ROBOT ASSISTED MINIMALLY INVASIVE ESOPHAGECTOMY FOR ESOPHAGEAL CANCER

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Robot assisted minimally invasive esophagectomy for esophageal cancer
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Robot geassisteerde minimaal invasieve oesofagectomie
als behandeling voor het oesofaguscarcinoom
(met een samenvatting in het Nederlands)

PROEFSCHRIFT

ter verkrijging van de graad van doctor aan de Universiteit Utrecht
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door

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Voor mijn ouders

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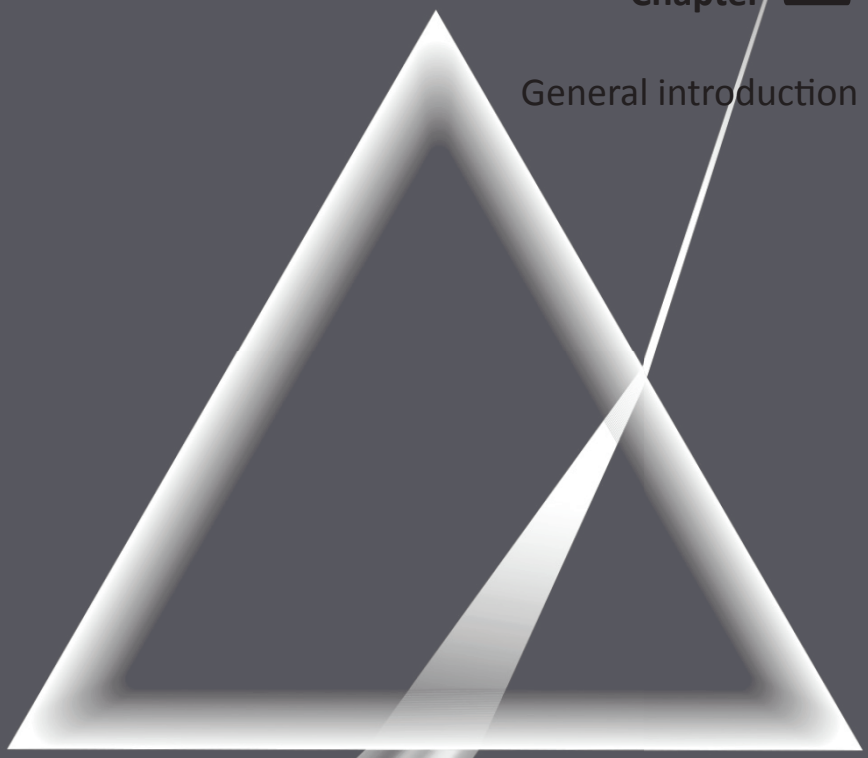
General introduction



INTRODUCTION

Esophageal cancer is the 8th most common malignancy and the 6th leading cause of cancer-related mortality worldwide with more than 450.000 new cases and 400.000 esophageal cancer related deaths.[1] Esophageal cancer is therefore one of the most aggressive and fatal cancers with an overall 5-survival rate of 15-25%.[2,3]
In general, esophageal cancer is 3 to 4 times more common among males than females.[4] There are two major histological types of esophageal cancer: esophageal squamous cell carcinoma (SCC) usually occurring in the middle or proximal one-third of the esophagus and esophageal adenocarcinoma (AC) usually occurring in the lower one-third or gastro-esophageal junction.[4,5]
In Western countries, smoking, alcohol and diets low in fruits and vegetables are considered to be the main risk factors for developing ESCC.[4,5] Incidence rates for ESCC are declining in western countries due to reductions in risk factors such as alcohol consumption and tobacco use.[4]
For EAC, smoking, obesity and chronic esophageal disorders such as achalasia and gastroesophageal reflux disease (GERD) resulting in Barrett's esophagus are the major risk factors.[4] A meta-analysis combing results of 5 different studies showed that weekly symptoms of GERD increase the odds of EAC 5-fold (OR = 4.92; 95% CI = 3.90-6.22). Daily symptoms even increase the odds 7-fold (OR = 7.40, 95% CI = 4.94-11.1).[5] The annual risk of developing AC in Barrett's esophagus patients is increased 30-fold compared to general population with an absolute risk of 0.12 percent / year.[5,6] The increase in incidence in EAC in Western countries is one the fastest increasing of all gastrointestinal cancer types and is attributable to the increase in the prevalence of known risk factors for EAC an Barrett's esophagus such as overweight and obesity.[4,5]

Clinical Findings

The diagnostic pathway of esophageal cancer is a multi step process to confirm the diagnosis of esophageal cancer and to evaluate oncological and functional operability. In case of suspected esophageal cancer, a detailed medical history and a thoroughly physical examination at the outpatient department precede diagnostic tests. Common symptoms of esophageal cancer are associated with a poor passage of food to the stomach. However, during development most esophageal cancers remain asymptomatic and therefore early diagnosis of esophageal cancer remains difficult ever since no symptoms are observed until passage problems occur. The most common symptoms are in general: dysphagia (74%), weight loss (57%), gastrointestinal reflux (20%), odynophagia (17%), and dyspnea (12%).[7] Besides the presence of current symptoms, the anamnesis should include details about familiarly predisposition for esophageal cancer and a medical history of risk factors for esophageal cancer such as chronic alcohol and tobacco abuse and a prior diagnosis of Barrett´s esophagus or achalasia. Furthermore, a history of cardiopulmonary co-morbidity possibly influencing the functional operability should be determined. Physical examination intends to obtain an impression of the general state of health. Enlarged (cervical) lymph nodes, indicating advanced disease, are checked and the nutritional status is assessed. Cardiopulmonary exercise test-

ing is used to determine the patient's clinical condition to decide whether a patient is able to undergo a major surgical procedure.[7]

Preoperative Testing

Esophagogastroscopy with endoscopic biopsy is the standard procedure for detection and confirmation of the diagnosis of esophageal cancer. Endoscopic ultrasound (EUS) is used to determine tumor stage (T-stage) and regional lymph node involvement (N-stage) and cervical ultrasonography is used for evaluation of suspected cervical lymph nodes. Computed tomography (CT) of thorax and abdomen is generally used for detection of distant (lymph node) metastases.[8,9] Positron emission tomography (PET) with ^{18}F-Fluoro-deoxy-D-glucose (FDG) combined with CT-scan is also used for determining regional lymph node involvement, but the most important role is to identify distant metastases pre-treatment or after neoadjuvant therapy.[10,11]

Indications for multimodality treatment and surgery

Based on preoperative testing and determined physical status, resectability is determined. Esophageal cancer is staged according to the 7th edition of the Tumor Node metastasis classification (TNM7).[12] The TNM 7 classification is sown in table 2. Esophageal tumors classified as cT4b and cM1 are considered to be irresectable.

Table 1. The 2009 TNM-7 classification of esophageal cancer.

T - Primary Tumor
TX Primary tumor cannot be assessed
T0 No evidence of primary tumor
Tis High grade dysplasia
T1 Tumor invades lamina propria or submucosa
T2 Tumor invades muscularis propria
T3 Tumor invades adventitia
T4a Resectable cancer invades adjacent structures (for example, pleura, pericardium, diaphragm).
T4b Unresectable cancer invades adjacent structures (for example, aorta, vertebral body, trachea).
N - Regional lymph nodes
NX Regional lymph nodes cannot be assessed
N0 no regional lymph node metastasis
N1 1 to 2 positive regional lymph nodes.
N2 3 to 6 positive regional lymph nodes.
N3 Greater than or equal to 7 positive regional lymph nodes.
M - Distant metastasis
MX Distant metastasis cannot be assessed
M0 No distant metastasis
M1 Distant metastasis

For patients with locally advanced esophageal cancer, radical esophageal esophagectomy including surrounding lymph nodes offers the best chance for survival with an average 5-year survival of 36%.[13] In order to improve outcome, multimodality treatment including

neo-adjuvant chemoradiotherapy and perioperative chemotherapy has become standard of care in recent years.[14,15] A meta-analysis calculated hazard ratios for all cause mortality with chemotherapy (0.87 (0.79-0.96; p=0.005) and chemoradiotherapy (0.78 (95% CI 0.70-0.88; p<0.0001) compared with surgery alone. These data suggest a survival benefit of neoadjuvant chemoradiotherapy or chemotherapy over surgery alone in patients with esophageal carcinoma. However, a clear advantage of neoadjuvant chemoradiotherapy over neoadjuvant chemotherapy has not been established yet.[14,15]
If patients with potentially operable cancer are physically unfit to undergo esophagectomy definitive chemoradiotherapy is the procedure of choice.[16] In case of advanced disease or distant metastases palliative measures are indicated.

Surgical treatment of esophageal cancer
Following neoadjuvant treatment, resection of the esophagus with en-bloc lymphadenectomy is the cornerstone of curative treatment for patients with locally advanced esophageal cancer.[1] The choice of surgical approach depends on the location of the tumor and the experience of the surgeon. Treatment in high-volume centers with experienced surgeons and the availability of critical-care support is associated with improved outcomes and lower morbidity and mortality.[17,18] The two main surgical approaches for locally advanced esophageal cancer are transthoracic or transhiatal esophagectomy.[1]

Transthoracic versus transhiatal esophagectomy
A transthoracic esophagectomy with two-field lymph node dissection and gastric conduit reconstruction is worldwide the preferred procedure for resection of esophageal cancer.[19] A transthoracic esophagectomy includes a laparotomy and thoracotomy with a mediastinal lymph node dissection. A gastric conduit is created and gastrointestinal continuity is restored by an intrathoracic anastomosis (Ivor Lewis approach) or cervical anastomosis (McKeown approach, which includes a cervicotomy).[20,21]
Transhiatal esophagectomy is performed through laparotomy and cervical incision, without thoracotomy. The transhiatal esophagectomy was designed to reduce postoperative morbidity and mortality by avoiding thoracotomy. A transhiatal blunt esophagectomy is performed with a limited lymph node dissection, which only includes the lower mediastinal lymph nodes. Continuity is restored by creating a gastric conduit with a cervical anastomosis.[22,23]
The largest randomized clinical trial (RCT), the HIVEX trial, compared an extended transthoracic resection with a limited transhiatal resection for adenocarcinoma of the esophagus and included 220 patients.[24] A total of 106 patients were assigned to undergo transhiatal esophagectomy, and 114 to undergo transthoracic esophagectomy. Transhiatal esophagectomy was associated with lower morbidity and shorter intensive care unit (ICU) and hospital stay compared to transthoracic esophagectomy with extended en bloc lymphadenectomy.[24] There was no significant overall survival benefit for either approach.[24,13] However, compared with limited transhiatal resection, extended transthoracic esophagectomy for type I esophageal adenocarcinoma shows an trend towards better 5-year survival (51% vs. 37%, P = 0.33) in subgroup analyses.[13] Patients with a limited number of positive lymph nodes (1 to

8 positive lymph nodes) in the resection specimen showed a improved 5-year locoregional disease-free survival advantage if operated via the transthoracic route (23% vs. 64%, P = 0.02).[13]
This RCT was included in a meta-analysis including 8 studies (5 cohort studies and 3 RCTs). In total 1155 patients (639 underwent transthoracic esophagectomy and 516 underwent transhiatal esophagectomy) were included.[25] Results from the meta analysis showed that a transhiatal esophagectomy was associated with decreased hospital stay (WMD = 1.92, 95%CI: 1.63-2.22, P < 0.00001), lower 30-day hospital mortality (OR = 3.21, 95%CI: 1.13-9.12, P = 0.03) and decreased pulmonary complications (OR = 2.95, 95%CI: 1.95-4.45, P < 0.00001), without differences in blood loss, duration of surgery, anastomotic leaks, cardiovascular complications, extent of lymph node dissection and survival.[25]
The current available evidence shows that a transhiatal esophagectomy is associated with lower morbidity compared to a transthoracic esophagectomy, without a difference in overall survival.[25] However, based on the subgroup analysis of the 5-year results of the HIVEX trial, a transthoracic esophagectomy with two-field lymph node dissection and gastric conduit reconstruction remains the preferred surgical procedure for resection of intrathoracic esophageal cancer with clinical mediastinal lymph node metastases. [13,19]

Open esophagectomy versus minimally invasive esophagectomy
Minimally invasive esophagectomy (MIE) was developed to improve the postoperative mortality and morbidity by reducing the surgical trauma in 1992 and 1995.[26,27] Minimally invasive procedures have been gaining popularity in the recent years and a trend towards the use of MIE was found worldwide.[19,28]
Currently there is 1 randomized controlled trial which compared MIE to open transthoracic esophagectomy (TIME-trial).[29] In this trial, 56 patients were randomized to open esophagectomy and 59 to MIE. Compared to open transthoracic esophagectomy, MIE resulted in a lower incidence of pulmonary infections within 2 weeks after surgery (RR 0·30, 95%CI 0·12–0·76, p=0·005), a shorter hospital stay (11 versus 14 days, p=0.044) and better short-term quality of life with equal short term oncological outcome.[29]
Results of this RCT were included in a meta-analysis of 48 studies (1 RCT and 47 observational studies), which compared minimally invasive procedures (thoracoscopy-assisted and all minimally invasive procedures, n = 4509) to open surgery (n = 9973).[30] It was concluded that MIE was superior in decreasing the incidence of in-hospital mortality compared to open esophagectomy (3.0% versus 4.6%, pooled odds ratio 0.69, 95% confidence interval 0.55–0.86) and the incidence of pulmonary complications (17.8% versus 20.4%, pooled relative risk 0.69, 95%CI 0.61–0.77).[30] Furthermore, a reduction in incidence of pulmonary embolism (pooled odds ratio 0.71, 95%CI 0.51–0.99) and atrial arrhythmias (pooled odds ratio 0.79, 95%CI 0.68–0.92) was observed, without a difference in incidence of anastomotic leakage.[30] In the United Kingdom (UK) and the United States of America (USA) population-based comparisons between the two surgical approaches showed similar oncological results, but increased incidence of re-interventions after MIE .[31,32]
Even though superiority for MIE over open esophagectomy was shown in aforementioned meta-analysis, MIE is not widely routinely applied as a standard approach for esophageal

cancer worldwide.[19] This might be attributable to limited scientific evidence on long term outcomes in combination with the learning curve associated with complex minimally invasive procedures.[31]
Recently, 3-year follow-up results were published from the TIME-trial.[33] Combined overall 3-year survival was 40.4% (SD 7.7%) in the open group versus 50.5% (SD 8%) in the minimally invasive group (P = 0.207). The hazard ratio (HR) was 0.883 (0.540 to 1.441) for MIE compared with open surgery. Disease-free 3-year survival was 35.9% (SD 6.8%) in the open versus 40.2% (SD 6.9%) in the MIE group [HR 0.691 (0.389 to 1.239).[33] Very recently, the French randomized trial data were presented on open versus hybrid (open thoracic and laparoscopic abdominal) approach (MIRO-trial). There was a survival benefit in the hybrid group, probably as a result of less postoperative complications.[34] These results, together with aforementioned short-term results, support the use of minimally invasive surgical techniques in the treatment of esophageal cancer.[28-34]

Robot assisted minimally invasive esophagectomy (RAMIE).

Whereas MIE may have advantages for the esophageal cancer patients, many surgeons worldwide choose for an open thoracic approach because of their concern of the high technical complexity of a minimally invasive procedure.[31,35,36]
Robot-assisted minimally invasive thoraco-laparoscopic esophagectomy (RAMIE) was developed in 2003 to overcome the technical limitations of conventional MIE.[36-38] RAMIE was shown to be feasible and safe in a cohort of Western European patients with advanced esophageal cancer.[38,39] RAMIE was oncologically effective with a high percentage of radical resections and adequate lymphadenectomy.[39] Whether RAMIE is superior to open transthoracic esophagectomy is currently investigated in the ROBOT trial, a randomized controlled trial which compares RAMIE to the open transthoracic esophagectomy.[40] The inclusion for this RCT is completed and results are expected in the near future.

Extend of lymphadenectomy (Number of resected lymph nodes)

The presence of lymph node metastasis is an important prognostic factor for survival in patients with curable esophageal cancer.[41-43,] Due to the unique submucosal lymphatic drainage system of the esophagus, lymphatic spread of esophageal tumors is unpredictable and highly variable.[44] To increase the chance of radical removal of all positive lymph nodes and thereby improve regional tumor control and long-term survival, transthoracic esophagectomy with an extended lymphadenectomy is generally recommended.[44-47]

A survival benefit of neoadjuvant chemoradiotherapy (nCRT) added to surgery has been demonstrated and therefore is regarded as standard of care for patients with locally advanced esophageal cancer in many countries.[48,49] The 5-year survival rates of patients undergoing nCRT followed by esophagectomy are now approaching 50%.[48,49]

The appropriate extent of lymphadenectomy after nCRT is currently debated. Recent studies, including patients treated with nCRT followed by esophagectomy suggested that lymph node yield (LNY) was not associated with survival.[50-52] However, these studies were con-

ducted with relatively small sample sizes (n=89-358) yielding limited statistical power, and therefore validation in larger cohorts of patients is needed. [50-52] A recent population-based study from The Netherlands demonstrated that a high LNY after nCRT was associated with improved overall survival. Furthermore, a high LNY was associated with favorable hazard ratios across all subgroups, including both squamous cell carcinoma and adenocarcinoma patients, both cN0 and cN+ patients, both transthoracic and transhiatal approaches, and both ypN0 and ypN+ patients.[53]

CONCLUSION

Until now, all studies comparing different surgical techniques for resection of esophageal cancer did not show a difference in overall survival. A transthoracic esophagectomy allows more complete lymphadenectomy of the mediastinum compared to transhiatal esophagectomy, without an improvement in overall survival. A transthoracic esophagectomy is associated with an increase in pulmonary complications and prolonged hospital stay. Any survival benefit of extensive lymphadenectomy remains to be proven.
Minimally invasive surgery are gaining popularity in the recent years and a trend towards the use of MIE was found worldwide. MIE was associated with a reduction in cardiopulmonary complications compared to open esophagectomy with comparable oncological outcomes. New surgical techniques, such as RAMIE look promising. Neoadjuvant treatment and the results of RAMIE will be investigated in this thesis.

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THESIS OUTLINE AND RESEARCH QUESTIONS

The aim of the research included in this thesis was to evaluate different therapeutic strategies which are involved in the treatment of esophageal cancer with emphasize on neoadjuvant and perioperative multimodality treatment strategies with curative intent (part I) and robot assisted minimally invasive esophagectomy (RAMIE) (part II) to reduce treatment related toxicity, postoperative complications, to improve quality of life and survival. Furthermore, different surgical techniques in relation to postoperative complications are investigated in part III.

Research questions
The following research questions are addressed in this thesis:

Part 1: neoadjuvant therapy

Chapter 2
Wat is the safety, efficacy, and long-term follow-up for perioperative epirubicin, cisplatin, and capecitabine chemotherapy in esophageal resection for adenocarcinoma?

Chapter 3
Local and systemic recurrence are important sources of treatment failure following surgical resection of esophageal adenocarcinoma. Does the addition of preoperative cetuximab and radiotherapy to perioperative epirubicin, cisplatin, and capecitabine increase treatment efficacy with acceptable toxicity?

Chapter 4
What are the differences between neoadjuvant chemoradiotherapy and perioperative chemotherapy for patients with resectable esophageal or gastroesophageal junction (GEJ) adenocarcinoma in terms of toxicity, postoperative complications, pathological response and survival?

Chapter 5
What are the differences between neoadjuvant chemoradiotherapy and perioperative chemotherapy for patients with resectable esophageal or gastroesophageal junction (GEJ) adenocarcinoma in terms of toxicity, postoperative complications, pathological response and survival within a single center?

Part 2: Robot assisted minimally invasive esophagectomy for esophageal cancer (RAMIE)

Chapter 6
Wat is the current evidence and further potential for robot assisted minimally invasive esophagectomy (RAMIE) for esophageal cancer.

Chapter 7
What are the oncologic long term results of robot-assisted minimally invasive thoraco-laparoscopic esophagectomy with two-field lymphadenectomy for esophageal cancer

Chapter 8
How is the learning curve defined for robot assisted minimally invasive esophagectomy (RAMIE) for esophageal cancer and what is the efficacy of a structured proctoring program for introducing a novice surgeon into this technique?

Chapter 9
What are the statistic and epidemiological backgrounds for the ROBOT trial to evaluate the efficacy, risks, quality of life and cost-effectiveness of robot assisted minimally invasive esophagectomy (RAMIE) as an alternative to open transthoracic esophagectomy as treatment for esophageal cancer?

Chapter 10
What are the differences between robot assisted minimally invasive esophagectomy (RAMIE) and open transthoracic esophagectomy considering postoperative, functional recovery, postoperative pain, quality of life costs and oncologic outcomes?

Part III: surgical techniques and complications

Chapter 11
What are the differences between End-to-end and end-to-side cervical esophagogastric anastomoses regarding postoperative outcomes?

Chapter 12
Pneumonia is a frequently observed complication following esophagectomy. The lack of a uniform definition of pneumonia leads to large variations of pneumonia rates in literature. Which diagnostic determinants affected the decision to treat pneumonia and could this be translated in a scoring system for the definition of pneumonia after esophagectomy?

Chapter 13
For patients with locally recurrent disease only, a potential survival benefit with operation has been suggested. Are there any surgical options for patients with recurrent esophageal carcinoma?

PART I

Neoadjuvant therapy

Chapter 2

Safety, efficacy, and long-term follow-up evaluation of perioperative epirubicin, Cisplatin, and capecitabine chemotherapy in esophageal resection for adenocarcinoma

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Ann Surg Oncol. 2015; 22:1555-63

ABSTRACT

Background

Perioperative epirubicin, cisplatin and capecitabine (ECC) chemotherapy was evaluated in patients that underwent esophageal resection for adenocarcinoma of the esophagus or gastro-esophageal junction (GEJ).

Patients and methods

A cohort of 93 consecutive patients was analyzed. Median follow up was 60 months. Source data verification of adverse events was performed by two independent observers.

Results

All 3 planned preoperative chemotherapy cycles were administered in 65 patients (69.9%). Only 27% of patients completed pre- and postoperative chemotherapy. The reasons for not receiving postoperative adjuvant chemotherapy could be separated in two main problems; toxicity of the preoperative chemotherapy and postoperative problems with difficulty in recovery and post-operative complications. Finally, 25 patients (27 %), completed 3 preoperative and 3 postoperative cycles.

Grade 3 and 4 non-hematological adverse events of preoperative chemotherapy mainly consisted of thromboembolic events (16.2%) and cardiac complications (7.5%). A history of cardiac and vascular disease was independently associated with discontinuation of preoperative chemotherapy and the occurrence of grade 3 or higher adverse events. In total 94% of all patients who started with ECC chemotherapy underwent surgery. A radical resection (R0) was achieved in 93% of all patients. A complete pathological response was observed in 8% of all patients.

After a median follow up of 60 months, median disease free survival was 28 months and median overall survival was 36 months. The 3 year overall survival was 50% and 5 year overall survival 42%.

Conclusion

In patients with adenocarcinoma of the esophagus or GEJ, the administration of 6 cycles of ECC based perioperative chemotherapy is associated with a relatively high number of adverse events. Although this toxicity did not affect esophageal resectability rate, this regimen should be used with caution in this patient population .

BACKGROUND

For patients with locally advanced esophageal cancer, radical esophagectomy offers the best chance for cure.[1] Despite radical surgery, 83% of patients experience local or systemic recurrence with an average 5-year survival of 36%.[2] In order to improve surgical results, multimodality treatment has been introduced in several trials.[3,4,5,6] One of these, the Medical Research Council Adjuvant Gastric Infusional Chemotherapy (MAGIC) trial, included a mix of patients with resectable adenocarcinoma of the gastric (74%), gastric-esophageal junction (GEJ) (11.2%) and esophageal adenocarcinoma (14.8%) that were treated with perioperative chemotherapy using epirubicin, cisplatin and 5-fluorouracil (ECF). This treatment strategy conferred a significant overall 5-year survival benefit of 13.3%.[7] In a subsequent study it was found that capecitabine was as effective as fluorouracil in this population.[8,9] Subset analyses performed in the MAGIC study did not find obvious differences in response to treatment between esophageal and GEJ on the one hand and gastric cancer on the other hand. Therefore we have treated patients with esophageal and GEJ adenocarcinoma with perioperative chemotherapy, consisting of 3 preoperative and 3 postoperative cycles of epirubicin, cisplatin and capecitabine (ECC).
In this study, we evaluated toxicity and feasibility of this regime in a population based consecutive retrospective study cohort for patients with esophageal and GEJ adenocarcinoma

PATIENTS AND METHODS

Patient population

In this retrospective study, we analyzed the clinical data from 93 consecutive patients treated with perioperative ECC for resectable esophageal or GEJ adenocarcinoma (Siewert type I and II locally advanced adenocarcinoma) between October 2006 and June 2011 in the St. Antonius hospital Nieuwegein and the University Medical Center Utrecht in the Netherlands. Median follow up was 60 months since the start of ECC chemotherapy. The last date of follow up was the 1st of June 2014. All patients had ECOG performance status 0-2. Patients with a higher ECOG performance status did not undergo neoadjuvant chemotherapy, but directly underwent surgery alone. Underlying diseases, such as cardiac, vascular, pulmonal or oncologic (other than esophageal), had to be stable and under control of their treating physician. Approval to start neoadjuvant chemotherapy had to be given by the multidisciplinary tumor board. All experimental protocols were approved by the appropriate institutional review committee and meet the guidelines of their responsible governmental agency. A part of this cohort was described before.[10]

Data collection

Clinical data were collected by using electronic medical records. Baseline characteristics included sex, BMI, alcohol, smoking, medical history, medication and baseline adverse events. We recorded routine diagnostic work up including upper endoscopy, endoscopic ultrasound (EUS), CT thorax and abdomen and ultrasound of the neck region. The use of PET scanning and fine needle aspiration (FNA) of suspected lymph nodes was also recorded.

Pre-operative and postoperative treatment characteristics were collected, including chemotherapy regimens, numbers of chemotherapy doses, dose reductions and dose density. Statistics on surgical procedures and complications were collected from a prospectively collected surgical database.
All patients were routinely seen starting 4 weeks after discharge at the outpatient department. Every 6 months patients were evaluated for disease recurrence.

Chemotherapy
Patients were scheduled to receive 3 preoperative ECC chemotherapy cycles and 3 postoperative ECC cycles. Pre- and postoperative chemotherapy cycles consisted of intravenous administration of epirubicin (50 mg/m2) and cisplatin (60 mg/m2), followed by 625 mg/m2 of capecitabine twice daily for 14 or 21 days. Adaptations to the regimen such as dose reduction or change of regimen to oxaliplatin or 5-fluoruracil (5-FU) were applied when necessary. Out of 93 patients, 78 patients were treated with perioperative ECC for esophageal or GEJ adenocarcinoma, 13 received EOC by medical indication (renal failure, hearing impairment, peripheral neuropathy) and 2 received ECF due to dysphagia for solid foods.
We generally performed a 2nd CT-scan after the 2nd course of chemotherapy to monitor the therapeutic effect. All patients were discussed in a multidisciplinary oncology meeting with surgeons, gastroenterologists, medical oncologists, radiotherapists and radiologists prior to treatment. Prior to resection all patients were seen by an anesthesiologist.

Toxicity
Source data verification of all grade 3 and higher adverse events was performed by two independent observers according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.[11] Grade 3, 4 and 5 adverse events were graded by consensus of three authors (PCS, IU, ML).

Surgery
Patients underwent surgery as soon as possible after completion of chemotherapy (preferably, within 6 weeks). The transthoracic esophagectomy was the favored surgical approach. Patients with severe cardiopulmonary co-morbidity underwent a transhiatal esophagectomy as the risk of complications associated with a transthoracic approach was considered too high.
Lymph node dissection around the celiac trunc was carried out in all patients. Gastric-tube reconstruction with a hand sewn cervical end to side anastomosis was the preferred technique for restoring the continuity of the digestive tract.

Pathological analysis
The resection specimen was evaluated using a standard protocol, with emphasis on margins, tumor type, extension of the tumor, and presence of lymph nodes. The 7th edition of the International Union Against Cancer (UICC) was used for TNM-classification, tumor grade, and stage grouping.[12] For all transthoracic esophagectomy, a two-field lymph node dissection was performed including mediastinal, periesophageal and celiac lymph nodes.

The (circumferential) resection margins were evaluated using the College of American Pathologist (CAP) criteria.[13]

Statistical analysis

Statistical analysis was performed using SPSS version 15.0 (SPSS, Chicago, IL). We considered a $p<0.05$ to be statistically significant. All skewed continuous data were presented as medians with range. Multivariate logistic regression analysis was performed for all outcomes with $p<0.10$ in the univariate analysis.

Survival time was calculated as the duration from the day of start of chemotherapy to death or the last date of follow-up. Disease-free interval was calculated from the day of start of chemotherapy to the day of definitive diagnosis of recurrent tumor. All patients were evaluated according to the intention-to-treat analysis.

RESULTS

Baseline characteristics

Baseline characteristics are summarized in Table 1. Patients included 80 men and 13 women, with a median age of 63 years (range: 36–78) and a BMI of 26,4 (range 19-36kg / m2). All patients had locally advanced cancer. Co-morbidity, consisting of a history of vascular, cardiac, pulmonary and oncologic disease, was observed frequently within this cohort.

Toxicity of chemotherapy

As a first determinant of toxicity, we assessed the ability to deliver the planned treatment schedule (Figure 1). All 3 planned preoperative cycles were administered in 65 patients (69.9%). Postoperative chemotherapy was initiated in 38 patients (41%). The reasons for not receiving postoperative adjuvant chemotherapy could be separated in two main problems. The first main reason was the toxicity of the preoperative chemotherapy mainly due to unresolved toxicity or early stopping pre-operative chemotherapy. The other main event was post-operative problems with difficulty in recovery and post-operative complications. Finally, 25 patients (27 %), completed 3 preoperative and 3 postoperative cycles. After the first course of chemotherapy, 2 patients died due to DPD deficiency.

In 68 patients (73.1%), adverse events (AE) (grade ≥1) occurred. These led to the early discontinuation of treatment in 31 (33.3%) patients. Grade 3 and 4 non-hematological adverse events in the pre-operative chemotherapy cycles mainly consisted of thromboembolic events in 15 patients (16.2%) of which 6 (6.5%) were clinically relevant pulmonary emboli (table 2). The other 9 thromboembolic events were sub clinical findings and observed on follow-up CT-scans. Cardiac complications were seen in 7 (7.5%) patients (Table 2).

Binary regression analysis showed that a history of cardiac (OR: 0.32 (95% CI:0.12 – 0.82), p: 0.018) and vascular disease (OR: 0.32 (95% CI: (0.12 – 0.81) p: 0.016) were associated with discontinuation of preoperative chemotherapy (table 3).

Multivariate analysis of all analyzed risk factors showed that a history of cardiac (OR: 0.33 (95%: 0.11-0.98), p=0.045) and vascular disease (OR: 0.31 (95% CI: 0.11-0.86, p: 0.024) were

Table 1. Baseline characteristics

	Cohort (*N*=93)
Age	
< 60 yr – no (%)	31 (33)
60 – 69yr - no (%)	44 (47)
≥70yr – no. (%)	18 (19)
Median – year	63
Range – year	36-78
Gender	
Male	80 (86)
Female	13 (14)
Smoking	
Yes	60 (65)
No	33 (35)
Alcohol	
Yes	61 (66)
No	32 (34)
BMI	
< 25 – no (%)	31 (33)
25 – 29.9 - no (%)	44 (47)
≥30 – no. (%)	18 (19)
Median	26,4
Range	19-36
History	
Cardiac	27 (29)
Vascular	45 (48)
Pulmonal	12 (12)
Oncologic	5 (5)
Site of tumor	
Lower oesophagus – no. (%)	75 (80)
GEJ – no. (%)	18 (19)
Stomach	0 (0.0)
Clinical stage (EUS – TNM7)	
T2N0 – no. (%)	4 (4)
T2N1 – no. (%)	2 (2)
T2N2 – no. (%)	1 (1)
T3N0 – no. (%)	17 (18)
T3N1 – no. (%)	23 (24)
T3N2 – no. (%)	29 (31)
T3N3 – no. (%)	7 (7)
T4aN3 – no. (%)	4 (4)
No pass	6 (6)
Length of tumor	
0.0-3.9 cm – no (%)	28 (30)
4.0-7.9 cm – no (%)	51 (55)
8.0-11.9 cm – no (%)	14 (15)
Median -cm	4.0
Therapy	
ECX – no (%)	78 (84)
EOX – no (%)	13 (14)
ECF – no (%)	2 (2)

* percentages may not total 100 because of rounding

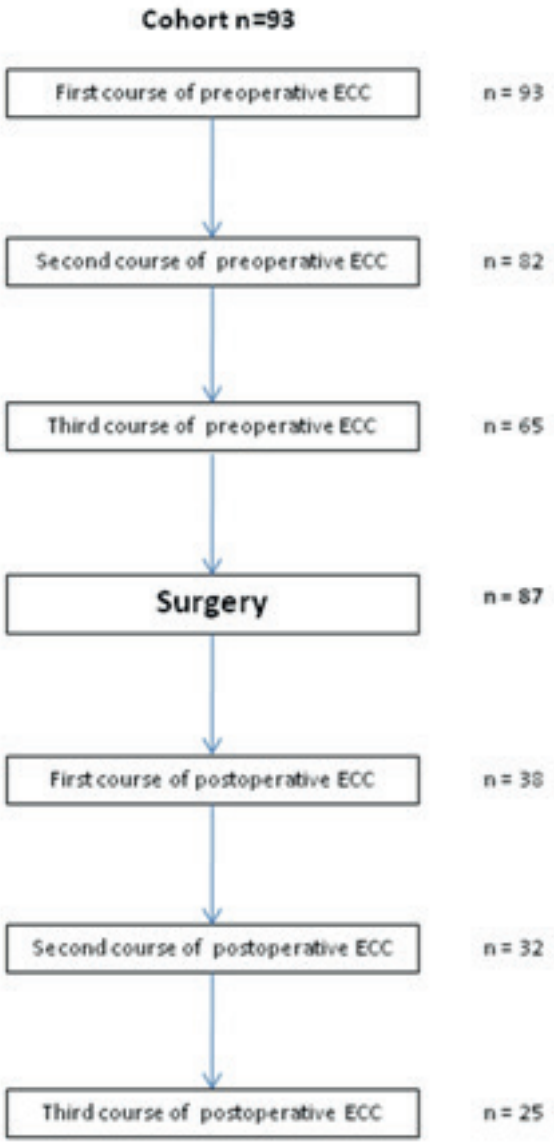

Figure 1. Feasibility Flowchart.
The flowchart shows the feasibility of ECC and ECF chemotherapy for our cohort.

associated with the occurrence of grade ≥3 adverse events. Out of 93 patient, 38 (41%) underwent postoperative adjuvant chemotherapy. Toxicity of the post-operative chemotherapy was shown in table 2.

Surgical results and postoperative complications

After the first course of chemotherapy, 2 patients died due to DPD deficiency and 3 patients developed metastases and 1 patient an inoperable tumor before surgery at re-evaluation after the 2nd course of chemotherapy. In total 87 (93.5%) patients underwent surgery with a median time between the completion of chemotherapy and surgery of 36 days (range 12–118 days). Transthoracic esophagectomy was performed in 51 patients (58.6%), transhiatal esophagectomy in 35 patients (40.2%) and distal esophagectomy combined with total gastrectomy in one patient (1.1%)

Postoperative complications occurred in 55 (63.2%) patients (Table 4). These complications

Table 2. Pre and post operative haematological toxicity and non-haematological toxicity (Grade 3,4 and 5)

Cohort (*N* (%))	**Preoperative (n=93)**		**Postoperative (n=38)**	
	Grade 3 and 4	**Grade 5**	**Grade 3 and 4**	**Grade 5**
Thromboembolic event	15 (16.1)		1 (2.6)	
Neutropenia	14 (15.1)		5 (13.1)	
Leukopenia	13 (14.0)		1 (2.6)	
Nausea	9 (9.7)		2 (5.2)	
Vomiting	9 (9.7)		2 (5.2)	
Diarrhea	8 (8.6)		1 (2.6)	
Febrile neutropenia	6 (6.5)	2 (2.2)	1 (2.6)	
Hand-foot syndrome	6 (6.5)		2 (5.2)	
Mucositis	4 (4.3)		3 (7.9)	
Dehydration	4 (4.3)		1 (2.6)	
Cardiac complications	7(7.5)		0 (0.0)	
Hyponatremia	3 (3.2)		0 (0.0)	
Hypokalemia	3 (3.2)		0 (0.0)	
Anemia	2 (2.2)		0 (0.0)	
Sepsis	2 (2.2)		0 (0.0)	
Colitis	2 (2.2)		0 (0.0)	
Thrombocytopenia	1 (1.1)		0 (0.0)	
Hypertension	1 (1.1)		0 (0.0)	
Urinary tract infection	1 (1.1)		0 (0.0)	
Allergic reaction	1 (1.1)		0 (0.0)	
Anorexia	1 (1.1)		0 (0.0)	
Respiratory infection	1 (1.1)		0 (0.0)	
Syncope	1 (1.1)		0 (0.0)	
Hyperglycemia	1 (1.1)		0 (0.0)	
Fatigue	0 (0.0)		3 (7.9)	

Table 3. Univariate and multivariate analysis of the association between risk factors and completion of chemotherapy treatment during the 3 preoperative cycles

Characteristic	Unadjusted OR (95%CI), univariate	P	Unadjusted OR (95%CI), Multivariate	P
Age	**1.001 (0.951 - 1.055)**	**0.955**		
Gender	**0.964 (0.270 - 3.438)**	**0.955**		
BMI	**1.073 (0.940 – 1.224)**	**0.296**		
Smoking	**0.809 (0.316 – 2.071)**	**0.659**		
Alcohol	**0.683 (0.261 – 1.789)**	**0.438**		
Cardiac	**0.317 (0.123 – 0.818)**	**0.018**	**0.333 (0.114 – 0.977)**	**0.045**
Vascular	**0.316 (0.124 – 0.805)**	**0.016**	**0.309 (0.112 – 0.855)**	**0.024**
Pulmonal	**5.500 (0.674 – 44.851)**	**0.111**		
Oncologic	**1.770 (0.189 - 16.592)**	**0.617**		
Site of tumor	**1.647 (0.490 – 5.537)**	**0.402**		
Therapy	**1.954 (0.570 – 6.693)**	**0.286**		

Table 4. Postoperative complications *(N=87)*

	Cohort
None	32 (37)
Complications	55 (63)
Pulmonary	35 (40)*
Pneumonia	30 (35)
Atelectasis	8 (9)
Pulmonary embolism	5 (5)
Pneumothorax	2 (2)
Anastomotic leakage	16 (18)
Mediastinitis	4 (5)
Thorax empyema	2 (2)
Atrial fibrillation	9 (10)
Chylothorax	9 (10)
Vocal cord paralysis	8 (9)
Bleeding	4 (5)
Wound infection	4 (5)
Other	4 (5)#
In-hospital death	3 (3)

* 10 patients had more than 1 pulmonary event

3 sepsis, 1 tracheoesophageal fistula

were mainly pulmonary (42%), including 30 (34.5%) pneumonias (Table 4). Anastomotic leakages were observed in 16 patients (18.3%), resulting in mediastinitis in 4 patients (4.6%) and thoracic empyema in 2 patients (2.3%). Other post-operative complications occurred less frequently. Median post-operative hospital stay was 14 days (range 12-118 days). Postoperatively, 3 patients died corresponding to an in-hospital mortality rate of 3.4%. Caus-

es of death included sepsis due to anastomotic leakage, sepsis after tracheo-esophageal fistula and sepsis after pneumonia with respiratory insufficiency.
During follow-up, 33 of 87 (37.9%) patients who underwent surgery required dilatations because anastomotic stricture. The dilations resolved the dysphagia in all patients and eventually all patients were able to eat solid food and had an adequate food intake.

Pathological results
Pathological results were shown in table 3. Histology of the resection specimens revealed that a radical resection (R0-resection) was obtained in 81 patients (87% of the total population, 94% of all operated patients). No gross irradical resections (R2 resections) were performed. In 6 patients (6.4%) a microscopic irradical resection (R1 resection) was obtained, which included 5 patients with a positive circumferential resection margin and 1 patient with a positive distal resection margin.
Postoperative lymph node status showed that 25.3% of patients who were preoperatively clinically diagnosed with N1 disease, had N0 disease. In 10 patients (10.7%) the N0-stage, as assessed by EUS, was changed towards a N1 or higher -stage postoperatively. Moreover, 7 patients had no residual adenocarcinoma in the resection specimen or regional lymph nodes, corresponding to a pathological complete response (pCR) rate of 8%.

Survival
All 93 patients were included in the survival analysis. Median follow-up time was 60 months. With the current follow up, 51 patients (54.8% of all patients) had tumor recurrence, 12.9% locoregional recurrence only, 25.8% distant metastases only and 16.1% both. Until now, 53 (57.0%) patients died. After a median follow up of 60 months, median disease free survival

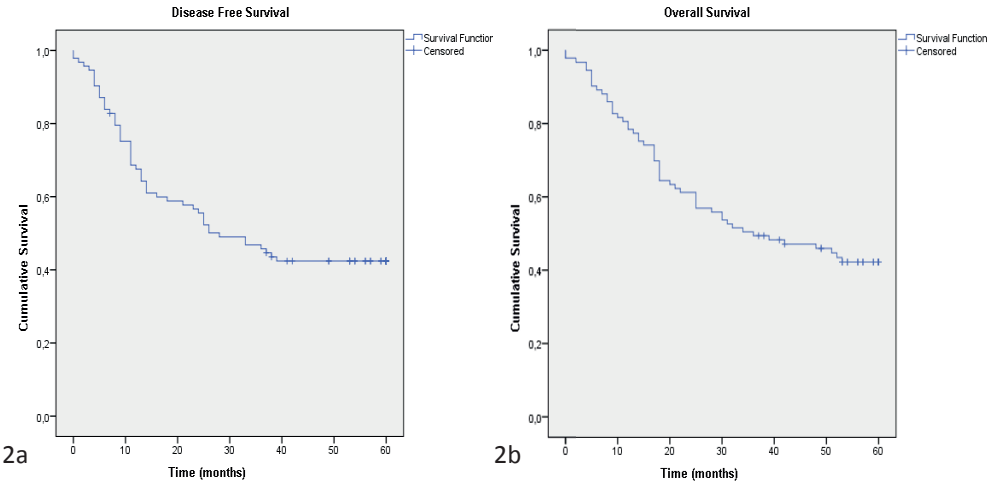

Figure 2a. Disease free survival for patients who underwent perioperative ECC chemotherapy for esophageal and GEJ adenocarcinoma. Figure 2b. Overall survival for patients who underwent perioperative ECC chemotherapy for esophageal and GEJ adenocarcinoma.

was 28 months and median overall survival was 36 months. Three year overall survival was 50% and 5 year overall survival 42%. Kaplan Meier Curves for disease free survival (DFS) were shown in figure 2a Kaplan Meier Curves for overall survival were shown in figure 2b.

DISCUSSION

This is the first series describing the use of perioperative ECC based chemotherapy in a homogeneous population of patients with adenocarcinoma of the esophagus that underwent esophageal resection. Only 66% of patients received the preoperative chemotherapy regimen of 3 ECC cycles due to toxicity. This toxicity was higher than initially reported in the MAGIC trial.[7] The observed high toxicity did however not negatively effect the ability to undergo surgery. In 93.5% of patients an esophageal resection could be performed with

Table 5. Pathological results *(N=87)*

	Cohort
Response	
Complete response	7 (8)
Radicality	
R0	81 (93)
R1	6 (7)
Lymph nodes	
Median – number (range)	20 (2-57)
Positive lymph nodes	
Median – number (range)	1 (0-29)
Ratio	5.0%
Tumor differentiation grade	
Poorly	44 (51)
Moderately	25 (29)
Well	11 (13)
NA	7 (8)
Pathological stage	
T0N0 – no. (%)	7 (8)
T1N0 – no. (%)	6 (7)
T1N1 – no. (%)	3 (3)
T1N2 – no. (%)	1 (1)
T2N0 – no. (%)	5 (6)
T2N1 – no. (%)	4 (5)
T2N2 – no. (%)	3 (3)
T2N3 – no. (%)	4 (5)
T3N0 – no. (%)	20 (23)
T3N1 – no. (%)	16 (18)
T3N2 – no. (%)	7 (8)
T3N3 – no. (%)	9 (10)
T4aN2 – no. (%)	1 (1)
T4aN3 – no. (%)	1 (1.1)

a radicallity rate of 94% and a pCR rate of 8%. Only 27% of patients completed pre- and postoperative chemotherapy, which showed that postoperative ECC chemotherapy was not feasible for patients with adenocarcinoma of the esophagus and GEJ.
We observed a significant number of clinically relevant thromboembolic and cardiovascular events (grade ≥3) in 16% of patients during the preoperative chemotherapy. The original report of the MAGIC trial, where the ECC chemotherapy schedule for gastro-esophageal cancer was described, did not report these events.[7] We chose to replace infusional 5-FU with oral capecitabine to increase convenience of treatment for our patients.[8,9] However, the choice of chemotherapy in our study may have affected the incidence of thromboembolic events. Both capecitabine and cisplatin were reported to cause vasoconstriction, vascular endothelium damage and were both reported to be associated with thromboembolic events in cancer.[14,15] A recent phase II trial with pre-operative ECC showed comparable results as obtained in the MAGIC trial with ECF treatment.[9] Although capecitabine is known to induce coronary spasms, capecitabine and infusional 5-FU show comparable cardiac toxicity.[16] Therefore, replacing 5-FU by capecitabine should not be a major factor in explaining the toxicity profile observed in our cohort.
Baseline characteristics showed that our patients matched to those randomized in the MAGIC trial chemotherapy arm with regard to age, sex and tumor size and stage (Table 1). However, 75 (80.6%) patients in our cohort had distal esophageal and 18 (19.4%) GEJ adenocarcinoma. This was different from the MAGIC trial, in which 74% of all patients had gastric adenocarcinomas.
Esophageal and gastric adenocarcinomas differ in their etiology, patient population and clinical characteristics. More importantly the surgical treatment is substantially different, comprising gastrectomy versus esophagectomy. The incidence of esophageal adenocarcinoma is increasing with approximately 5% each year, whereas the incidence of gastric adenocarcinomas is decreasing in Western countries.[17] In contrast to gastric cancer, esophageal adenocarcinoma has a clear sex preference with a 5 times higher incidence in men and is unrelated with low socioeconomic status.[18] The main risk factor for esophageal adenocarcinomas is gastro-esophageal reflux disease (GORD) and not H. pylori infection suggesting a different etiology.[19,20,21] These differences suggest that esophageal and GEJ adenocarcinomas form a separate entity from more distal gastric adenocarcinomas. Therefore translating results from trials predominantly including gastric cancer patients to esophageal and GEJ cancer patients might not be sensible.

Whether esophageal and esophagogastric-junction adenocarcinomas should be treated with perioperative chemotherapy or with preoperative chemoradiotherapy alone, is still unclear. Based on the intention to treat results of the MAGIC trial we decided to treat patients with esophageal adenocarcinoma with perioperative ECC chemotherapy. Within our cohort, this regimen is accompanied with serious toxicity as described before.
There are only two published randomized trials who directly compare chemotherapy with chemoradiotherapy. In 2009, Stahl et al. published the results of a phase III randomized controlled trial (POET trial) of preoperative chemotherapy compared with chemoradiotherapy in patients with locally advanced adenocarcinoma of the esophagogastric junction. The

study was closed early and statistical significance differences between the two arms were not reached. However, results show a trend towards a survival advantage for preoperative chemoradiotherapy compared with preoperative chemotherapy in adenocarcinomas of the esophagogastric junction.[22]

This is in concordance with results from a randomized phase II trial which were published in 2011.[23] Despite no significant difference in survival, histopathological response rates were significantly better in the chemoradiotherapy arm with acceptable toxicity in both arms. Thromboembolic complications were observed in 6% of patients in the chemoradiotherapy arm.[23]

Recently, the results from the Dutch CROSS-2 trial were published.[24] Patients with both squamous cell and adenocarcinoma of the distal esophagus ad GEJ were randomized between neoadjuvant chemoradiotherapy followed by surgery and surgery alone. In the chemoradiotherapy arm, the most commonly reported hematological adverse events were leukopenia (6%) and neutropenia (2%). The most common non-hematological adverse events were anorexia (5%) and fatigue (2%). The toxicity associated with chemoradiotherapy in this randomized controlled trial was acceptable and lower than observed in our cohort. Baseline characteristics did not differ between our cohort and the chemoradiotherapy arm of the CROSS-2 trial.[24] Resectability rates and postoperative results, such as pulmonary complications, anastomotic leakage and mortality were comparable.[24]

In our cohort, in 12.9% of all cases the first site of symptomatic tumor recurrence was locoregional or in the locoregional lymph nodes. Locoregional recurrence was observed in 7% of all cases after chemoradiotherapy followed by esophagectomy as reported in literature.[25] Distant metastases were observed in 26.8% of all patients, compared to 28% for patients who underwent neoadjuvant chemoradiotherapy and surgery.[25] The percentage of patients who had simultaneous locoregional recurrence and systemic metastases was 16% in our cohort and 13% after neoadjuvant chemoradiotherapy and surgery.[25]

The acceptable toxicity, in combination with better locoregional control suggests that neoadjuvant chemoradiotherapy is possibly a better therapeutic option for patients with resectable adenocarcinoma of the distal esophagus ad GEJ. However, prospective comparative studies are needed to prove the superiority of chemoradiotherapy over chemotherapy for this patient group. Patient selection and risk profiles are pivotal to obtain the best therapeutic strategy for esophageal adenocarcinoma patients.

In conclusion, we find a toxicity profile of perioperative chemotherapy in patients with esophageal and GEJ cancer patients that is more pronounced than expected. Postoperative ECC chemotherapy was not feasible. Translating findings from trials mainly containing gastric cancer patients towards esophageal cancer patients may lead to more toxicity and should thus be used with caution.

Conflict of interest statement

There was no conflict of interest.

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Chapter 3

Adding pre-operative radiotherapy plus cetuximab to peri-operative chemotherapy for resectable oesophageal adenocarcinoma: a single-centre prospective phase II trial

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AUTHOR SUMMARY

Background
Local and systemic recurrence are important sources of treatment failure following surgical resection of esophageal adenocarcinoma. We hypothesized that adding preoperative cetuximab and radiotherapy (cetux-RT) to perioperative chemotherapy would increase treatment efficacy with acceptable toxicity.

Patients and methods
In this prospective phase II trial patients were treated with three cycles of chemotherapy (epirubicin, cisplatin and capecitabine (ECX)), followed by cetux-RT. After surgery with curative intent, patients received three more cycles of ECX. Primary endpoints were efficacy determined with histopathological complete response (pCR) rate, and safety assessed with resectability rate.

Results
Of the twelve patients enrolled in this trial, six received at least one dose of cetux-RT. In five patients, Cetux-RT was not started due to adverse events (AEs) related to preoperative chemotherapy; one patient had progressive disease. Addition of cetux-RT was well tolerated and did not interfere with the resectability rate (100%). However, the pCR rate was 0 and 50% of patients experienced serious adverse events (SAEs) postoperatively.

Conclusion
Lack of initial signs of efficacy and a high incidence of postoperative SAEs prompted us to end this study prematurely. Perioperative ECX was associated with considerable toxicity and further treatment intensification is problematic.

Discussion
Long-term survival in patients with resectable esophageal adenocarcinoma remains poor (five-year survival 20-42%). Perioperative ECX chemotherapy has improved survival rates, but failed to deliver a significant proportion of pathologic complete responses. Since better locoregional control would probably improve survival rates, we added cetux-RT preoperatively (Figure 1).
We found that intensification of the preoperative treatment was poorly feasible as 42% of patients discontinued treatment due to toxicity of preoperative ECX. Addition of cetux-RT was well tolerated and did not interfere with the resectability rate; however the extension of the preoperative treatment led to a high postoperative complication rate. The combination of the extensive surgical procedure, the type of disease, the prolonged preoperative period and the high preoperative toxicity may have contributed to the postoperative toxicity of this regimen.

Although we did not complete full accrual, analysis of the six evaluable patients showed disappointing efficacy, as none of the resected tumors showed pCR. Previous studies with cetux-RT in patients with esophageal cancer did show an increase in pCR to 27-33%. However cetux-RT efficacy appears to be limited to squamous cell carcinomas.
Since there we no preliminary signs of efficacy we feel that our study does not warrant further investigation of cetux-RT for resectable esophageal adenocarcinoma. Furthermore, since intensification of ECX will be problematic, alternative multi-modality neoadjuvant schedules need to be identified.

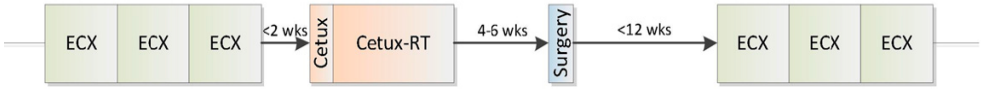

Figure 1. Treatment schedule. ECX: epirubicin (day 1,50mg/m$^{2)}$ cisplatin (day 1,60 mg/m^2) capecitabine (days 1-21, 1,250 mg/m^2) Cetux: cetuximab (day 1, 400 mg/m^2); Cetux-RT: cetuximab 250 mg/m^2 weekly, radiotherapy 45 Gy (25x1.8 Gy).
Abbreviations: Cetux, cetuximab; Cetux-RT, cetuximab plus radiotherapy; ECX: epirubicin, cisplatin, and capecitabine; wks, weeks.

Table 1. Adverse events related to cetux-RT

Name	*NC/NA	1	2	3	4	5	All Grades
Rash: acne/acneiform	16%	33%	50%	0%	0%	0%	83%
Fatigue (asthenia, lethargy, malaise)	50%	16%	33%	0%	0%	0%	50%
Nail changes	83%	0%	16%	0%	0%	0%	16%
Dysphagia (difficulty swallowing)	83%	0%	16%	0%	0%	0%	16%
Hypertension	83%	0%	16%	0%	0%	0%	16%
Rash: hand-foot skin reaction	83%	0%	16%	0%	0%	0%	16%
Dry skin	66%	33%	0%	0%	0%	0%	33%
Cough	66%	33%	0%	0%	0%	0%	33%
Nausea	66%	33%	0%	0%	0%	0%	33%
Pain in irradiated area	66%	33%	0%	0%	0%	0%	33%

* No Change from Baseline/ No Adverse Event

DISCUSSION

Over the past decades, the incidence of esophageal adenocarcinoma has increased in the Western world, partly attributable to the prevalence of risk factors as obesity and inactivity.[1,2] At our institution, perioperative chemotherapy with epirubicin, cisplatin, and capecitabine (ECX) is the standard treatment for patients with resectable esophageal adenocarcinoma based on results of the MAGIC trial[3]. Despite addition of this schedule, long-term survival remains poor. The five-year survival rate is estimated at 20-42%, depending on the number and location of lymph nodes involved, and is mainly limited by the high propensity for local recurrence and distant metastases.[4] Even after complete resection, locoregional recurrences occur in 30-40% of patients.[5]

Better local control is therefore important to improve long-term survival. Neoadjuvant concurrent chemoradiotherapy significantly reduces local recurrence rates and improves survival compared to surgery alone.[6–10] However, chemoradiation does not have a survival benefit over chemotherapy[9], presumably due to a lack of systemic efficacy, as chemoradiotherapy could not reduce the rate of distant recurrence compared to surgery alone.[6] To increase the systemic effects, induction chemotherapy could be an effective neoadjuvant therapy.[11] Chemotherapy followed by chemoradiotherapy is unfeasible because of significant toxicity.[12,13]

The epidermal growth factor receptor (EGFR) is overexpressed in a third of esophageal adenocarcinomas and is associated with poor prognostic factors.[14] Cetuximab is a monoclonal antibody that targets the EGFR. In combination with chemotherapy it has improved response rate and survival of patients with head and neck cancer[15] and advanced colorectal cancer[16]. The combination of cetuximab and radiotherapy mainly results in skin toxicity, which is more pronounced in irradiated areas.[17] This toxicity can be managed readily and does not overlap with the toxicity of perioperative chemotherapy. We performed a prospective single-arm phase II trial to investigate whether addition of preoperative cetuximab and radiotherapy (Cetux-RT) to standard care increases treatment efficacy with acceptable toxicity in patients with resectable esophageal adenocarcinoma.

Of the twelve patients enrolled in this trial, six (50%) underwent planned treatment with cetux-RT. Histopathological complete remission was chosen to assess local response to neoadjuvant therapy. Clinical response was deemed less reliable and could not predict prognosis, whereas histopathological evaluation had a good correlation with prognosis for patients with esophageal squamous cell carcinoma treated with chemoradiation.[18] Although we did not reach our primary endpoint, analysis of the six evaluable patients showed disappointing efficacy, as no pCR was attained. The pCR rate could be underestimated by our strict definition of complete response. However, our survival results do not support such an optimistic view. EGFR inhibition may therefore have limited efficacy in potentiating radiotherapy in esophageal adenocarcinoma. Previous studies with cetuximab-RT in patients with esophageal cancer did show an increase in pCR, with pCR rates ranging from 27-33%.[19–21] Two of these studies combined cetuximab with chemoradiotherapy; it is unclear how much of the effect is attributable to cetuximab.[19,20] Furthermore, De Vita et al. only observed pCR in squamous cell carcinomas.[21] This suggests that Cetux-RT may be less effective in esophageal adenocarcinomas, as noted by Lee et al.[22] Overall we feel that our study does not warrant further exploration of Cetux-RT for esophageal adenocarcinoma.

Cetux-RT did not interfere with the resectability rate (100%). However, all patients had postoperative complications and 50% (3/6) experienced a SAE postoperatively. The incidence of postoperative complications was 45% in the MAGIC trial, but it is unclear whether this includes all AEs or only the serious complications.[3] If the former is true, postoperative toxicity was indeed more pronounced in our study. In our Dutch retrospective cohort of 93 patients with resectable esophageal adenocarcinoma treated with perioperative ECX, postoperative complications were also more common (63%) than in the MAGIC trial. We believe that the type of disease, the surgical procedure, and the higher preoperative toxicity resulted in a

high complication rate. Furthermore, although Cetux-RT did not add to the toxicity in this trial, it prolonged the duration of preoperative treatment. Patients with an unfavorable preoperative nutritional condition experience significantly more complications after surgery for esophageal carcinoma.[23] Dysphagia, gastrointestinal side effects of preoperative therapy and a pro-inflammatory state induced by tumor cells all contribute to deterioration of the nutritional status.[24] With prolonged neoadjuvant therapy these factors potentially increase the risk of postoperative AEs.

Feasibility of the treatment protocol was limited by toxicity of preoperative chemotherapy, which led to discontinuation in 33% of patients. In the MAGIC trial, only 5% of patients could not complete all three preoperative cycles because of toxicity.[3] Replacement of 5-FU with capecitabine is unlikely to account for this difference, since a recent phase II trial with preoperative ECX showed feasibility comparable to the MAGIC trial.[25] The high toxicity rate of ECX in this trial could be a type II statistical error due to the small number of patients. Nevertheless, the toxicity profile is more pronounced in this patient group than previously described. Furthermore, the toxicity observed in the current trial corresponds with results from our Dutch cohort, in which pre-operative treatment with ECX was discontinued in 33% of patients due to AEs. The aforementioned trials studied patients with gastric cancer and esophageal cancer as a single population.[3,25] We solely included patients with esophageal adenocarcinoma, which could explain the increased toxicity. Chemotherapy toxicity profiles have not yet been compared for these two disease entities. To assess whether there truly is a difference in toxicity, adverse events should be reported separately for gastric and esophageal cancer in future trials.
In conclusion, perioperative ECX is a schedule with considerable toxicity, making further treatment intensification problematic. Furthermore, this trial showed no preliminary signs of efficacy of Cetux-RT. To increase survival of patients with resectable adenocarcinoma of the esophagus, alternative multi-modality neoadjuvant schedules need to be identified.

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Chapter 4

Preoperative Chemoradiotherapy and perioperative chemotherapy result in an equal survival for patients with resectable esophageal or gastroesophageal junction adenocarcinoma

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ABSTRACT

Purpose

This study compares neoadjuvant chemoradiotherapy (nCRT) to perioperative chemotherapy (pCT) for patients with resectable esophageal or gastroesophageal junction (GEJ) adenocarcinoma in terms of toxicity, postoperative complications, pathological response and survival.

Patientes and methods

313 patients with resectable esophageal or GEJ adenocarcinoma who treated with either nCRT (carboplatin/paclitaxel/41.4Gy, n = 176) or pCT (epirubicin, cisplatin and capecitabine, n = 137) were retrospectively analyzed and compared.

Results

Baseline and tumor characteristics were similar in both groups. The ability to deliver all planned preoperative cycles was higher in the nCRT group (92.0% versus 76.6%). nCRT was associated with a higher rate of grade 3-4 esophagitis. pCT was associated with a higher rate of grade 3-4 thromboembolic events, febrile neutropenia, nausea, vomiting, diarrhea, hand foot syndrome, mucositis, cardiac complications and electrolyte imbalances. In the pCT group two patients died during neoadjuvant treatment due to febrile neutropenia. Postoperative cardiac complications were higher in the nCRT group. All other postoperative complications and the in-hospital mortality rate (nCRT: 4.7% and pCT: 2.3%) were comparable. The pathologic complete response (pCR) rate was 15.1% following nCRT and 6.9% following pCT. Radicality of surgery was comparable (R0: 93.0% versus 91.6%). Median overall survival was 35 months after nCRT versus 36 months after pCT.

Conclusion

In conclusion, for patients with esophageal or gastroesophageal junction adenocarcinoma, chemoradiotherapy with paclitaxel, carboplatin and concurrent radiotherapy and perioperative chemotherapy with epirubicin, cisplatin and capecitabin lead to equal oncologic outcomes in terms of radical resection rates, lymphadenectomy, patterns of recurrent disease and (disease free) survival. However, neoadjuvant chemoradiotherapy is associated with a considerable lower level of severe adverse events and should therefore be the preferred protocol until a well powered randomized controlled trial provides different insights.

INTRODUCTION

Esophageal and gastroesophageal junctional (GEJ) adenocarcinoma are usually diagnosed in an advanced stage[1]. Due to rapid dissemination the prognosis is dismal in the majority of patients, resulting in overall survival rates between 15-25 percent[1,2]. Surgical resection is the cornerstone of curative treatment in selected patients without distant metastases. Key objective in this surgical approach is the achievement of a radical (R0) resection with an appropriate lymphadenectomy.

Unsatisfying results of surgery without neoadjuvant therapy incited development of multimodal approaches in the treatment of esophageal cancer[3]. Both neoadjuvant chemoradiotherapy (nCRT) and perioperative chemotherapy (pCT) have been demonstrated to show a survival benefit in multiple randomized clinical trials compared to surgery alone[4–9]. Results of an updated meta-analysis are in concordance with these results and provide strong evidence for a survival benefit of neoadjuvant chemoradiotherapy or chemotherapy over surgery alone in patients with esophageal adenocarcinoma[9].

Until now, direct evidence comparing nCRT and pCT is limited to 3 small randomized controlled trials and inconclusive regarding patient outcomes such as postoperative morbidity, mortality, radicality of surgery and survival[9–12].

In Europe and North America, chemoradiotherapy is nowadays the preferred neoadjuvant strategy. The most widely used chemoradiation regimen with paclitaxel, carboplatin and 41.4 Gy/23 fractions radiotherapy, is based on the CROSS-2 trial[8]. In the United Kingdom, perioperative chemotherapy with epirubicin, cisplatin and fluorouracil (ECF) is considered standard of care, based on the OEO 2 study and MAGIC trial[4, 5]. After publication of the REAL2 trial, in which the non-inferiority of substituting oral capecitabine for infused 5FU was shown, ECF was changed to ECX (epirubicin, cisplatin and capecitabine) in many clinics[13,14]. Until now, no direct comparisons have been made between pCT with ECX chemotherapy and nCRT with paclitaxel, carboplatin and 41.4 Gy/23 fractions.

The aim of this study was to compare perioperative ECX-based chemotherapy and chemoradiotherapy with paclitaxel, carboplatin and concurrent radiotherapy, in terms of toxicity, postoperative complications, pathological response, long term survival and disease recurrence.

PATIENTS AND METHODS

Patient population

Between April 2005 and November 2011 patients with resectable esophageal or junctional adenocarcinoma were treated in 3 high volume referral centers in The Netherlands with two different neoadjuvant regimes. In the Academic Medical Center (Amsterdam, The Netherlands) patients received neoadjuvant chemoradiotherapy (nCRT). In the University Medical Center Utrecht (Utrecht, The Netherlands) and Antonius Hospital (Nieuwegein, the Netherlands) received perioperative chemotherapy (pCT).

All patients who started neoadjuvant treatment were included in the analysis. They had WHO performance status 0-2. Underlying diseases, such as cardiac, vascular, pulmonary

or oncologic (other than esophageal), had to be stable and under control of their treating physician. All patients were discussed in a multidisciplinary oncology meeting with surgeons, gastroenterologists, medical oncologists, radiation oncologists and radiologists prior to treatment. Patients were not asked to provide informed consent for this specific study because the data was primarily recorded as part of standard care. The local ethics committees approved this approach.

Data collection
Primary endpoints were toxicity, postoperative complications, pathological response, long-term survival and disease recurrence. Data was extracted from the prospectively collected databases of all centers. Baseline characteristics included age, sex, BMI, comorbidity, and ASA score. Routine diagnostic work-up included upper endoscopy with biopsy, endoscopic ultrasound (EUS), computed tomography (CT) of thorax and abdomen and ultrasound of the neck region. Integrated ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET/)CT scanning and fine needle aspiration (FNA) of suspected lymph nodes were used on indication.
Preoperative and postoperative treatment characteristics were collected, including chemotherapy regimens, number of chemotherapy doses, dose reductions, dose density and the necessity to interrupt or cease treatment because of adverse events.

Chemotherapy
Patients were scheduled to receive three preoperative ECX chemotherapy cycles and three postoperative ECX cycles. Pre- and postoperative chemotherapy cycles consisted of intravenous administration of epirubicin (50 mg/m2) and cisplatin (60 mg/m2), followed by 1000 mg/m2 of capecitabine twice daily for 14 days or 625 mg/m2 of capecitabine twice daily for 21 days. Adaptations to the regimen such as dose reduction or change of regimen to oxaliplatin or 5-fluorouracil (5-FU) were applied when necessary. A second CT-scan after the second course of chemotherapy was made to monitor the therapeutic effect.

Chemoradiotherapy
On days 1, 8, 15, 22, and 29, carboplatin targeted at an area under the curve of 2 mg per milliliter per minute and paclitaxel at a dose of 50 mg per square meter of body-surface area were administered intravenously. A total radiation dose of 41.4 Gy conformal external beam radiotherapy was given in 23 fractions of 1.8 Gy each, with five daily fractions per week, starting on the first day of the first chemotherapy cycle[8].

Toxicity
Source data verification of all grade 3 and higher adverse events was performed by two separate observers (PCS, MCJA) according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.11. Grade 3, 4 and 5 adverse events were graded by consensus of two authors (PCS, MCJA).

Surgery

Different types of open and minimally invasive transthoracic and transhiatal surgery were performed during the inclusion period. Esophagectomy was performed by means of a transthoracic or transhiatal approach. A three-stage (minimally invasive) transthoracic esophagectomy was the standard surgical approach. Patients with a tumour located at the gastroesophaegal junction or reduced performance status (and therefore inability to undergo transthoracic esophagectomy) underwent transhiatal esophagectomy.

In short, during transhiatal esophagectomy, the esophagus was dissected under direct vision through the widened hiatus of the diaphragm up to the inferior pulmonary vein. The tumour and its adjacent lymph nodes were dissected en bloc. The paracardial, lesser curvature, left gastric artery (along with the lesser curvature), celiac trunk, common-hepatic-artery, and splenic-artery nodes were dissected, and a 3-cm wide gastric tube was constructed. After left-sided mobilization of the cervical oesophagus, the intrathoracic oesophagus was bluntly stripped from the neck to the upper level of the inferior pulmonary vein by using a vein stripper.

The transthoracic oesophagectomy was performed with a two-field lymphadenectomy. The specimen included the lower and middle mediastinal, subcarinal, and right-sided paratracheal lymph nodes (dissected en bloc). In the abdmominal phase, a lymph node dissection was performed identical to the transhiatal approach, as was the construction of a gastric tube and the cervical anastomosis. Finally, a feeding jejunostomy was placed.

Postoperative complications

All complications were graded using the modified Clavien-Dindo classification (MCDC) of surgical complications[16]. Anastomotic leakage included all clinical and radiological findings of anastomotic dehiscence or fistula. Thoracic empyema and mediastinitis following anastomotic leakage were defined as intrathoracic manifestation of anastomotic leakage.

Pathological analysis

The resected specimen was evaluated using a standard protocol, with emphasis on proximal, distal and circumferential resection margins, tumor type, extension of the tumor and the presence and localization of lymph nodes. The 7th edition of the International Union Against Cancer (UICC) was used for TNM-classification, tumor grade, and stage grouping[17].

Recurrent disease

For patients with recurrent esophageal cancer, the same protocol was used in all centers. First line palliative chemotherapy treatment consisted of capecitabine and oxaliplatin chemotherapy. Second line chemotherapy consisted of paclitaxel with ramucirumab or rinotecan or docetaxel. Irradiation was used to relieve symptoms of metastases.

Statistical analysis

Statistical analysis was performed using SPSS version 23.0 (SPSS, Chicago, IL, USA) To evaluate significance of differences between the two groups, the chi-square test was used for categorical variables and the Mann-Whitney U-test was used for non-parametric

continuous variables. Disease-free and overall-survival were analyzed using Kaplan-Meier curves. Differences in survival were analyzed using the log-rank test. A p-value of <0.05 was considered statistically significant.

Table 1: Baseline characteristics (n=313)

	Chemoradiotherapy (n=176) (n (%))	**Chemotherapy (n=137) (n (%))**	**P-value**
Age (y)	63	63	0.570
Gender (n (%))			
M	147 (83.5)	113 (82.5)	0.808
F	29 (16.5)	24 (17.5)	
BMI (kg / m²)	25.9	26.2	0.175
Co-morbidity			
Vascular	79 (44.8)	63 (46.0)	0.846
Cardiac	36 (20.4)	31 (22.6)	0.642
Pulmonal	17 (9.7)	17 (12.4)	0.438
Oncologic	12 (6.8)	10 (7.3)	0.869
ASA score (n (%))			
1	35 (19.9)	27 (19.7)	0.781
2	112 (63.6)	91 (66.4)	
3	28 (15.9)	19 (13.9)	
4	1 (0.6)	0 (0)	
Histology (n (%))			
Adenocarcinoma	176 (100)	137 (100)	
Location tumor			
Mid / Distal esophagus	129 (73.3)	104 (75.9)	0.589
Gastro-esophageal junction	47 (26.7)	33 (24.1)	
Neoadjuvant treatment*			
Chemoradiotherapy (CROSS)	176 (100)		
Chemotherapy (MAGIC)		137 (100)	
ECX		116 (84,7)	
EOX		19 (13.9)	
ECF		2 (1,5)	
Clinical stage*			
1	13 (7.4)	5 (3.6)	0.216
2	47 (26.7)	31 (22.6)	
3	116 (65.9)	101 (73.7)	
Surgical approach			
No operation	4 (2.3)	6 (4.4)	0.270
Transthoracic	115 (65.3)	78 (56.9)	
Transhiatal	57 (32.4)	52 (38.0)	
Total gastrectomy with distal esophagectomy	0 (0.0)	1 (0.7)	

*Due to rounding, some of the percentages do not add up.

RESULTS

Patient characteristics
Between April 2005 and November 2011, 176 patients underwent nCRT and 137 patients underwent pCT followed by esophagectomy. There were no significant differences in baseline characteristics (Table 1). The baseline characteristics were representative for patients with esophageal or junctional adenocarcinoma in West-European countries. Figure S1 (Supplemental1) represents a flow chart in which the clinical course of patients from both groups is shown.

Toxicity profile
As a first determinant of toxicity, the ability to complete the delivery of the planned treatment schedule was assessed (Figure S2, supplemental 2). The full 5 cycles of nCRT were administered in 162 of 176 patients (92.0%). A total of 105 out of 137 patients (76.6%) received the full treatment regimen of 3 preoperative cycles of chemotherapy (p=0.000) (Figure S2, supplemental 2). Postoperative continuation of chemotherapy was started in 60 patients (43.8%). The proportion of patients who underwent surgery after initiation of neoadjuvant therapy with curative intent was comparable in both groups (97.7% after nCRT vs. 95.6% after pCT; p = 0.293).
nCRT was associated with a higher rate of grade 3-4 esophagitis (p = 0.000). pCT was associated with a higher rate of grade 3-4 thromboembolic events (p = 0.000), febrile neutropenia (p = 0.038), nausea (p = 0.001), vomiting (p = 0.001), diarrhea (p = 0.001), hand foot syndrome (p = 0.005), mucositis (p = 0.005), cardiac complications (p = 0.002), and electrolyte imbalances. In the pCT group two patients died during neoadjuvant treatment due to febrile neutropenia (grade 5 toxicity). Pre- and postoperative toxicity for patients who underwent pCT are shown in Table 2.

Postoperative complications
Surgical results and postoperative complications are demonstrated in Table 3. In the chemoradiotherapy group, 104 of 172 patients (60.5%) had a complicated course whereas in the chemotherapy group, a complicated postoperative course was observed in 79 of 131 patients (60.3%), (p = 0.978). The incidence of postoperative cardiac complications was significantly higher in the chemoradiotherapy group compared to the chemotherapy group (17.4% vs. 6.9%, p = 0.006). The incidence of all other postoperative complications were comparable between both groups. There were no differences in median overall Clavien Dindo complication grades. Postoperative hospital stay was 11 days in the nCRT group and 13 days in the PCT group (p = 0.224) Postoperative overall in-hospital mortality was not significantly different between the chemoradiotherapy and chemotherapy group (4.7% vs. 2.3%, respectively; p = 0.276) (Table 3).

Pathological results
Pathological results are shown in Table 4. A R0 resection was achieved in 160 of 172 (93.0%) in the chemoradiotherapy group as compared to 120 of 131 patients (91.6%) in

Table 2: Haematological toxicity and non- haematological toxicity (Grade 3,4 and 5)

Preoperative toxicity						**Postoperative toxicity**	
Cohort (*n* (%))	**Chemoradio-therapy (n = 176)**		**Chemotherapy (n=137)**			**Chemotherapy (n = 60)**	
	Grade 3 and 4	**Grade 5**	**Grade 3 and 4**	**Grade 5**	**P-value**	**Grade 3 and 4**	**Grade 5**
Thromboembolic event	1 (0.6)		22 (16.1)		0.000	2 (3.3)	
Neutropenia	10 (5.7)		15 (10.9)		0.088	5 (8.5)	
Leukopenia	20 (11.4)		14 (10.2)		0.747	3 (5.0)	
Nausea	2 (1.1)		13 (9.5)		0.001	8 (13.3)	
Vomiting	2 (1.1)		13 (9.5)		0.001	8 (13.3)	
Diarrhea	0 (0.0)		9 (6.6)		0.001	2 (3.3)	
Febrile neutropenia	0 (0.0)		3 (2.2)	2 (1.5)	0.038	1 (1.7)	
Hand-foot syndrome	0 (0.0)		6 (4.4)		0.005	2 (3.3)	
Mucositis	0 (0.0)		6 (4.4)		0.005	3 (5.0)	
Dehydration	2 (1.1)		4 (2.9)		0.254	1 (1.7)	
Cardiac complications	0 (0.0)		7 (5.1)		0.002	1 (1,7)	
Hyponatremia	0 (0.0)		6 (4.4)		0.005	0 (0.0)	
Hypokalemia	0 (0.0)		4 (2.9)		0.023	0 (0.0)	
Anemia	1 (0.6)		2 (1.5)		0.422	0 (0.0)	
Thrombocytopenia	4 (2.3)		1 (0.7)		0.280	0 (0.0)	
Urinary tract infection	0 (0.0)		1 (0.7)		0.256	0 (0.0)	
Allergic reaction	0 (0.0)		1 (0.7)		0.256	0 (0.0)	
Anorexia	2 (1.1)		1 (0.7)		0.714	0 (0.0)	
Respiratory infection	0 (0.0)		1 (0.7)		0.256	1 (1,7)	
Peripheral neuropathy	0 (0.0)		2 (1.5)		0.108	2 (3.3)	
Fatigue	3 (1.7)		0 (0.0)		0.125	3 (5.0)	
Esophagitis	19 (11.0)		0 (0.0)		0.000	0 (0.0)	
Hypophosphatemia	0 (0.0)		1 (0.7)		0.256	0 (0.0)	
Tinnitus	0 (0.0)		0 (0.0)		1.000	1 (1,7)	

the chemotherapy group (p = 0.644). In the chemoradiotherapy group significantly more downstaging occurred with lower ypT-stages and more favorable tumor regression grades compared to the chemotherapy group (p = 0.007 and p = 0.000, respectively) (Table 4).

Survival and recurrence

All patients were included in the survival analysis (Figure 1). Median follow-up time was 42 months for nCRT and 41 months for pCT. Median overall survival was 41 months after nCRT versus 37 months after pCT (p = 0.707). Median disease free survival was 26 months for both nCRT and pCT (p=0.675).

In the nCRT group, 98 out of 172 patients (57%) had no signs of recurrent disease. In the pCT group 64 out of 131 patients did not have recurrent disease (49%, p = 0.467). Locoregional recurrence was observed in 8 patients (5%) in the nCRT group versus 10 patients in the pCT group (8%). Distant metastases were observed in 45 patients in the nCRT group (26%) and in 38 patients in the pCT group (19%). Combined locoregional and distant metastases were observed in 21 patients in the nCRT group (12%) versus 19 patients in the pCT group (15%) (Table S1, supplemental 3).

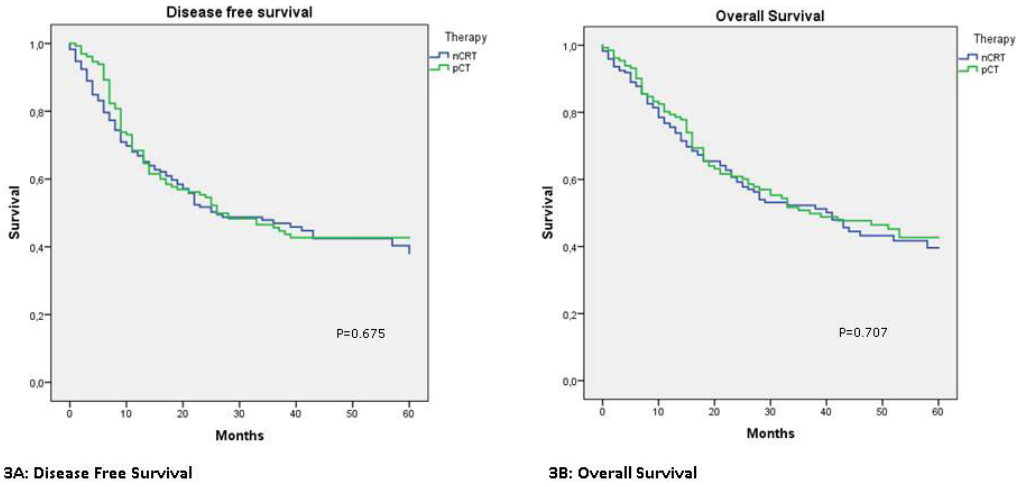

Figure 1. Disease free and overall survival for nCRT and pCT for esohageal and GEJ adenocarcinoma

DISCUSSION

This is the first study that compares neoadjuvant treatment with chemoradiotherapy using paclitaxel, carboplatin plus concurrent radiotherapy (CROSS[8]) and perioperative chemotherapy consisting of epirubicin, cisplatin and capecitabin (MAGIC[4]) for patients with resectable adenocarcinoma of the esophagus or GE-junction. Although nCRT was associated with better tumor downstaging and more favorable tumor regression grades, equal rates of radical resections and comparable disease-free and survival overall outcomes were observed. The risk of serious adverse events and the necessity to interrupt treatment was significantly higher in patients treated with pCT.

Table 3. Postoperative complications (n=303)

	Chemoradiotherapy (n=172)	Chemotherapy (n =131)	P-value
No complications (n (%))	104 (60.5)	79 (60.3)	0.978
Complications (n (%))	68 (39.5)	52 (39.7)	
Pneumonia (n (%))	35 (20.3)	39 (29.8)	0.059
Pulmonary embolism (n (%))	2 (1.2)	6 (4.6)	0.066
Anastomotic leakage (n (%))	22 (12.8)	25 (19.1)	0.134
Cardiac complications (n (%))	30 (17.4)	9 (6.9)	0.006
Chylothorax (n (%))	14 (8.1)	16 (12.2)	0.252
Vocal cord paralysis (n (%))	21 (12.2)	11 (8.4)	0.285
Bleeding (n (%))	1 (0.6)	4 (3.1)	0.094
Wound infection (n (%))	3 (1.7)	7 (5.3)	0.082
In-hospital mortality	8 (4.7)	3 (2.3)	0.276
Overall Clavien-Dindo grade (median)	2	2	0.967
Hospital stay (median days)	11	13	0.224

Table 4. Surgical and Pathological results (n=303)

	Chemoradiotherapy (n=172)	Chemotherapy (n =131)	P-value
Response (n (%))			
Complete response (Mandard 1)	26 (15.1)	9 (6.9)	0.000
Partial response (Mandard 2,3)	99 (57.6)	38 (29.0)	
No response (mandard 4,5)	47 (27.3)	85 (64.1)	
Radicality (n (%))			
R0	160 (93.0)	120 (91.6)	0.644
R1	12 (7.0)	11 (8.4)	
Lymph nodes (n (%))			
Median – number (range)	20	22	0.738
Pathological stage (n (%))			
0	26 (15.1)	9 (6.9)	0.007
1	34 (19.8)	16 (12.2)	
2	50 (29.1)	36 (27.5)	
3	62 (36.0)	70 (53.4)	

Oncologic results and survival

Both perioperative chemotherapy and neoadjuvant chemoradiotherapy have been found to improve survival for adenocarcinoma when compared to surgery alone[4–6, 8, 9]. In a meta-analysis by Sjoquist et al, two small randomized controlled trials directly comparing neoadjuvant chemoradiotherapy with chemotherapy were included[9]. These two trials

reported similar R0 resection rates between treatment groups, but significantly higher pathologically complete response rates and lower locoregional recurrence rates in the neoadjuvant chemoradiotherapy plus surgery groups. However, these findings did not result in a survival benefit for nCRT compared to pCT[10, 11].

In our study, similar results were shown. We showed that nCRT leads to better downstaging of esophageal adenocarcinomas than pCT, without differences in R0 resection rates between nCRT (93%) and pCT (92%) (p=0.644). No statistically significant differences in the risk of locoregional tumor recurrence, disease free survival and overall survival between nCRT and pCT at the long term follow up were found. After a follow up of approximately 41 months, median disease free survival was 26 months for both nCRT and pCT (p=0.675). Median overall survival was 41 months after nCRT versus 37 months after pCT (p = 0.707). Interestingly, survival results for pCT for esophageal adenocarcinoma were better than reported before, which could be attributed to improved preoperative staging techniques, improved peri-operative care and centralization of esophageal surgery.[4,18]

Based on the results of this study and in accordance with the literature, we conclude that nCRT and pCT are equally safe in terms of oncologic outcomes.

Table 5. Disease recurrence (n=303)

	Chemoradiotherapy (n=172)	Chemotherapy (n =131)	P-value
No Recurrence (n (%))	98 (57)	64 (49)	0.467
Recurrence (n (%))			
Locoregional	8 (5)	10 (8)	
Distant	45 (26)	38 (29)	
Both	21 (12)	19 (15)	

Toxicity and postoperative complications

As a first determinant of toxicity, we assessed the ability to deliver the planned treatment schedule. While 92.0% of nCRT patients completed the planned protocol, only 31.8% of patients completed the pCT schedule, emphasizing the low feasibility of the postoperative chemotherapy courses for patients with esophageal and GEJ adenocarcinoma. This can be attributed to the initial performance status and the morbidity associated with esophageal surgery and the higher level higher level of toxicity associated with pCT[14]. Compared to nCRT, in our series pCT led to a wider range and a higher frequency of severe adverse events.

Another important clinical parameter is the incidence of postoperative complications after nCRT or pCT. Beside a higher incidence of cardiac complications in the nCRT group, no statistically significant differences in postoperative complications and postoperative mortalitiy were observed between nCRT and pCT. This corresponds with the results from a meta-analysis describing postoperative morbidity and perioperative mortality in patients receiving neoadjuvant chemotherapy or chemoradiotherapy for resectable esophageal and gastro-esophageal junctional cancers[19].

This observation was confirmed in a recent study by Klevebro et al. in which 181 patients with esophageal adenocarcinoma and squamous cell carcinoma were randomized to neoadjuvant chemotherapy or neoadjuvant chemoradiotherapy[12]. It was concluded that

neoadjuvant chemoradiotherapy was not associated with a higher overall incidence of postoperative complications or postoperative mortality after esophagectomy compared to chemotherapy. However the complications that occurred in patients who received chemoradiotherapy were more severe with a higher median Clavien-Dindo score. This provides a level of ambiguity regarding the safety of adding radiotherapy as an adjunct to the neoadjuvant chemotherapy.

With no difference in oncologic outcomes, one could argue what the indication might be for both therapies. The rationale for the addition of irradiation to chemotherapy for resectable esophageal carcinoma is based on good evidence of increased tumor downsizing and improved local control[11].
Besides local control and downstaging, it is remarkable that carboplatin and paclitaxel based nCRT also exhibits a profound systemic effect which is reflected by a comparable percentage of systemic metastases as shown after pCT. This finding is supported by recent studies in which the systemic effect of these agents was demonstrated in both locoregional and metastatic adenocarcinoma of the esophagus[20,21].
Well-powered randomized controlled trials with long term follow up are needed to address the question which therapy regimen is preferable for treatment of resectable esophageal adenocarcinoma. The Neo-AEGIS randomized clinical trial (NCT01726452) directly compares the nCRT (CROSS) regimen with the pCT (MAGIC) regimen as described in our studies. Results are awaited in the coming years[22].

Finally, comparing results between high volume referral centers for esophageal carcinoma might introduce bias by indication, surgery and postoperative care differences. However, the process of data validation by two separate authors and comparable surgical training might limit the amount of bias in this study. Furthermore, our data represent consecutive patients in all centers and therefore the role of patient selection is minimized.

In conclusion, for patients with esophageal or gastroesophageal junction adenocarcinoma, chemoradiotherapy with paclitaxel, carboplatin and concurrent radiotherapy and perioperative chemotherapy with epirubicin, cisplatin and capecitabin lead to equal oncologic outcomes in terms of radical resection rates, lymphadenectomy, patterns of recurrent disease and (disease free) survival. However, neoadjuvant chemoradiotherapy is associated with a considerable lower level of severe adverse events and should therefore be the preferred protocol until a well powered randomized controlled trial provides different insights.

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S. van der Horst, physician assistant
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SUPPLEMENTARY INFORMATION

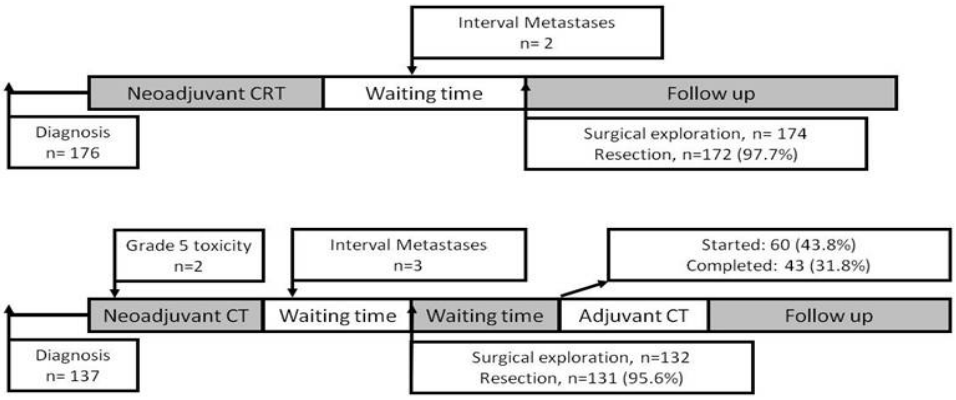
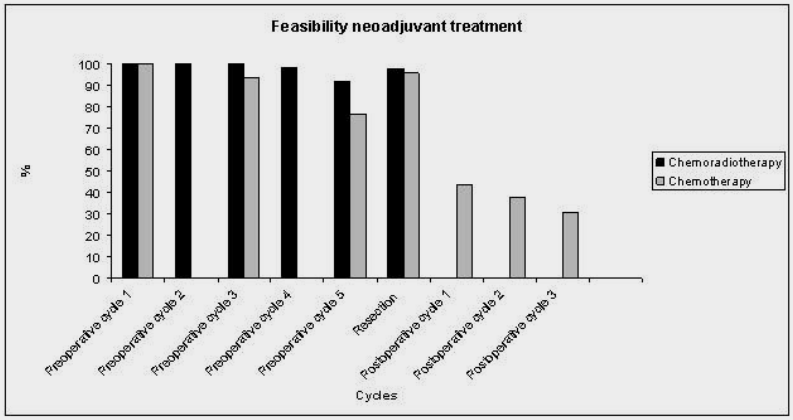


Figure 1. Clinical flowchart (Supplemental 1, S1)



	Chemoradiotherapy (n=176)	Chemotherapy (n=137)	P-value
Preoperative cycle 1	176 (100)	137 (100)	
Preoperative cycle 2	176 (100)	NA	
Preoperative cycle 3	176 (100)	128 (93.4)	0.001
Preoperative cycle 4	173 (98.2)	NA	
Preoperative cycle 5	162 (92.0)	105 (76.6)	0.000
Resection	172 (97.7)	131 (95.6)	0.293
Postoperative cycle 1	NA	60 (43.8)	
Postoperative cycle 2	NA	52 (38.0)	
Postoperative cycle 3	NA	42 (30.7)	

Figure 2. Feasibility of administration of neoadjuvant treatment for patients with esophageal or GEJ adenocarcinoma per cycle.

Chapter 5

Perioperative chemotherapy versus neoadjuvant chemoradiotherapy for esophageal or gastroesophageal junction adenocarcinoma: a propensity score matched analysis comparing toxicity, pathologic outcome, and survival

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ABSTRACT

Objectives

To evaluate toxicity, pathologic outcome, and survival after perioperative chemotherapy (pCT) compared to neoadjuvant chemoradiotherapy (nCRT) followed by surgery for patients with resectable esophageal or gastroesophageal junction (GEJ) adenocarcinoma.

Methods

Consecutive patients with resectable esophageal or GEJ adenocarcinoma who underwent pCT (epirubicin, cisplatin and capecitabine) or nCRT (paclitaxel, carboplatin, and 41.4 Gy) followed by surgery in a tertiary referral center in the Netherlands were compared. Propensity score matching was applied to create comparable groups.

Results

Of 193 eligible patients, 21 were discarded after propensity score matching; 86 and 86 patients who underwent pCT and nCRT, respectively, remained. Grade ≥3 thromboembolic events occurred only in the pCT group (19% vs. 0%, $p<0.001$), whereas grade ≥3 leukopenia occurred more frequently in the nCRT group (14% vs. 4%, $p=0.015$). No significant differences regarding postoperative morbidity and mortality were found. Pathologic complete response was more frequently observed with nCRT (18% vs. 11%, $p<0.001$), without significantly improving radicality rates (95% vs. 89%, $p=0.149$). Both strategies resulted in comparable 3-year progression-free survival (pCT vs. nCRT: 46% vs. 55%, $p=0.344$) and overall survival rates (49% vs. 50%, $p=0.934$). At 3-year follow-up, fewer locoregional disease progression occurred in the nCRT group (19% vs. 37%, p=0.024).

Conclusions

Compared to perioperative chemotherapy, neoadjuvant chemoradiotherapy achieves higher pathologic response rates and a lower risk of locoregional disease progression, without improving survival.

Key-words

Capecitabine, Cisplatin, Epirubicin, Carboplatin, Paclitaxel, Gastroesophageal junction adenocarcinoma, Esophageal adenocarcinoma, Chemotherapy, Radiotherapy, Chemoradiotherapy, Esophagectomy.

INTRODUCTION

Esophageal cancer is the sixth most common cause of cancer-related mortality worldwide, and the incidence of esophageal adenocarcinoma is rapidly increasing[1, 2]. Resection of the esophagus with en-bloc lymphadenectomy is the mainstay of curative treatment for patients with esophageal cancer[3]. However, a multimodality treatment approach is increasingly utilized since both perioperative chemotherapy (pCT) and neoadjuvant chemoradiotherapy (nCRT) have shown a survival benefit over surgery alone[4-7]. Response to neoadjuvant treatment has been associated with a higher percentage of radical surgical resection rates (R0), a reduced risk of tumor recurrence, and improved overall survival rates[8-10]. Currently, the optimal multimodality treatment strategy for resectable esophageal or gastroesophageal junction (GEJ) adenocarcinoma has not been established[5, 11].

The use of perioperative chemotherapy for esophageal cancer has yielded varying outcomes in terms of toxicity, pathologic outcome, and survival[12-14]. The MAGIC-trial showed a significant benefit of perioperative epirubicin, cisplatin, and fluorouracil chemotherapy over surgery alone with regard to R0 resection rates and survival[4]. Consecutive studies found that oral capecitabine was as effective as fluorouracil in this group of patients[15, 16]. Nevertheless, these treatment regimens are associated with a high toxicity profile, mainly consisting of thromboembolic events[4, 17]. In the recent CROSS trial, chemoradiotherapy followed by surgery was compared to surgery alone for patients with resectable esophageal cancer[10]. This trial recorded significantly increased R0 and survival rates, and achieved a significant rate of pathologic complete response (pathCR), favoring the multimodality group. This improvement was found to be clinically relevant for both squamous cell carcinoma and adenocarcinoma[6]. Due to the relatively low percentage of adverse events in combination with improved oncologic results, neoadjuvant chemoradiotherapy followed by surgery is now the preferred treatment strategy in the U.S. National Comprehensive Cancer Network (NCCN) guidelines[18]. Meanwhile, perioperative chemotherapy remains the preferred treatment option for resectable esophageal or GEJ adenocarcinoma according to the British Society of Gastroenterology guidelines[19].
Currently, direct comparisons between perioperative chemotherapy with epirubicin, cisplatin and capecitabine (ECC) and neoadjuvant chemoradiotherapy consisting of paclitaxel, carboplatin and concurrent radiotherapy (CROSS) for patients with esophageal or GEJ adenocarcinoma are limited. Therefore, the current study aimed to compare these two treatment regimens with regard to toxicity, pathologic outcome, and survival.

PATIENTS AND METHODS

Patient population
From a prospectively acquired database consecutive patients treated with perioperative ECC or preoperative nCRT according to CROSS with the intention to receive surgery for resectable esophageal or GEJ adenocarcinoma (Siewert type I and II) were analyzed. Patients were treated between October 2006 and September 2015 at our tertiary referral center. In

May 2012 the standard treatment with curative intent was switched from perioperative chemotherapy to neoadjuvant chemoradiotherapy. Diagnostic work-up consisted of endoscopy with biopsy, endoscopic ultrasound (EUS), ultrasonography of the neck, and either standalone computed tomography (CT) or integrated ^{18}F-fluorodeoxyglucose positron emission tomography (^{18}F-FDG PET)/CT scanning for clinical staging. All patients had a WHO performance status of 0-2 and biopsy-proven resectable adenocarcinoma (clinical stage T1N1-3 or T2-4aN0-3) with no evidence of distant metastases at initial staging.

Treatment protocols
Chemotherapy consisted of pre- and postoperative three-week cycles of an intravenous bolus of epirubicin (50 mg/m^2) and cisplatin (60 mg/m^2), followed by 625 mg/m^2 of capecitabine twice daily for 21 days[17]. The chemoradiotherapy regimen consisted of a total radiation dose of 41.4 Gy in 23 fractions of 1.8 Gy in 5 weeks with concurrent weekly administration of carboplatin (targeted at an area under the curve of 2 mg/ml per minute) and paclitaxel (50 mg/m^2 of body-surface area)[10]. After completion of neoadjuvant treatment, patients were scheduled for transthoracic esophagectomy with en-bloc two-field lymphadenectomy followed by gastric conduit reconstruction with cervical anastomosis end-to-side with hand-sewn continuous sutures in monolayer[20]. Patients with severe cardiopulmonary co-morbidity were scheduled for a transhiatal esophagectomy as the risk of complications associated with a transthoracic resection was considered too high.

Data collection and follow-up
Clinical patient characteristics, treatment details (e.g. chemotherapy regimens, surgical approach) and surgical outcome data (e.g. anastomotic leakage, hospital stay) were collected from the prospectively maintained database. Grading of toxicity was performed retrospectively by two independent observers according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0[21]. After esophagectomy, patients were routinely followed with an interval of 3 months in the first year, 6 months during the second year, and 12 months until 5 years after surgery. Diagnostic imaging was only performed in case of clinically suspected tumor recurrence. Recurrence was confirmed by histology or by clinical follow-up. Locoregional recurrence was defined as recurrence at the anastomotic site, mediastinum or upper abdomen, while distant recurrence was defined as recurrence in distant organs or distant lymph nodes. Progression-free survival (PFS) and overall survival (OS) were calculated from the date of first chemotherapy infusion to either the date of recurrence or last follow-up, or the date of death or last follow-up, respectively. Death from non-disease-related causes (e.g. myocardial infarction) were censored in the PFS analysis.

Postoperative course
Postoperative complications were graded according to the Clavien-Dindo classification[22, 23]. Definitions of the reported complications are presented in Table 3. Postoperative complications were prospectively registered and discussed weekly.

Pathological analysis
The resected specimens were processed according to a standardized protocol in accordance with the 7th edition of the International Union Against Cancer for ypTNM-classification[24]. The (circumferential) resection margin was evaluated using the College of American Pathologist criteria[25]. The degree of histopathologic tumor regression was graded according to the system proposed by Mandard et al[26].

Statistical analysis
Statistical analysis was performed using SPSS version 23.0 (IBM Corp., Armonk, NY) and R 3.1.2 open-source software (http://www.R-project.org; 'MatchIt' and 'optmatch' packages). To evaluate significance of differences between the two groups, the chi-square test was used for categorical variables, and the Student's T-test and Mann-Whitney U-test were used for parametric and non-parametric continuous variables, respectively. Overall survival and PFS were assessed using the Kaplan-Meier method, with the log-rank test to determine significance. A p-value of <0.05 was considered statistically significant.
To reduce the effect of confounding influences of covariates on the assessed outcome between the two study groups (pCT versus nCRT), propensity score matching was used to build comparable groups. First, a propensity score (the probability [ranging from 0 to 1] that a patient was assigned to the chemotherapy or chemoradiotherapy group given the individual profile of potential confounders) was calculated for each patient using logistic regression, based on all covariates (n=9) marked in Table 1. Next, propensity score matching with the 'optimal matching' technique was used to generate matched pairs of cases (1:1) in which the average within-pair difference in propensity scores was minimized[27]. Patients who fell outside the joint range of propensity scores (i.e. range of common support) were discarded.

RESULTS

Patient characteristics
In the study period a total of 106 patients underwent pCT and 87 underwent nCRT. In the original cohort differences were observed regarding patient and treatment-related characteristics. Using propensity score matching, 86 chemotherapy and 86 chemoradiotherapy patients could be matched without large imbalances of the used covariates. After propensity score matching balance among the two treatment arms improved substantially (Table 1). The results of the propensity score-matched cohort will be discussed here in further detail as this cohort consisted of groups with improved comparability.

Toxicity
A total of 66 out of 86 patients (79%) received the complete treatment regimen of three preoperative chemotherapy cycles. Postoperative continuation of chemotherapy was administered in 34 patients (40%). The 5 cycles of chemotherapy within the nCRT group were completed in 63 of 86 patients (73%), whereas 85 (99%) received all 23 fractions of radiotherapy. The main reason for not completing all chemotherapy cycles in the nCRT

Table 1. Comparison of baseline characteristics according to neoadjuvant treatment protocol, before and after propensity score matching.

	Original cohort			**Propensity score matched cohort**		
Variables	**pCT (n=106)**	**nCRT (n=87)**	***p* value**	**pCT (n=86)**	**nCRT (n=86)**	***p* value**
Male gender*	87 (82.1)	77 (88.5)	0.214	73 (84.9)	76 (88.4)	0.502
Age (years)*	62.5 ± 8.8	64.6 ± 8.1	0.099	62.9 ± 8.9	64.5 ± 8.1	0.232
BMI (kg/m^2)*†	26.3 ± 3.8	26.3 ± 4.1	0.873	26.4 ± 3.9	26.2 ± 4.1	0.744
ASA score*			0.183			0.445
I	30 (28.3)	16 (18.4)		21 (24.4)	16 (18.6)	
II	68 (64.2)	60 (69.0)		58 (67.4)	59 (68.6)	
III	8 (7.5)	11 (12.6)		7 (8.1)	11 (12.8)	
WHO performance status*			0.086			0.169
0	57 (53.8)	36 (41.4)		45 (52.3)	36 (41.9)	
1	49 (46.2)	51 (58.6)		41 (47.7)	50 (58.1)	
COPD	11 (10.4)	10 (11.5)	0.804	8 (9.3)	10 (11.6)	0.618
Cardiac co-morbidity	25 (23.6)	30 (34.5)	0.095	20 (23.3)	30 (34.9)	0.093
Diabetes mellitus	11 (10.4)	13 (14.9)	0.339	10 (11.6)	13 (15.1)	0.502
History of smoking*	59 (55.7)	60 (69.0)	0.059	47 (54.7)	59 (68.6)	0.060
Surgical approach*			**0.035**			0.485
Transhiatal	23 (21.7)	9 (10.3)		12 (14.0)	9 (10.5)	
Transthoracic	83 (78.3)	76 (89.7)		74 (86.0)	77 (89.5)	
Tumor length on endoscopy (cm)†	5.3 ± 2.5	4.8 ± 2.3	0.219	5.3 ± 2.6	4.8 ± 2.3	0.191
Clinical T-stage*‖			0.301			0.514
T1	2 (1.9)	2 (2.3)		1 (1.2)	2 (2.3)	
T2	9 (8.5)	15 (17.2)		9 (10.5)	15 (17.4)	
T3	91 (85.8)	68 (78.2)		73 (84.9)	67 (77.9)	
T4	4 (3.8)	2 (2.3)		3 (3.5)	2 (2.3)	
Clinical N-stage*§			0.323			0.866
N0	25 (23.6)	26 (29.9)		24 (27.9)	25 (29.1)	
N+	81 (76.4)	61 (70.1)		62 (72.1)	61 (70.9)	

Note. Data are numbers of patients with percentages in parentheses.

*Variables used for propensity matching.

†Data are mean ± standard deviation.

‖Clinical tumor stage (cT) classified according to the 7th edition of the International Union Against Cancer (UICC) tumor-node-metastasis (TNM) classification[24].

§Clinical lymph-node (cN) stage classified according to the 7th edition of the UICC TNM classification[24].

BMI: Body Mass Index. ASA: American Society of Anesthesiologists. WHO: World Health Organization. COPD: Chronic Obstructive Pulmonary Disease.

group was leukopenia. Grade ≥3 adverse events in the pCT group mainly consisted of clinically relevant thromboembolic events, which occurred only in the pCT group and not in the nCRT group (19 vs. 0%, p<0.001), 9 of which were symptomatic pulmonary emboli. The remaining 7 thromboembolic evens were asymptomatic (aortic or pulmonary emboli) and were detected during follow-up CT scans. Also grade ≥3 diarrhea occurred only in the chemotherapy group (8 vs. 0%, p=0.014). On the contrary, the incidence of grade ≥3 leukopenia in the nCRT group was significantly higher than observed in the chemotherapy group (14% vs. 4%, p=0.015). Other preoperative grade ≥3 adverse events did not differ significantly between the chemotherapy and chemoradiotherapy group (Table 2).
After surgery 34 (40%) of the patients in the pCT group started with adjuvant chemotherapy. The reason why 60% of the patients did not start the intended postoperative therapy was predominantly due to early cessation of the preoperative chemotherapy (n=20), postoperative complications or difficulty with recovery after surgery (n=20), postoperative mortality (n=3), disease progression (n=7), or patient decision (n=2). There were no statistical differences in preoperative patient-related characteristics, and tumor characteristics between patients who did and did not undergo postoperative chemotherapy.

Table 2. Comparative analysis of toxicity (grade 3 or higher) during neoadjuvant treatment.*

Toxicity criteria	**pCT (n=86)**	**nCRT (n=86)**	***p* value**
Thromboembolic event (grade ≥3)	16 (18.6)	0 (0.0)	**<0.001**
Neutropenia (grade ≥3)	2 (2.3)	7 (8.1)	0.168
Febrile neutropenia (grade ≥3)	5 (5.8)	2 (2.3)	0.443
Leukopenia (grade ≥3)	3 (3.5)	12 (14.0)	**0.015**
Thrombocytopenia (grade ≥3)	1 (1.2)	5 (5.8)	0.210
Anemia (grade ≥3)	1 (1.2)	0 (0.0)	1.000
Nausea (grade ≥3)	7 (8.1)	5 (5.8)	0.549
Vomiting (grade ≥3)	8 (9.3)	3 (3.5)	0.119
Diarrhea (grade ≥3)	7 (8.1)	0 (0.0)	**0.014**
Dehydration (grade ≥3)	2 (2.3)	3 (3.5)	0.650
Anorexia (grade ≥3)	1 (1.2)	0 (0.0)	1.000
Esophageal perforation (grade ≥3)	0 (0.0)	1 (1.2)	1.000
Gastric hemorrhage (grade ≥3)	0 (0.0)	1 (1.2)	1.000
Dyspnea (grade ≥3)	0 (0.0)	1 (1.2)	1.000
Allergic reaction (grade ≥3)	1 (1.2)	1 (1.2)	1.000
Acute coronary syndrome (grade ≥3)	1 (1.2)	0 (0.0)	1.000
Any adverse event (grade ≥3)	39 (45.3)	34 (39.8)	0.440
Premature discontinuation	20 (23.3)	23 (26.7)	0.597
Post-operative continuation	34 (39.5)	NA	NA

Note. Data are numbers of patients with percentages in parentheses.
*Adverse events graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0[21].

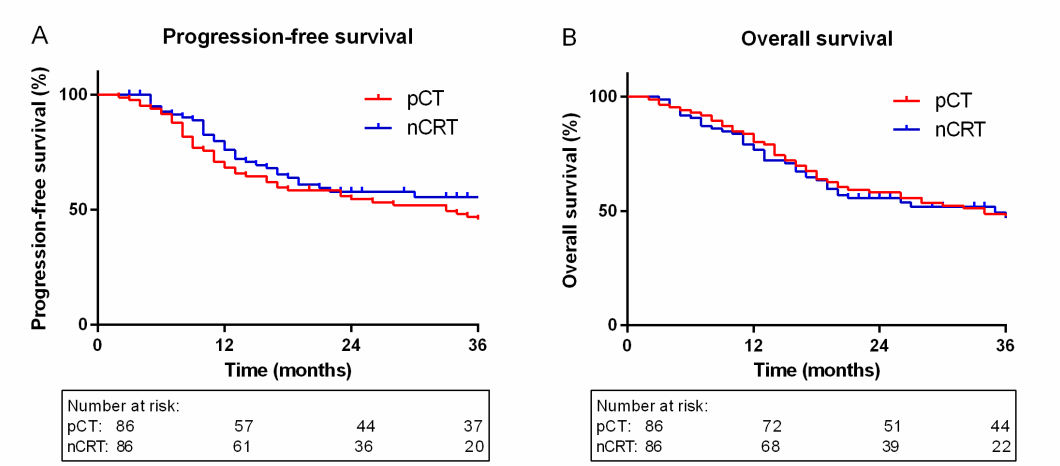

Figure 1. Comparison of progression-free survival (A) and overall survival (B) in propensity score-matched perioperative chemotherapy and neoadjuvant chemoradiotherapy followed by esophagectomy groups.

Postoperative course

In the chemotherapy group, 84 of 86 (98%) patients underwent esophageal resection, compared to 84 of 86 (98%) in the chemoradiotherapy group. Reasons to refrain from resection were disease progression during therapy (1 patient in the pCT group) and diagnosis of metastatic disease during surgery (1 patient in the pCT group and 2 patients in the nCRT group). Surgical results and postoperative complications are demonstrated in Table 3. In the pCT group, a complicated postoperative course occurred in 58 of 84 patients (69%), whereas in the nCRT group 61 of 84 patients (73%) had a complicated course (p=0.661). Severity and incidences of specific postoperative complications were comparable between both groups. Also, duration of hospital stay and postoperative 30-day mortality were comparable. In the pCT group, 5 of 84 (6%) patients died within 90 days after surgery, compared to 6 of 84 (7%), in the nCRT group (p=0.755). Of the 5 deaths in the pCT group 3 died due to postoperative complications and 2 patients died due to rapid-tumor progression without severe postoperative complications. In the nCRT group all 6 patients died due to severe postoperative complications.

Pathological assessment

Pathologic results are presented in Table 4. A pathCR was more frequently observed in patients who underwent nCRT compared to pCT (18% vs. 11%, respectively, p<0.001). Also a good response (Mandard 1 and 2) occurred more often in the nCRT group compared to the pCT group (37% vs. 17%, p=0.003). An R0 resection was achieved in 75 of 84 surgical patients (89%) in the chemotherapy group, compared to 80 of 84 (95%) in the chemoradiotherapy group (p=0.149).

Table 3. Comparative analysis of postoperative course.*

Outcome measure	pCT (n=84)	nCRT (n=84)	*p* value
Complicated postoperative course	58 (69.0)	61 (72.6)	0.661
Anastomotic leakage†	20 (23.8)	24 (28.6)	0.483
Pneumonia‡	29 (34.5)	29 (34.5)	1.000
Cardiac arrhythmia§	11 (12.6)	20 (23.8)	0.058
Chyle leak‖	14 (16.7)	12 (14.3)	0.870
Recurrent nerve paresis	6 (7.1)	8 (9.5)	0.577
Wound infection	3 (3.6)	5 (6.0)	0.469
Postoperative bleeding	2 (1.2)	2 (2.4)	1.000
Thromboembolic event	5 (6.0)	5 (6.0)	1.000
Clavien-Dindo grade¶			0.334
I	7 (8.3)	8 (9.5)	
II	28 (33.3)	19 (22.6)	
IIIa	0 (0.0)	3 (3.6)	
IIIb	6 (7.1)	14 (16.7)	
IV	15 (17.9)	11 (13.1)	
V	3 (3.6)	6 (7.1)	
Grade IIIb or higher	23 (27.4)	31 (36.9)	0.186
Duration of hospital stay (days)#	15 [11-23]	16 [11-27]	0.465
Duration of ICU stay (days)#	1 [1-4]	1 [1-4]	0.563
30-day mortality	1 (1.2)	2 (2.4)	1.000
90-day mortality	5 (6.0)	6 (7.1)	0.755

Note. Data are numbers of patients with percentages in parentheses.

*Of the 86 and 86 patients treated with neoadjuvant chemotherapy and chemoradiotherapy, 84 and 84 underwent surgery, respectively.

†Anastomotic leakage included all clinical and radiological findings of anastomotic dehiscence or fistula.

‡Pneumonia was defined by the universal pneumonia score[40].

§Cardiac arrhythmia were defined as any change in rhythm on an electrocardiogram requiring treatment.

‖Chyle leak was defined as elevated levels of triglycerides in intrathoracic fluid requiring treatment.

¶Clavien-Dindo classification, a surgical complication grading system[22,23].

#Data presented as median with interquartile range [IQR] between brackets.

Survival

In the intention-to-treat analysis (including all patients who did and did not undergo surgical resection after propensity score matching), median follow-up was 34 months (range 2-97) in the pCT group and 21 months (range 3-47) in the nCRT group, respectively. At 3 years follow-up, OS (49% vs. 50%; log-rank test p=0.934) and PFS (46% vs. 55%; log-rank test p=0.344) were comparable between the pCT and nCRT group, respectively (Figure 1). Further analysis showed that at 3 years follow-up, locoregional disease progression occurred less frequently in the nCRT group compared to the pCT group (19% vs. 37%, respectively; log-rank test p=0.024). No significant difference in the incidence of distant disease progression at 3 years was observed between the pCT and nCRT group (50% vs. 44%; log-rank test p=0.441), respectively.

Table 4. Comparative analysis of postoperative histopathology.*

Outcome	pCT (n=84)	nCRT (n=84)	*p* value
Pathologic T-stage†			0.131
ypT0	9 (10.7)	15 (17.9)	
ypT1b	12 (14.3)	10 (11.9)	
ypT2	12 (14.3)	19 (22.6)	
ypT3	48 (57.1)	38 (45.2)	
ypT4	3 (3.6)	2 (2.4)	
Pathologic N-stage‡			0.353
ypN0	36 (42.9)	42 (50.0)	
ypN1	48 (57.1)	42 (50.0)	
Tumor regression grade§			**<0.001**
I	9 (10.7)	15 (17.9)	
II	5 (6.0)	16 (19.0)	
III	17 (20.2)	27 (32.1)	
IV	18 (21.4)	22 (26.2)	
V	35 (41.7)	4 (4.8)	
Radicality of resection‖			0.149
R0	75 (89.3)	80 (95.2)	
R1	9 (10.7)	4 (4.8)	

Note. Data are numbers of patients with percentages in parentheses.

*Of the 86 and 86 patients treated with neoadjuvant chemotherapy and chemoradiotherapy, 84 and 84 underwent surgery, respectively.

†Pathological tumor stage (pT) classified according to the 7th edition of the International Union Against Cancer (UICC) tumor-node-metastasis (TNM) classification[24].

‡Pathological lymph-node (pN) stage classified according to the 7th edition of the UICC TNM classification[24].

The (circumferential) resection margin was evaluated using the College of American Pathologist (CAP) criteria.

§Histopathologic tumor regression graded according to the system proposed by Mandard et al.[26].

‖The (circumferential) resection margin was evaluated using the College of American Pathologist criteria[25].

DISCUSSION

In this propensity score-matched cohort study, outcomes of perioperative chemotherapy were compared to neoadjuvant chemoradiotherapy for patients with resectable esophageal or GEJ adenocarcinoma. No significant improvements were achieved with nCRT as compared to pCT in terms of radical resection rates or progression-free survival and overall survival. However, nCRT was associated with improved tumor downstaging and a higher pathCR rate compared to chemotherapy. This observation likely translated into the observed decrease in locoregional disease progression in the nCRT group.

According to recent literature, pCT and nCRT both improve survival compared to surgery

alone in patients treated for esophageal or GEJ adenocarcinoma[4, 6]. In two meta-analyses, indirect treatment comparisons have suggested a greater survival benefit of nCRT over pCT[5, 7]. However, in both meta-analyses the difference between the two groups did not reach statistical significance. This finding corresponds with the direct comparison in our study that showed no significant survival benefit for one of the regimens.

Until now, three randomized trials have made a similar attempt to directly compare nCRT with pCT for patients with esophageal or GEJ adenocarcinoma[28-30]. Stahl et al., randomly allocated 119 patients to either chemotherapy (cisplatin, 5-FU, leucovorin) or chemoradiotherapy (cisplatin, 5-FU, leucovorin, 30 and Gy) both followed by surgery[28]. The chemoradiotherapy arm showed a higher probability of pathologic complete response (2% after chemotherapy vs. 16% after nCRT, p=0.03) and a reduction in locoregional recurrence (41% after chemotherapy vs. 23% after nCRT; p=0.06). Although the study was closed early due to slow patient accrual, there was a trend towards a 3-year overall survival advantage (28% vs. 48%, p=0.07) for the nCRT group. In a comparable trial by Burmeister et al., 75 patients were randomized to receive either preoperative chemotherapy (cisplatin, 5-FU) or preoperative chemoradiotherapy (cisplatin, 5-FU, and 35 Gy)[29]. This study showed a higher histopathological complete response (13% vs. 0%) and R0 resection rate (100% vs. 89%) for patients treated with chemoradiotherapy compared to chemotherapy, respectively but no difference in survival was observed[29]. A recent randomized controlled trial of 181 patients by Klevebro et al., again showed a higher pathCR rate (28% vs. 9%; p=0.002) in patients treated with nCRT (platin, 5-FU, and 40 Gy) compared to neoadjuvant chemotherapy (platin, 5-FU), with comparable survival between the two groups [30].

Our finding that nCRT increases the pathCR rate corresponds with the studies discussed above. The nCRT group yielded a 18% pathCR rate compared to 11% in the pCT group ($p<0.001$), respectively. Additionally, in the current series a significantly lower incidence of locoregional tumor progression and a trend towards a higher R0 resection rate was found after nCRT. This supports the theory of effective tumor downstaging in this group. Pathologic response after neoadjuvant treatment is a major determinant of survival in patients with esophageal cancer[8, 26, 31-33]. Interestingly, in the current study and in the mentioned comparative studies, increased pathCR rates and improved local control did not translate into a significant survival benefit for the nCRT group. However, given that the majority of patients undergoing either nCRT or pCT will have distant disease progression, there is need for feasible_(adjuvant) treatments that result in effective systemic tumor elimination of micrometastases. As local control after nCRT is reasonable, currently the interest in adjuvant chemotherapy in these patients to increase systemic control is increasing. A recent cohort study has shown that this approach may improve survival in patients with residual nodal disease[34]. Future trials are underway and should answer whether the addition of new adjuvant therapies will improve survival by reducing distant disease progression[35, 36].

In addition to improving oncologic results, objective evaluation of the risk and benefits must be considered when comparing different types of neoadjuvant therapy. One of the well-established limitations of perioperative chemotherapy regimens is that adjuvant chemotherapy is less feasible than preoperative chemotherapy[4, 13, 37]. In the MAGIC and FNCLCC/FFCD trials, for example, the proportion of patients who received postoperative

chemotherapy was 55% and 48%, respectively[4, 13]. Also in the current study a limited number of patients initiated postoperative chemotherapy (40%). However, despite the fact that compliance with postoperative chemotherapy is often limited, a clear survival benefit of perioperative chemotherapy over surgery alone has been well established[4, 13]. The role of postoperative chemotherapy may be debated, as a recent meta-analysis showed no difference in survival between treatment with perioperative chemotherapy and preoperative chemotherapy only[38]. The feasibility problems of the currently available perioperative chemotherapy regimens favor the use of neoadjuvant treatment.

Another disadvantage of neoadjuvant therapies is the associated toxicity, which could contribute to an increase in postoperative morbidity and mortality[39]. In the current study, both treatment strategies caused substantial regimen-specific toxicity that are comparable with earlier reports[10, 15, 17]. Also, no significant difference with regard to severity and incidence of postoperative morbidity or perioperative mortality between the pCT and nCRT groups were observed. These results are consistent with two recent meta-analyses that compared postoperative morbidity and mortality between patients treated with pCT or nCRT for esophageal (adeno)carcinoma and found no differences[40, 41]. On the other hand, in a recent randomized controlled trial more severe postoperative complications were observed after nCRT compared to chemotherapy[42].

The anastomotic leak rates of 24-29% in the current series were substantially higher compared to other studies[40, 43, 44]. However, our definition of anastomotic leakage was rather un-restricted including any sign of clinical, endoscopic or radiological prove of anastomotic leakage. As such, the leakage rate in this study appears to be comparable with the leakage rates of 22% to 30% that were presented in the recent CROSS-trial[10].

Strengths of this study include the use of predominantly prospective collected data. Furthermore, the sample size of this study is relatively large compared to previous comparative studies. Lastly, this is one of the first studies that directly compares two highly recommended multimodality treatment regimens (ECC vs. CROSS) for patients with esophageal or GEJ adenocarcinoma. Potential limitations of this study include its retrospective character and lack of randomization. In order to adjust for the potentially resulting confounding bias, propensity score matching was performed to improve the comparability of the two groups. However, the inability of propensity score matching to adjust for unknown confounders that could explain some of our findings remains a limitation. Due to the inclusion of two groups receiving treatment in different time periods it is possible that unknown confounders have changed over time which to some extent might have created differences between the two groups. Survival, for example, could have been influenced by developments in available therapies for treatment of esophageal adenocarcinoma upon recurrence. Recent studies have demonstrated that treatment with ramucirumab monotherapy and ramucirumab combined with paclitaxel improves survival compared to placebo in patients with recurrent GEJ adenocarcinoma[45, 46]. Therefore, treatment of recurrent disease may not have been the same throughout the whole study period, which may have improved the prognosis of the nCRT patients that were included later in this study. Also, the addition of a diagnostic ^{18}F-FDG PET/CT as part of initial staging in more recent years may to some extent have improved the prognosis of these patients, through improved patient selection for treatment

with curative intent. Furthermore, the median-follow up in the nCRT group was relatively short. Therefore, subtle effects on progression-free survival and overall survival cannot be excluded. Currently, several randomized trials comparing chemotherapy and nCRT regimens are underway and should resolve the limitations in the current literature (CROSS versus MAGIC [NCT01726452], NEOSCOPE-trial [NCT01843829][47], TOPGEAR-trial [NCT01924819] [48]).

In conclusion, perioperative chemotherapy and neoadjuvant chemoradiotherapy are both associated with substantial regimen-specific adverse events and postoperative morbidity. Neoadjuvant chemoradiotherapy achieves higher pathologic complete response rates and a lower risk of locoregional disease progression, with similar survival compared to perioperative chemotherapy.

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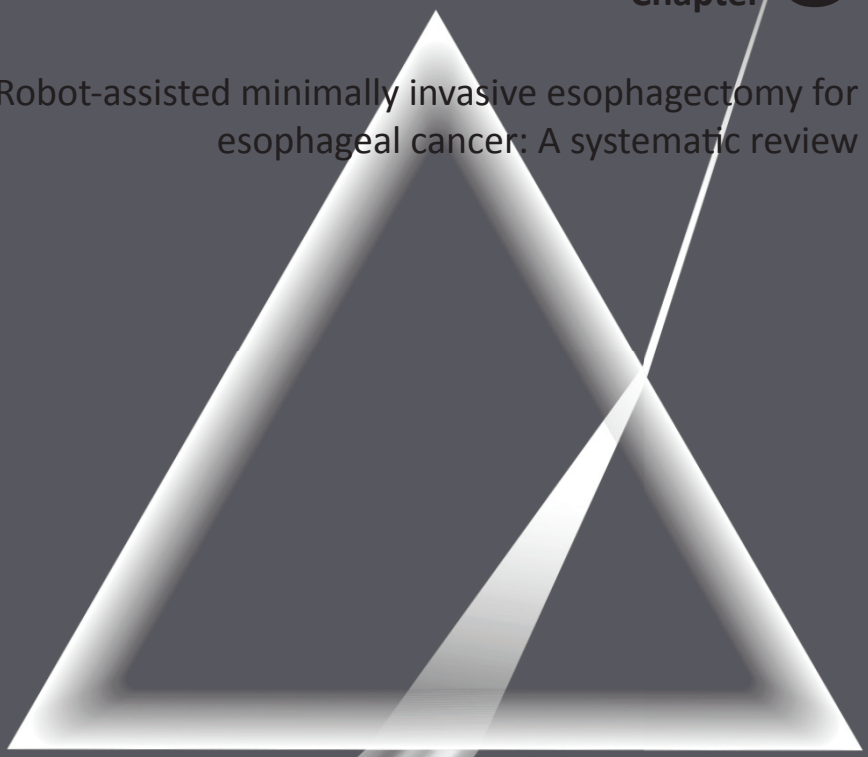
PART II

Robot assisted minimally invasive esophagectomy for esophageal cancer (RAMIE)

Chapter 6

Robot-assisted minimally invasive esophagectomy for esophageal cancer: A systematic review



J.P Ruurda, P.C. van der Sluis, S. van der Horst, R. van Hillegersberg

J Surg Oncol. 2015; 112:257-65

ABSTRACT

This paper describes the technique of robot-assisted minimally invasive esophagectomy. (RAMIE) Also, a systematic literature search was performed. Safety and feasibility of RAMIE was demonstrated in all reports. Short term oncologic results show radical resection rates of 77-100% and 18-43 lymph nodes harvested. RAMIE offers great visualization of the mediastinum and enables meticulous dissection in the mediastinum from diaphragm to thoracic inlet.

Keywords
RAMIE
esophageal surgery
RATE
ROBOT-assisted
minimally invasive

BACKGROUND

Radical esophagolymphadenectomy is the cornerstone of the multimodality treatment of esophageal cancer.[1] A transthoracic esophagectomy is the preferred surgical approach allowing for optimal resection of the tumor and the surrounding lymph nodes.[2] However, the percentage of cardiopulmonary complications associated with this procedure is high (50-70%).[2]
A minimally invasive approach reduces the surgical trauma of an open (transthoracic) esophagectomy, which results in lower rates of morbidity and mortality.[3] Short-term oncologic results for MIE are comparable with oncologic results after open esophagectomy.[3] However, minimally invasive esophagectomy (MIE) is not widely adapted around the world. In the UK, for instance, only 15,6 % of all esophagectomies are performed by minimally invasive.[4] Some centers even stopped their MIE programs because of safety issues. Whereas the thoracoscopic approach has obvious advantages for the patients, surgeons choose for an open thoracic approach because of their concern of the high technical complexity of a minimally invasive procedure and therefore MIE is not routinely applied around the world as a standard approach for esophageal cancer.[4]
A robot-assisted thoraco-laparoscopic minimally invasive esophagectomy (RAMIE) was initiated at our institute from 2003.[5,6] We envisioned the benefits of robotic assistance to aid with the complexity of this minimally invasive procedure.[7] The main goal was reducing the morbidity of esophagectomy, while enabling a safe and oncologically optimal resection. The aim of this paper is to describe the technical aspects of RAMIE and to review the literature on RAMIE in a systematic way for study design, postoperative complications and oncologic results.

METHODS

Indications

In general selection criteria to RAMIE are identical to standard transthoracic open or minimally invasive esophagectomy. Some relative contra-indications exist, such a prior thoracic surgery and poor performance status (especially poor pulmonary functioning). To our experience RAMIE is especially indicated in procedures where a dissection of the upper thoracic region (mediastinal lymph node stations 2 and 4 or proximal intrathoracic esophageal tumors) has to be performed. In most studies, results for RAMIE for early stage esophageal carcinomas were reported.

Operative Procedure at UMCU

For the thoracic phase, the patient is positioned in the left lateral decubitus position, tilted 45° towards the prone position. The robotic system (daVinci Si system, Intuitive Surgical Inc., Sunnyvale, CA, USA) is brought into the field at the dorsocranial side of the patient. Three ports are placed for the robotic system as well as 2 thoracoscopic ports for the assistant (figure 1). After selective desufflation of the right lung and incision and installation of the operation robot , the pulmonary ligament is divided. Hereafter, the parietal pleura

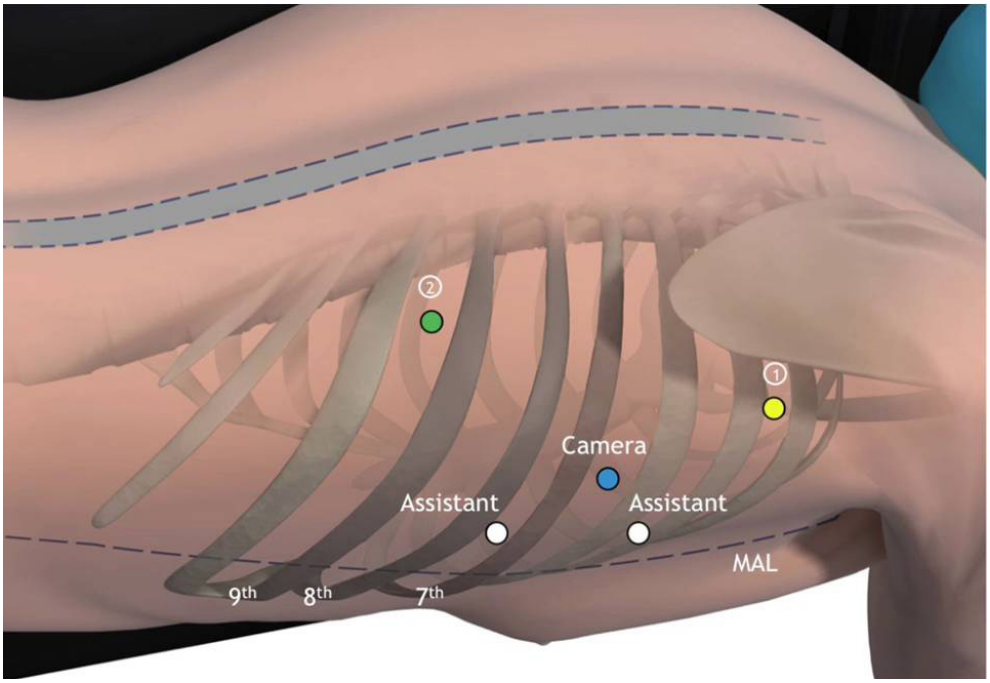
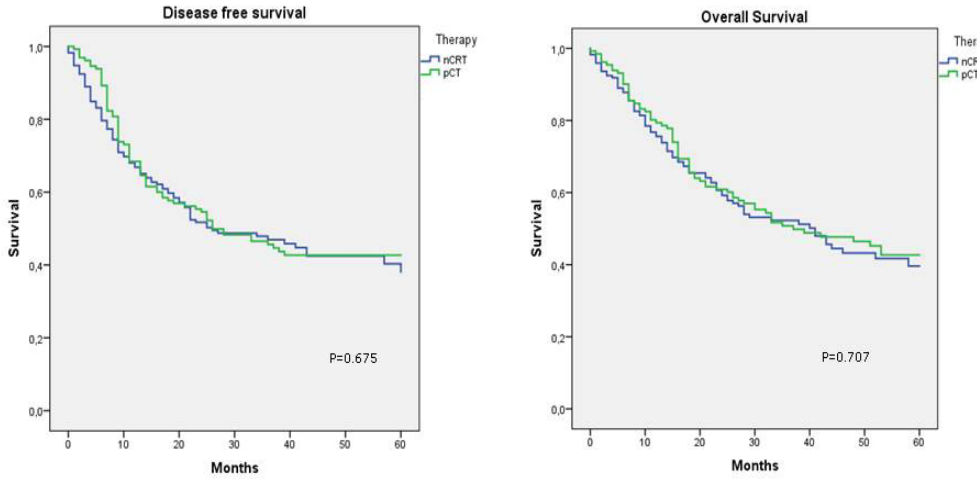


Figure 1. Robotic arm and trocars position in the thoracic phase of RAMIE.
1: left robotic arm, 2: right robotic arm, camera: robotic camera, assistant: assistant trocars ports (6).

is dissected at the anterior side of the esophagus from the diaphragm up to the azygos arch. The azygos vein is ligated with Hem-o-lok (Teleflex Medical, Weck Driv, NC, USA) and divided. Dissection of the parietal pleura is continued above the azygos arch to establish dissection of the right paratracheal lymph nodes. At the posterior side of the esophagus, the parietal pleura is dissected cranially to caudally along the azygos vein, including the thoracic duct. The thoracic duct is clipped with a 10-mm endoscopic clipping device (EndoclipTM II; Covidien, Mansfield, Massachusetts, USA) to prevent chylous leakage. To facilitate esophageal mobilization a penrose drain is placed around the esophagus to manipulate the esophagus for further mobilization. The esophagus is resected en bloc with the surrounding mediastinal lymph nodes. Figure 2 shows pictures of the thoracic phase of the operation. The resection specimen will contain the same lymph nodes as described for the open procedure. For the abdominal phase, the patient is placed in supine position. Figure 3 shows the position of the laparoscopic trocars. The lesser omentum is opened and transected closely to the liver, until the left crus of the diaphragm is reached. Hereafter, the greater gastric curvature is dissected using a harmonic ace. An abdominal lymphadenectomy is performed including lymph nodes surrounding the celiac trunk, along the left gastric and splenic artery and the lesser omental lymph nodes. The left gastric artery is ligated with Hem-o-lok (Teleflex Medical, Weck Driv, NC, USA) and transected at its origin.

Figure 1: Disease free and overall survival for nCRT and pCT for esophageal and GEJ adenocarcinoma



3A: Disease Free Survival **3B: Overall Survival**

Figure 2. Thoracic phase of RAMIE.
2aThe azygos vein (AV) is identified and ligated with Hem-o-lok 2b. The thoracic duct (TD) is extensively clipped and divided at the level of the diaphragm. 2c. A penrose drain (PD) is placed to facilitate mobilization of the esophagus (E). 2d. Lymph node dissection at the level of the carina (C)

Through a left-sided vertical incision along the sternocleidomastoid muscle, cervical phase of esophagectomy is initiated to facilitate mobilization of the cervical esophagus. No formal cervical lymph node dissection is carried out. The cervical esophagus is transected and a cord is attached to the specimen. The dissected esophagus with en-bloc the surrounding lymph nodes are pulled down through the mediastinum under laparoscopic view.
Hereafter, the left para-umbilical trocar port is widened to a 5-7-cm transverse transabdominal incision. The resection specimen is removed through this incision with a wound drape (3M, St. Paul, Minnesota, USA) to create the gastric conduit extracorporally. A linear stapler (GIATM 80, 3•8 mm; Covidien, Mansfield, Massachusetts, USA) is used to create a gastric conduit 4 cm wide, which is routinely oversewn. The gastric conduit is pulled up through the mediastinum along the original anatomic tract of the esophagus with the aid of a plastic tube (laparoscopic camera bag). A cervical handsewn end-to-side anastomosis is created between the gastric tube and the cervical esophagus using a 3/0 polydioxanone single-layer running suture. A feeding jejunostomy is placed in the second loop after the ligament of Treitz for postoperative feeding. The abdomen is closed in layers with PDS loop for the fascia and skin intracutaneously with monocryl.

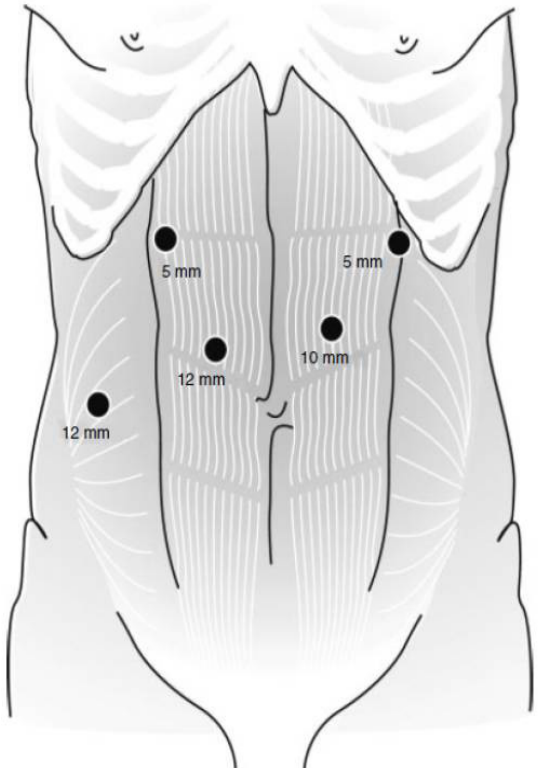


Figure 3. Trocars positions in the abdominal laparoscopic phase.
The camera is inserted through the 10mm port and the 5 mm ports are used as working ports for the operating surgeon. The liver retractor is inserted through the 12 mm pararectal port en de 12mm paraumbilical port is used for insertion of the harmonic scalpel (ultracision) (6).

Literature search

Databases Pubmed, Embase, were searched for: “esophagus” AND “robot”, and their synonyms or abbreviations. No additional search software or special features were used. The search sensitivity was checked by cross referencing the included articles and relevant reviews at Web of Science. The search was limited to papers describing original patient data of series >10 patients in the English language.

The final search was performed on February 27th. The investigators (JR and PvdS) independently performed the screening and article selection procedures. All articles, which fulfilled the eligibility criteria, were included in the systematic review. Duplicate publications with derivative patients were excluded. The search results and selection process were summarised in a flowchart (figure 4).

Each article was screened for first author, year of publication, number of subjects, study population characteristics and study design. Furthermore, postoperative complications and oncologic results were assessed. The level of evidence was assigned to each article by two authors (JR and PS) as determined by the Oxford Centre for Evidence-based Medicine Levels of Evidence.[8] The results were not statistically weighted.

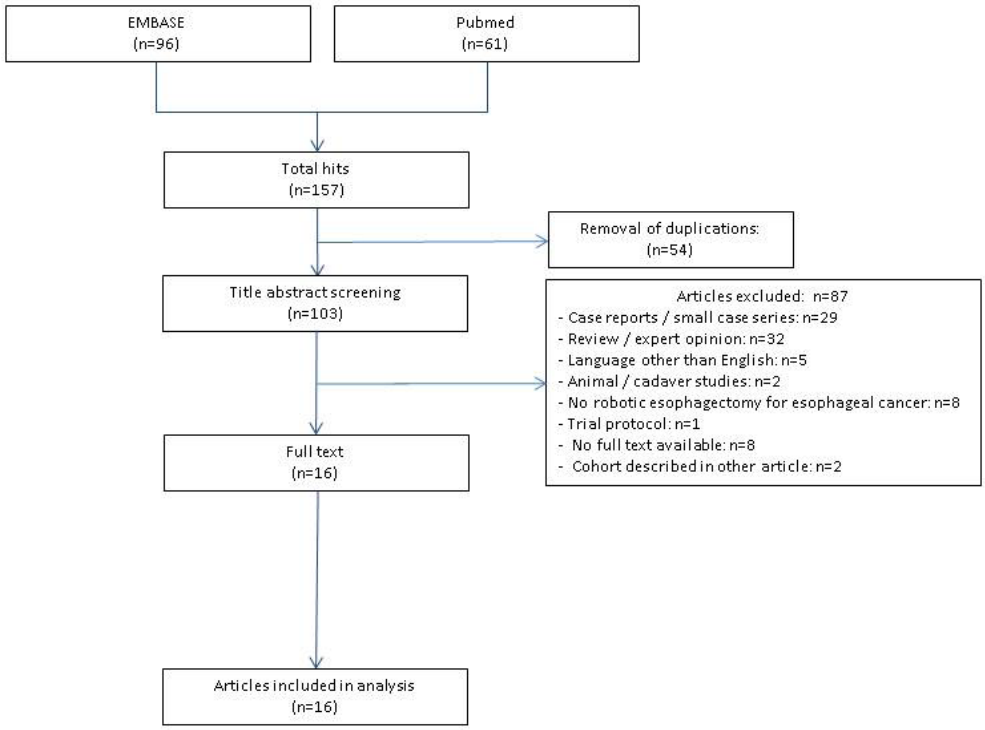


Figure 4. Flowchart Search strategy.

RESULTS

Literature

After applying the selection criteria to 103 abstracts, 16 papers remained available for analysis (Table 1). All papers contained case-series differing from 11 to 108 cases, published between 2007 and 2014 and reflect the early experience of the teams involved. Various approaches (transhiatal /transthoracic, intrathoracic /cervical anastomosis) are reported, with robotic assistance during different phases of the procedure (Table 1).[6,9-23]

Robot assisted transhiatal esophagectomy (RATE)

Five papers report on a transhiatal procedure (RATE).[9,11,14,18,21] In these procedures the robot is used in the abdomen only. One of these only reports on a single case in a patient with cardiopulmonary problems[9], 2 others are from a single institution, who started their learning curve in early stage cancer and proceeded to more advanced tumors.[11,21] The total number of cases is limited to 118, but in conclusion, the procedure is reported to be safe and effective in selected patients. Intraoperative statistics are shown in table 2. Operative times are shorter than for transthoracic procedures ranging from 231-312 minutes. Blood-loss was limited to 100 ml or less. Only in one publication conversions were mentioned and needed in 12,5 % of patients. Hospitalization ranged from 9 to 10 days and median ICU stay was 1 day. Postoperative complications are in line with existing literature concerning transhiatal procedure without the robot, and reported in Table 3, although one series reports a high rate of post-operative diaphragmatic herniations.[14] Mortality was reported in 2 cases only. Oncologic results are presented in table 4. The radical resection rate was reported in two series and the case report and was 91, 95 and 100% respectively. The number of lymph nodes harvested ranged from 15 to 22. All series report on short-term results and therefore survival was not reported.

Robot assisted minimally invasive esophagectomy (RAMIE)

All other procedures report on a transthoracic procedure, either 2 (intrathoracic anastomosis) or 3 stage (cervical anastomosis) (table 1). Only about 300 cases are reported in all papers combined, reflecting the early stage of robotic adaptation for this procedure. Mainly two strategies are used to position the patient: a prone position and a left lateral/semi-prone position. Trocar arrangements vary slightly, and some papers use an additional robotic arm (Table 1).

In the transthoracic series, operative times are generally longer than through a RATE (transhiatal) approach, ranging from 367 to 693 minutes except for one study that demonstrates extremely fast procedures[10]. The more extensive nature of the surgical procedure compared to RATE is also reflected by blood-loss, ranging from 75 to 640 ml. Conversions ranged from 0 to 21%. Length of stay (7-21 days) andICU stay (0.5-3.5 days) are within normal ranges. Complications are reported in most papers and in line with existing literature concerning open transthoracic esophagectomy, although definitions are unclear most of the times. Most common are pneumonia 6-45%, anastomotic strictures (10-68%), cardiac complications (often atrial fibrillation, 5-36%) and in case of 3-stage esophagectomy, recurrent nerve injury (4-35%). Anastomotic leakage varies between studies and is reported to be 4-38%. Mortality is low (0-6%). Oncologic results are not always reported, but radical resection rates range between 81-100% and the number of lymph nodes range between 18-38.

DISCUSSION

This paper represents the growing experience with and interest for RAMIE and RATE. Various groups have reported on feasibility and safety, with promising initial results in a wide range of approaches to esophagectomy.

In these publications, initial feasibility and safety have been demonstrated with good short-term oncologic results. No technical problems with robotic-assistance have been noted and the results encourage to further explore the role of robotic assistance for esophagectomy. Compared to a standard open approach, short-term oncologic results are at least comparable.[1,2,6] Long term overall survival data were not reported yet.

Concerning complications, challenges remain. At first glance, it seems that some complications occur more often after RAMIE than in large series of MIE or open surgery.[24] But, definition of complications is not reported in most studies this might influence the results. Anastomotic leakage and stricture rates vary between these publications. Anastomotic techniques, the site of anastomosis and possibly the administration of neoadjuvant therapy are probably the most important factors contributing to this complication and this moment no conclusions can be drawn whether robotic-assistance helps to overcome this complication. This is also the case for cardiac complications. The range of complications mentioned after RAMIE is broad, but can most probably not be contributed to the procedure on itself.[25-29]

Also, the RAMIE results reflect the early adaptation phase whereas the results from large series in MIE and open surgery that are reported are the results from long-term dedication to these procedures. However, a serious reduction of complication rates should be the goal of the teams that are currently developing the RAMIE approach further. Pulmonary complications, can hopefully be further reduced by shortening operating times. These are relatively long at this moment, compared to operating times of the very experienced teams that perform MIE on a regular base and report operating times of 329 minutes.[3] Possibly a prone position, without double lumen intubation might also reduce pulmonary complications.[1,26,29] However, the hypothesized benefit of such as a position has not been proven and the insufflation of carbon dioxide seems to collapse the lung for a substantial part in this position as well. so, the disadvantages of a prone position, especially when problems necessitating a conversion occur, have prevented us from modifying our operative technique.

Results of the implementation of fast recovery protocols are encouraging. These protocols have not completely been adopted by the teams that are currently involved in RAMIE, but the combination of a limited operative trauma and such fast-track regimens might reduce the onset of complications.[30]

The value of robotic assistance is hard to express in a true measure and therefore a randomized controlled trial, comparing robot-assisted and open three-phase esophagectomy was initiated. Short-term results are expected at the end of 2015.[31] Even though evidence is lacking, we attribute the good oncologic results presented to the use of robotic assistance. The stable, three-dimensional image allows for a very close observation of the operative field. This enables a fine dissection of the esophagus and surrounding tissue, closer to the structures that need to be preserved. In this way, were able to visualize the correct

dissection planes in a better way. We were also able to see a tiny meso-esophageal layer using this technique, as described recently.[32] To our opinion, the steady and up till ten times magnified field of view is especially helpful when operating on moving structures in the mediastinum, caused by breathing and pulsatile movements of the heart and aorta. We emphasize the need to express this subjective feeling in a true patient related outcome measure and think that radicality percentages in advanced tumors might be one of these measures. Therefore, we started operating downstaged T4b esophageal tumors (after long-course chemoradiotherapy) using the da Vinci robot and were able to achieve radical resections in all patients operated on so far (manuscript in preparation).

Also, it was experienced that the upper mediastinum (above the carina) and especially the upper thoracic aperture could be reached with much more ease than through a conventional laparoscopic approach or even a thoracotomy. Ergonomically, an open approach, but also a standard thoracoscopic approach often leads to neck and shoulder complaints.[33,34] In open surgery, the ribcage hampers a direct look at the operative field in the upper mediastinum. Obtaining good exposure, with a clear illumination of the operative field is often difficult and a strong flexure of the surgeons neck is needed. A thoracoscopic approach might overcome this disadvantage, but by working in the upper thoracic aperture, the instruments have to reach deep into the thorax, imposing problems in manipulation, through the fulcrum effect at the ribs.[7] Also, in the thoracic inlet, instruments tend to approach the operative field in a parallel way, therefore compromising maneuverability. The advantages the robotic system offers eliminate these problems in manipulation, visualization and ergonomics and enable us (and others) to do a dissection along the border of the superior caval vein and along the recurrent nerves, up to the level of the clavicle and down to the aortic arch.[22]

Cost-efficacy is a major point to address regarding robot-assisted surgery. The current monopoly of Intuitive Surgical is undesirable. Costs remain too high, competition is slowed down by patents and this puts the possible benefits of robotic surgery in the shades. We look forward to competitors entering the market in order to speed up developments and decrease costs. In that way, we will be able to assess the true cost-effectiveness of robotic-assistance and discover the full potential of placing a computer in between the surgeon's hands and his/her instruments.

In esophagectomy, potential benefits of robotic surgery to discover might hide in using advanced diagnostic imaging, such as fluorescence for sentinel node detection, intra-operative margin detection and visualization of anatomic structures that are not to be injured.[35] Also, image overlay can help us to identify anatomic landmarks and is a tool to judge vascularization of the gastric conduit.[36,37] This might further enhance oncologic results, but also reduce complication (leak) rates and therefore justify increased costs.[38]

In conclusion, literature but also our own experiences demonstrate technical and oncologic safety of RAMIE. We feel that robotic-assistance enablesa meticulous dissection of the mediastinum, which is translated in good short-term oncologic outcomes.

Table 1. Inclusive studies involving the robotic-assisted esophagectomy for esophageal cancer and the taken approach

									Approach						
Author	**Reference**	**Year**	**Study type**	**Level of evidence**	**Cases (n)**	**operation**	**Position**	**Tube**	**Robotic arms used**	**Thorax**	**Abdomen**	**Esophago-gastrostomy**	**Anastomosis technique (%)**	**Anastomosis position**	**30 day mortality (n (%))**
Anderson	14	2007	case series	4	25	TT/TH	Left lateral / supine	NR	3	Robotic	Robotic (3)	NR	Stapled	Cervical	0
Kernstine§	15	2007	case series	4	14	TT	Left lateral towards prone	Double lumen	3	Robotic	Robotic (8)	End-to-end	Stapled	Cervical	0
Galvani	16	2008	case series	4	18	TH	Semilithotomy	NR	3	NA	Robotic	NR	Hand sewn (75) / Stapled (25)	Cervical	0
Kim	17	2010	case series	4	21	TT	Prone	Bronchial blocker	3	Robotic	Robotic (4) / laparoscopy (14) / laparotomy (3)	Side-to-side	Stapled	Cervical	0
Boone	11	2011	case series	4	47	TT	Left lateral towards prone	Double lumen	3	Robotic	laparoscopy	End-to-side	Hand sewn	Cervical	3(6)
Puntam-bekar	18	2011	case series	4	32	TT	Prone	NR	3	Robotic	laparoscopy	NR	Hand sewn	Cervical	0
Sutherland	19	2011	case series	4	36	TH	Supine	NR	3	NA	Robotic	NR	Stapled	Cervical	NR
Hernandez	20	2012	case series	4	52	TT	Left lateral	NR	3	Robotic	Robotic	NR	Stapled	Intrathoracic	0
Weksler	21	2012	case series	4	11	TT	Left lateral towards prone	Double lumen	3	Robotic	laparoscopy	NR	Stapled	Cervical	0

Table 1. (continued)

Author	Reference	Year	Study type	Level of evidence	Cases (n)	operation	Position	Tube	Robotic arms used	Thorax	Abdomen	Esophago-gastrostomy	Anastomosis technique (%)	Anastomosis position	30 day mortality (n (%))
Cerfolio	22	2013	case series	4	22	TT	Left lateral towards prone	NR	4	Robotic	laparoscopy	End-to-end	Hand sewn (73) / Stapled (17)	Intrathoracic	0
Dunn#	23	2013	case series	4	40	TH	Supine	Standard endotracheal	3	NA	Robotic	End-to-end	Stapled	Cervical	1 (2.5)
Sarkaria	24	2013	case series	4	21	TT	Left lateral	NR	4	Robotic	Robotic	End-to-end	Stapled	Intrathoracic	1 (4.8)
Suda	25	2013	case series	4	16	TT	Prone	Double lumen	4	Robotic	laparoscopy	End-to-side (10) / End-to-end (6)	NR	Cervical	0
Coker	26	2014	case series	4	23	TH	Supine split leg	NR	3	NA	Robotic	Side-to-side	Stapled	Cervical	1 (4)
Kim	27	2014	case series	4	40	TT	Left lateral towards prone	Bronchial blocker	4	Robotic	laparoscopy	Side-to-side	Stapled	Cervical	1 (2.5)
Trugeda	28	2014	case series	4	14	TT	Prone	NR	3	Robotic	laparoscopy	NR	Hand sewn	Intrathoracic	0

2 benign cases

§ for 8 patients who underwent the complete robotic procedure

* mean instead of median

Table 2. Peroperative statistics

Author	Year	cases (n)	operation	perioperative complications (n (%))	Blood loss (ml)	Total operative time (min)	Thoracic phase / Console (min)	Conversions (n (%))
Anderson	2007	9	TT/TH	0	350	482	NR	1 (4)
Kernstine§	2007	10	TT	Bronchus injury 1 (7)	275	672	294	1 (7.1)
Galvani	2008	11	TH	0	54	267	NA	0
Kim	2010	12	TT	0	150	410	108.8	0
Boone	2011	6	TT	Bleeding 1 (2)	625	450	180	7 (15)
Puntambekar	2011	13	TT	NR	80	210	100	0
Sutherland	2011	14	TH	NR	97	312	NA	NR
Hernandez	2012	15	TT	NR	NR	442*	NR	0
Weksler	2012	16	TT	0	200	439	NR	0
Cerfolio	2013	17	TT	NR	60 / 75	367	NR	1 (4.5)
Dunn#	2013	18	TH	NR	97.2	311	NA	5 (12.5)
Sarkaria	2013	19	TT	NR	307	556	NR	2 (9.5)
Suda	2013	20	TT	NR	144.5	692.5	335.5	NR
Coker	2014	21	TH	0	100	231	NA	0
Kim	2014	22	TT	Bleeding 1 (3)	156.7	428.6*	186.7*	1 (2.5)
Trugeda	2014	23	TT	NR	75	NR	222	0

2 benign cases

§ for 8 patients who underwent the complete robotic procedure

* mean instead of median

Table 3. Postoperative outcomes

Author	cases (n)	Operation	Tumor site	Postoperative complications (n (%))	Anastomotic leakage rate (n (%))	Overall complications rate (n (%))	Median ICU stay (days)	Median hospital stay (days)
Anderson	25	TT/TH	NR	Pneumonia 4 (16) Chylothorax 2 (8) Empyema 1 (4) Vocal cord paralysis 1 (4)	4 (16)	Major 8 (32)	NR	11
Kernstine§	14	TT	Upper 0 Middle 2 Lower 10	Atrial fibrillation 5 (36) Vocal cord paralysis 2 (14) Anastomic stricture 2 (14)	2 (14)	Major 4 (29) Minor 13 (93)	1	13-18
Galvani	18	TH	Upper 0 Middle / Lower 18	Anastomotic stricture 6 (33) Atrial fibrillation 2 (11) Thoracic duct injury 1 (5) Vocal cord paralysis 1 (5)	6 (33)	NR	1.8*	10*
Kim	21	TT	Upper 3 Middle 7 Lower 11	Vocal cord paralysis 6 (29) Anastomotic stricture 2 (10) Chylous ascties 1 (5) Intra-abdominal bleeding 1 (5) Atrial fibrillation 1 (5)	4 (19)	NR	2	21
Boone	47	TT	Middle 12 Lower 35	Pulmonary complications 21 (45) Vocal cord paralysis 9 (19) Cardiac complications 6 (13) Chylothorax 6 (13) Wound infection 4 (9) Empyema 4 (9)	10 (21)	NR	3	18
Puntambekar	32	TT	NR	Chylothorax 3 (9) Pulmonary complications 2 (6)	3 (9)	NR	NR	NR

Table 3. Postoperative outcomes (continued)

Author	cases (n)	Operation	Tumor site	Postoperative complications (n (%))	Anastomotic leakage rate (n (%))	Overall complications rate (n (%))	Median ICU stay (days)	Median hospital stay (days)
				Vocal cord paralysis 2 (6)				
Sutherland	36	TH	Esophageal 8 GI junction 18	Incarcerated hiatal hernias 7 (19)	NR	NR	NR	9
Hernandez	2012	52	NR	Pneumonia 5 (10) Chylothorax 2 (4)	2 (4)	14 (27)	NR	NR
Weksler	11	TT	NR	Pulmary embolism 1 (9) Pneumonia 1 (9) Vocal cord paralysis 1 (9) Atelectasis 1 (9) Wound infection 1 (9) Urinary tract infection 1 (9)	1 (9)	4 (44)	3.5	8.7
Cerfolio	22	TT	NR	Atrial fibrillation 2 (9) Empyema 1 (5) Colon herniation 1 (5) Chylothorax 1 (5) Urinary retention 1 (5)	2 (9)	Major 5 (23) Minor 3 (14)	NR	7
Dunn#	40	TH	middle 1 Lower 7 GI-junction 29	Anastomotic stricture 27 (68) Pleural effusion 18 (45) Vocal cord paralysis 14 (35)	10 (25)	NR	1	9
			Stomach 1	Pneumonia 8 (20)				
Sarkaria	21	TT	Siewert I 7	upper-gastrointestinal airway fistulas 3 (14)	6 (29)	NR	NR	10
			Siewert II 9 Siewert III 2 NA 3	Pulmary embolism 2 (10) Respiratory failure 2 (10) Vocal cord paralysis 1 (5)				

Table 3. Postoperative outcomes (continued)

Author	cases (n)	Operation	Tumor site	Postoperative complications (n (%))	Anastomotic leakage rate (n (%))	Overall complications rate (n (%))	Median ICU stay (days)	Median hospital stay (days)
				Urinary tract infection 1 (5) Delayed gastric emptying 1 (5) Pneumonitis 1 (5) Atrial fibrillation 1 (5) Anastomotic stricture 1 (5) Wound infection 1 (5) Empyema 1 (5)				
Suda	16	TT	Upper 2 Middle 7 Lower 7	Laryngopharyngeal disfunction 9 (56) Vocal cord paralysis 6 (38) Hoarseness 3 (19) Aspiration 6 (38) Arrhythmia 2 (13) Pneumonia 1 (6)	6 (38)	NR	0.5	22
Coker	23	TH	NR	Anastomotic stricture 7 (30) Delayed gastric emptying 4 (17) Atrial fibrillation 4 (17) Dysphagia 3 (13) Pneumonia 2 (9) Pleural / pericardial effusion 2 (9) Urinary tract infection 2 (9) Urine retention 2 (9) ARDS 1 (5) Pulmary embolism 1 (5)	2 (9)	NR	NR	9
Kim	40	TT	Upper 2 Middle 25	Vocal cord paralysis 8 (20) Pulmonary complications 5 (13)	4 (10)	NR	1	14

Table 3. Postoperative outcomes (continued)

Author	cases (n)	Operation	Tumor site	Postoperative complications (n (%))	Anastomotic leakage rate (n (%))	Overall complications rate (n (%))	Median ICU stay (days)	Median hospital stay (days)
			Lower 13	Atrial fibrillation 2 (5) Chylothorax 2 (5)				
Trugeda	14	TT	Middle 0 Lower 14	Chylothorax 2 (14)	4 (28) 1 syptomatic 3 radiological	NR	NR	13

Table 4. Oncologic outcomes

Author	cases (n)	operation	Pathological stage	Tumor type (n)	R0 resections (n (%))	Median lymph nodes (n)	Median Follow up (months)	Recurrence (n (%))	Median DFS (months)	Median OS (months)	Survival
Anderson	25	TT/TH	NR	NR	25 (100)	22	6	1 (4)	NR	NR	NR
Kernstine§	14	TT	HGD (2) IIa (1) IIb (2) III (7) IV (2)	AC (8) SCC(4) HGD (2)	14 (100)	18	9	3 (21)	NR	NR	17 months 87%
Galvani	18	TH	HGD (9) 0 (2) I (5) IIa (2)	AC (_9) HGD (9)	NR	14	22	3 (17)	NR	NR	NR
Kim	21	TT	0 (1) I (8) IIb (5) III (4) IV (3)	AC (1) SCC (20)	20 (95)	38	NR	NR	NR	NR	NR
Boone	47	TT	I (2) IIa (6) IIb (3) III (8) IV (28)	AC (29) SCC (18)	36 (77)	29	30	30 (64)	15	NR	NR
Puntambekar	32	TT	NR	NR	NR	NR	NR	NR	NR	NR	NR
Sutherland	36	TH	NR	AC (32) SCC (2) HGD (1)	NR	NR	NR	NR	NR	NR	NR

Table 4. Oncologic outcomes

Author	**cases (n)**	**operation**	**Pathological stage**	**Tumor type (n)**	**R0 resections (n (%))**	**Median lymph nodes (n)**	**Median Follow up (months)**	**Recurrence (n (%))**	Median DFS (months)	Median OS (months)	Survival
				Benign stricture (1)							
Hernandez	52	TT	NR	AC (46) SCC (3) Neuroendocrine (1) HGD (2)	52 (100)	20	NR	NR	NR	NR	NR
Weksler	11	TT	0 (4) I (2) IIa (1) IIb (1) III (3)	Adenocarcinoma (11)	11 (100)	19	NR	NR	N	NR	NR
Cerfolio	22	TT	NR	AC (18) SCC (4)	22 (100)	18	5	NR	NR	NR	NR
Dunn#	40	TH	0 (5) IA (10) IB (6) IIA (1) IIB (7) IIIA (3) IIIB (4) IV (2)	AC (36) SCC (2)	36 (95)	20	29	16 (44%)	20	NR	NR
Sarkaria	21	TT	0 (8) I (5) IIa (1)	AC (18) SCC (2) GIST (1)	17 (81)	20	NR	NR	NR	NR	NR

Table 4. Oncologic outcomes

Author	cases (n)	operation	Pathological stage	Tumor type (n)	R0 resections (n (%))	Median lymph nodes (n)	Median Follow up (months)	Recurrence (n (%))	Median DFS (months)	Median OS (months)	Survival
Suda	16	TT	IIb (4) III (2) Other (1) I (7) II (3) III (6)	SCC (16)	14 (88)	38	NR	NR	NR	NR	NR
Coker	23	TH	0 (9) I (7) II (3) III (4)	AC(23)	21 (91)	15 (mean)	7	NR	NR	NR	2 year 57 %
Kim	40	TT	I (19) II (14) III (7)	SCC (40)	39 (97.5)	43	NR	NR	NR	NR	NR
Trugeda	14	TT	0 (2) I (2) II (3) III (7)	AC (9) SCC (5)	14 (100)	18	NR	NR	NR	NR	NR

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Chapter 7

Oncologic Long-Term Results of Robot-Assisted Minimally Invasive Thoraco-Laparoscopic Esophagectomy with Two-Field Lymphadenectomy for Esophageal Cancer

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ABSTRACT

Background

Open transthoracic esophagectomy is worldwide the gold standard in the treatment of resectable esophageal cancer. Robot-assisted minimally invasive thoraco-laparoscopic esophagectomy (RAMIE) for esophageal cancer may be associated with reduced blood loss, shorter intensive care stay, less cardiopulmonary morbidity. However, long-term oncologic results were not reported to date.

Methods

Between June 2007 and September 2011, 108 patients with potentially resectable esophageal cancer underwent RAMIE in the UMC Utrecht with curative intent. All data were recorded prospectively.

Results

The median duration of the surgical procedure was 381 (range 264-636) minutes. Pulmonary complications were most common and observed in 36 patients (33%). Median intensive care (ICU stay) was 1 day and median overall postoperative hospital stay was 16 days. In hospital mortality was 5%.

The majority of patients (78%) presented with T3 and T4 disease and 68% of patients had nodal positive disease (cN1-3) In 65% of patients neoadjuvant treatment (chemotherapy 57%, chemoradiotherapy 7%, radiotherapy 1%) was administered. In 103 (95%) patients a radical resection (R0) was achieved. The median number of lymph nodes was 26. Median follow up was 58 months. Five year overall survival was 42%. Median disease-free survival was 21 months and median overall survival was 29 months. Tumor recurrence occurred in 51 patients and was locoregional only in 6 (6%), systemic only in 31 (30%) and combined in 14 (14%).

Conclusion

RAMIE was shown to be oncologically effective with a high percentage of R0 radical resections and adequate lymphadenectomy. RAMIE provided good local control with a low percentage of local recurrence at long term follow up.

BACKGROUND

In 2008, an estimated 482,300 people were diagnosed with esophageal cancer, and 406,800 patients died of the disease worldwide.[1] Radical esophagolymphadenectomy is the cornerstone of the multimodality treatment with curative intent.[2-5]
Open transthoracic esophagectomy is the preferred surgical approach worldwide for esophageal cancer allowing resection of the tumor with en-bloc the surrounding para-tracheal, subcarinal and para-esophageal lymph nodes.[6,7] However, the percentage of cardiopulmonary complications associated with the open transthoracic approach is high (50-70%).[6]
Minimally invasive esophagectomy (MIE) was designed to reduce surgical trauma, resulting in lower rates of morbidity and mortality. With regard to MIE, review of literature shows a substantial decrease in blood loss, postoperative complications and days of hospital stay, with comparable short-term oncologic results.[8-13] These results were confirmed in a recently published randomized controlled trial, where MIE was compared to open transthoracic esophagectomy.[14] However, the open transthoracic esophagectomy remains the gold standard worldwide for the treatment of esophageal cancer.[7]
In 2003 robot-assisted thoraco-laparoscopic esophagectomy (RAMIE) was developed at the University Medical Center Utrecht (UMC Utrecht), The Netherlands.[15] Robot-assisted thoraco-laparoscopic esophagectomy facilitates complex minimally invasive procedures with an enlarged, 3 dimensional field of view. The articulated instruments facilitate dissection with 7 degrees of freedom. [13,15,16,17,18]
From our first experience, reported in 2006 and 2009, it was concluded that RAMIE is a feasible and safe technique, associated with reduced blood loss, shorter intensive care unit stay and a lower percentage of cardiopulmonary complications compared to literature reports of open transthoracic esophagectomy.[6,15,16]
Following these initial reports of RAMIE, the current article presents our subsequent series with a focus on long-term oncologic results.

METHODS

Patients

Between June 2007 and September 2011, consecutive patients with potentially curative resectable esophageal cancer were operated on in the UMC Utrecht. In our institute, transthoracic esophagectomy is the standard treatment for patients with esophageal cancer. The standard neoadjuvant treatment for patients with esophageal adenocarcinoma was preoperative chemotherapy (epirubicin, cisplatin and capecitabin (ECC)).[19] Patients with esophageal squamous cell carcinoma underwent preoperative chemoradiotherapy (carboplatin and taxol + 41,4 Gy).[20] Data on surgical procedures were registered prospectively in the operating room. All complications and follow up were registered in a prospective surgical database.
We prospectively recorded baseline characteristics and routine diagnostic work up including use and results of upper endoscopy, endoscopic ultrasound (EUS), CT thorax and abdomen

and ultrasound of the neck region. PET scanning with fine needle aspiration (FNA) of suspected lymph nodes was used at indication and recorded prospectively. All patients were discussed at a multidisciplinary oncology board meeting.
Patients received postoperative follow up at the outpatient department according to the standard follow up regimen described in the Dutch guidelines. Patients visited the outpatient department at 6 weeks, 3, 6, 9 and 12 months in the first year. In the 2nd, 3rd , 4th and 5th year postoperatively. Patients received follow up every 6 months. In case of symptoms of tumor recurrence occur, patients underwent a CT thorax and abdomen. All patients had at least 29 months of follow up and were followed for 5 years postoperatively.

Operative Procedure
The operative technique of thoracolaparoscopic esophagectomy with two field lymphadenectomy was described previously.[15,16] For the thoracic phase, the patient is positioned in the left lateral decubitus position, tilted 45° towards the prone position. The trocar arrangement during the robot-assisted thoracoscopic phase and laparoscopic phase are shown in figure S1.[15] Robot assisted esophagectomy included a thoracic lymphadenectomy, which included the right-sided paratracheal (lymph node station 2R), tracheobronchial (station 4), aortopulmonary window (Lymph nodes in the window dorsal to the aortic arch, cranially to the left main bronchus up until the pulmonary artery, station 5), carinal (station 7), perioesophageal (station 8) lymph nodes.[15]
The patient was placed in the supine position hereafter to facilitate a laparoscopic gastric mobilization, truncal lymph node dissection and gastric tube formation with cervical hand sewn end-to-side esophago-gastrostomy.[21]

Postoperative Management
Mechanical ventilation was continued until patients were transferred to the intensive care unit (ICU), where patients were extubated 2-3 hours after ending the operation. After 1 day, patients were transferred to the medium care unit (MCU) and to the surgical ward on postoperative day 2.
All patients were placed on a nil-by-mouth routine with enteral tube feeding by a needle-catheter jejunostomy the first 7 days postoperatively. Nasogastric tubes were routinely placed. No postoperative swallow tests were performed as the sensitivity rat of detecting leakage was considered to be too low to change postoperative decision making.[22] In absence of signs of anastomotic dehiscence, patients started with sips of water and the oral intake was gradually increased to solid food. There was no enhanced recovery program.

Postoperative complications
All complications were graded using the modified Clavien-Dindo classification (MCDC) of surgical complications. All reported complications were grade 2 and higher.[23]

Pathological analysis
The resected specimen was evaluated using a standard protocol, with emphasis on resection margins, tumor type, extension of the tumor and the presence of lymph nodes. The 7th

edition of the International Union Against Cancer (UICC) was used for TNM-classification, tumor grade, and stage grouping.[24] The (circumferential) resection margins were evaluated using the College of American Pathologist (CAP) criteria.[25]

Statistical analysis

Statistical analysis was performed using SPSS version 20.0 (SPSS, Chicago, IL, USA). We considered a P-value of <0.05 to be statistically significant. All skewed continuous data were presented as medians with range. Survival time was calculated as the duration from the day of surgery to death or the last date of follow-up. Disease-free interval was calculated from the day of surgery to the day of definitive diagnosis of recurrent tumor.

RESULTS

Between June 2007 and September 2011, 123 consecutive patients with potentially curative resectable esophageal cancer were eligible for transthoracic esophagectomy. In 7 patients with locally advanced T4 tumors an indication for open transthoracic esophagectomy was made preoperatively. Intraoperatively, irresectable disease was observed in 8 patients, leaving 108 patients eligible for RAMIE.

Baseline characteristics are summarized in Table S1. Patients included 76 men and 32 women, with a median age of 62 years (range: 42–78) and a BMI of 26 (range 16-36kg / m^2). The majority of patients (78%) were clinically staged cT3 and higher and 68% of patients had clinically positive nodal disease (cN1-N3). Co-morbidity, consisting of a history of vascular, cardiac, pulmonary and oncologic disease, was observed frequently within this cohort.

In 20 patients (19%) a conversion to an open transthoracic or open transhiatal procedure was needed. Conversion to thoracotomy (n=11) was necessary due to bulky adhesive tumor in the mediastinum (n=4), insufficient collapse of the right lung (n=2) or inadequate thoracosopic trocar position (n=1). Four patients had a bleeding that could not be controlled thoracoscopically (n=4). One patient had a bleeding from the bronchial artery, two patients had a bleeding from the azygos vein and one patient had an iatrogenic lung bleeding. Conversion to a transhiatal procedure (n= 9) was necessary due to insufficient collapse of the right lung (n=6), inadequate thoracoscopic port position (n=1), pleural adhesions (n=1) or enlarged right cardiac atrium (unusual anatomy) (n=1).

Conversion of the laparoscopic abdominal phase to laparotomy was required in 3 patients due to bleeding that could not be controlled laparoscopically (n=1), locally advanced tumor requiring total gastrectomy with colonic interposition (n=1) or very low position of the greater curvature (n=1). Patients who underwent intraoperative conversion did not statistically differ in baseline characteristics from patients who underwent a full RAMIE. There was a significant decrease in the percentage of conversions between the first 54 and second 54 patients (13 (24%) versus 7 (13%) respectively; P < 0·001).

Operative results

The patient operative data of 108 patients are shown in Table 1. The median duration of the total procedure was 381 (range 264–550) minutes. The thoracoscopic phase (88 patients)

Table 1: Patient operative data (n=108)

	n (%)	Median	Range
Total OR time (min)		381	264 - 636
Thoracoscopic phase		175	108 – 281
Total Blood loss (ml)		340	50 - 3800
Conversion thoracoscopy	20 (19)		
Reason conversion			
Respiratory problems	8 (7)		
Bleeding	4 (4)		
Bulky tumor	4 (4)		
Trocars problems	2 (2)		
Pleural adhesions	1 (1)		
Unusual anatomy	1 (1)		
Conversion laparoscopy	3 (3)		
Reason conversion			
Advanced tumor	1 (1)		
Bleeding	1 (1)		
Unusual anatomy	1 (1)		

had a median duration of 175 (range 108–241) minutes. There was a significant decrease in thoracoscopic operative time between the first 44 and second 44 patients who completed the thoracic phase thoracoscopically (199 min versus 166 min respectively; P < 0·001).

Postoperative results

Postoperative data were summarized in Table 2. An uncomplicated postoperative course was observed in 37 (34%) patients. Pulmonary complications were most common. Pneumonia was diagnosed and treated in 36 (33%) patients. Anastomotic leakage of the esophago-gastrostomy was seen in 20 (19%) of patients of whom 6 (6%) also had intrathoracic manifestation. Chylothorax was seen in 19 (18%) patients. In 15 out of 19 the leakages were low volume and could be treated conservatively showing that the leakage was only from small side branches of the thoracic duct.

Vocal cord paralysis occurred in 10 (9%) patients. Out of these 10 patients, paralysis was temporary in 8 patients. The permanent recurrence paralysis rate was 2%. Wound infections were seen in 7 (6%) patients; 5 patients were diagnosed with a cervical wound infection of whom 1 also had a thoracic wound infection. The other 2 patients had abdominal wound infections. Postoperative pneumothorax requiring additional chest tube placement was seen in 6 (6%) patients. Thromboembolic complications were seen in 6% of patients.

Patients were ventilated at the ICU for a median of 0 (range 0–64) days. Median ICU stay was 1 (range 1-76) day and overall postoperative hospital stay 16 (range 9-123) days.. In hospital mortality was 5% (4 patients). One patient died from a myocardial infarction, one from a tracheo–neo-esophageal fistula, one from anastomotic leakage with respiratory insufficiency, and one from a mediastinal septic bleeding following anastomotic leakage.

Table 2: Postoperative data

	n=108	Median	Range
Uncomplicated procedures – no. (%)	37 (34)		
Complications – no. (%)	71 (66)		
Pulmonary – no. (%)	36 (33)		
Pneumonia – no. (%)	36 (33)		
Atelectasis – no. (%)	6 (6)		
Anastomotic leakage– no. (%)	20 (19)		
Intrathoracic manifestations– no. (%)	6 (6)		
Chylothorax– no. (%)	19 (18)		
Vocal cord Paralysis[#] – no. (%)	10 (9)		
Cardiac– no. (%)	10 (9)		
Atrial fibrillation– no. (%)	9 (8)		
MI– no. (%)	1 (1)		
Wound infection– no. (%)	7 (6)		
Thrombo embolic event– no. (%)	6 (6)		
Pneumothorax– no. (%)	6 (6)		
Other*– no. (%)	3 (3)*		
In-hospital death	5 (5)		
ICU stay (days)		1	1 - 76
Hospital stay (days)		16	9 - 123

[#] 8 temporary, 2 permanent

*1 omentum necrosis, 1 tracheoesophageal fistula, 1 bleeding

Histopathological results

An overview of the histopathological results is shown in Table 3. The majority of the tumors were adenocarcinomas (78%). In 10 (9%) patients, no viable tumor cells were detected in the resected specimen, corresponding to a pathological complete response (pCR) rate to neoadjuvant therapy of 14%. The majority of tumors were located in the distal esophagus or at the GOJ (85%). In 102 (94%) patents a radical resection (R0) was achieved. No gross irradical resections (R2 resections) were performed. In 108 operations, 2794 lymph nodes were retrieved. The median number of lymph nodes was 26 (range 5-53). In total, 264 positive lymph nodes were dissected, with a median of 1 positive lymph node (range 0-22). The distribution of dissected lymph nodes is shown in figure S2. In total, 15% of all patients had lymph node metastases located at subcarinal level and higher.

Recurrence and outcome

At the time of analysis, a median of 58 months after surgery, all patients had undergone esophagectomy at least 29 months previously. No patients were lost to follow-up. Median overall survival was 29 months. Kaplan Meier curves for overall survival were shown in figure 1. Overall 5 year survival was 42%.

Out of 108 patients, 5 patients died postoperatively. Therefore, 103 patients were included in the recurrence analysis. Median disease free survival was 21 months. In 42 patients

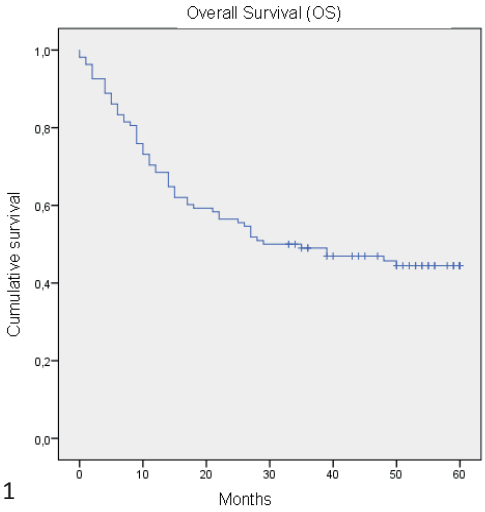
Table 3: Histopathological data

	n=108	Median	Range
Histological type			
Adenocarcinoma	78 (72)		
Squamous cell carcinoma	20 (19)		
No viable tumor cells	10 (9)		
Site of tumor			
Mid or upper esophageal	16 (15)		
Lower esophageal and GEJ	92 (85)		
Radicality			
R0	103 (95)		
R1	5 (5)		
Retrieved LN	2794	26	5 - 57
Positive LN	264	1	0 - 22
Pathological T-stage			
pT0 – no. (%)	10 (9)		
pT1 – no. (%)	20 (19)		
pT2 – no. (%)	11 (10)		
pT3 – no. (%)	65 (60)		
pT4a – no. (%)	2 (2)		
Pathological N-stage			
pN0 – no. (%)	48 (44)		
pN1 – no. (%)	30 (28)		
pN2 – no. (%)	20 (19)		
pN3 – no. (%)	10 (9)		

(52%), no signs of recurrent disease were observed after a median follow-up of 34 months. The remaining 39 patients developed symptomatic recurrent disease. In 52 out of 103 patients (%), no signs of recurrent disease were observed after a median follow-up of 34 months. The remaining 51 patients developed symptomatic recurrent disease. The first site of symptomatic tumor recurrence was in 6 (6%) patients locoregional only, in 31 (30%) systemic only and combined in 14 (14%) (table S2). Kaplan Meier curves for disease free survival are shown in figure 2.

DISCUSSION

This article presents our experience with RAMIE of a new cohort following our initial reports in 2006 and 2009 which showed this technique to be feasible and safe. In the current group of consecutive patients we focused on the oncologic long-term follow up. RAMIE was shown to be effective with a high percentage of R0 radical resections (95%) and adequate lymphadenectomy. RAMIE provided local control with a low percentage of local recurrence. This high percentage of radical resections in our cohort with a majority of locally advanced T3 tumors (60%) may be the result of the robotic surgical approach. Mainly the 3D, magnified surgical view combined with the high degrees of freedom of the articulating



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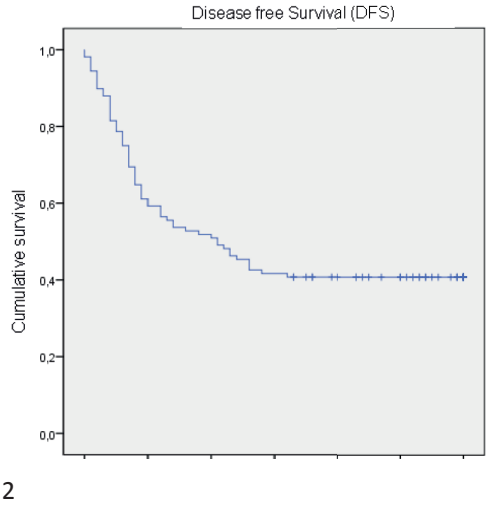

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Figure 1. Kaplan Meier Curves for overall survival (OS) in months.
Figure 2. Kaplan Meier Curves for disease free survival (DFS) in months

surgical instruments facilitate a precise dissection in a confined operating space.[18]
Nodal positive disease (pN+) was observed in 56% of all patients. A proper mediastinal lymphadenectomy was performed, including the right-sided paratracheal (lymph node station 2R), tracheobronchial (station 4), aortopulmonary window (station 5), carinal (station 7) and perioesophageal (station 8) lymph nodes.with a median of 26 dissected lymph nodes. This number is comparable to series of open transthoracic esophagectomy from literature.[6] For convential MIE the median number of dissected lymph nodes was 21. Overall survival of RAMIE was comparable to results after MIE.[26,27]
For recurrence, results after RAMIE in this study with 65% neoadjuvant treatment were comparable with results compared to open esophagectomy reported, in which all patients received neoadjuvant chemoradiotherapy.[28] In only 6% of all cases the first site of symptomatic tumor recurrence was locoregional or in the locoregional lymph nodes. This is comparable with results after chemoradiotherapy where locoregional recurrence was observed in 7% of all cases.[28] Distant metastases were observed in 30% of all patients, compared to 28% for patients who underwent neoadjuvant chemoradiotherapy.[28] The percentage of patients who had simultaneous locoregional recurrence and systemic metastases was 14% in our cohort and 13% after neoadjuvant chemoradiotherapy.[28]
Pneumonia (34%) was the most observed complication after RAMIE. We compared our results to a recent randomized controlled trial, where patients with resectable esophageal cancer were randomized between neoadjuvant chemoradiation and surgery alone. In this trial, only open esophagectomies were included showing a pneumonia rate of 44%.[20] Another recent randomized controlled trial compared conventional MIE to open transthoracic esophagectomy.[14] Results from this trial showed a reduced pulmonary complication rate in the MIE group compared to the open group.[14] The percentage of in hospital pulmonary

infections after MIE in that trial was lower (12%) than in our study.[14] However, different definitions of postoperative pneumonia were used. Our definition of pneumonia, was defined as the decision to treat suspected pneumonia (Modified Clavien Dindo Classification (MCDC (grade II).[23] The definition of pneumonia used in the randomized controlled trial was more strict (infiltrate on pulmonary radiography combined with a positive sputum culture) leading to a lower percentage of pneumonia. Applying this definition on our cohort, yields a pneumonia rate of 18%, which is comparable to MIE.[14] Reporting of postoperative pneumonia and postoperative outcomes after esophagectomy in general, are heterogeneous and inconsistent. This makes comparison between different studies difficult and a consensus approach to reporting clinical outcomes should be considered.[29,30]

Besides aforementioned advantages of RAMIE, there were also disadvantages of RAMIE such as the high costs of acquisition of Da Vinci surgical system, disposable instruments and a prolonged operative time compared to open esophagectomy.[18] Introduction of RAMIE in a hospital needs careful proctoring by surgeons skilled and trained in RAMIE to reduce postoperative complications and to facilitate a steep learning curve.[15] Centralization of robotic surgery in high volume centers leads to lower rate of post-operative complications and more efficient use of operating time.[31]

In this article we described a decrease in thoracoscopic operative time between the first 43 and second 42 patients (199 min versus 166 min respectively; $P < 0{\cdot}001$) emphasizing the learning curve. The median duration of the full procedure is 381 minutes. Currently we are performing the RAMIE procedure within 6 hours. Furthermore, a significant decrease in the percentage of conversions was observed between the first 54 and second 54 patients (13 (24%) versus 7 (13%) respectively; $P < 0{\cdot}001$). Currently our RAMIE conversion RATE is 4%.

Our results from robot-assisted esophagectomy are in concordance with a recently published systematic review.[18] This systematic review included 9 articles (130 cases) describing robot-assisted esophagectomy. The level of evidence for robot-assisted minimally invasive thoraco-laparoscopic esophagectomy was suboptimal and based on case series or expert opinions only (Level 4 or 5).[18] The aforementioned systematic review strongly emphasized the need for well conducted randomized controlled trials and long-term survival studies within a framework of measured and comparable outcomes to prove the superiority of robot-assisted minimally invasive thoraco-laparoscopic esophagectomy over the worldwide current standard open transthoracic esophagectomy.[18] Therefore, we initiated the ROBOT-trial (ClinicalTrial.gov Identifier: NCT01544790) in January 2012 to compare RAMIE with open transthoracic esophagectomy.[32]

In conclusion, RAMIE with 2-field lymphadenectomy was shown to be feasible and safe in a cohort of Western European patients with advanced esophageal cancer. Furthermore, RAMIE was shown to be oncologically effective with a high percentage of R0 radical resections with adequate lymphadenectomy. RAMIE provided adequate local control with a low percentage of local recurrence.

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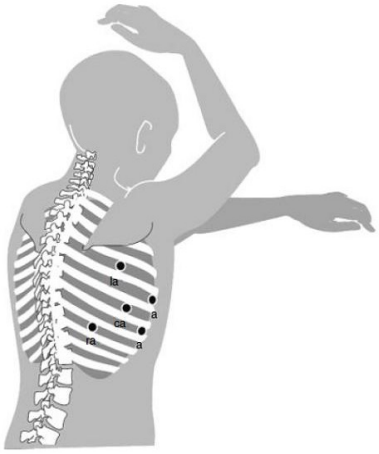
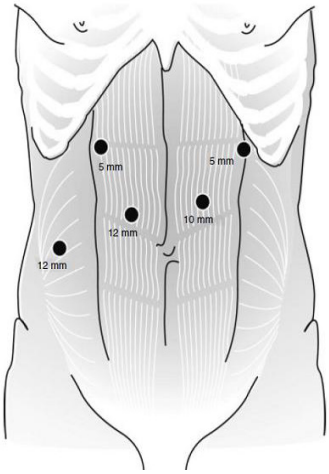
SUPPLEMENTARY INFORMATION





S1a S1b

Figure S1. Trocar arrangement during the (a) robot-assisted thoracoscopic phase and (b) laparoscopic phase.[15]

Figure S1a. Trocar arrangement during robot-assisted thoracoscopic phase. La: Left robotic arm (4th intercostal space); a: assistant thoracoscopic working port (5th and 7th intercostal space); ca: robotic camera arm (6th intercostal space); ra: right robotic arm (8th or 9th intercostal space).

Figure S1b. Trocar arrangement during the laparoscopic phase. The camera was inserted through the 10-mm para-umbilical trocar port and two 5-mm trocars were used as laparoscopic working ports. The liver retractor was inserted through the 12-mm right para-rectal trocar port. The harmonic ace was inserted through the 12-mm paraumbilical port. (with permission Boone et al).

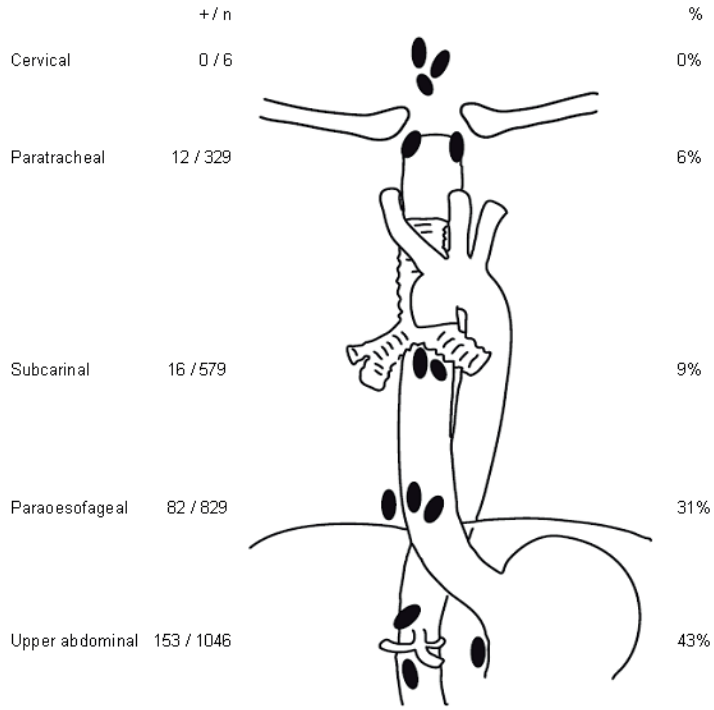


Figure S2. Distribution of resected lymph nodes. Total number of lymph nodes (n), number of positive lymph nodes (+) and percentage of positive lymph nodes (%) at each location out of 85 patients.

Table S1: Patient demographics and tumor characteristics (n=108)

	n (%)	Median	Range
Age (y)		62	42 - 78
Gender			
M	76 (70)		
F	32 (30)		
BMI (kg / m²)		26	16 – 36
Co-morbidity			
Vascular	36 (33)		
Cardiac	25 (23)		
Pulmonal	15 (14)		
Oncologic	15 (14)		
Previous thoracic / abdominal operation	29 (27)		
ASA score			
1	25 (23)		
2	74 (69)		
3	9 (8)		
Clinical T stage			
cT1	12 (11)		
cT2	12 (11)		
cT3	77 (71)		
cT4	7 (7)		
Ultrasound N stage			
cN0	35 (32)		
cN1-N3	83 (68)		
Tumor type			
Adenocarcinoma	85 (79)		
Squamous cell carcinoma	23 (21)		
Neoadjuvant treatment			
No therapy	39 (36)		
Chemotherapy	61 (57)		
Chemoradiotherapy	7 (7)		
Radiotherapy	1 (1)		

Table S2: Recurrence patterns after RAMIE (n=103)

	n (%)
No Recurrence	52 (50)
Recurrence	51 (50)
Locoregional*	6 (6)
Distant#	31 (30)
Both$	14 (14)

* Recurrence of primary tumor or tumor in locoregional lymph nodes

Hematogenous distant metastases or distant lymph node metastases

$ Synchronous locoregional recurrence and distant metastases

Chapter 8

The learning curve for robot-assisted minimally invasive thoraco-laparoscopic esophagectomy for esophageal cancer: results from 312 cases

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ABSTRACT

Background and aims

Robot-assisted minimally invasive thoraco-laparoscopic esophagectomy (RAMIE) was developed in 2003. RAMIE was shown to be safe and oncologically effective. The aim of this study was to assess the learning curve and the proctoring program for a newly introduced surgeon (surgeon 2).

Methods

The "learning curve" was defined as the number of operations that must be performed by a surgeon to achieve a steady level of performance. Measures of proficiency to describe the learning curve of the proctor and the newly introduced surgeon 2 included: operating time, blood loss and conversion rates and were analyzed using the cumulative sum (CUSUM) method. Results of the newly introduced surgeon were compared to the proctor in the same period of time.

Results

The proctor performed 232 of 312 procedures (74%) and surgeon 2 performed 80 of 312 procedures (26%). The proctor reached proficiency after 70 procedures in 55 months. The structured proctoring program for surgeon 2 started with 20 procedures as assisting table surgeon, followed by 5 observational and 15 supervised cases. Surgeon 2 performed at the same level as the proctor concerning operating time, blood loss, conversion rates, radicality and complications. For surgeon 2, the learning phase of RAMIE was completed within 24 cases (15 supervised and 9 independent cases) in 13 months; a reduction of 66% in the number of operations and a reduction of 76% in time, compared to the proctor.

Conclusion

The learning phase of RAMIE consisted of 70 procedures in 55 months. Using a structured proctoring program, surgeon 2 reached comparable postoperative and short term oncologic results within a reduced learning phase of 24 cases in 13 months.

BACKGROUND

In 2012 an estimated 455.800 people were diagnosed with esophageal cancer and 400,200 deaths occurred in 2012 worldwide.[1] Currently, the standard treatment for locally advanced esophageal cancer is preoperative chemoradiotherapy followed by open esophagectomy.[2,3] However, the open transthoracic esophagectomy is associated with high morbidity and mortality. [4] Minimally invasive esophagectomy (MIE) was designed to improve the outcome of esophagectomy. Systematic reviews and results from a randomized controlled trial comparing MIE to open transthoracic esophagectomy showed decreased blood loss, fewer postoperative complications and shorter hospital stay, with comparable short-term oncologic results.[5,6]

However, MIE is not widely applied. Technical limitations and concerns about oncologic efficacy have been the main reasons for a limited application of this technique. Hence, the open procedure remains the preferred approach in most centers worldwide.[4,7]

Robot-assisted minimally invasive thoraco-laparoscopic esophagectomy (RAMIE) was developed in 2003 to overcome the technical limitations of conventional MIE.[8,9] RAMIE was shown to be feasible and safe in a cohort of Western European patients with advanced esophageal cancer.[10] RAMIE was shown to be oncologically effective with a high percentage of radical resections and adequate lymphadenectomy with good local control with a low percentage of local recurrence at the long term follow up.[10]

The interest in RAMIE is expanding, with an increasing number of centers performing this technique worldwide.[11] Little is known about the “learning curve” for RAMIE. The “learning curve” is defined as the number of operations that must be performed by a surgeon to achieve a steady level of performance.[12,13]

In this article we describe the learning curve and proctoring results of introducing a second surgeon for RAMIE for esophageal cancer.

METHODS

Patients

Between October 2003 and August 2016, patients with resectable esophageal cancer who underwent RAMIE in the University Medical Center Utrecht, (Utrecht, the Netherlands) were included in the analysis. Data on surgical procedures were registered prospectively in the operating room. The thoracoscopic phase was defined as the time from the first incision for placement of the thoracic trocars until closure of the thoracic wounds. Total procedure operating time was defined as time from incision until closure (minutes) for both the thoracic and the abdominal phase of the procedure. All complications were graded using the modified Clavien-Dindo classification (MCDC) of surgical complications.[14]

Operative Procedure and postoperative management

All patients were discussed in a multidisciplinary cancer board to determine optimal treatment. All patients underwent a 3-stage RAMIE with 2-field lymphadenectomy by using the Da Vinci® robotic system (Intuitive Surgical Inc., Sunnyvale, California, USA).

An epidural catheter was placed to provide adequate postoperative analgesia.[8,9] For the robot assisted thoracoscopic phase, the patient was positioned in the left lateral decubitus position, tilted 45° towards prone position (semiprone). The thoracic phase included a mediastinal lymphadenectomy, including the paratracheal (station 2), tracheobronchial (station 4), aorto-pulmonary window (station 5)), carinal (station 7) and peri-esophageal (station 8) lymph nodes.[15] The nodes in the aorto-pulmonary window were resected by retracting the esophagus from the left main bronchus and aortic arch. The dissection was performed between the lateral border of the left main bronchus and the aortic arch les to the aortopulmonary window nodes. The patient was hereafter placed in the supine position to facilitate the laparoscopic abdominal phase of gastric mobilization, truncal lymph node dissection and gastric tube formation with cervical hand sewn end-to-side oesophago-gastrostomy (McKeown approach).[8,9] Mechanical ventilation was continued until patients were transferred to the intensive care unit (ICU). All patients were placed on a nil-by-mouth routine with jejunostomy tube feeding the first 4 days postoperatively. A nasogastric tube and bilateral chest tubes were routinely placed. Patients started with sips of water at day 5 and the oral intake was gradually increased to solid food. There was no enhanced recovery program.[8,9]

Pathological analysis

The resected specimen was evaluated using a standard protocol.[15] The 7th edition of the International Union Against Cancer (UICC) was used for TNM-classification, tumor grade, and stage grouping.[16] The (circumferential) resection margins were evaluated using the College of American Pathologist (CAP) criteria.[17]

Learning curve analysis

The cumulative sum (CUSUM) analysis transforms raw data into the running total of data deviations from the group mean, enabling investigators to visualize the data for trends not discernible with other approaches.[18] The "learning curve" is defined as the number of operations that must be performed by a surgeon to achieve a steady level of performance.[13,18] This could be an improvement in performance over time or a change in the ability to complete a task until failure is reduced to a constant minimum acceptable rate.[18] Our measures of proficiency included: thoracoscopic and total procedure operating time, thoracoscopic and total procedure blood loss and conversions. Data for each patient in the series were plotted from left to right on the horizontal axis chronologically. The following formula was used:

$$CUSUM = \sum_{i}^{n} (xi\text{-}\mu)$$

X_i represents the measure of proficiency of each case and μ represents the mean of the examined variable.[19] This was repeated until the last patient within this series of 312.

For the binary variable conversion of the thoracoscopic phase, the CUSUM was defined as: CUSUM = $\Sigma(X_i - X_0)$, where $X_i = 0$ for success (no conversion), $X_i = 1$ for a failure (conversion).[20] As previously published, the conversion rate for the thoracoscopic phase of the operation was 19%.[10] Therefore in this study, X_0, was set at 0.19. This was repeated until the last

patient within this series of 312. The percentage of radical resections (R0) and the number of resected lymph nodes were not included in the CUSUM analyses due to the introduction of neoadjuvant therapy in 2006.

Proctoring

A newly introduced surgeon 2 was introduced in September 2011 to RAMIE. After 20 procedures as assisting table surgeon and 5 observational cases during the proctor program, surgeon 2 performed 15 RAMIE procedures under strict supervision by the proctor. At this moment, the proctor had experience with over 150 RAMIE procedures and a steady state of performance was reached considering surgical and oncological results. The results of the learning curve of surgeon 2 were compared to the results of the proctor in the same period of time (Phase 3) and to the initial results of the proctor . CUSUM analyses for surgeon 2 were performed for thoracoscopic operating time, total operating time, thoracoscopic and overall blood loss.

Statistical analysis

Statistical analysis was performed using SPSS version 23.0 (SPSS, Armonk, NY: IBM Corp.). We considered a P-value of <0.05 to be statistically significant. All skewed continuous data were presented as medians with range. To evaluate significance of differences between the two groups, the chi-squared test or Fisher's exact test were used as appropriated for categorical variables and the non-parametric Mann-Whitney U-test was used for continuous variables. CUSUM curves were computed with previously described formulae using Microsoft Excel 2011 (Microsoft Corporation, Redmond, WA).

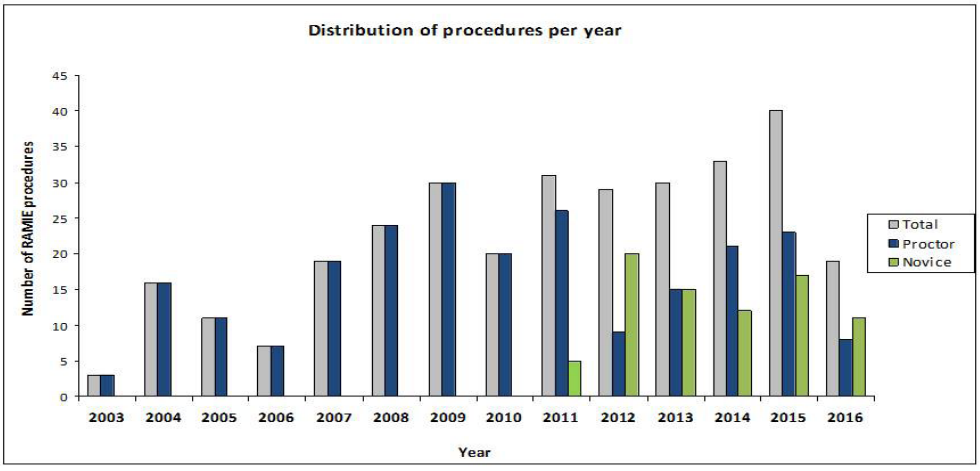

Figure 1. Number of RAMIE procedures performed per year.

Table 1: Patient demographics and tumor characteristics (n=312)

	n (%)	Median	Range
Age (y)		65	41 - 79
Gender			
M	225 (72)		
F	87 (28)		
BMI (kg / m²)		25	16 – 42
Co-morbidity			
No comorbidity	105 (34)		
Vascular	101 (32)		
Cardiac	65 (21)		
Diabetes	33 (11)		
Pulmonal	52 (17)		
Oncologic	42 (14)		
Previous thoracic / abdominal operation	81 (26)		
ASA score			
1	76 (24)		
2	197 (63)		
3	39 (13)		
Clinical stage			
IA	17 (5)		
IB	23 (7)		
IIA	49 (16)		
IIB	24 (8)		
IIIA	112 (36)		
IIIB	46 (15)		
IIIC	41 (13)		
Tumor location			
Upper esophageal	17 (5)		
Middle esophageal	53 (17)		
Lower esophageal / GEJ	242 (78)		
Tumor type			
Adenocarcinoma	209 (67)		
Squamous cell carcinoma	103 (33)		
Neoadjuvant treatment			
No therapy	90 (29)		
Chemotherapy	89 (29)		
Chemoradiotherapy	132 (42)		
Radiotherapy	1 (0)		
RAMIE			
Thoraco-laparoscopy	286 (92)		
Thoraco-laparotomy	26 (8)		
Reconstruction			
Gastric conduit (cervical, handsewn, end-to-side)	304 (97)		
Gastric conduit (intrathoracic, handsewn, end-to-side)	4 (1)		
Gastric conduit (intrathoracic, handsewn, end-to-end)	1 (0)		
Gastric conduit (intrathoracic, stapled, end-to-side)	2 (1)		
Colonic interposition (cervical, handsewn, end-to-side)	1 (0)		
Cervical lymph node dissection	6 (2)		

RESULTS

Between October 2003 and October 2016, 312 out of 539 (58%) consecutive patients with potentially resectable esophageal cancer underwent RAMIE. Patients with tumors of the distal esophagus or gastro-esophageal junction (GEJ) who had severe cardiopulmonary co-morbidity underwent a (laparoscopic) transhiatal esophagectomy. The number of procedures performed each year are shown in figure 1. The median number of RAMIE procedures was 22 per year (Figure 1).
Baseline characteristics for 312 patients are summarized in table 1. Conversions were observed in 37 patients (11%). A radical resection (R0) was achieved in 286 patients (92%).

Learning curve
In total 232 (74%) RAMIE procedures were performed by the proctor. The CUSUM curves are shown in figure 2a-c. The learning curve of the thoracoscopic and total operating time could be divided into 3 phases. Phase 1 included the first 70 cases, representing the learning curve. Phase 2 (between case 71–case 174) represented the increasing competence of the surgeon. Phase 3 represents technically more difficult cases, such as patients with upper esophageal cancer with suspected upper mediastinal lymph node metastases, cT4b esophageal cancer and patients with suspected cervical lymph node metastases undergoing a 3-field cervical dissection were included (Figure 2a).
According to the CUSUM curves for blood loss, the learning curve of thoracoscopic and total procedure blood loss could be divided into two phases. Phase 1 included the first 70 cases representing the initial learning phase. Phase 2 (case 71-case 174) represented the accumulation of additional experience of the surgeon. Even though indications were extended at case 175, an increase in blood loss was not observed in phase 3 (Figure 2b).
Comparisons for peri- and postoperative statistics between the 3 phases are presented in Table 2. Thoracoscopic operating time decreased from 199 to 170 minutes ($p = 0.006$) and total operating time decreased from 411 to 375 minutes ($p = 0.019$) comparing phase 1 to phase 2. Thoracoscopic blood loss decreased from 250 ml to 100 ml and total procedure blood loss decreased fro 500 tp 360 m comparing phase 1 to phase 2 ($p = 0.000$). Hospital stay decreased from 19 to 15 days ($p = 0.001$) and ICU stay decreased from 3 to 1 days comparing phase 1 to phase 2 ($p =0.010$). No differences were observed in postoperative complications (table 2).
According to the CUSUM curve for conversions (figure 2c), the learning curve of conversions could be divided into 3 phases. Phase 1 included the first 70 cases, with the line crossing the origin, representing the initial learning curve. After 70 patients, a steady state level of conversions was reached. After 125 procedures with the obtained additional experience, a definitive decline in the percentage of conversions was observed. According to the CUSUM curve for conversions (figure 2c), the learning curve of conversions could be divided into 3 phases. Phase 1 included the first 70 cases, with the line crossing the origin, representing the initial learning curve. After 70 patients, a steady state level of conversions was reached. After 125 procedures with the obtained additional experience, a definitive decline in the percentage of conversions was observed.

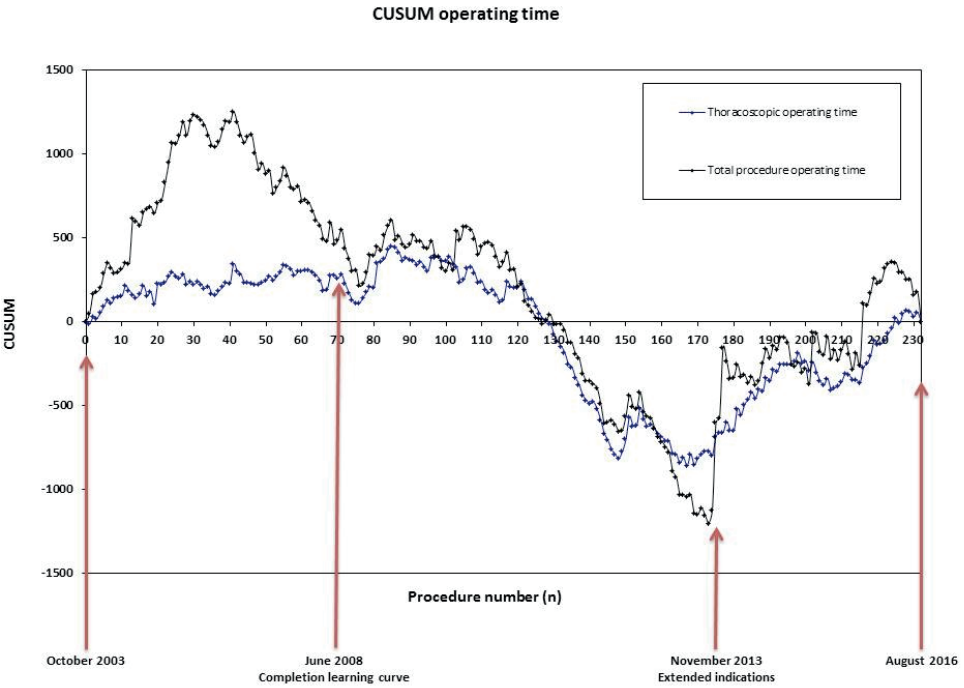

Figure 2a. CUSUM analysis for thoracoscopic and total procedure operating time versus procedure number in chronologic order.

Based on all the CUSUM curves we defined the learning curve completed for RAMIE after 70 cases, which were completed within 55 months.

Proctoring results

In total 80 out of 312 procedures were performed by surgeon 2 (26%). After 20 procedures as assisting table surgeon and 5 observational cases, surgeon 2 performed 15 RAMIE procedures under strict supervision by the proctor. These were included in the learning curve analysis (figure 3a and 3b).

Results from phase 1 and phase 3 of the proctor were compared to results of surgeon 2 (n=80). Baseline results are shown in table 2.

Beside a higher incidence of pulmonary (P=0.004) and oncologic comorbidity (P=0.044) all baseline characteristics were comparable between phase 3 of the proctor and the 80 procedures performed by surgeon 2. Median thoracoscopic operative time was 207 minutes for the proctor and 156 minutes for the surgeon 2 (p=0.000). Median total operative time was 401 minutes for the proctor and 338 minutes for surgeon 2 (p=0.001). All other variables, such as thoracoscopic and total procedure blood loss, the percentage of radical resections, the percentage of conversions, hospital and ICU stay and complications did not differ significantly between the proctor and surgeon 2 (Table 3). However, compared to the initial results of the proctor (phase 1), thoracoscopic and overall operating time, thoracoscopic

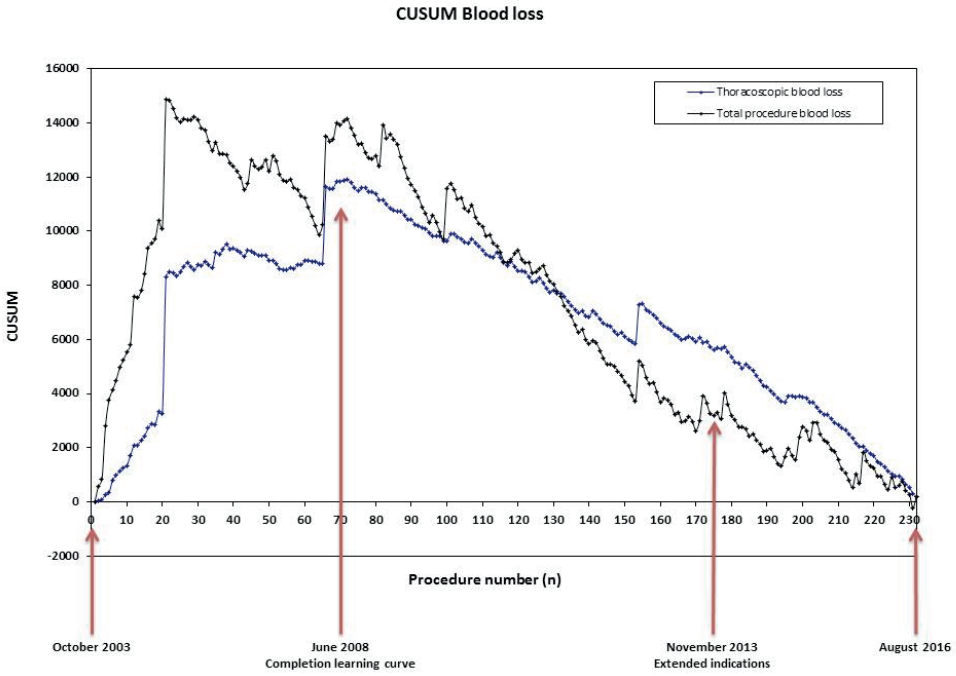

Figure 2b. CUSUM analysis for thoracoscopic and total procedure blood loss versus procedure number in chronologic order.

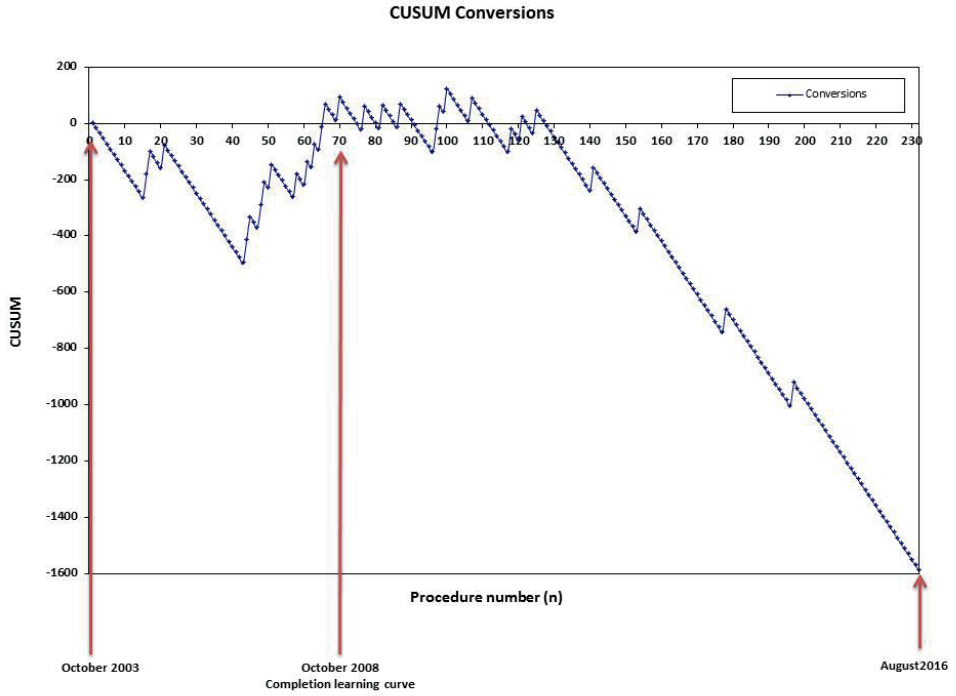

Figure 2c. CUSUM analysis for conversions versus procedure number in chronologic order.

Table 2: RAMIE results for proctor

	Proctor Phase 1 (case 1 - 70)	Proctor Phase 2 (Case 71 - 174)	Proctor Phase 3 (Case 175 -232)	P-value Phase 1 vs. Phase 2	P-value Phase 1 vs. Phase 3	P-value Phase 2 vs. Phase 3
Thoracoscopic operative time (min)	199	170	207	0.006	0.261	0.003
Total procedure operating time (min)	411	375	401	0.019	0.745	0.103
Thoracoscopic blood loss (ml)	250	100	100	0.000	0.000	0.545
Total blood loss (ml)	500	360	383	0.000	0.031	0.313
Conversions (n (%))	17 (24)	15 (14)	3 (5)	0.100	0.003	0.072
Thoracic phase	14 (20)	12 (12)	2 (3)	0.125	0.005	0.089
Abdominal phase	3 (4)	3 (3)	1 (3)	0.686*	0.626*	1.000*
Radicality (R0) (n (%))	57 (81)	99 (95)	53 (91)	0.003	0.107	0.334
Lymph nodes (n)	23	22	25	0.484	0.212	0.029
In hospital mortality (n (%))	4 (6)	6 (6)	3 (5)	1.000*	1.000*	1.000*
ICU stay (days)	3	1	1	0.010	0.002	0.458
Hospital stay (days)	19	15	16	0.001	0.047	0.914
Postoperative complications (n (%))						
Anastomotic leakage	20 (29)	22 (21)	14 (24)	0.262	0.572	0.661
Pneumonia	26 (37)	37 (36)	17 (29)	0.833	0.350	0.417
Postoperative bleeding	0 (0)	1 (1)	2 (3)	1.000*	0.117*	0.292*
RLN palsy	12 (17)	9 (9)	10 (17)	0.092	0.988	0.103
Cardiac complications	9 (13)	9 (9)	10 (17)	0.372	0.487	0.103
Wound infection	2 (3)	9 (9)	1 (2)	0.203*	1.000*	0.079

#Fisher's exact test 2-sided

and total procedure blood loss, conversions, ICU and hospital stay were significantly better in favor of surgeon 2.

Learning curve for surgeon 2.

For thoracoscopic operating time and total procedure operating time for surgeon 2, the CUSUM analysis could be dived in 3 phases (Figure 3a). Phase 1 included the first 24 cases, representing the learning curve. Out of the 24 first cases, the first 15 cases were supervised cases and hereafter 9 procedures were performed independently by the surgeon 2. The CUSUM curve for operating time increased in these 9 cases. After 24 procedures, a plateau phase was reached and hereafter the surgeon showed increasing competence (case 25-48). Case 49 represented the first case of a patient with cT4b esophageal cancer who was

operated by surgeon 2. Hereafter, more difficult cases were included. Inclusion of these cases resulted in longer operating times and an increase in the CUSUM curves.
The CUSUM curves for the surgeon 2 for thoracoscopic and total procedure blood loss could also be divided into 3 phases (figure 3b). Phase 1 included the first 24 cases representing the learning phase. After the first 15 supervised cases, an increase in the CUSUM curve for blood loss is observed in the 9 independent cases. After 24 cases, the CUSUM curve maximum was reached. Hereafter, accumulation of additional experience and a steady state of performance were reached (phase 2, case 25–48). Phase 3 (case 49-80) represented the

Table 3: Baseline characteristics for proctor versus surgeon 2

	Proctor Phase 1 (case 1 - 70)	Proctor Phase 3 (Case 175 -232)	Surgeon 2 (Case 1-80)	P-value Phase 1 vs. Surgeon 2	P-value Phase 3 vs. Surgeon 2
Age (y)	62	66	66	0.491	0.390
Gender					
M	52 (74)	44 (76)	64 (80)	0.404	0.561
F	18 (26)	14 (24)	16 (20)		
BMI (kg / m²)	25	25	25	0.625	0.596
Co-morbidity					
No comorbidity	45 (64)	14 (24)	20 (25)	0.000	0.116
Vascular	9 (13)	22 (38)	34 (43)	0.000	0.590
Cardiac	10 (14)	9 (16)	20 (25)	0.102	0.177
Diabetes	6 (9)	7 (12)	8 (10)	0.764	0.700
Pulmonary	6 (7)	19 (33)	10 (13)	0.437	0.004
Oncologic	3 (4)	15 (26)	10 (13)	0.074	0.044
Previous thoracic / abdominal operation	3 (4)	21 (36)	26 (33)	0.000	0.650
ASA score				0.462	0.842
1	21 (30)	10 (17)	17 (21)		
2	36 (56)	39 (67)	51 (64)		
3	10 (14)	9 (16)	12 (15)		
Clinical stage				0.000	0.776
IA	5 (7)	2 (3)	3 (4)		
IB	1 (1)	5 (9)	9 (11)		
IIA	13 (19)	6 (10)	14 (18)		
IIB	2 (3)	7 (12)	5 (6)		
IIIA	42 (60)	14 (24)	16 (20)		
IIIB	3 (4)	14 (24)	17 (21)		
IIIC	4 (6)	10 (17)	16 (20)		
Tumor location				0.335	0.165
Upper esophageal	1 (1)	7 (12)	5 (6)		
Middle esophageal	12 (17)	10 (17)	16 (20)		
Lower esophageal / GEJ	57 (81)	41 (71)	59 (74)		
Cervical lymph node dissection	0 (0)	5 (9)	1 (1)	1.000*	0.082

#Fisher's exact test 2-sided

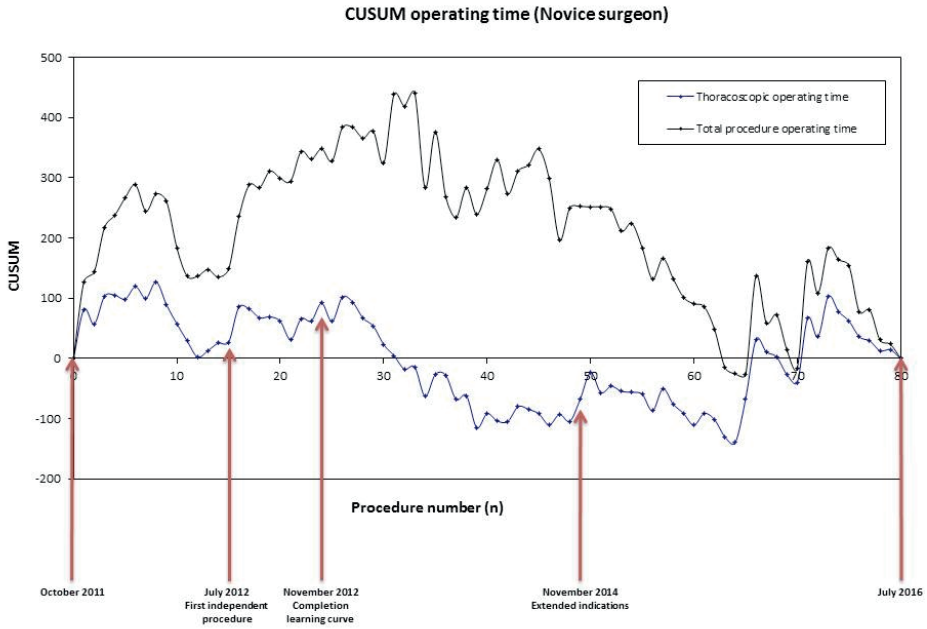

Figure 3a. CUSUM analysis for thoracoscopic and total procedure operating time for surgeon 2 surgeon in chronologic order.

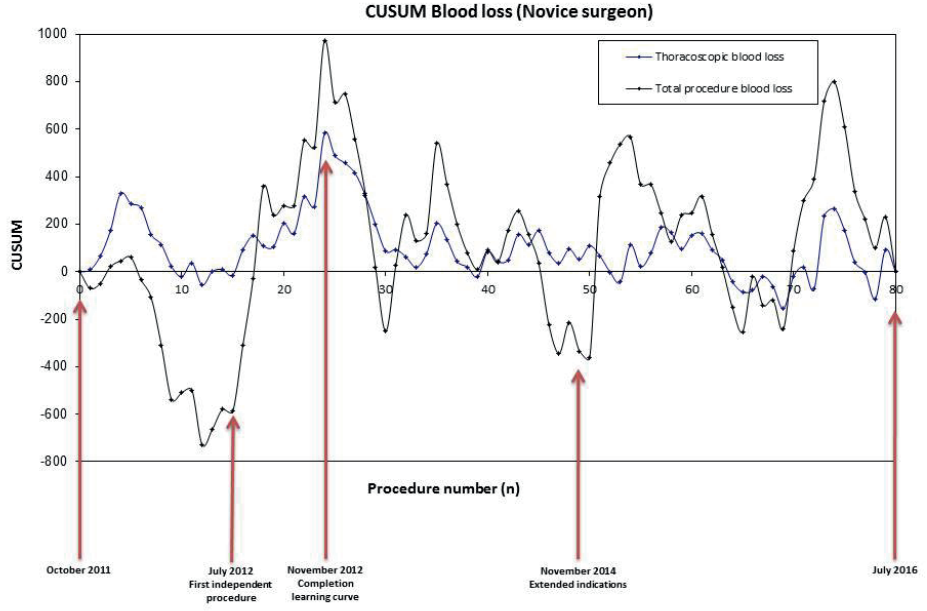

Figure 3b. CUSUM analysis for thoracoscopic and total procedure blood loss for surgeon 2 in chronologic order.

inclusion of more advanced cases with as a result an increase in blood loss in some patients. The CUSUM analysis for thoracoscopic conversions was not performed, as no thoracoscopic conversions occurred for surgeon 2 (Table 3).
Based on all the CUSUM curves we defined the learning curve for RAMIE for surgeon 2 as 24 cases (15 supervised cases and 9 independent cases) in our series. These 24 cases were completed within 13 months.

DISCUSSION

In this study, we presented our 13 years' experience with RAMIE to define the learning curve and to show the proctoring results for a newly introduced surgeon into RAMIE (surgeon 2). CUSUM analyses divided the learning curve for all measures of proficiency into 3 phases. Phase 1 included the first 70 cases, representing the initial learning curve. In phase 2 (case 70-175), a plateau phase was reached and the competence of the surgeon was increased.

Table 4: RAMIE results for proctor versus surgeon 2

	Proctor Phase 1 (case 1 - 70)	Proctor Phase 3 (Case 175 -232)	Surgeon 2 (case 1-80)	P-value Phase 1 vs. Surgeon 2	P-value Phase 3 vs. Surgeon 2
Thoracoscopic operative time (min)	199	207	156	0.000	0.000
Total procedure operating time (min)	411	401	338	0.000	0.000
Thoracoscopic blood loss (ml)	250	100	105	0.000	0.165
Total blood loss (ml)	500	383	365	0.000	0.194
Conversions (n (%))	17 (24)	3 (5)	2 (3)	0.000	0.407
Thoracic phase	14 (20)	2 (3)	0 (0)	0.000	0.175*
Abdominal phase	3 (4)	1 (3)	2 (3)	0.665*	1.000*
Radicality (R0) (n (%))	57 (81)	53 (91)	77 (96)	0.003	0.227
Lymph nodes (n)	23	25	25	0.249	0.756
In hospital mortality (n (%))	4 (6)	3 (5)	3 (4)	0.569*	0.696*
ICU stay (days)	3	1	1	0.000	0.399
Hospital stay (days)	19	16	14	0.000	0.268
Postoperative complications (n (%))					
Anastomotic leakage	20 (29)	14 (24)	21 (26)	0.750	0.778
Pneumonia	26 (37)	17 (29)	32 (40)	0.720	0.195
Postoperative bleeding	0 (0)	2 (3)	1 (1)	1.000*	0.572*
RLN palsy	12 (17)	10 (17)	7 (9)	0.123	0.134
Cardiac complications	9 (13)	10 (17)	14 (18)	0.431	0.968
Wound infection	2 (3)	1 (2)	1 (1)	0.599*	1.000*

In phase 3 (case 175-232), the indications for RAMIE were extended with cT4b tumors, patients with upper esophageal cancer with suspected upper mediastinal lymph nodes and patients with cervical lymph nodes metastases who underwent 3 field dissection (NODE study: NCT02426879). According to the CUSUM analyses, proficiency was reached after 70 procedures in June 2008, 55 months after the first RAMIE procedure with significant differences in thoracoscopic and total procedure operating time, thoracoscopic and total procedure blood loss and a reduction in ICU and hospital stay.

In this study, the Da Vinci® robotic system was used for the thoracoscopic phase. The robot could be used for the abdominal phase as well, however, at the time of introduction of RAMIE, there were no robotic endowristed coagulating instruments available. The dissection of the greater curvature along the gastroepiploic vessels with a rigid robotic ultrasonic scalpel did not add to conventional laparoscopic dissection. Furthermore, the dexterity of the robotic arms was insufficient to reach the duodenum, greater curvature and hiatus within a single docking. With the recently introduced robotic bipolar coagulator (vessel sealer®) and newest generation robot (Xi®) these limitations have been solved.

Until now, there are only 2 articles that described the learning process for RAMIE in 100 patients or less in clustered cohorts.[13,21] A learning process was noted after 20 cases and 30-45 cases, respectively.[13,21] No clear statements about completion of the learning curve were made. The learning curve for conventional MIE was also described in several articles.[22,23] By using CUSUM analyses it was concluded that approximately 35-44 procedures are needed to reach proficiency.[22,23] The limitation of all these studies was that these were early reports with insufficient numbers to identify the plateau of the learning curve. Data derived from studies describing learning curves in robot-assisted laparoscopic prostatectomy (RALP), suggest that approximately 80-300 procedures were needed to complete the learning curve for the whole procedure.[24] When these results are extrapolated to both MIE and RAMIE, at least 300 procedures are needed to be performed to draw firm conclusions about different phases of the learning curve.

After completion of the learning curve we introduced surgeon 2 into the RAMIE technique in October 2011. Surgeon 2 performed 80 out of 312 (26%) RAMIE procedures of whom 15 were under strict supervision. In the beginning of the proctoring process, cases were carefully selected with fewer patients with a history of pulmonary and oncologi disease The first 48 cases for surgeon 2 did not include more complicated cases. With this case selection and a strict supervision by the proctor in the first 15 patients, shorter thoracoscopic and total procedure operating times were observed for surgeon 2 ($p = 0.000$). Blood loss, conversions, radicality of surgery (R0) and postoperative outcomes such as hospital stay and postoperative complications were comparable. It was concluded that surgeon 2 performed RAMIE at least at the same level of performance compared to the proctor. The next aim was to assess whether surgeon 2 was able to complete his learning curve within a lower number of procedures and shorter time as compared to the proctor. CUSUM analyses were performed for thoracoscopic operating time and total procedure operating time, thoracoscopic and total procedure blood loss. According to these CUSUM analyses, proficiency was reached after 24 procedures (15 supervised and 9 independent cases) within 13 months, which is a reduction of 66% in the number of operations and a reduction of 76% in time compared to

the initial learning phase for the proctor.
These results support the effectiveness of the proctor program. After a limited introduction process with 20 procedures as assisting table surgeon, 5 observational and 15 supervised cases, surgeon 2 was able to show the same level performance as the proctor, with a shorter learning curve.
However, we do realize that many factors may have influenced the learning curve of surgeon 2. After finishing a 18 month upper gastrointestinal surgery fellowship with an emphasize on both open and minimally invasive esophagectomy, surgeon 2 was familiar with the surgical procedure. Furthermore, with 25 procedures (20 as a resident and 5 as esophageal surgeon) as assisting table surgeon, surgeon 2 was familiar with all steps of the RAMIE procedure. The previous experience of the proctor combined with the experience of the operative team including a physician assistant specialized in robotic surgery, dedicated anesthesiologists, and operation room scrub nurses resulted in standardization of the RAMIE procedure. All these factors might have contributed to a shorter learning curve for surgeon 2.
The question remains, whether these results can be extrapolated to other hospitals. Beside the newly introduced surgeon, the complete operating team should be trained as well.[36] For RAMIE, 2 motivated surgeons, a dedicated anesthesiologist and RAMIE specialized scrub nurses should be involved in the proctoring program. A sufficient case load (>20/year) and guaranteed access to a robotic system are of crucial importance.
In urology, proctoring has proven to be an essential mechanism for successful implementation of RALP and this approach may be comparable in RAMIE.[37] We started with a proctoring program for surgeons from other hospitals in 2014 and designed a structured training program for RAMIE for this purpose. The proctored surgeons should have experience in esophageal surgery and preferably in minimally invasive GI surgery. The program started with 2-3 case observations in our RAMIE expert center, followed by a basic and dedicated esophageal robotic course in a cadaveric lab. The first case at the own hospital was always proctored by an expert, preferably within two weeks following the last case observation. Hereafter, the proctor supervised the surgeon for the first 2-10 cases and reviewed the of skills after the first 20-25 procedures.[25] Until now, 8 surgeons from 4 hospitals were proctored according to this program. The results of this program will be evaluated in the near future.
In conclusion, for RAMIE, the first 70 cases formed the learning phase upon reaching proficiency after development of this technique in 2003. After a structured proctoring program, surgeon 2 was able to show the same level performance as the proctor. The learning phase for the surgeon 2 consisted of 24 cases (15 supervised and 9 independent cases) in 13 months, which is a reduction of 66% in the number of operations and a reduction of 76% in time, compared to the proctor. Proctoring is pivotal to reduce the learning curve of RAMIE for newly introduced surgeons and secure a flawless introduction of this technique.

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Chapter 9

Robot-assisted minimally invasive thoraco-laparoscopic esophagectomy versus open transthoracic esophagectomy for resectable esophageal cancer, a randomized controlled trial (ROBOT trial)

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Trials. 2012; 13:230

ABSTRACT

Background

For patients with esophageal cancer, radical esophagolymphadenectomy is the cornerstone of the multimodality treatment with curative intent. Transthoracic esophagectomy is worldwide the preferred surgical approach allowing for en-bloc resection of the tumor with the surrounding lymph nodes. However, the percentage of cardiopulmonary complications associated with the transthoracic approach is high (50-70%).

Recent studies have shown that robot-assisted minimally invasive thoraco-laparoscopic esophagectomy (RATE) was at least equivalent to the open transthoracic approach for esophageal cancer in terms of short-term oncological outcomes. RATE was accompanied with reduced blood loss, shorter intensive care unit stay and improved lymph node retrieval compared to open esophagectomy and the pulmonary complication rate, hospital stay and perioperative mortality were comparable.

Objectives

The objective is to evaluate the efficacy, risks, quality of life and cost-effectiveness of RATE as an alternative to open transthoracic esophagectomy as treatment for esophageal cancer.

Methods

This is an investigator-initiated and investigator-driven monocenter randomized controlled parallel-group, superiority trial. All adult patients (age ≥18 and ≤ 80 years) with histologically proven, surgically resectable (cT1-4a, N0-3, M0) esophageal carcinoma of the intrathoracic esophagus and with European Clinical Oncology Group performance status 0, 1 or 2 will be assessed for eligibility and included after obtaining informed consent. Patients (n=112) with resectable esophageal cancer are randomized at the outpatient department to either RATE (n=56) or open three-stage transthoracic esophageal resection (n=56). The primary outcome of this study is the percentage of overall complications (Grade 2 and higher) as stated by the modified Clavien-Dindo classification of surgical complications (MCDC).

Conclusion

This is the first randomized controlled trial designed to compare RATE with open transthoracic esophagectomy as surgical treatment for resectable esophageal cancer. If our hypothesis is proven correct, RATE will result in a lower percentage of postoperative complications, lower blood loss, shorter hospital stay, but with at least similar oncologic outcomes and better postoperative quality of life compared with the open transthoracic esophagectomy.

The study started in January 2012. Follow up will be 5 years. Short term results will be analyzed and published after discharge of the last randomized patient.

BACKGROUND

In 2008, an estimated 482,300 people were diagnosed with esophageal cancer, and 406,800 patients died of the disease worldwide.[1] Radical esophagolymphadenectomy is the cornerstone of the multimodality treatment with curative intent.[2-5]
Transthoracic esophagectomy is worldwide the preferred surgical approach allowing for en-bloc resection of the tumor with the surrounding para-tracheal, subcarinal and para-esophageal lymph nodes.[6,7] However, the percentage of cardiopulmonary complications associated with the transthoracic approach is high (50-70%).[6]
Minimally invasive esophagectomy (MIE) was designed to reduce surgical trauma, resulting in lower morbidity and mortality rates. With regard to MIE, review of literature shows a substantial decrease in blood loss, postoperative complications and days of hospital stay, with comparable oncologic results.[8-12]
In 2003 the robot-assisted thoraco-laparoscopic approach was developed at the University Medical Center Utrecht (UMCU), The Netherlands.[14] Robot-assisted thoraco-laparoscopic esophagectomy (RATE) facilitates complex minimally invasive procedures with an enlarged, 3 dimensional field of view. The articulated instruments allow dissection with 7 degrees of freedom.[14,15]
Until now, there are no prospective randomized controlled trials comparing robot-assisted minimally invasive esophagectomy with conventional open transthoracic esophagectomy. We present the protocol of the first randomized controlled trial comparing these 2 surgical approaches.

Aim of the study

This is a randomized controlled parallel-group, superiority trial of robot-assisted thoraco-laparoscopic esophagectomy versus open three-stage transthoracic esophagectomy in patients with resectable intrathoracic esophageal cancer.

METHODS

Objectives

Patients with resectable esophageal cancer are randomized at the outpatient department to either (a) robot-assisted thoraco-laparoscopic esophagectomy or (b) open three-stage transthoracic esophageal resection. The objective is to evaluate the efficacy, risks and cost-effectiveness of robot-assisted thoraco-laparoscopic esophagectomy as an alternative to open transthoracic esophagectomy as treatment for esophageal cancer. We hypothesize that the robot-assisted minimally invasive thoraco-laparoscopic esophagectomy leads to a lower postoperative complication rate, less blood loss and a shorter hospital stay, with similar oncologic outcomes and better postoperative quality of life compared with the open transthoracic esophagectomy (current reference standard of care).

Study design
This is an investigator-initiated and investigator-driven randomized controlled parallel-group, superiority trial comparing robot-assisted thoraco-laparoscopic esophagectomy with traditional open three-stage transthoracic esophageal resection
This study is conducted in accordance with the principles of the Declaration of Helsinki [17] and Good Clinical Practice Guidelines[18]. The independent ethics committee of the University Medical Center Utrecht (UMCU) has approved the study. Written informed consent will be obtained from all participating patients. Clinical trial monitoring will be conducted by an independent data monitor (Julius Clinical Research, Zeist, The Netherlands).

Study population
All adult patients (age ≥18 and ≤ 80 years) with histologically proven, surgically resectable (cT1-4a, N0-3, M0) squamous cell carcinoma, adenocarcinoma or undifferentiated esophageal carcinoma of the intrathoracic esophagus will be assessed for eligibility. Patients should have a performance status 0, 1 or 2 according to the European Clinical Oncology Group (ECOG) (table 1).

Table 1. Patients' In- and exclusion criteria

Inclusion criteria
- Histologically proven squamous cell carcinoma, adenocarcinoma or undifferentiated carcinoma of the intrathoracic esophagus (including Siewert I and II)
- Surgically resectable (T1-4a, N0-3, M0)
- Age ≥ 18 and ≤ 80 years
- European Clinical Oncology Group (ECOG) performance status 0,1 or 2
- Written informed consent

Exclusion criteria
- Carcinoma of the cervical esophagus
- Carcinoma of the gastro-esophageal junction (GEJ) with the main part of the tumor in the gastric cardia (Siewert type III)
- Prior thoracic surgery at the right hemithorax or thoracic trauma)

Study protocol
Patients are informed about the trial by one of our surgeons (R. van Hilegersberg or J.P. Ruurda) at the outpatient department. After receiving the information, all patients get one week time to consider their consent. After one week patients are contacted by the coordinating researcher (P.C. van der Sluis) to make an appointment to obtain and register informed consent.
After obtaining informed consent, randomization is done by computer generated random

numbers. Concealment of allocation is done by using sealed opaque envelops. There is no blinding for the patient, surgeon and coordinating researcher because this is difficult in daily practice. However the independent data monitoring safety committee is blinded to the allocated intervention. Within 1 week patients will be informed about the allocated treatment. This study is completed funded by the department of Surgery in the UMC Utrecht. Multiple esophageal cancer biopsies for pathological analysis will be obtained through esophagogastroscopy of which 4 biopsies will be snap frozen and stored for translational research. The physical status of the patient is assessed and preoperative testing is guided by institutional guidelines.[19]

Neoadjuvant (radio)chemotherapy will be administered according to the current policy in the Netherlands and the UMC Utrecht.[19] Two additional blood samples will be obtained for translational research (proteomics) at the following times: before start of neoadjuvant treatment, day of operation, after adjuvant treatment and with suspicion of recurrent disease.

After finishing preoperative neoadjuvant treatment, patients will be evaluated with a second CT-scan for metastases and resectability. When the tumor is considered to be resectable, patients will undergo the randomized intervention either robot-assisted thoraco-laparoscopic esophagectomy or open three-stage transthoracic esophagectomy depending on randomization.

All resection specimens will be preserved and stored (biobank, tissue-microarray) for translational research.

The study has started on January 1st 2012. Inclusion will take approximately 3 years. Follow up for each patient will be 5 years. Total duration of the study will be 8 years.

Surgery

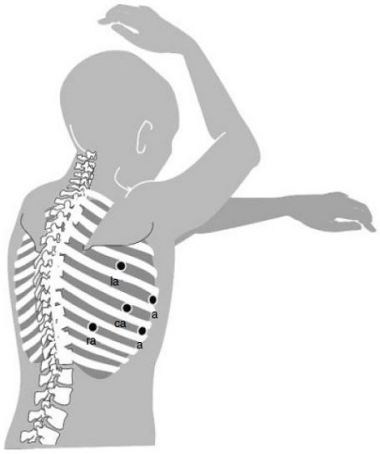
All procedures (robot-assisted thoraco-laparoscopic esophagectomy or open transthoracic esophagectomy) will be carried out by the same experienced surgeons in the UMC Utrecht (JR and RvH). All patients will receive an epidural catheter to provide adequate postoperative analgesia. Patients will be intubated with a left-sided double-lumen tube to enable selective desufflation of the right lung during the thoracic phase in both procedures.

Prophylactic antibiotics Cefazolin (2000 mg) and metronidazole (500 mg) antibiotic prophylaxis will be administered 30 minutes prior to incision.[15] An intravenous injection of 10 mg/kg methylprednisolone will be administered 30 minutes prior to incision to minimize postoperative pulmonary complications.[20] During single-lung ventilation, a pressure-controlled ventilation strategy will be used with a maximum pressure of 20 cm H_2O.[21]

Open three stage transthoracic esophagectomy

The patient is placed in a left lateral decubitus position and the procedure commences with a right posterolateral thoracotomy. After incision and desufflation of the right lung the pulmonary ligament is incised followed by identification of the azygos vein. The azygos vein is clipped and ligated at the level of the azygos arch. The thoracic duct is identified, clipped and ligated. The esophagus is resected en bloc with the surrounding mediastinal lymph nodes. The resected specimen will contain right-sided paratracheal (lymph node station

2R), tracheobronchial (lymph node station 4), aortopulmonary window (station 5), carinal (station 7) and peri-esophageal (station 8) lymph nodes.[23]
Chest tubes are placed and the thoracotomy wound is closed using intracutaneous closure with absorbable sutures.
The patient is turned to a supine position for the abdominal phase via supra-umbilical laparotomy. The stomach is mobilized with special care for the gastroepiploic and short gastric vessels. The left gastric artery is identified, clipped and ligated. Lymph node dissection is performed around the celiac trunk and the lesser omentum. A linear stapler (GIATM 80, 3•8 mm; Covidien, Mansfield, Massachusetts, USA) is used to create a gastric conduit 4 cm wide, which is routinely oversewn.[24] The gastric conduit is pulled up through the mediastinum along the original anatomic tract of the esophagus with the aid of a plastic tube (laparoscopic camera bag). A cervical handsewn end-to-side anastomosis is created between the gastric tube and the cervical oesophagus using a 3/0 polydioxanone single-layer running suture. A feeding jejunostomy is placed in the second loop after the ligament of Treitz for postoperative feeding. The abdomen is closed in layers with PDS loop for the fascia and skin intracutaneously with monocryl. Patients are transferred to the intensive



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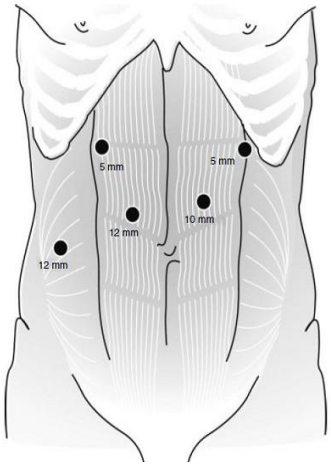

1b

Figure 1. Trocar arrangement during robot-assisted thoracoscopic phase
Figure 1a. Trocar arrangement during robot-assisted thoracoscopic phase. La: Left robotic arm (4th intercostal space); a: assistant thoracoscopic working port (5th and 7th intercostal space); ca: robotic camera arm (6th intercostal space); ra: right robotic arm (8th intercostal space).[15]
Figure 1b. Trocar arrangement during the laparoscopic abdominal phase. The camera was inserted through the 10-mm para-umbilical trocar port and two 5-mm trocars were used as laparoscopic working ports. The liver retractor was inserted through the 12-mm right para-rectal trocar port. The harmonic scalpel was inserted through the 12-mm paraumbilical port.[15]

care unit (ICU) after the surgical procedure.

Robot-assisted minimally invasive thoraco-laparoscopic esophagectomy

The RATE was described previously.[15] For the thoracic phase, the patient is positioned in the left lateral decubitus position, tilted 45° towards the prone position. The robotic system (daVinci Si system, Intuitive Surgical Inc., Sunnyvale, CA, USA) is brought into the field at the dorsocranial side of the patient. Three ports are placed for the robotic system as well as 2 thoracoscopic ports for the assisting surgeon (figure 1a). After incision and installation of the operation robot and selective desufflation of the right lung, the pulmonary ligament is divided. Hereafter, the parietal pleura is dissected at the anterior side of the esophagus from the diaphragm up to the azygos arch. The azygos vein is ligated with Hem-o-lok (Teleflex Medical, Weck Driv, NC, USA) and divided.[22] Dissection of the parietal pleura is continued above the azygos arch to establish dissection of the right paratracheal lymph nodes. At the posterior side of the esophagus, the parietal pleura is dissected cranially to caudally along the azygos vein, including the thoracic duct. The thoracic duct is clipped with a 10-mm endoscopic clipping device (EndoclipTM II; Covidien, Mansfield, Massachusetts, USA) to prevent chylous leakage. To facilitate esophageal mobilization a penrose drain is placed around the esophagus to manipulate the esophagus for further mobilization. The esophagus is resected en bloc with the surrounding mediastinal lymph nodes. The resection specimen will contain the same lymph nodes as described for the open procedure.

For the abdominal phase, the patient is placed in supine position. Figure 1b shows the position of the laparoscopic trocars. The lesser omentum is opened and transected closely to the liver, until the left crus of the diaphragm is reached. Hereafter, the greater gastric curvature is dissected using a harmonic ace. An abdominal lymphadenectomy is performed including lymph nodes surrounding the celiac trunk, along the left gastric and splenic artery and the lesser omental lymph nodes. The left gastric artery and vein are ligated with Hem-o-lok (Teleflex Medical, Weck Driv, NC, USA) and transected at their origin.

Through a left-sided vertical incision along the sternocleidomastoid muscle, cervical phase of esophagectomy is initiated to facilitate mobilization of the cervical esophagus. No formal cervical lymph node dissection is carried out, but macroscopically suspected cervical lymph nodes are dissected. The cervical esophagus is transected and a cord is attached to the specimen. The dissected esophagus with en-bloc the surrounding lymph nodes are pulled down through the mediastinum under laparoscopic view.

Hereafter, the left para-umbilical trocar port is widened to a 5-7-cm transverse transabdominal incision. The resection specimen is removed through this incision with a wound drape (3M, St. Paul, Minnesota, USA) to create the gastric conduit extracorporally. A linear stapler (GIATM 80, 3•8 mm; Covidien, Mansfield, Massachusetts, USA) is used to create a gastric conduit 4 cm wide, which is routinely oversewn.[24] The gastric conduit is pulled up through the mediastinum along the original anatomic tract of the esophagus with the aid of a plastic tube (laparoscopic camera bag). A cervical handsewn end-to-side anastomosis is created between the gastric tube and the cervical esophagus using a 3/0 polydioxanone single-layer running suture. A feeding jejunostomy is placed in the second loop after the ligament of Treitz for postoperative feeding. The abdomen is closed in layers with PDS loop for the fascia and skin intracutaneously with monocryl. Patients are transferred to the intensive care unit

(ICU) after the surgical procedure.

Outcome measurements

In terms of short-term oncological outcomes, we expect the robot-assisted esophagectomy to be equivalent to the open approach for survival, but is accompanied with fewer complications.[9-12] Therefore, the primary outcome of this study is the percentage of overall complications (Grade 2 and higher) as stated by the modified Clavien-Dindo classification of surgical complications (MCDC).[25]

Secondary biochemical outcomes include individual components of the primary endpoint (Major complications (MCDC grade II-IV)) including: myocardial infarction, anastomotic leakage (clinical or radiologic diagnosis), anastomotic stenosis, chylothorax (chylous leakage, presence of chylous in chest tubes or indication to start low fat (2%) containing tube feeding (Vivonex® T.E.N., Nestlé), gastric tube necrosis (proven by gastroscopy), pulmonary embolus, deep vein thrombosis, vocal cord palsy or paralysis. Minor complications (MCDC grade I) will also be recorded. These include for example wound infections, pleural effusions and delayed gastric emptying.

Length of ICU-MCU stay (days), length of hospital stay (days), in hospital mortality (IHM) and mortality within 30 and 60 days will be reported. For all patients, the cause of death will be noted. If applicable, the results of the autopsy report will be noted. Two, 3 and 5 year disease free and overall survival will
be reported.

Operation time is defined as time from incision until closure (minutes) for both the thoracic and the abdominal phase of the procedure. For the robotic procedure, set up time will be recorded separately. Unexpected events and complications occurring during the operation will be recorded (e.g. hemorrhage requiring transfusion, perforation of other organs) as well as blood loss during operation (ml, per phase). In case of conversion to thoracotomy or laparotomy the reason for conversion has to be explained (absolute numbers/percentage).

The resected specimen will be marked by the surgical team for the position of lymph node dissection. Evaluation will be performed by an experienced pathologist using standard protocols. Stage grouping will take place according to the Union Internationale Contre le Cancer (UICC) protocol using the TNM-7 classification.[26] Exact localization of the lymph nodes is an essential part of the pathologic examination.[23] The pathology report contains the following parameters: site of tumor, type and gradation, extension in the esophageal wall, margins of the resection, extent of resection (R0, R1 or R2)[27], lymph node status with the number of lymph nodes, Tumor Regression Grade (TRG, according to Mandard)[28], vaso-invasion and perineural growth. Quality control of pathology will be provided by a specialized gastrointestinal pathologist (FJWtK).

Type and dose of used analgesics will be noted during the hospital admission period. Visual Analogue Scale (VAS) for pain will be noted at following times: pre-operatively and the first

10 days after surgery and a fixed periods during follow up (6 weeks, 6 months and yearly post-operatively up to 5 years).
Quality of life questionnaires will be required at following times: SF-36, EORTC QLQ-C30 (Dutch), EORTC OES18 (Dutch) and EQ-5D (Appendix 1 & 2) pre-operative < 5 days and 6 weeks, 6 months and yearly up to 5 years post-operatively.

The approach for the cost-analysis is comparing actual direct medical costs incurred with both strategies up until 5 years after the operation. Costs estimates will be based on the recorded volumes and unit costs associated with both procedures. This includes the costs of operation rooms, hospital and ICU stay, costs associated with complications and re-operations.

Sample size calculation
Hypothesis: Compared with an open transthoracic esophagectomy, robot-assisted thoraco-laparoscopic esophagectomy will result in a lower percentage of overall complications (MCDC Grade 2 and higher). In a prospective analysis of our own series, MCDC grade 2-5 complications were observed in 69% of all patients who underwent robot-assisted thoraco-laparoscopic esophagectomy and in 91% of all patients who underwent open transthoracic esophagectomy in our won series in the UMC Utrecht (2003-2010). We calculated that 102 patients (51 in each arm) with resectable esophageal cancer would be required to detect this 22% reduction in the absolute risk of overall complications (from 91% to 69% of patients) based on a two-sided significance level (alpha) of 0.05 and a power of 0.80. An estimated compensation of 10% for drop out is included in the total number of patients resulting in total 112 patients, 56 in each arm. The flowchart visualizes the final design (figure 2).

Statistical analysis
All prospective data will be statistically analyzed by the use of the statistical software SPSS. Data analysis will be performed in accordance with the intention-to-treat principle; additional per-protocol analysis will also be performed for tumor type, tumor stage and type of neoadjuvant treatment.
To evaluate significance of differences between the two groups, chi-squared and Fisher's exact test will be used as appropriate for categorical variables, and the non-parametric Mann-Whitney U-test for continuous variables.
To evaluate differences in disease free and overall survival, Kaplan-Meier survival curves will be computed. Survival curves will be compared by log-rank test and multivariable analysis will be accomplished by the Cox regression model. Significance level will be set at 5%.
The approach for the cost-analysis is comparing actual direct medical costs incurred with both strategies up until 5 years after the operation. Costs estimates will be based on the recorded volumes and unit costs associated with both procedures. This includes the costs of operation rooms, hospital and ICU stay, costs associated with complications and re-operations.
Pain scores will be analyzed using a linear mixed model using repeated measures analysis. The quality of life questionnaires will be compared by using covariance analysis (pre-

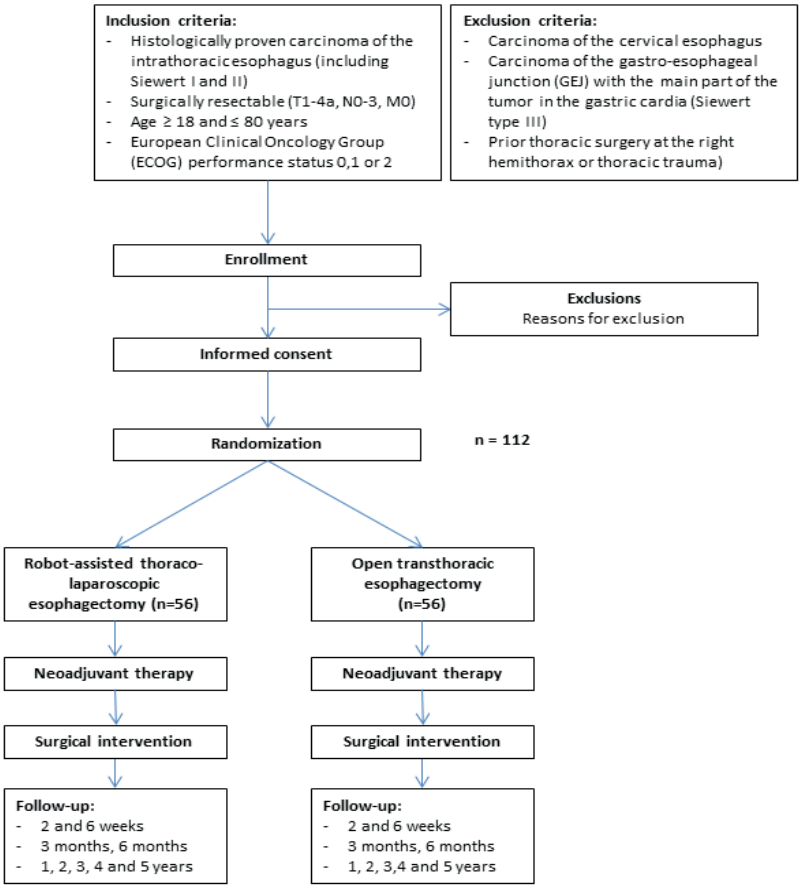

Figure 2. Flow chart ROBOT trial.

operative scores as co-variables). The cost-effectiveness analysis will compare the mean costs and effects for both strategies and result in an incremental cost-effectiveness ratio. Uncertainty in the balance between costs and effects will be assessed with bootstrapping. A time horizon of 5 years will be applied, and costs and effects will be discounted according to Dutch guidelines.
If the baseline characteristics differ after randomization, i.e. there is a lack of balance in the confounding factors; this will be corrected using the multivariate analysis or by using a net benefit regression approach.

Interim-analysis
There will be one interim-analysis. The stopping rule used for efficacy (i.e. better outcome for minimally invasive for the primary endpoint) is the Peto-approach, meaning a p-value <0.001. The trial will not be stopped for futility (i.e. no difference) as the robot-assisted

minimally-invasive approach is being used by a growing numbers of centers worldwide and the outcome of all endpoints of this first randomized trial on this subject are relevant to health care professionals involved with this procedure in those hospitals. As is advised by the Dutch Central Committee on Research involving Human Subjects (CCMO) there is no formal stopping rule for harm.
After every 25 patients, individualized patient description charts including safety parameters will be presented to the Data Safety Monitoring Committee (DSMC). The DSMC will discuss these in a plenary or telephone conference with the study coordinator and principal investigator present. If the suspects harm (i.e. worse outcome for minimally invasive) they will inform the trial research group. The trial research group will discuss in a plenary session together with the DSMC the potential harm per patient and determine whether a relationship can be drawn between the minimally-invasive procedure and the adverse events. Consensus will be reached and the METC will be informed.

DISCUSSION

To the best of our knowledge this is the first randomized controlled trial designed to compare robot-assisted minimally invasive thoraco-laparoscopic esophagectomy (RATE) with open transthoracic esophagectomy as surgical treatment for resectable esophageal cancer.
In the 2010 revised Dutch esophageal carcinoma guidelines, open transthoracic esophagectomy is considered to be the procedure of first choice for patients with resectable esophageal carcinoma.[19] However, the open transthoracic esophagectomy is accompanied with significant morbidity, which is predominantly through cardiopulmonary complications.[6]
To reduce surgical trauma and morbidity of the open transthoracic esophagectomy, minimally invasive procedures have been designed to overcome this problem. However, conventional (thoraco)scopic surgery has some important limitations, such as a 2-dimensional view, disturbed eye-hand coordination and limited degrees of freedom, which might limit the surgeon in performing an optimal radical esophageal and mediastinal lymph node dissection.[13]
To overcome the limitations of conventional (thoraco)scopic surgery, the robot-assisted minimally invasive thoraco-laparoscopic esophagectomy was developed in the UMC Utrecht in 2003.[15] Despite these unchallengeable technical advantages, the evidence behind its superiority over the conventional open transthoracic esophagectomy is still lacking. From a systematic review, which included 9 articles (130 cases) related to robot-assisted esophagectomy, it was concluded that robot-assisted esophagectomy was a feasible and safe technique.[16] In terms of short-term oncological outcomes, RATE was at least equivalent to the open transthoracic approach for esophageal cancer.[9-12,16] Robot-assisted minimally invasive thoraco-laparoscopic esophagectomy was accompanied with reduced blood loss, shorter intensive care unit stay and improved lymph node retrieval compared to open esophagectomy and the pulmonary complication rate, hospital stay and perioperative mortality were comparable.[16] Disadvantages of the robot-assisted thoraco-laparoscopic esophagectomy were reported to be a prolonged operative time and high costs consisting of acquisition of an operation robot and disposable tools.[16]

The level of evidence for robot-assisted minimally invasive thoraco-laparoscopic esophagectomy is suboptimal and based on case series or expert opinions only (Level 4 or 5).[16] The systematic review strongly emphasized the need for well conducted randomized controlled trials and long-term survival studies within a framework of measured and comparable outcomes to prove the superiority of robot-assisted minimally invasive thoraco-laparoscopic esophagectomy over the worldwide current standard open transthoracic esophagectomy.[16]
Recently, 2 articles about conventional minimally invasive esophagectomy were published.[29,30] Results from both articles show that minimally invasive esophagectomy in general is superior over open esophagectomy. [29,30] This suggests that robot assisted esophagectomy might be superior as well. One could argue that the real question is if robotic assisted esophagectomy can improve outcomes when compared to coventional minimally invasive esophagectomy. However, with limited evidence available for the superiority of robot-assisted esophagectomy over open esophagectomy, it is yet too early to compare robot-assisted esophagectomy with conventional minimally invasive esophagectomy. Differences between these groups will probably be small and therefore large numbers of patients are needed to ensure enough statistical power. Such a clinical trial can only be done worldwide in a multicenter fashion by surgeons who are experienced in both techniques to avoid bias. The UMC Utrecht has the largest experience worldwide with robot-assisted thoraco-laparoscopic esophagectomy. Combined with a completed learning curve, our centre is considered to be the best place to compare robot-assisted esophagectomy with the open transthoracic esophagectomy. We have started this monocenter randomized controlled trial in 2012. This monocenter randomized controlled superiority trial can provide further evidence supporting the robot-assisted minimally invasive thoraco-laparoscopic esophagectomy as treatment for resectable esophageal cancer.
It is anticipated that the inclusion for this study will take three years to complete. The study started in January 2012, follow up will be 5 years. Short term results will be analyzed and published after discharge of the last randomized patient.

CONCLUSION

This is the first randomized controlled trial designed to compare robot-assisted minimally invasive thoraco-laparoscopic esophagectomy with open transthoracic esophagectomy as surgical treatment for resectable esophageal cancer
If our hypothesis is proven correct, robot-assisted minimally invasive thoraco-laparoscopic esophagectomy will result in a lower percentage of postoperative complications, lower blood loss, shorter hospital stay, but with at least similar oncologic outcomes and better postoperative quality of life compared with the open transthoracic esophagectomy (current standard).

Trial status
Recruiting of patients started in January 2012.

Abbreviations

CT	Computed tomography
DSMC	Data Safety Monitoring Committee
ECOG	European Clinical Oncology Group
EUS	Endoscopic ultrasonography
FDG	[18F] Fluorodeoxyglucose
GEJ	Gastro-esophageal junction
GI	Gastro-intestinal
ICU	Intensive care unit
MCDC	Modified Clavien-Dindo classification
METC	Medisch Ethische Toetsingscommissie
MCU	Medium care unit
MIE	Minimally invasive esophagectomy
PET	Positron emission tomography
R0	Oncological radical resection
TNM	Tumor, Node, Metastasis
UICC	Union Internationale Contre le Cancer
UMC	Universitair Medisch centrum
VAS	Visual Analogue Scale
WMO	Wet maatschappelijke ondersteuning

Competing interests
All authors declare to have no competing interests.

Authors' contributions
PCS, JPR, SH, RJJV, MGHB, and RH were involved in developing the original study design. PCS, JPR, SH, RJJV, MGHB, and RH developed the research protocols. JPR, IHMBR, JCAJ, FJWK, ACK, MSL, MPJKL, OR, MEIS, ES, FPV, EEV, PDS and RH are responsible for the clinical input. HK will be responsible for the economic and quality of life analysis. PCS, JPR and RH drafted the paper. All authors provided input into revisions of the paper and have approved the final manuscript.

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Chapter 10

Robot-assisted minimally invasive thoraco-laparoscopic esophagectomy versus open transthoracic esophagectomy for resectable oesophageal cancer: a randomized controlled trial

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ABSTRACT

Background
The standard curative treatment for patients with esophageal cancer is perioperative chemotherapy or preoperative chemoradiotherapy followed by open transthoracic esophagectomy (OTE). Robot-assisted minimally invasive thoraco-laparoscopic esophagectomy (RAMIE) may reduce perioperative complications and improve functional recovery.

Methods
A single center randomized controlled trial was conducted, assigning 112 patients with resectable intrathoracic esophageal cancer to either RAMIE or OTE. The composite primary endpoint was the occurrence of overall surgery-related postoperative complications (modified Clavien–Dindo classification (MCDC) grade 2-5).

Results
Overall surgery-related postoperative complications occurred less frequently after RAMIE (59%) compared to OTE (80%) (risk ratio with RAMIE (RR) 0.74 (95% Confidence interval (CI), 0.57-0.96; P=0.02). RAMIE resulted in less median blood loss (400ml versus 568ml, P<0.001), a lower percentage of pulmonary complications (RR 0.54 (95%CI, 0.34-0.85; P=0.005) and cardiac complications (RR 0.47 (95%CI, 0.27-0.83; P=0.006)) and lower mean postoperative pain (visual analogue scale, 1.86 versus 2.62; p<0.001) compared to OTE. Functional recovery at postoperative day 14 was better in the RAMIE group (RR 1.48 (95%CI, 1.03–2.13; P=0.038)) with better quality of life score at discharge (mean difference quality of life score 13.4 (2.0-24.7, p=0.02) and 6 weeks post-discharge (mean difference 11.1 quality of life score (1.0-21.1; p=0.03)). Oncological outcomes at short-term (radicality, number of lymph nodes) and long-term (overall and disease-free survival) were comparable at a medium follow up of 40 months.

Conclusions
RAMIE resulted in a lower percentage of overall, surgery-related and cardiopulmonary complications with lower postoperative pain, better short-term quality of life and a better short-term postoperative functional recovery compared to OTE. Oncological outcomes were equal and in concordance with the highest standards nowadays. This randomized controlled trial provides evidence for the use of RAMIE to improve postoperative outcome in patients with resectable esophageal cancer.

INTRODUCTION

The standard treatment for locally advanced esophageal cancer with curative intent is perioperative chemotherapy or preoperative chemoradiotherapy followed by esophagectomy with 2-field lymphadenectomy.[1] Worldwide, an open transthoracic esophagectomy (OTE), consisting of thoracotomy and laparotomy, with gastric conduit reconstruction is the standard operative technique.[2,3]
Minimally invasive esophagectomy (MIE) was developed to improve the postoperative outcome by reducing the surgical trauma, with comparable short-term oncologic results.[4,5,6] However, MIE is a highly complex procedure associated with a long learning curve.[2,6]
In 2003, robot-assisted minimally invasive thoraco-laparoscopic esophagectomy (RAMIE) was developed to overcome the technical limitations of MIE.[6] Robotic surgery benefits from a stable 3-dimensional, magnified view and articulated instruments enabling precise dissection with 7 degrees of freedom of movement.[7,8]
Results from several cohort studies show that RAMIE is feasible and safe combining the benefits of the minimally invasive approach with good oncological outcome.[7,8,9] However, no randomized comparison between RAMIE and OTE has been performed yet.[10,11]
In this randomized controlled trial, RAMIE was compared to OTE in a center that passed the learning curve with 10 years of RAMIE experience. The primary objective of this randomized controlled trial was to investigate differences between the two surgical approaches on postoperative complications (i.e. primary outcome). Secondary outcomes were functional recovery, postoperative pain, (short-term) quality of life costs and oncologic outcomes.

METHODS

Study design and oversight

The ROBOT (**ROB**ot-assisted minimally invasive thoraco-laparoscopic esophagectomy versus **O**pen **T**ransthoracic esophagectomy) trial was an investigator-initiated and investigator-driven randomized superiority controlled parallel-group, single center trial comparing robot-assisted minimally invasive thoraco-laparoscopic esophagectomy (RAMIE) (Da Vinci® robotic system Intuitive Surgical Inc., Sunnyvale, California, USA) with open transthoracic esophagectomy (OTE). The design and rationale of the ROBOT trial were reported previously.[11] The ROBOT trial followed the Consolidated Standards of Reporting of Trials (CONSORT) guidelines for patient reported outcomes.[12] A data safety monitoring board (DSMB) of 5 independent, non-participating physicians assessed safety during the trial in 3 meetings, of which 1 contained an interim analysis after 56 patients. The stopping rule for efficacy in the interim analysis was the Peto approach, meaning $P_{interim}<0.001$.

Patients and staging

The inclusion period of the trial was from January 2012 - August 2016 in the University Medical Center Utrecht, Utrecht, the Netherlands. The in- and exclusion criteria were described previously (supplementary methods S1).[11] The study was conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice Guidelines.[14,15] The

independent medical ethics committee of the University Medical Center Utrecht approved the study. Written informed consent was obtained from all participating patients. Clinical trial monitoring was conducted by an independent data monitor (Julius Clinical Research, Zeist, The Netherlands).
All patients were discussed in a multidisciplinary cancer board to determine optimal treatment. Diagnostic work-up of all patients consisted of endoscopy with biopsy, endoscopic ultrasound (EUS), ultrasonography of the neck, and either standalone computed tomography (CT) or integrated 18F-fluorodeoxyglucose positron emission tomography (18F-FDG PET)/CT scanning for clinical staging. At the time of initiation of the trial in January 2012, perioperative chemotherapy according to the MAGIC trial (epirubicin, cisplatin and capecitabine) was the standard treatment for patients with esophageal adenocarcinoma.[16] After publication of the CROSS trial in May 2012, the standard treatment was switched from perioperative chemotherapy to neoadjuvant chemoradiotherapy (carboplatin and paclitaxel with concurrent radiotherapy).[17] All cT0 patients who underwent esophagectomy had irradical endoscopic mucosal resection or endoscopic submucosal dissection before and did not undergo neoadjuvant treatment.

Randomization and quality control
Patients were screened at the outpatient department for inclusion in the ROBOT trial and received the trial information. Patients had at least 1 week time to consider informed consent for inclusion in the trial. After obtaining written informed consent, patients were randomized by the study coordinators distant and separate from the surgeons who informed the patients for inclusion in the trial. Allocation of concealment was performed using computer generated random numbers in sealed opaque envelopes corresponding to either RAMIE or OTE. Operator blinding for the procedure was not possible. All surgical procedures were performed by the same experienced surgeons in the UMC Utrecht (JPR and RvH) who performed at least 50 RAMIE and OTE procedures before. All outcomes were discussed in a weekly multidisciplinary meeting, where the participants were unaware of treatment allocation. All trial patients were included in the national registry Dutch Upper Gastrointestinal Cancer Audit (DUCA) in order to facilitate a transparent way to register complications.

Surgical procedures
The surgical procedures were described in detail previously.[7-11] An epidural catheter was placed routinely in both treatment arms to provide adequate postoperative analgesia. The intraoperative ventilation technique of single lung ventilation was the same in the 2 treatment arms. The patient positioning and surgical resection technique was also similar for the open and minimally invasive approach. For the thoracic phase, the patient was positioned in the left lateral decubitus position, tilted 45° towards prone position (semiprone). The length of the trocars incisions in the thoracic phase were 2x 8mm and 3x 12mm. The thoracic phase included a mediastinal lymphadenectomy, including the paratracheal (station 2), tracheobronchial (station 4), aorto-pulmonary window (lymph nodes in the window dorsal to the aortic arch, cranially to the left main bronchus up until

the pulmonary artery (station 5)), carinal (station 7) and periesophageal (station 8) lymph nodes.[18] The patient was thereafter placed in the supine position to facilitate the abdominal phase of gastric mobilization, truncal lymph node dissection and gastric tube formation with cervical hand sewn end-to-side esophago-gastrostomy.[7-11] A tube feeding jejunostomy was placed in all patients. In both arms the jejunostomy catheter was created by an open surgical technique, using either the median laparotomy or the transverse incision which was created for removing the resection specimen.
The resected specimen was evaluated by a specialized gastrointestinal pathologist using a standard protocol, with emphasis on resection margins, radicality of resection (R0-2), tumor type, extension of the tumor, the presence and localization of lymph nodes and tumor regression grades.[18,19] The 7th edition of the International Union Against Cancer (UICC) was used for TNM-classification and tumor grade.[20] The (circumferential) resection margins were evaluated using the College of American Pathologist (CAP) criteria.[21]

Postoperative Management
For all patients, irrespective of randomization to RAMIE and OTE, the same postoperative protocol was followed. Mechanical ventilation was continued until patients were transferred to the intensive care unit (ICU), where patients were extubated 2-3 hours after ending the operation. At postoperative day 1, patients were transferred to the medium care unit (MCU) and to the surgical ward on postoperative day 2. All patients were placed on a nil-by-mouth routinely with jejunostomy tube feeding during the first 4 days postoperatively. A nasogastric tube and bilateral chest tubes were routinely placed.[7-11] No postoperative swallow tests were performed.[22] In absence of clinical signs of anastomotic dehiscence, patients started with sips of water at day 5 and the oral intake was gradually increased to solid food. Enhanced recovery after surgery (ERAS) guidelines were not used in the postoperative protocol.

End points and follow up
The primary endpoint of this study was the percentage of overall surgery-related postoperative complications modified Clavien–Dindo classification (MCDC) surgical complications grade ≥2.[11,23]
Secondary endpoints (MCDC grade ≥2) were the individual components of the primary endpoint and included pulmonary complications (pneumonia, pneumothorax, pulmonary embolus and acute respiratory distress syndrome (ARDS), cardiac complications (atrial fibrillation, cardiac asthma, myocardial infarction), postoperative bleeding and dehiscention of the abdominal fascia.[11,23] Anastomotic leakage, mediastinitis, gastric conduit necrosis, chylothorax and recurrent laryngeal nerve injury were graded according to definitions stated by the Esophagectomy Complications Consensus Group (ECCG).[24] Minor complications (MCDC grade I) included wound infections.[11] In-hospital mortality and mortality within 30 and 60 days, length of intensive care unit (ICU) and hospital stay (days) were recorded.
The operation time was defined as time from incision until closure (minutes) for both the thoracic phase and the abdominal phase of the procedure. Intraoperative complications and blood loss during operation (milliliters per phase) were recorded. In case of conversion, the reason for conversion was explained.

Overall survival (OS), disease free survival and recurrence patterns were reported. Overall survival was calculated from the date of surgery to the date of death or last follow-up. Disease free survival was calculated from the date of surgery to recurrence or death related to disease and/or treatment or last date of follow-up.
Postoperative functional recovery was defined as: removal of thoracic tubes, no requirement of intravenous fluid resuscitation, tolerance for solid oral intake, the ability to mobilize independently and adequate pain control with oral analgesics. The percentage of patients discharged with or without jejunostomy tube feeding was recorded. Postoperative anastomotic dilatation was determined in both groups.[11] A visual analogue scale (VAS 1-10 scale) for pain was noted at the following times; preoperatively and every day during the first 14 days after surgery. VAS scores and functional recovery were measured each morning after clinical examination.
After surgical treatment, patients were followed at 2, 6 weeks, 6 months and 1 year after discharge. This follow-up continued up to 5 years after surgery. Preoperatively, at discharge and during postoperative outpatient department visits, quality of life (QoL) questionnaires (Short Form-36, EORTC Quality-of-life Questionnaire Core 30, EORTC OES18 and EQ-5D) were completed. The results of Quality-of-life Questionnaire Core 30 at discharge and 6 weeks post discharge are presented in this article.[25] A difference of 10 points or higher between groups has been shown to be clinically relevant.[26] All other quality of life scores will be reported when the long-term follow-up has been completed.
The response rate for preoperative and immediate postoperative QoL was in the beginning of the trial 33%. To improve this rate, the logistics of collecting the patient data were changed after 36 patients, which improved response rate to 71%.

Sample size and statistical Analysis
In a prospective analysis of our own series (2003–2010), MCDC grade ≥2 overall surgery-related complications were observed in 69% of all patients who underwent RAMIE and in 91% of all patients who underwent OTE. We calculated that 102 patients (51 in each arm) with resectable esophageal cancer would be required to detect a 22% reduction in the absolute risk of overall surgery-related complications (from 91% to 69% of patients) based on a two-sided significance level (alpha) of 0.05 and a power of 0.80. An estimated compensation of 10% for drop out was included in the total number of patients, resulting in a total of 112 patients, 56 in each arm.
All analyses were performed according to the intention-to-treat (ITT) principle. Results are presented as risk ratios with corresponding 95% confidence intervals (CI). To evaluate significance of differences between groups, chi-squared and Fisher's exact test were used as appropriate for categorical variables and the student's T-test and non-parametric Mann-Whitney U-test for continuous variables.
Differences over time in quality of life and pain scores between and within treatment groups were assessed using linear mixed-effects models adjusted for the baseline value. Survival analyses were explorative and served as quality control. Overall and progression-free survival curves were estimated with the Kaplan-Meier method and compared with the log-rank test. All reported P-values were two-sided. Significance level was set at 0.05. Given the

multiple comparisons we made for the secondary outcomes without adjusting for multiple testing, we would expect one or two false results by chance if all of these comparisons were actually null.

RESULTS

Patients

Between January 2012 and August 2016, 236 patients with resectable intrathoracic esophageal cancer were screened in the UMC Utrecht, of whom 138 patients were considered eligible for the ROBOT trial (figure 1). Finally, 112 patients (allocation ratio 81%) were randomized in a 1:1 fashion to undergo either RAMIE or OTE. For reasons independent of group assignment, 3 patients did not undergo scheduled surgery. In the RAMIE group, 1 patient died and 1 patient developed metastases during neoadjuvant treatment. In the OTE group, 1 patient physically deteriorated to WHO-ECOG 3 after neoadjuvant treatment and refused surgery. These patients were not included in the intention-to-treat analysis. In the RAMIE group, 1 patient had an esophageal perforation during neoadjuvant treatment and underwent emergency laparoscopic transhiatal esophagectomy. One crossover occurred: 1 patient assigned to the OTE group underwent RAMIE due to a WHO-ECOG score of 3 after neoadjuvant treatment. In the RAMIE group, 2 patients were found to have irresectable disease intraoperatively. In 1 patient tumor ingrowth to the aorta was found and in 1 patient liver metastases were discovered intraoperatively. All these patients were included in the intension-to-treat analysis. In total, 54 and 55 patients were analyzed in the RAMIE and OTE group, respectively (Figure1). Demographic and clinical characteristics were similar at baseline (Table 1 and Table S2). In both groups, over 70% of patients had clinically ^{3}T3 disease and over 65% had clinically ^{3}N1 disease (Table S2)

Clinical End Points

The primary endpoint of the occurrence of overall surgery-related postoperative complications (MCDC grade ≥2) occurred in 32 of 54 patients after RAMIE (59%) and in 44 of 55 patients after OTE (80%) (RAMIE risk ratio (RR) 0.74 (95% Confidence interval with RAMIE (CI), 0.57-0.96; P=0.02)) (Table 2). Overall postoperative complications (surgery-related and unrelated (MCDC grade ≥2)) occurred in 34 of 54 (63%) patients after RAMIE and in 44 of 55 (80%) patients after OTE (RR, 0.79; 95%CI 0.62-1.00; P=0.049).

Pulmonary complications were the most frequent secondary endpoint and occurred in 17 of 54 patients in the RAMIE group (32%) and in 32 of 55 patients in the OTE group (58%) (RR 0.54 (95%CI, 0.34-0.85; P=0.005). Pulmonary complications consisted mainly of pneumonia. Cardiac complications were observed in 17 of 45 patients in the RAMIE group (22%) and in 26 of 55 patients in the OTE group (47%) (RR 0.47 (95%CI ,0.27-0.83; P=0.006)). Cardiac complications consisted mainly of atrial fibrillation (AF). There were no statistically significant differences in all other complications, readmission to the intensive care unit (ICU), reoperations, readmissions and in hospital mortality, 30 and 60 day mortality. In the RAMIE group 2 patients died from mediastinitis after anastomotic leakage and in the OTE group 1 patient died in hospital due to a tracheo-esophageal fistula. Median ICU stay was 1

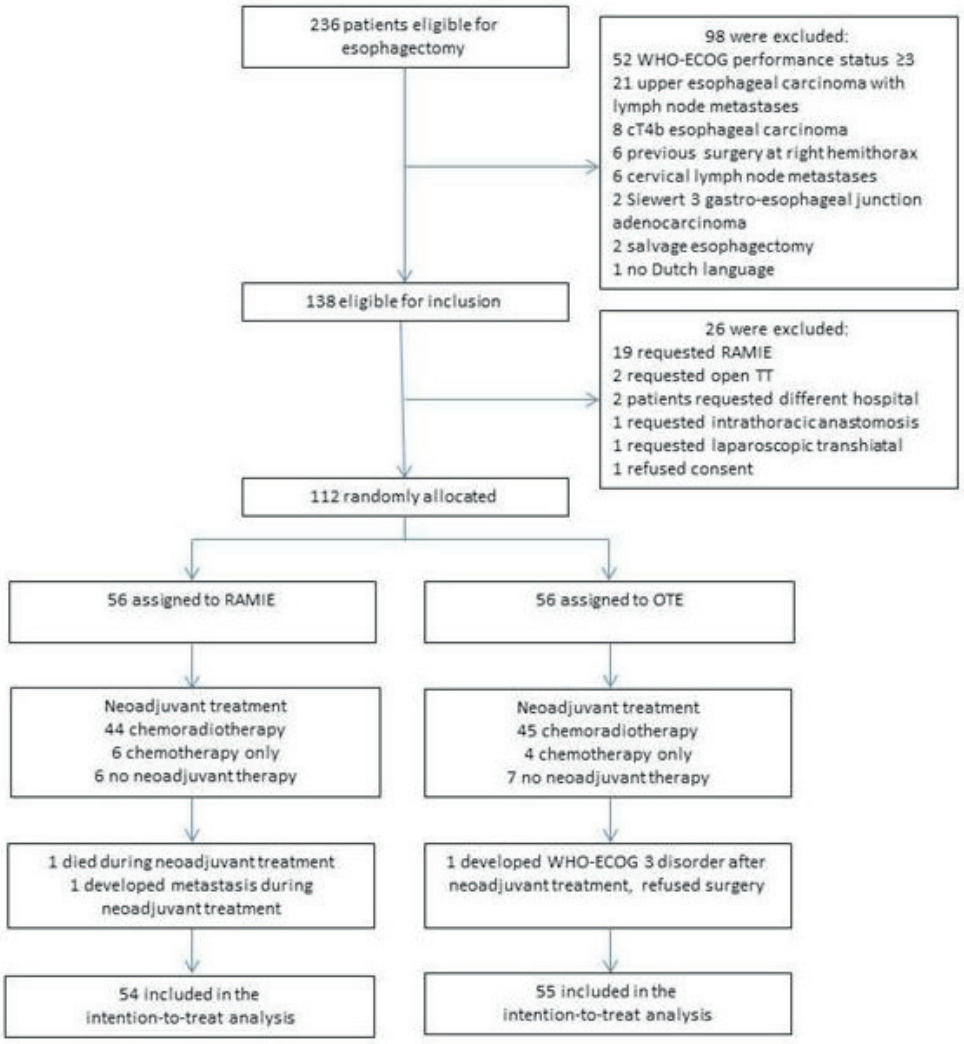


Figure 1. Enrollment, randomization and outcomes

day in both groups (p=0.45) and median hospital stay was 14 days in the RAMIE group and 16 days in the OTE group (p=0.33) (Table 2).

Functional recovery, pain, short-term quality of life and costs

Functional recovery at postoperative day 14 was significantly better in the RAMIE group (38 of 54 patients (70%) compared to the OTE group (28 of 55 patients, 51%) (RR 1.48 (95%CI,1.03–2.13; P=0.04)). There were only 2 patients, 1 in each arm, who did never recover on the item tolerance for solid oral intake. The median day of functional recovery was 10 days in the RAMIE group and 13 days in the OTE group (p=0.14). In the RAMIE group,

Table 1: Baseline characteristics (n=109)

	RAMIE (n=54)	OTE (n=55)
Age (year) ¶	64 (±8.9)	65 (±8.2)
Gender (n (%))		
M	46 (85)	42 (76)
F	8 (15)	13 (24)
BMI (kg / m²) ¶ †	26.1 (±4.4)	25.5 (±4.7)
ASA score (n (%))#		
1	13 (24)	11 (20)
2	37 (69)	34 (62)
3	6 (11)	10 (18)
Type of carcinoma (n (%))		
Adenocarcinoma	41 (76)	43 (78)
Squamous cell carcinoma	13 (24)	12 (23)
Location of tumor (n (%))		
Upper third	1 (2)	0 (0)
Middle third	5 (9)	8 (15)
Lower third	26 (48)	29 (53)
Gastro-esophageal junction	22 (41)	18 (33)
Neoadjuvant treatment (n (%))		
Chemoradiotherapy	42 (79)	44 (80)
Chemotherapy	6 (11)	4 (7)
None	6 (11)	7 (13)
Tumor length (cm – range) ¶	5.0 (±2.1)	4.4 (±1.8)
Comorbidity (n (%))		
Yes	43 (80)	41 (75)
No	11 (20)	14 (26)

¶Plus–minus values are means ±SD

#ASA denotes American Society of Anesthesiologists

significantly more patients were discharged without the need for additional jejunostomy tube feeding as compared to the OTE group (42% and 18%, respectively; RR 1.90 (95%CI,1.10-3.29; P=0.008,Table 2)).

Epidural catheters were placed successfully in 49 of 54 patients (91%) in the RAMIE group and 52 of 55 patients in the OTE group (94%) (p=0.489). The need for additional patient controlled analgesia in the first 4 days postoperatively was equal in both groups (p=0.697) (Table 2). Mean postoperative pain on a visual analogue scale (VAS) during the first 14 days was significantly lower after RAMIE compared to OTE (1.86 versus 2.62, p<0.001, Figure 2). Both at discharge as well as 6 weeks post-discharge, short-term quality of life (QoL) was higher after RAMIE compared to OTE (mean difference 13.4 (2.0-24.7, p=0.02) and 11.1 (1.0 - 21.1; p=0.03), respectively). Also physical functioning was higher in the RAMIE group as compared OTE (13.5 (1.2-25.7, p=0.03) and 10.7 (0.04–21.4; p=0.049) at discharge and 6-week post-discharge, respectively).

Table 2: Postoperative statistics (n=109)

	RAMIE (n=54)	OTE (n=55)	P-value
Primary endpoint (n (%))			
Related complications (MCDC 2, 3, 4 and 5)#	32 (59)	44 (80)	0.02
No related complications (MCDC 0,1)	22 (41)	11 (20)	
Secondary endpoints (n (%))			
Pulmonary complications	17 (32)	32 (58)	0.005
Pneumonia	15 (28)	30 (55)	
Pneumothorax	0 (0)	3 (6)	
Pulmonary embolism	3 (6)	1 (2)	
ARDS	0 (0)	1 (2)	
Cardiac complications	12 (22)	26 (47)	0.006
Atrial fibrillation	12 (22)	25 (46)	
Cardiac asthma	1 (2)	1 (2)	
Wound infections	2 (4)	8 (14)	0.09*
Cervical	2 (4)	1 (2)	
Thoracic	0 (0)	5 (9)	
Abdominal	0 (0)	2 (4)	
Anastomotic leakage¶			0.57
Type I (conservative)	0 (0)	0 (0)	
Type II (Non-surgical intervention)	1 (2)	0 (0)	
Type III (Surgical intervention)	12 (22)	11 (20)	
Mediastinitis¶	12 (22)	11 (20)	0.42
Thoracic empyema¶	2 (4)	3 (6)	
Gastric conduit necrosis¶			
Type III (Conduit necrosis extensive, treated with resection and diversion)	1 (2)	2 (4)	
Chylothorax¶			0.69
Type I (Dietary, low fat elemental formula gavage)	9 (17)	6 (11)	
Type II (Total Parenteral Nutrition)	6 (11)	5 (9)	
Type III (operative)	2 (4)	1 (2)	
Recurrent Laryngeal Nerve injury¶			0.78
Type I (No therapy)	5 (9)	6 (11)	
Reoperations	13 (24)	18 (33)	0.32
Readmission Intensive care unit	7 (13)	9 (16)	0.61
In hospital mortality	2 (4)	1 (2)	0.62*
Hospital stay (days – IQ range) §	14 (11 – 25)	16 (11 – 27)	0.33
Intensive care unit stay (days – IQ range) §	1 (1 – 2)	1 (1 – 3)	0.45
Functional recovery and short-term quality of life			
Functional recovery within first 2 weeks (n (%))	38 (70)	28 (51)	0.04
Day functional recovery (median – IQ range) §	10 (9-13)	13 (9 – 34)	0.14
Hospital readmission within 30 days (n (%))	6 (12)	4 (7)	0.52*
Short-term quality of life (QLQ-C30)##30,31			
Health-related quality of life (discharge)**	57.9 (49.9-66.1)	44.6 (36.7-52.5)	0.02
Health-related quality of life (6 weeks)**	68.7 (61.5-75.9)	57.6 (50.6-64.6)	0.03
Physical functioning (discharge)**	54.5 (45.8-63.3)	41.0 (32.4-49.6)	0.03
Physical functioning (6 weeks)**	69.3 (61.6-76.9)	58.6 (51.1-66.0)	0.049

Related complications are MCDC grade 2 complications and higher (pulmonary complications, cardiac complications, wound infections, postoperative bleeding and dehiscention of abdominal fascia[23] or Type II and higher complications according to ECCG defintions (anastomotic leakage, mediastinitis, thoracic empyema, chylothorax, and recurrent laryngeal nerve injury).[24]

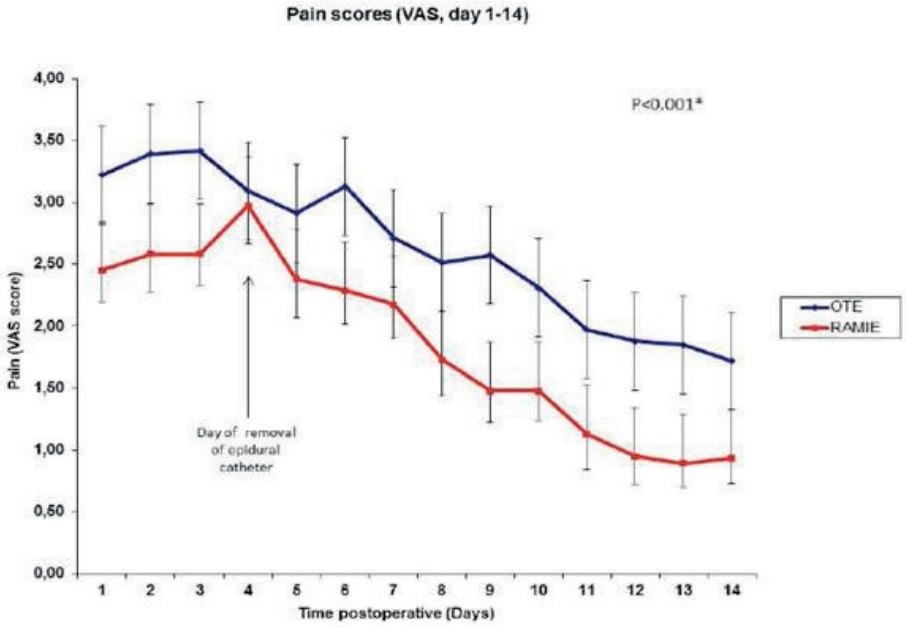
¶ Complications graded according to ECCG defintions[24]

§ IQ range denotes interquartile range** 95% CI ## In total, 64 patients (59%) were included in the quality-of-life analysis, 31 in the RAMIE group and 33 in the OTE group.

Intraoperative outcomes

For RAMIE the mean thoracic operating time was 170 minutes versus 134 minutes for OTE (p<0.001). The mean abdominal and cervical operating time (min) for RAMIE was 186 minutes versus 161 minutes for OTE (p<0.001). This resulted in a significantly longer mean total operating time in the RAMIE groups (349 minutes (versus) 296 minutes in the OTE group (p<0.001)(Table 3).

For RAMIE the median thoracic blood loss was 120 ml versus 200 ml for OTE (p<0.001). Total median blood loss was significantly lower after RAMIE (400 ml) compared to OTE (568 ml)(P<0.001). Conversions of RAMIE were observed in 3 of 54 patients (5%). In 1 RAMIE procedure, the thoracic phase was converted to a laparoscopic transhiatal esophagectomy due to pleural adhesions. In 2 patients the laparoscopic abdominal phase was converted to a laparotomy, due to intra-abdominal bleeding. All other intraoperative outcomes were comparable (Table 3).



	1	2	3	4	5	6	7	8	9	10	11	12	13	14	Overall
RAMIE	2.45	2.58	2.58	2.97	2.38	2.29	2.18	1.73	1.48	1.48	1.13	0.95	0.89	0.93	1.86
OTE	3.22	3.39	3.41	3.09	2.91	3.13	2.71	2.51	2.58	2.31	1.97	1.88	1.85	1.72	2.62
SE#	0.40	0.40	0.40	0.40	0.40	0.40	0.39	0.39	0.39	0.39	0.39	0.40	0.40	0.40	0.13
P-value	0.05	0.04	0.04	0.76	0.18	0.03	0.15	0.05	0.01	0.03	0.03	0.02	0.02	0.05	<0.001

Figure 2. Mean pain scores Visual analogue scale (VAS) in the first 14 days postoperatively corrected for preoperative pain scores. On day 4 the epidural catheter was removed.

*During the first 14 days, overall pain (VAS scores) was significantly lower for RAMIE compared to OTE using a miced effects linear model adjusted for basline pain.

SE denotes standard error of the mean.

Table 3: Intraoperative and pathological statistics (n=109)

	RAMIE (n=54)	OTE (n=55)	P-value
Operating time¶			
Thoracic Operating time (min)	170 (±34.6)	135 (±23.3)	<0.001
Abdominal and cervical operating time (min)	186 (±38.7)	161 (±30.1)	<0.001
Total Operating time (min)	349 (±56.9)	296 (±33.9)	<0.001
Blood loss§			
Thoracic Blood Loss (ml – IQ range)	120 (78 – 200)	200 (195 – 313)	<0.001
Total blood loss (ml – IQ range)	400 (258 – 581)	568 (428 – 800)	<0.001
Conversion (n (%))	3 (5)	NA	
Conversion Thorax	1 (2)	NA	
Conversion Abdomen	2 (4)	NA	
Intraoperative complications (n (%))	7 (13)	9 (16)	0.62
Resection (n (%))			0.24*
Esophagectomy	52 (96)	55 (100)	
Irresectable disease	2 (4)	0 (0)	
Liver metastases	1 (2)	0 (0)	
Aortic ingrowth	1 (2)	0 (0)	
Type of reconstruction (n (%))			0.22
Gastric conduit (Cervical, hand sewn, end-to-side)	52 (96)	54 (98)	
Colonic interposition (Cervical, hand sewn, end-to- end)	0 (0)	1 (2)	
Irresectable	2 (4)	0 (0)	
Radicality of Surgery (n (%))			0.35
R0	50 (93)	53 (96)	
R1	2 (4)	2 (4)	
Irresectable disease	2 (4)	0 (0)	
Lymph nodes number (number – IQ range)	27 (17 - 33)	25 (17 – 31)	0.41
Type of carcinoma (n (%))			0.78
Adenocarcinoma	41 (76)	43 (78)	
Squamous cell carcinoma	13 (24)	12 (22)	
Pathologic stage (n (%))			0.62
pT0N0	10 (19)	10 (18)	
pT0N1	6 (11)	3 (6)	
pT1aN0	1 (2)	0 (0)	
pT1aN1	1 (2)	1 (2)	
pT1bN0	1 (2)	2 (4)	
pT1bN1	3 (6)	1 (2)	
pT1bN2	0 (0)	1 (2)	
pT2N0	6 (11)	8 (15)	
pT2N1	4 (7)	2 (4)	
pT2N2	0 (0)	1 (2)	
pT2N3	1 (2)	0 (0)	
pT3N0	6 (11)	12 (22)	
pT3N1	6 (11)	7 (13)	
pT3N2	4 (7)	2 (4)	
pT3N3	2 (4)	4 (7)	
pT4aN1	0 (0)	1 (2)	
pT4aN3	1 (2)	0 (0)	
Irresectable disease	2 (4)	0 (0)	
Tumor regression (Mandard) (n (%))##			0.35
1	15 (28)	10 (18)	
2	10 (19)	7 (13)	
3	8 (15)	18 (33)	
4	11 (20)	11 (20)	
5	3 (6)	2 (4)	

¶Plus–minus values are means ±SD

§ IQ range denotes interquartile range

Additional resections are described in table S4

According to Mandard et al[16]

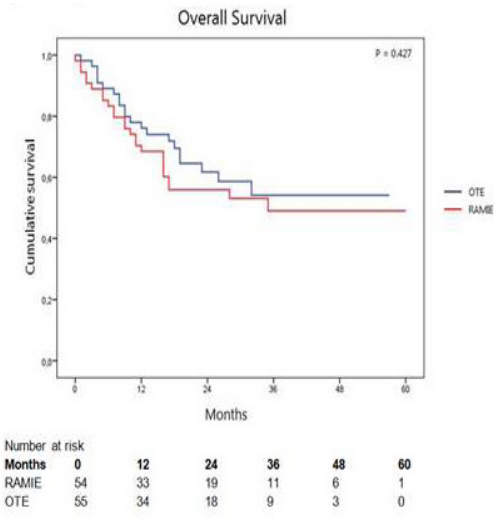


Figure 3a. Overall Survival (OS) for RAMIE versus OTE.

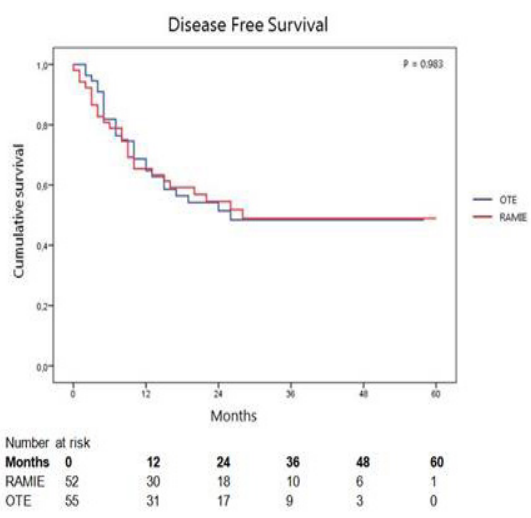


Figure 3b. Disease Free Survival (DFS) for RAMIE versus OTE.

Figure 3. Kaplan Meier curves for overall and disease free survival

Oncologic outcomes

Pathological examination of the resected specimen showed that a radical resection (R0) was achieved in 50 of 54 patients after RAMIE (93%) and in 53 of 55 patients after OTE (96%) (p=0.35). The number of retrieved lymph nodes and all pathologic outcomes were comparable in both groups (Table 3 and table S4).

All patients were included in the overall survival (OS) analysis. Median follow up was 40 months for both groups and median overall survival was not yet reached. There were no statistically significant differences in OS (log rank test, p = 0.427) (Figure 3a).

Out of 109 patients, 107 were included in the disease-free survival (DFS) and recurrence analyses (2 irresectable patients in the RAMIE group were excluded). In the OTE group there were 2 deaths without recurrence and in the RAMIE group there were 3 deaths without recurrence. These were all related to a complicated postoperative course after surgery and were therefore included in the DFS analysis.

There were no statistically significant differences in median DFS between groups (26 months for RAMIE and 28 months for OTE, log rank test, p = 0.983)(Figure 3b). In both groups, there were no isolated locoregional recurrences and recurrence patterns were comparable (Table S5).

DISCUSSION

This is the first randomized controlled trial worldwide, comparing robot-assisted minimally invasive thoraco-laparoscopic esophagectomy (RAMIE) to open transthoracic

esophagectomy (OTE) in patients with advanced esophageal cancer. RAMIE was associated with a significant lower percentage of overall surgery-related postoperative complications compared to OTE. RAMIE was also associated with less blood loss, a lower percentage of pulmonary complications and cardiac complications compared to OTE. Postoperative pain during the first 14 days was lower after RAMIE compared to OTE. RAMIE resulted in a higher proportion of patients who were functionally recovered within 14 days. Compared to OTE, short-term Quality of life after RAMIE was better, both at discharge and 6 weeks after discharge. There was no significant difference in oncologic outcome parameters, such as R0 resection rate, the number of lymph nodes, recurrence patterns, OS and DFS. Both RAMIE and OTE provided good local oncological control, with no isolated locoregional recurrences in both groups at a median follow up of 40 months.

In this study, RAMIE was compared to OTE, which is considered to be the gold standard for resectable esophageal cancer worldwide.[2] Before any comparison of a novel surgical technique to the gold standard can be performed, the learning curve has to be completed. In 2012, when the trial was initiated, our center was the only center worldwide that had clearly passed the learning phase with a joint experience of >170 RAMIE procedures.[27] Hence, it was decided to perform a single center randomized controlled trial.[11,27]

The single center design could be considered a limitation of this study and might hamper generalizability of these results to other centers. However, during the past years more than 5 centers across Europe were proctored to perform RAMIE as their preferred surgical approach with excellent results. Therefore, with a completed learning curve for RAMIE , the results presented in this trial should be reproducible in the other centers as well.[28]

Strengths of this study are the randomized design, the fact the surgeons passed the learning curve, the use of the IDEAL recommendations for the assessment of surgical innovation[29] and the use of overall surgery-related complications as the primary outcome.

In this study, consecutive patients were included without selection based on comorbidity or tumor size.

The primary endpoint of this study was the percentage of overall surgery-related postoperative complications according to the modified Clavien–Dindo classification (MCDC) of surgical complications grade ≥2.[23] For esophagectomy specific complications, the definitions stated by the Esophagectomy Complications Consensus Group (ECCG) were used.[24] The registration of complications in this trial was performed prospectively in a weekly multidisciplinary meeting. The advantage of this method in a single center setting, is that all complications are noted meticulously and uniformly, leading to a complete overview of all possible complications after esophagectomy. This explains a relatively high rate of overall complications recorded in this trial.

Pulmonary complications were most common and mainly consisted of pneumonia (table 2) The incidence of pneumonia is highly dependent on definition.[30] In this study, the decision to start antibiotics to treat pneumonia was used (MCDC≥2).[23] This resulted in a pneumonia rate of 28% in the RAMIE group and a 55% pneumonia rate in the OTE group. In the previously published CROSS study, a different definition was used for pneumonia, namely the isolation of pathogen from sputum culture and a new or progressive infiltrate on chest radiograph, resulting in a 44% pulmonary complication rate.[17] Applying the same

definition for pneumonia as used in the CROSS trial in our study would decrease the rate of pneumonia to 7% in the RAMIE group and 32% in the OTE group (p=0.004, RR0.488, 95% CI 0.328–726). However, as the sputum culture outcome becomes available after the decision to treat pneumonia, this is not independently associated with pneumonia treatment.[30] We therefore used the decision to start antibiotics to treat pneumonia as the definition for pneumonia (MCDC≥2) in this randomized controlled trial.[23]

Cardiac complications were also frequently observed and consisted mainly of atrial fibrillation (table 2).

The incidence of cardiac complications is directly related to the presence of cardiovascular comorbidity.[31] A history of cardiac disease was present in 29% of patients and a history of vascular disease was present in 33% of patients. These percentages represent the population of patients with esophageal cancer in a Western world. With similar baseline characteristics in both the RAMIE group and the OTE group, differences in postoperative cardiac complications were indeed related to the surgical approach in favor of RAMIE.

The incidence of anastomotic leakage the ROBOT trial was relatively high and comparable in both arms.[17] In this study, a cervical esophagogastric anastomosis was used to restore gastrointestinal continuity. Recent studies show that a cervical anastomosis is associated with a higher incidence of anastomotic leakage compared to an intrathoracic anastomosis.[32,33] In this trial all clinical or non-clinical signs of anastomotic leak were scored prospectively, which probably resulted in relatively higher leak rates in both trial arms. As the previously published studies on this topic use various definitions for anastomotic leak rate, the outcomes are difficult to compare.[17,24]

In this trial, an anastomotic leakage with any sign of mediastinal involvement (mediastinitis) was treated with prolonged antibiotic treatment and surgical drainage of the mediastinum through the cervical incision. This is an effective procedure, usually taking no more than 15 min. These interventions were scored as type III anastomotic leakage (reoperation) according to the ECCG definitions, explaining the percentage of reinterventions in both arms.[24]

The incidence of chylothorax was relatively high, reflecting a radical en-bloc esophagolymphadenectomy including a thoracic duct resection. The vast majority of patients only required treatment with dietary modification (Type 1). Also for chylothorax many different definitions are used in the literature, which makes a proper comparison with other studies difficult.[24]

Due to a radical paratracheal lymph node dissection and a radical lymph node dissection in the aorto-pulmonary window combined with a cervical anastomosis, a recurrent laryngeal nerve complication rate of around 10% was observed in both arms. All observed recurrent laryngeal nerve injuries were type I (hoarseness), temporary and required no intervention. This percentage is comparable to other studies where routine paratracheal lymph node dissections were performed in combination with a cervical anastomosis.[32,33]

Not many studies use the overall surgery-related complications as primary endpoint. Comparisons between studies can only be performed if the same definitions for complications are used and comorbidities are reported in detail. For all surgical studies for esophageal cancer in the future, it is highly recommended to use ECCG definitions in order to facilitate comparison between studies.[24]

The question arises whether RAMIE is superior to other minimally invasive surgical techniques. The conventional minimally invasive esophagectomy (MIE) has shown comparable benefits compared to open surgery in a randomized trial (TIME-trial).[5] Outcomes of a randomized trial comparing the hybrid technique consisting of laparoscopy and open thoracotomy versus OTE are awaited (MIRO-trial).[34] To show the benefits of RAMIE over conventional MIE in a multicenter randomized trial would require a large number of patients as outcome differences are probably subtle. Therefore, comparing RAMIE to MIE in a multi-center randomized trial might not be feasible. Future initiatives such as the ESODATA prospective international registry, using the uniform ECCG scoring system would allow for comparisons between RAMIE or MIE.[24]

Within this trial, postoperative pain, quality of life and postoperative recovery were better in favor of RAMIE compared to OTE. This is an important secondary endpoint most probably attributed to the reduced surgical trauma. These results need to be confirmed in large prospective studies.

Although functional recovery was achieved in a median of 10 days in the RAMIE group, logistics keep the patient regularly longer in the hospital than needed resulting in prolonged hospital stay. We observed a non-significant decrease from 16 to 14 days in LOS within this trial in favor of RAMIE without the use of an enhanced recovery after surgery (ERAS) program in both arms. A possible reduction of 2 days is in the range of trials comparing open versus laparoscopic colectomy, such as the COLOR trial.[35] In the COLOR trial, a significant 1 day reduction in LOS was observed in favor of laparoscopic surgery. With larger groups, a significant decrease in hospital stay might be observed with the RAMIE procedure. At the time of initiation of this trial in 2012, there was no ERAS program in applied after esophagectomy. Recent studies have shown a substantial improvement of postoperative results using the ERAS program following esophageal resection[36] .

In conclusion. in this single center randomized controlled trial, RAMIE resulted in a lower percentage of overall surgery-related and cardiopulmonary complications with lower postoperative pain, better short-term quality of life and a better short-term postoperative functional recovery compared to OTE. Oncological outcomes were equal and in concordance with the highest standards nowadays. This randomized controlled trial provides evidence for the use of RAMIE to improve short-term postoperative outcomes in patients with resectable esophageal cancer.

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Conflict of interest:
J.P. Ruurda and R. van Hillegersberg are proctors for Intuitive Surgical Inc., Sunnyvale, California, USA. No funding was obtained for this study.

SUPPLEMENTARY INFORMATION

Supplementary methods (S1)

Inclusion and exclusion criteria

All adult patients (age ≥18 and ≤80 years) with histologically proven, surgically resectable (cT1-4a, N0-3, M0) cancer of the intrathoracic esophagus were assessed for eligibility between January 2012 and august 2016 in the University Medical Center (UMC) Utrecht (Utrecht, The Netherlands). All patients had a performance status 0, 1 or 2 according to the World Health Organization (WHO) at randomization. Patients with cancer of the cervical esophagus, gastro-esophageal junction type III carcinoma (Siewert classification)[12] and patients with prior thoracic surgery or thoracic trauma of the right hemithorax were excluded.

Supplemental 2: Baseline statistics (continued)

Table S2: Baseline characteristics (n=109)

	RAMIE (n=54)	OTE (n=55)
Clinical stadium (n (%))		
cT1N0	4 (7)	4 (7)
cT1N1	1 (2)	2 (4)
cT2N0	5 (9)	3 (6)
cT2N1	4 (7)	4 (7)
cT2N2	1 (2)	0 (0)
cT2N3	1 (2)	0 (0)
cT3N0	6 (11)	12 (22)
cT3N1	12 (22)	21(38)
cT3N2	13 (24)	6 (11)
cT3N3	6 (11)	2 (4)
cT4aN2	1 (2)	0 (0)
cT4aN3	0 (0)	1 (2)
Medical history (n (%))		
Cardiac	15 (28)	16 (29)
Vascular	22 (41)	18 (33)
Diabetes	3 (6)	6 (11)
Pulmonal	10 (19)	9 (16)
Neurologic	7 (13)	9 (16)
Intestinal	8 (15)	6 (11)
Urologic	2 (4)	3 (5)
Trombo-embolic	3 (6)	4 (7)
Malignancy	3 (6)	8 (15)
Previous abdominal operation	20 (37)	19 (35)

Supplemental 3: Postoperative statistics (continued)

Table S3: Postoperative statistics (n=109)

	RAMIE (n=54)	OTE (n=55)	P-value
Complications grade (MCDC)[23]			
MCDC grade 2	**26 (48)**	**43 (78)**	
MCDC grade 3a	**4 (7)**	**4 (7)**	
MCDC grade 3b	**11 (20)**	**16 (29)**	
MCDC grade 4a	**6 (11)**	**7 (13)**	
MCDC grade 4b	**0 (0)**	**2 (4)**	
MCDC grade 5	**2 (4)**	**1 (2)**	
Postoperative bleeding	2 (4)	2 (4)	
Dehiscention of abdominal fascia	0 (0)	1 (2)	
30 day mortality	1 (2)	0 (0)	
60 day mortality	3 (6)	1 (2)	
Postoperative anastomotic dilatation	28 (52)	26 (47)	
Epidural insufficiency (first 4 days, additional PCA) ©	24 (44)	22 (41)	
Additional PCA after removal of epidural (n (%))©	1 (2)	5 (9)	

© PCA denotes patient controlled analgesia

Supplemental 4: Intraoperative and pathological statistics (continued)

Table S4: Intraoperative and pathological statistics (n=109)

	RAMIE (n=54)	OTE (n=55)	P-value
Length thoracotomy incision¶			
External (Skin, cm)	NA	17.9 (±1.5)	
Internal (thoracic wall, cm)	NA	19.6 (±1.5)	
Intraoperative complications (n (%))	7 (13)	9 (16)	
Bleeding	3 (5)	2 (4)	
Atrial fibrillation	2 (4)	1 (2)	
Splenic injury	2 (4)	2 (4)	
Lung injury	0 (0)	4 (7)	
Aortic adventitia injury	1 (2)	0 (0)	
Additional resections (n (%))	5 (9)	10 (18)	
Spleen	3 (6)	1 (2)	
Greater omentum	1 (2)	3 (6)	
Lung (wedge)	1(2)	2 (4)	
Diaphragm	1(2)	1 (2)	
Right crus	1 (2)	2 (4)	
Stomach	0 (0)	1 (2)	
Pleura	0 (0)	1 (2)	
Pericardium	0 (0)	1 (2)	
Gall Bladder	0 (0)	1 (2)	
Azygous Vein	1 (2)	0 (0)	
Grade of differentiation (n (%))			
Grade cannot be assessed (Gx)	8 (15)	3 (6)	
Well differentiated (G1)	5 (9)	3 (6)	
Moderately differentiated (G2)	15 (28)	19 (35)	
Poorly differentiated (G3)	21 (39)	23 (42)	
Undifferentiated (G4)	3 (6)	7 (13)	
Irresectable disease	2 (4)	0 (0)	
Epidural failure (prior to surgery) (n (%))	5 (9)	3 (6)	*

¶ Plus–minus values are means ±SD.

Supplemental 5: Recurrence

Table S5: Recurrence (n=107)

	RAMIE (n=52)	OTE (n=55)	P-value
Recurrence (n (%))			0.32
No recurrence	29 (56)	32 (58)	
Locoregional only	0 (0)	0 (0)	
Distant	10 (19)	15 (27)	
Locoregional and distant	13 (25)	8 (15)	
Organ recurrence (n (%))			
Locoregional lymph nodes (mediastinal, truncal)	11 (21)	7 (13)	
Distant lymph nodes	7 (14)	8 (15)	
Gastric conduit	3 (6)	2 (4)	
Lung	4 (8)	3 (6)	
Liver	4 (8)	8 (15)	
Adrenal	1 (2)	3 (6)	
Bone	4 (8)	3 (6)	
Brain	3 (6)	1 (2)	
Muscle	1 (2)	0 (0)	
Pleura / pleuritis carcinomatosa	4 (8)	3 (6)	
Peritoneal / peritonitis carcinomatosa	3 (6)	3 (6)	
Operation Wound / Thoracic wall	0 (0)	4 (7)	

PART III

surgical techniques and complications

Chapter 11

End-to-end cervical esophagogastric anastomoses require a higher number of stricture dilations compared to end-to-side anastomoses after esophagectomy

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ABSTRACT

Background
Leakage and benign strictures occur frequently after esophagectomy. The objective of this study was to analyze the outcome of hand-sewn end-to-end versus end-to-side cervical esophagogastric anastomoses.

Methods
A series of 390 consecutive patients who underwent esophagectomy with gastric conduit reconstruction was analyzed.

Results
The end-to-end technique was performed in 112 (29%) patients and the end-to-side in 278 (71%) patients. Anastomotic leakage occurred in 20 (18%) patients with an end-to-end anastomosis versus 58 (21%) patients with an end-to-side anastomosis (*p=0.50).* A higher incidence in anastomotic strictures was seen in end-to-end anastomoses (48 (43%)) compared with end-to-side anastomoses (89 (32%); *p=0.04*). Moreover, a median of 11 (7-17) dilations was necessary in patients with a benign anastomotic stricture in the end-to-end group compared with 4 (2-8) dilations in patients with a benign anastomotic stricture in the end-to-end group (*p<0.036*). After multivariate analysis the difference in anastomotic leakage rates remained non-significant (*p=0.74*), whereas anastomotic stricture rate and number of dilations were higher in the end-to-end group (*p=0.03* and *p=0.01*, respectively).
Conclusion: The technique of anastomosis is not significantly related to anastomotic leakage rate. However, patients with end-to-end anastomoses develop postoperative strictures more frequently, requiring a higher number of dilations compared to end-to-side anastomoses.

Keywords
Esophagectomy; surgical anastomosis; anastomotic leakage; anatomotic stricture.

INTRODUCTION

For patients with locally advanced esophageal cancer, esophageal resection (esophagectomy) offers the best chance for cure with an average 5-year survival of 36% [1]. Postoperative complications are often related to the esophagogastric anastomosis. Anastomotic leakage occurs in up to 40% [2]. The mortality associated with anastomotic leakage can be as high as 15%, while the reported mortality rate in patients without anastomotic leakage is around 4% [3]. Another anastomotic complication is the formation of a benign stricture at the cervical anastomosis, which occurs in up to 40% of all esophagectomies [4,5]. Benign esophageal anastomotic strictures lead to a reduction in quality of life [6].

At present, the association between anastomotic leakage and stricture formation with regard to the surgical anastomotic technique remains unclear. A limited number of studies have compared end-to-end (ETE) versus end-to-side (ETS) anastomoses with variable results for both procedures [2,7]. The general consensus among gastrointestinal surgeons is to perform an ETS anastomosis, however, a recent randomized controlled trial showed a reduction in anastomotic leakage rate in the ETE group [2]. In addition, the number of dilations required per anastomotic type has not been adequately investigated.

Since anastomotic leakage and stricture formation are common unsolved problems after esophagectomy and literature is inconclusive about superiority of anastomotic techniques, we performed a cohort study in a tertiary referral center. The aim of our study was to compare ETE versus ETS anastomoses in patients who underwent esophagectomy with gastric conduit reconstruction.

Material & Methods

This study was designed to evaluate the change in policy of hand-sewn esophagogastrostomy in our tertiary referral center, University Medical Center Utrecht, in patients who underwent esophagectomy. From 1991-2003 the ETE technique was the standard procedure for cervical anastomosis, whereas from 2004-2011 the ETS technique was the standard of care.

Patients who had undergone esophagectomy with gastric conduit formation in the period 1991-2011 were included in the database. In total 426 patients were identified. Patients who underwent other or additional procedures were excluded (n=28); i.e., primary tumor in the larynx (3), colon interposition (14), jejunal interposition (4), and Roux-en-Y reconstruction (7). In another 8 patients, the medical record had no detailed description of the anastomotic technique. Finally, a total of 390 consecutive patients were available for statistical analysis.

Esophagolymphadenectomy was performed by means of an open (transthoracic or transhiatal) or minimally invasive (thoracolaparoscopic, thoracolaparotomic, or laparoscopic transhiatal) approach. The gastric conduit was placed in the posterior mediastinum in all patients. Generally, the gastric conduit staple line was oversewn by hand. All esophagogastrostomies were created in the neck. All 390 anastomoses were created with

Figure 1: Technique of ETE vs. ETS anastomosis

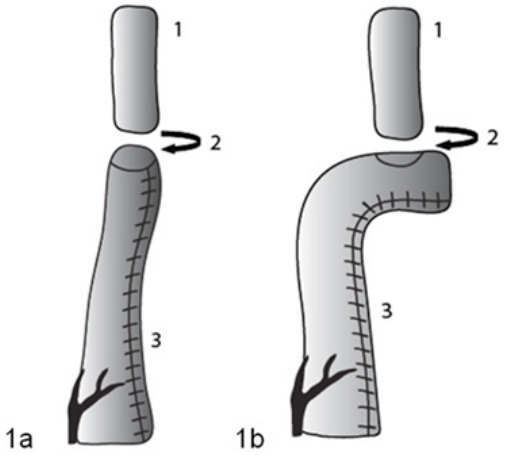

Figure 1a: ETE esophagogastrostomy, in which the end of the esophageal stump (1) is connected to end of the gastric conduit (3) at the site of the anastomosis (2). 1b: ETS esophagogastrostomy, in which the end of the esophageal stump (1) is connected to the side of the gastric conduit (3) at the site of the anastomosis (2).

a hand-sewn single-layered technique (3-0 PDS). For the ETE anastomosis, the distal end of the cervical esophagus and the proximal end of the gastric conduit were connected in a straight line (Figure 1a). For the ETS anastomosis, the distal end of the cervical esophagus was positioned perpendicular to the side of the proximal gastric conduit (Figure 1b). The anastomoses were constructed by experienced surgeons who were accustomed to the ETE and ETS techniques and had completed the learningcurves for these anastomoses. After construction of the ETS anastomosis, the tip of the gastric conduit was removed with the use of a stapler (GIA, Covidien, Mansfield, MA, USA).

The definition anastomotic leakage was applicable if there were clinical signs and symptoms of leakage, such as subcutaneous emphysema, passage of air, saliva, or other luminal contents through the cervical incision. During follow-up after surgery, symptoms of dysphagia were evaluated. Potential anastomotic strictures were evaluated with the use of upper endoscopy. In case an anastomotic stricture was diagnosed, endoscopic dilations by means of Savary dilation were performed according to standardized protocol. This was done by experienced gastroenterologists at the UMC Utrecht.

Data were analyzed with SPSS for Windows (version 15.0, SPSS Inc. Chicago, Illinois, 2006). Statistical tests used were Pearson X^2 for binary and categorical values and the nonparametric Mann-Whitney U test for continuous variables with a non-Gaussian distribution. Results were presented as median (lower quartile- upper quartile). Variables with p-values <0.10 in univariate analysis (age, COPD, smoking, tumor stage, surgical approach) were regarded as

potential confounders and were included in a multivariate analysis. Also, period of surgery (1991-1995, 1996-2000, 2001-2005, and 2006-2011) was added to the multivariate analysis. Binary logistic regressions and linear regression were performed to correct for these confounders. P-values <0.05 were considered to be significant and confidence intervals (CI) of 95% were used. Data were reported as (Odds Ratio [CI]; p-value).

Table 1: baseline characteristics for patients with ETE and ETS anastomoses.

	ETE (n=112)	**ETS (n=278)**	**Significance (p value)**
Age (years)*	61 (52-68)	65 (58-71)	<0.001
Gender (male)	86 (77%)	198 (71%)	0.264
Body Mass Index (kg/m2)*	24 (21-27)	25 (22-28)	0.117
Comorbidities:			
Diabetes Mellitus	5 (4%)	35 (12%)	0.113
COPD	4 (4%)	32 (12%)	0.014
Cardiovascular disease	16 (15%)	53 (19%)	0.263
Smoking	72 (64%)	146 (53%)	0.044
Alcohol	70 (63%)	168 (60%)	0.849
Tumor stage TNM7:			
Benign	1 (1%)	3 (1%)	<0.001
Cis/Dysplasia	2 (2%)	17 (6%)	
Ia	6 (5%)	30 (11%)	
Ib	9 (8%)	11 (4%)	
IIa	12 (10%)	51 (18%)	
IIb	10 (9%)	19 (7%)	
IIIa	29 (26%)	57 (20%)	
IIIb	22 (20%)	28 (10%)	
IIIc	11 (10%)	10 (4%)	
IV	10 (9%)	52 (19%)	
Surgical approach:			<0.001
Open transhiatal	75 (67%)	96 (35%)	
Transthoracic	29 (26%)	30 (11%)	
Thoracolaparoscopic	0 (0%)	108 (39%)	
Thoracolaparotomic	8 (7%)	17 (6%)	
Laparoscopic transhiatal	0 (0%)	27 (9%)	

*Median (lower quartile- upper quartile)

RESULTS

Over a time period of 20 years, ETE anastomoses were performed in 112 (29%) patients, whereas ETS anastomoses were constructed in 278 (71%) patients (Table 1). Tumor stage was more advanced in patients with an ETE anastomosis, since 72 (65%) patients in the ETE group had T3-T4 stage esophageal cancer compared with 147 (53%) patients in the ETS group (p<0.04). Minimally invasive procedures, such as thoracolaparoscopic, thoracolaparotomic and laparoscopic transhiatal esophagectomy were perfomed in 8 (7%) patients in the ETE group compared to 152 (55%) patients in the ETS group (p<0.001).

Table 2: postoperative outcomes in univariate analysis and multivariate analysis performed with correction for: age, COPD, smoking, tumor stage, surgical approach, and year of surgery.

	ETE	***ETS***	***Univariate analysis***		***Multivariate analysis***	
	N= 112	**N=278**	**OR / B† (95% CI)**	***P***	**OR / B† (95% CI)**	***P***
Anastomotic leakage	20 (18%)	58 (21%)	1.213 (0.690, 2.131)	0.502	0.872 (0.394, 1.931)	0.735
Anastomotic stricture	48 (43%)	89 (32%)	0.628 (0.400, 0.986)	0.043	0.489 (0.250, 0.957)	0.031
Number of dilations*†	11 (7-17)	4 (2-8)	-4.570 (-8.828, -0.312)	0.036	-6.375 (-11.202, -1.549)	0.010
Cervical wound infection	7 (6%)	21 (8%)	1.226 (0.506, 2.970)	0.652	2.060 (0.687, 6.171)	0.197
Recurrent nerve lesion	7 (6%)	30 (11%)	1.815 (0773, 4.261)	0.171	0.840 (0.293, 2.407)	0.746
Empyema	1 (1%)	12 (4%)	5.008 (0.643, 38.975)	0.124	2.771 (0.303, 25.325)	0.367
Mediastinitis	2 (2%)	5 (2%)	1.007 (0.193, 5.270)	0.993	0.000 (0.000,-)	0.994
Pneumonia	17 (15%)	77 (28%)	2.141 (1.200, 3.820)	0.010	0.788 (0.376, 1.654)	0.529
Postoperative hospital stay (d)*†	17 (14-28)	17 (14-26)	-0.479 (-5.367, 4.408)	0.790	-2.406 (-8.111, 3.300)	0.407
Intensive care stay (d)*†	3 (2-7)	3 (1-5)	0.185 (-2.857, 3.226)	0.949	-0.908 (-4.248, 2.432)	0.593

* Median (lower quartile-upper quartile)

† Regression coefficient

Anastomotic leakage occurred in 20 (18%) patients in the ETE group, in contrast to 58 (21%) patients in the ETS group (1.213 [0.690, 2.131]; p=0.50) (Table 2). A benign anastomotic stricture occurred in 48 (43%) patients with an ETE anastomosis, compared to 89 (32%) patients with an ETS anastomosis (0.628 [0.400, 0.986]; p=0.04). Moreover, the median number of dilations performed in the ETE group was 11 (7-17), whereas this was 4 (2-8) in the ETS group (-4.570 [-8.828, -0.312]; p=0.04). The incidence of anastomotic stricture formation was not found to be related to anastomotic leakage. In 32 (41%) patients with anastomotic leakage an anastomotic stricture developed, compared with 104 (33%) patients without anastomotic leakage (p=0.23). In the ETE group 10 (50%) patients with anastomotic leakage had a benign stricture, compared with 22 (38%) patients in the ETS group (p=0.35). In the ETE group, 17 (15%) patients developed pneumonia compared with 77 (28%) patients in the ETS group (2.141 [1.200, 3.820]; p=0.01). These values were further analysed in multivariate analysis.

The postoperative hospital stay was 17 (14-28) days in the ETE group compared with 17 (14-26) days in the ETS group (0.479 [5.67, 4.408]; p=0.85). Duration of intensive care stay was 3 (2-7) days in patients with an ETE anastomosis compared with ETS anastomosis, 3 (1-5) days

(0.185 [2.857, 3.226]; p=0.91).

The presentation of anastomotic leakage occurred after a median of 7 (2-22) days after surgery in patients with an ETE anastomosis and at postoperative day 8 (1-36) in patients with an ETS anastomosis (p=0.78).

A multivariate analysis was performed to correct for potential confounders (Table 2). It was found that anastomotic leakage was comparable in both groups (0.872 [0.394, 1.931]; p=0.735), while postoperative strictures developed more frequently in the ETE anastomosis (0.489 [0.250, 0.957]; p=0.031). A higher number of dilations were required to treat strictures in the ETE group compared with the ETS group (-6.375 [-11.202, -1.549]; p=0.010). After correction for confounders, pneumonia rate did not differ between both groups (0.788 [0.376, 1.654]; p=0.529).

DISCUSSION

In this study, we demonstrated that patients who underwent esophagectomy with an ETE or ETS esophagogastric anastomosis developed anastomotic leakage at a comparable rate. However, benign anastomotic strictures developed at a higher rate in patients with an ETE anastomosis, compared to patients with an ETS anastomosis. The number of endoscopic dilations required to treat strictures was also significantly higher in patients with an ETE anastomosis compared to those with an ETS anastomosis.
A possible explanation for the better long term results of an ETS anastomosis compared to an ETE anastomosis may well be the fact that an ETS anastomosis commonly is wider than an ETE anastomosis. It was hypothesized that 3 possible mechanisms might have contributed to this wider anastomosis. First, by using the ETS technique, the length of the gastric conduit can be tailored to the position of the esophageal stump. As a result, the anastomosis will be less prone to traction. This allows for optimal blood supply and healing, and ischemia and necrosis of the gastric conduit is likely to be reduced. Second, the size of the created lumen in the gastric conduit can be exactly adjusted to the size of the esophageal lumen. This is not the case in an ETE anastomosis where mostly an inlay technique is needed to overcome the difference in luminal size, which may lead to stenosis. Third, the proximal part of the gastric conduit, which is used to create the ETS anastomosis, has a more profound vasculatory system than the anastomotic gastric tip which constitutes part of the ETE anastomosis [8].
The etiology of anastomotic leakage is mulitfactorial. Next to technical factors, other factors such as the presence of bacterial flora may influence the occurrence of anastomotic leakage. We chose to focus on the technical aspects of anastomotic leakage in this study.
Previous reports on the risk of leakage and stricture formation related to the type of anastomosis have shown conflicting results. A retrospective cohort study showed non significant differences in the occurrence of anastomotic leakage and benign stricture formation in ETS versus ETE hand-sewn anastomoses [7]. This study included merely 118 patients (28 ETE, 90 ETS), and therefore might be underpowered. A more recent randomized clinical trial found that ETS anastomoses were associated with a reduction in

benign stricture formation, but led to a higher rate of anastomotic leakage compared to ETE anastomoses [2]. The results of the last study can possibly be explained by a learning curve in the construction of an ETS anastomosis. As the surgeons from the institution in which this trial was conducted, were used to the ETE technique, they may not have completed the learning curve for the ETS technique at the time of the study [9]. Such learning curves have previously been described in esophageal surgery [10, 11].

Since both ETE and ETS techniques show comparable anastomotic leakage rates, the worldwide preference of surgeons for ETS (50%) or ETE (33%) cervical anastomosis seems justified [12]. Nevertheless, the present study demonstrates that ETE anastomoses are associated with a significantly higher anastomotic stricture rate. Moreover, a higher number of dilations are required in patients with an ETE anastomosis, compared to ETS. This should be taken into account when opting for either of both anastomotic techniques, because this can be of significant influence on the patients' quality of life [13].

The higher pneumonia rate in the ETS group in univariate analysis can be explained by the difference in surgical approach between both techniques. The majority (67%) of the ETE population underwent transhiatal esophagectomy, whereas the most patients (56%) in the ETS group underwent a transthoracic approach. After correction for this confounder in multivariate analysis, the rate of pneumonia was comparable in both groups.

It should be mentioned that the design of this study is observational, rather than a randomized controlled trial. The findings of this study can therefore not be directly extrapolated into a treatment advice. The present study might have been subject to a possible historical bias. During a period of 20 years, surgical approaches and postoperative care have improved, which may have influenced the results. Therefore, we included the period of surgery as a potential confounder in the multivariate analysis. As shown in the results section, the period of surgery did not significantly influence the postoperative outcomes.

CONCLUSION

In our observational study, no significant difference in anastomotic leakage rate was found between ETE and ETS cervical anastomoses in patients who underwent esophagectomy with gastric conduit reconstruction. However, ETE anastomoses were associated with a significantly higher postoperative benign stricture rate. Moreover, ETE anastomoses required a significantly higher number of dilations compared with ETS cervical esophagogastric anastomoses.

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Chapter 12

A New Clinical Scoring System to Define Pneumonia following Esophagectomy for Cancer

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ABSTRACT

Background
Pneumonia is a frequently observed complication following esophagectomy. The lack of a uniform definition of pneumonia leads to large variations of pneumonia rates in literature. This study was designed to to develop a scoring system for diagnosing pneumonia following esophagectomy at the hospital ward.

Methods
In a prospective cohort study of esophagectomy patients, known risk factors for pneumonia, temperature, leukocyte count, pulmonary radiography and sputum culture added were evaluated. Primary outcome was defined as the decision to treat suspected pneumonia. Multivariate Cox regression analysis with backward selection was used to identify predictors of pneumonia treatment.

Results
The majority of postoperative pneumonia treatments (88.2%) occurred at the hospital ward, where treatment was observed in 67 (36.2%) of 185 patients. Independent diagnostic determinants for pneumonia treatment were temperature (HR=1.283, P=0.073), leukocyte count (HR=1.040, P=0.078) and pulmonary radiography (HR>11.0, P=0.000). Sputum culture did not influence the decision to treat pneumonia. These findings were used to develop a scoring system which includes temperature, leukocyte count and pulmonary radiography.

Conclusion
The decision to treat pneumonia is based on temperature, leukocyte count and pulmonary radiography findings. The proposed clinical scoring system for pneumonia following esophagectomy at the hospital ward has the potential to aid clinical practice and improve comparability of future research in esophageal cancer surgery.

INTRODUCTION

Esophagectomy for cancer is accompanied with high postoperative morbidity rates.(1-3) Respiratory complications, dominated by pneumonia, are most common (20-60%), associated with an increased risk of mortality (up to 5-10%) and the principle cause of postoperative death.(1;4;5) Furthermore, postoperative complications after esophagectomy have been reported to correlate with recurrence of disease.(6-8)

Pneumonia in hospitalized patients can be divided into ventilator-associated pneumonia (VAP) and hospital acquired pneumonia (HAP).(9-11) Pneumonia is often difficult to diagnose. Criteria with high sensitivity and low specificity, such as fever, leukocytosis, infiltrative abnormalities on pulmonary radiographies and bacterial growing on sputum culture, are used to establish the diagnosis.(10)

VAP is defined as pneumonia in patients receiving mechanical ventilation for at least 24 hours and can be diagnosed with the Clinical Pulmonary Infection Score.(12-16) HAP is defined as pneumonia in patients with a first positive bacterial respiratory culture finding >2 days from admission who do not meet the VAP criteria.(11) However, no clinical scoring system is available for diagnosing HAP in non-ventilated patients. The use of different definitions in literature limits interpretation and comparison of postesophagectomy pneumonia rates across studies.(17)

A frequently used traditional definition of pneumonia in clinical studies is the presence of infiltrative findings on pulmonary radiography combined with a positive sputum culture.(2;18) Other authors prefer a general classification of complications adapted to the respiratory system (Modified Clavien Dindo Classification; MCDC).(17;19)

In this prospective observational cohort study the objective was to define the diagnostic determinants that affected the decision to treat pneumonia. Furthermore, we aimed at developing a new scoring system for the definition of pneumonia after esophagectomy in non-ventilated patients.

PATIENTS AND METHODS

Inclusion

A prospective database was maintained from October 2003 including all esophageal resections in a tertiary referral center (University Medical Center Utrecht, the Netherlands) as approved of by the institutional review board with patient consent. Database entries included standard patient characteristics with medical history and prospectively collected per- and postoperative data. All patients operated up to March 2011 were selected. Patients were included when they had undergone esophagectomy with gastric conduit reconstruction for esophageal cancer.

Procedure

Patients underwent either transhiatal esophagectomy (THE), transthoracic esophagectomy (TTE) or minimally invasive robot-assisted thoracolaparoscopic esophagectomy (RATE). Enteral continuity was restored with a gastric conduit with a cervical esophagogastrostomy.

All patients received bilateral chest tubes and a feeding jejunostomy.
Postoperatively, all patients were transferred to the intensive care unit (ICU). The criteria for weaning from mechanical ventilation were hemodynamic stability without high dose positive inotropic or vasoconstrictive agents, core temperature >36°C, peripheral temperature >31°C, SaO2 >94% with FiO2 ≤40% and PEEP ≤8 cm H_2O, physiological respiratory impulse (respiratory frequency 10-20 per minute) and adequate consciousness. After weaning, patients were discharged to the hospital ward. Adequate nutritional intake was ensured through the feeding jejunostomy. Oral feeding was discontinued for one week without signs of anastomotic leakage. The jejunostomy remained in place during hospital stay and was removed in the outpatient clinic only after re-establishment of sufficient oral intake.

Primary outcome
In the absence of a reliable gold standard for diagnosing pneumonia, primary outcome was defined as *the decision to treat suspected pneumonia* (MCDC grade II, see table 1). The decision to treat pneumonia was cross referenced with registration of antibiotic medication use in the electronic medical records from the pharmacology department. Unless contra-indicated, patients diagnosed with pneumonia were treated intravenously with ceftriaxon 2000mg/day according to hospital protocol. If sputum culture indicated resistance of microorganisms to specific antibiotics, the antibiotic regimen was adjusted accordingly.

Table 1. Classification of surgical complications with clinical examples of the respiratory system (as proposed by Dindo et al.[19] and adapted by D'Journo et al.[17])

Grade	Definition	Respiratory system
I	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic, and radiological interventions Allowed therapeutic regimens are drugs as antiemetics, antipyretics, analgesics, diuretics, electrolytes, and physiotherapy	Secretion retention or atelectasis requiring physiotherapy
II	Any deviation from the normal postoperative course requiring pharmacological treatment with drugs other than such allowed for grade I complications Blood transfusions and total parenteral nutrition are also included	Pneumonia treated with antibiotics on the ward
III	Any deviation from the normal postoperative course requiring surgical, endoscopic, or radiological intervention	Suction during bronchoscopy
IIIa	Intervention not under general anesthesia	
IIIb	Intervention under general anesthesia	
IV	Life-threatening complication requiring IC/ICU management	
Iva	Single-organ dysfunction (including dialysis)	Respiratory failure requiring endotracheal or non-invasive ventilation
IVb	Multi-organ dysfunction	Respiratory failure with failure of another organ
V	Death of a patient	Death

Data collection
With the use of electronic medical records, the following 4 diagnostic determinants were collected which were registered during patients' stay at the MCU or the hospital ward; temperature (degrees Celsius), leukocyte count (n x10^9/L), pulmonary radiography findings and sputum culture (analogous to the CPIS criteria for VAP(12)).
The diagnostic determinants were performed at the moment during which pneumonia was clinically suspected and before commencing antibiotic treatment. In cases where there had been no suspicion of pneumonia, data were collected on the fourth day at the hospital ward to ensure a sufficient time from ICU discharge. The time-to-treatment of pneumonia at the hospital ward was calculated from the day of discharge from the ICU department.

Statistical analysis
The association of each individual risk factor and diagnostic determinant with the decision to treat patients for pneumonia was examined in univariate analysis using separate Cox regression models for each variable. Subsequently, those factors with a P-value ≤0.20 in univariate analysis were selected for multivariate analysis, together with variables which were considered clinically relevant based on literature reports. The selected risk factors and diagnostic determinants were then entered in two separate multivariate Cox models, respectively, from which relevant variables were selected using AIC based backwards selection. Finally, two models were obtained; one model for risk factors and one model for diagnostic determinants.

RESULTS

Between October 2003 and March 2011, a consecutive series of 206 patients underwent esophagectomy with gastric conduit reconstruction. Temperature recordings, leukocyte counts, pulmonary radiographies and sputum culture results were all retrieved from 185 patients. Patients were excluded in case of missing data for temperature (n=7), leukocyte count (n=6) or pulmonary radiography (n=8).

Pneumonia
Pneumonia was suspected and treated accordingly in 70 of 185 (37.8%) patients (see table 2). During postoperative ICU stay, 9 (4.9%) patients were treated for pneumonia. At the surgical ward, 67 (36.2%) patients were treated for pneumonia. The latter group was used for further analysis.
The median time between the day of ICU discharge until the day at which pneumonia treatment was started at the hospital ward was 4 (range 0-21) days. Overall, the median hospital length of stay was 21 (range 10-105) days. Patients who were treated for pneumonia had a median hospital stay of 22 (range 10-182) days, compared to 15 (range 3-98) days for patients who were not treated for pneumonia at the hospital ward (Mann-Whitney U test, p=0.000). We analyzed all patients based on the intention to treat principle and therefore included all patients. This includes all patients who did not undergo esophagectomy based on metastatic disease discovered preoperatively and patients who died postoperatively.

Table 2. Postoperative outcomes

			n (%) (total n=185)
Treated for pneumonia *(MCDC grade II)*		During total hospital stay	70 (37.8)
		During postoperative ICU stay	9 (4.9)
		During hospital ward stay	67 (36.2)
Time-to-treatment of pneumonia (days)*		median (range)	4 (0-21)
Anastomotic leakage			35 (18.9)
Chylus leakage			26 (14.1)
Wound infection	Neck		5 (2.7)
	Thorax		1 (0.5)
	Abdomen		5 (2.7)
Recurrent nerve	pareses		18 (9.7)
	paralysis		4 (2.2)
Atrial fibrillation			23 (12.4)
Myocardial infarction			4 (2.2)
In hospital mortality (*MCDC grade V)*			5 (2.7)
Length of stay (days)	ICU postoperative	median (range)	1 (1-65)
	ICU total	median (range)	2 (1-65)
	Hospital total	median (range)	21 (10-105)
Length of postoperative mechanical ventilation (days)		median (range)	0 (0-64)

Values are n (%) unless indicated otherwise

* Time-to-treatment of pneumonia at the hospital ward was calculated from the day of discharge from the ICU department

Abbreviations: MCDC - Modified Clavien Dindo classification, ICU - Intensive care unit.

A total of 34 (18.4%) patients were readmitted to the ICU department (MCDC grade IV). In most cases, 33 of 34 (97%) patients, this was due to respiratory failure. Patients who were treated for pneumonia at the hospital ward were at increased risk of getting readmitted to the ICU department when compared to patients who were not treated for pneumonia (35.8% vs. 8.5%, OR 6.0, Chi-square test p=0.000).

The in-hospital mortality rate related to pneumonia and respiratory failure (MCDC grade V) was 2.7% in the study population. In patients treated for pneumonia at the hospital ward, the in-hospital mortality rate was 4.5% compared to 1.7% among patients without pneumonia (OR 2.7, Chi-square test P=0.262).

Regression analysis of risk factors for pneumonia

Descriptive data on the distribution of pre- and perioperative risk factors for pneumonia are presented in table 3. In the univariate Cox regression models, age, gender, history of COPD, BMI, neoadjuvant therapy and the number of resected lymph nodes were significantly associated with an increased risk of pneumonia treatment, when employing a liberal criterion of a P value ≤0.20.

Results from the multivariate Cox model, with AIC based backward selection of relevant

Table 3. Univariate Cox regression analysis of risk factors for pneumonia

			Treated for pneumonia				
Risk factor			**Total n=185 n (%)**	**Yes n=67 n(%)**	**No n=118 n (%)**	**HR**	***P value†***
Age [years]		mean (SD)	63.9 (9.0)	65.4 (9.3)	63.0 (8.8)	1.02	***0.118***
Gender [male]			141 (76.2)	56 (83.6)	85 (72.0)	1.80	***0.059***
BMI		mean (SD)	25.5 (4.2)	26.2 (4.0)	25.2 (4.3)	1.04	***0.146***
COPD			23 (12.4)	12 (17.9)	11 (9.3)	1.72	***0.109***
Cardiac disease			37 (20.0)	16 (23.9)	21 (17.8)	1.28	*0.397*
Diabetes			26 (14.1)	11 (16.4)	15 (12.7)	1.18	*0.622*
Tobacco use			95 (51.4)	34 (50.7)	61 (51.7)	1.01	*0.969*
Alcohol use			102 (55.1)	41 (61.2)	61 (51.7)	1.30	*0.286*
Neoadjuvant therapy			71 (38.4)	30 (44.8)	41 (34.7)	1.41	***0.169***
ASA score	1		47 (25.4)	15 (22.4)	32 (27.1)	1.00	*0.764*
	2		106 (57.3)	40 (59.7)	66 (55.9)	1.22	
	3-4		32 (17.3)	12 (17.9)	20 (16.9)	1.28	
Operative approach [transthoracic extended]			134 (72.4)	52 (77.6)	82 (69.5)	1.43	*0.208*
Operative blood loss [milliliters]		median (range)	360 (6490)	360 (3770)	375 (6490)	1.00	*0.399*
Operative time [minutes]		median (range)	402 (522)	417 (412)	386 (501)	1.00	*0.417*
pT*	0-1		45 (24.3)	17 (25.4)	28 (23.7)	1.00	*0.790*
	2		16 (8.6)	4 (6.0)	12 (10.2)	0.70	
	3-4		124 (67.0)	46 (68.7)	78 (66.1)	0.97	
Total number of LNN resected [n]		median (range)	19 (63)	19 (45)	19 (63)	0.98	***0.164***
Postoperative ICU stay [days]		median (range)	1 (131)	1 (130)	1 (40)	1.01	*0.538*
Postoperative mechanical ventilation [days]		median (range)	0 (119)	0 (119)	0 (35)	1.01	*0.449*
Pneumonia during postoperative ICU stay			9 (4.9)	6 (9.0)	3 (2.5)	1.62	*0.294*

Values are n (%) unless indicated otherwise

* according to the TNM staging system, 7th edition

† variables with a P value <0.20 were selected for multivariate analysis

Abbreviations: HR - Hazard ratio, COPD - Chronic obstructive pulmonary disease, BMI - Body mass index, ASA - American Society of Anesthesiologists, pT - depth of tumor infiltration, pN - lymph node involvement, ICU - Intensive care unit.

predictors, are presented in table 4. The overall univariate P value for operative approach (transhiatal vs. transthoracic) was P=0.208. This variable was included in the multivariate Cox regression model (before commencing with the backwards selection) based on clinical relevance and its' well known association with pulmonary complications in literature.(2;20) In the multivariate Cox model, obtained after backwards selection, variables significantly

Table 4. Multivariate Cox regression analysis of risk factors for pneumonia

Risk factor	HR	*P value*
Operative approach [transthoracic extended]	2.393	***0.007***
Age	1.034	***0.027***
Gender [male]	2.379	***0.011***
History of COPD	1.985	***0.037***
Total number of LNN resected	0.972	***0.025***

Abbreviations: HR - Hazard ratio, COPD - Chronic obstructive pulmonary disease, LNN - lymph nodes.

Table 5. Univariate Cox regression analysis of diagnostic determinants for pneumonia

			Treated for pneumonia			
Diagnostic determinant		**Total n=185**	**Yes n=67**	**No n=118**	**HR**	***P value***
Temperature [°C]	median (range)	37.3 (4.6)	38.0 (4.6)	37.1 (3.0)	2.18	***0.000***
Leukocyte count [x10^9/L]	median (range)	11.3 (30.2)	14.4 (29.8)	9.7 (28.6)	1.10	***0.000***
Pulmonary radiography	No infiltrate	126 (68.1)	13 (10.3)	113 (89.7)	1.00	***0.000***
	Diffuse (or patchy) infiltrate	36 (19.5)	31 (86.1)	5 (13.9)	15.51	
	Well-circumscribed infiltrate	23 (12.4)	23 (100.0)	0 (0.0)	19.17	
Sputum culture	No sputum culture	41 (22.2)	11 (26.8)	30 (73.2)	1.00	***0.000***
	No PMO	77 (41.6)	19 (24.7)	58 (75.3)	0.89	
	PMO for pneumonia	59 (31.9)	29 (49.2)	30 (50.8)	1.88	
	PMO for pneumonia with corresponding gram stain	8 (4.3)	8 (100.0)	0 (0.0)	7.57	

Abbreviations: HR - Hazard ratio, PMO - pathogenic microorganism.

associated with treatment of pneumonia included transthoracic operative approach (Hazard Ratio=2.393, P=0.007), age (HR=1.034, P=0.027), male gender (HR=2.379, P=0.011), history of COPD (HR=1.985, P=0.037) and total number of resected lymph nodes (HR=0.972, P=0.025). BMI and neoadjuvant therapy were rejected from the regression model.

Regression analysis of diagnostic determinants for treatment of pneumonia

Associations between temperature, leukocyte count, pulmonary radiography and sputum culture with treatment of pneumonia are presented in table 5. All four diagnostic determinants showed significant associations in univariate Cox regression analysis (all overall P values <0.001) and were consequently entered into multivariate analysis.

Sputum culture was excluded from the multivariate Cox regression model through backward selection (see table 6). Temperature and leukocyte count remained in the model (HR=1.283, P=0.073; HR=1.040, P=0.078, respectively). Abnormal pulmonary radiography was an

Table 6. Multivariate Cox regression analysis of diagnostic determinants for pneumonia

Diagnostic determinant		**HR**	***P value***
Temperature		1.283	*0.073*
Leukocyte count		1.040	*0.078*
Pulmonary radiography	No infiltrate	1.000	*0.000*
	Diffused (or patchy) infiltrate	11.473	
	Well-circumscribed infiltrate	13.389	

Abbreviations: HR - Hazard ratio.

independent predictor of pneumonia treatment (P=0.000) with HRs of 11.5 and 13.4 for diffused infiltrate and well-circumscribed infiltrate, respectively.
A scoring model was created based on the outcomes of the multivariate analysis. Sputum culture was not included since it was already excluded from the regression model. Temperature recording and leukocyte count were included because they were borderline significant and because they can easily be obtained in the clinical setting. Analogous to the CPIS scoring system (12), each diagnostic determinant was assigned a score (see table 7) of which the sum yields an overall score ranging from 0 to 5 points. Figure 1 shows the total scores grouped by the negative or positive decision to treat patients for pneumonia. The pivot point of pneumonia treatment in this scoring model was at 2 points. Of all 66 patients with a score of 2 or higher, 58 patients were treated for pneumonia. In a subset of 30 patients with a sum score of 2 points, who were treated for pneumonia, 25 patients scored at least 1 point for infiltrative signs on pulmonary radiography (24 patients with a diffused infiltrate, and 1 patient with a well circumscribed infiltrate). The remaining 5 patients scored 1 point for temperature and 1 point for leukocyte count. Out of 119 patients scoring 0 or 1 points, 9 patients were treated for pneumonia. There was only 1 patient who had a sum of 3 points without radiologic findings on the thoracic x-ray.

Table 7. Utrecht Pneumonia Scoring System for the decision to treat pneumonia at the hospital ward after esophagectomy *

Diagnostic determinant	Range	Score
Temperature [^{o}C]	≥ 36.1 and ≤ 38.4	0
	≥ 38.5 and ≤ 38.9	1
	≥ 39.0 and ≤ 36.0	2
Leukocyte count [x10^{9}/L]	≥ 4.0 and ≤ 11.0	0
	< 4.0 or > 11.0	1
Pulmonary radiography	No infiltrate	0
	Diffused (or patchy) infiltrate	1
	Well-circumscribed infiltrate	2

* A sum score of 2 points or higher, of which at least 1 point is assigned due to infiltrative findings on pulmonary radiography, indicates treatment of pneumonia.

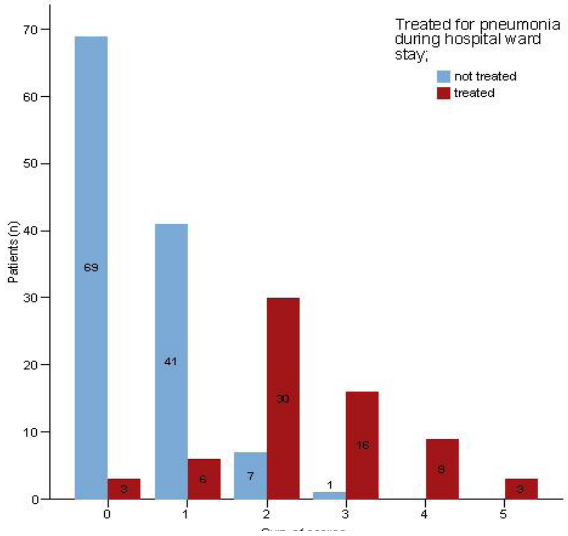

Figure 1.Numbers of patients with and without treatment for pneumonia arranged by the sum of scores of the Utrecht Pneumonia Scoring System

DISCUSSION

Esophagectomy is associated with a high risk of postoperative morbidity, mostly respiratory infections. Hence, studies on resection techniques in esophageal cancer surgery focus mainly on a reduction of morbidity, particularly respiratory complications and pneumonia. It is remarkable that these studies use different definitions of pneumonia(18;21) or fail to provide a definition altogether.(22-26) Consequently, the reported pneumonia rates vary widely.

In this prospective series of patients who underwent esophageal resection with gastric conduit reconstruction, treatment of pneumonia (MCDC grade II) at the hospital ward was found in 36.2% of patients. Pneumonia was associated with respiratory failure and consequent readmission to the ICU (MCDC grade IV). When a different and frequently used definition of pneumonia is applied on our cohort (i.e. infiltrate on pulmonary radiography combined with a positive sputum culture(2;18)), the pneumonia rate decreases to 18.9%. It seems that a discrepancy exists between the diagnosis of pneumonia for clinical purposes and how pneumonia is potentially reported in literature. This illustrates the urgent need for a standardized approach towards pneumonia following esophagectomy.

Risk factors

In multivariate regression analysis of all relevant pre- and perioperative risk factors, a transthoracic operative approach was the strongest independent predictive factor followed by male gender and history of COPD. Increasing age was also associated with

pneumonia treatment. The number of resected lymph nodes was negatively associated with postoperative pneumonia treatment (HR<1.0). Since lymph node harvest is generally higher during transthoracic surgery this was contrary to what we expected. Though significant, its' effect was minor.

The strong correlation of COPD with postoperative pneumonia treatment indicates that our results correspond with other studies, which report high predictive values of lung function and comorbidity for postoperative complications.(5;20) Operative approach (transhiatal vs. transthoracic) is also reported to be highly correlated to the development of pulmonary complications.(2;20) In accordance with other reports, ASA score and BMI were not associated with treatment of pneumonia in our series.(20;27)

Other authors have described nomograms and risk models to predict occurrence and/or severity of complications after esophagectomy.(5;20;28;29) However, available prediction models suffer from low discriminative ability.(28;30) Pre- and perioperative risk factors play an important role, but the pathogenesis of postoperative complications is highly complex and dependent on a multitude of factors. Anesthesiological considerations, such as epidural analgesia and anesthetic management during surgery also influence postoperative outcomes.(31) Furthermore, genetic and immunological concepts may contribute in the development of complications as well.(32)

Diagnostic determinants

Nomograms aid in risk stratification and patient selection for surgery, but do not facilitate the diagnostic process. Therefore, the second regression model focused on how diagnostic determinants for pneumonia had been used in clinical practice. Factors that play a role in the clinical decision-making process are general physical examination (chest auscultation, respiratory rate, coughing, presence and aspect of sputum, temperature) complemented with leukocyte count, arterial blood gas, pulmonary radiography and sputum culture.(10) The sensitivity of physical examination has been questioned in literature due to a high interobserver variability.(33) In this study it is impossible to assess its' contribution in the diagnostic process. C-reactive protein not only lacks specificity, but is highly responsive to major surgery and was therefore not included.(34) The determinants of pneumonia that could be objectively assessed are temperature recordings, leukocyte count, pulmonary radiography and sputum culture.

These four diagnostic variables were examined for their influence on the diagnostic process. Multivariate analysis showed a large effect of pulmonary radiography. It was the preferred or most important instrument for diagnosing pneumonia in clinical practice. Temperature and leukocyte also affected the decision to treat pneumonia. Although their effects appear minor, it must be noted that the risk increases exponentially with each incremental unit. This means that with an increase in leukocyte count of 20 units, the estimated risk (HR) of pneumonia treatment increases as 1.040^{20}=2.191. Sputum culture was excluded during backward selection and did not independently correlate with the decision to treat pneumonia.

The findings correlate with the guidelines of the American Thoracic Society and the Infectious Diseases Society of America for the management of adults with HAP. The diagnosis of HAP is suspected if the patient has an infiltrate on pulmonary radiography which is new or

progressive, along with clinical findings suggesting infection, such as fever, purulent sputum, leukocytosis, and decline in oxygenation.(10) The results of sputum culture, of which sensitivity is debatable(10), become available after the decision to treat has already been taken. This is reflected in our findings which show that sputum culture is not independently associated with pneumonia treatment. It could be argued that pneumonia is overdiagnosed when sputum culture is not included in the decision process. Without a reliable gold standard it is impossible to adequately determine over- or undertreatment rates. Though sputum culture does not influence the decision to treat pneumonia, it should always be performed to identify the responsible pathogen and to assess whether a switch of antibiotic medication is indicated.

Scoring model for pneumonia

To facilitate the diagnosis of VAP and improve comparability between clinical trials, the Clinical Pulmonary Infection Score (CPIS) is often used in clinical practice and literature.(12;13;35-40) Such a scoring system is not available for diagnosing HAP. Moreover, the majority of pneumonias in the studied cohort were diagnosed after discharge from the ICU. Hence, a standardized model for pneumonia at the hospital ward could be of great value in esophageal cancer research.

A clinical scoring model of the diagnostic determinants, analogous to the CPIS(12), was created based on multivariate Cox regression analysis. The model includes temperature, leukocyte count and pulmonary radiography, all easily obtainable from the non-ventilated patient. In contrast to the CPIS, no data was included on oxygenation (PaO_2/FiO_2 in mmHg) and tracheal secretions (number of required secretions) since these can only be assessed in mechanically ventilated patients. The presented scoring model accurately corresponds with the clinical practice of how pneumonia was diagnosed and treated accordingly in the studied series. It indicates that patients scoring 2 or higher were treated for pneumonia. The majority of patients scoring 2 points also had infiltrative signs on pulmonary radiography. Moreover, pulmonary radiography exercised the greatest effect (HR>11.0) in multivariate analysis. Based on these findings, we suggest a straightforward model which directs the decision to treat pneumonia after esophagectomy at the hospital ward. Patients with a sum score of 2 points or higher, of which at least 1 point is assigned due to infiltrative findings on pulmonary radiography, should be treated for pneumonia. Future studies should validate the utility of this model in the design, conduct, and evaluation of clinical research regarding pneumonia after esophagectomy.

Conclusion

In our series, a transthoracic operative approach, male gender and history of COPD were the strongest predictors for postoperative pneumonia treatment at the hospital ward. These risk factors are important for risk stratification and patient selection. However, the decision to treat pneumonia is composed by the outcomes of diagnostic determinants. In case of clinical suspicion of pneumonia after discharge from postoperative ICU stay, clinicians are guided by temperature, leukocyte count and pulmonary radiography findings. Sputum culture does not influence the decision to treat pneumonia, but is required to identify pathogens and

appropriate antibiotic treatment.
The lack of a uniform definition leads to underreporting of pneumonia rates in literature. We strongly advocate a standardized definition that includes the clinical decision to treat pneumonia. Pneumonia following esophagectomy is mostly diagnosed at the hospital ward and the decision to treat is based on temperature, leukocyte count and pulmonary radiography findings. After validation, the proposed scoring model has the potential aid clinical practice and to improve comparability of future research in esophageal cancer surgery.

Disclosures and Freedom of Investigation
No form of funding was received for this study. There are no conflicts of interest to disclose.
All authors had full control of the design of the study, the methods used, the outcome parameters and results, the analysis of data and production of the written manuscript.

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Chapter 13

Gastric conduit resection and jejunal interposition for recurrent esophageal cancer

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We describe the case of a 58-year-old man with recurrent adenocarcinoma at the site of an esophagogastrostomy that we treated by radical surgical resection and jejunal interposition. Oral intake was started on the 6th postoperative day and the patient was discharged on the 11th postoperative day. Seven months after the surgical procedure no signs of tumor recurrence were detected. Resection of localized (recurrent) esophageal cancer may well be a valuable treatment option and is therefore an interesting therapeutic option in patients with recurrent disease. However this needs to be investigated in a randomized controlled trial.

The incidence of esophageal adenocarcinoma is rapidly increasing [1]. For patients with locally advanced disease, radical esophagectomy offers the best chance for survival, with a mean 5-year survival rate of 36% [2]. Despite potentially curative local therapy, most patients will have locoregional or systemic recurrent disease [2, 3]. Recurrent disease is the major cause of death in patients who undergo esophagectomy, with a median survival of 7 months after recurrence [3]. Approximately 10% of patients who undergo resection will have recurrent disease at the site of the esophagogastric anastomosis [4, 5]. Therapeutic options for locally recurrent esophageal carcinoma are limited and depend on the tumor (extension of the tumor) and patient (clinical condition and symptoms) characteristics. In most cases, local radiotherapy or chemotherapy is given with palliative intent. For patients with locally recurrent disease, a potential survival benefit for surgical resection has been suggested [6]. Here we report a case of a patient with recurrent adenocarcinoma at the site of the esophagogastrostomy treated by surgical resection.

In April 2009, a 58-year-old male patient was diagnosed with cT3N1 (TNM 7 [7]) adenocarcinoma of the distal esophagus. The patient underwent 3 cycles of chemotherapy with ECC (epirubicin, cisplatin, capecitabine), followed by radiotherapy and experimental cetuximab. Thereafter he underwent an uncomplicated laparoscopic transhiatal esophagectomy with gastric conduit reconstruction. Histologic examination of the resection specimen showed a radically resected T2N0Mx esophageal adenocarcinoma with partial response to neoadjuvant therapy (Mandard grade 2). Postoperatively the patient underwent another 3 cycles of (adjuvant) ECC chemotherapy. One year later he returned with fatigue, anemia, and headache. Esophagogastroscopy showed a bleeding semicircular recurrent tumor of 3.0 cm length 2 cm below the esophagogastric anastomosis. Biopsy specimens showed high-grade dysplasia that was suspected of being malignant. Endomucosal resection of the recurrent tumor was not possible because of infiltration into the submucosa. Intraluminal radiotherapy (brachytherapy) was suggested, but in the absence of metastases a local resection with free jejunal interposition was chosen by the patient.

The cervical esophagus and esophagogastric anastomosis were mobilized through a left longitudinal cervical incision. Because of the absence of transmural ingrowth in the gastric conduit wall, the tumor could not be identified. After transillumination, the position of the tumor was identified and the distal tumor margin was marked and then resected (Fig 1). Frozen sections showed that the margins were tumor free. The vascular supply for the jejunal graft was then prepared by identifying and clipping the superior thyroid artery. The internal jugular vein was dissected to be used as the acceptor vein for the microvascular anastomosis.

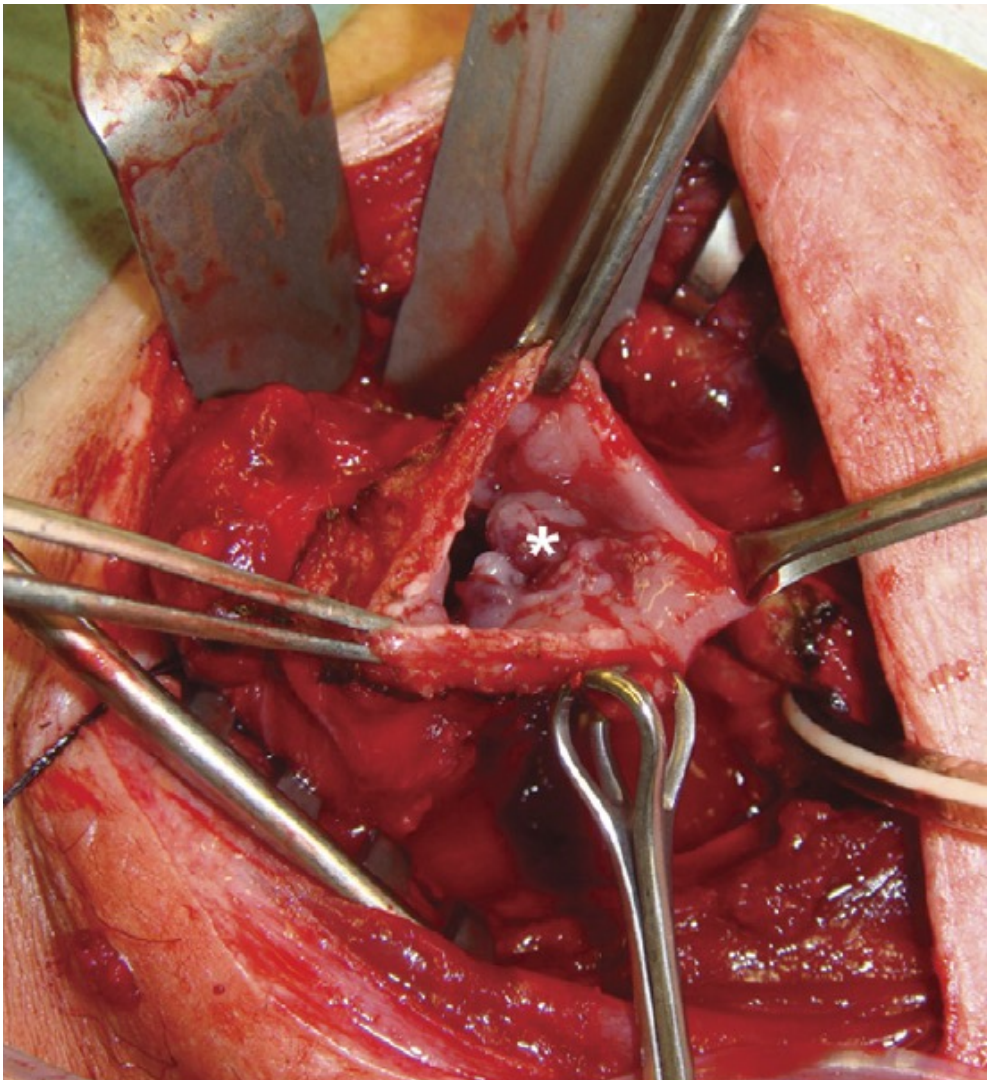

Fig 1. The alimentary tract lumen with tumor visible after the distal esophagus is transected. The tumor (*) is localized 2 cm distal to the esophagogastrostomy.

For the jejunal autograft, a midline laparotomy was performed. After transillumination of the mesentery artery, a long jejunal segment distal to the Treitz ligament was selected for reconstruction (Fig 2). The distal end of the jejunal segment was marked to ensure an isoperistaltic orientation in the neck. A feeding jejunostomy was placed and small-bowel continuity was reestablished with an end-to-end jejunojejunostomy. The distal end-to-end jejunogastrostomy was performed first, followed by creation of the proximal end-to-end esophagojejunostomy with a little tension on the suture line (Fig 3). The latter is important to

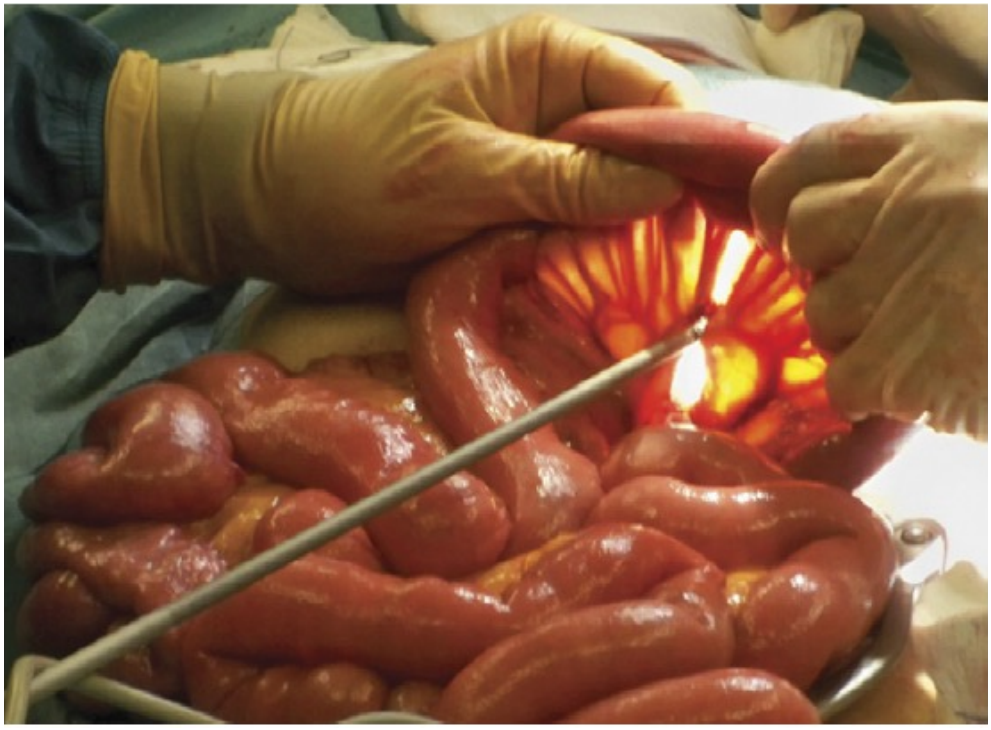

Fig 2. Transillumination of the mesentery allows the surgeon to select the segment of the jejunum to be harvested.

prevent regurgitation and dysphagia. The gastric conduit remained well vascularized during the whole procedure. After completion of the enteric anastomoses, the arterial end-to-end anastomosis was created between the jejunal branch of the superior mesenteric artery and the superior thyroid artery. The venous end-to-side anastomosis was created between the venous branch of the jejunal autograft and the internal jugular vein (Fig 4). After release of the clamps, vascularization and coloring of the jejunal autograft were restored.
Histologic examination of the resection specimen showed a T3N0 esophageal adenocarcinoma, 3.7 cm in length, which was radically resected. Jejunal tube feeding was started using the feeding jejunostomy. In the absence of signs of anastomotic leakage, oral intake was started on the 6th postoperative day. On the 11th postoperative day, the patient was discharged. Nine months after the surgical procedure, there were no signs of tumor recurrence.

COMMENT

Recurrent disease is the leading cause of death in patients undergoing curative resection for esophageal carcinoma. Therapeutic options for locally recurrent esophageal carcinoma are limited. Combined multimodality treatment can be offered to improve survival or improve

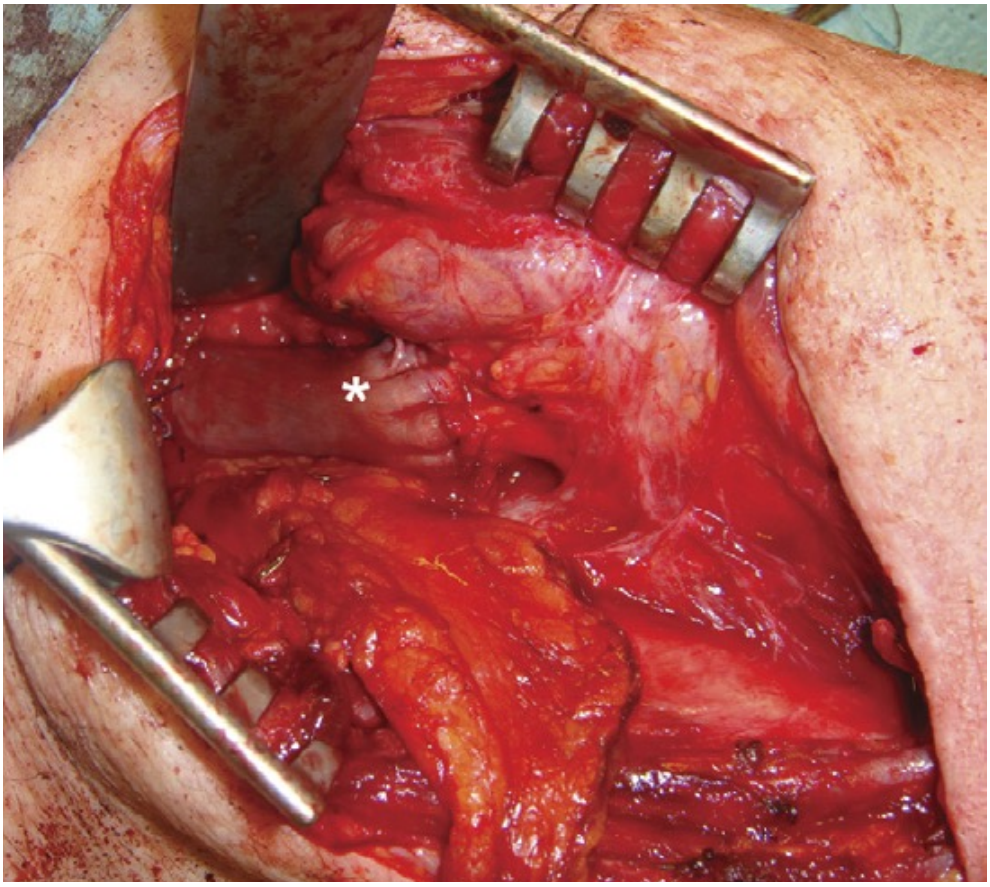

Fig 3. The distal end-to-end jejunogastrostomy is performed first, placing the jejunal autograft in an isoperistaltic position. The proximal end-to-end esophagojejunostomy (*) is then created with just a little tension on the suture line (lateral view from the left side).

clinical symptoms [8]. For patients with locally recurrent disease only, a potential survival benefit with operation has been suggested [6]. Our patient had shown a partial response to previous preoperative neoadjuvant chemoradiotherapy. Therefore a radical resection of the recurrent tumor was considered the best therapeutic option in this patient. One-year, 3-year, and 5-year overall survival rates for radically resected recurrent esophageal cancer have been reported to be 62%, 44%, and 35%, respectively [6].

Gastroscopic surveillance was performed 6 months after operation. It is currently 9 months after the surgical procedure, and our patient has no signs of tumor recurrence. If tumor recurrence takes place, it will most likely be in the first year after operation (38%) [6].

The absence of systemic metastases and only a partial response to preoperative chemoradiotherapy made our multidisciplinary oncology committee decide that a radical surgical procedure without postoperative adjuvant chemotherapy would be the best

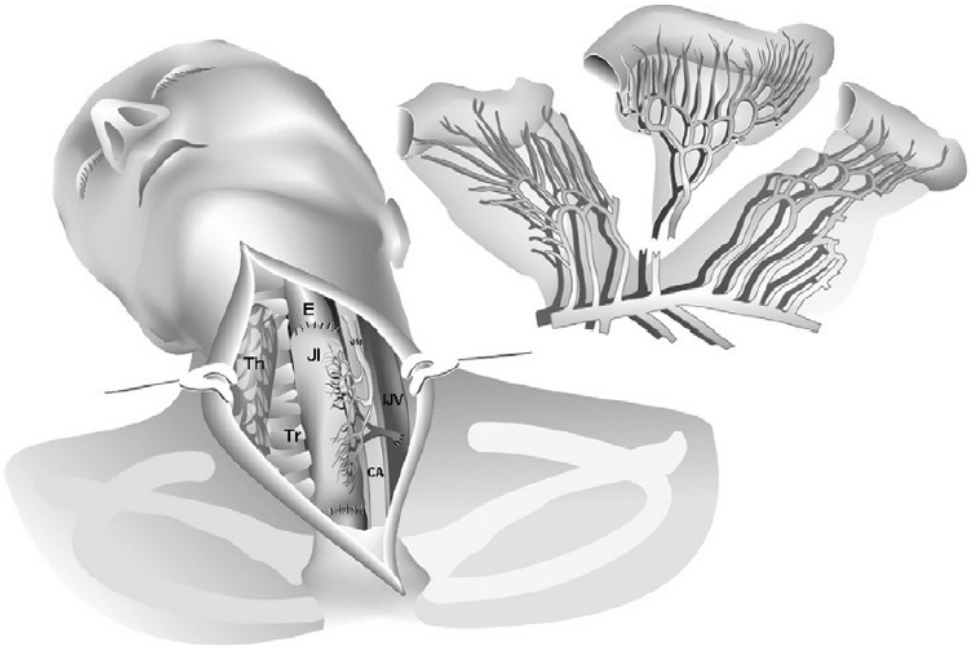

Fig 4. Microvascular anastomoses. Jejunal segment is selected and harvested and the vascular pedicle is dissected. The microvascular arterial end-to-end anastomosis is created between the jejunal branch of the superior mesentericartery and the superior thyroid artery. The microvascular venous end-to-side anastomosis is created between the venous branch of the jejunal autograft and the internal jugular vein. (CA = carotid artery; E = esophagus, IJV = internal jugular vein; JI = jejunal interposition; Th = thyroid; Tr = trachea.)

therapeutic option for our patient. Irradiation in the cervical anastomotic area might compromise the microvascularity of a free graft. Therefore no adjuvant radiotherapy was administered. Resection of locally recurrent esophageal cancer with jejunal interposition can be technically challenging because of fibrosis from the previous resection and previous chemoradiotherapy. Furthermore, special care should be taken of the vascularization of the gastric conduit to avoid ischemia and necrosis [6].

As described here, this surgical procedure turned out to be technically feasible and safe, with a short hospitalization time and no postoperative complications. Radical resection of localized (recurrent) esophageal carcinoma may well lead to long-term survival and is therefore an interesting therapeutic option in patients with recurrent disease [6].

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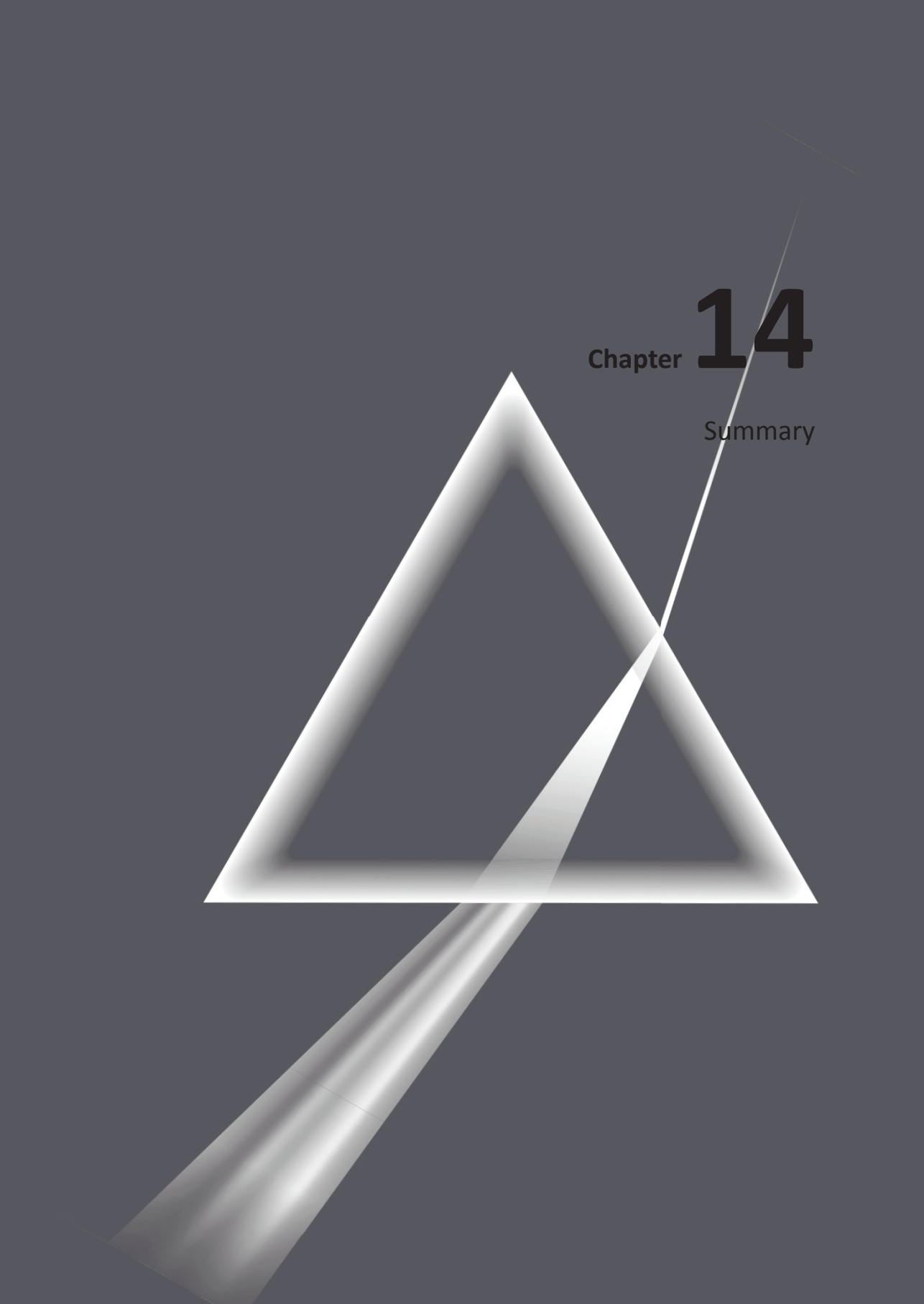

Chapter 14

Summary

PART I: NEOADJUVANT THERAPY

In **Chapter 2,** the first series to report the use of perioperative ECC-based chemotherapy in a homogeneous population of patients with adenocarcinoma of the esophagus or gastroesophageal junction (GEJ) was described. Due to toxicity, only 66 % of the patients received the preoperative chemotherapy regimen of three ECC cycles. Multivariate analysis of all the analyzed risk factors showed that a history of cardiac disease or vascular was associated with the occurrence of grade 3 or higher adverse events. This toxicity was higher than initially reported in the MAGIC trial and REAL2 trial, where these regimens were first described. This could be due to a difference in population included in the study. In the MAGIC trial, 74 % of all the patients had gastric adenocarcinomas whereas in our cohort, 81% of patients had distal esophageal adenocarcinomas. Esophageal and gastric adenocarcinomas differ in their aetiology, patient population, and clinical characteristics. More importantly, the surgical treatment is substantially different, consisting of gastrectomy instead of esophagectomy. These differences suggested that esophageal and GEJ adenocarcinomas form an entity separate from more distal gastric adenocarcinomas and translating results from trials predominantly including gastric cancer patients to esophageal and GEJ cancer patients might not be sensible.
The observed high toxicity, however, did not negatively affect the ability to undergo surgery. For 94 % of the patients, an esophageal resection could be performed with a radicality rate of 94 % and a pCR rate of 8%. Only 27 % of the patients completed the pre- and postoperative chemotherapy, which showed that postoperative ECC chemotherapy was not feasible for most patients with adenocarcinoma of the esophagus or GEJ.
In **Chapter 3**, a phase II study was performed, where patients were treated with three cycles of epirubicin, cisplatin, and capecitabine (ECC), followed by cetuximab and radiotherapy. After surgery with curative intent, patients received three more cycles of ECC. Primary endpoints were efficacy, determined by histopathological complete response (pCR) rate, and safety, which was assessed with resectability rate. With 12 patients enrolled, the lack of initial signs of efficacy and a high incidence of postoperative serious adverse events prompted us to end this study prematurely. Perioperative ECX was associated with considerable toxicity and it was concluded that further treatment intensification was problematic.
In **Chapter 4**, neoadjuvant chemoradiotherapy (nCRT) according to the CROSS regimen (carboplatin/paclitaxel/41.4Gy, n=176), was compared to perioperative chemotherapy (pCT) according to the MAGIC regimen (epirubicin, cisplatin and capecitabine, n=137) for patients with resectable esophageal or gastroesophageal junction (GEJ) adenocarcinoma in tertiary referral centers in the Netherlands. Primary endpoints were toxicity, postoperative complications, pathological response, long-term survival and disease recurrence. It was concluded that nCRT and pCT lead to equal oncologic outcomes in terms of radical resection rates, lymphadenectomy, patterns of recurrent disease and (disease free) survival. However, neoadjuvant chemoradiotherapy was associated with a considerable lower level of severe adverse events and is therefore be the preferred protocol until a well powered randomized controlled trial provides different insights.

In **Chapter 5**, in a propensity score-matched cohort study, outcomes of perioperative chemotherapy were compared to neoadjuvant chemoradiotherapy for patients with resectable esophageal or GEJ adenocarcinoma within a single center. No significant improvements were achieved with nCRT as compared to pCT in terms of radical resection rates or progression-free survival and overall survival. However, nCRT was associated with improved tumor downstaging and a higher pCR rate compared to pCT. This observation likely translated into the observed decrease in locoregional disease progression in the nCRT group.

PART II: ROBOT ASSISTED MINIMALLY INVASIVE THORACO-LAPAROSCOPIC ESOPHAGECTOMY (RAMIE) FOR ESOPHAGEAL CANCER

A systematic review of studies describing robot assisted minimally invasive thoraco-laparoscopic esophagectomy for esophageal cancer (RAMIE) was performed in **Chapter 6.** A literature search yielded 16 eligible papers describing case series of RAMIE. The review demonstrated the growing experience with and the growing interest for RAMIE. Furthermore, in this systematic review, RAMIE was shown to be technically and oncologically safe.

In **Chapter 7**, in a cohort of 108 Western European patients with advanced esophageal cancer, RAMIE with two-field lymphadenectomy was shown to be feasible and safe. Furthermore, RAMIE was shown to be oncologically effective, with a high percentage of R0 radical resections with adequate lymphadenectomy. RAMIE provided adequate local control, with a low percentage of local recurrence.

In **Chapter 8**, the learning curve for RAMIE was described in a cohort of 312 esophageal cancer patients. For the pioneers of RAMIE, the first 70 RAMIE cases formed the learning phase upon reaching proficiency after start-up of this technique in 2003. After a structured proctoring program, a newly introduced surgeon, who was introduced to the RAMIE technique, was able to show the same level performance as the proctor. The learning phase for the novice surgeon consisted of 24 cases (15 supervised and 9 independent cases) in 13 months, which showed a reduction of 66% in the number of operations and a reduction of 76% in time, compared to the proctor. This chapter showed that proctoring is pivotal to reduce the learning curve of RAMIE for novice surgeons and secure a flawless introduction of this technique.

In **Chapter 9**, the trial protocol was described for the ROBOT trial. The ROBOT trial was a randomized controlled parallel-group, superiority monocenter trial comparing robot-assisted minimally invasive esophagectomy (RAMIE) with open transthoracic esophagectomy (OTE) (ClinicalTrials.gov Identifier: NCT01544790). The primary composite endpoint of this study was the percentage of overall and related complications (grade 2 and higher) as stated by the modified Clavien–Dindo classification (MCDC) of surgical complications.

In **Chapter 10**, results of the ROBOT trial were described. In this randomized controlled monocenter trial, 112 patients with resectable intrathoracic esophageal cancer were randomly assigned to RAMIE or OTE. The composite primary endpoint of this study was the occurrence of overall complications (modified Clavien–Dindo classification (MCDC) grade 2-5).

RAMIE was associated with a lower percentage of overall and surgery related complications compared to OTE. Furthermore, RAMIE was associated with less blood loss, a lower percentage of pulmonary complications and a lower percentage of cardiac complications compared to OTE. Postoperative pain in the first 14 days was lower after RAMIE compared to OTE. RAMIE resulted in a higher proportion of patients who were functionally recovered within 14 days and in a higher proportion of patients who could be discharged without the need for additional jejunostomy tube feeding. Short term quality of life after RAMIE was better, both at discharge and 6 weeks after discharge.
Together with the previous randomized trial on MIE versus OTE (TIME trial), results of this randomized controlled trial provide evidence to change the surgical standard of care into minimally invasive surgery for esophageal cancer patients who need esophageal resection.

PART III: SURGICAL TECHNIQUES AND COMPLICATIONS

In **Chapter 11,** the postoperative outcomes of hand-sewn end-to-end versus end-to-side cervical esophagogastric anastomoses were compared. The technique of anastomosis was not significantly related to anastomotic leakage rate. However, patients with cervical end-to-end anastomoses developed postoperative strictures more frequently, requiring a higher number of dilations compared to cervical end-to-side anastomoses.
In **Chapter 12**, a new clinical scoring system to define pneumonia following esophagectomy for cancer was proposed. Pneumonia is a frequently observed complication following esophagectomy. The lack of a uniform definition of pneumonia leads to large variations of pneumonia rates in literature. This study was designed to develop a scoring system for diagnosing pneumonia following esophagectomy at the hospital ward. In a prospective cohort study of esophagectomy patients, known risk factors for pneumonia, temperature, leukocyte count, pulmonary radiography and sputum culture added were evaluated. Primary outcome was defined as the decision to treat suspected pneumonia. This study showed that the decision to treat pneumonia was based on temperature, leukocyte count and pulmonary radiography findings. The proposed clinical scoring system for pneumonia following esophagectomy at the hospital ward has the potential to aid clinical practice and improve comparability of future research in esophageal cancer surgery.
In **Chapter 13**, a case was described of a patient with recurrent adenocarcinoma at the site of the esophagogastrostomy (gastric conduit). The gastric conduit was radically resected and continuity of the digestive tract was restored by jejunal interposition. Resection of localized (recurrent) esophageal cancer may well be a valuable treatment option and is therefore an interesting therapeutic option in patients with recurrent disease.

Chapter 15

General discussion and future directions

GENERAL DISCUSSION AND FUTURE DIRECTIONS

In the last years tremendous progress has been established in the treatment of esophageal cancer both in the fields of perioperative treatment and surgery. This thesis evaluated different treatment strategies for esophageal cancer including neoadjuvant therapy and robot assisted minimally invasive thoraco-laparoscopic esophagectomy (RAMIE) for esophageal cancer. Furthermore surgical techniques and compilations were evaluated This general discussion will elaborate on the most important new insights for neoadjuvant treatment, RAMIE and will explain the implications for current practice and future directions.

Neoadjuvant therapy

Both neoadjuvant chemoradiotherapy (nCRT) followed by surgery and perioperative chemotherapy (pCT) have been demonstrated to show a survival benefit in multiple randomized clinical trials compared to surgery alone for esophageal adenocarcinoma.[1] In Europe and North America, chemoradiotherapy is nowadays the preferred neoadjuvant strategy based on the CROSS trial.[2] In the United Kingdom, perioperative chemotherapy is considered standard of care, based on the modified MAGIC regimen.[3] These 2 therapeutic regimens were compared in chapter 5 and chapter 6 of this thesis.[4,5] Perioperative chemotherapy and neoadjuvant chemoradiotherapy were both associated with substantial regimen specific adverse events and postoperative morbidity. However, nCRT was associated with a considerable lower level of severe adverse events. Neoadjuvant chemoradiotherapy achieved higher pathologic complete response rates and a lower risk of locoregional disease progression, with similar survival compared to pCT. Based on a different toxicity profile, combined with higher pathologic complete response rates, nCRT is currently the preferred protocol for resectable esophageal adenocarcinoma in The Netherlands including our hospital.

However until no, there are no short and long term results available from well powered randomized controlled trials which directly compare nCRT according to the CROSS regimen and pCT according to the MAGIC regimen. This level 1 evidence is needed to definitely provide the answer to which therapy regimen is preferable for treatment of resectable esophageal adenocarcinoma. Currently, the Neo-AEGIS randomized clinical trial (NCT01726452) and POWERRANGER randomized clinical trial (NCT01404156) directly compare the nCRT (CROSS) regimen with the pCT (MAGIC) regimen as described in our studies and are recruiting participants. Results are awaited in the coming years.[6]

Currently, the 5-year overall survival for patients with esophageal cancer after nCRT followed by esophagectomy is approximately 50%.[2,7] A radical resection (R0) was achieved in 92% of patients.[2] Despite achieving a radical resection in 92% of patients, 50% of patients will not be alive 5 years after surgery. Long term results of the CROSS trial show locoregional progression in 22% of patients and distant progression (systemic metastases) in 39% of patients in the nCRT group. This suggests that local control could still use some improvement but also that the majority of cancer related deaths were due to systemic metastases [7] To improve survival in esophageal cancer patients, 2 strategies could be explored; first to improve locoregional control and second to reduce the amount of systemic metastases after radical esophagectomy.

Strategies to improve survival after esohagectomy

The long term results of the CROSS trial show that 45% of patients received a transhiatal esophagectomy.[7] With a transhiatal esophagectomy a limited lymph node dissections was performed including an upper abdominal lymphadenectomy, resection of nodes along the hepatic artery, splenic artery, and left gastric artery. The intrathoracic lymph nodes were not dissected. A Population-based Cohort Study in the Netherlands, including 2698 patients showed that a higher lymph node yield was significantly associated with improved overall survival, indicating a therapeutic value of extended lymphadenectomy during esophagectomy.[8] Therefore, a transthoracic esophagectomy with an extended lymphadenectomy should be the standard of care for patients with esophageal cancer after nCRT. It would be interesting to see the subgroup analysis for transhiatal versus transthoracic esophagectomy from esophageal adenocarcinoma patients included in the CROSS trial considering oncologic outcomes.

Robot-assisted minimally invasive thoraco-laparoscopic esophagectomy (RAMIE) might improve local control with radical resections (R0) in 93% of patients combined with an adequate intrathoracic and abdominal lymphadenectomy with a median number of 27 resected lymph nodes.[9] After neoadjuvant treatment, RAMIE provided good local oncological control, with no isolated locoregional recurrences in the currently presented RCT (Chapter 10) after 40 months of follow up.[9] The question, whether RAMIE will improve locoregional control for esophageal cancer will be answered in the future when the complete 5-year follow up will be analyzed.

Aforementioned strategies could improve locoregional control. However, reducing the amount of systemic metastases after radical esophagectomy should be the primary focus. Despite achieving a radical resection in over 90% of patients, 50% of patients will not be alive 5 years after surgery.[2,9] After radical esophagectomy, no visible esophageal cancer is observed, but in a large group of patients, micrometastases are present which will develop in systemic metastases and will result in cancer related death. On could argue that after radical esophagectomy, adjuvant treatment should be initiated after radical esophagectomy to target these micrometastases.[10] But what should this therapy be? In chapter 2 it was shown that postoperative epirubicin, cisplatin, and capecitabine (ECC) chemotherapy was not feasible after esophagectomy, due to the combination of an extensive surgical procedure and high toxicity of this regimen.[11] But are there agents available for postoperative adjuvant chemotherapy after radical esophagectomy with comparable efficacy and lower toxicity to target micrometases? Carboplatin and paclitaxel, as used in the CROSS trial also exhibit a profound systemic effect which is reflected by a comparable percentage of systemic metastases as shown after pCT.[4,5] Furthermore, the systemic effect of these agents was demonstrated in irresectable and metastatic adenocarcinoma of the esophagus.[12] In esophageal squamous cell cancer, results are promising, postoperative adjuvant therapy improved survival in pathologic non-responders after neoadjuvant chemoradiation for esophageal squamous cell carcinoma.[13] Currently, in a prospective single arm study (NCT02347904) the feasibility of administering adjuvant S-1 and Oxaliplatin (SOX) in patients with esophageal cancer after neoadjuvant chemoradiotherapy with paclitaxel and carboplatin and esophagectomy is assessed. The study is currently recruiting participants and results are awaited.

Besides adjuvant chemotherapy, treatment of esophageal cancer turned towards biologic therapies to offer a more tailored, and potentially effective, treatment option (targeted therapy) nowadays. The following potential biologic targets in esophageal, esophagogastric, and gastric malignancies have been evaluated to date: HER-2, EGFR, VEGF and VEGFR, c-MET, mTOR, PD-1.[13] However, no trials have been completed so far in an adjuvant or peri-operative setting and evidence for targeted therapy is limited to recurrent and metastatic gastroesophageal cancer.

There are 2 agents who showed positive results in clinical studies for in recurrent en metastatic esophageal and gastric malignancies (trastuzumab and ramucirumab).From 2005 to 2009, the Trastuzumab for Gastric Cancer(ToGA) randomized controlled trial evaluated the safety and clinical efficacy of Trastuzumab (Her2) for locally advanced, recurrent or metastatic adenocarcinoma of the gastroesophageal junction or stomach.[14] Patients receiving trastuzumab with chemotherapy (capecitabine or fluorouracil plus cisplatin) did have a significant improvement in median overall survival compared to the chemotherapy only arm (13.8 vs.11.1 months), with no difference in toxicity (grade 3 or 4 adverse events). Improvement in overall survival was even more pronounced in patients with immunohistochemistry (IHC) 3+ or IHC 2+ with positive fluorescent in situ hybridization (FISH) (16.0 vs. 11.8 months) with longer progression free survival and higher rates of overall tumor response.[14] For patients with recurrent or metastatic esophagogastric/gastric adenocarcinoma with HER2 overexpression, chemotherapy with Trastuzumab is now the standard treatment.[13,14]

Ramucirumab, a VEGFR-2 inhibitor was assessed as a second line therapy after platinum or fluoropyrimidine therapy for recurrent or metastatic gastroesophageal junction or gastric cancer in a randomized, multicentre, placebo controlled, phase 3 trial (REGARD).[15] A significant increase in median overall survival (5.2 months in the ramucirumab arm versus.3.8 months in the placebo arm), and median progression free survival (2.1 vs. 1.3 months,respectively).was observed.[15]

In the RAINBOW trial, Ramucirumab with concurrent paclitaxel was compare to paclitaxel and placebo in metastatic esophagogastric or gastric adenocarcinoma with disease progression after first line chemotherapy. Patients that received ramucirumab with paclitaxel experienced longer median overall

survival (9.6 vs. 7.4 months) compared to paclitaxel.[16] Based on the results of the REGARD and RAINBOW trial, ramucirumab is now a preferred second-line therapy for metastatic or locally advanced esophagogastric or gastric adenocarcinoma and esophageal adenocarcinoma.[13,15,16]

With proven efficacy in the metastatic setting for gastroesophageal adenocarcinoma, these agents will be evaluated in the neoadjuvant and adjuvant setting in the future.[13] Next-generation sequencing and genome wide association studies are required to predict clinical outcome, prognostications and to show distinct molecular subtypes with potential therapeutic relevance to select the optimal personalized targeted therapy.[17,18]

Surgical therapy for esophageal cancer

Worldwide, there is still debate what the best surgical technique should be to perform a transthoracic esophagectomy: open transthoracic esophagectomy (OTE), conventional minimally invasive esophagectomy (MIE), robot-assisted minimally invasive esophagectomy (RAMIE) or the hybrid technique consisting of laparoscopy and open thoracotomy.

In a randomized controlled trial MIE was compared to OTE (TIME-trial).[19] Compared to OTE, MIE resulted in a lower incidence of pulmonary infections within 2 weeks after surgery, a shorter hospital stay and better short-term quality of life with equal short term oncological outcome.[19]

In the ROBOT trial, a single center randomized controlled trial, presented in chapter 10, RAMIE was compared to OTE (ROBOT-trial).[9] RAMIE resulted in a lower percentage of overall, surgery-related and (cardio)pulmonary complications with lower postoperative pain, better short term quality of life and a better short term postoperative functional recovery compared to OTE, without differences in oncological outcomes.[9]

Outcomes of two important randomized trials are currently awaited: the MIRO-trial, comparing the hybrid technique consisting of laparoscopy and open thoracotomy versus OTE are currently awaited (MIRO-trial).[21] and the ROMIO trial, comparing open, hybrid and minimally invasive surgical procedures for esophagectomy in the treatment of cancer are awaited [20,21]

Results from the TIME-trial and ROBOT-trial provided evidence for the use of MIE or RAMIE to improve postoperative outcome in patients with resectable esophageal cancer.[9,19] The question rises whether RAMIE is superior to conventional minimally invasive esophagectomy or hybrid esophagectomy. To show the benefits of RAMIE over conventional MIE in a randomized trial would require a large number of patients as differences will be more subtle compared to the open surgical technique. Such a trial could only performed in a worldwide multicenter fashion, where participating surgeons should be skilled in both conventional MIE and RAMIE and for both reasons, such a randomized controlled might night be feasible. A large number of patients included in national or worldwide prospective database registries, with a defined protocol for registering complications according to the definitions stated by the Esophagectomy Complications Consensus Group (ECCG)[22] and reporting of patient comorbidities could answer the question whether RAMIE or MIE is superior to open esophagectomy or to each other.

Differences between MIE and RAMIE in postoperative complications and oncologic outcomes might be marginal. Quality of life, better ergonomics for the surgeon and cost effectiveness might be important endpoints in these prospective registry studies

Independently of the surgical technique which is used, we strongly would like to emphasize the effect of centralization of high complex surgical procedures. Centralization of esophagectomy, to a minimum of 20 resections/year has been successfully introduced in the Netherlands.[23] However, increasing hospital volume from 20 procedures per year to 40 and 60 procedures per year was associated with a decrease in 6 month mortality. Beyond 60 procedures per year, no further decrease was detected. Until 50 esophagectomies, a higher hospital volume was associated with a decreased 2 year mortality.[23] We therefore suggest introduction of a centralization to a minimum of 50 resections per year in The Netherlands.

Comparisons between surgical techniques should only be performed in high volume centers. With centralization to minimum of 50 resection per year, the Netherlands would be an ideal country to perform nationwide randomized clinical studies. When all high volume centers are willing to participate, the inclusion of patients in multicenter randomized controlled trials could be finished within 1 year and improve survival for esophageal cancer patients.

Robot-assisted minimally invasive esophagectomy (RAMIE)

RAMIE is a complex surgical intervention, which is influenced by factors that depend on the surgeon, team and hospital setting. For the development of RAMIE by our group, a 5-stage development process for the assessment of surgical innovation (IDEAL) was recognized.[24]

Our first experience, with 21 patients undergoing RAMIE (stage 1, Idea), was described in a prospective cohort study in 2006.[25] Technical feasibility and early technical modifications were described in 2009 in a prospective cohort study including 47 patients (stage 2a, Development).[26] In 2015, the oncological long-term follow up was described in a prospective cohort study including 108 patients (stage 2b, Exploration) (Chapter 7).[27] Finally, in the ROBOT trial (Chapter 10), a single center randomized controlled trial, stage 3 (Assessment) was investigated.[9] Stage 4 (Long term study) is currently assessed with the extension of indications for RAMIE and registration of cases in the national registry database the Dutch Upper gastrointestinal Cancer Audit (DUCA).[28,29] In our opinion, all new surgical techniques should be introduced using the IDEAL criteria.[24]

In the ROBOT trial, RAMIE was compared to OTE, which is considered to be the gold standard for resectable esophageal cancer worldwide.[9,30] Before any comparison of a novel surgical technique to the gold standard can be performed, the learning curve has to be completed. In 2012, when the trial was initiated, our center was the only centre worldwide that had clearly passed the learning phase with a joint experience of >170 RAMIE procedures.[31] Hence, it was decided to perform a single center randomized controlled trial, as no other institution had comparable surgical expertise.[30,31]

The question arises whether the RAMIE results from the ROBOT trial, obtained within a single center randomized trial, are reproducible to other centers worldwide. What would be the best strategy to introduce RAMIE into other centers?

We showed that the first 70 cases formed the initial learning phase for RAMIE and that structured proctoring program reduced the learning phase to 24 cases, which corresponded to a reduction of 66% in the number of operations and a reduction of 76% in time.[31]

We started with a proctoring program for surgeons from other hospitals and designed a structured training program for RAMIE. The following conditions have to be applicable in order for the proctoring program to be successful for newly introduced surgeons: 2 motivated surgeons experienced in esophageal surgery and preferably in minimally invasive gastrointestinal surgery, a dedicated anesthesiologist and RAMIE specialized scrub nurses, a sufficient case load (>20 cases/year) and guaranteed access to a robotic system.[31] The program started with 2-3 case observations in our RAMIE expert center, followed by a basic and dedicated esophageal robotic course in a cadaveric lab. The first case at the own hospital was always proctored by an expert. Hereafter, the proctor supervised the surgeon for the first 2-10 cases and reviewed the skills after the first 20-25 procedures.[31] We have

trained now 5 centers in Europe that are performing RAMIE as their preferred surgical approach with very good results. These results which will be analyzed in the near future. In our opinion, it seems possible to reproduce these results in other centers, after passing the learning curve for RAMIE. We therefore conclude that these results are generizable and reproducible in other centers.

Future directions

Future directions for RAMIE include modifications of different steps of the operation. In all our studies, the Da Vinci® robotic system was used for the thoracoscopic phase only.[9,25,26,27,29,31] The next step would be to introduce the robotic system for the abdominal phase of the operation.[31] At the time of introduction of RAMIE in 2003, there were no robotic endowristed coagulating instruments available. The dissection of the greater curvature along the gastroepiploic vessels with a rigid robotic ultrasonic scalpel did not add to conventional laparoscopic dissection. Furthermore, the dexterity of the robotic arms was insufficient to reach the duodenum, greater curvature and hiatus within a single docking. With the recently introduced robotic bipolar coagulator (vessel sealer®) and newest generation robot (Xi®) allowing multiquadrant surgery, these limitations have been solved and the robotic abdominal phase could be of technical benefit.[31]

Technical developments within esophageal surgery are encouraged and might be introduced in the RAMIE procedure in the near future. For example, indocyanine green fluorescence angiography (ICG-FA) is a newly developed technique to measure perfusion of the gastroepiploic artery, the gastric conduit and the esohpagogastric anastomosis intraoperatively and could possibly predict anastomotic leakage.[32]

Recently, a version of a robotic 45 mm stapler (EndoWrist Stapler System (EWSS) was developed for use with the da Vinci Xi Surgical System The robotic stapler is mounted to da Vinci instrument arms and controlled from the surgical console. The robotic stapler offers articulation with 108° total side-to-side and 54° total up and down and is equipped with SmartClamp™ feedback. This feedback system detects whether the stapler is adequately closed on tissue or when excessive tissue is present within the stapler. When excessive tissue is present, the device does not allow firing and requires adequate tissue allocation before activation. This 45 mm robotic stapler and the soon to be expected 60 mm robotic stapler look very promising for the future.[33]

All relevant patents of Da Vinci were listed in 1999 and will expire in 2019. Therefore, new robotic systems are coming into the market, such as: TITAN, Cambridge Medical, Transenterix VERB, the Medtronic robot, the Avatera Robot, REVO-I, and Medicaroid with a possible reduction in costs.[34] The technological developments in these new robotic devices focus on specific features of the robotic arms, instruments, console and video technology. Clinical applicability and costs will be the most important factors for implementation of aforementioned systems and will be compared to the gold standard the Da Vinci robot. The question whether these technical developments will result in better outcomes for our patients will be answered in the upcoming years.[34] But moreover these platforms will allow surgeons to use the forces of computing power between their hands and their patients. This allows for smart tools and artificial intelligence to be introduced into the field of surgery.

For restoration of gastrointestinal continuity a cervical handsewn gastroesophageal anastomosis was used in our studies. In al our studies, the percentage of anastomotic leakage was approximately 14-24%.[9,25,26,27,29] Some studies suggested that a cervical anastomosis is associated with a higher incidence of anastomotic leakage compared to an intrathoracic anastomosis.[35,36] In our opinion a robot assisted handsewn intrathoracic anastomosis is technically very well feasible and may further improve the outcome of RAMIE. We recently started with performing a robot assisted handsewn intrathoracic anastomosis during the RAMIE procedure The introduction of the robot assisted handsewn intrathoracic anastomosis will be reported in the future.

The question remains whether we could increase our indications for using RAMIE in esophageal cancer. In stage 4 of the IDEAL criteria, indications for RAMIE are extended, such as RAMIE for upper esophageal cancer with upper mediastinal lymph node metastases[29], cT4b esophageal cancer or other types of salvage surgery for esophageal cancer.[31] This analysis of this extension of indications for RAMIE are awaited with great interest.

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Chapter 16

conclusions

CONCLUSIONS

The conclusions derived from this thesis are summarized:

Part I: Neoadjuvant therapy

Chapter 2:
- In patients with adenocarcinoma of the esophagus or GEJ, epirubicin, cisplatin and capecitabine (ECC) perioperative chemotherapy is associated with a relatively high number of adverse events.
- A history of cardiac or vascular disease is associated with the occurrence of grade 3 or higher adverse events.
- Postoperative ECC chemotherapy was not feasible, due to unresolved toxicity or early stopping of the preoperative chemotherapy or post-operative problems with difficulty in recovery.

Chapter 3.
- Perioperative ECC was associated with considerable toxicity and further treatment intensification with cetuximab and radiotherapy was not feasible.

Chapter 4.
- Neoadjuvant chemoradiotherapy was associated with a considerable lower level of severe adverse events and with better tumor regression grades compared to perioperative chemotherapy.
- Neoadjuvant chemoradiotherapy and perioperative chemotherapy lead to equal oncologic outcomes in terms of radical resection rates, lymphadenectomy, patterns of recurrent disease and (disease free) survival.

Chapter 5:
- Neoadjuvant chemoradiotherapy was associated with improved tumor downstaging and a higher complete pathological response rate compared to perioperative chemotherapy
- No significant improvements were achieved with neoadjuvant chemoradiotherapy as compared to perioperative chemotherapy in terms of radical resection rates or progression-free survival and overall survival.

Part II: Robot assisted minimally invasive thoraco-laparoscopic esophagectomy (RAMIE) for esophageal cancer

Chapter 6:
- Robot assisted minimally invasive thoraco-laparoscopic esophagectomy (RAMIE) is technically feasible and oncologically safe

Chapter 7.
- RAMIE is oncologically effective, with a high percentage of R0 radical resections and adequate lymphadenectomy. RAMIE provided adequate local control, with a low percentage of local recurrence.

Chapter 8.
- The first 70 cases formed the initial learning phase for RAMIE
- A structured proctoring program reduced the learning phase for a newly introduced surgeon to 24 cases, which corresponded to a reduction of 66% in the number of operations and a reduction of 76% in time.

Chapter 9:
- This single center randomized controlled superiority trial could provide further evidence supporting the robot-assisted minimally invasive thoraco-laparoscopic esophagectomy as treatment for resectable esophageal cancer.
- Publishing of a clinical trial protocol is important to reduce bias and for quality control

Chapter 10:
- Compared to an open transthoracic esophagectomy. RAMIE resulted in a lower percentage of overall, surgery-related and (cardio)pulmonary complications with lower postoperative pain, better short term quality of life and a better short term postoperative functional recovery, without differences in oncological outcome.

Chapter 11:
- Patients with cervical end-to-end anastomoses developed postoperative strictures more frequently and required a higher number of dilations compared to cervical end-to-side anastomoses.

Chapter 12:
- The decision to treat pneumonia after esophagectomy was based on temperature, leukocyte count and pulmonary radiography findings
- The proposed clinical scoring system for pneumonia following esophagectomy at the hospital ward has the potential to aid clinical practice and improve comparability of future research in esophageal cancer surgery.

Chapter 13.
- Resection of localized (recurrent) esophageal cancer was technically feasible and safe.
- Radical resection of localized (recurrent) esophageal carcinoma may well lead to long-term survival and is therefore an interesting therapeutic option in patients with recurrent disease.

ADDENDA

Dutch Summary
Acknowledgements
List of publications
Curriculum Vitae

DUTCH SUMMARY (NEDERLANDSE SAMENVATTING)

Slokdarmkanker is wereldwijd de 8e meest voorkomende vorm van kanker en de 6e meest voorkomende vorm van kanker gerelateerde sterfte met meer dan 450.000 nieuwe gevallen en 400.000 slokdarmkanker gerelateerde sterfgevallen per jaar. Slokdarmkanker is daarom een van de meest agressieve vormen van kanker met 5-jaars overleving van 15-25%.
De 2 meest voorkomende vormen van slokdarmkanker zijn het slokdarm plaveiselcelcarcinoom en het slokdarm adenocarcinoom. Het slokdarm plaveiselcelcarcinoom komt het meest voor in Aziatische landen en ontstaat in het bovenste gedeelte en in het midden van de slokdarm. In westerse landen is het slokdarm adenocarcinoom het meest voorkomend en deze vorm ontstaat in het onderste gedeelte van de slokdarm en de slokdarm-maag overgang. Chirurgie is de hoeksteen van de curatieve behandeling van slokdarmkanker. Hierbij wordt de slokdarm en het bovenste gedeelte van de maag en de omliggende lymfeklieren chirurgisch verwijderd, waarbij er van de maag een buismaag wordt gemaakt om er voor te zorgen dat het voedsel via deze weg de darmen kan bereiken. Dit is een grote operatie met een hoog percentage complicaties en sterfte.
De laatste jaren is er veel vooruitgang geboekt om de complicaties en sterfte te verminderen en om de overleving te verbeteren, maar toch blijven er nog veel uitdagingen over. Het onderzoek in dit proefschrift is er op gericht om de overleving van patiënten met slokdarm te verbeteren en om de complicaties te verminderen. Een strategie om de overleving te verbeteren is het geven van chemotherapie of chemoradiotherapie. In deel I van dit proefschrift worden chemotherapie en chemoradiotherapie met elkaar vergeleken om te evalueren welke therapie de beste therapie is voor patiënten met een slokdarm adenocarcinoom.
Een strategie om complicaties te verminderen is om in plaats van een open operatie, waarbij grote operatie wonden worden gemaakt, gebruik te maken van een robot geassisteerde kijkoperatie om de slokdarm te verwijderen. Dit zou kunnen lijden tot minder complicaties en een sneller herstel. In deel II van dit proefschrift worden alle aspecten van een robot geassisteerde kijkoperatie om de slokdarm te verwijderen geëvalueerd.
In deel III van dit proefschrift worden verschillende operatietechnieken om de buismaag aan te sluiten en een complicatie scoring model voor longontsteking en een nieuwe operatietechniek beschreven voor terugkerende kanker beschreven.

DEEL 1: NEOADJUVANTE THERAPIE VOOR SLOKDARM ADENOCARCINOOM

In **Hoofdstuk 2** wordt de eerste serie wereldwijd van Epirubicine, Cisplatinum en Capecitabine (ECC) chemotherapie beschreven bij patiënten met een slokdarm adenocarcinoom. Vanwege hoge toxiciteit werd slechts bij 66% van alle patiënten de preoperatieve chemotherapie afgemaakt. Risicofactoren hiervoor zijn een medische voorgeschiedenis van hart en vaatziekten. Ondanks deze hoge toxiciteit, kon 94% van de patiënten wel een operatie ondergaan waarbij de slokdarm verwijderd werd. Slechts 27% van de patiënten kon de postoperatieve kuren ook afmaken. Dit laat zien dat de postoperatieve ECC chemotherapie

niet haalbaar is voor de meeste patiënten met een slokdarm adenocarcinoom.
In **Hoofdstuk 3** worden de resultaten beschreven van een fase II onderzoek, waarbij patiënten met een slokdarm adenocarcinoom werden behandeld met 3 kuren Epirubicine, Cisplatinum en Capecitabine (ECC) chemotherapie, gevolgd door cetuximab en radiotherapie. Dit werd gegeven met als doel een betere lokale controle te krijgen. Na de operatie volgen nog 3 ECC chemotherapie kuren. De primaire eindpunten waren veiligheid (het percentage patiënten dat aan een operatie toekomt) en effectiviteit (het percentage complete pathologische respons). De analyse na 12 patiënten liet een hoog percentage toxiciteit en postoperatieve complicaties zien gecombineerd met een laag percentage effectiviteit. Daarom werd de fase II studie voortijdig gestopt en er werd geconcludeerd dat het toevoegen van cetuximab en radiotherapie aan het ECC chemotherapie schema niet haalbaar is.

In **Hoofdstuk 4** werden de meeste voorkomende therapieën voor het slokdarm adenocarcinoom; neoadjuvante chemoradiotherapie volgens het CROSS schema (carboplatin/paclitaxel/41.4Gy) en perioperatieve chemotherapie volgens het MAGIC schema (epirubicin, cisplatin and capecitabine) gevolgd door een slokdarmresectie, met elkaar vergeleken in tertiaire verwijscentra in Nederland. De eindpunten waren toxiciteit, postoperatieve complicaties, pathologische respons en overleving en terugkeer van de ziekte. Neoadjuvante chemoradiotherapie en perioperatieve chemotherapie hadden vergelijkbare oncologische uitkomsten zoals het aantal radicale resecties, het aantal lymfeklieren, terugkerende ziekte en overleving. Neoadjuvante chemoradiotherpie was geassocieerd met een lagere toxiciteit en is op dit moment de standaard therapie in Nederland.

In **Hoofdstuk 5** werden neoadjuvante chemoradiotherapie volgens het CROSS schema (carboplatin/paclitaxel/41.4Gy) en perioperatieve chemotherapie volgens het MAGIC schema (epirubicin, cisplatin and capecitabine) vergeleken in 1 centrum, het UMC Utrecht, middels een propensity score gematched cohort studie. Neoadjuvante chemoradiotherapie was geassocieerd met een hoger percentage tumor downstaging een hogere pathologische complete respons, maar dit leidde niet tot een hoger percentage radicale resectie, verminderde terugkeer van ziekte en betere overleving.

PART II: ROBOT GEASSISTEERDE MINIMAAL INVASIEVE SLOKDARMRESECTIE ALS BEHANDELING VOOR SLOKDARMKANKER

In **Hoofdstuk 6** werd alle beschikbare literatuur over robot geassisteerde minimaal invasieve slokdarmresectie als behandeling voor slokdarmkanker vergeleken in een systematische review. Dit leverde 16 artikelen op. Deze artikelen lieten zien dat robot geassisteerde minimaal invasieve slokdarmresectie als behandeling voor slokdarmkanker een zowel technisch als oncologisch een veilige techniek is.

In **Hoofdstuk 7** werd een prospectief cohort beschreven waarin 108 patiënten een robot geassisteerde minimaal invasieve slokdarmresectie als behandeling voor slokdarmkanker ondergingen. Dit cohort liet zien dat deze techniek veilig kon worden toegepast. Qua

oncologische uitkomsten bleek een robot geassisteerde minimaal invasieve slokdarmresectie als behandeling voor slokdarmkanker een effectieve therapie met hoog percentage radicale resecties en een adequate lymfeklierdissectie. Dit resulteerde in een goede lokale controle met een laag percentage terugkeer van ziekte in het operatieveld en in een overleving vergelijkbaar met de hoogste standaarden wereldwijd.

In **Hoofdstuk 8** werd de learning curve beschreven van robot geassisteerde minimaal invasieve slokdarmresectie als behandeling voor slokdarmkanker. Bij elke nieuwe techniek ondergaan zowel de operateur als het operatieteam een learning curve, waarbij in het begin er een leer fase is waarbij het enige tijd duurt voordat de resultaten stabiel worden. In een cohort van 312 slokdarmkanker patiënten, vormde de eerste 70 patiënten de learning curve voor de pionier van deze techniek. Er werd ook een 2^{e} chirurg geïntroduceerd die zorgvuldig werd getraind en begeleid (proctoring). Tijdens zijn learning curve leverde dit dezelfde resultaten op als bereikt door de proctor in dezelfde periode, alleen werd de learning curve afgerond na 24 patiënten in 13 maanden. Dit was een reductie van 66% in het aantal operaties en 76% in de tijd. Een goede begeleiding tijdens de leerfase (proctoring) is belangrijk en levert een reductie op van de learning curve.

In **hoofdstuk 9** werd het protocol beschreven van de ROBOT trial (ClinicalTrials.gov Identifier: NCT01544790). In deze gerandomiseerde trial werd een robot geassisteerde minimaal invasieve slokdarmresectie vergeleken met een open transthoracale slokdarmresectie als behandeling voor slokdarmkanker. Het primaire eindpunt was het percentage postoperatieve complicaties volgens de “modified Clavien–Dindo classification (MCDC) of surgical complications” graad 2 en hoger.

In **Hoofdstuk 10** werden de resultaten van de ROBOT trial beschreven. In deze monocenter gerandomiseerde trial werden 112 patiënten gerandomiseerd tussen een robot geassisteerde minimaal invasieve slokdarmresectie vergeleken en een open transthoracale slokdarmresectie. Het primaire eindpunt was het percentage postoperatieve complicaties volgens de “modified Clavien–Dindo classification (MCDC) of surgical complications” graad 2 en hoger.
Een robot geassisteerde minimaal invasieve slokdarmresectie resulteerde in een lager percentage postoperatieve (cardiopulmonaire) complicaties, minder bloedverlies, minder pijn, betere korte termijn kwaliteit van leven en een beter postoperatief herstel vergeleken met een open transthoracale slokdarmresectie. De oncologische uitkomsten in beide groepen waren niet verschillend en vergelijkbaar met de hoogste standaarden wereldwijd.

DEEL III: CHIRURGISCHE TECHNIEKEN EN COMPLICATIES

In **Hoofdstuk 11** werden de postoperatieve uitkomsten vergeleken tussen een handgelegde end-to-end en een end-to-side anastomose voor het aansluiten van de buismaag. Er waren geen verschillen in naadlekkage, maar patiënten met een end-to-end anastomose ontwikkelde een hoger percentage postoperatieve stricturen welke een endoscopische

dilatatie nodig hadden vergeleken met een end-to-side anastomose.

In **Hoofdstuk 12** werd een nieuw klinisch scoringsysteem voor postoperatieve pneumonie op de afdeling ontwikkeld na een slokdarmresectie. Pneumonie is de meest voorkomende complicatie en er was geen uniforme definitie beschikbaar, wat leidde tot een grote variatie in de percentages voor postoperatieve pneumonie in de literatuur wereldwijd. In een prospectieve cohort studie werden bekende risico factoren, zoals temperatuur, leukocytose, X-thorax en sputum kweek geëvalueerd. De primaire uitkomst was de beslissing om pneumonie te behandelen met antibiotica. Deze studie liet zien dat de beslissing om een pneumonie na een slokdarmresectie te behandelen op de verpleegafdeling gebaseerd is op temperatuur, leukocytose en afwijkingen op de X-thorax. Dit scoringsysteem kan helpen bij een klinische beslissing om een pneumonie na een slokdarmresectie te behandelen en om verschillende studies beter te vergelijken in de toekomst door gebruik te maken van dezelfde definitie in de toekomst.

In **Hoofdstuk 13** werd een casus beschreven van een patiënt met een recidief slokdarmkanker ter plaatste van de anastomose van de buismaag. Deze afwijking werd chirurgisch verwijderd en de continuïteit werd hersteld met een gevasculariseerd jejunuminterponaat. Deze casus laat zien dat resectie van een recidief slokdarmkanker ter plaatste van de anastomose van de buismaag een goede therapeutische optie is voor patiënten met een recidief slokdarmcarcinoom.

CONCLUSIE:

In dit proefschrift werden meerder strategieën geëvalueerd om de overleving van patiënten met slokdarmkanker te verbeteren en complicaties te verminderen. Perioperatieve chemotherapie voor patiënten met een slokdarm adenocarcinoom leidt tot hoge toxiciteit waardoor de postoperatieve chemotherapie voor veel patiënten niet haalbaar is. Het is ook niet haalbaar om radiotherapie en cetuximab toe te voegen aan de preoperatieve chemotherapie. Chemoradiotherapie en chemotherapie leveren vergelijkbare resultaten op qua overleving en mogelijk heeft chemoradiotherapie een lager toxiciteitprofiel.
De interesse in robot geassisteerde minimaal invasieve slokdarmresectie neem toe wereldwijd om complicaties te verminderen vergeleken met een open transthoracale slokdarm resectie. Robot geassisteerde minimaal invasieve slokdarmresectie is een technisch en oncologisch veilige techniek. De learning curve van de robot geassisteerde minimaal invasieve slokdarmresectie ligt op 70 procedures en proctoring verkort de learning curve aanzienlijk. Vergeleken met een open transthoracale slokdarmresectie resulteert een robot geassisteerde minimaal invasieve slokdarmresectie in een lager percentage postoperatieve (cardiopulmonaire) complicaties, minder bloedverlies, minder pijn, betere korte termijn kwaliteit van leven en een beter postoperatief herstel met oncologische uitkomsten die vergelijkbaar zijn met de hoogste standaarden wereldwijd.

Review Committee

Prof. dr. C. Veenhof
Prof. dr. B.L.A.M. Weusten
Prof. dr. M.R. Vriens
Prof. dr. G.J.A. Offerhaus
Prof. dr. M.I. van Berge Henegouwen

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Dear prof. dr. J.V. Reynolds and prof. dr. M. Nillson, I feel honored to have you as members of the opposition at my PhD defense today and as special guests at the symposium this morning. I'm looking forward to work with you in the future.

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Submitted for publication to the 2nd edition of the Textbook of Robotic Surgery (publisher: McGraw Hill).

Robotic Surgery for esophageal cancer.
R. van Hillegersberg, **P.C. van der Sluis**, J.P. Ruurda
Submitted for publication to Expertise Oberer Gastrointestinaltrak, Edited by: Hölscher, Mönig, Meyer.

CURRICULUM VITAE

Pieter Christiaan van der Sluis was born on the 8th of May 1982 in Amsterdam, The Netherlands. He lived most of his childhood in Mijdrecht. After graduating from the Alkwin Kollege in Uithoorn in 1999, he started with the study Biomedical Sciences at the VU University Amsterdam and obtained the Bachelor's degree in 2003. Hereafter het completed the Master's degree in Oncology at the VU University Amsterdam in 2005 after completing an internship in the H. Lee Moffitt Cancer Center in Tampa Bay, Florida.

In 2005 het started with the Selective Utrecht Medical Master (SUMMA) and completed his Medical degree in 2010. The research presented in this thesis was started in august 2010 under supervision of prof. dr. R. van Hillegersberg and dr. J.P. Ruurda. In 2012 he started as a surgical resident (not in training) in the UMC Utrecht in Utrecht.

In January 2013, the surgical training was initiated for the first 2 years in the UMC Utrecht in Utrecht under supervision of prof. dr. M.R. Vriens. Hereafter, he continued his surgical training in the Diakonessenhuis in Utrecht under supervision of dr. T. van Dalen. In the 5th year of surgical training, the differentiation in gastro-intestinal oncologic surgery was started in the Diakonessenhuis under supervision of dr. P.H. Davids and Dr. A. Pronk. Nowadays, for the 6th and final year of the surgical training he is working in the UMC Utrecht to complete a differentiation in gastro-intestinal and oncologic surgery, with emphasize on colorectal, HIPEC and upper GI surgery. Currently, he is the supervising examinator for the Student Outpatient Clinic in Surgery course for the Selective Utrecht Medical Master (SUMMA).