiated on transthoracic esophagectomy versus transhiatal extended gastrectomy for “true cardia” type II gastroesophageal junction (GEJ) adenocarcinoma with their midpoint between ≤1 cm proximal and ≤2 cm distal from the top of gastric folds. The incidence of GEJ cancer is markedly increasing. However, the optimal surgical approach for type II GEJ tumors has

not yet been determined, as an international survey showed that 73% of responding surgeons perform gastrectomy, whereas 27% perform esophagectomy. Indeed, all studies that investigated both surgical procedures only consisted of retrospective series showing ambiguous results on survival and postoperative morbidity. We hypothesize that transthoracic esophagectomy will allow for a higher rate of radical resections and a more complete mediastinal lymph node dissection, resulting in a longer overall survival, while providing an acceptable quality of life and cost-effectiveness. The CARDIA-trial is the first randomized trial to compare both surgeries and will help determine the optimal surgical approach.

Conclusion

Results from the multicenter randomized LOGICA-trial, performed in a Western population with mainly locally advanced gastric adenocarcinoma, demonstrated that postoperative complications, postoperative recovery, quality of life and oncological efficacy were comparable between laparoscopic and open gastrectomy. In laparoscopic gastrectomy, adequate pain control was achieved, generally without epidural analgesia. In addition, fewer patients used oral opioids at discharge, compared to the open gastrectomy. Differences in costs were limited between both treatments, though they might slightly favor open gastrectomy. These results support centers to choose, based upon their own preference, whether or not to (de)implement laparoscopic gastrectomy as an alternative to open gastrectomy.

Three nationwide retrospective studies were performed in patients with less common subtypes of gastroesophageal cancer: diffuse type carcinoma (including signet ring cell carcinoma), (MA)NEC and gastroesophageal cancer with hepatic or pulmonary oligometastases. The results provide insights that can help guide treatment decisions at multidisciplinary tumor boards.

Two new clinical trials were designed and initiated as part of this thesis. The CARDIA-trial includes patients with Siewert type 2 GEJ cancer and the ISCON-trial includes patients with esophageal cancer selected on preoperative CT-scan to be at high risk for postoperative morbidity. Once completed, the results will help guide and further improve surgical treatment strategies for these patients.

CHAPTER 12

General discussion and future perspectives

Gastric adenocarcinoma is the most common type of gastric cancer and gastrectomy with multimodal treatment is the cornerstone of curative treatment. The first aim of this thesis was to compare the two most important approaches of gastrectomy: laparoscopic versus open (part I). The second aim of this thesis was to evaluate treatment for less common subtypes of gastroesophageal cancer and treatment in patients at high risk for postoperative complications to work towards a more personalized treatment of gastroesophageal cancer (part II).

LAPAROSCOPIC VERSUS OPEN GASTRECTOMY FOR GASTRIC CANCER

Implementation of laparoscopic gastrectomy

Open gastrectomy has long been the gold standard in curative multimodal treatment of gastric cancer worldwide(1,2). However, laparoscopic gastrectomy for locally advanced gastric cancer is rapidly being adopted, attempting to reduce surgical trauma(3). Large Western population-based studies and Eastern randomized trials reported reduced hospital stay, equal or reduced postoperative complications, equal radical resection rates and lymph node yield after laparoscopic gastrectomy, compared to open gastrectomy(4–9). Nevertheless, randomized trials in Western populations with predominantly locally advanced gastric cancer were lacking(10). Due to the lack of level-1 evidence, concerns of a reduced lymph node yield in patients with locally advanced gastric cancer still existed and Western guidelines did not generally consider laparoscopic gastrectomy a standard treatment option(11,12).

The LOGICA-trial provided this randomized evidence and observed no difference between laparoscopic and open gastrectomy regarding postoperative hospital stay, oncological efficacy, postoperative complications and postoperative quality of life (chapter 2). Together with the recently published European STOMACH-trial on laparoscopic versus open total gastrectomy (n=96), which found similar short-term results, these were the first multicenter randomized results in a Western population on laparoscopic versus open gastrectomy(13,14). Furthermore, the datasets of both trials are currently being merged for additional analysis and these results are still awaited. The LOGICA and STOMACH-trial results are exciting as they support the application of laparoscopic gastrectomy as a safe alternative to open gastrectomy in Western populations.

The impact of the LOGICA-trial, the STOMACH-trial, large Western population-based studies and Eastern randomized trials on laparoscopic versus open gastrectomy has been substantial. Over one million new cases of gastric cancer are diagnosed each year worldwide(15). The majority of patients that are eligible for curative treatment will receive

a gastrectomy. The proportion of laparoscopic gastrectomy for locally advanced gastric cancer in the Netherlands has increased from 5% in 2012 to nearly 80% in 2020 and worldwide from 6-9% in 2014 to 33-39% in 2020. For early gastric cancer, these percentages are even higher(3,8,16).

Similarity of laparoscopic and open gastrectomy

The LOGICA-trial demonstrated the safety of performing the same operation laparoscopically or open, as radical resection rate, lymph node yield and 1-year survival did not differ between treatment arms (chapter 2). This is an achievement on its own. However, the fact that it is the same operation could also explain why no improvements were observed after laparoscopic gastrectomy regarding postoperative hospital stay, complications or quality of life, compared to open gastrectomy for gastric cancer.

In contrast, Western randomized trials on esophageal cancer comparing (robot-assisted) thoracolaparoscopic esophagectomy to open equivalent did show reduced postoperative pulmonary and cardiac complications, reduced postoperative pain and better postoperative recovery and short-term quality of life, in favor of the minimally invasive procedure (17,18). Esophagectomy consists of at least a thoracic phase and an abdominal phase, of which the abdominal phase is largely comparable to total gastrectomy. The advantages of the thoracolaparoscopic esophagectomy are likely due to the fact that patients are spared from the thoracotomy, which is the most invasive part of the procedure. Sparing patients from the laparotomy could still be relevant, but appears to be so to a lesser degree.

Indeed, for locally advanced gastric cancer, only the Eastern randomized KLASS-trial demonstrated reduced postoperative complications after laparoscopic distal gastrectomy, whereas all other Eastern trials, the LOGICA-trial and STOMACH-trial demonstrated comparable postoperative complications between laparoscopic and open gastrectomy(7,10,13,14). Furthermore, even though previous Western population based studies found reduced postoperative hospital stay after laparoscopic gastrectomy, these results could not be reproduced in the randomized setting(8,9,13,14). In population based studies, the reduced hospital stay after laparoscopic gastrectomy might actually have been the result of the simultaneously implemented enhanced recovery after surgery (ERAS) programs(19). For example, these studies could have been biased due to ERAS programs being more strictly enforced in the early adopting hospitals of laparoscopic gastrectomy, or in patients receiving laparoscopic gastrectomy in general, compared to patients receiving open gastrectomy(8,19,20). These results underline the importance of conducting randomized trials. The LOGICA-trial had comparable postoperative complications and the same ERAS protocol was used in both treatment arms, hence it is perhaps unsurprising that no relevant differences were found between treatment arms regarding postoperative hospital stay(14,21).

Even though the open and laparoscopic gastrectomy are in essence the same operation, the current laparoscopic technique does provides 2 possible advantages: 1. reduced damage to the abdominal wall and 2. reduced internal trauma due to a better and more close-up view of the surgical field and anatomical planes, as was demonstrated by the significantly reduced blood loss in the LOGICA-trial(14). Hypothetically, these advantages could result in reduced wound infections, improved postoperative mobilisation and recovery, reduced systemic inflammatory and thereby reduced postoperative pneumonia and atrial fibrillation and reduced long-term incisional herniations(21). However these hypothetical advantages were not observed in the LOGICA-trial (chapter 2). Apparently, these 2 possible advantages are not the most important factor for the patients undergoing this procedure, as they did not translate to actual reduced complications or improved quality of life after laparoscopic gastrectomy. Perhaps these 2 possible advantages pale compared to the challenges these patients face: regardless whether the approach is open or laparoscopic, in both cases major surgery is performed with the same resection of (part of) the stomach, the same D2 lymphadenectomy and performance of the same anastomosis. In addition, the same perioperative chemotherapy is applied. In a population of >65 year old patients, often with multiple comorbidities and often in poor nutritional condition, resulting in 5-year survival rates of only 35% after both open or laparoscopic gastrectomy in the context of multimodal treatment(9,16). Frankly put, perhaps these patients have larges issues than whether their gastrectomy is performed laparoscopically or open.

Quality of life

In the LOGICA-trial, no improvements in quality of life up to 1 year postoperatively were observed after laparoscopic gastrectomy, compared to open gastrectomy (chapter 2). This is in line with the reasoning in the paragraphs above. Nevertheless, it should be noted that the first time point to measure quality of life in the LOGICA-trial was 6 weeks post-operatively, observing no difference between treatment arms. It is a wasted opportunity that quality of life was not measured at 7 days and 30 days postoperatively. Indeed, for distal gastrectomy in an Eastern population, increased quality of life was observed especially at 7 and 30 days postoperatively after laparoscopic gastrectomy(22). Quality of life was also improved at 90 days postoperatively, but the results were less pronounced than at 7 and 30 days(22). Likewise, in a different field of study, the LEOPARD trial on laparoscopic versus open distal pancreatectomy demonstrated increased quality of life after laparoscopic surgery at 7 and 30 days postoperatively, but comparable quality of life between treatment arms at 90 days(23). I believe it could be possible that laparoscopic (distal) gastrectomy provides a small clinically relevant improvement in quality of life within these first postoperative weeks in Western populations, mainly due to smaller wounds and less pain (as demonstrated by the reduced oral opioid consumption at discharge), which normalizes after a few weeks

once the first healing of the surgical wounds has passed(24). Unfortunately, no randomized data is available to prove this hypothesis.

Incisional hernia and adhesions

Laparoscopic gastrectomy may reduce long-term incisional hernia and adhesion related morbidity, as is the case of laparoscopic surgery in general(25–27). However, it will likely be difficult to ever prove this hypothesis for gastrectomy in the Western populations specifically, as enormous sample sizes would be required for adequate power(25–27).

Pain and opioid consumption

In contrast to the hypothetical advantages mentioned previously, the LOGICA-trial was able to demonstrate a minor advantage relevant for the patient: adequate pain control was achieved without epidural analgesia in the laparoscopic gastrectomy group and fewer patients used opioid at discharge after laparoscopic gastrectomy, compared to open gastrectomy (chapter 3).

Advantages of laparoscopic gastrectomy for locally advanced cancer?

If we recap on the above, it appears laparoscopic gastrectomy is not the answer for the major challenges that patients with locally advanced gastric cancer face (chapter 2). Nevertheless, the LOGICA trial did demonstrate minor advantages regarding epidural analgesia and opioid consumption after laparoscopic gastrectomy (chapter 3). In addition, there are minor hypothetical advantages, such as improved quality of life within the very first weeks after surgery and reduced incisional hernia and adhesion associated morbidity many years after surgery. Even though these improvements are minor, they could still have a relevant impact in gastric cancer care, due to the large amount of gastrostomies being performed globally on a yearly basis, as described previously(15).

Advantages of laparoscopic distal gastrectomy for early cancer?

In contrast to locally advanced gastric cancer, multiple Eastern randomized trials on early gastric cancer have demonstrated clear benefits regarding postoperative complications, recovery and quality of life for laparoscopic distal gastrectomy, compared to open distal gastrectomy(5–7,22,28). One could hypothesize that, since these patients are often in better condition, do not undergo perioperative chemotherapy and receive only a resection of part of the stomach, the stress of the initial treatment is less. Hence, the reduced damage of the abdominal wall and improved dissection according to the anatomical planes in laparoscopic surgery becomes more relevant. For patients with early gastric cancer that are not eligible for an endoscopic resection/dissection, laparoscopic distal gastrectomy appears to be the superior treatment(5–7,22,28).

Cost-effectiveness of laparoscopic gastrectomy

As described, in a Western population with predominantly locally advanced gastric cancer, only a modest clinical benefit has been demonstrated for laparoscopic gastrectomy (chapter 2 & 3). In light of these results and the rapid adaptation of laparoscopic gastrectomy worldwide, it was highly relevant to evaluate the cost-effectiveness of laparoscopic versus open gastrectomy for gastric cancer(3). Thus far, literature on cost-effectiveness of laparoscopic versus open gastrectomy was retrospective or model based(29–32). To the best of our knowledge, the LOGICA-trial was the first prospective multicenter randomized trial worldwide that evaluated this subject thoroughly. The results demonstrated that, even though the laparoscopic gastrectomy itself was more expensive, after 1-year follow-up differences in both total costs and effectiveness were limited between laparoscopic and open gastrectomy (chapter 4). This comparable cost-effectiveness supports centers to choose, based upon their own preference, whether or not to (de)implement laparoscopic gastrectomy as an alternative to open gastrectomy (chapter 2, 3 & 4).

Robot-assisted laparoscopic gastrectomy

Current advantages of robot-assisted laparoscopic procedures include high-definition vision controlled by the operator, better ergonomics and easier instrument movement with more degrees of freedom(33). Nevertheless, in Western gastric cancer populations, it has not been demonstrated that these advantages translate to improved outcomes that are relevant for the patient(33). In Western populations, no randomized trials have yet been performed comparing robot-assisted laparoscopic gastrectomy to either conventional laparoscopic or open equivalent(33). As described earlier, only conventional laparoscopic gastrectomy has been compared to open gastrectomy in the LOGICA and STOMACH trials, which did not demonstrate reduced complications (chapter 2)(13,14). Furthermore, the observational studies that have been performed on robot-assisted laparoscopic gastrectomy demonstrated no clear reproducible advantages that are relevant for the patient, compared to conventional laparoscopic or open equivalent(33).

In Eastern populations, results from randomized trials on robot-assisted laparoscopic gastrectomy versus open gastrectomy are also not available(34). However the results of 2 randomized trials (one single-center, the other two-center) on robot-assisted laparoscopic gastrectomy versus conventional laparoscopic gastrectomy were published in 2021(35,36). These trials support the safety of the robot-assisted procedure(35,36). Strikingly, surgical postoperative complications did not differ between treatment arms, whereas medical complications (mainly pulmonary complications) were reduced after the robot-assisted procedure(35,36). It is hypothesized that this is due to less internal trauma during the robot-assisted procedure and consequently a milder postoperative inflammatory response(35,36). These results cannot necessarily be extrapolated to the Western population,

since the randomized comparisons of conventional laparoscopic versus open gastrectomy did not lead to reduced pulmonary complications in the Western LOGICA and STOMACH trials (chapter 2)(13,14). Hence, it would be surprising if comparing the robot-assisted versus conventional laparoscopic procedure does result in a relevantly reduced inflammatory response. Nevertheless, the Eastern randomized results do provide arguments to initiate trials on robot-assisted versus conventional laparoscopic gastrectomy in Western populations, preferable in centers that have completed the learning curve for both procedures and with blinded scoring of postoperative pneumonia according to clear definitions, such as the Uniform Pneumonia Score(37).

Cost-effectiveness of robot-assisted laparoscopic gastrectomy

Costs of the robot-assisted procedure are higher compared to the conventional laparoscopic procedure. This was demonstrated in the single-center randomized trial: even though pulmonary complications were reduced, total costs of the robot-assisted procedure were higher, compared to the conventional laparoscopic procedure (median US$13,423 versus US$10,165 $p<0.001$)(36). The total costs included costs of the equipment, operation and postoperative care. Hence, in Western populations, the robot-assisted procedure should currently only be performed in innovation driven hospitals. A broader implementation to all hospitals should not be initiated until randomized studies in Western populations demonstrate either improved outcomes that are relevant for the patient, preferably measured as increased quality-adjusted life-years (QALYs), or until comparable costs between the robot-assisted procedure and the alternative procedure are achieved. In contrast, even though the LOGICA-trial did not demonstrate increased QALYs after conventional laparoscopic gastrectomy, compared to open gastrectomy, it did indicate comparable costs (chapter 4). Hence, conventional laparoscopic gastrectomy can be implemented more broadly as an alternative to open gastrectomy (chapter 4).

Total versus distal gastrectomy: anastomotic leakage

Anastomotic leakage is the most important complication following gastrectomy, leading to postoperative morbidity and even mortality(38). In the LOGICA-trial, leakage rates did not significantly differ between laparoscopic and open gastrectomy (chapter 2). However, strikingly, leakages rates did markedly differ between total gastrectomy (19.8%) and distal gastrectomy (2.4%) (chapter 4, supplementary material 4). This is in line with population data from the Dutch Upper GI Cancer Audit (DUCA)(39). Hence, the gastrojejunostomy performed in patients that were eligible for distal gastrectomy resulted in a solid anastomosis. On the other hand, the esophagojejunostomy performed in patients that required total gastrectomy is still unsatisfactory, as leakage rates of 20% are observed. This difference between total and distal gastrectomy is likely explained by the technical challenges of

performing the more proximal esophagojejunostomy near the esophageal hiatus in the diaphragm, inherent disadvantages of connecting the jejunum to the distal esophagus, as opposed to the proximal stomach and patient characteristics. For example, patients requiring total gastrectomy have a worse outcome in general. Efforts should be made to overcome these technical challenges and improve the esophagojejunostomy. A logical first step of research would be to compare the esophagojejunostomy leakages rates in the DUCA or multinational registries between circular and linear stapled (the two most common anastomotic techniques), each technique corrected for learning curve per hospital and per surgeon, hospital, annual volume and case-mix(16,40,41). In addition, multicenter analyses of anastomotic technique by detailed video review could help optimise the technical aspects(42). Lastly, detailed comparative studies on esophagojejunostomy technique between Western and Eastern hospitals could be beneficial, as hospitals in Eastern populations report markedly lower leakage rates(43,44).

Total versus distal gastrectomy: functional outcome

Unpublished data of the LOGICA-trial shows improved quality of life and functional outcomes in patients that underwent distal gastrectomy, compared to open gastrectomy. Though the abovementioned difference in anastomotic leakage could play a role, the most likely cause of this difference in quality of life is a functional proximal stomach still being in situ after distal gastrectomy. Hence, from a viewpoint of postoperative complications and quality of life, distal gastrectomy should be performed when oncologically feasible.

FUTURE PERSPECTIVES OF LAPAROSCOPIC GASTRECTOMY

Centralization and learning curve

The LOGICA-trial is likely only the beginning of laparoscopic gastrectomy in the Western populations. Eventually, a plateau will be reached of how far the outcomes of gastrectomy can be improved: the performance of gastrectomy will presumably always be associated with certain morbidity, since even after uncomplicated surgery, the patient will have to live without his/her (proximal) stomach. Nevertheless, it appears this plateau has not yet been reached(45). In the past decade, a start of centralization of gastrectomy was initiated in the Netherlands with hospitals currently having to perform at least 20 gastrectomies annually(46). This has reduced postoperative mortality and improved survival(45,46). Nevertheless, one could argue whether real centralization has yet been achieved in the Netherlands, as the annual volume is still relatively low. For example, 13 hospitals in the South-Korean KLASS-02 trial performed at least 80 gastrectomies annually(7,44). Indeed, hospitals performing >200 or even >500 gastrectomies annually are not uncommon in

Eastern populations(3,44). As described previously, the outcomes of gastrectomy for gastric cancer are better in Eastern populations, compared to Western populations(43). In part this is due to better patient condition and more favourable disease stages, but it can also be contributed to the increased surgical experience and routine in hospitals, due to these large annual volumes(43,45).

A complementary concept to annual hospital volumes is the learning curve of the surgeon and hospital; meaning the amount of laparoscopic gastrectomy cases the surgeon has performed and the hospital personal has provided care for thus far(40). It is possible that the learning curve for laparoscopic gastrectomy (and more specifically, laparoscopic *total* gastrectomy) is as low as 20 cases, as is in line with the best available data in 2015 when the LOGICA-trial was initiated(8,21). Hence, centers in the LOGICA-trial were required to have performed at least 20 cases of laparoscopic gastrectomy prior to their first inclusion, as a quality control measurement. However, more recent data demonstrate that the learning curve might be as high as >100 cases and thus remains to be reached by the majority of Dutch hospitals(40,44,47). Hopefully the current trend continues in Western populations and postoperative complications and mortality after (laparoscopic) gastrectomy will be further reduced as increased annually volumes per hospital lead to increased surgical experience and routine(45,46).

Technical innovations

A major future potential of laparoscopic gastrectomy lies in the fact that a computer is placed between the eyes (and hands in case of robot-assisted surgery) of the surgeon and the patient. This allows for implementation of many (future) technical innovations. Examples from current clinical practices are indocyanine green (ICG) lymphangiography for a more radical or tailored lymphadenectomy and ICG angiography of blood vessels to guide the construction of the anastomosis(48,49). Furthermore, video recording already allows for comparison and standardization of technique between hospitals worldwide and will soon open the doors to long-distance proctoring (telementoring), both of which can improve the quality of surgery(44,50–52). Indeed, as surgical quality control is essential during the learning curve of surgical teams and in randomized controlled trials on gastroesophageal cancer, the easier quality control due to video recordings are an advantage of laparoscopic surgery(14,44,53). Perhaps the most exciting but more abstract future application will be from artificial intelligence. By collecting video recordings of thousands of surgeries, processing these via artificial intelligence and coupling these to large international datasets with patient characteristics and postoperative outcomes, tools can be created that give live guidance to surgeons for intraoperative decisions(42,54,55). As gastrectomy typically takes 3-4 hours to perform and such video recordings will have countless degrees of freedom, it will be important to start with a narrow focus. An obvious

first point of focus for gastroesophageal surgery research is to use thousands of videos of the anastomosis construction (manual construction by the surgeon and ICG angiography evaluation), coupled with preoperative patient related risk factors of anastomotic leakage (including preoperative CT-scan data) and the outcome anastomotic leakage(38,42,49,56,57).

Perioperative care

Importantly, it cannot be overstated that substantial improvements have been made in the past decades, especially in the care surrounding the gastrectomy. Gastric cancer patients' outcomes have improved, for example due to developments in preoperative staging such as the added value of diagnostic laparoscopy to detect peritoneal metastases, the added value of perioperative chemotherapy and improved chemotherapy regimens such as the FLOT-regimen and enhanced recovery after surgery protocols(1,2,19,58). In the upcoming decades, I believe the following developments will take place: staging and detection of microscopic distant metastatic disease will further improve due to techniques such as circulating tumor DNA, systemic treatments for gastroesophageal cancer will improve due to new targeted therapies and immunotherapies, local treatment of the primary tumor or (oligo)metastases will improve due to improvements in radiotherapy (such as magnetic resonance imaging guided radiotherapy, proton therapy and stereotactic radiotherapy), selecting the optimal treatment for each individual tumor biology will improve by techniques such as patient-derived organoids that allow in vitro testing of pre-operative treatments in each individual patient and by a better understanding of the molecular different subtypes of gastroesophageal cancer and patient selection will improve by selecting the optimal treatment for each individual patient, based upon the patients' condition, comorbidity and genotype(59–71).

Organ sparing treatment

The CRITICS II and TOPGEAR trials are recruiting patients to investigate whether preoperative chemoradiotherapy for gastric cancer improves outcomes(72,73). Interim analysis have shown this treatment to be safe(74). If preoperative chemoradiotherapy leads to downstaging of the tumor or even a pathological complete response, it could be oncologically feasible to perform a distal gastrectomy instead of a total gastrectomy in a larger proportion of patients, leading to reduced postoperative anastomotic leakage and better functional outcomes (unpublished data LOGICA-trial)(39). For more proximal gastric cancers following preoperative chemoradiotherapy, perhaps a proximal gastrectomy with curative intent will become a feasible and safe option in Western populations(75). In addition, if a pathological complete response following chemo(radio)therapy can be achieved and accurately predicted without requiring pathological analysis of a resection specimen, active surveillance strategies could become feasible, in which (partial)

gastrectomy is only offered to patients as a salvage therapy in case of recurrent local disease, as is currently being introduced as standard clinical care in rectal cancer patients and being investigated in esophageal cancer patients (clinicaltrials.gov NCT04460352)(76–78). In the future, if organ sparing treatment becomes an oncologically safe option in a selection of patients with gastric cancer, this will result in major improvements in quality of life.

Currently, for many gastric cancers, gastrectomy is the only potentially curative treatment and will thus be an essential treatment for many decades to come. Nevertheless, it is my belief the largest improvements in gastroesophageal cancer care for the next decades will not come from improvements of the gastrectomy procedure, but from improved staging and multimodal therapies, which are tailored to specific tumor biology, patient genome and patient condition.

PERSONALIZED TREATMENT OF GASTROESOPHAGEAL CANCER

Currently, a relatively large proportion of patients with locally advanced gastroesophageal cancer receive the same treatment with curative intent: preoperative chemoradiotherapy followed by resection or perioperative chemotherapy combined with resection(1,2,79). To improve outcomes, this relative "one size fits all" approach should be further tailored to the individual patient, based upon the anatomical location of the tumor (and its metastases), the tumor genome and its unique susceptibility to specific treatments and the patient's genome and condition and its unique susceptibility to side effects of specific treatments(56,57,59,65,76,78,80–82).

Personalized treatment by patient characteristics

Despite recent improvements in surgical technique, major postoperative complications (Clavien-Dindo grade ≥3) still occur in 19% of patients after gastrectomy and 29% of patients after esophagectomy(83). Within the group of patients that are deemed fit enough to undergo surgery (based upon clinical condition and comorbidity), it is currently not possible to accurately predict which patients will develop major complications and which patients do not(56,84,85). Additional information from preoperative CT-scans could further help predict the risk for a postoperative complication. Examples are body composition parameters to determine increased risk for postoperative complications after surgery and the uniform calcification score to determine increased risk of anastomotic leakage after esophagectomy (chapter 5 & 9). Such scores are currently not broadly implemented in clinical practice. Here lies an opportunity for improvement. Such parameters should be derived from CT-scans by automated software and linked with large datasets such as the DUCA that contain baseline characteristics and treatment outcomes of thousands of

patients. Tools can then be created to automatically predict the risk of patients undergoing a major complication at multidisciplinary tumor boards, such as the GRACE risk score calculator for mortality after acute coronary syndromes (https://www.mdcalc.com/grace-acs-risk-mortality-calculator)(85,86).

Next, for such high risk patients, alternative treatment strategies need to be developed. The ISCON-trial in the current thesis is an example in which a the previously validated uniform calcification score is determined by preoperative CT-scan to select patients at increased risk of anastomotic leakage and offer them an alternative surgical strategy: laparoscopic ischemic conditioning 14 days prior to esophagectomy (chapter 9). Other non-surgical examples of such strategies are definitive chemoradiotherapy for patients with squamous cell esophageal cancer or irinotecan based perioperative chemotherapy for neuroendocrine carcinomas in patients with UGT1A1 genotype *1*1 or *1*28 (making these patients less susceptible to toxicity from irinotecan) (clinicaltrials.gov NCT04460352) (81). Ideally, multiple local and systemic treatment options should be available, with a predicted risk (complications) and benefit (control of disease) for each individual patient.

Personalizing treatment by tumor characteristics

For many specific tumor characteristics, the optimal treatment remains to be eluded. For Siewert type II gastroesophageal junction carcinoma with their midpoint between ≤1 cm proximal and ≤ 2 cm distal from the top of gastric folds, no consensus has been reached on the optimal surgery(87). Worldwide, 73% of hospitals perform a (extended) total gastrectomy, whereas 27% perform an esophagectomy(87). This reflects the limited literature on this subject: only retrospective studies are available and they show ambiguous results on survival and postoperative morbidity(88). The CARDIA-trial presented in the current thesis is a multinational, multicenter, randomized trial that will compare both surgeries and will help determine the optimal surgical approach (chapter 10).

For less common tumor biologies, such as (signet ring cell) diffuse type gastric cancer, gastroesophageal (mixed adeno)neuroendocrine carcinoma and gastroesophageal cancer with pulmonary or liver oligometastases, the current thesis attempted to provide answers to some of the clinical dilemmas (chapter 6, 7 and 8). Nevertheless, it can be acknowledged that these are only small pieces of the puzzle. To solve the larger puzzle, a broader understanding of the differences in staging and tumor biology is likely required. For example, why do certain patients with cT3N1M0 staged gastric adenocarcinoma achieve cure with gastrectomy only, whereas other patients require perioperative chemotherapy and gastrectomy to achieve cure and yet the majority of patients does not achieve cure, despite the most intensive treatment available(1,2,89)?

I believe a large part of the answer lies in insufficient staging and insufficient acknowledgement of the subtypes of gastric cancer. Likely, part of the uncured patients

already had microscopically distant metastatic disease. Hopefully, new techniques such as circulating tumour DNA can help increase staging of such patients(61,62,71). In addition, even gastric adenocarcinoma is likely not "one disease", as 4 subtypes have been identified based upon tumor genomics: (1) Epstein-Barr virus (EBV) infection, (2) microsatellite instability (MSI), (3) chromosomal instability (CIN) and (4) genomic stability (GS)(65,90). Future studies are required in all these different subtypes and stages of gastroesophageal cancer to test what is the optimal combination of currently available and future treatment options (such as surgery, radiotherapy, chemotherapy, immunotherapy and targeted therapy) and why (what pathophysiological mechanism renders certain tumors more susceptible to certain therapies) whilst every time balancing the predicted risk (complications) and benefit (control of disease) for each individual patient(56,57,59,65,76,78,80–82).

FINAL REMARKS

This thesis provided evidence from a multicenter randomized trial that laparoscopic gastrectomy is a safe and effective alternative to open gastrectomy in a Western population with predominantly locally advanced gastric cancer. Differences in both costs and effectiveness were limited between treatment strategies. This supports hospitals to choose, based upon their own preference, whether or not to (de)implement laparoscopic gastrectomy as an alternative to open gastrectomy.

Even though new technical developments have the potential to further improve surgical technique, perhaps the most important improvements in gastroesophageal cancer care can be expected from novel local and systemic therapies which are tailored to specific tumor biology, patient genome and patient condition.

CONCLUSIONS

Part I. Laparoscopic versus open gastrectomy for gastric cancer (LOGICA-trial)

- In a Western population with predominantly locally advanced gastric cancer, laparoscopic gastrectomy did not lead to shorter hospital stay. In addition, oncological efficacy, postoperative complications and postoperative quality of life did not differ between laparoscopic gastrectomy and open gastrectomy (Chapter 2).
- Postoperative pain scores were acceptable after laparoscopic and open gastrectomy. After laparoscopic gastrectomy, this was generally achieved without epidural analgesia, with significantly lower opioid consumption at postoperative day 1-2 and with reduced opioid prescriptions at discharge (chapter 3).

- Even though the laparoscopic gastrectomy procedure itself was more expensive, after 1-year follow-up, differences in both total costs and effectiveness were limited between laparoscopic and open gastrectomy (Chapter 4).
- Low skeletal muscle mass and high visceral and subcutaneous adipose tissue radiation attenuation (indicating fat depleted of triglycerides) as measured on preoperative CT-scans are predictors for major postoperative complications after treatment with preoperative chemotherapy and gastrectomy (chapter 5).

Part II. Personalized treatment of gastroesophageal cancer

- In patients with gastric or gastroesophageal junction diffuse type adenocarcinoma, including signet ring cell carcinoma, preoperative chemotherapy prior to surgery was associated with better survival, compared to surgery alone (chapter 6).
- Gastroesophageal (mixed adeno)neuroendocrine carcinoma ((MA)NEC) are often misdiagnosed as adenocarcinoma on endoscopic biopsies. However, if (MA)NECs are recognized, biopsy diagnosis is reliable. Patients with localized gastroesophageal (MA)NEC that underwent resection had a 5-year survival of 35-39% (chapter 7).
- In highly selected patients with gastroesophageal cancer and hepatic or pulmonary metastases, metastasectomy was performed with relatively limited morbidity and mortality and offered a 5-year overall survival of 31–53% (chapter 8).
- A prospective single-arm safety and feasibility trial is underway to evaluate the safety and feasibility of performing laparoscopic ischemic conditioning prior to esophagectomy in patients with esophageal cancer and arterial calcifications as measured on pre-operative CT-scan (ISCON-trial) (Chapter 9).
- A multinational, multicenter, randomized controlled trial is underway, comparing transthoracic esophagectomy and transhiatal extended gastrectomy for “true cardia” type II gastroesophageal junction adenocarcinoma. It is hypothesized that transthoracic esophagectomy will lead to better oncological efficacy and survival, while providing acceptable quality of life and cost-effectiveness (CARDIA-trial) (chapter 10).

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Appendices

DUTCH SUMMARY (NEDERLANDSE SAMENVATTING)

Hoofdstuk 1. Algemene inleiding

Maag- en slokdarmkanker zijn wereldwijd de derde en zesde meest voorkomende oorzaken van kankergerelateerde sterfte. Met name in westerse populaties neemt de incidentie van adenocarcinomen toe. Daar bij gaat het om adenocarcinomen in de proximale maag, op de maag-slokdarmovergang en in de distale slokdarm. Van deze patiënten heeft slechts iets meer dan de 50% een mogelijk te genezen ziekte bij het stellen van de diagnose. De behandeling gericht op genezing bestaat uit een chirurgische resectie van de ziekte en/of chemo(radio)therapie. Deze behandeling heeft echter een hoge morbiditeit tot gevolg en minder dan 40% van de patiënten die deze behandeling ondergaat wordt ook daadwerkelijk genezen. De meerderheid van de patiënten ondergaat een vergelijkbare behandeling en deze behandeling is dus relatief weinig toegespitst op de individuele patiënt. Om uiteindelijk tot betere uitkomsten te komen is het nodig om deze behandelingen meer te personaliseren. Het eerste doel van dit proefschrift is om de twee belangrijkste operatietechnieken te vergelijken van het relatief veel voorkomende adenocarcinoom van de maag: de laparoscopische versus open maagresectie (deel I). Het tweede doel van dit proefschrift is om de behandeling te evalueren van relatief weinig voorkomende subtypes van maag- en slokdarmkanker en de behandeling van patiënten met een verhoogd risico op postoperatieve complicaties, om zo tot een meer gepersonaliseerde behandeling te komen van maag- en slokdarmkanker (deel II).

Deel I. Laparoscopische versus open maagresectie voor maagkanker (LOGICA-trial)

Hoofdstuk 2. Postoperatief herstel en oncologische effectiviteit

De multicenter gerandomiseerde LOGICA-trial werd verricht naar de laparoscopische versus open maagresectie in de westerse populatie met voornamelijk lokaal gevorderde maagkanker. De ziekenhuisopnameduur, het aantal postoperatieve complicaties, het aantal radicale resecties, de lymfeklieropbrengst, de 1-jaars algehele overleving en de globale gezondheidsgerelateerde kwaliteit van leven verschilden niet tussen de laparoscopische en open maagresectie. Wel was er minder bloedverlies na de laparoscopische maagresectie, maar ook een langere operatieduur. De bovengenoemde resultaten ondersteunen het gebruik van de laparoscopische maagresectie als een gelijkwaardig alternatief voor de open maagresectie.

Hoofdstuk 3. Pijn en opiaatgebruik

Er werd een secundaire analyse verricht van de LOGICA-trial naar postoperatieve pijn en opiaatgebruik. De gemiddelde pijnscores waren zowel bij de laparoscopische als bij de open maagresectie acceptabel en onderling vergelijkbaar op alle postoperatieve opnamedagen

en bij ontslag. In de laparoscopiegroep werd dit over het algemeen bereikt zonder epidurale ruggenprik, in tegenstelling tot in de opengroep. Hiernaast was in de laparoscopiegroep het gemiddelde opiaatgebruik in de eerste twee dagen na de operatie en op de dag van ontslag significant lager dan in de opengroep. Dit kunnen relevante voordelen zijn van de laparoscopische maagresectie, ook met oog op de huidige opiaten-epidemie.

Hoofdstuk 4. Kosteneffectiviteit
Er werd een prospectieve kosteneffectiviteitsanalyse verricht in de LOGICA-trial. De laparoscopische maagresectie op zichzelf was duurder dan de open maagresectie, vanwege de langere operatieduur en duurdere wegwerpmaterialen (€ 7.380 versus € 5.972). De totale kosten na 1 jaar waren € 26.084 voor de laparoscopische maagresectie versus € 25.332 voor de open maagresectie. De voor kwaliteit van leven gecorrigeerde levensjaren bedroegen respectievelijk 0.665 versus 0.686. Gezien deze verschillen relatief klein zijn ten opzichte van de onzekerheid in de analyse, kan worden aangenomen dat de totale kosten en de effectiviteit weinig verschillen tussen de laparoscopische en open maagresectie. Deze vergelijkbare kosteneffectiviteit stelt ziekenhuizen in staat om, op basis van eigen voorkeur, de laparoscopische maagresectie te (de)implementeren als alternatief voor de open maagresectie.

Chapter 5. Lichaamssamenstelling als voorspeller voor complicaties
Er werd een prospectieve zijstudie verricht in de LOGICA-trial naar het verband tussen de lichaamssamenstelling, die op de CT-scan voorafgaand aan de maagresectie werd gemeten, en de postoperatieve complicaties. Patiënten met een lage skeletspiermassa hadden een significant hoger risico op het ontwikkelen van een ernstige complicatie, na behandeling middels chemotherapie gevolgd door maagresectie. Patiënten met een laag triglyceridengehalte in visceraal of subcutaan vet (op CT-scan zichtbaar als een hoge stralingsverzwakking) hadden ook een hoger significant risico op het ontwikkelen van een ernstige postoperatieve complicatie. Deze bevindingen kunnen bijdragen aan een betere preoperatieve screening van patiënten die een hoog risico lopen op ernstige postoperatieve complicaties.

Deel II. Gepersonaliseerde behandeling voor maag- en slokdarmkanker

Hoofdstuk 6. Diffuus type carcinoom van de maag of maag-slokdarmovergang
Er werd een nationaal retrospectief cohortonderzoek verricht naar patiënten met een diffuus type carcinoom (inclusief zegelringcelcarcinoom) in de maag of op de maag-slokdarmovergang. Dit type wordt beschouwd als meer agressief en minder reactief op chemotherapie, vergeleken met het intestinaal type adenocarcinoom. Desalniettemin laat onze studie zien dat voor beide types preoperatieve chemotherapie gevolgd door chirurgie

geassocieerd was met een betere overleving, vergeleken met enkel chirurgie. Derhalve dient het toedienen van preoperatieve chemotherapie de standaard behandeling te blijven voor deze patiënten. Hiernaast werd een verband gevonden tussen enerzijds ziekenhuizen die jaarlijks weinig patiënten opereren met een diffuus type maag-slokdarmovergang carcinoom en anderzijds meer irradicale resecties en een lagere algehele overleving. Derhalve wordt voor deze patiëntengroep centralisatie van zorg geadviseerd.

Hoofdstuk 7. (Gemengd adeno)neuro-endocrien carcinoom van de maag en slokdarm
Er werd een nationaal retrospectief cohortonderzoek verricht naar patiënten met een (gemengd adeno)neuro-endocrien carcinoom van de maag of slokdarm ((MA)NEC). Dit uiterst zeldzame subtype is agressief en de overlevingskansen worden, met name in oudere literatuur, als somber beschouwd. Onze studie laat zien dat patiënten met de definitieve diagnose (MA)NEC op resectie, vooraf middels endoscopische biopten vaak verkeerd als adenocarcinoom waren gediagnosticeerd. Echter, als een (MA)NEC vooraf wel werd herkend middels biopt, dan is deze diagnose betrouwbaar en kan op basis hiervan de behandelstrategie worden bepaald. Helaas kunnen we ervan uit gaan dat de meerderheid van patiënten uitgezaaide ziekte hebben bij het stellen van de diagnose. Onze studie liet echter zien dat voor patiënten zonder uitzaaiingen op afstand de 5-jaars overleving 35-39% bedroeg. Het inzetten van een behandeling gericht op genezing is voor deze patiënten dus een valide optie die dient te worden besproken in een multidisciplinair overleg.

Hoofdstuk 8. Lever- en long-oligometastasen van maag- en slokdarmkanker
Er werd een nationaal retrospectief cohortonderzoek verricht naar patiënten die een resectie met intentie tot genezing ondergingen van lever- of longmetastasen van maag- of slokdarmkanker. De standaardbehandeling voor deze patiënten bedroeg gedurende de studieperiode ofwel ondersteunende zorg gericht op comfort, danwel palliatieve chemotherapie. Deze behandelingen resulteren in een mediane overleving van minder dan een half jaar. Onze studie includeerde uiterst geselecteerde patiënten, vermoedelijk in een klinisch goede conditie en met relatief gunstige tumorkenmerken zoals metachrone oligometastasen. Het operatief verwijderen van lever- of longmetastasen leidde tot relatief weinig postoperatieve morbiditeit en mortaliteit. Het resulteerde bij de geïncludeerde patiënten in een 5-jaars overleving van 31-53%. Deze resultaten rechtvaardigen de uitvoering van toekomstige prospectieve studies met strikte inclusiecriteria, waarin geëvalueerd wordt of een lokale behandeling van maag- of slokdarm-oligometastasen in deze uiterst geselecteerde patiënten leidt tot een verbetering in overleving en kwaliteit van leven.

Hoofdstuk 9. ISCON-trial
Er werd een prospectief eenarmig veiligheids- en haalbaarheidsonderzoek gestart in 2 Europese ziekenhuizen naar het verrichten van laparoscopische ischemische conditionering (ISCON). ISCON werd 12-18 dagen voorafgaand aan een slokdarmresectie verricht bij patiënten met slokdarmkanker en slagaderverkalking op de preoperatieve CT-scan. Een algeheel matige cardiovasculaire status bij deze patiënten leidt vermoedelijk tot een verminderde doorbloeding van de buismaagreconstructie na slokdarmresectie, met als gevolg een grotere kans op naadlekkage met geassocieerde morbiditeit en mortaliteit. ISCON zou mogelijk de doorbloeding van de buismaag kunnen verbeteren door een herverdeling van de bloeddoorstroming, met als gevolg een kleinere kans op naadlekkage. Wij verwachten dat ISCON veilig en haalbaar is. Als dit wordt bevestigd in deze eenarmige studie zal een multicenter gerandomiseerd gecontroleerd onderzoek worden opgezet om te onderzoeken of ISCON ook daadwerkelijk leidt tot een kleinere kans op naadlekkage en een minder ernstig beloop van naadlekkage bij patiënten met een hoog risico hierop.

Hoofdstuk 10. CARDIA-trial
Er werd een multinationaal, multicenter, gerandomiseerd gecontroleerd onderzoek gestart naar de transthoracale slokdarmresectie versus de transhiataal uitgebreide maagresectie, voor type II cardiacarcinomen op de maag-slokdarmovergang. Het centrum van deze carcinomen ligt tussen ≤1 cm proximaal en ≤2 cm distaal van de top van de maagplooien. De incidentie van kanker op de maag-slokdarmovergang neemt toe. De optimale chirurgische behandeling is echter nog onduidelijk. Zo liet een internationale enquête zien dat voor deze type II cardiatumoren 73% van de ondervraagde chirurgen een maagresectie verricht en 27% een slokdarmresectie. Tot dusver zijn er alleen retrospectieve onderzoeken verricht die beide operaties vergelijken, met tussen de onderzoeken tegenstrijdige resultaten wat betreft overleving en postoperatieve morbiditeit. Onze hypothese luidt dat de transthoracale slokdarmresectie leidt tot een hoger percentage radicale resecties en tot een completere mediastinale lymfeklierdissectie. De verwachting is dat dit resulteert in een betere algehele overleving, met acceptabele kwaliteit van leven en kosteneffectiviteit. De CARDIA-trial is het eerste gerandomiseerde onderzoek dat beide operaties vergelijkt en zal helpen te bepalen wat de optimale operatie is.

Conclusie

De multicenter gerandomiseerde LOGICA-trial was uitgevoerd in een westerse populatie met voornamelijk lokaal gevorderde maagkanker. De resultaten laten zien dat de postoperatieve complicaties, herstel, kwaliteit van leven en de oncologische effectiviteit vergelijkbaar zijn tussen de laparoscopische en de open maagresectie. De postoperatieve pijn is acceptabel na beide operaties, echter na de laparoscopische maagresectie werd dit

meestal bereikt zonder epidurale ruggenprik. Hiernaast gebruiken na de laparoscopische maagresectie significant minder patiënten bij ontslag nog orale opiaten, vergeleken met na de open maagresectie. Het verschil in totale kosten was beperkt tussen beide operaties, al zou de open maagresectie mogelijk iets goedkoper kunnen zijn. Deze resultaten stellen ziekenhuizen in staat om, op basis van eigen voorkeur, de laparoscopische maagresectie te (de)implementeren als alternatief voor de open maagresectie.

Hiernaast werden er drie nationale retrospectieve cohortonderzoeken verricht naar patiënten met relatief weinig voorkomende subtypes van maag- en slokdarmkanker: diffuus type carcinoom (inclusief zegelringcelcarcinoom), (MA)NEC en maag- of slokdarmkanker met lever- of long-oligometastasen. Deze resultaten kunnen bijdragen aan het maken van betere behandelbeslissingen tijdens multidisciplinaire overleggen.

Tot slot werden er twee klinische onderzoeken ontworpen en gestart in het kader van dit proefschrift. De CARDIA-trial includeert patiënten met kanker op de maag-slokdarmovergang en de ISCON-trial includeert patiënten met slokdarmkanker die op basis van de preoperatieve CT-scan een verhoogd risico op postoperatieve morbiditeit hebben. Zodra deze onderzoeken zijn voltooid, zullen de resultaten bijdragen aan het verbeteren van de chirurgische behandeling voor deze patiënten.

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ACKNOWLEDGEMENTS (DANKWOORD)

Gedurende mijn promotietraject heb ik met buitengewoon veel mensen mogen samenwerken. Graag wil ik iedereen bedanken die heeft bijgedragen aan de totstandkoming van dit proefschrift, met in het bijzonder de onderstaande personen.

Patiënten
Allereerst wil ik graag alle patiënten bedanken voor hun deelname aan de verschillende studies.

Promotiecommissie
Geachte prof. dr. R. van Hillegersberg, beste Richard, ik heb genoten van je goede leiderschap, goede feedback en slimme opmerkingen. Het was ontzettend leuk om met je te sparren over de verschillende onderwerpen, waaronder de resultaten van de LOGICA trial. Ik ken geen onderzoeker die zo "street-smart" is als jij en het was een groot plezier om samen ten strijde te trekken bij de METC voor de opzet van de ISCON en CARDIA trials. Ook de internationale contacten blijven me bij, natuurlijk met onze collega's uit Keulen maar bijvoorbeeld ook toen we om 05:45 met slaperige ogen bij een Esodata vergadering zaten op een congres in Wenen. Gedurende mijn promotietraject hadden we meerdere contactmomenten per week en dat is een luxe die promovendi uit andere onderzoeksgroepen niet altijd kennen. Uiteraard betekende dit ook dat ik op die momenten niet met lege handen kon komen aanzetten, het tempo zat er goed in en voor uitstelgedrag was geen tijd. Ik wil je bedanken voor de vrijheid en het vertrouwen. Bedankt voor de leuke tijd. Bedankt voor alles wat ik gedurende mijn promotietraject heb mogen leren.

Geachte prof. dr. J.P. Ruurda, beste Jelle, ik heb genoten van je intellect, humor en scherpe opmerkingen. Als ik dreigde te verzanden in alle details dan probeerde jij me weer op de grote lijn te laten richten. Bedankt hiervoor. Het is mooi om te zien met wat voor efficiëntie jij te werk gaat en hier van te leren. Bedankt voor je snelle reacties en goede feedback op mijn presentaties en manuscripten. Ik ben er trots op deel uit te maken van deze geweldige onderzoeksgroep die je samen met Richard leidt.

Beoordelingscommissie
Geachte leden van de beoordelingscommissie, hartelijk dank voor het lezen en beoordelen van mijn proefschrift. Ik kijk uit naar de gedachtewisseling tijdens mijn verdediging.

Opleiders Radiotherapie
Geachte dr. J.L. Noteboom en drs. I.E. van Dam, beste Juus en Iris, op voorhand was ik

sterk tegen het volgen van een promotietraject "in je vrije tijd." Eigenlijk ben ik dit nog steeds. Mijn droombaan als arts in opleiding tot radiotherapeut kwam echter op mijn pad, wat maakte dat ik de afgelopen twee jaar mijn promotietraject toch heb moeten afronden naast mijn baan bij de Radiotherapie. Het zal een cliché zijn dat dit zo is gelopen. Graag wil ik jullie bedanken voor de extra ruimte die jullie mij geboden hebben voor het afronden van mijn promotietraject.

Collega's

Beste Oesmaag-onderzoeksgroep, een meer inspirerende groep collega's kon ik me niet wensen. Jullie maakten het promoveren leuk. Beste Maarten, in 2016 kwam ik voor het eerst als student, toen tijdelijk wonend in Duitsland, naar Utrecht afgereisd om bij onze onderzoeksgroep te kijken. Bedankt voor je goede en humorvolle begeleiding destijds. Zonder deze goede aftrap was er nu geen promotie geweest. Beste Hylke, bedankt voor het opstarten van de prachtige LOGICA trial samen met Leonie en Maarten. Bedankt voor het meedenken over de resultaten en je talent om met het snoeimes door mijn manuscripten te gaan. Beste Emma, samen vertegenwoordigden wij het maagteam in de kelder. Bedankt voor de goede samenwerking. Het samen schrijven van het zegelringcelmanuscript ging gesmeerd! Beste Eline, bedankt voor je goede grappen in de kelder en je talent om niet alles serieus te nemen. Onmisbaar in een promotietraject. Scherp dat Emma en jij al snel een overeenkomst zagen tussen mijn naam en mijn favoriete statistiekprogramma. Beste Cas, bedankt voor je inzet en altijd opgewekte humeur. Geweldig dat je samen met Eline en ook Lianne een aantal studies voortzet. Beste Gino, mooi dat dankzij Eline en jou het ICG-project geen verspilde moeite was. Beste Mando, officieel niet van de oesmaag-groep, maar mooi dat we de kelder nog hebben mogen delen! Beste Tiuri, uitstekende keuze om radiotherapeut te worden, en dan ook nog in het mooie Zwitserland. Succes! Beste Sylvia, Gijs, Pieter, Teus, Lucas, Alicia, Ingmar, Daan en Bernadette, bedankt voor het groepsgevoel, de gezelligheid en jullie waardevolle input.

Beste Feike, eerst hebben we als studenten nog een enkele maand tegenover elkaar gezeten in het Q-gebouw en later kwam ik je achterna naar de promovendi kelder zonder daglicht. Bedankt voor het wegvangen van mijn vele vragen in de beginfase en het sparren over alle verschillende onderzoeken. Bedankt voor de uitstekende sfeer in de kelder en je collegialiteit. Ik ben vereerd dat je mijn paranimf bent en hopelijk treffen we elkaar nog vaak bij het multidisciplinair overleg!

Beste Anne May, bedankt dat je me geleerd hebt om correct een gerandomiseerde trial te analyseren. Dat kwam wel van pas in dit proefschrift. Beste Miriam van der Meulen, bedankt voor je fijne samenwerking omtrent de kostenanalyse, het uitwisselen van R-codes

en je geduld wanneer ik iets nog preciezer wilde uitzoeken. Beste Marije Marsman en Lodewijk Brosens, bedankt voor de samenwerking.

Beste Mark Ramaekers en Thaís Tweed, ook jullie bedankt voor de goede samenwerking. Mark, knap hoe je de opiatendata van de LOGICA-trial verzameld hebt. Stelling nummer 10 zal ook jou niet vreemd in de oren klinken.

Beste Romy, je weet als geen ander hoe uitdagend de logistiek is met 2 drukbezette professoren en een grote groep promovendi. Hartelijk dank dat je altijd wilde meedenken om de afspraken in goede banen te leiden. We konden altijd op je vertrouwen. Beste Marielle en Fatiha, jullie ook bedankt voor jullie bijdrage hieraan. Beste Antoinette, bedankt voor je hulp bij het opzetten van de klinische trials.

Beste Wendy van wenzid.nl, bedankt voor het vormgeven van mijn proefschrift. Ik vind het een prachtig geheel geworden. Je bent erg goed in je werk, dus dat was prettig samenwerken.

Beste collega AIOS van de afdeling Radiotherapie, het is fantastisch om wederom deel uit te maken van zo'n slimme en sociale groep. Bedankt voor het overnemen van mijn diensten toen ik een aantal maanden fulltime aan de afrondingen van mijn proefschrift ging werken.

Beste collega's van de afdeling Chirurgie en in het bijzonder alle promovendi, bedankt voor het leuke contact.

Beste chirurgen die hebben meegewerkt aan de hoofdstukken over (gemengd adeno) neuroendocriene carcinomen en long- of lever-oligometastasen, bedankt voor de gastvrijheid toen ik als student met mijn OV-kaart langs bijna alle ziekenhuizen in Nederland reisde voor de dataverzameling.

En "last but not least", beste LOGICA-trial chirurgen, arts-onderzoekers, research nurses, studenten en iedereen die heeft bijgedragen aan de trial, hartelijk dank voor jullie continue enthousiasme en inzet.

Colleagues from Cologne

Dear Christiane Bruns, Wolfgang Schröder, Laura Knepper and all other colleagues of the University Hospital of Cologne, Germany, many thanks for the wonderful collaboration between Utrecht and Cologne on the CARDIA and ISCON trials. I am especially grateful that you employed me as the CARDIA-trial International Medical Coordinator during the later stages of my PhD studies. I am looking forward to the trial results!

Vrienden en familie
Lieve vrienden en familie, mijn contacten met jullie zijn mijn meest waardevolle bezit.

Lieve oudbestuursgenoten, lieve Eva, Michelle, Joost, Claire, Julia en Nadja. Inmiddels is het tien jaar geleden sinds we een jaar op elkaars lip zaten en er vriendschappen voor het leven zijn ontstaan. Geweldig dat we nog steeds lief en leed delen. De gelijkenis tussen ons bestuurshok destijds en mijn promotiekelderkamer is treffend. Eigenlijk wat ik de hele dag deed ook: goochelen met getallen. Eva, bedankt voor het proeflezen van enkele Nederlandstalige hoofdstukken, handig dat jij wél Nederlandstalige televisie keek vroeger.

Lieve bandgenoten van "Hart Geruis", onze weekenden vol met muziek en gezelligheid blijven de beste ontspanning. Laten we hiermee doorgaan totdat we écht oud zijn. Dwight en Eke, wat mij betreft blijven jullie nog lang "om de hoek" wonen!

Lief tennisteam, bij deze kunnen jullie eindelijk mijn proefschrift lezen, of enkel een blik op de voorkant werpen. Toch spijtig dat Duco het steevast "een werkstuk" noemt. Wie weet zit ik er vanaf nu wat energieker bij op de donderdagavond. Tot op de tennisbaan en ernaast!

Lieve vrienden uit Groningen en Utrecht die niet specifiek onder één van de groepen hierboven vallen, in het bijzonder Jorrit van Zwieten, Bart, Niels, Jacomien en Frank, bedankt voor alle gezelligheid en de nodige afleiding gedurende mijn promotietraject. Bart, bedankt voor de leuke telefoongesprekken over onze promoties tijdens de COVID-lockdown. Frank, wat heb jij een fantastische nieuwgierige levensblik. Bijzonder handig om een vriend te hebben die voor zijn plezier proefschriften proefleest. Bedankt dat je er met de stofkam doorheen bent gegaan. Je zal tot één van de weinigen behoren die mijn proefschrift van kaft tot kaft heeft gelezen.

Lieve ooms, tantes en nichten van der Veen, het is best bijzonder dat jullie mij hebben zien opgroeien sinds ik een klein mannetje was. Ik ben benieuwd wat jullie van dit proefschrift vinden.

Lieve schoonfamilie, lieve Ronald, Ingrid, Lars, Eva, Rens en Olivia. Bedankt voor de warme ontvangst in jullie familie. Ik waardeer jullie enthousiasme en betrokkenheid enorm. Hiernaast wil ik jullie bedanken voor de interesse in mijn promotietraject. Je schoonfamilie kun je niet kiezen, maar ik heb het behoorlijk goed getroffen.

Lieve broer, lieve Jorrit, van jongs af aan was jij mijn grote voorbeeld. Je bent enorm sociaal en daar was ik toen we opgroeiden wel eens jaloers op. Vroeger had ik in jou altijd een

speelmaatje en later volgde ik je naar Groningen om daar te gaan studeren. We zitten vaak op dezelfde golflengte en dat is ontzettend leuk. Als getuige op mijn bruiloft heb je mooi kunnen oefenen voor het paranimfschap. Ik prijs mezelf gelukkig dat ik jou als broer heb.

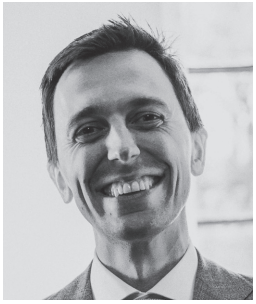
Dear Aurore, I am happy to have you as my sister-in-law. It is great to see how passionate you can be about things and that you make Jorrit happy. Thank you for immigrating to the Netherlands, we are lucky to have Jorrit and you living nearby.

Lieve Zoé, het is leuk om te zien hoe trots jouw (groot)ouders op je zijn. Je bent nu nog klein, maar misschien sla jij ooit dit boek open en zie je hier je eigen naam staan, dat zou grappig zijn. Wie weet inspireert het je om ook een wetenschapper te worden.

Lieve ouders, lieve Geert en Jannie, bedankt voor jullie onvoorwaardelijke liefde. Jullie hebben me altijd gesteund, inmiddels al 30 jaren lang, zowel in mijn opleidingen als daarbuiten. Als zoon ben je geneigd dit als "normaal" te zien, maar dat is het niet. Het is bijzonder. Betere ouders had ik me niet kunnen wensen.

Lieve Sanne, we hebben elkaar in de eerste maand van mijn promotietraject ontmoet en enkele maanden voorafgaand aan de verdediging van dit proefschrift zijn we getrouwd. We zijn blijkbaar nog niet zo goed in het spreiden van onze life-events. Van iedereen die hier genoemd is, ben jij de enige die écht weet hoeveel werk en aandacht er in dit proefschrift is gegaan. Bedankt voor al je steun. Bedankt dat je mijn grootste fan bent en me er altijd aan hebt herinnerd dat het toch wel speciaal is om te promoveren. Jij bent het belangrijkste in mijn leven en ik hoop dat we samen oud mogen worden, tot in het verpleeghuis.

CURRICULUM VITAE



Arjen van der Veen was born on the 1st of August 1992 in Leeuwarden, the Netherlands. He is the son of Geert van der Veen and Jannie de Jager. He has one older brother, Jorrit van der Veen.

After graduating (*cum laude*) from the Piter Jelles Montessori, Leeuwarden, Arjen started medical school at the Rijksuniversiteit Groningen in 2010. He paused his studies in 2012 to take seat in the board of the Medical Faculty Association Panacea as treasurer. Afterwards he continued his studies, performed the 5th year in Oldenburg, Germany and subsequently followed an internship of tropical medicine in Zambia. He developed an interest in cancer research and completed his final year of medical school at the Department of Surgical Oncology of the University Medical Center Utrecht.

Following graduation as a medical doctor in December 2017, Arjen started as a PhD candidate at the same Department of Surgical Oncology, under the supervision of prof. dr. R. van Hillegersberg and prof. dr. J.P. Ruurda. During his PhD program, he collaborated with many hospitals throughout the Netherlands to complete the LOGICA trial on laparoscopic versus open gastrectomy for gastric cancer, which was published in the Journal of Clinical Oncology in 2021. In addition, he performed multiple nationwide database studies on the treatment of gastroesophageal cancer and initiated the ISCON and CARDIA trials in a multinational collaboration with the University Hospital of Cologne, Germany.

At the end of 2020, Arjen started his clinical career as a radiation oncology resident in training at the University Medical Center Utrecht. In his spare time, he enjoys playing tennis and music, reading and spending time with friends and family. He currently lives in Utrecht with his wife Sanne.