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Optimal classification and management of complications after curative esophagectomy for cancer

In the era of neoadjuvant chemoradiotherapy and minimally invasive surgery

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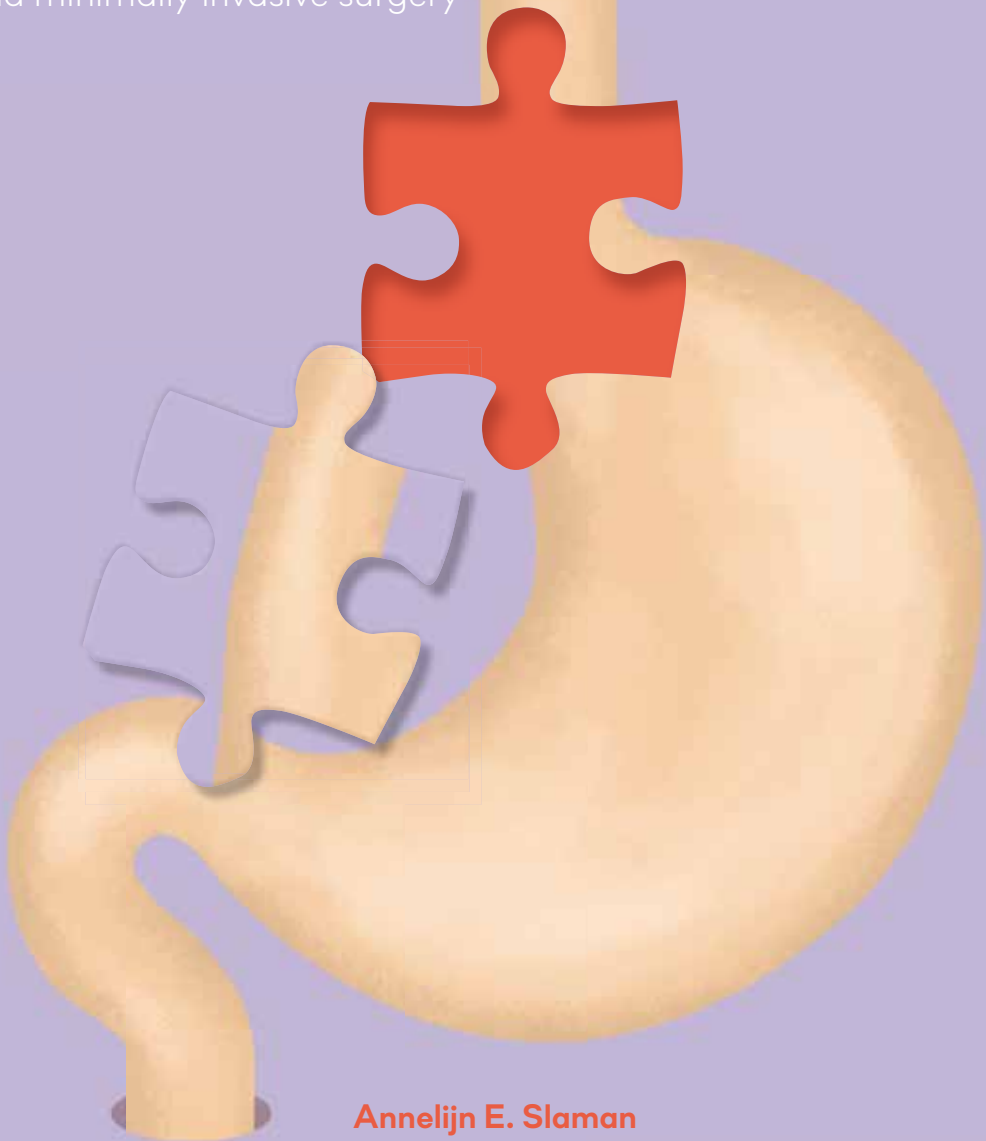
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In the era of neoadjuvant chemoradiotherapy and minimally invasive surgery



Annelijn E. Slaman

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Optimal classification and management of complications after curative esophagectomy for cancer

ACADEMISCH PROEFSCHRIFT

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aan de Universiteit van Amsterdam

op gezag van de Rector Magnificus

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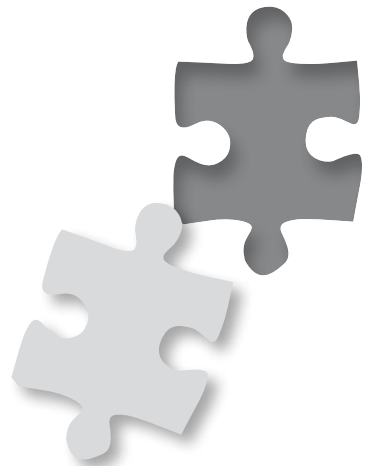
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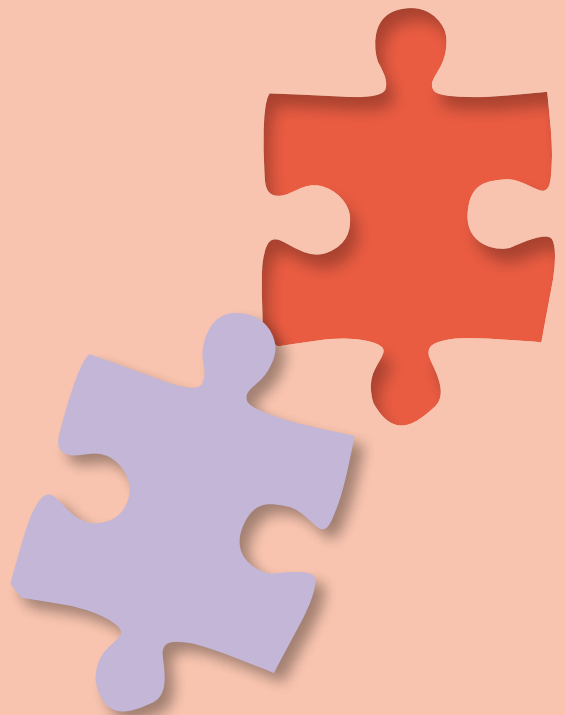


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CHAPTER 1

Introduction and general outline of the thesis





Esophageal cancer

The incidence of esophageal cancer is rising, with 604 100 new cases worldwide in 2020.¹ To put this in perspective, the incidence of esophageal cancer in the Netherlands has increased by almost 400% between 1989 and 2020.² The two most common histologic subtypes are adenocarcinoma and squamous cell carcinoma. Whilst high body mass index, gastroesophageal reflux disease, Barret's esophagus and cigarette smoking are risk factors for adenocarcinomas, substantial alcohol consumption and cigarette smoking increase the risk for developing squamous cell carcinomas. Most patients present with weight loss and dysphagia. To confirm the diagnosis and assess the spread of esophageal cancer, gastroscopy with biopsies, computed tomography (CT) scans of the neck, thorax and abdomen combined with positron emission tomography (PET) and frequently endoscopic ultrasound and ultrasound of the neck are performed. Esophageal cancer treatments can be applied with curative (33%) or palliative intent (67%), depending on the presence of (distant) metastases. In general, esophageal cancer has one of the lowest 5-year overall survival rates of all cancer types (20%). In 2010, neoadjuvant chemoradiotherapy is added to the standard curative treatment of patients with cT0-1N+ and cT2-4aNO-3MO carcinomas. This has increased the 5-year OS up to 50-60% in patients eligible for esophagectomy.^{3,4}

Esophagectomy

The first total esophagectomy was introduced by dr. Franz John A. Torek in 1913 (New York, USA), starting with a left thoracotomy to dissect the esophagus followed by subcutaneous tunneling of the proximal esophagus and creation of an external rubber conduit.⁵ It was dr. Ivor Lewis who described the intrathoracic anastomosis after esophagectomy in 1946 (United Kingdom), consisting of a 2-staged transthoracic esophagectomy.⁶ Dr. Kenneth McKeown proceeded with 3-staged transthoracic esophagectomy with creation of right-sided cervical anastomosis in 1976 (United Kingdom).⁷ The first successful transhiatal esophagectomy was performed by dr. Grey Turner, but dr. Mark Orringer described the first (blind) transhiatal esophagectomy with cervical anastomosis without the necessity of thoracotomy in 1984.⁸ These procedures are still performed in general practice nowadays. However, after many years of surgical refinement, esophagectomy for cancer still results in morbidity and mortality rates of 50-65% and 2-5%. This is relatively high as compared to other oncologic gastrointestinal operations.^{4,9-11}

Postoperative complications

The most recent changes in the surgical technique of esophageal cancer consist of minimally invasive surgery and the transition to transthoracic esophageal

resections with intrathoracic anastomosis.^{12,13} However, next to the negative influence of the high morbidity rate after esophagectomy on patients' quality of life, the workload of nurses and clinicians, and healthcare costs, recent studies show that complications after esophagectomy independently impair survival rates of these patients.^{3,14} This reinforces the importance of reducing complications after esophagectomy for cancer.

Complication registry

Reducing postoperative complications in general goes beyond the improvement of operation techniques alone. Knowing how to reduce complications starts with awareness of complications and evaluation of the burden of complications on patients. Postoperative complication registry is mandatory in the Netherlands. However, detection of (the severity of) complications is not 100% accurate. To improve complication registration at surgical departments, different registry methods are developed over the past years. In the Netherlands, postoperative complications were registered in the 'Landelijke Heelkundige Complicatie Registratie' (LHCR) database until 2018. The Dutch Upper gastrointestinal Cancer Audit (DUCA) is responsible for the evaluation of complications in patients after esophagectomy for cancer since 2011. To assess the severity of surgical complications, the most common methods are the Clavien–Dindo classification and more recently, the Comprehensive Complication Index (CCI).^{15–17} However, reports evaluating the accuracy of these complication severity classifications are scarce.

Aim of the thesis

This thesis aims to 1) improve the accuracy of complication registration and classification of their severity at surgical departments of tertiary referral centers in the Netherlands, and 2) to improve the short-term outcomes after esophagectomy in patients with esophageal cancer in the era of minimally invasive surgery and neoadjuvant chemoradiotherapy in the Netherlands by investigating different surgical techniques.

General outline of the thesis

To achieve the aim of this thesis, it is divided into two parts. **Part I** explores the accuracy of specific complication registry methods and severity classifications in surgical patients of tertiary referral centers in the Netherlands. **Part II** investigates associations between specific esophagectomy techniques and short-term outcomes in patients with esophageal cancer.

Part I. Registration of surgical complications

In many Dutch centers, registry of complications is performed during a verbal

inventory meeting at a surgical department. However, this method is associated with detection of less than 90% of all complications.¹⁸ In an attempt to improve the detection rate, **Chapter 2** compares the sensitivity of a novel trigger tool to that of the verbal inventory. Regarding complication severity, the Clavien–Dindo classification is based on the most invasive complication treatment of a patient using grades between I and V (death). The comprehensive complication index (CCI) incorporates the treatment of all complications in a patient using a score between 0 (no complication) and 100 (death). **Chapter 3** investigates differences between correlations of the CCI versus the Clavien–Dindo classification with traditional outcome parameters. **Chapter 4** further explores differences in complication severity after esophagectomy alone as compared with esophagectomy following neoadjuvant chemoradiotherapy (nCRT).

Part II. The influence of different surgical techniques on specific postoperative outcomes

In order to assess the influence of surgical techniques, this part compares postoperative outcomes after different esophagectomy techniques. **Chapter 5** compares anastomotic leakages after transthoracic esophagectomy between patients with cervical anastomosis (McKeown esophagectomy) and intrathoracic anastomosis (Ivor Lewis esophagectomy). **Chapter 6** explores potential severity differences of anastomotic leakage after McKeown esophagectomy as compared to Ivor Lewis esophagectomy. **Chapter 7** investigates whether the novel ‘flap and wrap’ reconstruction reduces the number of anastomotic leakages after the implementation of Ivor Lewis esophagectomy.

Diaphragmatic hernia is a rare, but serious complication after esophagectomy. In **Chapter 8**, the incidence, symptoms, and treatments of symptomatic diaphragmatic hernias is investigated and a potential decreasing incidence of diaphragmatic hernia when performing cruroplasty after esophagectomy is explored. At the end of the thesis, **Chapter 9** provides a general overview regarding trends in patients’ characteristics, oncological and surgical treatments, short-term outcomes and survival over the last 25 years.

References

1. Sung H, Ferlay J, Siegel RL, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin.* 2021;71(3):209-249. DOI:10.3322/caac.21660
2. Nederlandse Kankerregistratie (NKR). Incidence of esophageal cancer 1989-2020.; 2021.
3. Kalff MC, Fransen LFC, de Groot EM, et al. Long-term survival after minimally invasive versus open esophagectomy for esophageal cancer: A nationwide propensity-score matched analysis. *Ann Surg.* 2020; Publish Ah. DOI:10.1097/sla.0000000000004708
4. Nuytens F, Dabakuyo-Yonli TS, Meunier B, et al. Five-year survival outcomes of hybrid minimally invasive esophagectomy in esophageal cancer: Results of the MIRO randomized clinical trial. *JAMA Surg.* 2021;156(4):323-332. DOI:10.1001/jamasurg.2020.7081
5. Dubez A, Schwartz SI, Franz John A, Torek. *Ann Thorac Surg.* 2008;85(4):1497-1499. DOI:10.1016/j.athoracsur.2007.10.106
6. Lewis I. The surgical treatment of carcinoma of the esophagus with special reference to a new operation for growths of the middle third. *Br J Surg.* 1946;34(133):18-31. DOI:10.1002/bjs.18003413304
7. McKeown KC. Total three stage esophagectomy for cancer of the esophagus. *Br J Surg.* 1976;63(4):259-262. DOI:10.1002/bjs.1800630403
8. Orringer M. Transhiatal esophagectomy without thoracotomy for carcinoma of the thoracic esophagus. *Ann Surg.* 1984;200(3):282-288. DOI: 10.1097/0000658-198409000-00005
9. Schröder W, Raptis DA, Schmidt HM, et al. Anastomotic techniques and associated morbidity in total minimally invasive transthoracic esophagectomy: Results from the EsoBenchmark database. *Ann Surg.* 2019;270(5):1. doi:10.1097/SLA.0000000000003538
10. Mertens AC, Kalff MC, Eshuis WJ, Van Gulik TM, Van Berge Henegouwen MI, Gisbertz SS. Transthoracic versus transhiatal esophagectomy for esophageal cancer: a nationwide propensity score-matched cohort analysis. *Ann Surg Oncol.* 2021;28(1):175-183. DOI:10.1245/s10434-020-08760-8
11. An Y, Roodbeen SX, Talboom K, Tanis PJ, Bemelman WA, Hompes R. A systematic review and meta-analysis on complications of transanal total mesorectal excision. *Color Dis.* 2021;23:2527-2538. DOI:10.1111/codi.15792
12. Biere SSAYAY, Van Berge Henegouwen MI, Maas KW, et al. Minimally invasive versus open esophagectomy for patients with esophageal cancer: A multicenter, open-label, randomised controlled trial. *Lancet.* 2012;379(9829):1887-1892. DOI:10.1016/S0140-6736(12)60516-9
13. Haverkamp L, Seesing MFJJ, Ruurda JP, et al. Worldwide trends in surgical techniques in the treatment of esophageal and gastresophageal junction cancer. *Dis Esophagus.* 2016;00(00):1-7. DOI:10.1111/dote.12480
14. Van Der Werf LR, Wijnhoven BPL, Fransen LFC, et al. A national cohort study evaluating the association between short-term outcomes and long-term survival after esophageal and gastric cancer surgery. *Ann Surg.* 2019;270(5). DOI:10.1097/SLA.0000000000003520
15. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: A new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg.* 2004;240(2):205-213. DOI:10.1097/01.sla.0000133083.54934.ae
16. Slankamenac K, Graf R, Barkun J, Puhana MA, Clavien PA. The comprehensive complication index: A novel continuous scale to measure surgical morbidity. *Ann Surg.* 2013;258(1):1-7. DOI:10.1097/SLA.0b013e318296c732
17. Low DE, Alderson D, Ceconello I, et al. International consensus on standardization of data collection for complications associated with esophagectomy: Esophagectomy Complications Consensus Group (ECCG). *Ann Surg.* 2015;262(2):286-294. DOI:10.1097/SLA.0000000000001098
18. Ubbink DT, Visser A, Gouma DJ, Goslings JC. Registration of surgical adverse outcomes: A reliability study in a university hospital. *BMJ Open.* 2012;2(3):1-6. DOI:10.1136/bmjopen-2012-000891

PART 1

Evaluation of registry methods for postoperative complications at a surgical department



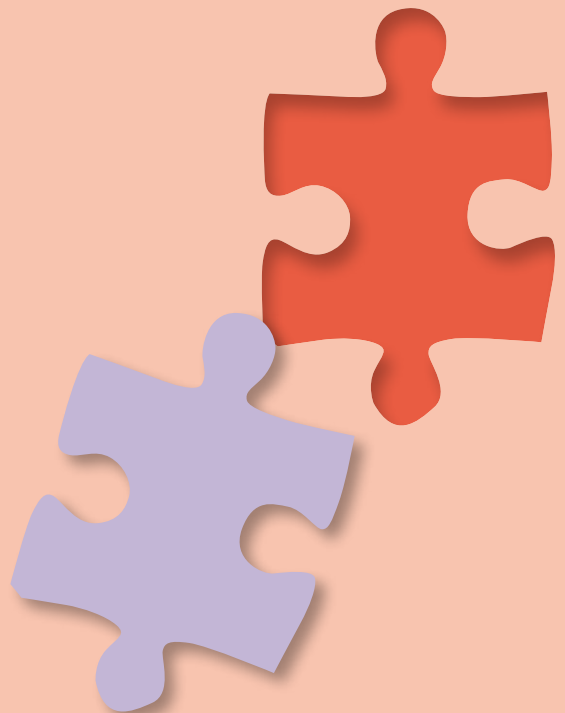


CHAPTER 2

Trigger tool versus verbal inventory to detect surgical complications

Langenbeck's Archives of Surgery 2015

Annelies Visser
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ABSTRACT

Purpose: Traditionally, registering complications after surgery is based on voluntary reporting or incident reports. These methods may fail to detect the total number of complications. A trigger tool was developed to detect complications in hospitalized surgical patients. In this diagnostic study, we compared its sensitivity and specificity with the verbal inventory used by surgical staff and residents.

Methods: A set of 31 potential triggers was chosen based on a systematic review and existence of the triggers in hospital databases. The trigger tool was developed using multivariate regression and receiver operating characteristic (ROC) analyses. The reference standard consisted of 300 patients, 150 with and 150 without complications. Sensitivity and specificity of the trigger tool and verbal inventory were determined.

Results: The final trigger tool consisted of nine triggers. Sensitivities of the trigger tool and verbal inventory were 70.7 and 78.7%, respectively, while specificities were 70.0 and 100.0%, respectively. Sensitivity values to detect major complications were 97.2 and 80.6% for the trigger tool and verbal inventory, respectively.

Conclusions: The proposed customized trigger tool for a university center appeared to be as accurate as a verbal inventory in respect of detecting surgical patients with complications and was even more accurate when detecting major complications.

INTRODUCTION

Registration of surgical complications is important for assessing and improving the quality of surgical care.¹ In addition, analyzing surgical complication registration outcomes can and should lead to improved patient outcomes.² Despite widespread acknowledgement that complications should be reduced, controversy exists in respect of how to detect and record these complications.³

Traditional efforts to detect complications have focused on voluntary reporting or incident reports.⁴ These methods had often poor success rates in the detection of complications.³ For example, registration during verbal hand-off meetings yields a registration rate of only 86% of all complications.⁵ Moreover, to achieve adequate reporting of complications, a sufficient number and surgeons with different fields of surgical interest should participate in daily verbal hand-off meetings, but this would be time-consuming for highly qualified surgeons. Hence, hospitals would benefit from a more effective way to identify complications and to complete their registration.

In an attempt to design a more uniform, practical, and efficient complication registration method, the Institute for Healthcare Improvement (IHI) developed the Global Trigger Tool (GTT).⁴ A trigger can be defined as a specific factor that is derived from the patient's medical record and is associated with an increased risk of complications. These factors can be patient-specific (e.g., laboratory results, body mass index (BMI)), surgical-procedure-specific (e.g., complexity of the procedure), or hospitalization-specific (e.g., length of hospital stay). A trigger tool is a set of triggers that identifies patients who are likely to have suffered a complication and thereby indicates which patient records should be checked for complications, for instance by a data manager. The benefits of (some form of) the Global Trigger Tool to detect complications have been studied in terms of interrater reliability among different reviewers of reporting complications.^{3,6-12} Two studies showed high specificity (92.0 and 99.0%), but low sensitivity (23.0 and 28.0%).^{13,14} High specificity means that the methods could be used to replace expensive manual chart reviews because fewer false-positive charts would need to be checked. However, in order not to miss any complications, the sensitivity of the method should also be high.

The aim of this study was to develop a new trigger tool and assess its accuracy and usefulness compared with the verbal inventory.

METHODS

Patients and setting

This study comprised a model development and diagnostic accuracy study, based on a 1-year sample of hospitalized surgical patients. The study was performed at the department of surgery of a tertiary referral university center in Amsterdam. All patients (n=4534) above the age of 17 admitted to the hospital or operated on by a surgeon from this department between July 2012 and June 2013 were included in this study. This surgical department provides general, gastrointestinal, hepatopancreatobiliary, vascular, and trauma surgical services.

Verbal inventory and registry of complications

Currently, surgical residents collect preoperative, intraoperative, and postoperative data for each surgical patient in real-time. During the morning hand-off, the attending staff may add patient complications to the data. Subsequently, the database manager retrospectively reviews the charts of patients previously identified with a complication for possible additional complications. In case of uncertainties, the data manager consults the surgeon responsible for the registration. The identification and collection of complication data by surgical residents and during the morning hand-off is defined as 'verbal inventory'.

All complications are registered and categorized by severity based on the Clavien–Dindo classification in the department's complication database.¹⁵ The complication registry categorizes each complication into four grades of severity: grade 1, temporary health disadvantage recovering without reoperation (grade 1 management includes radiological or endoscopic interventions, similar to Dindo grades I, II, and IIIa), grade 2, recovery after reoperation (similar to Dindo grade IIIb), grade 3, (probably) permanent damage or function loss (similar to Dindo grade IV when permanent), and grade 4, death (similar to Dindo grade V).

A complication is defined according to national and international standards as 'an unintended and unwanted outcome or state during medical care that is so harmful to the patient's health that it requires (adjustment of) treatment or leads to permanent damage'.¹⁶ Complications that occur after discharge are not registered unless the patient is readmitted within 30 days after discharge.

Development of the trigger tool

A set of potentially relevant triggers was chosen based on the following: (a) a previous systematic review of the literature in which these triggers were found

to be significantly associated with surgical complications, (b) questionnaires containing questions regarding the potential triggers found in the literature, answered by 12 surgeons within our hospital to validate or supplement this set of potential triggers, and (c) existence of the trigger in electronic hospital databases.¹⁷ Completeness of complication data was checked by two investigators by reading patient files in the hospital's database. Subsequently, two different investigators independently extracted the potential trigger data from the hospital's database belonging to the records of patients in the study period. To ensure correctness of the data entry into the new dataset, one investigator (AES) checked a random set of 20 patient records per trigger as entered by the other investigator (CMvL) and vice versa. Univariate logistic regression analyses were performed to find triggers that occurred substantially more often in the group with complications in the department's complication database. Variables with $P < 0.20$ were entered into a stepwise multivariate logistic regression analysis to find significant independent triggers ($P < .05$). This association was expressed as their odds ratio (OR), 95% confidence intervals, (CI) and P values. Continuous variables were dichotomized. Different ranges of cut-off values based on clinical relevance and the literature were tested for each variable and analyzed with the final cut-off limits. The most significant value was set.

Reference standard

Of all patients with complications, 86% of patients were recorded in the existing database.⁵ In order to validate and compare the trigger tool, a reference standard database was formed from a random sample of 150 records with complications and 150 records without complications, meaning oversampling for complications. For each potential trigger, a minimum of 10 records (as a rule of thumb) should be included in the reference standard in a regression analysis. A sample of 150 records was considered to be adequate as a reference standard to enable detection of 15 possible independent predictors. The medical files of all patients in the reference standard were reviewed by two investigators (AES and CMvL). If the investigators found complications in the records without complications, these records were removed from the sample without complications and added to that with complications. In the event of uncertainties when interpreting the texts of the resources about complications, the investigators consulted each other or their supervisors. This procedure continued until the group without complications also contained 150 verified records.

Validation of the trigger tool

The independent triggers from the department's complication database were subsequently entered in another multivariate analysis, now using the reference

standard in order to check their validity. Triggers were kept in the model if they again contributed significantly to the model. If not, the trigger was removed from the model unless the trigger had a low incidence (<10 patients) in the reference standard and was a significant factor in the univariate analysis. The remaining independent triggers formed the final trigger tool.

Comparing the verbal inventory with the trigger tool

The verbal inventory and trigger tool were compared with the reference standard in order to calculate their sensitivity and specificity in respect of the detection of one or more complications and the severity, type, and number of complications registered. All statistical analyses were performed using IBM SPSS Statistics version 20 (IBM, Armonk, NY, USA).

RESULTS

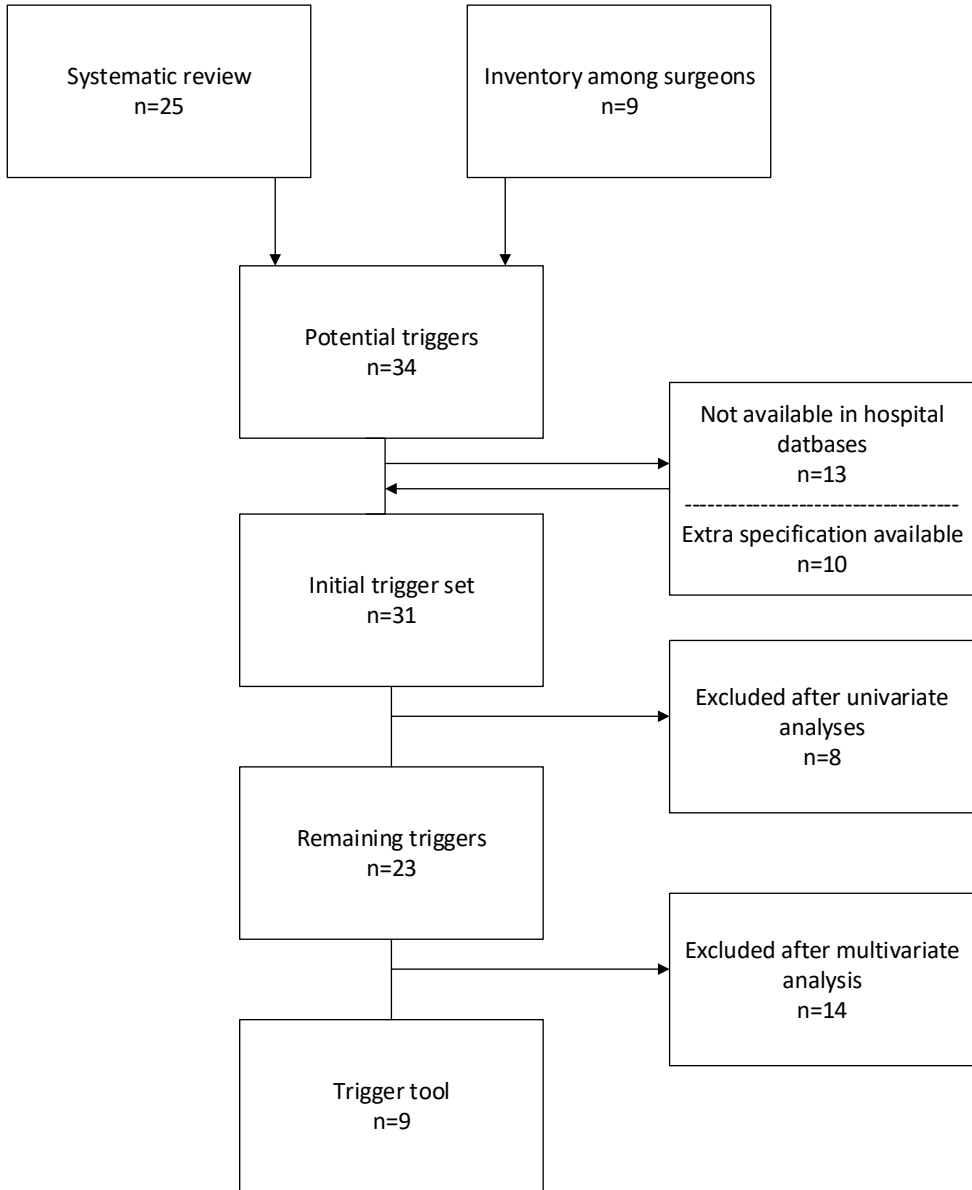
Patients and setting

A total of 4534 patients admitted to the hospital between June 2012 and July 2013 were included in this study. Their mean age was 55 years (range 18–99). Of these, 2529 (55.8%) were men and 2005 (44.2%) were women. Of all patients, 2520 (55.6%) underwent operative treatment. In 795 of the 4534 (17.5%) patient records, one or more complications were documented in the department's database.

Development of the trigger tool

The systematic review provided 25 potential triggers that were significantly associated with the occurrence of surgical complications.¹⁷ The verbal inventory conducted by the surgeons yielded 9 additional potential triggers (Fig. 1). This led to a total of 34 potential triggers for data collection. Of these, 21 were readily available in hospital databases and an extra 10 specifications of these potential triggers were recruited from the hospital's database. For example, the trigger 'emergency operation' resulted in two triggers: (1) emergency operation during admission and (2) the highest urgency classification of emergency surgery during admission.

Figure 1. Flow chart of the triggers eventually included in the trigger tool.



Univariate analyses found 23 out of 31 potential triggers with $P < 0.20$ (Table 1). Some of the triggers influenced each other, for example, an esophageal resection was associated with admission at the ICU and a higher complexity of surgery. To study the separate effects of the triggers, we developed three models: (1) a general model for patients who underwent a surgical procedure, (2) a model focusing on specific surgical procedures that were prone to resulting in postoperative complications, and (3) a model for patients who did not undergo surgery, but who could still be burdened with complications during the admission period or during the 30 days after discharge (Table 1).

Table 1. Outcome of univariate analysis of variables possibly associated with complications (n=4534).

Variables	P value	95% CI	No. of samples (n)
Retrieved from the systematic review			
Sex	.090	0.749-1.021	4534
Age (years)	<.001	1.007-1.011	4534
Body mass index (kg/m ²)	.678	0.984-1.026	2154
ASA	<.001	1.239-1.678	2121
MET score	.963	0.945-1.062	1643
Emergency procedure	<.001	1.873-2.650	4534
Urgency code at moment of admission	.298	0.881-1.511	4534
Highest urgency code in admission period	<.001	1.470-1.742	4534
Duration greater than scheduled procedure time	<.001	1.007-1.011	2254
Do not resuscitate	<.001	0.309-0.464	4168
Smoking	.220	0.912-1.491	1956
COPD/asthma/emphysema	.003	1.148-1.990	2209
Hypertension	.230	0.920-1.412	2288
Increased serum creatinine	.666	0.734-1.218	1856
Hyponatremia	.098	0.952-1.792	1427
Hypernatremia	.769	0.417-3.263	1427
Sodium level outside reference range	.091	0.959-1.773	1427
Increased leukocyte count	.015	1.062-1.757	1556
Decreased serum albumin	<.001	2.811-7.382	665
Use of corticosteroids	.188	0.919-1.535	4534
Active alcohol abuse	.737	0.852-1.120	2066
Retrieved from the inventory among surgeons			
Surgical procedure (yes/no)	<.001	1.966-2.747	4534
Esophageal resection	<.001	4.397-11.171	4534
Whipple procedure	<.001	6.451-18.328	4534
Acute Abdominal Aortic Aneurysm	<.001	4.574-22.513	4534
Multiple trauma patient	<.001	1.629-5.538	4534
Length of stay	<.001	7.350-10.815	4534
Admission to ICU	<.001	4.290-6.396	4534
Reoperation	<.001	10.917-18.540	4534
Increased C-reactive protein level	.035	1.030-2.270	980
Complexity of procedure	<.001	1.139-1.240	2520

CI confidence interval, ASA American Society of Anesthesiologists, MET score fitness score based on anesthesiology questionnaire, COPD chronic obstructive pulmonary disease, ICU intensive care unit

This resulted in 11 independent triggers, 4 of which were continuous variables: length of hospital stay, extension of standard surgical procedure time, complexity of procedure, and age. Their cut-off values were set to the following: length of stay ≥ 14 days, technical complexity of procedure \geq class 6, age ≥ 85 years, and time required above the scheduled procedure time ≥ 110 min. Table 2 shows the results of the trigger tool with the 11 potential triggers again tested in the multivariate analysis, now dichotomized based on these cut-off values.

Validation of the trigger tool

The triggers were tested using the reference standard (Table 3). The reference standard is not representative of the total population in the department's complication database due to oversampling of records with complications. Due to the smaller size of this group, we also studied the incidence of the triggers. The multivariate analysis, now using the reference standard, showed 6 out of the 11 potential triggers to be significant (Table 3). The triggers 'time required above the scheduled procedure time ≥ 110 minutes' and 'age ≥ 85 ' were found not to be significantly associated with the presence of complications ($P > .20$). The incidence of 3 potential triggers was low (esophagectomy (n=6), Whipple procedure (n=7), and abdominal aortic aneurysm surgery (n=6)), but these triggers were significant in the univariate analyses. Nevertheless, these triggers were included in the trigger tool.

Table 2. Multivariate analysis using the departments' database (n=4534)

Trigger	P value	OR (95% CI)
Model 1		
Length of stay ≥ 14 days	<.001	4.948 (3.754–6.523)
Do not resuscitate	<.001	2.177 (1.501–3.155)
Reoperation	<.001	7.755 (5.384–11.168)
Whipple procedure	<.001	8.201 (4.494–14.964)
Acute abdominal aortic aneurysm	<.001	8.913 (1.995–39.816)
Esophageal resection	<.001	4.906 (2.818–8.542)
Age ≥ 85 years	.009	2.944 (1.237–7.005)
Duration greater than scheduled procedure time ≥ 110 min	<.001	3.660 (2.407–5.562)
Model 2		
Do not resuscitate	<.001	2.937 (2.166–3.982)
Duration greater the scheduled procedure time ≥ 110 min	<.001	4.731 (3.307–6.767)
Complexity of surgery	<.001	2.007 (1.578–2.552)
Urgency of operation	<.001	1.613 (1.290–2.016)
Model 3		
Length of stay ≥ 14 days	<.001	6.399 (5.208–7.863)
ICU stay	<.001	2.796 (2.226–3.512)
DNR	<.001	2.256 (1.799–2.830)

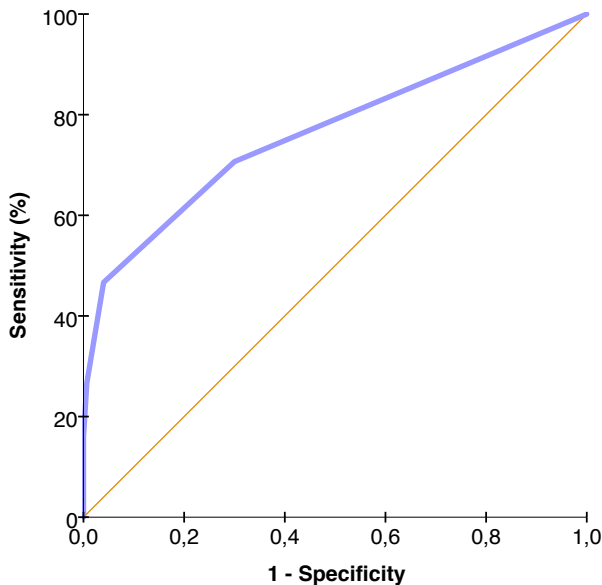
OR odds ratio, CI confidence interval, ICU intensive care unit

Table 3. Multivariate analysis using reference standard (n=300)

Trigger	P value	OR (95% CI)
Model 1		
Length of stay ≥14 days	<.001	35.139 (8.253-149.616)
Do not resuscitate	.010	0.352 (0.159-0.777)
Reoperation	.008	16.379 (2.056-130.483)
Model 2		
Do not resuscitate	.001	0.086 (0.019-0.382)
Complexity of surgery ≥6	.001	4.273 (1.776-10.285)
Urgency operation	.073	1.849 (0.945-3.616)
Model 3		
Length of stay ≥14 days	<.001	38.016 (8.953-161.423)
ICU stay	.012	3.675 (1.327-10.177)
Do not resuscitate	.002	0.294 (0.136-0.634)

OR Odds ratio, CI confidence interval, ICU Intensive Care Unit

Thus, nine significant independent triggers were included in the final trigger tool, and these were as follows: emergency procedure, complexity of surgical procedure above class 6, do not resuscitate policy, ICU stay, length of hospital stay of more than 14 days, reoperation, esophagectomy, Whipple procedure, and acute (or ruptured) abdominal aortic aneurysm surgical procedure.



Optimum: sensitivity 0.707, specificity: 0.700. Area under the curve (AUC): 0.764

Figure 2. ROC curve showing the number of positive triggers needed to detect complications

A receiver operating characteristic (ROC) curve analysis was subsequently performed to determine the number of positive triggers needed to detect complications most accurately. The trigger tool performed best if one of the nine triggers in the trigger tool was present (sensitivity 70.7%, specificity 70.0%, AUC 0.764, Fig. 2).

Comparing the verbal inventory meeting with the trigger tool

Patient records

The sensitivity values for the verbal inventory and trigger tool methods to detect complications as compared to the reference standard were 78.7% (118/150) and 70.7% (106/150), respectively, while specificity values were 100% (150/150) and 70.0% (105/150), respectively. Therefore, the verbal method missed 21.3% of the records with complications, while the trigger method missed 29.3% (Table 4).

The sensitivity for detecting records with major complications (severity class ≥ 2 , reoperation,) was higher for the trigger tool than for the verbal method, with values of 97.2 and 80.6%, respectively (Table 4). When a combination of the trigger tool and the verbal inventory was used, 138 out of the 150 records with complications was detected (sensitivity 92.0%).

Missed complications

The verbal inventory missed 31 records with one or more complications (a total of 71 complications). The trigger tool missed 45 records (a total of 53 complications). All complications missed by the trigger tool were minor complications (severity class < 2), especially wound problems. The verbal inventory also missed mainly minor complications, but these were categorized as functional disturbance (i.e., hypertension or electrolyte derailment). Two severe complications were also missed by the verbal inventory (reoperation and death).

Table 4. Verbal inventory versus trigger tool, sensitivity (n=300).

	Verbal inventory (%)	Trigger tool (%)
Reference standard		
Records with complications	78.7	70.7
Records with complications with the highest severity ¹		
≥Severity 2	80.6	97.2
≥Severity 3	91.7	100
≥Severity 4	83.3	100

¹ Severity: 2) recovery after reoperation, 3) (probably) permanent damage or function loss, and 4) death

Discussion

Based on our study results, the proposed trigger tool appears to be as accurate as a verbal inventory in terms of sensitivity and specificity relating to the detection of complications that occur in hospitalized surgical patients. Furthermore, the trigger tool we developed detected more complications overall and more severe complications. Only certain mild complications have been missed, for example, wound infection with no need for reoperation or mild cardiac complications.

The verbal inventory during the morning hand-off promotes awareness of the complications suffered by patients and deliberation and reflection with and by hospital colleagues. The two methods were tested with regard to their ability to identify records with complications. To optimize the registration of complications, registry after using one of the methods must be referred to the surgeons, who should discuss these in order to undertake preventive actions by way of, for example, separate complication meetings.

This study is one of the few that have used a reference standard to assess the comprehensiveness of the detection of patients with complications by two methods, i.e., verbal inventory and a trigger tool. Most studies have used a 'silver' standard or even no reference standard at all.^{13,14,18} The sensitivity of the trigger tool in this study compares favorably to other forms of term searching tools, such as scanning discharge letters for words suggestive of complications, or natural language processing detection methods.^{13,14,18}

As an alternative to the detection methods investigated here, the clinical observation method involves the investigation of potential complications by a trained observer of all patients and providers, who is warned to check for complications by a predefined list of clinical event 'triggers'. Clinical observation is a powerful tool for identifying incidents and errors in medical care, especially when compared with self-reporting or voluntary reporting mechanisms.^{14,19} This observation method, however, uses clinical observers and also focus groups to identify complications, which would involve a huge manual effort. Another option, the IHI collaborative 'Global Trigger Tool' (GTT), appears to detect more complications than other conventional approaches but also requires substantial manual effort.^{3,4,7}

The proposed trigger tool (tailored to a Dutch hospital context) is expected to be highly resource-intensive and will require manual database searching by the database manager, but the surgeons' workload will probably be reduced. Further research is needed to determine the potential time and costs involved. A fully electronic database including all admitted patients and their health care

utilization characteristics would facilitate the use of this trigger tool. Unfortunately, symptoms, diagnoses, and physical findings are usually recorded as narrative texts, and are as yet unavailable in coded form. Nursing files and surgical discharge letters were found to be helpful in finding complications.⁵ The trigger tool method could be simplified by the retrieval of complications from patient nursing files and surgical discharge letters. In addition, nurses could play an important role in the process of complication registration. Application of the trigger tool could also be simplified by way of systematized electronic storage information in hospital data systems, in order to detect patients 'at risk' more easily.

Limitations

The study was a single-center study. However, the predictive factors used as potential triggers were derived from a systematic review based on studies from various institutions. Although certain triggers (for example, highly specialized surgical interventions performed only in high-volume centers) may not be relevant in some centers, the remaining triggers may well be. Three out of the nine triggers consisted of specific major surgical procedures in a university hospital. These procedures are not undertaken in all hospitals. There has been a tendency for health organizations to rush towards inadequately justified 'one fits all' solutions, but the effectiveness of these global tools varies widely and they do not provide the robust data on which hospitals need to base their decisions to optimize patient safety.¹³ However, the absence of certain triggers or surgical procedures in some hospitals does not imply that this trigger tool is invalid. The use of a customized set of triggers to detect surgical complications, as provided in this study, could result in high sensitivity, especially for the detection of major complications. The potential triggers identified in a previous systematic review can be used as a new set of potential triggers, and this article provides a method for use by other hospitals to develop a customized trigger tool based on their own type of surgery.¹⁷ It should also be noted that the definition of the DNR status may be culturally sensitive. We do not, however, think this will have a major impact on the validity of the trigger tool, but only on the predictive power of this particular trigger.

Although tested on a reliable reference standard (n=300), little is known about the risks of the trigger tool in a larger population regarding missed complications. For practical reasons, the number of patients in the reference standard was limited, which may have led to fewer significant triggers. Further external validation is warranted to assess the value of this trigger tool before it can be implemented in clinical practice. The reference standard datasets are a subgroup of the department's complication database. Composing the reference

standard in this way might not be statistically appropriate. Since it incorporates a set of total department's patient population, we assume the influence on the study outcomes will be small.

Cut-off values were based on practical grounds and clinical relevance. Determining cut-off values by means of ROC analysis would have resulted in identifying more than 70% of patients who might have suffered a complication (e.g., the optimum cut-off value for age would be >57 years, while the patients' mean age was 55 years).

This trigger tool is helpful after discharge in relation to the detection of complications by identifying high-risk patients' records. Another use of 'triggers' could be their functioning as so-called red flags, highlighting patients who are at risk of developing complications, which could be useful in the improvement of complication prevention in clinics. Not all of our triggers could function as red flags before admission. The type of surgery and planned intensive care admission are known before admission. Nevertheless, if these red flags occur during admission, the patient can be marked as having a high risk of developing complications, either in order to detect them early or even to take action to prevent (more) complications during admission. Although studies on the Global Trigger Tool are common, little is known about the use of a customized trigger tool or sensitivity outcomes against a reference standard.¹⁶ The need for an efficient and inexpensive means to detect complications makes further research on an electronic (trigger tool) approach attractive.

Conclusions

The use of a customized set of triggers as proposed here by a university hospital for detecting surgical complications could result in high sensitivity for the detection of major complications in an academic hospital. However, mild complications could be missed, for example, wound infection with no need for a reoperation. The proposed trigger tool appears to be as accurate as a verbal inventory in terms of sensitivity and specificity in relation to the detection of minor and major complications. This study provides a method by which other hospitals could develop a customized trigger tool based on their own type of surgery to detect more severe complications, provided that it is simplified by systematized electronic storage of patients' characteristics and valuable trigger information in hospital data systems.

References

1. Veen EJ, Janssen-Heijnen MLG, Leenen LPH, Roukema JA. The registration of complications in surgery: A learning curve. *World J Surg.* 2005;29(3):402-409. doi:10.1007/s00268-004-7358-8
2. Nicolay CR, Purkayastha S, Greenhalgh A, et al. Systematic review of the application of quality improvement methodologies from the manufacturing industry to surgical healthcare. *Br J Surg.* 2012;99(3):324-335. doi:10.1002/bjs.7803
3. Resar RK, Rozich JD, Simmonds T, Haraden CR. A trigger tool to identify adverse events in the intensive care unit. *Jt Comm J Qual Patient Saf.* 2006;32(10):585-590. DOI:10.1016/S1553-7250(06)32076-4
4. Griffin FA, Resar RK. IHI Global Trigger Tool for measuring adverse events (second edition). Cambridge, MA: Institute for Healthcare Improvement; 2009 (available on www.IHI.org).
5. Ubbink DT, Visser A, Gouma DJ, Goslings JC. Registration of surgical adverse outcomes: A reliability study in a university hospital. *BMJ Open.* 2012;2(3):1-6. doi:10.1136/bmjopen-2012-000891
6. Griffin FA, Classen DC. Detection of adverse events in surgical patients using the trigger tool approach. *Qual Saf Heal Care.* 2008;17(4):253-258. doi:10.1136/qshc.2007.025080
7. Mattsson TO, Knudsen JL, Lauritsen J, Brixen K, Herrstedt J. Assessment of the global trigger tool to measure, monitor and evaluate patient safety in cancer patients: Reliability concerns are raised. *BMJ Qual Saf.* 2013;22(7):571-579. doi:10.1136/bmjqs-2012-001219
8. Naessens JM, O'Byrne TJ, Johnson MG, Vansuch MB, Mcglone CM, Huddleston JM. Measuring hospital adverse events: Assessing inter-rater reliability and trigger performance of the Global Trigger Tool. *Int J Qual Heal Care.* 2010;22(4):266-274. doi:10.1093/intqhc/mzq026
9. Schildmeijer K, Nilsson L, Årestedt K, Perk J. Assessment of adverse events in medical care: Lack of consistency between experienced teams using the Global Trigger Tool. *BMJ Qual Saf.* 2012;21(4):307-314. doi:10.1136/bmjqs-2011-000279
10. Von Plessen C, Kodal AM, Anhøj J. Experiences with Global Trigger Tool reviews in five Danish hospitals: An implementation study. *BMJ Open.* 2012;2(5):1-8. doi:10.1136/bmjopen-2012-001324
11. Szekendi MK, Sullivan C, Bobb A, et al. Active surveillance using electronic triggers to detect adverse events in hospitalized patients. *Qual Saf Heal Care.* 2006;15(3):184-190. doi:10.1136/qshc.2005.014589
12. O'Leary KJ, Devisetty VK, Patel AR, et al. Comparison of traditional trigger tool to data warehouse based screening for identifying hospital adverse events. *BMJ Qual Saf.* 2013;22(2):130-138. doi:10.1136/bmjqs-2012-001102
13. Forster AJ, Andrade J, Van Walraven C. Validation of a discharge summary term search method to detect adverse events. *J Am Med Informatics Assoc.* 2005;12(2):200-206. doi:10.1197/jamia.M1653
14. Melton GB, Hripcsak G. Automated detection of adverse events using natural language processing of discharge summaries. *J Am Med Informatics Assoc.* 2005;12(4):448-457. doi:10.1197/jamia.M1794
15. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: A new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg.* 2004;240(2):205-213. doi:10.1097/01.sla.0000133083.54934.ae
16. Kievit J, Jeekel J, Sanders F. Complicaties registreren. Landelijke database voor beter inzicht. *Medisch Contact.* 1999;54:1363-1365.
17. Visser A, Geboers B, Gouma DJ, Goslings JC, Ubbink DT. Predictors of surgical complications: A systematic review. *Surgery* 2015;158(1):58-65. doi:10.1016/j.surg.2015.01.012
18. Murff HJ, Forster AJ, Peterson JF, Fiskio JM, Heiman HL, Bates DW. Electronically screening discharge summaries for adverse medical events. *J Am Med Informatics Assoc.* 2003;10(4):339-350. doi:10.1197/jamia.M1201
19. Backman C, Forster AJ, Vanderloo S. Barriers and success factors to the implementation of a multi-site prospective adverse event surveillance system. *Int J Qual Heal Care.* 2014;26(4):418-425. doi:10.1093/intqhc/mzu052

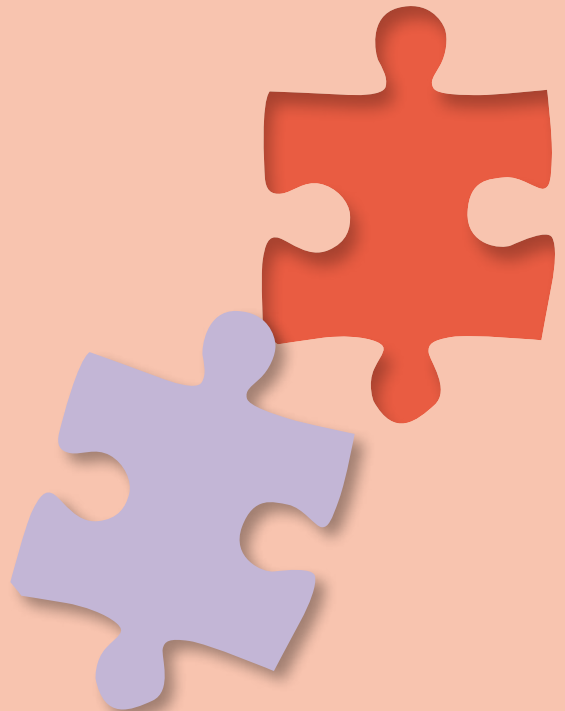


CHAPTER 3

A quantified scoring system for postoperative complication severity as compared to the Clavien–Dindo classification

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ABSTRACT

Background: Esophagectomies are associated with high morbidity. To assess complication severity, the Clavien–Dindo classification grades only the most severe complication. However, it ignores additional complications with equal to or lower severity than that one complication. The Comprehensive Complication Index (CCI) incorporates all complication severities. It might therefore be a better system for assessing severities. The aim of this study was to validate the CCI and to compare it to the Clavien–Dindo classification.

Methods: A prospective database was used to analyze 621 patients, each of whom underwent an esophagectomy between 1993 and 2005. The CCI was calculated and its relation with traditional parameters was assessed and compared to the relation of the Clavien–Dindo classification with the same parameters.

Results: Complications occurred in 429 patients (69.1%). The correlation between the CCI and the Clavien–Dindo classification was $r=0.987$, $P < .010$. The relation of the CCI with 3 out of 7 parameters was not significantly different compared to the relation of the Clavien–Dindo classification ($P > .05$). There was a significantly stronger relation ($P < .05$) of the CCI with length of stay ($r=0.663$ versus 0.646), a prolonged length of stay ($r=0.542$ versus 0.530), reintervention ($r=0.437$ versus 0.422), and reoperation rate ($r=0.489$ versus 0.471) than the Clavien–Dindo classification.

Conclusion: The Comprehensive Complication Index is a promising scoring system that could be used to identify risks in surgical patient groups.

INTRODUCTION

Esophagectomy for cancer is associated with high postoperative mortality and morbidity. Mortality rates have been reduced from approximately 16 to 3.2% over the past years, and attention to postoperative complications has increased.¹⁻³ Quality of healthcare cannot be assessed only by the occurrence of complications per se, the severity of these complications is also important. Complications after esophagectomy can range from relatively small (e.g., urinary tract infection) to severe complications (e.g., intensive care unit (ICU) admission after anastomotic leakage).

In the past years, several registry systems with a focus on complication severity have been developed to assess the risks of surgical procedures and to measure quality of care.⁴⁻⁶ The Clavien–Dindo classification is one method that is now widely used by many surgical specialties to assess and compare the severity of postoperative complications.^{5,7-11} This severity classification grades the most severe complications that occur in the patient's admission period based on the treatment used for these complications. However, it ignores all additional complications that are equal to or less severe than the one complication with the highest Clavien–Dindo classification grade.

The Comprehensive Complication Index (CCI) was developed for involvement of the severity of each complication that occurred after surgery.⁶ All complications are scored separately according to the severity classes of the Clavien–Dindo classification. The Comprehensive Complication Index can then be calculated as the sum of all different severity classes using a formula that has been developed using an adopted operating–risk–index and can easily be assessed using the CCI-calculator available at https://www.assessurgery.com/about_cci-calculator/.^{6,12} The CCI values range from 0 to 100, a value of 0 reflects the absence of complications, while a CCI of 100 indicates that the patient has died due to complications.

A recently published study investigated the Comprehensive Complication Index of the intervention versus control groups of 3 different randomized controlled trials. It showed that there was a significant difference between the arms in 2 out of 3 randomized controlled trials (pancreas and esophageal resections) if the Comprehensive Complication Index was used as a measure for complication severity, while there was no difference in either the number of complications or the Clavien–Dindo classification between those arms.¹³ In the third randomized controlled trial (colon resections), the Comprehensive Complication Index confirmed the absence of a difference between the 2 arms. Based

on the results of this study, the Comprehensive Complication Index might be considered a useful and possibly a more accurate method to assess risks in surgical procedures, but whether the Clavien–Dindo classification can be completely replaced by the Comprehensive Complication Index in future studies is still unknown. After all, while the Comprehensive Complication Index requires a calculation, scoring only the worst complication can more easily assess severity scores in patients by using the Clavien–Dindo classification.

The aim of this study is, therefore, to investigate the accuracy of the Comprehensive Complication Index compared to the Clavien–Dindo classification. The relation of the Comprehensive Complication Index with parameters such as (a prolonged) length of hospital stay, (a prolonged) ICU length of stay, re-intervention, reoperation, and reintubation rate was compared to the Clavien–Dindo classification in a large patient cohort. If the Comprehensive Complication Index shows a stronger relation with these parameters compared to the Clavien–Dindo classification, the Comprehensive Complication Index could be a more valuable method with which to assess preoperative and postoperative risks in esophageal cancer and it could be used postoperatively as a measure of quality of care.

METHODS

Patients and Setting

The patient group that was analyzed in this study had already been investigated in the O-POSSUM validation study.¹⁴ An existing prospective database was used to perform the validation study, which contained all patients who underwent a potentially curative esophagectomy for adenocarcinoma or squamous cell carcinoma at the department of surgery of a tertiary referral university hospital in Amsterdam, The Netherlands, between January 1993 and August 2005. In this study, patients were excluded from the analyses if they died due to the occurrence of complications, since the CCI is then always 100 in spite of the severity of preceding complications in these patients. Patients were also excluded if data with information about their complication treatment could not be obtained.

Data Collection

The Clavien–Dindo classification of the most severe complication, hospital length of stay (in days), a prolonged length of stay, ICU length of stay (in days), a prolonged ICU length of stay, reinterventions, reoperations, and reintubations had already been described in the existing database, and were used for the

analyses. A prolonged ICU length of stay was considered the ICU length of stay greater than the median ICU length of stay. A reintervention was defined as 'a surgical, endoscopic or radiological intervention not under general anaesthesia as a treatment for the complications'.⁵ All medical records were checked for additional complications. A complication was defined as 'an unintended and unwanted outcome or state that occurred during or following medical care that is so harmful to the patient's health that it requires (adjustment of) treatment or leads to permanent damage'.¹⁵ Complications were registered if they occurred during the hospital stay or if the patient was readmitted to the hospital within 30 days after surgery. Each individual complication was further graded according to the Clavien–Dindo classification. These grades were entered into the CCI-calculator to assess the CCI values per patient.¹² The values were used to calculate the correlation coefficients.

The relation of the Comprehensive Complication Index and the Clavien–Dindo classification with all parameters

A scatterplot was generated to assess the relation of the Comprehensive Complication Index with length of stay (in days) and ICU length of stay (in days) and to check the data for outliers. Spearman's rank test was used to calculate the correlation coefficient of the CCI with (a prolonged) length of stay, (a prolonged) ICU length of stay, reintervention (e.g., radiologically guided drainage), reoperation, and reintubation rates. The correlation of the Clavien–Dindo classification with (a prolonged) length of stay, (a prolonged) ICU length of stay, reintubation, reoperation, and reintervention rate were also calculated using Spearman's rank test. Outcome values were expressed as correlation coefficients Rho (r_s) and P values. Correlation coefficients of $r_s=0.10$ – 0.29 , $r_s=0.30$ – 0.49 , and $r_s=0.50$ – 1.0 were considered small, moderate, and strong correlations, respectively.¹⁶ Hotelling's two-sample dependent test for correlations was used to calculate the significant differences between the correlation coefficients of the parameters with the Clavien–Dindo classification and the Comprehensive Complication Index (in P values). IBM SPSS Statistics version 22.0.0.0 (IBM, Armonk, N.Y., USA) was used for the calculation of the correlation coefficients. R Console version 2.15.0 was used to perform Hotelling's two-sample dependent test for correlation. For all analyses, $P < .050$ was considered to be statistically significant.

RESULTS

Patients and setting

The database contained 663 patients who underwent an intentionally curative esophagectomy for adenocarcinoma or squamous cell carcinoma of the esophagus proven by biopsy. Twenty-four patients (3.6%) were excluded from the analysis because they died due to the occurrence of complications. For 18 patients (2.7%), treatment of the complication(s) was not described in med-

Table 1. Characteristics of 621 patients who underwent elective esophagectomy.

Variable	n (%)
Age (median), years (range)	64 (30–85)
Sex ratio (male:female)	475:146
Tumor type	
Adenocarcinoma	431 (69.4)
Squamous cell carcinoma	181 (29.1)
Adenosquamous cell carcinoma	9 (1.4)
Neoadjuvant chemoradiotherapy	117 (18.8)
Preoperative stages [‡]	
0	11 (1.8)
I	54 (8.9)
IIa	187 (30.9)
IIb	44 (7.3)
III	293 (48.3)
IV	17 (2.8)
Operation	
Transhiatal esophagectomy	400 (64.4)
Trans thoracic esophagectomy	221 (35.6)
Reconstruction	
Gastric tube	602 (96.9)
Colon interposition	19 (1.3)
Anastomosis	
Cervical	612 (98.6)
Intrathoracic	9 (1.4)
Postoperative stages [¥]	
I	79 (12.7)
IIa	129 (20.8)
IIb	51 (8.2)
III	248 (40.0)
IVa	113 (18.2)

[‡]Data were missing for 15 patients.

[¥]Data were missing for 1 patient.

Table 2. Types of complications (if ≥ 5) that occurred in patients who underwent esophagectomy

Type of complication	n (%)
Pneumonia	164 (19.9)
Vocal cord paralysis	71 (8.6)
Anastomotic or conduit leak or necrosis	63 (7.6)
Atrial fibrillation	56 (6.8)
Atelectasis	54 (6.5)
Pneumothorax	41 (5.0)
Chyle leak	34 (4.1)
Delirium	30 (3.6)
Urinary tract infection	28 (3.4)
Iatrogenic lesion of the iliac artery treated with splenectomy	21 (2.5)
Postoperative bleeding	17 (2.1)
Wound dehiscence	16 (1.9)
Abscess	14 (1.7)
Ileus	14 (1.7)
Pleural effusion	13 (1.6)
Pulmonary embolism	12 (1.6)
Wound infection	12 (1.6)
Respiratory failure	10 (1.2)
Pleural empyema	9 (1.1)
Pseudomembranous colitis	9 (1.1)
Bladder retention	8 (0.9)
Diaphragmatic herniation	8 (0.9)
Sepsis	7 (0.8)
Acute respiratory distress syndrome	6 (0.7)
Anastomotic stenosis	6 (0.7)
Pulmonary edema	6 (0.7)
Clostridium difficile infection	6 (0.7)
Central line-associated bloodstream infection	5 (0.6)
Delayed gastric emptying	5 (0.6)
Other cardiac	20 (2.4)
Other gastrointestinal	16 (1.9)
Other pulmonary	15 (1.8)
Other neurologic	10 (1.2)
Other	21 (2.5)
Total	826 (100)

ical files, or medical files were missing. Hence, a total of 621 patients were eligible for the analyses (Table 1).

All patients underwent an open esophageal resection. The mean hospital length of stay was 23 days (range 8–143), the mean ICU length of stay was 5 days (range 1–102). The mean hospital and ICU length of stay were significantly different between patients without complications versus patients with one or more complications (14 versus 26 days and 2 versus 6 days, respectively), both $P < .001$. The median hospital and ICU length of stay of the total group were 16 and 2 days, respectively. Prolonged hospital and ICU length of stay were therefore considered as an length of stay greater than 16 days (17 or longer) and as ICU length of stay greater than 2 days (3 days or longer), respectively.

There were 429 patients (69.1%) with one or more complications. The median number of complications of all patients was 1 (Interquartile range (IQR) 0–2) with a median CCI of 12.2 (IQR 0–33.7). The median number of complications for the patients who had complications was also 1 (IQR 1–2) with a median CCI of 22.6 (IQR 8.7–43.3). A total of 829 individual complications occurred in these patients (Table 2).

Reintubation was required in 69/620 (11.1%) patients after complications were noticed. There were 73/621 patients (11.8%) who underwent reoperation and 71/619 patients (11.5%) who needed an intervention as the treatment for one complication or more. It was not possible to obtain reintervention and reintubation data for all 621 patients ($n=619$ and 620 , respectively).

Table 3 shows the median CCI per Clavien–Dindo grade for 621 patients. It shows that a Clavien–Dindo grade II was correlated with CCI values ranging from 20.9 to 37.2 (with a median CCI of 22.6) in this study. The maximum CCI value in this Clavien–Dindo grade overlaps the lower CCI in the Clavien–

Table 3. The median CCI value as compared to the Clavien–Dindo grade of 621 analyzed patients who underwent esophagectomy

Clavien–Dindo grade	n (%)	CCI, median (range)
0	192 (30.9)	0 (0)
I	120 (19.3)	8.7 (8.7–5.0)
II	133 (21.4)	22.6 (20.9–37.2)
IIIa	31 (5.0)	27.6 (26.2–50.0)
IIIb	34 (5.6)	39.7 (33.7–62.6)
IVa	96 (15.3)	48.1 (42.4–78.7)
IVb	15 (2.4)	69.9 (46.2–92.5)

CCI/ Comprehensive Complication Index

Dindo grade IIIa in this patient group (with a median CCI of 27.6, ranging from 26.2 to 50.0). The table shows that the overlap of the values is also fitted in other Clavien–Dindo grades.

The relation between the Comprehensive Complication Index and the Clavien–Dindo classification with all parameters

A scatterplot suggested a positive curvilinear relationship of the CCI with hospital and ICU length of stay. A correlation coefficient of $r_s=0.987$ was found between the CCI and the Clavien–Dindo classification ($P < .010$). The correlation of both registry methods with (a prolonged) hospital length of stay, (a prolonged) ICU length of stay, and reoperation was calculated for 621 patients. The correlation coefficients for reintervention and reintubation were calculated for 619 and 620 patients, respectively.

Spearman’s rank test showed a significant moderate or strong correlation of the Comprehensive Complication Index and the Clavien–Dindo classification with all parameters ($P < .001$). A strong correlation coefficient was found between the Comprehensive Complication Index and hospital length of stay ($r=0.663$), a prolonged hospital length of stay ($r=0.542$), ICU length of stay ($r=0.514$), and reintubation rate ($r=0.520$). A moderate correlation coefficient was found between the Comprehensive Complication Index and a prolonged ICU length of stay ($r=0.484$), reintervention rate ($r=0.437$), and reoperation rate ($r=0.489$). The Clavien–Dindo score also showed a strong correlation with hospital length of stay ($r=0.646$), ICU length of stay ($r=0.517$), and reintubation rate ($r=0.520$) and showed a moderate relation with a prolonged length of stay ($r=0.530$), a prolonged ICU length of stay ($r=0.486$), reintervention rate ($r=0.422$), and reoperation rate ($r=0.471$). There was a significantly stronger correlation between the Comprehensive Complication Index and length of stay ($P < .001$), a prolonged length of stay ($P = .028$), reintervention rate ($P = .010$), and reoperation rate ($P = .001$) than between the Clavien–Dindo classification

Table 4. Correlation coefficients for the CCI and the Clavien–Dindo classification of 621 patients

	CCI (r_s)	Clavien–Dindo classification (r_s)	P value
Hospital length of stay	0.663	0.646	<.001
Hospital length of stay >16 days	0.542	0.530	.028
ICU length of stay	0.514	0.517	0.589
ICU length of stay >2 days	0.484	0.486	0.724
Reintervention [‡]	0.437	0.422	.010
Reoperation	0.489	0.471	.001
Reintubation*	0.520	0.520	1.000

All correlation coefficients (r_s) were significant with $P < .010$. CCI Comprehensive Complication Index. [‡]n=619 due to missing values. *n=620 due to 1 missing value.

and these parameters. The relations of the Comprehensive Complication Index with other parameters were not significantly different compared to the Clavien–Dindo classification ($P > .05$, Table 4).

DISCUSSION

The Comprehensive Complication Index shows a moderate to strong relation with all parameters (prolonged) hospital length of stay, (prolonged) ICU length of stay, reintervention, reoperation, and reintubation rate). As compared to the relation of the Clavien–Dindo classification with (prolonged) ICU length of stay, and reintubation, the relation of the CCI with these variables is not significantly different. However, 4 out of 7 parameters showed a significantly higher correlation with the CCI than with the Clavien–Dindo classification, that is, (a prolonged) length of stay, reintervention, and reoperation.

This could be explained by the occurrence of multiple complications among patients who were classified into the same Clavien–Dindo grade. For example, there were 2 patients with a Clavien–Dindo classification IIIb (reoperation). One patient underwent reoperation only after the occurrence of a wound dehiscence (CCI 33.7, length of stay: 20 days), while the other patient (CCI 62.6, LOS 143 days) suffered from the following conditions: anastomotic leakage drained at the bedside (Clavien–Dindo classification grade I), pneumonia treated with antibiotics (grade II), wound dehiscence treated with reoperation (grade IIIb), underwent a second reoperation indicated by ileus (grade IIIb), delirium treated with antipsychotic medicine (grade II), and an anastomotic stenosis treated with endoscopic dilatation (grade IIIa). The last patient showed an increase in both the CCI as well as the length of stay, but not in the Clavien–Dindo grade.

In most Clavien–Dindo grades, the upper CCI value per Clavien–Dindo grade overlaps the lower CCI that correlates with the following Clavien–Dindo grade. As shown in Table 3, Clavien–Dindo grade IIIb is fitted with an upper CCI that is higher than the lower CCI of Clavien–Dindo grade IVa. Apparently, Clavien–Dindo grade IIIb (reoperation) could be correlated with a more severe postoperative course than Clavien–Dindo grade IVa (admission to the ICU for single organ failure) for patients with multiple complications who underwent reoperation. Therefore, we can conclude that the severity of the complications does not depend only on the treatment of the most severe complications.

Considering the stronger relation of the CCI with (a prolonged) length of stay,

reintervention, and reoperation rate than the relation of the Clavien–Dindo classification with these parameters, comparison of the severity of the post-operative complications among patients is therefore more accurate when the CCI is used. Since the relations of the Comprehensive Complication Index and the Clavien–Dindo classification with the other parameters are equal, the Comprehensive Complication Index can be used to assess differences in the severity of complications in other patients.

Another frequently used system with which to classify the severity of complications is the Accordion Severity Grading System (ASGS), which is a severity grading system derived from the Clavien–Dindo classification.⁴ It contains a contracted classification for smaller studies and an expanded classification for larger studies, especially for complex procedures such as esophageal resections. Compared to Clavien–Dindo classification grades IVa and IVb, which contain complications requiring ICU admission due to single or multiple organ failure, Accordion level 5 is based only on multiple organ failure regardless of ICU admission. This is caused by the fact that some patients require monitoring on the ICU if moderate complications occur in the presence of comorbidities. The development of the CCI incorporates the patients' perspective and the severity of complications is therefore based more on the impact that the complications have on the patients instead of on the severity of the complication itself. Second, the Accordion Severity Grading System and other scoring systems derived from the Clavien–Dindo classification are mostly ordinal scales that are less accurate for comparing patient groups in scientific studies than quantitative methods.^{9,17,18}

The values of the CCI range from 0 to 100 and could therefore provide a more comparable registry method for researchers instead of ordinal values such as those used in the Clavien–Dindo classification. When complications cause death, however, a CCI value of 100 does not reflect the severity of complications that arise in the period before the moment of death. For example, patients could die of a cerebral vascular accident without any other accessory complication, or they could die after a period of cumulative complications eventually leading to multiple organ failure and death. The CCI could possibly give more insight into the severity of complications if the occurrence of complications in the period before death were separately incorporated into the calculation. This is also supported by the development of the Postoperative Morbidity Index (PMI), another quantitative severity scoring system derived from the Accordion Severity Grading System and the National Surgical Quality Improvement Program, which showed that the value of death was not always scored as 100 by 43 surgical experts using a scale from 1 (minimal complication) to

100 (maximal complication).^{19,20} Unfortunately, the calculation of the Postoperative Morbidity Index is complex and it ignores the patients' perspective in assessing complication severity, whereas the incorporation of the patients' perspective by the Comprehensive Complication Index is a major change in the use of a quantified complication severity scoring system.

Limitations

Since the O-POSSUM validation study, postoperative morbidity has decreased, which is mostly attributable to the decrease in pulmonary complications.²¹ This could be explained by the introduction of minimally invasive surgery (which was not yet implemented in this patient group) and improvements in postoperative care and enhanced recovery. In addition, neoadjuvant chemoradiotherapy is now standard care, whereas in this patient cohort, only 18.8% of patients were treated with neoadjuvant therapy.²² The results of this study must therefore be carefully interpreted and applied to recent patient cohorts. More research on a representative patient group should therefore be performed. In addition, this study was based on patients from a prospectively maintained database and complication treatment data were retrospectively added to this database. As a consequence of missing treatment data, 18 patients were excluded from the analysis.

Conclusions

The equal and stronger correlation of the Comprehensive Complication Index with the traditional parameters in our study and the results of the earlier study show that the Comprehensive Complication Index is a more accurate registry method for complication severity than the Clavien–Dindo classification.¹³ Although the calculation of Comprehensive Complication Index is more complex and time consuming when compared to the Clavien–Dindo classification, the Comprehensive Complication Index could be a valuable severity scoring system with which to identify risks for the occurrence of complications in patient groups in retrospective studies, and it could also be used to compare postoperative morbidity more accurately than the Clavien–Dindo classification in future randomized controlled trials.

References

1. Whooley BP, Law S, Murthy SC, Alexandrou A, Wong J. Analysis of reduced death and complication rates after esophageal resection. *Ann Surg.* 2001;233(3):338-344.
2. McCahill LE, May M, Morrow JB, et al. Esophagectomy outcomes at a mid-volume cancer center utilizing prospective multidisciplinary care and a 2-surgeon team approach. *Am J Surg.* 2014;207(3):380-386.
3. Davies AR, Sandhu H, Pillai A, et al. Surgical resection strategy and the influence of radicality on outcomes in esophageal cancer. *Br J Surg.* 2014;101(5):511-517. doi:10.1002/bjs.9456
4. Strasberg SM, Linehan DC, Hawkins WG. The accordion severity grading system of surgical complications. *Ann Surg.* 2009;250(2):177-186. doi:10.1097/SLA.0b013e3181afde41
5. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: A new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg.* 2004;240(2):205-213. doi:10.1097/01.sla.0000133083.54934.ae
6. Slankamenac K, Graf R, Barkun J, Puhán MA, Clavien PA. The comprehensive complication index: A novel continuous scale to measure surgical morbidity. *Ann Surg.* 2013;258(1):1-7. doi:10.1097/SLA.0b013e318296c732
7. Clavien P a, Barkun J, de Oliveira ML, et al. The Clavien-Dindo classification of surgical complications: five-year experience. *Ann Surg.* 2009;250(2):187-196.
8. Casadei R, Ricci C, Pezzilli R, et al. Assessment of complications according to the Clavien-Dindo classification after distal pancreatectomy. *JOP.* 2011;12(2):126-130.
9. Seely AJE, Ivanovic J, Threader J, et al. Systematic classification of morbidity and mortality after thoracic surgery. *Ann Thorac Surg.* 2010;90(3):936-942.
10. Yoon PD, Chalasani V, Woo HH. Use of Clavien-Dindo classification in reporting and grading complications after urological surgical procedures: analysis of 2010 to 2012. *J Urol.* 2013;190(4):1271-1274.
11. Rogmark P, Petersson U, Bringman S, et al. Short-term outcomes for open and laparoscopic midline incisional hernia repair: a randomized multicenter controlled trial: the ProLOVE (prospective randomized trial on open versus laparoscopic operation of ventral eventrations) trial. *Ann Surg.* 2013;258(1):37-45.
12. Slankamenac K, Graf R, Barkun J, Puhán M a, Clavien P-A. CCI®-Calculator. AssesSurgery GmbH. http://www.assessurgery.com/calculator_single/. Published 2013.
13. Slankamenac K, Nederlof N, Pessaux P, et al. The comprehensive complication index: a novel and more sensitive endpoint for assessing outcome and reducing sample size in randomized controlled trials. *Ann Surg.* 2014;260(5):757-763.
14. Lagarde SM, Maris a KD, de Castro SMM, Busch ORC, Obertop H, van Lanschot JJB. Evaluation of O-POSSUM in predicting in-hospital mortality after resection for esophageal cancer. *Br J Surg.* 2007;94(12):1521-1526.
15. Goslings JC, Gouma DJ. What is a surgical complication? *World J Surg.* 2008;32(6):952.
16. Pallant J. SPSS survival manual. A step by step guide to data analysis using SPSS. In: 4th ed. Crows Nest NSW: Allen & Unwin; 2011:134.
17. Harris DY, McAngus JK, Kuo Y-F, Lindsey RW. Correlations Between a Dedicated Orthopaedic Complications Grading System and Early Adverse Outcomes in Joint Arthroplasty. *Clin Orthop Relat Res.* November 2014:0-7. doi:10.1007/s11999-014-4058-z
18. Mazeh H, Cohen O, Mizrahi I, et al. Prospective validation of a surgical complications grading system in a cohort of 2114 patients. *J Surg Res.* 2014;188(1):30-36. doi:10.1016/j.jss.2013.12.004
19. Strasberg SM, Hall BL. Postoperative morbidity index: a quantitative measure of severity of postoperative complications. *J Am Coll Surg.* 2011;213(5):616-626. doi:10.1016/j.jamcollsurg.2011.07.019
20. Porembka MR, Hall BL, Hirbe M, Strasberg SM. Quantitative weighting of postoperative complications based on the accordion severity grading system: demonstration of potential impact using the american college of surgeons national surgical quality improvement program. *J Am Coll Surg.* 2010;210(3):286-298.
21. Biere SSAY, Van Berge Henegouwen MI, Maas KW, et al. Minimally invasive versus open esophagectomy for patients with esophageal cancer: A multicenter, open-label, randomised controlled trial. *Lancet.* 2012;379(9829):1887-1892.
22. van Hagen P, Hulshof MCCM, van Lanschot JJB, et al. Preoperative chemoradiotherapy for esophageal or junctional cancer. *N Engl J Med.* 2012;366(22):2074-2084. doi:10.1056/nejmoa1112088



CHAPTER 4

Using the Comprehensive Complication Index to assess
the impact of neoadjuvant chemoradiotherapy on
postoperative complications after esophagectomy for cancer

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ABSTRACT

Background: Neoadjuvant chemoradiotherapy (nCRT) followed by surgery for patients with esophageal or junctional cancer has become a standard of care. The Comprehensive Complication Index (CCI) has recently been developed and accounts for all postoperative complications. Hence, CCI better reflects the burden of all combined postoperative complications in surgical patients than the Clavien–Dindo score alone, which incorporates only the most severe complication. This study was designed to use the comprehensive complication index to evaluate the severity of complications in patients treated with nCRT followed by esophagectomy versus patients who underwent esophagectomy alone.

Methods: All patients included in the CROSS study—a randomized, clinical trial on the value of nCRT followed by esophagectomy—were included. Complications were assessed and graded using Clavien–Dindo classification. CCI was derived from these scores, using the CCI-calculator[®] available online (www.assessurgery.com). The CCI of patients who underwent nCRT followed by surgery was compared with the CCI of patients who underwent surgery alone.

Results: In both groups 161 patients were included. The median (and interquartile range) CCI of patients with nCRT and surgery was 26.22 (17.28–42.43) versus 25.74 (8.66–43.01) in patients who underwent surgery alone ($P = .58$). There also was no difference in CCI between subgroups of patients with anastomotic leakage, pulmonary complications, cardiac complications, thromboembolic events, chyle leakage, and wound infections.

Conclusions: Neoadjuvant chemoradiotherapy according to CROSS did not have a negative impact on postoperative complication severity expressed by CCI compared with patients who underwent surgery alone for potentially curable esophageal or junctional cancer.

INTRODUCTION

Esophageal cancer remains one of the most common cancers worldwide.¹ Treatment for patients with potentially curable esophageal cancer involves an esophagectomy with gastric tube reconstruction. Meta-analyses of randomized, controlled trials comparing neoadjuvant chemoradiotherapy plus surgery to surgery alone showed that multimodality treatment improves overall survival, but side-effects (e.g., radiation fibrosis, suppressed immune function, impaired nutritional and hematological status) could increase morbidity and mortality after esophagectomy.²⁻¹⁷ The largest published, randomized clinical trial on the value of neoadjuvant chemoradiotherapy (CROSS trial) also showed a survival benefit.¹⁴ Importantly, there was no difference in the frequency of complications and postoperative mortality between the patients who were treated with neoadjuvant chemoradiotherapy followed by surgery and the patients who underwent surgery alone.

In the past decades, the frequency and severity of postoperative complications have become important quality measures in surgical studies. In addition, patients' reported grading of complications provides a better insight into the burden of a complicated postoperative course. Therefore, several severity-scoring systems have been developed.¹⁸⁻²² A novel and validated scoring system is the Comprehensive Complication Index.^{20,23} The Comprehensive Complication Index summarizes the frequency, severity, and patients' rating of complications by using the adopted "operating risk index" in a single score that ranges between 0 (no complication) and 100 (death) based on the established Clavien-Dindo classification.²² A recent study showed that the Comprehensive Complication Index is a sensitive method that is superior to traditional endpoints, because it summarizes the whole burden of postoperative complications to the patient.²⁰ Whereas traditional endpoints showed no significant differences in the incidence of postoperative complications within the CROSS trial, the current study was designed to evaluate the overall effect of neoadjuvant chemoradiotherapy on the severity of postoperative complications and the overall burden on patients taking part in the CROSS trial. Therefore, the Comprehensive Complication Index was compared between patients with esophageal or esophagogastric junction cancer who underwent chemoradiotherapy plus surgery versus patients who underwent surgery alone.

METHODS

Patients with esophageal cancer or cancer of the gastroesophageal junction (cT1-4aN0-3M0) who underwent a curative surgical resection of the esophagus and who participated in the CROSS trial were selected from the study database. The CROSS trial was a multicenter, randomized, controlled trial that compared overall survival for patients who were treated with neoadjuvant chemoradiotherapy followed by esophagectomy and patients who underwent esophagectomy alone. The inclusion and exclusion criteria as well as staging procedures have been described previously.²⁴ As the study focuses on complication severity after esophagectomy, patients who did not undergo resection were removed from the study cohort.

Complications

Complications were defined using the complete and commonly applicable National Cancer Institute's Common Terminology Criteria for Adverse Events, 4.0.²⁵ Because these criteria do not provide a definition of anastomotic leakage, the definition according to Bruce et al. was used.²⁶ 'drainage of saliva or gastrointestinal content from the surgical join between the esophagus and gastric tube. The luminal contents may emerge externally or internally or may be collected near the anastomosis with or without systemic complications'. Only complications within 30 days after the operation and/or during the hospital stay were assessed.

Comprehensive Complication Index (CCI)

The Comprehensive Complication Index is a complication index that was introduced by Slankamenac and colleagues in 2013 and is based on the Clavien-Dindo classification (see Appendix).^{20,22} In the development of the Comprehensive Complication Index, data on common postoperative complications were gathered and rated by both patients and physicians. In this method each complication is validated and given a fixed number, and also includes the patient's perspective regarding the severity. After this, a score is calculated for each grade in the Clavien-Dindo classification. To calculate the Comprehensive Complication Index, all complications that a patient develops after surgery are summarized and computed through the operation risk index approach that is commonly used in economics. This can be done easily and free of charge at <https://www.assessurgery.com>. The final index yields a score from 0 (no complication) to 100 (death).²⁷ To investigate whether postoperative complication severity is influenced by neoadjuvant treatment, the severity of all combined complications was measured using the Comprehensive Complication Index. Based on results in earlier studies of patients who underwent esophageal can-

cer surgery in which specific complications showed an increase in incidence, six subgroups were formed in this study. For example, some studies showed the influence of neoadjuvant treatment on pulmonary complications, due to the radiation field. In subgroup 2, patients with pulmonary complications were compared. Only patients with the specific complication were used to calculate the specific complication Comprehensive Complication Index.

Grading of complications

We used the original database of the CROSS study in which postoperative complications were scored by data managers in each participating center. Cross-checking of these complications and grading every complication according to the Clavien–Dindo classification was done by one of the authors (NN). The Comprehensive Complication Index was calculated afterwards. In addition, for each patient the traditional endpoints, the total number of complications, the presence of any complication (yes/no) and the most severe complications (grade IIIb according to the Clavien–Dindo classification) were assessed.

Treatment

As previously described, patients randomized to neoadjuvant chemoradiotherapy underwent five weekly cycles of chemoradiotherapy (carboplatin/paclitaxel with 41.1 Gy concurrent radiotherapy) followed by surgery that would preferably be performed within 4–6 weeks after chemoradiation.²⁴ Patients randomized to the surgery alone arm underwent esophagectomy as soon as possible.

Statistical analyses

Adjustment for possible confounders was not necessary, because the data were controlled for confounding by randomization. Baseline continuous data were described as means with standard deviation or, in the case of variables that were not normally distributed, with the median and interquartile range. Normal distribution was calculated using the Kolmogorov–Smirnov test. Groups were compared using the nonparametric Mann–Whitney U test. For cross-tabulations, Pearson’s chi-square test with continuity correction was used. All statistical analyses were performed on the statistical package SPSS 22.0 (SPSS Inc., Chicago, IL). Two-sided $P < .050$ was considered to be statistically significant.

RESULTS

Of the 368 patients randomized in the CROSS trial, 322 patients were included in the present study.¹⁴ An overview of inclusion and exclusion of patients in the present study is shown in Figure 1.

Patients' characteristics, including age, sex, comorbidity, and surgical approach, were similar between both groups (Table 1). More radical (R0) resections were performed in patients who received neoadjuvant chemoradiotherapy before esophagectomy ($P < .001$). In patients who were analyzed in the current study ($n=322$), the combined treatment group of 136 (85%) patients developed at least one complication versus 125 (78%) of the surgery alone group (Table 2).

Figure 1. Flow chart of patients

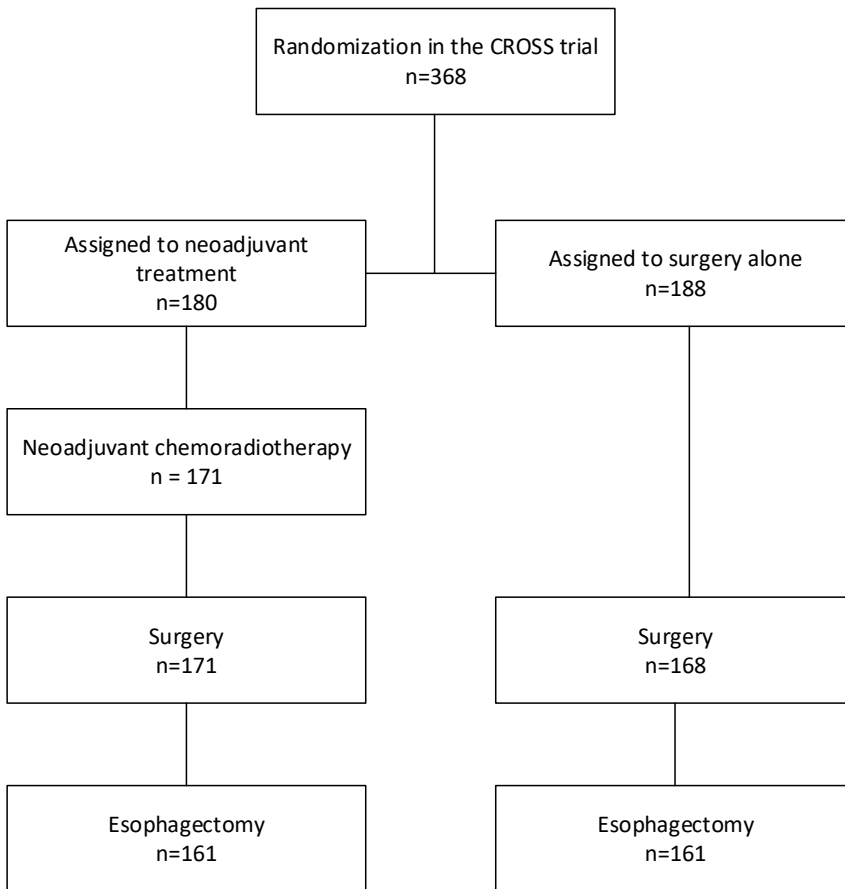


Table 1. Baseline characteristics

	nCRT and surgery (n=161)	Surgery alone (n=161)	P value
Age (year)	60 (37-76)	60 (36-76)	.72
Sex (male:female)	129:34	123:38	.41
WHO performance status			
0	27 (16.7)	20 (12.4)	.28
1	134 (83.2)	140 (87.0)	.34
Comorbidity			
Cardiovascular	45 (28.0)	40 (24.8)	.48
Respiratory	17 (10.6)	19 (11.8)	.69
Diabetes mellitus	14 (8.7)	11 (6.8)	.55
Histology			
Squamous cell carcinoma	37 (23.0)	37 (23.0)	1.00
Adenocarcinoma	121 (75.2)	120 (74.5)	1.00
Undifferentiated carcinoma	3 (1.9)	4 (2.5)	1.00
Tumor site			
Proximal esophagus	2 (1.2))	3 (1.9)	1.00
Mid esophagus	24 (14.9)	16 (9.9)	.23
Distal esophagus	112 (69.6)	123 (76.4)	.20
Gastroesophageal junction	23 (14.3)	17 (10.6)	.40
Mortality			
30-day	3 (1.9)	4 (2.5)	1.00
In-hospital	5 (3.1)	6 (3.7)	.99
Surgical approach			
Transhiatal esophagectomy	72 (44.7)	72 (44.7)	1.00
Transthoracic esophagectomy	89 (55.3)	87 (54.0)	.91
RO resections	148 (91.9)	111 (68.9)	<.001

WHO: World Health Organization, nCRT: neoadjuvant chemoradiotherapy, RO resections: resections with tumor-free margins. Age is presented in median (range). Percentages may not add up to 100 because of rounding

Grade I complications were seen in 43.5% of patients after neoadjuvant chemoradiotherapy plus surgery versus 49.1% of patients after surgery alone ($P = .37$). In addition, there was no statistically significant difference for grade II-V complications (Table 2). Analyses in six subgroups showed that respiratory complications, i.e., pneumonia, were the most common (30.4 versus 24.8%, $P = .32$), followed by anastomotic leakage (22.9 versus 30.4%, $P = .13$) and cardiac arrhythmias (18.6 versus 13.7%, $P = .29$). Significantly more infections of the chest wound were found in patients with neoadjuvant treatment who underwent a transthoracic esophagectomy (0 versus 5.6%, $P = .007$). The incidence of all other complications was not significantly different between the two groups.

Table 2. Frequencies of Clavien–Dindo classification grades and postoperative complications in patients in the current study

	nCRT and surgery (n=161)	Surgery alone (n=161)	P value
Any complication	136 (84.5)	125 (77.6)	.13
Grade I complication	70 (43.5)	79 (49.1)	.37
Grade II complication	90 (55.9)	85 (52.8)	.65
Grade IIIa complication	58 (36.0)	52 (32.3)	.56
Grade IIIb complication	25 (15.5)	28 (17.3)	.76
Grade IVa complication	28 (17.3)	33 (20.5)	.57
Grade IVb complication	3 (1.9)	6 (3.7)	.50
Grade V complication	5 (3.1)	6 (3.7)	1.00
Subgroup 1: Anastomotic leakage	37 (22.9)	49 (30.4)	.16
Subgroup 2: Pulmonary complication	81 (50.3)	82 (50.9)	1.00
Subgroup 3: Cardiac complications	34 (21.1)	23 (14.2)	.57
Subgroup 4: Thromboembolic events	6 (3.7)	4 (2.5)	1.00
Subgroup 5: Chyle leakage	16 (9.9)	11 (9.1)	.41
Subgroup 6: Wound infection	18 (11.1)	21 (13.0)	.60
Anastomotic leakage	37 (22.9)	49 (30.4)	.16
Leakage requiring surgical intervention	8 (4.9)	6 (3.7)	.59
Pneumonia	49 (30.4)	40 (24.8)	.32
Atelectasis	17 (10.6)	22 (13.7)	.49
Empyema	14 (8.7)	25 (15.5)	.09
Pneumothorax	10 (6.2)	14 (8.7)	.52
Respiratory insufficiency	29 (18.0)	33 (20.5)	.67
Reintubation	33 (20.5)	33 (20.5)	1.00
Thromboembolism	6 (3.)	4 (2.5)	.75
Cardiac arrhythmia	30 (18.6)	22 (13.7)	.29
Myocardial infarction	0	1 (0.6)	1.00
Cardiac decompensation	4 (2.5)	0	.13
Mediastinitis	6 (3.7)	11 (6.8)	.32
Chylothorax	16 (9.9)	11 (6.8)	.41
Vocal cord palsy	19 (11.8)	12 (7.5)	.66
Wound infection neck	9 (5.6)	6 (3.7)	.60
Wound infection thorax	0	9 (5.6)	.007
Wound infection abdomen	9 (5.6)	6 (3.7)	.60
Renal failure	4 (2.5)	1 (0.6)	.37
Sepsis	7 (4.3)	10 (6.2)	.62
Multiple organ failure	0	6 (3.7)	.13
Readmission to ICU	30 (18.6)	27 (16.8)	.66

nCRT neoadjuvant chemoradiotherapy, ICU intensive care unit

There was no statistically significant difference in the Comprehensive Complication Index between both groups. The median Comprehensive Complication Index in the combined treatment group was 26.22 (IQR 17.28–42.43) compared with 25.74 (IQR 8.66–43.01) in the surgery alone group ($P = .58$, Table 3). In subgroup analyses of the specific complications, the Comprehensive Complication Index for patients who underwent neoadjuvant chemo-

Table 3. Comprehensive Complication Index computed for the whole study group as well as subgroups of common postoperative complications

	CRT and surgery	Surgery alone	P value
Total group (n=322)	26.22 (17.28–42.43)	25.73 (8.66–43.01)	0.58
Patients with anastomotic leakage (n=86)	8.66 (8.66–33.73)	8.66 (8.66–33.73)	0.78
Patients with pulmonary complications (n=163)	20.92 (20.92–42.43)	20.92 (20.92–42.43)	0.59
Patients with cardiac complications (n=57)	20.92 (20.92–20.92)	20.92 (20.92–20.92)	0.64
Patients with thromboembolic complications (n=10)	20.92 (20.92–20.92)	20.92 (20.92–20.92)	1.0
Patients with chyle leakage (n=27)	8.66 (8.66–20.92)	14.79 (8.66–31.85)	0.65
Patients with wound infections (n=39)	8.66 (8.66–8.66)	8.66 (8.66–8.66)	0.93

Values are shown as the median Comprehensive Complication Index with interquartile range.

radiotherapy and developed an anastomotic leak was not statistically different from patients who underwent surgery alone: 8.66 (8.66–33.73) versus 8.66 (8.66–33.73), $P = .78$. The same was true for the other subgroups of patients who developed pulmonary or cardiac complications, a thromboembolic event, chyle leakage, or wound infection (Table 3).

DISCUSSION

The Dutch CROSS study showed an absolute 5-year survival benefit of 13% for patients who underwent neoadjuvant chemoradiotherapy followed by an esophagectomy for esophageal or junction cancer. Hence, neoadjuvant chemoradiotherapy is nowadays widely used in clinical practice. However, it is important to consider the potential harm caused by neoadjuvant chemoradiotherapy, because trials frequently focus on the benefits of the treatment.^{28–30} This may be caused by a lack of sensitive outcome parameters, by underreporting, and by the strict inclusion criteria of trials that are frequently broadened after closure of the trial and the specification of positive results. In addition, sample sizes are often rather small, masking the incidence of selectively rare but potentially serious complications.

In this study we used the novel outcome measure for a postoperative complicated course (the Comprehensive Complication Index) to compare the additive impact of neoadjuvant chemoradiotherapy on the severity of complications in patients after esophagectomy, as the incidence of complications was already reported in the CROSS study. Our results do not show significant differences in either the Comprehensive Complication Index between both groups or in the incidence of specific common complications.

The benefit of neoadjuvant treatment has been a topic of many studies but the potential harm has been described less extensively. The Cochrane review, published in 2010, demonstrates that postoperative complications are often either ill-described or not described at all.^{13,31} Therefore, in their meta-analysis no overall complication rate could be calculated.

In a retrospective study published by Morita et al. containing 686 patients, the total number of complications, as well as pulmonary complications and anastomotic leakage, developed more frequently in patients who underwent neoadjuvant treatment in comparison with patients who did not undergo neoadjuvant treatment.³² Bosch et al. confirmed an increase in cardiopulmonary complications in the neoadjuvant treatment group (pneumonia and cardiac arrhythmias).⁸ In a retrospective cohort study of 138 patients, Merrit et al. showed no increase in postoperative morbidity and mortality, but concluded that major postoperative complications are rather due to surgical techniques and preoperative morbidity rather than neoadjuvant therapy.¹⁶ Furthermore, Kelley et al. performed a prospective trial in 2004, which showed no significantly higher complication rate in patients who underwent preoperative chemoradiotherapy.⁵ In a study of 40 patients by Bagheri et al., respiratory complications were closely analyzed, and although there was a significant correlation between the number of microorganisms in the sputum and difficulty in weaning, there was no correlation found between neoadjuvant treatment and pulmonary complications.⁷

Several meta-analyses showed a decrease in mortality without any proof of a decrease in postoperative complications, but most trials failed to produce information about postoperative complications.^{10,12,13,19} Greer et al. found no difference in their meta-analysis and concluded that there was a need for large, randomized trials.¹¹

With the recently developed sensitive comprehensive complication index, it is possible to take the severity of all complications into consideration, thus improving the accuracy of reporting the impact of all side effects combined.^{20,22} The Comprehensive Complication Index has already been validated in different surgical trials, showing its value. The Comprehensive Complication Index incorporates patients' opinion on a complication, as well as the physicians' opinion. It also takes into account low-grade complications, which are not normally considered an endpoint but contribute to the patients' postoperative experience. Additionally, the Comprehensive Complication Index can be used to compare the severity of a specific complication (i.e., anastomotic leakage) between different patient groups (Table 3).

There are several limitations to the current study. Because our study included patients from seven participating hospitals, it may be possible that there is some difference in reporting and treatment of complications. All complications were reviewed by one of the authors to preserve uniformity in the application of the Clavien–Dindo classification. In the Netherlands, transference to the Medium or Intensive Care Unit for more intensive monitoring of patients is relatively low, which in the Clavien–Dindo system directly results in a grade IV complication but is not always accompanied by organ failure. The difference in complications scored in the CROSS trial differ because of the difference between the Clavien–Dindo classification and the Comprehensive Complication Index. In the CROSS study, only the most severe complication counted. In this study we only included early complications i.e., during the 30 days after surgery and/or within hospital admission. Later complications, e.g., stenosis or complications due to recurrence, were not included. Another possible limitation of this study is that postoperative complications were not the primary endpoint of the CROSS trial. The sample size calculation of the CROSS trial was based on expected differences in survival outcome as the main study outcome, therefore, the size of this study population might be too small to show differences in rare complications. However, as described by Slankamenac et al., when using the Comprehensive Complication Index as opposed to the original Clavien–Dindo classification as an endpoint, a meaningful comparison can be made with smaller sample sizes.²⁰

CONCLUSIONS

The Comprehensive Complication Index can be used as a tool to monitor postoperative recovery in a detailed and structured way. Because all data in the present study were prospectively registered, this study gives a realistic view of postoperative complications in patients with cancer of the esophageal and esophagogastric junction. This study shows that the frequency of complications described in patients extracted from the CROSS trial data is similar in the two groups, and the outcomes of specific complications in the two groups are similar. Neoadjuvant chemoradiotherapy does not have a negative impact on the overall postoperative morbidity as expressed by the Comprehensive Complication Index compared with patients who underwent surgery alone for potentially curable esophageal or esophagogastric junctional cancer.

References

1. Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. *Int J Cancer*. 2010;127(12):2893-2917. DOI:10.1002/ijc.25516
2. Kelsen DP, Winter KA, Gunderson LL, et al. Long-term results of RTOG trial 8911 (USA intergroup 113): A random assignment trial comparison of chemotherapy followed by surgery compared with surgery alone for esophageal cancer. *J Clin Oncol*. 2007;25(24):3719-3725. DOI:10.1200/JCO.2006.10.4760
3. Wijnhoven BPL, Van Lanschot JJB, Tilanus HW, Steyerberg EW, Van Der Gaast A. Neoadjuvant chemoradiotherapy for esophageal cancer: A review of meta-analyses. *World J Surg*. 2009;33(12):2606-2614. DOI:10.1007/s00268-009-0223-z
4. Kranzfelder M, Gertler R, Hapfelmeier A, Friess H, Feith M. Chylothorax after esophagectomy for cancer: Impact of the surgical approach and neoadjuvant treatment: Systematic review and institutional analysis. *Surg Endosc*. 2013;27(10):3530-3538. DOI:10.1007/s00464-013-2991-7
5. Kelley ST, Coppola D, Karl RC. Neoadjuvant chemoradiotherapy is not associated with a higher complication rate vs. surgery alone in patients undergoing esophagectomy. *J Gastrointest Surg*. 2004;8(3):227-232. DOI:10.1016/j.gassur.2003.11.024
6. Hii MW, Smithers BM, Gotley DC, et al. Impact of postoperative morbidity on long-term survival after esophagectomy. *Br J Surg*. 2013;100(1):95-104. DOI:10.1002/bjs.8973
7. Bagheri R, RajabiMashhadi MT, Ghazvini K, Asnaashari A, Zahediyan A, Sahebi MA. The effect of neoadjuvant chemoradiotherapy on airway colonization and postoperative respiratory complications in patients undergoing esophagectomy for esophageal cancer. *Interact Cardiovasc Thorac Surg*. 2012;14(6):725-728. DOI:10.1093/icvts/ivs009
8. Bosch DJ, Muijs CT, Mul VEM, et al. Impact of neoadjuvant chemoradiotherapy on postoperative course after curative-intent transthoracic esophagectomy in esophageal cancer patients. *Ann Surg Oncol*. 2014;21(2):605-611. DOI:10.1245/s10434-013-3316-8
9. Deng J, Wang C, Xiang M, Liu F, Liu Y, Zhao K. Meta-analysis of postoperative efficacy in patients receiving chemoradiotherapy followed by surgery for resectable esophageal carcinoma. *Diagn Pathol*. 2014;9(1):1-8. DOI:10.1186/1746-1596-9-151
10. GebSKI V, Burmeister B, Smithers BM, Foo K, Zalberg J, Simes J. Survival benefits from neoadjuvant chemoradiotherapy or chemotherapy in esophageal carcinoma: a meta-analysis. *Lancet Oncol*. 2007;8(3):226-234. DOI:10.1016/S1470-2045(07)70039-6
11. Greer S, Goodney P, Sutton J. Neoadjuvant chemoradiotherapy for esophageal carcinoma: A meta-analysis. *Surgery*. 2005;137(2):172-177. DOI: 10.1016/j.surg.2004.06.033
12. Urschel JD, Vasan H. A meta-analysis of randomized controlled trials that compared neoadjuvant chemoradiotherapy and surgery to surgery alone for resectable esophageal cancer. *Am J Surg*. 2003;185(6):538-543. DOI:10.1016/S0002-9610(03)00066-7
13. Malthaner R, Wong RKS, Spithoff K. Preoperative or postoperative therapy for resectable esophageal cancer: An updated practice guideline. *Clin Oncol*. 2010;22(4):250-256. DOI:10.1016/j.clon.2010.02.005
14. van Hagen P, Hulshof MCCM, van Lanschot JJB, et al. Preoperative chemoradiotherapy for esophageal or junctional cancer. *N Engl J Med*. 2012;366(22):2074-2084. DOI:10.1056/nejmoa1112088
15. Fiorica F, Di Bona D, Schepis F, et al. Preoperative chemoradiotherapy for esophageal cancer: A systematic review and meta-analysis. *Gut*. 2004;53(7):925-930. DOI:10.1136/gut.2003.025080
16. Merritt RE, Whyte RI, D'Arcy NT, Hoang CD, Shrager JB. Morbidity and mortality after esophagectomy following neoadjuvant chemoradiation. *Ann Thorac Surg*. 2011;92(6):2034-2040. DOI:10.1016/j.athoracsur.2011.05.121
17. Low DE, Kuppasamy M, Hashimoto Y, Traverso LW. Comparing complications of esophagectomy and pancreaticoduodenectomy and potential impact on hospital systems utilizing the accordion severity grading system. *J Gastrointest Surg*. 2010;14(11):1646-1652. DOI:10.1007/s11605-010-1325-5
18. Strasberg SM, Linehan DC, Hawkins WG. The accordion severity grading system of surgical complications. *Ann Surg*. 2009;250(2):177-186. DOI:10.1097/SLA.0b013e3181afde41
19. Strasberg SM, Hall BL. Postoperative morbidity index: a quantitative measure of severity of postoperative complications. *J Am Coll Surg*. 2011;213(5):616-626. DOI:10.1016/j.jamcollsurg.2011.07.019

20. Slankamenac K, Graf R, Barkun J, Puhan MA, Clavien PA. The comprehensive complication index: A novel continuous scale to measure surgical morbidity. *Ann Surg.* 2013;258(1):1-7. DOI:10.1097/SLA.0b013e318296c732
21. Mazeh H, Cohen O, Mizrahi I, et al. Prospective validation of a surgical complications grading system in a cohort of 2114 patients. *J Surg Res.* 2014;188(1):30-36. DOI:10.1016/j.jss.2013.12.004
22. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: A new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg.* 2004;240(2):205-213. DOI:10.1097/01.sla.0000133083.54934.ae
23. Slaman AE, Lagarde SM, Gisbertz SS, Van Berge Henegouwen MI. A quantified scoring system for postoperative complication severity compared to the Clavien-Dindo classification. *Dig Surg.* 2015;32(5):361-366. doi:10.1159/000433608
24. Van Heijl M, Van Lanschot JJB, Koppert LB, et al. Neoadjuvant chemoradiation followed by surgery versus surgery alone for patients with adenocarcinoma or squamous cell carcinoma of the esophagus (CROSS). *BMC Surg.* 2008;8(21). DOI:10.1186/1471-2482-8-21
25. Common Terminology Criteria for Adverse Events (CTCAE). U.S. Department of Health and Human Services. National Institutes of Health. National Cancer Institute. V4.03; June 14, 2010.
26. Bruce J, Krukowski ZH, Al-Khairi G, Russell EM, Park KGM. Systematic review of the definition and measurement of anastomotic leak after gastrointestinal surgery. *Br J Surg.* 2001;88(9):1157-1168. DOI:10.1046/j.0007-1323.2001.01829.x
27. Slankamenac K, Graf R, Puhan MA, Clavien PA. Perception of surgical complications among patients, nurses and physicians: A prospective cross-sectional survey. *Patient Saf Surg.* 2011;5(1):1-8. DOI:10.1186/1754-9493-5-30
28. Golder S, Loke YK. Sensitivity and precision of adverse effects search filters in MEDLINE and EMBASE: A case study of fractures with thiazolidinediones. *Health Info Libr J.* 2012;29(1):28-38. DOI:10.1111/j.1471-1842.2011.00972.x
29. Papanikolaou PN, Christidi GD, Ioannidis JPA. Comparison of evidence on harms of medical interventions in randomized and nonrandomized studies. *Cmaj.* 2006;174(5):635-641. DOI:10.1503/cmaj.050873
30. Vandembroucke JP. When are observational studies as credible as randomised trials? *Lancet.* 2004;363(9422):1728-1731. DOI:10.1016/S0140-6736(04)16261-2
31. Low D, Alderson D, Ceconello I, et al. International consensus on standardization of data collection for complications associated with esophagectomy: Esophagectomy Complications Consensus Group (ECCG). *Ann Surg.* 2015;262(2):286-294. DOI: 10.1097/SLA.000000000000109
32. Morita M, Masuda T, Okada S, et al. Preoperative chemoradiotherapy for esophageal cancer: Factors associated with clinical response and postoperative complications. *Anticancer Res.* 2009;29(7):2555-2562.

APPENDIX

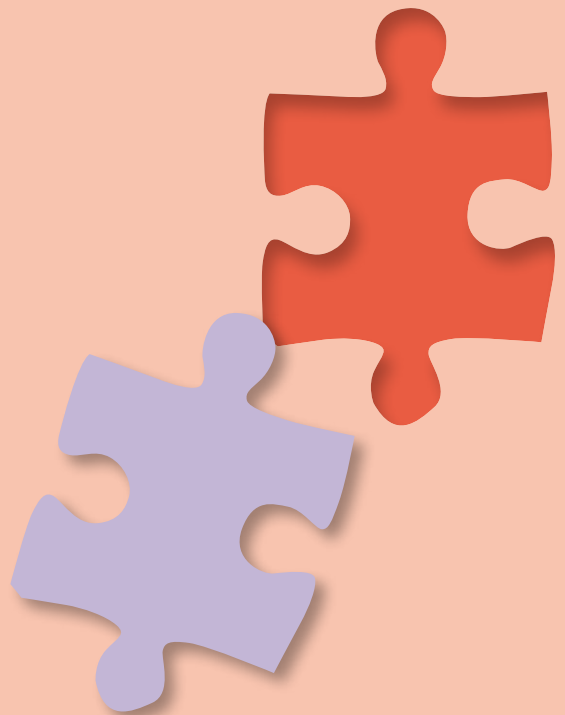
The Clavien–Dindo Classification²²

Grade	Description
Grade 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 anti-emetics, anti-pyretics, analgetics, diuretics, electrolytes, and physiotherapy. This grade also includes wound infections opened at the bedside.
Grade II	Requiring pharmacological treatment with drugs other than such allowed for grade I complications Blood transfusions and total parenteral nutrition are also included.
Grade III IIIa IIIb	Requiring surgical, endoscopic or radiological intervention. IIIa Intervention not under general anesthesia. IIIb Intervention under general anesthesia.
Grade IV IVa IVb	Life-threatening complication (including CNS complications)* requiring IC/ICU management. IVa Single organ dysfunction (including dialysis). IVb Multi-organ dysfunction.
Grade V	Death of a patient.
Suffix "d"	If the patient suffers from a complication at the time of discharge, the suffix "d" (for "disability") is added to the respective grade of complication. This label indicates the need for a follow-up to fully evaluate the complication.



PART II

The influence of different surgical techniques on complications after esophagectomy for cancer





CHAPTER 5

Propensity-score-matched analysis comparing minimally invasive Ivor Lewis versus minimally invasive McKeown esophagectomy

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ABSTRACT

Introduction: Totally minimally invasive esophagectomy (TMIE) is increasingly used for treatment of patients with esophageal carcinoma. However, it is currently unknown whether McKeown TMIE or Ivor Lewis TMIE should be preferred for patients in whom both procedures are oncological feasible.

Methods: The study was performed in 4 high-volume Dutch esophageal cancer centers using data of patients between November 2009 and April 2017. Prospectively collected data from consecutive patients with esophageal cancer localized in the distal esophagus or gastroesophageal junction undergoing McKeown TMIE or Ivor Lewis TMIE were included. Patients were propensity-score-matched for age, body mass index, sex, American Society of Anesthesiologists classification, Charlson Comorbidity Index, tumor type, tumor location, clinical stage, neoadjuvant treatment, and hospital of surgery. The primary outcome parameter was anastomotic leakage requiring reintervention or reoperation. Secondary outcome parameters were: operation characteristics, pathology results, complications, reinterventions, reoperations, length of stay, and mortality.

Results: Of the 787 included patients, 420 remained after matching. The incidence of anastomotic leakage requiring reintervention or reoperation was 23.3% after McKeown TMIE versus 12.4% after Ivor Lewis TMIE ($P = .003$). Ivor Lewis TMIE was significantly associated with a lower incidence of pulmonary complications (46.7 versus 31.9%), recurrent laryngeal nerve palsy (9.5 versus 0.5%), reoperations (18.6 versus 11.0%), 90-day mortality (7.1 versus 2.9%), shorter median intensive care unit length of stay (2 days versus 1 day) and shorter median hospital length of stay (12 versus 11 days), $P < .05$. R0 resection rate was similar between the groups. The median number of examined lymph nodes was 21 after McKeown TMIE and 25 after Ivor Lewis TMIE ($P < .001$).

Conclusions: Ivor Lewis TMIE is associated with a lower incidence of anastomotic leakage, 90-day mortality and other postoperative morbidity compared to McKeown TMIE in patients in whom both procedures are oncological feasible.

INTRODUCTION

Totally minimally invasive esophagectomy (TMIE) is increasingly used in the treatment of patients with esophageal carcinoma.¹ TMIE has been shown to reduce pulmonary complications, postoperative pain, and hospital length of stay compared to open esophagectomy, without compromising oncological safety.^{2,3}

There are several surgical approaches for TMIE: the Orringer procedure (laparoscopic transhiatal with cervical anastomosis), the McKeown procedure (thoracolaparoscopic with cervical anastomosis) and the Ivor Lewis procedure (thoracolaparoscopic with intrathoracic anastomosis).⁴⁻⁶ Transhiatal TMIE is currently not favored because no adequate thoracic lymph node dissection can be performed, which might compromise survival in selected patients.^{1,7} For patients with resectable esophageal carcinoma between the level of the carina and the gastroesophageal junction, both a McKeown TMIE and an Ivor Lewis TMIE esophagectomy are considered feasible and oncological appropriate. It is, however, currently unknown whether McKeown TMIE or Ivor Lewis TMIE is associated with lower postoperative morbidity.

A recent review and meta-analysis concluded that no randomized controlled trials, and only 5 comparative cohort studies, have been published comparing McKeown TMIE with Ivor Lewis TMIE.⁸ In addition, these 5 studies were single-center studies, included a limited number of patients, all studies were retrospective and none of the studies corrected for case-mix parameters.

Therefore, the aim of the present study was to compare postoperative morbidity in a multicenter setting, including case-mix correction by propensity score matching, for patients who had distal esophageal or gastroesophageal junction carcinoma and were undergoing McKeown TMIE or Ivor Lewis TMIE.

METHODS

Study Setting

This retrospective cohort study with prospectively collected data included patients undergoing McKeown TMIE and Ivor Lewis TMIE in 4 Dutch hospitals. All centers are regional referral centers for esophageal cancer surgery and perform at least 40 TMIEs per year. In addition, all centers experienced a transition from McKeown TMIE to Ivor Lewis TMIE as the preferred surgical procedure for patients with esophageal cancer during the study period. In all hospitals,

perioperative care pathways were implemented before the start of this study. In 3 out of the 4 hospitals, all operated patients went to the intensive care unit (ICU) for at least 1 day, and in 1 of the hospitals, patients were only transferred to the ICU on indication.

Patients

Consecutive patients with malignant tumors of the esophagus or gastroesophageal junction (cT1b–4a, N0–3, M0) undergoing elective, curative TMIE between November 2009 and April 2017 were included in this study. All patients with carcinoma of the proximal or middle esophagus and patients with carcinoma of the gastric cardia were excluded, to ensure that only patients in whom both McKeown TMIE and Ivor Lewis TMIE were feasible were included. Curative resection after neoadjuvant chemoradiotherapy according to the CROSS scheme was the standard treatment in the Netherlands during the study period.⁹ In selected cases, neoadjuvant chemotherapy was administered. Patients receiving definitive chemoradiation therapy and a subsequent salvage procedure were excluded from this analysis.

Surgeons and operative technique

All patients were operated on by a dedicated esophageal surgical team. Most procedures were performed by 2 surgeons. All patients underwent TMIE including a laparoscopic lymph node dissection in a supine position and thoracoscopic lymph node dissection in a prone position. Anastomotic techniques in the Ivor Lewis TMIE group were fully mechanical circular end-to-side anastomosis or semi-mechanical linear side-to-side (S-S) anastomosis. In the McKeown TMIE group, anastomotic technique was hand-sewn end-to-end, end-to-side, or side-to-side, semi-mechanical side-to-side or stapled side-to-side.^{10,11} Pyloric drainage procedures were not routinely performed.

Case-mix and outcome parameters

Case-mix parameters were patient sex, age, body mass index (BMI), American Society of Anesthesiologists (ASA) score, Charlson Comorbidity Index, clinical tumor stage, tumor location, tumor histology, and neoadjuvant treatment.

The primary outcome parameter was anastomotic leakage requiring reintervention or reoperation. The Esophagectomy Complications Consensus Group (ECCG) definition of anastomotic leakage was used: a full-thickness gastrointestinal defect involving the esophagus, anastomosis, staple line, or conduit.¹² Anastomotic leakage was diagnosed by contrast computed tomography scan, endoscopy, drainage of ingested materials or gastric content into chest tubes or signs of anastomotic leakage during reoperation or autopsy. Anastomotic

leakage was graded according to the ECCG: type I (no reintervention or reoperation required), type II (reintervention but no reoperation), and type III (requiring reoperation).¹²

Secondary outcome parameters were conversion rate, operative time, chyle leakage, pulmonary complications, pneumonia, cardiac complications, jejunostomy-related complications, overall morbidity (defined as 'the combined incidence of all complications'), hospital length of stay (LOS), ICU length of stay, readmissions within 30 days, and 30-day, 90-day, and in-hospital mortality and textbook outcome. Outcome parameters are described in more detail in online appendix I. In addition, RO resection rate and the number of examined lymph nodes were recorded. Textbook outcome, a composite outcome parameter of an 'ideal outcome' in a patient, was used and this was scored if the outcome in a patient met the following criteria: radical (RO) resection, 15 or more resected lymph nodes, no perioperative complications, no reinterventions or reoperations, no complications of Clavien–Dindo grade III or higher, no ICU readmission, no hospital length of stay greater than 21 days, no hospital readmission less than 30 days, no mortality of less than 30 days and no in hospital mortality.^{13,14} Reinterventions were subdivided into radiologic and endoscopic reinterventions. Endoscopic reinterventions were defined as any endoscopic procedures used to treat anastomotic leakage.

Statistical methods

A propensity-score-matched analysis was performed to minimize selection bias. Propensity scores were calculated using logistic regression. All case-mix factors and the hospital of surgery were entered into the regression model with the operative technique (McKeown TMIE or Ivor Lewis TMIE) as the dependent variable. The cases were matched for their propensity scores using a matching ratio of 1:1 and a nearest neighbor matching protocol with a caliper of 0.2. Cases were not reusable after matching.¹⁵

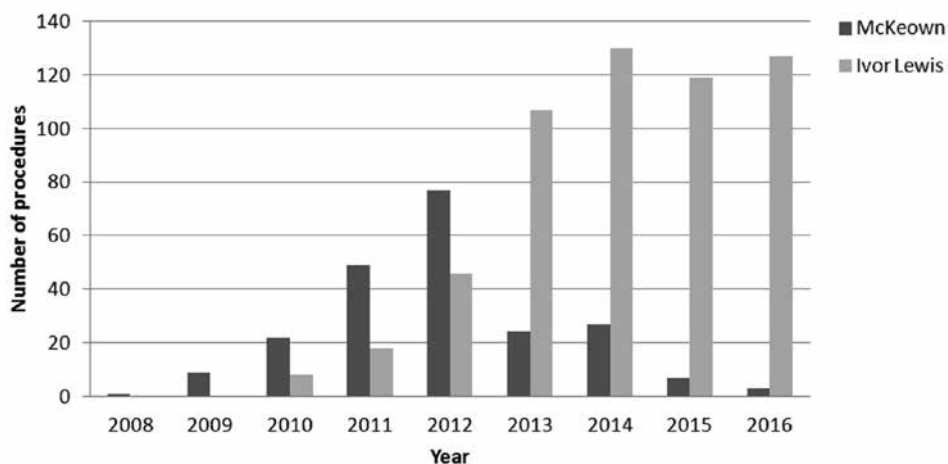
Outcome parameters were analyzed using IBM SPSS for Windows (version 22.0, Armonk, NY). The Chi-square test or Fisher's exact test was used when appropriate to evaluate whether differences in binomial variables were statistically significant. For continuous variables that did not display a normal distribution, the Mann–Whitney U test was used. Differences were considered statistically significant when the *P* value was less than .05.

RESULTS

Patient characteristics

Data from 787 consecutive patients were analyzed. The use of TMIE increased over time and a substantially higher proportion of patients underwent Ivor Lewis TMIE during later periods (Fig. 1). Before matching, significant differences between patients undergoing McKeown TMIE and Ivor Lewis TMIE were present for tumor type, tumor location, clinical stage, Charlson Comorbidity Index, and the hospital of surgery. After propensity score matching, 420 patients remained to be evaluated (210 in each group). After matching, only tumor type remained significantly different between the McKeown TMIE and Ivor Lewis TMIE groups, although the difference between the groups was reduced by the matching procedure. Details of patients' characteristics before and after matching are shown in Table 1.

Figure 1. Number of totally minimally invasive esophagectomies performed



Postoperative complications

Unmatched and matched outcome parameters are shown in Table 2. After matching, the incidence of anastomotic leakage requiring reintervention or reoperation was 23.3% in the McKeown TMIE group and 12.4% in the Ivor Lewis TMIE group ($P = .003$). No association between tumor type and anastomotic leakage requiring reintervention or reoperation was observed. The difference in anastomotic leakage between the groups persisted in a post-hoc binary logistic regression analysis that corrected for tumor type ($P = .004$). An additional post-hoc binary regression analysis showed that the difference in anastomotic leakage requiring reintervention or reoperation persisted after

correcting for year of surgery ($P = .018$). The total incidence of anastomotic leakage was 28.1% after McKeown TMIE and 13.8% after Ivor Lewis TMIE ($P < .001$). The incidence of pulmonary complications was 46.7% after McKeown TMIE and 31.9% after Ivor Lewis TMIE ($P = .002$). Atrial fibrillation occurred in 25.7% in the McKeown TMIE group and in 16.7% in the Ivor Lewis TMIE group ($P = .023$). The incidence of recurrent laryngeal nerve palsy was 9.5% after McKeown TMIE and 0.5% after Ivor Lewis TMIE ($P < .001$, Table 2).

Other outcome parameters

After matching, median operative time was 349 minutes for McKeown TMIE compared to 410 minutes for Ivor Lewis TMIE ($P < .001$). The reoperation rate was 18.6% in the McKeown TMIE group and 11.0% in the Ivor Lewis TMIE group ($P = .028$). Median ICU length of stay was 2 days after McKeown TMIE compared to 1 day after Ivor Lewis TMIE ($P < .001$) and median hospital length of stay was 12 days in the McKeown TMIE group and 11 days in the Ivor Lewis TMIE group ($P = .046$). The 30-day, 90-day, and in hospital mortality rates were 2.4, 7.1, and 5.2%, respectively, after McKeown TMIE compared to 1.0, 2.9, and 1.4%, respectively, after Ivor Lewis TMIE ($P = .253$, $P = .044$, and $P = .053$, respectively). The median number of examined lymph nodes was 21 after McKeown TMIE and 26 after Ivor Lewis TMIE ($P < .001$). The overall RO resection rate was 96.1% with no significant difference between groups. No other secondary outcome parameters were significantly different between groups (Table 2).

DISCUSSION

In this study, Ivor Lewis TMIE was associated with a significantly lower incidence of anastomotic leakage requiring reintervention or reoperation compared to McKeown TMIE. The widespread belief that anastomotic leakage after cervical anastomosis is less severe and can be solved with drainage through the cervical wound only is therefore not in line with the findings of the present study. In addition, Ivor Lewis TMIE was significantly associated with a lower incidence of pulmonary complications, recurrent laryngeal nerve palsy, atrial fibrillation, reoperations, 90-day mortality, and shorter ICU and hospital length of stay compared to McKeown TMIE. The strength of this study is that it is the first study to perform a multicenter, propensity-score-matched analysis comparing Ivor Lewis TMIE with McKeown TMIE in a substantial number of patients. Because only patients with tumors in the distal esophagus and gastroesophageal junction were included, the study population is more homogeneous because both Ivor Lewis TMIE and McKeown TMIE are both feasible and oncologically

Table 1. Comparison of case-mix characteristics for the overall population, and for those undergoing McKeown TMIE versus Ivor Lewis TMIE, before and after propensity score matching

Variables	All patients (n=787)	Before matching			After matching		
		McKeown (n=226)	Ivor Lewis (n=561)	P value	McKeown (n=210)	Ivor Lewis (n=210)	P value
Hospital				<.001			.974
1	185 (23.5)	16 (7.1)	169 (30.1)		16 (7.6)	15 (7.1)	
2	107 (13.6)	40 (17.7)	67 (11.9)		39 (18.6)	41 (19.5)	
3	177 (22.5)	18 (8.0)	159 (28.3)		18 (8.6)	20 (9.5)	
4	318 (40.4)	152 (67.3)	166 (29.6)		137 (65.2)	134 (63.8)	
Age	65.0 (12.4)	64.4 (13.6)	65.0 (12.2)	.359	64.5 (13.7)	64.9 (12.9)	.696
BMI	25.5 (5.4)	25.5 (5.3)	25.6 (5.4)	.259	25.6 (5.3)	25.3 (5.5)	.982
Sex				.052			.372
Male	649 (82.5)	177 (78.3)	472 (84.1)		169 (80.5)	176 (83.8)	
Female	138 (17.5)	49 (21.7)	89 (15.9)		41 (19.5)	34 (16.2)	
ASA classification				.277			.876
1	122 (15.5)	40 (17.7)	82 (14.6)		39 (18.6)	39 (18.6)	
2	492 (62.5)	146 (64.6)	346 (61.7)		132 (62.9)	130 (61.9)	
3	169 (21.5)	39 (17.3)	130 (23.2)		38 (18.1)	40 (19.0)	
4	4 (0.5)	1 (0.4)	3 (0.5)		1 (0.5)	1 (0.5)	
Charlson comorbidity index				<.001			.711
0	294 (37.4)	56 (24.8)	238 (42.4)		56 (26.7)	56 (26.7)	
1	164 (20.8)	44 (19.5)	120 (21.4)		36 (17.1)	36 (17.1)	
2	114 (14.5)	52 (23.0)	62 (11.1)		45 (21.4)	39 (18.6)	
3	133 (16.9)	48 (21.2)	85 (15.2)		47 (22.4)	49 (23.3)	
4	63 (8.0)	21 (9.3)	42 (7.5)		21 (10.0)	24 (11.4)	

5		16 (2.0)	5 (2.2)	11 (2.0)	5 (2.4)	6 (2.9)
6		2 (0.3)	0 (0)	2 (0.4)	0 (0)	0 (0)
7		1 (0.1)	0 (0)	1 (0.2)	0 (0)	0 (0)
	Tumor type				<.001	.010
	Adenocarcinoma	667 (84.8)	169 (74.8)	498 (88.8)	161 (76.7)	183 (87.1)
	Squamous cell carcinoma	98 (12.5)	45 (19.9)	53 (9.4)	38 (18.1)	24 (11.4)
	Other	22 (2.8)	12 (5.3)	10 (1.8)	11 (5.2)	3 (1.4)
	Tumor location				<.001	.721
	Distal	655 (83.2)	210 (92.9)	445 (79.3)	194 (92.4)	192 (91.4)
	Gastro-esophageal junction	132 (16.8)	16 (7.1)	116 (20.7)	16 (7.6)	18 (8.6)
	Clinical stage				<.001	.402
	I	150 (19.1)	25 (11.1)	125 (22.3)	25 (11.9)	26 (12.4)
	II	297 (37.7)	68 (30.1)	229 (40.8)	66 (31.4)	76 (36.2)
	III	340 (43.2)	133 (58.8)	207 (36.9)	119 (56.7)	108 (51.4)
	Neoadjuvant treatment	736 (93.5)	211 (93.4)	525 (93.6)	195 (92.9)	194 (92.4)
					.910	.852

Continuous parameters are displayed as median (interquartile range). CDC: Clavien Dindo classification, RO: radical resection, ICU: intensive care unit

safe in these patients. This resulted in a lower risk of selection bias than other studies that have been published on this subject.¹⁶⁻²⁰

A limitation of this study is that a difference in tumor type persisted between the groups after propensity score matching. However, a post-hoc regression analysis showed that this factor did not explain the differences observed in this study. In addition, most Ivor Lewis patients were operated on in a later time period (Fig. 1). To investigate whether it was likely that the outcomes of our study could be explained by other factors that changed over time (e.g., perioperative care), we performed an additional regression analysis, correcting for year of surgery for our primary outcome parameter. Although the observed difference between the groups was smaller in this analysis, the difference in anastomotic leakage requiring reintervention or reoperation remained significantly different and it is therefore unlikely that the primary findings of our study are explained by improving general care only.

Another limitation is the heterogeneous anastomotic techniques that are used in this study. The fact that no robust data are currently available regarding the association of the anastomotic technique (e.g., hand-sewn versus stapled or different types of anastomotic configuration) with differences in outcome led us to believe that the heterogeneous techniques probably do not contribute to the results of this study. Future research will have to clarify whether differences in anastomotic techniques are associated with differences in outcome after minimally invasive esophagectomy. Furthermore, a large proportion of the patients were included in one of the participating centers. Although the study was matched for the hospital in which the operation was performed and this is unlikely to have influenced the results, it does affect the general strength of this being a multicenter analysis.

Another concern is the occurrence of learning-curve bias, because it has been reported that outcomes of esophagectomy improve as surgical proficiency is gained.^{21,22} The time periods in which patients undergoing McKeown TMIE (mainly earlier period) and Ivor Lewis TMIE (mainly later period) were included were also characterized by surgical learning curves for McKeown TMIE and Ivor Lewis TMIE. Although patients were included during both the learning curves of McKeown TMIE and Ivor Lewis TMIE, it is unfortunately not possible to assess whether learning-curve effects were similar in both treatment groups. Steps that had been learned during the implementation of McKeown TMIE were probably also applied in Ivor Lewis TMIE and this might have positively affected the outcome in the Ivor Lewis TMIE group. However, large learning-curve effects have also been reported for Ivor Lewis TMIE and we therefore

Table 2. Comparison of outcome parameters between McKeown and Ivor Lewis esophagectomy

Variables	Before matching			After matching		
	McKeown (n=226)	Ivor Lewis (n=561)	P value	McKeown (m=210)	Ivor Lewis (n=210)	P value
Conversion abdomen	5 (2.2)	6 (1.1)	.217	5 (2.4)	1 (0.5)	.215
Conversion thorax	0 (0.0)	14 (2.5)	.014	0 (0)	3 (1.4)	.248
Operating time (min)	330 (72)	286.5 (138)	<.001	349.0 (114)	410.5 (216)	<.001
Anastomatic leakage type ≥2	50 (22.1)	70 (12.5)	.001	49 (23.3)	26 (12.4)	.003
Anastomatic leakage	60 (26.5)	81 (14.4)	<.001	59 (28.1)	29 (13.8)	<.001
Type I	10 (4.4)	11 (2.0)	.052	10 (4.8)	3 (1.4)	.087
Type II	23 (10.2)	36 (6.4)	.070	23 (11.0)	13 (6.2)	.081
Type III	27 (11.9)	34 (6.1)	.005	26 (12.4)	13 (6.2)	.029
Chyle leakage	30 (13.3)	49 (8.7)	.055	27 (12.9)	19 (9.0)	.211
Pulmonary complications	102 (45.1)	230 (41.0)	.288	98 (46.7)	67 (31.9)	.002
Pneumonia	56 (24.8)	156 (27.8)	.386	55 (26.2)	40 (19.0)	.080
Cardiac complications	61 (27.0)	117 (20.9)	.063	56 (26.7)	41 (19.5)	.082
Atrial fibrillation	59 (26.1)	96 (17.1)	.004	54 (25.7)	35 (16.7)	.023
Myocardial infarction	23 (10.2)	23 (4.1)	.001	19 (9.0)	12 (5.7)	.191
Asystole	25 (11.1)	25 (4.5)	.001	21 (10.0)	13 (6.2)	.152
Recurrent laryngeal nerve palsy	20 (9.0)	3 (0.5)	<.001	20 (9.5)	1 (0.5)	<.001
Overall complications	141 (62.4)	345 (61.5)	.816	134 (63.8)	117 (55.7)	.091
Major complications (CDC≥3)	58 (25.7)	187 (33.3)	.036	56 (26.7)	62 (29.5)	.515
Reoperation	40 (17.7)	88 (15.7)	.489	39 (18.6)	23 (11.0)	.028
Reintervention	58 (25.7)	161 (28.7)	.390	56 (26.7)	56 (26.7)	1.000
Radiologic	40 (17.7)	74 (13.2)	.104	39 (18.6)	34 (16.2)	.520
Endoscopic	22 (9.7)	48 (8.6)	.599	23 (11.0)	32 (15.2)	.193
RO resection	217 (96.0)	535 (95.4)	.688	201 (95.7)	199 (94.8)	.647
Examined lymph nodes	21 (16)	22 (11)	.082	21 (15)	26 (17)	<.001
ICU length of stay	2 (4)	1 (2)	.001	2 (4)	1 (2)	<.001
ICU readmission	50 (22.1)	100 (17.8)	.165	48 (22.9)	34 (16.2)	.085
Hospital length of stay	12 (14)	11 (10)	<.001	12 (18)	11 (9)	.046
Hospital readmission	37 (16.4)	83 (14.8)	.578	33 (15.7)	37 (17.6)	.600
Textbook outcome	98 (43.4)	264 (47.1)	.347	90 (42.9)	106 (50.5)	.118
Mortality						
In-hospital	11 (4.9)	17 (3.0)	.208	11 (5.2)	3 (1.4)	.053
30-day	5 (2.2)	13 (2.3)	.929	5 (2.4)	2 (1.0)	.253
90-day	16 (7.1)	25 (4.5)	.134	15 (7.1)	6 (2.9)	.044

Continuous parameters are presented as median (interquartile range). CDC Clavien–Dindo classification, ICU Intensive Care Unit

think it is unlikely that the findings of the present study can be solely explained by learning-curve bias.²³ In fact, the difference in anastomotic leakage incidence between McKeown TMIE and Ivor Lewis TMIE may be even larger than that demonstrated in the present study. This is supported by a post-hoc analysis showing that the incidence of anastomotic leakage in the Ivor Lewis TMIE group decreased from 12.7% in the first half of patients to 7.4% in the second half of patients. In contrast, no learning curve effect was found regarding anastomotic leakage in the McKeown TMIE group.

Median ICU length of stay and hospital length of stay were significantly shorter after Ivor Lewis TMIE compared to McKeown TMIE, which might be explained by the lower incidence of complications after Ivor Lewis TMIE. Postoperative mortality was also lower in the Ivor Lewis TMIE group and this was primarily caused by the relatively high incidence of in-hospital mortality in the McKeown TMIE group. Oncological R0 resection rate was high in both groups, but Ivor Lewis TMIE was associated with a higher number of retrieved lymph nodes. During this study period, the surgical extent and technique of the lymph node dissection was equal in both groups, and therefore this finding may reflect a learning curve for performing minimally invasive lymph node dissection or for the retrieval of lymph nodes in the resected specimen by the pathologist.

Five other studies have previously compared McKeown TMIE with Ivor Lewis TMIE.¹⁶⁻²⁰ A recent meta-analysis of these studies showed no significant difference in anastomotic leakage, but did find that Ivor Lewis TMIE was associated with a shorter hospital length of stay and less blood loss.⁸ The studies in this meta-analysis were heterogenic regarding the methodology and definitions used, which might explain why the outcome differs from the present study. However, the fact that findings in the present study are different from findings in previously published literature underlines that there is still uncertainty as to whether McKeown TMIE or Ivor Lewis TMIE should be the preferred surgical procedure for patients with resectable esophageal cancer.

Another important consideration is that there are no high-quality data regarding whether an intrathoracic anastomotic leakage is of equal severity as a cervical anastomotic leakage in terms of morbidity. It is therefore uncertain whether differences in anastomotic leakage should be assessed solely based on incidences of anastomotic leakage in comparative studies. Finally, data on long-term outcome parameters, survival, quality of life, and cost-effectiveness are lacking and these data are needed to fully justify a preferred TMIE technique. A randomized controlled ICAN trial, comparing McKeown TMIE with Ivor Lewis TMIE regarding anastomotic leakage, functional outcome, and

quality of life, is currently being conducted in the Netherlands.²⁴ The outcomes of this trial may further elucidate whether McKeown TMIE or Ivor Lewis TMIE should be preferred for patients with esophageal cancer.

CONCLUSIONS

Total minimally invasive Ivor Lewis esophagectomy was associated with lower postoperative morbidity and mortality than total minimally invasive McKeown esophagectomy for patients in whom both procedures are oncologically feasible. Results of a randomized controlled trial are warranted for level 1 evidence regarding whether total minimally invasive McKeown esophagectomy or Ivor Lewis esophagectomy should be preferred for patients with esophageal cancer.

References

1. Haverkamp L, Seesing MFJJ, Ruurda JP, et al. Worldwide trends in surgical techniques in the treatment of esophageal and gastroesophageal junction cancer. *Dis Esophagus*. 2016;00(00):1-7. DOI:10.1111/dote.12480
2. Biere SSAY, Van Berge Henegouwen MI, Maas KW, et al. Minimally invasive versus open esophagectomy for patients with esophageal cancer: A multicenter, open-label, randomised controlled trial. *Lancet*. 2012;379(9829):1887-1892. DOI: 10.1016/S0140-6736(12)60516-9
3. Dantoc MM, Cox MR, Eslick GD. Does minimally invasive esophagectomy (mie) provide for comparable oncologic outcomes to open techniques? A systematic review. *J Gastrointest Surg*. 2012;16(3):486-494. DOI:10.1007/s11605-011-1792-3
4. Orringer M. Transhiatal esophagectomy without thoracotomy for carcinoma of the thoracic esophagus. *Ann Surg*. 1984;200(3):282-288. DOI: 10.1097/00000658-198409000-0000
5. McKeown KC. Total three stage esophagectomy for cancer of the esophagus. *Br J Surg*. 1976;63(4):259-262. DOI:10.1002/bjs.1800630403
6. Lewis I. The surgical treatment of carcinoma of the esophagus with special reference to a new operation for growths of the middle third. *Br J Surg*. 1946;34(133):18-31. DOI:10.1002/bjs.18003413304
7. Omloo JMT, Lagarde SM, Hulscher JBF, et al. Extended transthoracic resection compared with limited transhiatal resection for adenocarcinoma of the mid/distal esophagus: Five-year survival of a randomized clinical trial. *Ann Surg*. 2007;246(6):992-1000. DOI:10.1097/SLA.0b013e31815c4037
8. van Workum F, Berkelmans GH, Klarenbeek BR, Nieuwenhuijzen GAP, Luyer MDP, Rosman C, McKeown K, Ivor Lewis totally minimally invasive esophagectomy for cancer of the esophagus and gastroesophageal junction: Systematic review and meta-analysis. *J Thorac Dis*. 2017;9:S826-S833. DOI:10.21037/jtd.2017.03.173
9. van Hagen P, Hulshof MCCM, van Lanschot JJB, et al. Preoperative chemoradiotherapy for esophageal or junctional cancer. *N Engl J Med*. 2012;366(22):2074-2084. DOI:10.1056/nejmoa1112088
10. Collard JM, Romagnoli R, Goncette L, Otte JB, Kestens PJ. Terminalized semimechanical side-to-side suture technique for cervical esophagogastrostomy. *Ann Thorac Surg*. 1998;65(3):814-817. DOI:10.1016/S0003-4975(97)01384-2
11. Iannettoni MD, Orringer MB, Marshall B, Iannettoni MD (2000) Eliminating the cervical esophagogastric anastomotic leak with a side-to-side stapled anastomosis. *J Thorac Cardiovasc Surg* 119:277-288. 2000;48109:277-288. DOI: 10.1016/S0022-5223(00)70183-8
12. Low D, Alderson D, Ceconello I, et al. International consensus on standardization of data collection for complications associated with esophagectomy: Esophagectomy Complications Consensus Group (ECCG). *Ann Surg*. 2015;262(2):286-294. DOI: 10.1097/SLA.0000000000001098
13. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: A new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg*. 2004;240(2):205-213. DOI:10.1097/01.sla.0000133083.54934.ae
14. Busweiler LAD, Schouwenburg MG, van Berge Henegouwen MI, et al. Textbook outcome as a composite measure in esophagogastric cancer surgery. *Br J Surg*. 2017;104(6):742-750. DOI:10.1002/bjs.10486
15. Austin PC. Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples. *Stat Med*. 2009;28(25):3083-3107. DOI:10.1002/sim.3697
16. Nguyen NT, Hinojosa MW, Smith BR, Chang KJ, Gray J, Hoyt D. Minimally invasive esophagectomy lessons learned from 104 operations. *Ann Surg*. 2008;248(6):1081-1091. DOI:10.1097/SLA.0b013e31818b72b5
17. Rajan PS, Vaithiswaran V, Rajapandian S, Senthilnathan P, Praveenraj P, Palanivelu C. Minimally invasive esophagectomy for carcinoma esophagus - Approaches and options in a high volume tertiary center. *J Indian Med Assoc*. 2010;108(10):642-644.
18. Luketich JD, Pennathur A, Awais O, et al. Outcomes after minimally invasive esophagectomy: review over 1000 patients. *Ann Surg*. 2012;256(1):95-103. DOI: 10.1097/SLA.0b013e3182590603
19. Hao Z, Zhenya S, Lei W. Esophageal-Gastric anastomosis in radical resection of esophageal cancer under thoracoscopy combined with laparoscopy. *J Coll Physicians Surg Pakistan*. 2014;24(10):754-756. DOI:10.2014/JCPS.754756

20. Zhai C, Liu Y, Li W, et al. A comparison of short-term outcomes between Ivor-Lewis and McKeown minimally invasive esophagectomy. *J Thorac Dis.* 2015;7(12):2352-2358. DOI: 10.3978/j.issn.2072-1439.2015.12.15
21. Mackenzie H, Markar SR, Askari A, Ni M, Faiz O, Hanna GB. National proficiency-gain curves for minimally invasive gastrointestinal cancer surgery. *Br J Surg.* 2016;103(1):88-96. DOI:10.1002/bjs.9963
22. Markar SR, Mackenzie H, Lagergren P, Hanna GB, Lagergren J. Surgical proficiency gain and survival after esophagectomy for cancer. *J Clin Oncol.* 2016;34(13):1528-1536. DOI:10.1200/JCO.2015.65.2875
23. Van Workum F, Stenstra MHBC, Berkelmans GHK, et al. learning curve and associated morbidity of minimally invasive esophagectomy: A retrospective multicenter study. *Ann Surg.* 2019;269(1):88-94. DOI:10.1097/SLA.0000000000002469
24. van Workum F, Bouwense SAW, Luyer MDP, et al. Intrathoracic versus cervical anastomosis after minimally invasive esophagectomy for esophageal cancer: study protocol of the ICAN randomized controlled trial. *Trials.* 2016;17(1):505. DOI: 10.1186/s13063-016-1636-2

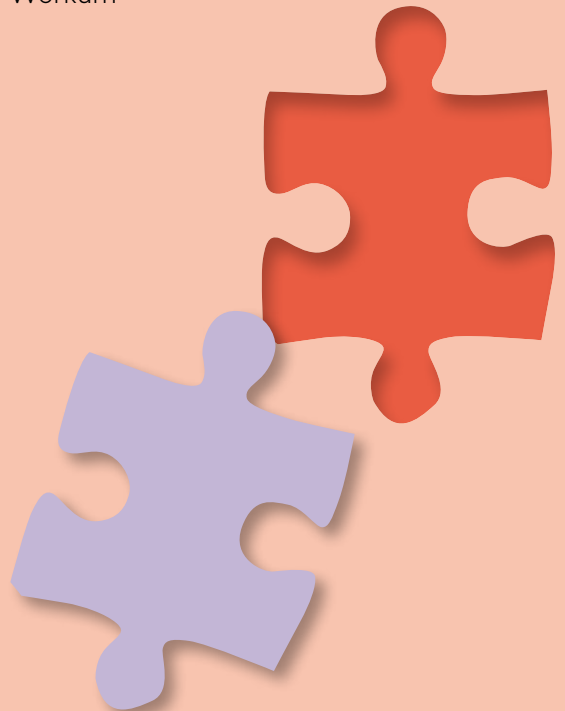


CHAPTER 6

Outcomes of patients with anastomotic leakage after transhiatal, McKeown or Ivor Lewis esophagectomy: a nationwide cohort study

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ABSTRACT

Background: Anastomotic leakage has a great impact on clinical outcomes after esophagectomy. Variations in anastomotic leakage severity between different types of esophagectomy (i.e., transhiatal, McKeown and Ivor Lewis) have never been studied in terms of postoperative mortality and morbidity.

Methods: All esophageal cancer patients with anastomotic leakage after transhiatal, McKeown or Ivor Lewis esophagectomy between 2011 and 2019 were selected from the Dutch Upper Gastrointestinal Cancer Audit (DUCA) registry. The primary outcome was 30-day/in-hospital mortality. Secondary outcomes included postoperative complications, reoperation and ICU readmission rate.

Results: Data from 1030 patients with anastomotic leakage after transhiatal (n=287), McKeown (n=397) and Ivor Lewis esophagectomy (n=346) were evaluated. The 30-day/in-hospital mortality rate was 4.5% in patients with leakage after transhiatal, 8.1% after McKeown and 8.1% after Ivor Lewis esophagectomy ($P = .139$). After correction for confounders, leakage after transhiatal resection was associated with lower mortality (OR 0.152–0.699, $P = .004$), but mortality after McKeown and Ivor Lewis esophagectomy was similar. Reoperation rate was 24.0% after transhiatal, 40.6% after McKeown and 41.3% after Ivor Lewis esophagectomy ($P < .001$). ICU readmission rate was 24.0% after transhiatal, 37.8% after McKeown and 43.4% after Ivor Lewis esophagectomy ($P < .001$).

Conclusion: This study in patients with anastomotic leakage confirms a strong association between severity of clinical consequences and different types of esophagectomy. It supports the hypothesis that cervical leakage is generally less severe than intrathoracic leakage. The clinical impact of anastomotic leakage should be taken into account, in addition to its incidence, when different types of esophagectomy are compared by clinicians or researchers.

INTRODUCTION

The incidence of esophageal cancer is increasing and it is the sixth most common cause of cancer-related death worldwide.¹ Approximately 30% of esophageal cancer patients will undergo an esophagectomy with curative intent.^{2,3} The most commonly performed procedures are transhiatal esophagectomy (transhiatal procedure with abdominal gastric mobilization, transhiatal dissection of the lower esophagus and cervical anastomosis), McKeown esophagectomy (three-stage esophagectomy with abdominal gastric mobilization, transthoracic esophageal dissection and cervical anastomosis) and Ivor Lewis esophagectomy (two-stage esophagectomy with abdominal gastric mobilization, transthoracic esophageal dissection and intrathoracic anastomosis).⁴

Anastomotic leakage is a severe complication and is associated with an increased mortality rate (2-12%), a prolonged hospital length of stay, a decreased quality of life and higher costs.⁵⁻⁷ Anastomotic leakage severity can be classified according to how the leakage was treated, but this does not necessarily reflect its clinical severity, which can be measured by parameters such as mortality and intensive care unit (ICU) readmission rate.⁸ Although it is often claimed that cervical anastomotic leakage is less severe than intrathoracic anastomotic leakage, there are insufficient data to support this.⁹ On the contrary, severe intrathoracic consequences of cervical anastomotic leakage have been described.¹⁰⁻¹³ In addition, there might be a difference in severity of anastomotic leakage between a transthoracic and transhiatal esophagectomy with cervical anastomosis because thoracic dissection might facilitate intrathoracic manifestations of cervical anastomotic leakage ("chute hypothesis"). Although this is supported by a study including 79 patients with cervical anastomotic leakage after a transthoracic versus transhiatal approach, patients undergoing esophagectomy with intrathoracic anastomosis were not included in that study.¹⁰

One study comparing mortality rates in patients with anastomotic leakage after transhiatal, McKeown and Ivor Lewis esophagectomy did not find any significant differences.¹⁴ However, that study only included a total of 119 leakage patients and therefore differences in anastomotic leakage severity between common types of esophagectomy remains to be studied in a large patient cohort.

The aim of this study was to investigate on a population level whether the clinical outcomes (severity) of anastomotic leakage varied in patients who had undergone different types of esophagectomy.

METHODS

Study setting

Data were retrieved from the Dutch Upper Gastrointestinal Cancer Audit (DUCA). This is a national clinical registry that includes all surgically treated patients in the Netherlands with esophageal, junctional or gastric cancer. Participation in the DUCA is obligatory and all hospitals in the Netherlands performing esophagogastric surgery for cancer are included. Case ascertainment for the DUCA was estimated at 97.8% of all primary esophageal and junction cancer resections, as registered in the Netherlands Cancer Registry.¹⁵ The study protocol was approved by the DUCA scientific committee and no ethical approval or informed consent was required for this study under Dutch law.

Patients

Our primary aim was to investigate the severity of anastomotic leakage after different types of esophagectomy in terms of postoperative mortality and morbidity. All patients with anastomotic leakage after primary esophagectomy with gastric tube reconstruction for intrathoracic esophageal cancer or junctional cancer between 2011 and 2019 were included. General outcome data for this cohort (i.e., including patients without anastomotic leakage) have previously been described.^{16,17} In the Netherlands, different types of esophagectomy are performed depending on the site of the lesion, patient comorbidity and surgeon preference. During the study period, esophagectomies for esophageal or junctional cancer were only performed in high-volume hospitals (>20 esophagectomies per year).

In this study, patients undergoing open or minimally invasive transhiatal esophagectomy or esophagectomy with two-field lymphadenectomy (McKeown or Ivor Lewis) were included. Regarding junctional tumors, patients with a Siewert I or II tumor who underwent an esophagectomy were included in this study. Patients younger than 18 years, patients undergoing palliative or emergency resection and patients with missing data regarding the inclusion or exclusion criteria were excluded.

Preoperative workup was in accordance with local protocols and oncological staging was performed by using the TNM classification. Only patients with anastomotic leakage were selected. Anastomotic leakage was defined as 'a full-thickness gastrointestinal defect involving the esophagus, anastomosis, staple line, or conduit irrespective of presentation or method of identification'.⁸

Outcome parameters and definitions

The primary outcome parameter was 30-day and/or in-hospital mortality (defined as: mortality from any cause during admission for esophagectomy or within 30-days after esophagectomy).

Secondary outcome parameters were pulmonary complications, cardiac complications, gastric tube necrosis (defined as a distinct outcome parameter), chyle leakage, reintervention rate (radiologic, endoscopic or surgical), reoperation rate (defined as: an operation for any complication during admission for esophagectomy) and ICU and hospital length of stay. In addition, a composite endpoint of reoperation and/or ICU readmission and/or 30-day/in-hospital mortality was chosen after discussions in the study team, because it reflects patients with severe clinical consequences of anastomotic leakage and does not only take into account the treatment given (as is the case for the ECCG and Clavien–Dindo classifications). Since 2015, postoperative anastomotic leakage and complications were additionally scored according to the ECCG and Clavien–Dindo classifications.^{8,18}

Statistical methods

Patients with anastomotic leakage were selected and divided into 3 groups according the type of surgery (transhiatal, McKeown and Ivor Lewis esophagectomy) and compared for baseline and outcome parameters. To evaluate differences in baseline characteristics between the three groups, the Chi-square test was used for binominal and ordinal variables. For continuous variables that did not fit a normal distribution, the Kruskal–Wallis test was used. Binomial logistic regression analysis was performed to evaluate the effect of the type of surgery on binomial outcome parameters both with and without adjustment for potential confounding variables. Potential confounders were selected based on clinical relevance, previous literature or mechanical arguments according to recent literature advocating this method.¹⁹ The following potential confounding variables were identified: age, sex, body mass index (BMI), American Society of Anesthesiologists (ASA) classification, neoadjuvant therapy, year of surgery and surgical approach (open or minimally invasive).^{16,20–22}

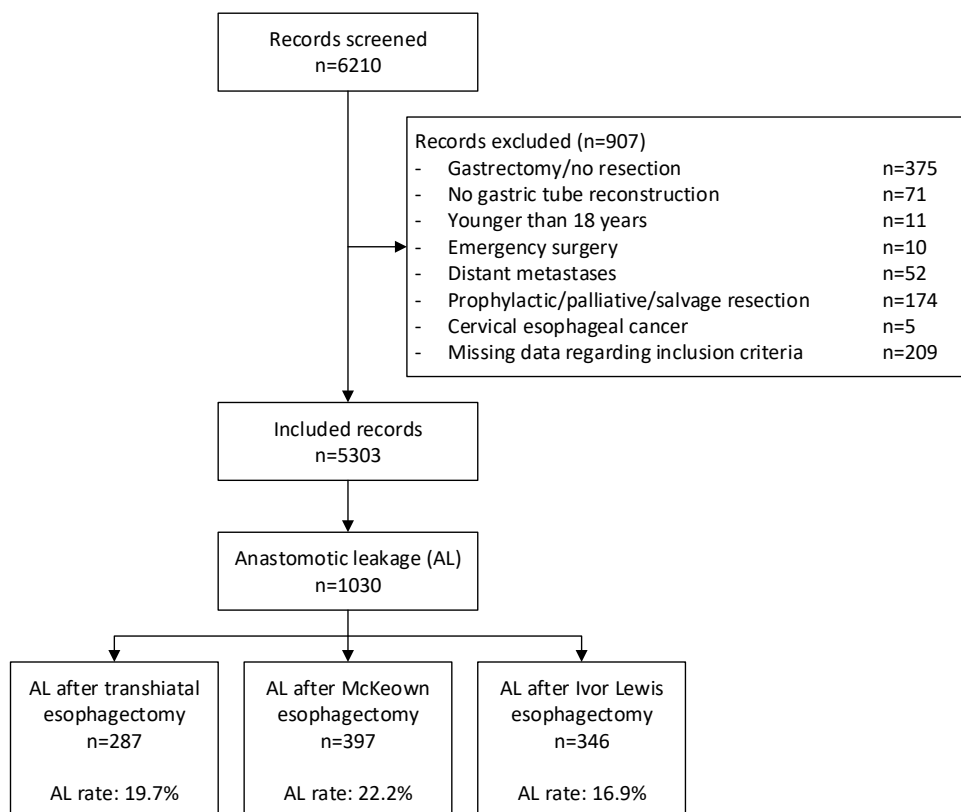
Outcomes are reported as odds ratio (OR) with a 95% confidence interval and, additionally, P values are presented. All analyses were performed using IBM SPSS statistics software, version 25.0 (IBM Corporation, Armonk, New York, USA).

RESULTS

Patient characteristics

A total of 1030 patients with anastomotic leakage after esophagectomy with gastric tube reconstruction for esophageal or junction cancer were included (Fig. 1). Of these 1030 anastomotic leakage patients, 287 patients underwent transhiatal esophagectomy, 397 patients underwent McKeown esophagectomy and 346 patients underwent Ivor Lewis esophagectomy. The anastomotic leakage rate was 19.7% after transhiatal esophagectomy, 16.9% after Ivor Lewis esophagectomy and 22.2% after McKeown esophagectomy. Patient, tumor and treatment characteristics according to the operation technique are shown in Table 1.

Figure 1. Flow chart



Primary outcome

The 30-day/in-hospital mortality rate was 4.5% (n=13) in patients with anastomotic leakage after transhiatal esophagectomy, 8.1% (n=32) in patients with anastomotic leakage after McKeown esophagectomy and 8.1% (n=28) in patients with anastomotic leakage after Ivor Lewis esophagectomy ($P = .139$). When adjusting for confounding variables, the mortality rate in patients with anastomotic leakage was significantly lower after transhiatal esophagectomy compared to Ivor Lewis esophagectomy (OR 0.33, 95% CI 0.15–0.70, $P = .004$). There were no differences between McKeown and Ivor Lewis esophagectomy regarding the primary outcome (OR 0.82, 95% CI 0.46–1.45, $P = .49$, Table 2).

Secondary outcomes

Secondary outcome parameters are presented in Table 3. The combined endpoint of reoperation and/or ICU readmission and/or 30-day/in-hospital mortality occurred in 36.6% of anastomotic leakage patients after transhiatal esophagectomy, 55.4% after McKeown esophagectomy and 61.6% after Ivor Lewis esophagectomy ($P < .001$).

Anastomotic leakage was the reason for reoperation in 79.5% of the patients and this comprised chyle leakage in 2.2%, bleeding in 2.3%, "other specified" in 3% and "other, not specified" in 13.0%. Pulmonary complication rate was highest in patients with anastomotic leakage after Ivor Lewis esophagectomy (55.2%, n=191) and this comprised 37.3% (n=107) after transhiatal and 45.6% (n=181) after McKeown esophagectomy ($P < .001$). Recurrent laryngeal nerve palsy was highest in patients with anastomotic leakage after McKeown esophagectomy (10.3%, n=41) and this comprised 7.3% (n=21) after transhiatal and 1.2% (n=4) after Ivor Lewis esophagectomy.

Details regarding the severity of anastomotic leakage according to the ECCG and Clavien–Dindo classifications were available for 414 patients (Table 4). Anastomotic leakage requiring endoscopic, radiologic or surgical reintervention (ECCG grade ≥ 2) was observed in 35.4% of the patients with anastomotic leakage after transhiatal esophagectomy, 62.0% after McKeown esophagectomy and 82.8% after Ivor Lewis esophagectomy ($P < .001$).

DISCUSSION

This is the first nationwide study that has compared the outcomes of patients with anastomotic leakage after different types of esophagectomy, investigat-

Table 1. Baseline characteristics

	All (n=1030)	Transhiatal (n=287)	McKeown (n=397)	Ivor Lewis (n=346)	P value
Age (years)	66 (12)	68 (13)	65 (11)	66 (11)	<.001
Body mass index (kg/m ²)	25.8 (5.6)	26.4 (6.1)	25.1 (5.6)	26.3 (5.6)	<.001
Sex					<.001
Male	814 (79.1)	237 (82.6)	287 (72.3)	290 (83.8)	
Female	215 (20.9)	50 (17.4)	110 (27.7)	55 (15.9)	
ASA classification					<.001
1	143 (13.9)	33 (11.5)	67 (16.9)	43 (12.4)	
2	596 (57.9)	144 (50.2)	231 (58.2)	221 (63.9)	
3	276 (26.8)	101 (35.2)	96 (24.2)	79 (22.8)	
4	9 (0.9)	5 (1.7)	2 (0.5)	2 (0.6)	
Unknown	6 (0.6)	4 (1.4)	1 (0.3)	1 (0.3)	
Tumor type					<.001
Adenocarcinoma	788 (76.5)	251 (87.5)	240 (60.5)	297 (85.8)	
Squamous cell carcinoma	210 (20.4)	26 (9.1)	143 (36.0)	41 (11.8)	
Other	25 (2.4)	8 (2.8)	11 (2.8)	6 (1.7)	
Unknown	7 (0.7)	2 (0.7)	3 (0.8)	2 (0.6)	
Tumor site					<.001
Proximal 1/3	17 (1.7)	1 (0.3)	16 (4.0)	0 (0)	
Middle 1/3	130 (12.6)	9 (3.1)	108 (27.2)	13 (3.8)	
Distal 1/3	658 (63.9)	171 (59.6)	220 (55.4)	267 (77.2)	
Junction	213 (20.7)	101 (35.2)	48 (12.1)	64 (18.5)	
Unknown	12 (1.2)	5 (1.7)	5 (1.3)	2 (0.6)	
cT stage					.082
T1	50 (4.9)	20 (7.0)	14 (3.5)	16 (4.6)	
T2	201 (19.5)	53 (18.5)	74 (18.6)	74 (21.4)	
T3	710 (68.9)	193 (67.2)	276 (69.5)	241 (69.7)	
T4	30 (2.9)	6 (2.1)	18 (4.5)	6 (1.7)	
Unknown	39 (3.8)	15 (5.2)	15 (3.8)	9 (2.6)	
cN stage					.040
N0	358 (34.8)	105 (36.6)	129 (32.5)	124 (35.8)	
N1	425 (41.3)	105 (36.6)	169 (42.6)	151 (43.6)	
N2	175 (17.0)	54 (18.8)	73 (18.4)	48 (13.9)	
N3	30 (2.9)	4 (1.4)	15 (3.8)	11 (3.2)	
N+	11 (1.1)	3 (1.0)	3 (0.8)	5 (1.4)	
Unknown	31 (3.0)	16 (5.6)	8 (2.0)	7 (2.0)	
Neoadjuvant treatment					<.001
None	84 (8.2)	39 (13.6)	19 (4.8)	26 (7.5)	
Chemotherapy	45 (4.4)	18 (6.3)	17 (4.3)	10 (2.9)	
Radiotherapy	1 (0.1)	1 (0.3)	0 (0)	0 (0)	
Chemoradiation	895 (86.9)	226 (78.7)	359 (90.4)	310 (89.6)	
Yes, type unknown	2 (0.2)	1 (0.3)	1 (0.3)	0 (0)	
Unknown	3 (0.3)	2 (0.7)	1 (0.3)	0 (0)	
Year of surgery					<.001
2011–2012	222 (21.6)	104 (36.2)	92 (23.2)	26 (7.5)	
2013–2014	243 (23.6)	71 (24.7)	98 (24.7)	74 (21.4)	
2015–2016	280 (27.2)	71 (24.7)	100 (25.2)	109 (31.5)	
2017–2018	285 (27.7)	41 (14.3)	107 (27.0)	137 (39.6)	
Esophagectomy					<.001
Open	248 (24.1)	146 (50.9)	67 (16.9)	35 (10.1)	
Hybrid	52 (5.0)	0 (0)	25 (6.3)	27 (7.8)	
Total minimally invasive	730 (70.9)	141 (49.1)	305 (76.8)	284 (82.1)	

Age and BMI are presented as median and interquartile range. ASA American Society of Anesthesiologists

ing whether leakage after different types of esophagectomies were associated with differences in severity. After correction for confounders (amongst others higher age and ASA in the anastomotic leakage after transhiatal esophagectomy group), anastomotic leakage after transhiatal esophagectomy was found to be associated with a clinically relevant lower mortality rate, although this difference did not reach the level of statistical significance. In addition, anastomotic leakage after transhiatal esophagectomy was associated with the least severe consequences in terms of reoperation and ICU readmission rate, followed by McKeown and finally Ivor Lewis esophagectomy. Although a causal relationship could not be established from this type of study, these results show a strong association between the severity of clinical consequences (i.e., reoperation, ICU readmission and mortality) in patients with anastomotic leakage and different types of esophagectomy. This indicates that anastomotic leakage severity should be taken into account, in addition to leakage incidence, when different types of esophagectomy are compared by clinicians or researchers. It also supports the view that a cervical anastomotic leak is often less severe than a leak from an intrathoracic anastomosis.

Table 2. Results of multivariate analysis with anastomotic leakage as outcome parameter

	Odds ratio	95% Confidence interval	P value
Age (years)	1.004	0.996-1.011	.365
Sex	0.897	0.649-1.239	.509
Body mass index (kg/m ²)	1.001	0.997-1.006	.602
Type of esophagectomy			
Transhiatal	0.277	0.188-0.407	<.001
McKeown	0.692	0.505-0.949	.022
Ivor Lewis	Ref.	Ref.	Ref.
ASA classification			
1	Ref.	Ref.	Ref.
2	1.740	1.171-2.584	.006
3	2.722	1.746-4.224	<.001
4	0.251	0.029-2.142	.206
Year of surgery			
2011-2012	3.326	2.161-5.120	<.001
2013-2014	2.536	1.729-3.719	<.001
2015-2016	2.120	1.484-3.029	<.001
2017-2018	Ref.	Ref.	Ref.
Neoadjuvant treatment			
None	1.342	0.825-2.183	.236
Chemotherapy	0.940	0.490-1.801	.852
Radiotherapy	0.000	0.000	1.000
Chemoradiotherapy	Ref.	Ref.	Ref.
Surgical approach			
Open	0.619	0.434-0.882	.008
Hybrid	1.141	0.619-2.105	.673
Total minimally invasive	Ref.	Ref.	Ref.

Age and BMI are presented as median and interquartile range. ASA American Society of Anesthesiologists

Limitations

In this study, transhiatal resection was performed in earlier years and it was more likely to have been reserved for patients with substantial comorbidity, possibly causing selection bias. In the Netherlands, practice shifted from transhiatal towards transthoracic esophagectomy because it is believed that transthoracic esophagectomy facilitates a more extended intrathoracic lymph node dissection and therefore may result in better survival outcomes. As a result, transhiatal esophagectomy became the reserved technique for patients with

Table 3.

Secondary outcomes of patients who underwent transhiatal, McKeown and Ivor Lewis esophagectomy

	All (n=1030)	Transhiatal (n=287)	McKeown (n=397)	Ivor Lewis (n=346)	P value
Reoperation, ICU readmission or mortality	538 (52.2)	105 (36.6)	220 (55.4)	213 (61.6)	<.001
Pulmonary complications	479 (46.5)	107 (37.3)	181 (45.6)	191 (55.2)	<.001
Pneumonia	89 (8.6)	9 (3.1)	26 (6.5)	54 (15.6)	<.001
Pleural effusion	52 (5.0)	8 (2.8)	14 (3.5)	30 (8.7)	.001
Pneumothorax	30 (2.9)	4 (1.4)	14 (3.5)	12 (3.5)	.197
Atelectasis	7 (0.7)	1 (0.3)	1 (0.3)	5 (1.4)	.103
Respiratory failure	48 (4.7)	6 (2.1)	14 (3.5)	28 (8.1)	.001
Acute aspiration	5 (0.5)	0 (0)	1 (0.3)	4 (1.2)	.079
ARDS	13 (1.3)	0 (0)	7 (1.8)	6 (1.7)	.079
Tracheobronchial defect	10 (1.0)	0 (0)	3 (0.8)	7 (2.0)	.061
Persistent air leak	8 (0.8)	0 (0)	5 (1.3)	3 (0.9)	.175
Cardiac complications	244 (23.7)	53 (18.5)	97 (24.4)	94 (27.2)	.034
Myocardial infarction	2 (0.2)	0 (0)	0 (0)	2 (0.6)	.138
Supraventricular arrhythmia	88 (8.5)	10 (3.5)	28 (7.1)	50 (14.5)	<.001
Ventricular arrhythmia	16 (1.6)	1 (0.3)	8 (2.0)	7 (2.0)	.151
Cardiac decompensation	2 (0.2)	0 (0)	2 (0.5)	0 (0)	.202
Pericarditis	2 (0.2)	0 (0)	0 (0)	2 (0.6)	.138
Cardiac arrest	2 (0.2)	0 (0)	0 (0)	2 (0.6)	.138
Gastric tube necrosis	34 (3.3)	6 (2.1)	21 (5.3)	7 (2.0)	.047
Chyle leakage	84 (8.2)	4 (1.4)	59 (14.9)	21 (6.1)	<.001
Reinterventions	688 (66.8)	117 (40.8)	268 (67.5)	303 (87.6)	<.001
Radiologic	277 (26.9)	46 (16.0)	108 (27.2)	123 (35.5)	<.001
Endoscopic	394 (38.3)	51 (17.8)	132 (33.2)	211 (61.0)	<.001
Reoperation	373 (36.2)	69 (24.0)	161 (40.6)	143 (41.3)	<.001
ICU length of stay (days)	3 (11)	2 (7)	4 (11)	5 (15)	<.001
ICU admission	369 (35.8)	69 (24.0)	150 (37.8)	150 (43.4)	<.001
Hospital length of stay (days)	22 (24)	15 (13)	22 (25)	29 (27)	<.001
Readmissions	247 (24.3)	67 (23.3)	94 (23.7)	86 (24.9)	.534
Mortality					
30-day	38 (3.7)	4 (1.4)	15 (3.8)	19 (5.5)	.024
In-hospital	65 (6.3)	11 (3.8)	31 (7.8)	23 (6.6)	.103

Continuous data are presented as medians (interquartile range).

ARDS acute respiratory distress syndrome, ICU intensive care unit.

Table 4.

Severity classifications of anastomotic leakage after transhiatal, McKeown and Ivor Lewis esophagectomy

	All (n=1030)	Transhiatal (n=287)	McKeown (n=397)	Ivor Lewis (n=346)	P value
ECCG classification					<.001
Grade I	135 (32.6)	41 (63.1)	62 (38.0)	32 (17.2)	
Grade II	180 (43.6)	18 (27.7)	57 (35.0)	105 (56.5)	
Grade III	98 (23.7)	5 (7.7)	44 (27.0)	49 (26.3)	
Unknown	1 (0.2)	1 (1.5)	0 (0.0)	0 (0.0)	
Clavien–Dindo classification					<.001
Grade I	79 (19.1)	26 (40.0)	45 (27.6)	8 (4.3)	
Grade II	63 (15.2)	18 (27.7)	22 (13.5)	23 (12.3)	
Grade IIIa	145 (35.0)	8 (12.3)	46 (28.2)	91 (48.9)	
Grade IIIb	76 (18.4)	9 (13.8)	35 (21.5)	32 (17.2)	
Grade Iva	35 (8.5)	2 (3.1)	12 (7.4)	21 (11.3)	
Grade IVb	6 (1.4)	2 (3.1)	0 (0.0)	4 (2.2)	
Grade V	9 (2.2)	0 (0.0)	3 (1.8)	6 (3.2)	
Unknown	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.5)	

ECCG Esophagectomy Complications Consensus Group

significant comorbidities. However, the expected direction of the effect of this selection bias (i.e., transhiatal patients treated in earlier years and with more comorbidities are expected to fare worse than patients undergoing McKeown or Ivor Lewis in later years and with fewer comorbidities) makes it unlikely that our study results were caused by selection bias. In fact, the difference between transhiatal and McKeown/Ivor Lewis that we found may even be larger than that described in the present study. However, chemoradiotherapy was given to a greater patient proportion in later years of surgery (when surgeons often chose McKeown or Ivor Lewis procedures) and it may be hypothesized that this precipitated more severe consequences of leakages. The main findings of the study persisted in the multivariate analysis, in which corrections were also made for year of surgery and neoadjuvant treatment.

Earlier studies mainly focused on anastomotic leakage incidence and showed a significantly lower incidence of anastomotic leakage in patients with an intrathoracic as compared to a cervical anastomosis.^{6,16,23,24} However, our study indicates that the severity of an anastomotic leakage is also clinically relevant, since cervical anastomotic leakage was associated with less severe consequences than intrathoracic anastomotic leakage. The most stated and most plausible explanation is that cervical anastomotic leakage can drain through the cervical wound, preventing intrathoracic consequences of the leak, although intrathoracic manifestations can also occur.¹⁰⁻¹² These intrathoracic manifestations of cervical anastomotic leakage occur more frequently after McKeown than after

transhiatal esophagectomy and were associated with prolonged hospital and ICU length of stay and mortality.¹⁰

The present study also observed anastomotic leakage after McKeown esophagectomy to be more severe than anastomotic leakage after transhiatal esophagectomy; this supports the clinical relevance of the 'chute hypothesis', which states that transthoracic dissection in two-field lymphadenectomy can facilitate intrathoracic manifestations of cervical anastomotic leakage.

The main strength of this study is that it is a large population-based cohort study with high-quality registry data, which also provides data on associations between outcome and type of esophagectomy in anastomotic leakage patients. Some limitations also have to be discussed. First, although the Dutch Upper gastrointestinal Cancer Audit is known as a good quality and complete data registry, not all parameters of interest were available. For example, the registry does not include the reason for ICU readmission and mortality, although this information might have contributed to understanding why patients with leakage after different procedures had different outcomes regarding these parameters. However, the reason for reoperation was available in the dataset (anastomotic leakage in 80% of the patients), suggesting that anastomotic leakage was the most important contributor to the outcomes observed.

Data regarding formal classification of anastomotic leakage according to the ECCG and Clavien–Dindo classification are only available in the DUCA registry for 2015 onwards. However, despite the smaller numbers in the subgroup analyses according to the ECCG and Clavien–Dindo classification, similar results in favor of the transhiatal resection compared to the entire cohort were found. This makes it unlikely that the outcome of this study would have been different if ECCG and Clavien–Dindo had been available for the whole study cohort and we therefore believe our results are robust.

Lastly, we cannot rule out the possibility that the outcomes were affected by a learning-curve. However, previous studies on learning curves in minimally invasive surgery found that the learning-curve contributed to increased anastomotic leakage rates, but did not find an increased severity of anastomotic leakage (e.g., mortality rate).²⁵ In addition, the results of this study, adjusted for both year of surgery and surgical approach (i.e., open, hybrid or totally minimally invasive), do not point in this direction.

The fact that anastomotic leakage severity varies after different types of esophagectomy has important implications for clinicians and for future clini-

cal research. The findings of this study should therefore be considered by clinicians who decide what type of esophageal resection they will perform for patients and this should be taken into account along with other characteristics of the types of procedures (e.g., complication incidence and oncological clearance).^{16,24,26-29}

Conclusion

This study confirms that anastomotic leakage after different types of esophagectomy is associated with differences in outcomes and supports the hypothesis that cervical anastomotic leakage is generally less severe than intrathoracic leakage. Leakage after transhiatal resection was associated with the lowest morbidity. For patients undergoing two-field lymphadenectomy, a McKeown procedure was associated with lower morbidity than Ivor Lewis esophagectomy, although mortality was similar. The clinical impact of anastomotic leakage should be taken into account, in addition to its incidence, when different types of esophagectomy are compared by clinicians or researchers.

References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin.* 2018;68(6):394-424. DOI:10.3322/caac.21492
2. Dikken JL, Lemmens VE, Wouters MWJM, et al. Increased incidence and survival for esophageal cancer but not for gastric cardia cancer in the Netherlands. *Eur J Cancer.* 2012;48(11):1624-1632. DOI:10.1016/j.ejca.2012.01.009
3. Pennathur A, Gibson MK, Jobe BA, Luketich JD. Esophageal carcinoma. *Lancet.* 2013;381(9864):400-412. DOI:10.1016/S0140-6736(12)60643-6
4. Stiles BM, Altorki NK. Traditional Techniques of Esophagectomy. *Surg Clin North Am.* 2012;92(5):1249-1263. DOI:10.1016/j.suc.2012.08.001
5. Alanezi K, Urschel J. Mortality secondary to esophageal anastomotic leak. *Ann Thorac Cardiovasc Surg.* 2004;10(2):71-75.
6. Biere SSAY, Maas KW, Cuesta MA, Van Der Peet DL. Cervical or thoracic anastomosis after esophagectomy for cancer: A systematic review and meta-analysis. *Dig Surg.* 2011;28(1):29-35. DOI:10.1159/000322014
7. Luketich JD, Pennathur A, Awais O, et al. Outcomes after minimally invasive esophagectomy: review over 1000 patients. *Ann Surg.* 2012;256(1):95-103. DOI: 10.1097/SLA.0b013e3182590603
8. Low D, Alderson D, Ceconello I, et al. International consensus on standardization of data collection for complications associated with esophagectomy: Esophagectomy Complications Consensus Group (ECCG). *Ann Surg.* 2015;262(2):286-294. DOI: 10.1097/SLA.0000000000001098
9. Orringer MB, Marshall B, Lannettoni M. Transhiatal esophagectomy for treatment of benign and malignant esophageal disease. *World J Surg.* 2001;25(2):196-203.
10. Van Heijl M, Van Wijngaarden AKS, Lagarde SM, Busch ORC, Van Lanschot JJB, Van Berge Henegouwen MI. Intrathoracic manifestations of cervical anastomotic leaks after transhiatal and transthoracic esophagectomy. *Br J Surg.* 2010;97(5):726-731. DOI:10.1002/bjs.6971
11. van Rossum PSN, Haverkamp L, Carvello M, Ruurda JP, van Hillegersberg R. Management and outcome of cervical versus intrathoracic manifestation of cervical anastomotic leakage after transthoracic esophagectomy for cancer. *Dis Esophagus.* 2017;30(1):1-8. DOI:10.1111/dote.12472
12. Korst RJ, Port JL, Lee PC, Altorki NK. Intrathoracic manifestations of cervical anastomotic leaks after transthoracic esophagectomy for carcinoma. *Ann Thorac Surg.* 2005;80(4):1185-1190. DOI:10.1016/j.athoracsur.2005.04.020
13. Mertens AC, Kalff MC, Eshuis WJ, Van Gulik TM, Van Berge Henegouwen MI, Gisbertz SS. Transthoracic versus transhiatal esophagectomy for esophageal cancer: a nationwide propensity score-matched cohort analysis. *Ann Surg Oncol.* 2021;28(1):175-183. DOI:10.1245/s10434-020-08760-8
14. Chidi AP, Etchill EW, Ha JS, et al. Effect of thoracic versus cervical anastomosis on anastomotic leak among patients who undergo esophagectomy after neoadjuvant chemoradiation. *J Thorac Cardiovasc Surg.* 2020;160(4):1088-1095. DOI:10.1016/j.jtcvs.2020.01.089
15. Busweiler LAD, Wijnhoven BPL, van Berge Henegouwen MI, et al. Early outcomes from the Dutch Upper gastrointestinal Cancer Audit. *Br J Surg.* 2016;103(13):1855-1863. DOI:10.1002/bjs.10303
16. Gooszen JAH, Goense L, Gisbertz SS, Ruurda JP, van Hillegersberg R, van Berge Henegouwen MI. Intrathoracic versus cervical anastomosis and predictors of anastomotic leakage after esophagectomy for cancer. *Br J Surg.* 2018;105(5):552-560. DOI:10.1002/bjs.10728
17. Van Der Werf LR, Busweiler LAD, Van Sandick JW, Van Berge Henegouwen MI, Wijnhoven BPL. Reporting national outcomes after esophagectomy and gastrectomy according to the esophageal complications consensus group (ECCG). *Ann Surg.* 2020;271(6):1095-1101. DOI:10.1097/SLA.0000000000003210
18. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: A new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg.* 2004;240(2):205-213. DOI:10.1097/01.sla.0000133083.54934.ae
19. Jager KJ, Zoccali C, MacLeod A, Dekker FW. Confounding: What it is and how to deal with it. *Kidney Int.* 2008;73(3):256-260. DOI:10.1038/sj.ki.5002650
20. Baranov NS, van Workum F, van der Maas J, et al. The influence of age on complications and overall survival after ivor lewis totally minimally invasive esophagectomy. *J Gastrointest Surg.* 2019;23(7):1293-1300. DOI:10.1007/s11605-018-4062-9

21. Biere SSAY, Van Berge Henegouwen MI, Maas KW, et al. Minimally invasive versus open esophagectomy for patients with esophageal cancer: A multicenter, open-label, randomised controlled trial. *Lancet*. 2012;379(9829):1887-1892. DOI: 10.1016/S0140-6736(12)60516-9
22. Mariette C, Markar SR, Dabakuyo-Yonli TS, et al. Hybrid minimally invasive esophagectomy for esophageal cancer. *N Engl J Med*. 2019;380(2):152-162. DOI:10.1056/nejmoa1805101
23. van Workum F, Berkelmans GH, Klarenbeek BR, Nieuwenhuijzen GAP, Luyer MDP, Rosman C. McKeown or Ivor Lewis totally minimally invasive esophagectomy for cancer of the esophagus and gastroesophageal junction: Systematic review and meta-analysis. *J Thorac Dis*. 2017;9:S826-S833. DOI:10.21037/jtd.2017.03.173
24. Van Workum F, Slaman AE, Van Berge Henegouwen MI, et al. Propensity score-matched analysis comparing minimally invasive ivor lewis versus minimally invasive mckeown esophagectomy. *Ann Surg*. 2020;271(1):128-133. DOI:10.1097/SLA.0000000000002982
25. Claassen L, van Workum F, Rosman C. Learning curve and postoperative outcomes of minimally invasive esophagectomy. *J Thorac Dis*. 2019;11(Suppl 5):S777-S785. DOI:10.21037/jtd.2018.12.54
26. Omloo JMT, Lagarde SM, Hulscher JBF, et al. Extended transthoracic resection compared with limited transhiatal resection for adenocarcinoma of the mid/distal esophagus: Five-year survival of a randomized clinical trial. *Ann Surg*. 2007;246(6):992-1000. DOI:10.1097/SLA.0b013e31815c4037
27. Visser E, Markar SR, Ruurda JP, Hanna GB, van Hillegersberg R. Prognostic Value of Lymph Node Yield on Overall Survival in Esophageal Cancer Patients: A Systematic Review and Meta-analysis. *Ann Surg*. 2019;269(2):261-268. DOI:10.1097/SLA.0000000000002824
28. Noordman BJ, Van Klaveren D, Van Berge Henegouwen MI, et al. Impact of surgical approach on long-term survival in esophageal adenocarcinoma patients with or without neoadjuvant chemoradiotherapy. *Ann Surg*. 2018;267(5):892-897. DOI:10.1097/SLA.0000000000002240
29. Hagens E, Van Berge Henegouwen MI, Gisbertz S. Ps02.158: Distribution of lymph node metastases in esophageal carcinoma [tiger study]: a multinational observational study. *Dis Esophagus*. 2018;31:166-166. DOI:10.1093/dote/doy089.ps02.158



CHAPTER 7

Improved anastomotic leakage rates after
the 'flap and wrap' reconstruction in Ivor Lewis
esophagectomy for cancer

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ABSTRACT

Background: Anastomotic leakage after esophagectomy has serious consequences. In Ivor Lewis esophagectomy, a shorter and possibly better vascularized gastric conduit is created than in McKeown esophagectomy. The intrathoracic anastomosis can additionally be wrapped in omentum and concealed behind the pleura ('flap and wrap' reconstruction). The aims of this study were 1) to observe anastomotic leakages after Ivor Lewis, transhiatal and McKeown esophagectomy, and 2) to evaluate whether anastomotic leakage rates decreased after the 'flap and wrap' reconstruction in Ivor Lewis esophagectomy.

Methods: Consecutive patients undergoing esophagectomy at a tertiary referral center between January 2013 and April 2019 were included. Primary outcome was the anastomotic leakage incidence. Secondary outcomes were postoperative outcomes, mortality, and 2-year overall survival (OS).

Results: A total of 463 patients were included. The incidences of anastomotic leakage after Ivor Lewis, transhiatal, and McKeown esophagectomy were 9.8% (32/328), 24.3% (9/37) and 31.6% (31/98), respectively ($P < .001$). In the Ivor Lewis esophagectomy group, the incidence was 7.3% after the 'flap and wrap' reconstruction and 28.2% when this was not performed ($P < .001$). If anastomotic leakages occurred after the 'flap and wrap' reconstruction, fewer reoperations (5.8 vs 27.0%) and ICU readmissions were observed (15.0 vs 43.2%) than without the 'flap and wrap' reconstruction (both $P < .001$).

Conclusion: Fewer anastomotic leakages are observed in patients who were selected for Ivor Lewis esophagectomy as compared to transhiatal and McKeown esophagectomy. The 'flap and wrap' reconstruction seems a promising technique to further reduce the anastomotic leakage incidence and severity in esophageal cancer patients who have an indication for Ivor Lewis esophagectomy.

INTRODUCTION

The first successful total transthoracic esophagectomy for esophageal carcinoma was performed by Franz Torek in 1913. Torek's review on literature described failure in more than 92% of patients.¹ Ivor Lewis presented the outcomes of a modified right-sided transthoracic esophageal resection in 1946, and the foundation of the well-known Ivor Lewis esophagectomy was formed.² Morbidity and mortality after esophagectomy have decreased over the years, but population-based studies from the Netherlands still report high anastomotic leakage rates (15–34%).^{3–5}

Despite the risk of anastomotic leakage and other complications, esophagectomy is still the most important component in the curative treatment for esophageal carcinomas, and has superior survival outcomes than chemo(radio)therapy alone.^{6,7} Esophageal anastomotic leakages are difficult to manage and have several negative consequences.⁸ On patient level, it results in a prolonged ICU or hospital stay, higher risk of mortality, impaired quality of life and worse long-term survival.^{9,10} On institutional and national levels, it is associated with higher workload for healthcare workers and with increased healthcare costs.¹¹ The prevention of anastomotic leakages after esophagectomy is important in the light of increasing numbers of surgically treatable esophageal carcinomas worldwide.¹²

To reduce the incidence of anastomotic leakage after esophagectomy, surgical techniques and perioperative care underwent various modifications over the last decades. A recent multicenter randomized trial has demonstrated the association between anastomotic leakages with the location of the anastomosis in transthoracic esophagectomy.⁵ Furthermore, an additional protective effect of omentoplasty on intrathoracic anastomosis is suggested by other reports.^{9,13}

The objectives of the present study are to assess the incidence of anastomotic leakage after different esophagectomy and reconstruction techniques in a tertiary, high-volume university hospital in the Netherlands, and to investigate whether the addition of omentoplasty and pleural flap concealment ('flap and wrap' reconstruction) to Ivor Lewis esophagectomy has a beneficial effect on the anastomotic leakage rate as compared to the Ivor Lewis anastomosis without 'flap and wrap' reconstruction.

METHODS

This observational cohort study included consecutive patients undergoing esophagectomy as part of curative cancer treatment at a tertiary referral hospital in the Netherlands between February 2013 and April 2019. Patients with mid-to-distal esophageal, gastroesophageal junction (GEJ) and cardiac carcinomas who were scheduled for open, hybrid or minimally invasive esophagectomy were selected from a prospective upper gastrointestinal surgery database. Patients were eligible for curative esophagectomy with gastric conduit reconstruction if they had histologically proven cT1-4aNO-1MO carcinoma. Palliative and/or emergency esophagectomy and colon reconstructions were excluded. Requirement for informed consent of patients was waived by the institutional review board of the Amsterdam UMC, which ethically assessed and approved the study. Patients of the upper gastrointestinal cancer department were informed that they had the general opportunity to opt-out for the use of data for research purposes at any time and data were consequently excluded from the database.

Cancer staging and oncologic treatments

Esophageal cancer staging was performed by endoscopy with biopsies, endoscopic ultrasound, ultrasound of the neck, computed tomography (CT) and positron emission tomography/computed tomography (PET/CT). The American Joint Committee on Cancer (AJCC) classification was used for staging (7th and 8th Ed.).^{14,15} Neoadjuvant chemoradiotherapy or perioperative chemotherapy was administered according to the Dutch guideline for esophageal cancer treatment.¹⁶ In the follow-up period after surgery, patients visited the outpatient clinic in 2 weeks, 6 weeks and every 3 months in the first year after surgery. Subsequently, patients were seen every 6 months until the fourth postoperative year and once more after 5 years. Endoscopies and radiographic imaging during follow-up were only performed on indication, as described by the Dutch guideline.¹⁶

Perioperative protocols

Patients' physical condition was optimized prior to esophagectomy by accompaniment of dietitians, and physiotherapists on indication. Postoperative patients were only admitted to the Intensive Care Unit (ICU) if this was required because of severe comorbidities or severe complications. If no complications occurred, patients were discharged at postoperative day seven according to the ERAS protocol.¹⁷

Esophagectomy

All surgeons had experience with minimally invasive and open transhiatal and McKeown esophagectomy before the start of the study. Ivor Lewis esophagectomy was introduced at the start of the inclusion period in February 2013. In January 2014, the Ivor Lewis esophagectomy was modified. The intrathoracic anastomosis was wrapped in omentum and concealed behind a pleural flap ('flap and wrap' reconstruction). On average, 80–100 esophageal resections were performed annually at this center.

The operative technique depended on the location of the tumor, radiation field and the physical fitness of the patient. For distal esophageal, junction and cardia carcinomas, minimally invasive Ivor Lewis esophagectomy became the standard technique following its introduction in 2013. Minimally invasive McKeown esophagectomy was the standard procedure for tumors in the middle and proximal third of the esophagus, and when the radiation field extended above the carina. Laparoscopic transhiatal esophagectomy was usually performed in patients who were considered not to be fit enough for transthoracic surgery, i.e. in case of severe pulmonary comorbidities. If minimally invasive surgery did not seem feasible beforehand, patients were scheduled for open esophagectomy (i.e. due to bulky tumors or previous upper gastrointestinal surgery).

All open and minimally invasive transhiatal and transthoracic resections were performed as previously described.¹⁸ All transthoracic procedures included a two-field lymphadenectomy, and an extended one-field lymphadenectomy towards the lower mediastinum (until the level of the pulmonary vein) was performed in transhiatal procedures. The right gastroepiploic and first part of the right gastric arteries and veins were preserved to supply blood to the gastric conduit. A 60 mm linear stapler was used for the gastric conduit of approximately 3 to 4 cm wide. Hand-sewn cervical anastomosis was created end-to-side or end-to-end with single-layered PDS 3.0. The intrathoracic anastomosis was created end-to-side with a double stapling technique using a 25 or 29 millimeter circular stapler (depending on the diameter of the esophageal stump), after securing the anvil with a purse-string suture.

The anastomosis of the 'flap and wrap' reconstruction was additionally wrapped in omentum followed by a single suture fixating and lifting the tip of the gastric conduit behind a pleural flap which was created superior to the transected arch of the azygos vein. With this technique, the gastric conduit is concealed with omentum and completely covered by the pleural flap. Also, the tensile forces on the circular anastomosis will be reduced.

Data collection

Eligible patients for esophagectomy were added in the prospective database on a weekly basis by regularly checking the operation schedule of the following week. Attending surgeons were asked to fill in a document with information about specific surgical and intraoperative outcomes directly after surgery in the operation room (Appendix A). Postoperative outcomes and complications were discussed with the surgeons every week before these data were registered in the database. Last follow-up data was collected on 26 August 2021.

Study outcomes and definitions

The primary outcome was the incidence of anastomotic leakage. Secondary outcome parameters were severity type of anastomotic leakage¹⁹, morbidity rate, the Comprehensive Complication Index (CCI)²⁰, reinterventions, reoperations, ICU admissions, reintubations, mortality, and 2-year overall survival (OS). Additionally, a proficiency-gain curve specific for the study center was assessed using the incidence of anastomotic leakage after Ivor Lewis esophagectomy. Anastomotic leakage was defined as 'full thickness gastrointestinal defect involving esophagus, anastomosis, staple line, or conduit irrespective of presentation or method of identification' in line with the definition of the Esophagectomy Complications Consensus Group (ECCG).¹⁹ Other definitions are described in Appendix B.

Statistical methods

Patients were classified into three groups: 1) Ivor Lewis (including patients with and without 'flap and wrap' reconstruction), 2) McKeown, and 3) transhiatal esophagectomy (THE). Secondly, subgroup analyses were performed for patients in the Ivor Lewis esophagectomy group with and without 'flap and wrap' reconstruction.

Centered weighted moving average was used to calculate the individual incidence of anastomotic leakage for each patient before plotting the proficiency-gain curve to bias of previous patients. Visual inspection was used to assess the plateau stage of the proficiency-gain curve. Chi-square and Fisher's exact tests were used to analyze categorical variables. To compare continuous variables, Mann-Whitney U (normally distributed variables) and Kruskal-Wallis tests (non-normally distributed variables) were performed. Univariate and multivariate analyses were performed to assess the predictive value of the 'flap and wrap' reconstruction on the occurrence of anastomotic leakages. Variables with $P < .20$ in the univariate analyses were included in the multivariate analysis. Multivariate analysis was performed using stepwise binary logistic regression with dichotomized variables. Kaplan-Meier curves were used to compare

2-year overall survival between groups. Differences with $P < .05$ were considered as significant. For all statistical analyses SPSS Statistics 26.0.0.1 (2019, Armonk, NY: IBM Corp.) was used.

RESULTS

A flow chart of the study is presented in Fig. 1. A total of 465 patients were included. Baseline characteristics differed significantly between patients who underwent transhiatal ($n=37$), McKeown ($n=98$) and Ivor Lewis esophagectomy ($n=330$), Table 1. Mean age was 64 years (95% CI 63–65) with a mean BMI of 25.9 kg/m² (95% CI 25.5–26.3). However, the Ivor Lewis esophagectomy group consisted of younger patients than transhiatal and McKeown patients (mean age of 63, 69 and 64 years respectively, $P < .001$) and contained a greater proportion of men (resp. 82.6, 67.6 and 67.3%, $P < .001$). Baseline characteristics of patients with and without and 'flap and wrap' reconstruction after Ivor Lewis esophagectomy were comparable (Appendix C). Median follow-up of surviving patients was 50.5 months (95% CI 39.1–61.9). Two McKeown and 6 Ivor Lewis esophagectomy patients were lost to follow-up (1.7%).

Figure 1. Flow chart

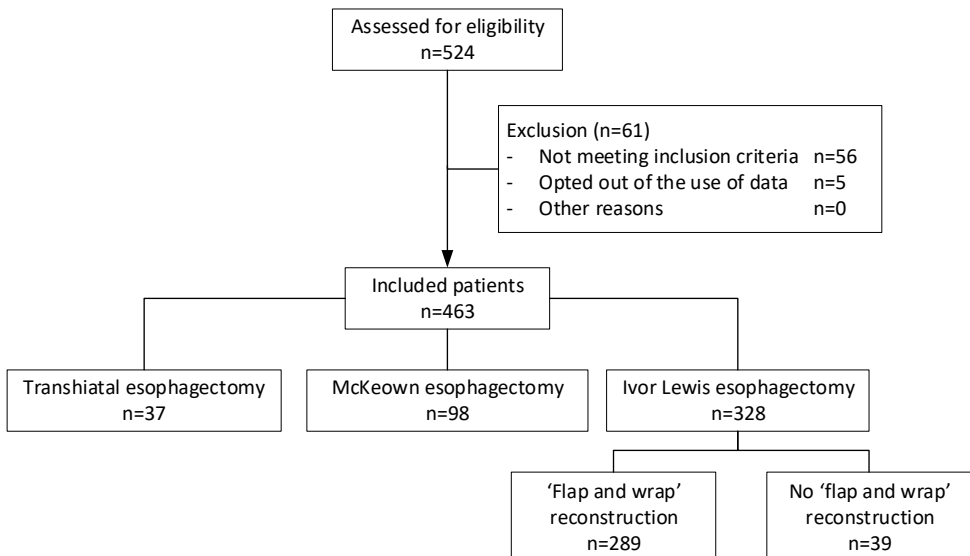
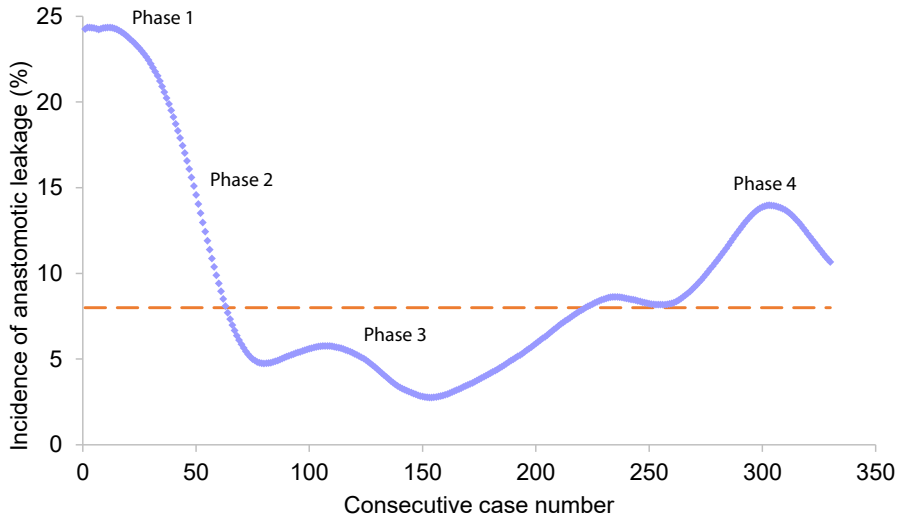


Figure 2. Proficiency-gain curve of Ivor Lewis esophagectomy



Ivor Lewis, transhiatal and McKeown esophagectomy

The incidence of anastomotic leakage of the total group was 15.5%. The incidences per procedure were 9.8% after Ivor Lewis esophagectomy, 24.3% after transhiatal esophagectomy, and 31.6% after McKeown esophagectomy ($P < .001$). The plateau phase in the proficiency-gain curve was reached after the 63th consecutive case (Fig. 2).

Transhiatal esophagectomy had the shortest operation time as compared to McKeown and Ivor Lewis esophagectomy (mean of 307, 419 and 421 minutes, $P < .001$), Table 2. Morbidity and pulmonary complication rates did not differ between the groups ($P > .05$). Patients after Ivor Lewis esophagectomy had shortest median ICU length of stay (LOS) (0 versus 1 and 1 day, $P = .002$). However, the Comprehensive Complication Index was not different between groups ($P = .30$). Highest mortality rates were found after McKeown esophagectomy, i.e., a 90-day mortality rate of 8.2% as compared to 0% and 1.2% after transhiatal and Ivor Lewis esophagectomy ($P < .001$).

Table 1. Baseline characteristics

	THE (n=37)	McKeown (n=98)	Ivor Lewis (n=328)	Total (n=471)	P value
Age (years)	69 (66–71)	64 (63–66)	63 (63–64)	64 (63–65)	.001
Sex (men)	25 (67.6)	66 (67.3)	271 (82.6)	362 (78.2)	.002
Body mass index (kg/m ²)	26.7 (25.1–28.2)	24.8 (23.9–25.7)	26.1 (25.7–26.6)	25.9 (25.5–26.3)	.013
ASA classification					.109
1	8 (21.6)	31 (31.6)	104 (31.7)	143 (30.9)	
2	18 (48.6)	56 (57.1)	161 (49.1)	235 (50.8)	
3	11 (29.7)	11 (11.2)	63 (19.2)	85 (18.4)	
Comorbidity					
Cardiovascular	14 (37.8)	35 (35.7)	143 (43.6)	192 (41.5)	.341
Diabetes mellitus	6 (16.2)	12 (12.2)	37 (11.3)	55 (11.9)	.674
COPD	4 (10.8)	4 (4.1)	15 (4.6)	23 (5.0)	.229
Previous upper gastrointestinal operation	0	1 (1.0)	12 (3.7)	13 (2.8)	.214
Tumor histology					<.001
High grade dysplasia	0	0	1 (0.3)	1 (0.2)	
Adenocarcinoma	34 (91.9)	49 (50.0)	286 (87.2)	369 (79.7)	
Squamous cell carcinoma	3 (8.1)	45 (45.9)	38 (11.6)	86 (18.6)	
Other	0	4 (4.1)	3 (0.9)	7 (1.5)	
Tumor site					<.001
Mid esophagus	0	35 (35.7)	20 (6.1)	55 (11.9)	
Distal esophagus	22 (59.5)	61 (62.2)	242 (73.8)	325 (70.2)	
GEJ	14 (37.8)	2 (2.0)	50 (15.2)	66 (14.3)	
Cardia	1 (2.7)	0 (0)	16 (4.9)	17 (3.7)	
T-stadium					.547
T1	4 (10.8)	6 (6.1)	26 (7.9)	36 (7.8)	
T2	8 (21.6)	24 (24.5)	52 (15.9)	84 (18.1)	
T3	24 (64.9)	66 (67.3)	243 (74.1)	333 (71.9)	
T4	1 (2.7)	2 (2.0)	7 (2.1)	7 (2.1)	
N-stadium					.005
N1	20 (54.1)	30 (30.6)	117 (35.8)	167 (36.1)	
N2	10 (27.0)	35 (35.7)	139 (42.5)	184 (39.8)	
N3	1 (2.7)	0 (0)	7 (2.1)	8 (1.7)	
Nx	0 (0)	2 (2.0)	0 (0)	2 (0.4)	
Neoadjuvant treatment					.009
None	9 (24.3)	9 (9.2)	29 (8.8)	47 (10.2)	
Chemotherapy	2 (5.4)	1 (1.0)	21 (6.4)	24 (5.2)	
Chemoradiotherapy	26 (70.3)	88 (89.8)	278 (84.8)	392 (84.7)	
Esophagectomy					.642
Open	1 (2.7)	1 (1.0)	10 (3.0)	12 (2.6)	
Minimally invasive	36 (97.3)	96 (98.0)	307 (93.6)	439 (94.8)	
Hybrid (thorax open)	n/a	1 (1.0)	7 (2.1)	8 (1.7)	
Hybrid (abdomen open)	n/a	0	4 (1.2)	4 (0.9)	

Continuous data are presented in mean (95% CI). GEJ Gastroesophageal junction

Table 2. Short-term outcomes of transhiatal, McKeown and Ivor Lewis esophagectomy

	THE (n=37)	McKeown (n=98)	Ivor Lewis (n=328)	P value
Conversions	0	0	9 (2.8)	.147
Intraoperative blood loss [‡] (mL)	150 (50–250)	150 (100–200)	200 (100–300)	<.001
Operation time (min)	307 (288–327)	419 (408–430)	421 (415–427)	<.001
Blood transfusions	3 (8.1)	12 (12.2)	32 (9.7)	.952
Intraoperative	1 (2.7)	2 (2.0)	5 (1.5)	
Postoperative	2 (5.4)	10 (10.2)	27 (8.2)	
Morbidity (any complication)	25 (67.6)	61 (62.2)	184 (55.8)	.247
Pulmonary complications	9 (24.3)	29 (29.6)	83 (25.2)	.659
Anastomotic leakage type [‡]				.020
I	1 (2.7)	3 (3.1)	1 (0.3)	
II	8 (21.6)	22 (22.4)	20 (6.1)	
III	0	6 (6.1)	11 (3.4)	
Comprehensive Complication Index	8.7 (0–25)	16.6 (0–40.5)	8.7 (0–27.6)	.303
Reinterventions	7 (18.9)	35 (35.7)	81 (24.5)	.049
Reoperations	2 (5.4)	10 (10.2)	25 (7.6)	.586
Reintubations	2 (5.4)	11 (11.2)	36 (10.9)	.568
ICU readmissions	4 (10.8)	17 (17.3)	60 (18.2)	.533
ICU length of stay	1 (0–1)	1 (0–3)	0 (0–1)	.002
Hospital length of stay	10 (8–17)	11 (8–17)	10 (8–16)	.429
Mortality				
In-hospital	0	4 (4.1)	2 (0.6)	.021
30-days	0	4 (4.1)	3 (0.9)	.057
Combined	0	6 (6.1)	3 (0.9)	.003
90-days	0	8 (8.2)	4 (1.2)	<.001
R0 resections	37 (100)	95 (96.9)	318 (97.0)	.559
Resected lymph nodes	22 (19–26)	33 (30–35)	34 (33–35)	<.001

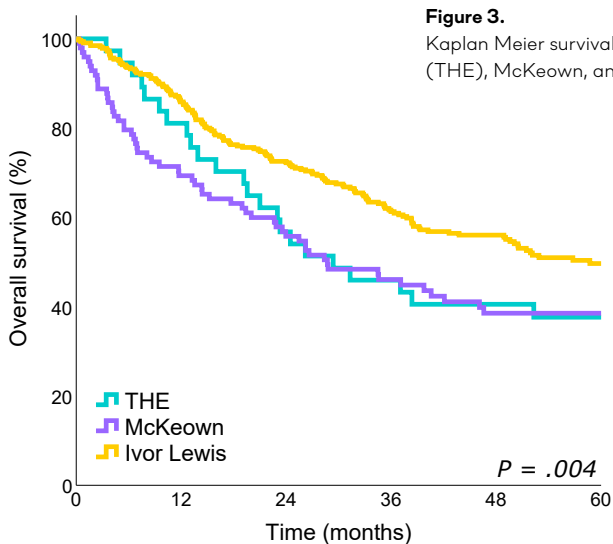
Intraoperative blood loss, (hospital/ICU) length of stay and Comprehensive Complication Index are presented in median (IQR). Operation time and resected lymph nodes are presented in means (95% CI).

[‡]Data was missing for 8 patients (1.7%)

The median number of resected lymph nodes was lower after transhiatal esophagectomy than after McKeown and Ivor Lewis esophagectomy (respectively 22, 33 and 34 lymph nodes, $P < .001$). Kaplan Meier curves are presented in Fig. 3. The 2-year overall survival rates were 72.2%, 54.1%, 55.8% after Ivor Lewis, transhiatal and McKeown esophagectomy ($P = .004$). The 5-year overall survival rates were respectively 49.7%, 38.5% and 37.6%, but this included 53.5% of censored patients in the Ivor Lewis group.

Flap and wrap reconstruction in Ivor Lewis esophagectomy

After the addition of the 'flap and wrap' reconstruction to the Ivor Lewis



No. at risk	0	12	24	36	48	60
Transhiatal	37	30	21	17	14	11
McKeown	98	67	53	36	30	24
Ivor Lewis	327	278	232	171	123	67

esophagectomy, the incidence of anastomotic leakage decreased from 28.2% without 'flap and wrap' reconstruction to 7.3% ($P < .001$). Overall morbidity and mortality in Ivor Lewis patients after the 'flap and wrap' reconstruction did not differ from those without 'flap and wrap' reconstruction ($P > .05$, Appendix D). However, the 'flap and wrap' reconstruction resulted in fewer pulmonary complications (21.8 versus 51.3%), reoperations (5.2 versus 25.6%), ICU readmissions (14.9 versus 43.6%), and reintubations (7.6 versus 35.9%) than after Ivor Lewis anastomosis without the 'flap and wrap' reconstruction. Median ICU length of stay (0 versus 1 day, $P < .001$) and hospital length of stay (10 versus 12 days, $P = .010$) were also shorter in patients after the 'flap and wrap' reconstruction. The 2-year overall survival did not change after applying the 'flap and wrap' reconstruction (79.5 versus 71.5%, $P = .312$)

Anastomotic leakages in patients with Ivor Lewis esophagectomy

The addition of the 'flap and wrap' reconstruction was an independent factor for fewer anastomotic leakages after esophagectomy, with an odds ratio of 0.214 (95% CI 0.107-0.427, $P < .001$) Appendix E. Reoperation was less frequently required if the anastomotic leakage occurred in patients with

Table 3. Short-term outcomes of anastomotic leakage patients after Ivor Lewis esophagectomy

	No flap and wrap reconstruction (n=39)	Flap and wrap reconstruction (n=289)	P value
Anastomotic leakage type			.013
I	0 (0)	1 (0.3)	
II	4 (10.2)	16 (5.5)	
III	7 (17.9)	4 (1.4)	
Comprehensive Complication Index	47.3 (43.3–57.0)	54.1 (40.3–70.1)	.457
ICU admissions due to AL	10 (25.6)	15 (5.2)	<.001
ICU length of stay	7 (4–12)	3 (0–7)	.137
Hospital length of stay	42 (25–49)	38 (13–57)	.999
Hospital readmissions due to AL	0 (0)	4 (1.4)	.460
Mortality due to AL	0 (0)	1 (0.3)	.999

Continuous values are presented in medians (IQR). AL anastomotic leakage

compared to without ‘flap and wrap’ reconstruction (19.0% versus 63.6%, $P = .012$). Severity of the anastomotic leakage was also lower after ‘flap and wrap’ reconstruction (Table 3). However, the median Comprehensive Complication Index of patients with anastomotic leakages were not significantly different (47.3 versus 54.1, $P = .457$).

DISCUSSION

This prospective cohort study investigates the incidence of anastomotic leakage after the introduction of Ivor Lewis esophagectomy, and subsequently evaluates the influence of the recent implementation of the ‘flap and wrap’ reconstruction in Ivor Lewis esophagectomy on the occurrence of anastomotic leakage. The study results show that the introduction of Ivor Lewis esophagectomy led to an anastomotic leakage incidence of less than 10% in this tertiary referral center. A plateau phase in the proficiency-gain curve for Ivor Lewis esophagectomy was reached after 63 patients, based on the incidence of anastomotic leakage. In general, Ivor Lewis esophagectomy resulted in shorter ICU stay and improved 2-year overall survival as compared to transhiatal and McKeown esophagectomy.

The shift to the ‘flap and wrap’ reconstruction in Ivor Lewis esophagectomy resulted in an anastomotic leakage rate of less than 8%. In patients with anastomotic leakages after Ivor Lewis esophagectomy, lower severity was found in patients with the ‘flap and wrap’ reconstruction than in patients without the ‘flap and wrap’ reconstruction.

The incidence of anastomotic leakage after Ivor Lewis esophagectomy lies within the range of previous studies (5–21%).^{5,21–26} However, no studies report the incidence of anastomotic leakage after transhiatal, Ivor Lewis and McKeown esophagectomy as primary outcome parameter. One observational multicenter study from the Netherlands investigated short-term outcomes of patients with anastomotic leakage after transhiatal, McKeown and Ivor Lewis esophagectomy.²⁷ The study reported lowest incidences after Ivor Lewis esophagectomy (17%), which was higher than that of the current study. The ‘flap and wrap’ reconstruction that was used in the current study may play a role in this difference. Mortality, reinterventions and reoperations after anastomotic leakages in that study were disadvantageous for the Ivor Lewis esophagectomy, which is also in contrast to the current study results. A recently published randomized study compared the incidence of anastomotic leakage requiring interventions between intrathoracic and cervical anastomosis, all with omentoplasty.⁵ An incidence of anastomotic leakage of 12% after Ivor Lewis esophagectomy in the Ivor Lewis arm was observed, which is comparable to the results of the current study. The authors hypothesized that this incidence may have been negatively influenced by the proficiency-gain curves that some participating centers were still going through. The proficiency-gain curve of Ivor Lewis esophagectomy in the present study follows an expected surgical course that consists of four phases: start of the training (phase 1), acquiring proficiency, competence and additional experience (phase 2), reaching a plateau (phase 3), and a drop of competence (phase 4)(Fig. 2).²⁸ The steep gradient in the second phase of the proficiency-gain curve corresponds to training of complex surgical procedures, such as esophagectomy. The fourth phase reflects an advanced period where surgeons start to operate on more complex patients due to confidence after previous promising results or start training the procedure to fellows or residents.²⁸ The number of cases needed to overcome the accepted anastomotic leakage rate of 8% after implementation of the Ivor Lewis esophagectomy is comparable to that of other centers.^{29,30}

It is difficult to compare the outcomes of the ‘flap and wrap’ reconstruction to other literature. The scarce number of studies that investigated omentoplasty in transthoracic esophagectomy have shown that anastomotic leakage incidences vary between 3 and 16%, which seems comparable to the outcomes of the ‘flap and wrap’ reconstruction.^{31–35} Almost all studies have shown that omentoplasty leads to lower anastomotic leakage rates. However, these studies were performed with small patient groups, often undergoing different esophagectomy procedures and/or were performed in the era prior to minimally invasive surgery and neoadjuvant chemoradiotherapy. In spite of this lack of homogeneity, omentoplasty was found to be a significant negative predictor

of anastomotic leakages in patients after esophagectomy by two systematic reviews.^{9,13}

The benefit of the 'flap and wrap' reconstruction concerning anastomotic leakage and its severity as compared to other procedures can be explained by several hypotheses. First, the gastric conduit in Ivor Lewis is shorter than in transthoracic and McKeown esophagectomy, resulting in better perfusion at the site of the anastomosis. Second, vertical traction on the anastomosis can be avoided by stitching the gastric conduit to the pleural flap. Third, covering the anastomosis behind the pleural flap and wrapping the greater omentum around it serve as mechanical protection mechanisms against the negative intrathoracic pressure, and also create barriers for infections to spread throughout the thoracic cavity. Additionally, angiogenic and growth factors that are produced by the omentum lead to revascularization to adjacent tissues, especially in the infected areas. This may lead to faster anastomotic leakage healing.³⁶ Furthermore, omentum has shown immunologic areas, that can react fast with immune cells in response to infection.³⁶ Consequently, anastomotic leakages may have a less severe course, leading to less invasive treatment possibilities, such as intraluminal vacuum therapy or endoscopic stenting instead of surgery.³⁷

A strength of the present study is that it shows change of a surgical technique using prospective data with information about anastomotic leakages after the implementation of Ivor Lewis esophagectomy followed by modification of the reconstruction. The study is a reflection of the daily esophageal cancer treatment in a tertiary referral center, where 80–100 esophagectomies per year are performed. In clinical practice, patients with curatively treatable esophageal cancer are usually selected for transthoracic surgery if they are physical fit (e.g., often younger patients), whilst the McKeown esophagectomy is reserved for patients with a tumor and/or radiation field that extends above the carina. The study shows assessment of the proficiency-gain curve is important when interpreting the results of a newly implemented technique. Furthermore, discussing postoperative data of each patient with surgeons of this center before entering the database and the use of ECGG definitions secure accurate data collection and generalizability of the study. A more precise analysis of the complication severity was pursued using the Comprehensive Complication Index instead of using the Clavien–Dindo classification.^{20,38}

This study has some limitations. The plateau phase of the proficiency-gain curve was reached after consecutive Ivor Lewis esophagectomy number 63, thus patients without 'flap and wrap' Ivor Lewis reconstruction may have experienced more learning-associated morbidity than patients with 'flap and wrap'

reconstruction. However, even with the learning-associated morbidity, Ivor Lewis esophagectomy seems feasible in terms of anastomotic leakages, secondary outcomes and 2-year overall survival as compared to the other procedures. Due to the study design, which shows results of treatment of esophageal cancer in daily practice ('natural occurring sample'), selection bias is likely to have influenced outcomes due to selection of a different patient group for Ivor Lewis esophagectomy. The objective of this study was not to show superiority of either technique, as there will always be indication for either technique due to patient and tumor characteristics. The aim was to describe the outcomes when patients are selected for either procedure in daily practice.

Conclusions

This observational study showed that the incidence and severity of anastomotic leakages differed between patients selected for transhiatal, McKeown and Ivor Lewis esophagectomy, with lowest incidences for the 'flap and wrap' reconstruction in Ivor Lewis esophagectomy. Therefore, Ivor Lewis esophagectomy with 'flap and wrap' reconstruction is the preferred curative procedure in patients with distal esophageal or gastro-esophageal junction cancer that are fit enough to undergo transthoracic esophagectomy. However, since transhiatal and McKeown esophagectomy will always remain essential procedures for selected patients, upper gastrointestinal surgeons must have proficiency in these procedures.

References

1. Torek F. The causes of failure in the operative treatment of carcinoma of the esophagus. *Ann Surg.* 1929;90(4):496-506. DOI:10.1097/00000658-192910000-00004
2. Lewis I. The surgical treatment of carcinoma of the esophagus with special reference to a new operation for growths of the middle third. *Br J Surg.* 1946;34(133):18-31. DOI:10.1002/bjs.18003413304
3. Hulscher JBF, van Sandick JW, de Boer AGEM, et al. Extended transthoracic resection compared with limited transhiatal resection for adenocarcinoma of the esophagus. *N Engl J Med.* 2002;347(21):1662-1669. DOI:10.1056/nejmoa022343
4. van Hagen P, Hulshof MCCM, van Lanschot JJB, et al. Preoperative chemoradiotherapy for esophageal or junctional cancer. *N Engl J Med.* 2012;366(22):2074-2084. DOI:10.1056/nejmoa1112088
5. Van Workum F, Versteegen MHP, Klarenbeek BR, et al. Intrathoracic vs cervical anastomosis after totally or hybrid minimally invasive esophagectomy for esophageal cancer: a randomized clinical trial. *JAMA Surg.* 2021;156(7):601-610. DOI:10.1001/jamasurg.2021.1555
6. Wang BY, Wu SC, Chen HC, et al. Survival after neoadjuvant chemoradiotherapy and esophagectomy versus definitive chemoradiotherapy for patients with esophageal squamous cell carcinoma. *Br J Surg.* 2019;106(3):255-262. DOI:10.1002/bjs.11004
7. Di Corpo M, Schlottmann F, Strassle PD, Nurczyk K, Patti MG. Treatment modalities for esophageal adenocarcinoma in the United States: Trends and survival outcomes. *J Laparoendosc Adv Surg Tech.* 2019;29(8):989-994. DOI:10.1089/lap.2019.0350
8. Versteegen MHP, Bouwense SAW, Van Workum F, et al. Management of intrathoracic and cervical anastomotic leakage after esophagectomy for esophageal cancer: A systematic review. *World J Emerg Surg.* 2019;14(1):1-12. DOI:10.1186/s13017-019-0235-4
9. Kamarajah SK, Lin A, Tharmaraja T, et al. Risk factors and outcomes associated with anastomotic leaks following esophagectomy: A systematic review and meta-analysis. *Dis Esophagus.* 2020;33(3):1-14. DOI:10.1093/dote/doz089
10. Van Der Werf LR, Wijnhoven BPL, Franssen LFC, et al. A national cohort study evaluating the association between short-term outcomes and long-term survival after esophageal and gastric cancer surgery. *Ann Surg.* 2019;270(5). DOI:10.1097/SLA.0000000000003520
11. Agzarian J, Visscher SL, Knight AW, et al. The cost burden of clinically significant esophageal anastomotic leaks—a steep price to pay. *J Thorac Cardiovasc Surg.* 2019;157(5):2086-2092. DOI:10.1016/j.jtcvs.2018.10.137
12. Kastelein F, Van Olphen SH, Steyerberg EW, et al. Impact of surveillance for Barrett's esophagus on tumor stage and survival of patients with neoplastic progression. *Gut.* 2016;65(4):548-554. DOI:10.1136/gutjnl-2014-308802
13. Grigor EJM, Kaaki S, Fergusson DA, Maziak DE, Seely AJE. Interventions to prevent anastomotic leak after esophageal surgery : a systematic review and meta - analysis. *BMC Surg.* 2021. DOI:10.1186/s12893-020-01026-w
14. Rice TW, Blackstone EH, Rusch VW. 7th edition of the AJCC Cancer Staging Manual: esophagus and esophagogastric junction. *Ann Surg Oncol.* 2010;17(7):1721-1724. DOI:10.1245/s10434-010-1024-1
15. Rice TW, Patil DT, Blackstone EH. 8th edition AJCC/UICC staging of cancers of the esophagus and esophagogastric junction: Application to clinical practice. *Ann Cardiothorac Surg.* 2017;6(2):119-130. DOI:10.21037/acs.2017.03.14
16. Vereniging van Maag-Darm-Leverartsen. Dutch guideline for esophageal cancer, version 3.1. Federatie Medisch Specialisten. https://richtlijnendatabase.nl/richtlijn/oesofaguscarcinoom/oesofaguscarcinoom_-_startpagina.html. Published 2015. Accessed: September 21, 2021.
17. Blom RLGM, Van Heijl M, Bemelman WA, et al. Initial experiences of an enhanced recovery protocol in esophageal surgery. *World J Surg.* 2013;37(10):2372-2378. DOI:10.1007/s00268-013-2135-1
18. Anderegg MCJJ, Gisbertz SS, van Berge Henegouwen MI. Minimally invasive surgery for esophageal cancer. *Best Pract Res Clin Gastroenterol.* 2014;28(1):41-52. DOI:10.1016/j.bpg.2013.11.002
19. Low DE, Alderson D, Ceconello I, et al. International consensus on standardization of data collection for complications associated with esophagectomy: Esophagectomy Complications Consensus Group (ECCG). *Ann Surg.* 2015;262(2):286-294. DOI:10.1097/SLA.0000000000001098
20. Slankamenac K, Graf R, Barkun J, Puhon MA, Clavien PA. The Comprehensive Complication Index: A novel continuous scale to measure surgical morbidity. *Ann Surg.* 2013;258(1):1-7. DOI:10.1097/SLA.0b013e318296c732

21. Straatman J, Van Der Wielen N, Cuesta MA, et al. Minimally invasive versus open esophageal resection. *Ann Surg.* 2017;266(2):232-236. DOI:10.1097/SLA.0000000000002171
22. Sabra MJ, Alwatari YA, Wolfe LG, et al. Ivor Lewis vs Mckeown esophagectomy: analysis of operative outcomes from the ACS NSQIP database. *Gen Thorac Cardiovasc Surg.* 2020;68(4):370-379. DOI:10.1007/s11748-020-01290-w
23. Schröder W, Raptis DA, Schmidt HM, et al. Anastomotic techniques and associated morbidity in total minimally invasive transthoracic esophagectomy: Results from the EsoBenchmark database. *Ann Surg.* 2019;270(5):1. DOI:10.1097/SLA.0000000000003538
24. Van Workum F, Slaman AE, Van Berge Henegouwen MI, et al. Propensity score-matched analysis comparing minimally invasive ivor lewis versus minimally invasive mckeown esophagectomy. *Ann Surg.* 2020;271(1):128-133. DOI:10.1097/SLA.0000000000002982
25. Seesing MFJ, Gisbertz SS, Goense L, et al. A propensity score matched analysis of open versus minimally invasive transthoracic esophagectomy in the Netherlands. *Ann Surg.* 2017;266(5):839-846. DOI:10.1097/SLA.0000000000002393
26. van Workum F, Berkelmans GH, Klarenbeek BR, Nieuwenhuijzen GAP, Luyer MDP, Rosman C. McKeown or Ivor Lewis totally minimally invasive esophagectomy for cancer of the esophagus and gastroesophageal junction: Systematic review and meta-analysis. *J Thorac Dis.* 2017;9:S826-S833. DOI:10.21037/jtd.2017.03.173
27. Verstegen MHP, Slaman AE, Klarenbeek BR, et al. Outcomes of patients with anastomotic leakage after transhiatal, McKeown or Ivor Lewis esophagectomy: a nationwide cohort study. *World J Surg.* 2021. DOI:10.1007/s00268-021-06250-w
28. Hopper AN, Jamison MH, Lewis WG. Learning curves in surgical practice. *Postgrad Med J.* 2007;83(986):777-779. DOI:10.1136/pgmj.2007.057190
29. Claassen L, van Workum F, Rosman C. Learning curve and postoperative outcomes of minimally invasive esophagectomy. *J Thorac Dis.* 2019;11(Suppl 5):S777-S785. DOI:10.21037/jtd.2018.12.54
30. Van Workum F, Stenstra MHBC, Berkelmans GHK, et al. Learning curve and associated morbidity of minimally invasive esophagectomy: A retrospective multicenter study. *Ann Surg.* 2019;269(1):88-94. DOI:10.1097/SLA.0000000000002469
31. Wiggins T, Markar SR, Arya S, Hanna GB. Anastomotic reinforcement with omentoplasty following gastrointestinal anastomosis: A systematic review and meta-analysis. *Surg Oncol.* 2015;24(3):181-186. DOI:10.1016/j.suronc.2015.06.011
32. Lu M, Luketich JD, Levy RM, et al. Anastomotic complications after esophagectomy: Influence of omentoplasty in propensity-weighted cohorts. *J Thorac Cardiovasc Surg.* 2020;159(5):2096-2105. DOI:10.1016/j.jtcvs.2019.09.157
33. Bhat MA, Dar MA, Lone GN, Dar AM. Use of pedicled omentum in esophagogastric anastomosis for prevention of anastomotic leak. *Ann Thorac Surg.* 2006;82(5):1857-1862. DOI:10.1016/j.athoracsur.2006.05.101
34. Tuo G, Jin G, Pang Y, et al. Omentoplasty decreases leak rate after esophagectomy: a meta-analysis. *J Gastrointest Surg.* 2020;24(6):1237-1243. DOI:10.1007/s11605-019-04284-z
35. Yuan Y, Zeng X, Hu Y, Xie T, Zhao Y. Omentoplasty for esophagogastrostomy after esophagectomy. *Cochrane Database Syst Rev.* 2014;2014(10). DOI:10.1002/14651858.CD008446.pub3
36. Wang AW, Prieto JM, Cauvi DM, Bickler SW, De Maio A. The greater omentum - a vibrant and enigmatic immunologic organ involved in injury and infection resolution. *Shock.* 2020;53(4):384-390. DOI:10.1097/SHK.0000000000001428
37. Tavares G, Tustumi F, Tristão LS, Bernardo WM. Endoscopic vacuum therapy for anastomotic leak in esophagectomy and total gastrectomy: a systematic review and meta-analysis. *Dis Esophagus.* 2021;34(5):1-11. DOI:10.1093/dote/daaa132
38. Slaman AE, Lagarde SM, Gisbertz SS, Van Berge Henegouwen MI. A quantified scoring system for postoperative complication severity compared to the Clavien-Dindo classification. *Dig Surg.* 2015;32(5):361-366. DOI:10.1159/000433608

Appendices

Appendix A. Data form that surgeons filled in at the operation room

Patient name:

Date of birth: [dd/mm/yy]

Scheduled date of surgery: [dd/mm/yy]

Exact date of surgery: [dd/mm/yy]

Indication

- Stomach:
 - Linitis plastica
 - Fundus
 - Antrum
 - Pylorus
 - Gastric tube anastomosis
 - Cardiac carcinoma
- Esophagus:
 - Proximal
 - Middle
 - Distal
 - Gastroesophageal junction
- High grade dysplasia
- Other, malignancy:
- Other, benign:
- Esophageal rupture

Surgical procedure

- Minimally invasive transthoracic esophagectomy
- Minimally invasive transhiatal esophagectomy
- Open transthoracic esophagectomy
- Open transhiatal esophagectomy
- Total gastrectomy
- Subtotal gastrectomy

Proximal anastomosis

- Cervical: [left/right]
- Intrathoracic esophagogastrostomy
- Intrathoracic esophagojejunostomy
- Intra-abdominal esophagojejunostomy
- Intra-abdominal gastrojejunostomy
- No reconstruction: [reason]

If applicable, reconstruction type

- Gastric conduit
- Colon interposition
- Other: [specify]

'Flap and wrap' reconstruction: yes no

If applicable, reconstruction route

- Prevertebral
- Retrosternal
 - Subcutaneous
 - Not applicable

Intubation

- Single lumen tube
- Double lumen tube
- Bronchial blocker

Epidural anesthesia: no yes

Patient position

- Prone
- Left lateral
- Right lateral

Harmonic device

- Ligasure
- Ultracision
- None
- Other: [specify]

Anastomosis technique

- Stapled: 21 mm 25 mm 29 mm
- Semi-mechanical
- Manual end-to-end
- Manual end-to-side

Other parameters

- Feeding jejunostomy
- Conversion, specification:
- Iatrogenic injury, specification:
- Additional resection, specification:
- Tumor perforation
- Macroscopically radical resection
- If R2, specify location of tumor rest:

Duration of surgery: [.....] minutes

Blood loss volume: [.....] mL

Postoperative destination: high care ICU

Detubated at: OR high care ICU

Transthoracic drainage

- Not applicable
- Left hemithorax
- Right hemithorax
- Both sides of thoracic cavity

Appendix B. Definitions of secondary outcomes

Severity of anastomotic leakage	According to the Esophageal Cancer Consensus Group: Type I: No change in therapy or treated medically or with dietary modification Type II: Requiring interventional therapy Type III: Requiring surgical therapy
Comprehensive Complication Index	Classification method for the severity of all postoperative complications together, ranging from 0 (no complications) to 100 (death)
Reinterventions	Treatment of complications by endoscopy or interventional radiology, not under general anesthesia
Reoperations	Treatment of complications by surgery under general anesthesia
ICU readmissions	As part of complication treatment
Reintubations	Intubation at the ICU needed as treatment of complications
Combined mortality	Death in the first 30 days after esophagectomy or during the hospital admission
2-year overall survival	Interval between esophagectomy and all-caused death

Appendix C. Baseline characteristics of patients who underwent Ivor Lewis esophagectomy

	No 'flap and wrap' reconstruction (n=39)	'Flap and wrap' reconstruction (n=289)	P value
Age (years)	63 (60-65)	64 (63-65)	.615
Sex (male)	31 (79.5)	240 (83.0)	.582
Body mass index (kg/m ²)	26.4 (25.2-27.5)	26.1 (25.6-26.6)	.747
Comorbidity			
Cardiovascular	19 (48.7)	124 (42.9)	.492
Diabetes mellitus	5 (12.8)	32 (11.1)	.746
COPD	0 (0)	15 (5.2)	.232
Previous upper gastrointestinal surgery	2 (5.1)	10 (3.5)	.602
ASA classification			.757
1	14 (35.9)	90 (31.1)	
2	17 (43.6)	144 (49.8)	
3	8 (20.5)	55 (19.0)	
Histology			.023
High grade dysplasia	1 (2.6)	0 (0)	
Adenocarcinoma	36 (92.3)	250 (86.5)	
Squamous cell carcinoma	2 (5.1)	36 (12.5)	
Other	0 (0)	3 (1.0)	
Tumor site			.095
Mid esophagus	0 (0)	20 (6.9)	
Distal esophagus	35 (89.7)	207 (71.6)	
Gastroesophageal junction	3 (7.7)	47 (16.3)	
Cardia	1 (2.6)	15 (5.2)	
Neoadjuvant treatment			.202
None	3 (7.7)	26 (9.0)	
Chemotherapy	0 (0)	21 (7.3)	
Chemoradiotherapy	36 (92.3)	242 (83.7)	
Esophagectomy			.865
Open	1 (2.6)	9 (3.1)	
Minimally invasive	36 (92.3)	271 (93.8)	
Hybrid (thorax open)	1 (2.6)	6 (2.1)	
Hybrid (abdomen open)	1 (2.6)	3 (1.0)	

Continuous data are presented as mean (95% confidence interval).

COPD chronic obstructive pulmonary disease, ASA American Society of Anesthesiologists

Appendix D. Short-term outcomes for patients with standard and ‘flap and wrap’ reconstruction in Ivor Lewis esophagectomy

	No ‘flap and wrap’ reconstruction (n=39)	‘Flap and wrap’ reconstruction (n=289)	P value
Blood transfusion			.003
Intraoperative	1 (2.6)	4 (1.4)	
Postoperative	9 (23.1)	18 (6.2)	
Morbidity	27 (69.2)	157 (54.3)	.078
Pulmonary complications	20 (51.3)	63 (21.8)	<.001
Comprehensive Complication Index	26.2 (0–50.1)	8.7 (0–26.2)	.003
Reinterventions	14 (35.9)	67 (23.2)	.084
Reoperations	10 (25.6)	15 (5.2)	<.001
ICU readmissions	17 (43.6)	43 (14.9)	<.001
Reintubations	14 (35.9)	22 (7.6)	<.001
ICU length of stay	1 (0–7)	0 (0–1)	<.001
Hospital length of stay	12 (9–34)	10 (8–15)	.011
Mortality			
In-hospital	1 (2.6)	1 (0.3)	.224
30-day	1 (2.6)	2 (0.7)	.317
Combined	1 (2.6)	2 (0.7)	.317
90-days	2 (5.1)	2 (0.7)	.071

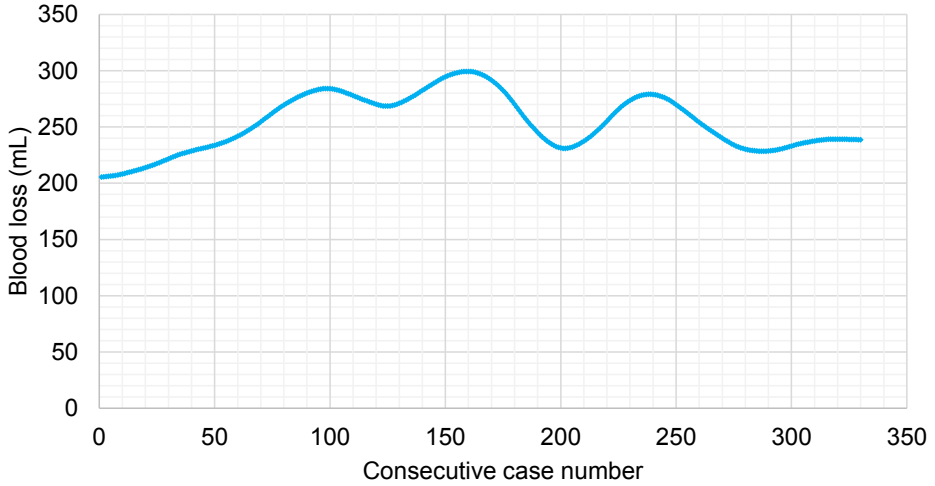
Continuous values are presented in medians (IQR)

Appendix E. Univariate and multivariate binary logistic regression analysis

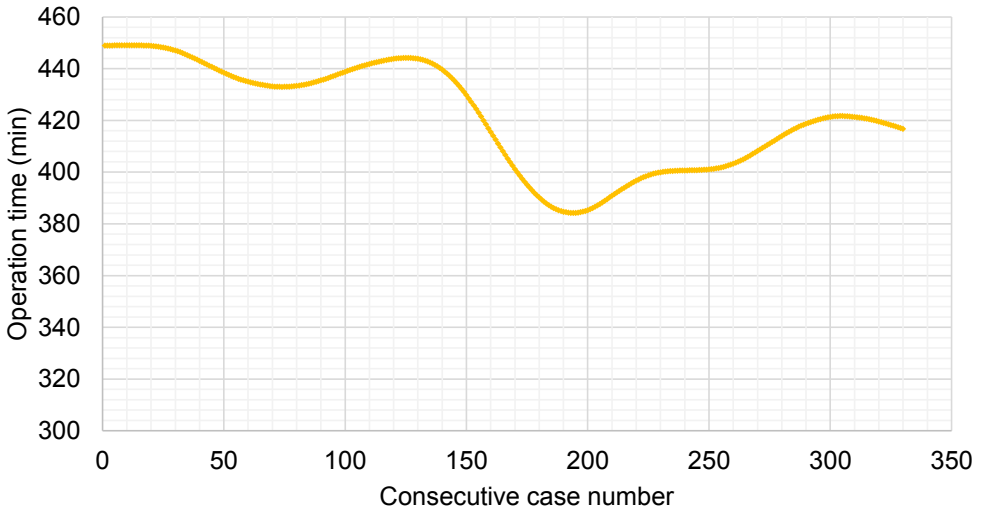
Variables	Univariate analysis		Multivariate analysis	
	OR (95% CI)	P value	OR (95% CI)	P value
Age				
>65 years	1.025 (0.620-1.695)	.923		
>70 years	0.983 (0.566-1.708)	.952		
>75 years	1.364 (0.602-3.086)	.457		
>80 years	2.779 (0.499-15.460)	.243		
BMI				
>25 kg/m ²	1.525 (0.903-2.576)	.115	not entered	
>30 kg/m ²	1.814 (0.996-3.303)	.051	2.182 (1.127-4.225)	.021
>35 kg/m ²	0.738 (0.172-3.478)	.738		
Cardiovascular morbidity	1.067 (0.642-1.773)	.803		
Diabetes mellitus	2.072 (1.063-4.039)	.032	0.921 (0.286-2.966)	.891
ASA classification				
≥2	1.286 (0.730-2.264)	.384		
≥3	1.53 (0.880-2.886)	.124	1.604 (0.824-3.124)	.164
Neoadjuvant chemoradiotherapy	0.717 (0.376-1.370)	.314		
Minimally invasive surgery	0.850 (0.238-3.035)	.802		
Transhiatal esophagectomy	1.612 (0.734-3.538)	.234		
McKeown esophagectomy	3.679 (2.154-6.285)	<.001	1.495 (0.751-2.979)	.253
Flap and wrap reconstruction	0.188 (0.108-0.325)	<.001	0.214 (0.107-0.427)	.001

Appendix F.

a) Proficiency-gain curve for Ivor Lewis esophagectomy: blood loss



b) Proficiency-gain curve for Ivor Lewis esophagectomy: operation time





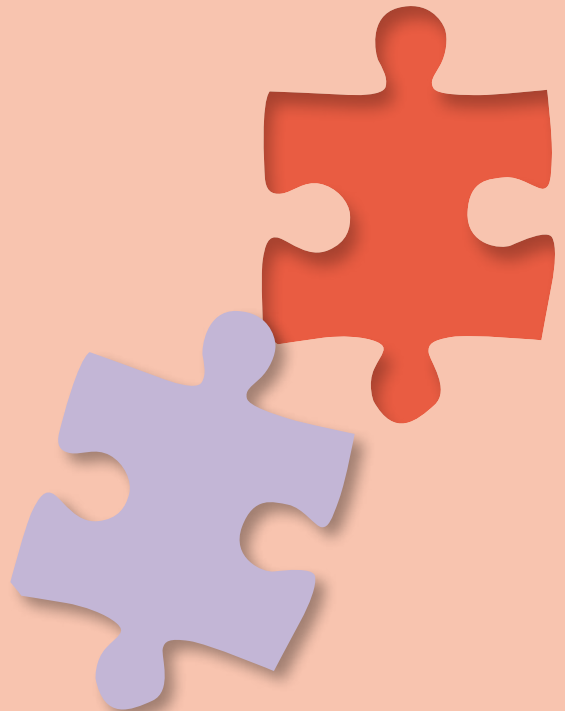
CHAPTER 8

Incidence and treatment of symptomatic diaphragmatic hernia after esophagectomy for cancer

Annals of Thoracic Surgery 2018

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ABSTRACT

Background: Diaphragmatic hernias after esophagectomy are mostly asymptomatic. However, they can also manifest with severe complications and be associated with high morbidity and mortality rates. The aims of this study were to assess the incidence, predictive factors, and preferred treatment of symptomatic diaphragmatic hernias and to evaluate the role of prophylactic cruroplasty in patients after esophagectomy for carcinomas of the esophagus or gastroesophageal junction.

Methods: A prospective database was used to retrospectively analyze consecutive patients who underwent esophagectomy between January 2005 and December 2015.

Results: A symptomatic diaphragmatic hernia was diagnosed in 21 (2.5%) of 851 included patients, 15 (4.3%) after 345 minimally invasive esophagectomies and 6 (1.2%) after 506 open esophagectomies ($P = .004$). Minimally invasive Ivor Lewis procedures had the highest incidence (9.4%, $P = .002$) as compared with all other procedures. Prophylactic cruroplasty did not decrease the incidence of symptomatic diaphragmatic hernias (2.1 vs 2.7%, $P = .608$). Surgical treatment consisted of cruroplasty, with reinforcement of Prolene pledgets (Ethicon, Somerville, NJ) in 11 patients. Major complications (Clavien–Dindo grade > IIIb) occurred in 3 patients, all after open repair ($n=9$). Recurrences were found in 4 patients (19.0%), three after laparoscopic repair and one after open repair.

Conclusions: The incidence of symptomatic diaphragmatic hernia after esophagectomy was 2.5%, with the highest incidence after minimally invasive Ivor Lewis esophagectomy (9.4%) as compared with other procedures. Although prophylactic cruroplasty is now the standard of care in patients undergoing minimally invasive esophagectomy, a significant lower hernia rate was not found in this study.

INTRODUCTION

The incidence of esophageal cancer is increasing worldwide, and this is mainly attributable to the increasing number of adenocarcinomas in Western countries.^{1,2} The best curative option for this disease is esophageal resection. However, esophageal resections are associated with high short-term and long-term morbidity rates.^{3,4} An uncommon complication after esophagectomy is diaphragmatic hernia, with an incidence that varies between 0 and 28%.⁵⁻⁷ Most diaphragmatic hernias are asymptomatic and are not always diagnosed in patients who underwent esophagectomy, whereas the incidence of symptomatic hernias ranges from 0% to 19%.⁵ The associated symptoms are non-specific (e.g., shortness of breath or abdominal pain), but they can suggest a life-threatening incarceration of intra-abdominal organs through the esophageal hiatus. Untreated symptomatic diaphragmatic hernias can be followed by imminent strangulation, necrosis, and perforation of the incarcerated tissue or organ.⁶⁻¹⁰ Symptomatic hernias after esophagectomy represent an absolute indication for surgical intervention, and treatment consists of reduction of the hernia and cruroplasty.¹¹ Despite the possible severity of this complication, the actual incidence is often underestimated, and the number of studies including patients with symptomatic hernias is limited. The aims of this study were to assess the incidence, predictive factors, and preferred treatment of symptomatic diaphragmatic hernias in a large consecutive patient group that underwent esophagectomy for carcinoma of the esophagus or gastroesophageal junction (GEJ) and to evaluate the role of prophylactic cruroplasty in the incidence of symptomatic diaphragmatic hernias.

METHODS

Study setting

A prospective database of a tertiary high-volume academic center (The Academic Medical Center, Amsterdam, the Netherlands) was used to perform this study. The database contained all consecutive patients with an adenocarcinoma or squamous cell carcinoma of the esophagus (or gastroesophageal junction) who were operated on between January 2005 and January 2016. Approval for this study and the requirement to gain informed consent were waived by the local medical ethical committee because participants in this study were not subjected to diagnostic or therapeutic procedures and were not required to follow rules of behavior. All adult patients (age >17 years) who underwent an elective transthoracic esophagectomy or transhiatal esophagectomy with curative intent and reconstruction were included. During salvage procedures a

reconstruction was usually not performed in this hospital, and these patients were consequently excluded. Patients with metastases (M1 tumors) did not undergo esophagectomy in our hospital and were also excluded from this study.

Definition of a symptomatic diaphragmatic hernia

A symptomatic diaphragmatic hernia was defined as a postoperative intrathoracic herniation of abdominal viscera that occurred after esophagectomy, confirmed by chest radiography or computed tomography (CT) and accompanied by related symptoms. If radiologic imaging showed a diaphragmatic hernia during follow up but patients did not experience related symptoms, the hernia was defined as asymptomatic and patients were not surgically treated.

Esophagectomy techniques

Transthoracic (McKeown or Ivor Lewis procedures) or transhiatal esophageal resections were performed in our center. Minimally invasive esophagectomy was implemented in 2009, and more than one half of the patients underwent minimally invasive esophagectomy in 2013. A 3- to 4-cm-wide gastric tube was the standard type of reconstruction. If the stomach was not suitable for reconstruction, a colonic interposition was created.

Prophylactic cruroplasty at initial surgery

During all transhiatal esophageal resections, the left and right crura were widened. To gain further access to the para-esophageal tissue, the diaphragm was opened anteriorly. The crus was not dissected during this procedure. In the final phase, cruroplasty was performed by closing the crus at the anterior side. Because the gastric conduit was positioned at the posterior side in all procedures, it was protected against iatrogenic injury. Cruroplasty was performed as a standard of care in all open transthoracic resections during the final part of the abdominal phase. However, the addition of cruroplasty during minimally invasive transthoracic esophagectomy was determined at the surgeon's discretion until January 2014. After January 2014 it was implemented as a standard of care for all transthoracic procedures. Ethibond non-absorbable sutures (Ethicon, Somerville, NJ) were used to close the widened crus until the hiatus measured a width of approximately 4 cm.

Postoperative follow-up after esophagectomy

Postoperative CT scans were not routinely performed during the outpatient clinic visits according to the Dutch guidelines unless this imaging was required as indicated by symptoms, complications, or suspicion of tumor recurrences.¹² Outpatient clinic visits were planned in the first 2 weeks after discharge, every 3 months in the first year, and every 6 months thereafter.

Surgical treatment of symptomatic diaphragmatic hernias

The choice of open or minimally invasive diaphragmatic hernia repair was made on the basis of the availability of minimally invasive surgery, the surgeon's discretion, and the surgeon's experience. During each procedure, contents of the hernia were repositioned into the abdominal cavity, followed by cruroplasty. Based on the surgeon's experience, cruroplasty was reinforced with pledgets of Prolene mesh (Ethicon, Somerville, NJ), 0.5 to 1 cm² on both sides of every stitch. Finally, the gastric conduit was sewn to the crus using Vicryl absorbable sutures (Ethicon, Somerville, NJ).

Data collection and statistics

Patients' characteristics, surgical data, and short-term outcomes were collected in a prospective database. The severity of complications was scored according to the Clavien–Dindo classification.¹³ All Clavien–Dindo classification grades higher than IIIa were considered major complications. Data on symptomatic diaphragmatic hernias were retrospectively identified from the hospital databases.

Univariate and multivariate analyses were performed to assess the role of assumed risk factors in the occurrence of symptomatic diaphragmatic hernias. The following parameters were entered into the univariate analyses: BMI, sex, age, ASA classification, type of neoadjuvant treatment, tumor location, minimally invasive procedure, type of esophagectomy, colonic reconstruction, intrathoracic anastomosis, and prophylactic cruroplasty. If parameters showed a significance of $P < 0.20$ in the univariate analyses, entering into a stepwise multivariate logistic regression analysis followed. Ten events (i.e., symptomatic diaphragmatic hernias) per variable were required to perform the multivariate analysis.¹⁴ Cross-tabulations were calculated by Chi-square analyses and Fisher's exact tests. Linear-by-linear association tests were used to compare ordinal scales between groups. $P < .05$ was considered to be statistically significant. IBM SPSS Statistics version 22.0 (IBM Corp, Armonk, NY) was used to perform all analyses.

RESULTS

A total of 851 patients with a median age of 64 years underwent curative esophagectomy for esophageal cancer between January 2005 and January 2016 (Table 1). Of all patients, open esophagectomy was performed in 506 patients, and minimally invasive esophagectomy was performed in 345 patients. Most patients underwent open transhiatal esophagectomy (n=232, 27.3%), followed by open McKeown esophagectomy (n=217, 25.5%), minimally invasive McKeown esophagectomy (n=184, 21.6%), minimally invasive Ivor Lewis esophagectomy (n=117, 13.7%), open Ivor Lewis esophagectomy (n=57, 6.7%), and minimally invasive THE (n=44, 5.2%; Table 2, Fig. 1). More than half of the patients were treated with neoadjuvant chemoradiotherapy (61.8%). The median length of stay was 14 days. The morbidity rate was 64.5%, and the 30-day mortality rate was 2.6%. For fewer than 5% of the patients, body mass index, ASA classification, and cruroplasty data were missing.

Incidence of symptomatic diaphragmatic hernia

During follow-up 21 patients (2.5%) were diagnosed with a symptomatic diaphragmatic hernia. Of these, 15 patients previously underwent minimally invasive esophagectomy (4.3%), and 6 patients underwent open esophagectomy (1.2%, $P = .004$). The highest incidence was found after minimally invasive Ivor Lewis esophagectomy (9.4%, $P < .001$) as compared with other techniques (Table 2).

Figure 1.

Overview of the annual incidence of symptomatic diaphragmatic hernia (SDH) after esophageal resections, prophylactic cruroplasty, and minimally invasive Ivor Lewis esophageal resections

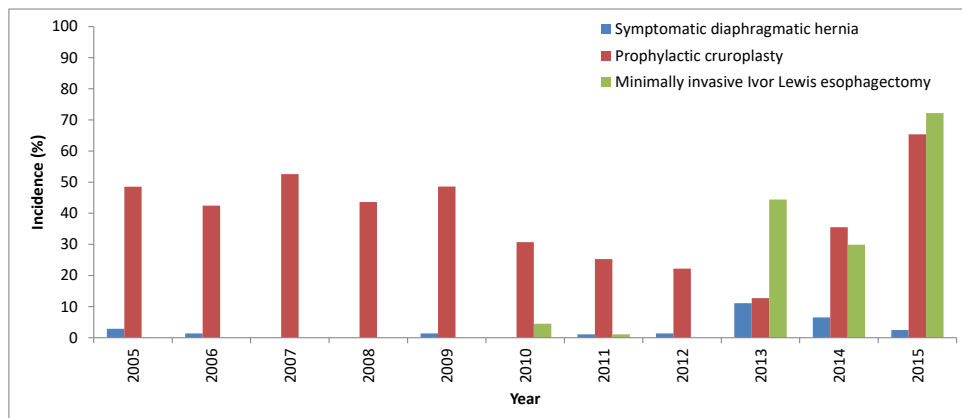


Table 1. Characteristics of 851 patients who underwent esophagectomy between January 2005 and December 2015.

	Total group (n=851)	Symptomatic diaphragmatic hernia (n=21)	P value
Age (years)	63 (24–85)	62 (45–79)	.481
Sex (male)	654 (76.9)	15 (3.3)	.551
Body mass index ^a (kg/m ²)	25.9 (16.5–46.3)	24.0 (19.5–34.4)	.278
ASA classification ^b			.470
1	161 (18.9)	6 (3.7)	
2	481 (56.5)	10 (2.1)	
3	204 (24.0)	5 (2.5)	
4	2 (0.2)	0	
Previous upper gastrointestinal surgery	22 (2.6)	0	1.000
Tumor site			.673
Proximal esophagus	3 (0.4)	0	
Mid esophagus	127 (14.9)	1 (0.8)	
Distal esophagus	538 (63.2)	16 (3.0)	
Gastroesophageal junction	151 (17.7)	3 (2.0)	
Cardia	32 (3.8)	1 (3.1)	
Neoadjuvant treatment			.023
No neoadjuvant treatment	301 (35.4)	2 (0.7)	
Chemotherapy	24 (2.8)	0	
Chemoradiotherapy	526 (61.8)	19 (3.6)	
Surgical approach			.004
Minimally invasive	345 (40.5)	15 (4.3)	
Open	526 (61.8)	6 (1.2)	
Reconstruction			.300
Gastric conduit	840 (98.7)	20 (2.4)	
Colon interposition	10 (1.2)	1 (10.0)	
Esophagojejunostomy	1 (0.1)	0	
Anastomosis site			<.001
Cervical	667 (79.6)	10 (1.5)	
Intrathoracic	163 (20.4)	11 (6.3)	
Cruroplasty ^c	328 (38.5)	7 (2.1)	.608
Postoperative histology			.352
Adenocarcinoma	622 (73.1)	16 (2.6)	
Squamous cell carcinoma	157 (18.4)	2 (1.3)	
High grade dysplasia	11 (1.3)	0	
Other malign	13 (1.5)	0	
No tumor cells	48 (5.6)	3 (6.3)	
Length of stay (days)	14 (3–304)	11 (7–71)	.682
Length of ICU stay (days)	1 (0–213)	1 (0–18)	.608
Morbidity after esophagectomy	551 (64.7)	15 (71.4)	.502
Clavien–Dindo classification			.304
I	104 (12.2)	2 (1.9)	
II	178 (20.9)	3 (1.7)	
IIIa	55 (6.5)	4 (7.3)	
IIIb	31 (3.6)	2 (6.5)	
IVa	104 (12.2)	2 (1.9)	
IVb	41 (4.8)	1 (2.4)	
V	36 (4.2)	1 (2.8)	
30-day mortality	22 (2.6)	0	1.000
In-hospital mortality	31 (3.8)	1 (3.1)	.557
Combined mortality	35 (4.2)	1 (2.8)	.601

Continuous data are presented as median (range). ASA American Society of Anesthesiologists, ICU intensive care unit. ^a Data were missing for 22 patients (2.6%), ^b Data were missing for 3 patients (0.4%),

Table 2. Incidence of symptomatic diaphragmatic hernias in all surgical procedures

Type of procedure	Total group	Symptomatic diaphragmatic hernia	P value
			.002
Open transhiatal esophagectomy	232 (27.3)	3 (1.3)	
Open Ivor Lewis esophagectomy	57 (6.7)	0	
Open McKeown esophagectomy	217 (25.5)	3 (1.4)	
Minimally invasive transhiatal esophagectomy	44 (5.2)	1 (2.3)	
Minimally invasive Ivor Lewis esophagectomy	117 (13.7)	11 (9.4)	
Minimally invasive McKeown esophagectomy	184 (21.6)	3 (1.6)	

Patients with a symptomatic diaphragmatic hernia did not have a medical history of gastric or esophageal surgical treatment, but 3 patients (14.3%) had a pre-existing diaphragmatic hernia (Table 3). One patient had colonic reconstruction after esophagectomy secondary to extensive ingrowth of the tumor in the stomach.

Prophylactic cruroplasty

The influence of prophylactic cruroplasty on the incidence of symptomatic diaphragmatic hernia could not be found in this study. There were seven symptomatic hernias after prophylactic cruroplasty versus 14 if cruroplasty was not performed during esophagectomy (resp. 2.1 versus 2.7%, $P = .608$). In a subgroup analysis of patients who underwent minimally invasive Ivor Lewis procedures, the difference in incidence of symptomatic diaphragmatic hernias after prophylactic cruroplasty ($n=2$) as compared with no cruroplasty ($n=9$) showed no significance (resp. 5.0 versus 12.2%, $P = .324$).

Predictive factors

Potential effects of neoadjuvant chemoradiotherapy, minimally invasive esophagectomy, minimally invasive Ivor Lewis esophagectomy, open transhiatal esophagectomy, colonic interposition, and intrathoracic anastomosis were tested in univariate analyses (Table 4).

Table 3. Clinical manifestations of 21 patients with symptomatic diaphragmatic hernia.

Variable	n (%)
Pre-existing diaphragmatic hernia	3 (14.3)
Short-term symptomatic diaphragmatic hernia	5 (23.8)
Time (days) from surgery to diagnosis	172 (1-1031)
Diagnosis	
Chest X-ray	3 (14.3)
CT scan	17 (81.0)
Laparoscopic exploration	1 (4.8)

Continuous data are presented as median (range). CT computed tomography.

Table 4. Possible predictive factors entered in the univariate analyses.

Variables	Odds ratio	95% confidence interval	P value
Body mass index (kg/m ²)	0.952	0.848-1.068	.399
Sex (male)	0.747	0.286-1.952	.552
Age (years)	0.984	0.941-1.029	.481
ASA classification			
>1	0.577	0.220-1.510	.262
>2	0.967	0.350-2.673	.948
>3	0	0	1.000
Tumor site			
Proximal esophagus	n/a	n/a	n/a
Mid esophagus	0.279	0.03-2.100	.215
Distal esophagus	1.888	0.685-5.205	.219
Gastroesophageal junction	0.768	0.223-2.641	.675
Cardia	1.289	0.168-9.913	.807
Neoadjuvant therapy			
Chemotherapy	0	0	.998
Chemoradiotherapy	6.052	1.400-26.157	.016
Minimally invasive esophagectomy	3.788	1.455-9.862	.006
Type of esophagectomy			
Open transhiatal	n/a	n/a	.020
Open McKeown	1.070	0.214-5.359	.934
Open Ivor Lewis	0	0	.997
MI transhiatal	1.775	0.180-17.469	.632
MI McKeown	1.265	0.252-6.343	.775
MI Ivor Lewis	7.921	2.165-28.985	.002
Colonic interposition	4.561	0.551-37.737	.159
Intrathoracic anastomosis	4.501	1.880-10.780	.001
Cruroplasty	0.787	0.314-1.970	.608

ASA American Society of Anesthesiologists, MI minimally invasive, n/a not applicable

Of these factors, neoadjuvant chemoradiotherapy, minimally invasive esophagectomy, minimally invasive Ivor Lewis esophagectomy, and intrathoracic anastomosis had $P < .20$. Of these, neoadjuvant chemoradiotherapy and minimally invasive Ivor Lewis esophagectomy were entered into the multivariate analysis.¹⁴ Only minimally invasive Ivor Lewis esophagectomy was an independent predictive factor for developing symptomatic diaphragmatic hernias in this model, with an odds ratio of 4.289 (95% CI 1.090-16.869; $P < .037$; Table 5).

Diagnosis

There was a median of 172 days (range 1-1031) between esophagectomy and the diagnosis of a symptomatic diaphragmatic hernia, with a median of 202 days (range 8-1031) after MIE, whereas this median was only 10 days (range 1-347 days) after open esophagectomy ($P = .010$). There were 6 patients who had a hernia during hospitalization for the initial esophagectomy. Of these,

Table 5. Multivariate analysis for 851 patients who underwent esophagectomy with 21 symptomatic patients

Variables	Odds ratio	95% confidence interval	P value
Neoadjuvant therapy			
None	Ref.	Ref.	Ref.
Chemotherapy	0	0	.998
Chemoradiotherapy	3.906	0.819-18.622	.087
Type of esophagectomy			
Open transhiatal	Ref.	Ref.	Ref.
Open McKeown	0.790	0.155-4.028	.777
Open Ivor Lewis	0.00	0.00	.997
Minimally invasive transhiatal	1.061	0.104-10.790	.960
Minimally invasive McKeown	0.650	0.122-3.482	.615
Minimally invasive Ivor Lewis	4.289	1.090-16.869	.037

Ref reference value

5 patients had a diagnosis in the first 30 days after esophagectomy (early hernias). The sixth patient had a diagnosis on day 37 but was still hospitalized for the initial esophagectomy at that time. The most common symptom in the early diagnosis (within 30 days postoperatively) was respiratory distress, although the most common symptoms were abdominal or thoracic pain during the late diagnosis. CT scans were used to diagnose more than 80% of the symptomatic diaphragmatic hernias (Table 3, Fig. 2).



Figure 2. Computed tomography scan of the thorax and abdomen of a patient 10 months after esophagectomy who reported dyspnea.

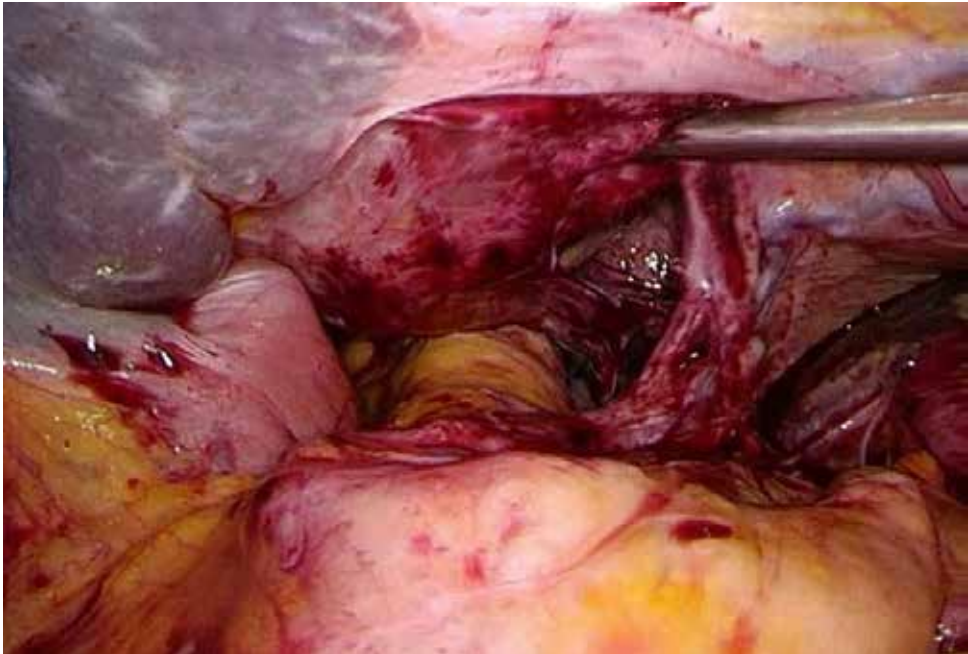
Surgical repair of symptomatic diaphragmatic hernia

The median time interval between the diagnosis of a symptomatic diaphragmatic hernia and surgical repair was 1 day (range 0–701). Most patients were operated on in an acute setting (71.4%) because of suspected intestinal strangulation or ischemia on the basis of clinical presentation or CT scan findings. In 11 patients (52.4%) minimally invasive repair was performed. Of these, conversion to open surgery was necessary in 1 patient as a result of pulmonary insufficiency during laparoscopy and poor abdominal view caused by distension of the large bowel. In 10 patients cruroplasty was reinforced with Prolene pledgets (Ethicon), and data on 1 patient were missing. Figure 3 and 4 show laparoscopic views of a diaphragm before and after closure with reinforcement of pledgets.

Outcomes after surgical repair of symptomatic diaphragmatic hernia

The morbidity rate after surgical repair was 42.9%, all after surgical procedures in an acute setting (Table 6). Major complications (Clavien–Dindo classification >grade IIIa) occurred in 4 patients (19.1%), all after open surgical repair. One of these patients died of cardiac arrest within 30 days after open repair. However, autopsy showed multiple diffuse metastases that were thought to be the cause of death. A second patient was admitted to the intensive care

Figure 3. Laparoscopic abdominal view of the diaphragmatic hernia.



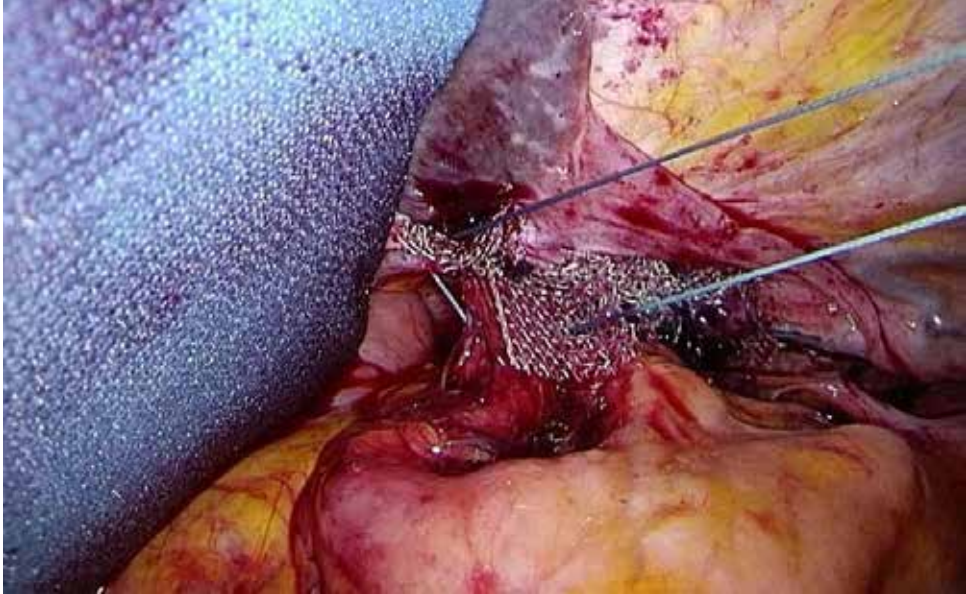


Figure 4. Abdominal view after laparoscopic repair of the diaphragmatic hernia with mesh reinforcement.

unit because of respiratory distress, deep venous thrombosis, anastomotic leakage related to the esophagectomy, and pneumonia after aspiration secondary to vocal cord paresis. The third patient was intubated as a result of cardiac decompensation after persistent atrial fibrillation, and the last patient was admitted to the intensive care unit as a consequence of sepsis resulting from perforation of the small bowel combined with worsening of pre-existing pneumonia. The median length of stay after hernia repair was 8 days (range 1–55).

The Mann–Whitney U test showed a lower length of stay after minimally invasive hernia repair (median of 4 days, range 1–20) as compared with open repair (median of 25 days, range 4–55, $P = .017$). Recurrences of symptomatic diaphragmatic hernias were found in 4 patients (19%). Three recurrences occurred after laparoscopy, two of these hernias were closed with primary sutures, and one was reinforced with pledgets. The recurrence after open esophagectomy was treated with open surgery and reinforcement of Prolene pledgets (Ethicon).

Table 6. Morbidity after surgical repair of symptomatic diaphragmatic hernias

Complications	n (%)
Atrial fibrillation	2 (9.5)
Heart failure	1 (4.8)
Delirium	3 (14.2)
Pulmonary embolism	1 (4.8)
Short bowel torsion	1 (4.8)
Anastomotic leakage	2 (9.5)
Chyle leakage	1 (4.8)
Pneumonia	2 (9.5)
Urine bladder infection	1 (4.8)
Wound infection	1 (4.8)
Pleural effusion	1 (4.8)
Pericarditis	1 (4.8)
Deep venous thrombosis	1 (4.8)
Wound abscess	1 (4.8)

DISCUSSION

In the present study we evaluated the incidence, risk factors, and treatment of symptomatic diaphragmatic hernias after esophagectomies. The incidence of symptomatic diaphragmatic hernias in patients after esophageal resections was 2.5%; 1.2% after open operation and 4.3% after MIE.

Subgroup analyses showed that the highest incidence of symptomatic diaphragmatic hernia was seen after minimally invasive Ivor Lewis esophagectomy (9.4%) as compared with other surgical techniques. This was also a risk factor for symptomatic diaphragmatic hernias in the multivariate analysis. In this single tertiary referral center series, an increase in symptomatic diaphragmatic hernias has been seen since 2013. This may have been the result of the increased numbers of minimally invasive Ivor Lewis esophagectomies performed, in which the hiatus is widened more compared with a minimally invasive McKeown procedure. Widening of the hiatus was reported to be a prognostic factor for postoperative diaphragmatic hernia by two studies (by Van Sandick and colleagues and Oor and colleagues).^{5,15}

Moreover, this increase could be a result of the early phase of the learning curve of surgeons for minimally invasive Ivor Lewis esophagectomy, which was introduced in 2012. Consequently, the procedure was refined over time; for example, by adding cruroplasty after a higher incidence of hernias in the first period of implementation. It is possible that the incidence of symptomatic diaphragmatic hernia has decreased since that time. Although a statistical significance

for the predictive value of cruroplasty could not be retrieved because of the low numbers in this study, a significant difference perhaps may be found in larger series.

The influence of minimally invasive surgery on the development of adhesions in a large patient group was investigated by Burns and colleagues.¹⁶ These investigators showed that minimally invasive surgery causes fewer adhesion-related complications after colorectal operations as compared with open procedures. After open esophageal resections, postoperative adhesions could prevent the abdominal viscera from herniation through the hiatus, a hypothesis that was also proposed by other investigators.^{8,10} This hypothesis seems to be supported by the short time interval between open esophagectomy and the diagnosis of symptomatic diaphragmatic hernias in the current study (a median of 10 days). Although it was not significant in the multivariate analysis in this study, neoadjuvant (chemo-)radiotherapy has been reported to be associated with impaired wound healing. If radiotherapy is performed in the area of the hiatus, as was the case in this study group, this could be a causal factor for the development of symptomatic diaphragmatic hernias. However, this effect could have been clouded by the implementation of minimally invasive surgery because it was introduced in the same period as neoadjuvant chemoradiotherapy.

The scarce number of studies that have investigated the incidence of diaphragmatic hernias after esophageal resections predominantly includes patients with both asymptomatic and symptomatic diaphragmatic hernias. Nonetheless, the study by Van Sandick and colleagues has shown that surgical treatment is not always indicated if patients have a diagnosis of diaphragmatic hernia.¹⁵ Besides, various definitions of diaphragmatic hernias have been used, and inclusion criteria are not homogeneous among studies. This disparity has led to a wide range of incidence of this complication.⁵⁻⁷ For example, two cross-sectional studies by Ganeshan and colleagues included patients only if CT scans were performed in the first year postoperatively.^{10,17} Patients who were not postoperatively monitored in the study of Geneshan et al. could have had a symptomatic diaphragmatic hernia, but they were excluded from the analysis. Furthermore, the recent study of Brenkman and colleagues performed CT scans on indication in 74% of their cohort.¹⁸ Patients who had evidence of diaphragmatic hernia on CT scans were subsequently asked whether they experienced symptoms, and this approach could have introduced an observational bias in their study.

Morbidity rates up to 60% after surgical repair of symptomatic diaphragmatic hernias were described in other studies, with a morbidity rate after laparoscop-

ic repair ranging from 11 to 56%.⁵ This finding is comparable to the morbidity in the present study, especially for the lower morbidity rate after laparoscopic repair. Thus, the best surgical treatment for symptomatic diaphragmatic hernias seems to be laparoscopic repair.

Limitations

According to the Dutch guidelines for esophageal cancer, CT scans are not performed as a standard of care in the postoperative period in the Netherlands.¹² Consequently, the incidence of asymptomatic diaphragmatic hernias could not be assessed in the present study. Although a prospective database with consecutive patients was used for this study, the selection of patients with symptomatic diaphragmatic hernias was retrospectively performed, and this could have led to missing data. For example, a pre-existing diaphragmatic hernia is interesting to investigate because the meta-analysis of Oor and colleagues showed that a pre-existing diaphragmatic hernia was a predictive factor in one of three studies that were included.⁵ Unfortunately, data on pre-operative diaphragmatic hernias could not be retrieved for the entire cohort from our prospective database. Another factor is that minimally invasive surgery was introduced in 2009, and the Ivor Lewis procedure has been the preferred procedure in our center since its introduction in 2012. Therefore, there is some heterogeneity among the current patient group. Further prospective investigations with a larger and homogeneous patient group are recommended to assess the incidence of symptomatic diaphragmatic hernias.

CONCLUSIONS

The incidence of symptomatic diaphragmatic hernias after esophagectomy was 2.5% in this study. A trend towards a greater incidence was observed for the last few years and, more specifically, in patients undergoing minimally invasive Ivor Lewis esophagectomy. Although prophylactic cruroplasty is now the standard of care in patients undergoing minimally invasive esophagectomy in this center, a significant lower hernia rate was not found in this study. The best treatment for patients with this serious complication seems to be laparoscopic repair with approximation of the crura, combined with placement of mesh pledgets in patients with a large symptomatic hernia.

References

1. Arnold M, Soerjomataram I, Ferlay J, Forman D. Global incidence of esophageal cancer by histological subtype in 2012. *Gut*. 2015;64(3):381-387. DOI: 10.1136/gutjnl-2014-308124
2. Ferlay J, Steliarova-Foucher E, Lortet-Tieulent J, et al. Cancer incidence and mortality patterns in Europe: estimates for 40 countries in 2012. *Eur J Cancer*. 2013;49(6):1374-1403. DOI: 10.1016/j.ejca.2012.12.027
3. van Workum F, van der Maas J, van den Wildenberg F, et al. Improved functional results after minimally invasive esophagectomy: intrathoracic versus cervical anastomosis. *Ann Thorac Surg*. 2017;103(1):267-273. DOI: 10.1016/j.athoracsur.2016.07.010
4. Luketich JD, Pennathur A, Franchetti Y, et al. Minimally invasive esophagectomy. Results of a prospective phase II multicenter trial—the eastern cooperative oncology group (E2202) study. *Ann Surg*. 2015;261(4):702-707. DOI: 10.1097/SLA.0000000000000993
5. Oor JE, Wiezer MJ, Hazebroek EJ. Hiatal hernia after open versus minimally invasive esophagectomy: a systematic review and meta-analysis. *Ann Surg Oncol*. 2016;23(8):2690-2698. DOI:10.1245/s10434-016-5155-x
6. Ulloa Severino B, Fuks D, Christidis C, Denet C, Gayet B, Perniceni T. Laparoscopic repair of hiatal hernia after minimally invasive esophagectomy. *Surg Endosc Other Interv Tech*. 2016;30(3):1068-1072. DOI:10.1007/s00464-015-4299-2
7. Matthews J, Bhandari S, Mitchell H, et al. Diaphragmatic herniation following esophagogastric resectional surgery: an increasing problem with minimally invasive techniques?: Post-operative diaphragmatic hernias. *Surg Endosc Other Interv Tech*. 2016;30(12):1-9. DOI:10.1007/s00464-016-4899-5
8. Price TN, Allen MS, Nichols FC, et al. Hiatal hernia after esophagectomy: analysis of 2,182 esophagectomies from a single institution. *Ann Thorac Surg*. 2011;92(6):2041-2045. DOI:10.1016/j.athoracsur.2011.08.013
9. Messenger DE, Higgs SM, Dwerryhouse SJ, et al. Symptomatic diaphragmatic herniation following open and minimally invasive esophagectomy: Experience from a UK specialist unit. *Surg Endosc Other Interv Tech*. 2015;29(2):417-424. DOI:10.1007/s00464-014-3689-1
10. Ganeshan DM, Correa AM, Bhosale P, et al. Diaphragmatic hernia after esophagectomy in 440 patients with long-term follow-up. *Ann Thorac Surg*. 2013;96(4):1138-1145. DOI:10.1016/j.athoracsur.2013.04.076
11. Benjamin G, Ashfaq A, Chang YH, Harold K, Jaroszewski D. Diaphragmatic hernia post-minimally invasive esophagectomy: a discussion and review of literature. *Hernia*. 2015;19(4):635-643. DOI:10.1007/s10029-015-1363-8
12. Vereniging van Maag-Darm-Leverartsen. National guideline for the treatment of esophageal cancer in the Netherlands, version 3.0. https://richtlijnendatabase.nl/richtlijn/oesofaguscarcinoom/oesofaguscarcinoom_-_startpagina.html. Published 2010.
13. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: A new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg*. 2004;240(2):205-213. DOI:10.1097/01.sla.0000133083.54934.ae
14. Peduzzi P, Concato J, Kemper E, Holford TR, Feinstein AR. A simulation study of the number of events per variable in logistic regression analysis. *J Clin Epidemiol*. 1996;49(12):1373-1379. DOI: 10.1016/s0895-4356(96)00236-3
15. Van Sandick JW, Kneijens JL, Van Lanschot JJB, Obertop H. Diaphragmatic herniation following esophagectomy. *Br J Surg*. 1999;86(1):109-112. DOI:10.1046/j.1365-2168.1999.00979.x
16. Burns EM, Currie A, Bottle A, Aylin P, Darzi A, Faiz O. Minimal-access colorectal surgery is associated with fewer adhesion-related admissions than open surgery. *Br J Surg*. 2013;100(1):152-159. DOI:10.1002/bjs.8964
17. Ganeshan DM, Bhosale P, Iyer R. Diaphragmatic hernia after esophagectomy for esophageal malignancy. *J Thorac Imaging*. 2013;28(5):308-314. DOI: 10.1097/RTI.0b013e3182776df7
18. Brenkman HJF, Parry K, Noble F, et al. Hiatal hernia after esophagectomy for cancer. *Ann Thorac Surg*. 2017;103(4):1055-1062. DOI:10.1016/j.athoracsur.2017.01.026

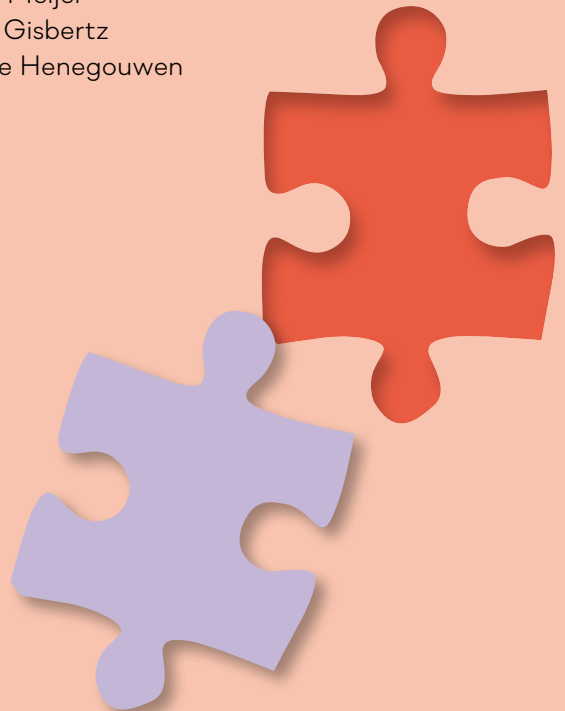


CHAPTER 9

Improved clinical outcomes and survival after esophagectomy for cancer in a tertiary referral center over 25 years

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ABSTRACT

Background: In recent decades, there have been major developments in the curative treatment of esophageal cancer, such as implementation of PET/CT, neoadjuvant chemoradiotherapy, minimally invasive surgery and enhanced recovery programs. This observational study examined clinical and survival outcomes of patients after esophagectomy for cancer over 25 years.

Methods: Consecutive patients who underwent esophagectomy for cancer at a tertiary referral center between 1 January 1993 and 1 January 2018 were selected from a prospectively maintained database. Patients were assigned to five periods: 1993–1997, 1998–2002, 2003–2007, 2008–2012, and 2013–2017. The primary outcome was 5-year overall survival using Kaplan–Meier with log-rank tests for trends.

Results: A total of 1612 patients were analyzed. The median follow-up of surviving patients was 80.4 months (IQR 58.5–123.2). The 5-year overall survival improved gradually from 32.5% to 47.7% over 25 years ($P < .001$). Length of stay reduced from a median of 16 days (IQR 14–24) in 1993–1997 to 11 days (IQR 8–18) in 2013–2017 ($P < .001$). No decrease in mortality was encountered over 25 years, although over the last 5 years, in-hospital and 90-day mortality dropped from 4.2% and 8.3% in 2013 to 0% in 2017 for both parameters ($P < .050$). Anastomotic leakages reduced from 26.4% in 2013 to 9.7% in 2017 ($P < .001$).

Conclusion: Over the last 25 years, clinical outcomes and 5-year overall survival significantly improved in patients who underwent esophagectomy for cancer at this tertiary referral center.

INTRODUCTION

The incidence of esophageal cancer is rising globally. In 2018, esophageal cancer was ranked as the sixth most deadly cancer.¹ Although squamous cell carcinoma remains the most frequent esophageal cancer type worldwide, adenocarcinoma has become most prevalent in Western countries.² Changing patient and treatment factors, such as (neo)adjuvant therapies, surgical techniques, and postoperative care protocols, may have improved outcomes after esophageal cancer treatment over the past decades.

Advanced diagnostic techniques (e.g., PET/CT) have led to better detection of metastases, resulting in more accurate patient selection for curative treatment.³ Other diagnostic developments have led to a growing number of patients with earlier cancer diagnosis who are treated by less invasive endoscopic mucosal resections.⁴ The remaining patients for esophagectomy could be in a relatively worse preoperative condition (e.g., by worse nutrition status), leading to deteriorated postoperative outcomes. However, multileaf collimators and intensity-modulated radiotherapy have recently improved radiation dose distribution in terms of lower doses to surrounding tissues, which could lead to fewer radiation adhesions during surgery.⁵ Besides, neoadjuvant chemoradiotherapy improves survival considerably after esophagectomy and has become the standard curative treatment of esophageal cancer worldwide.⁶

Most studies report outcomes after changing diagnostic and therapeutic methods for esophageal cancer for each method separately, without evaluating the effect of all changes together. Few studies have examined cumulative effects, but have often included non-surgical patients, or were performed before latest important changes were implemented.⁷⁻⁹ The aim of the present study was to evaluate short- and long-term outcomes in surgically treated esophageal cancer patients at a tertiary referral center over the past 25 years.

METHODS

Patients

This observational study was performed at the department of surgery of a tertiary referral center in the Netherlands. Consecutive patients between 1 January 1993 and 1 January 2018 were selected from a prospectively maintained database, guaranteeing a potential follow-up of 44 months. Patients with adenocarcinoma or squamous cell carcinoma of the esophagus, gastroesophageal junction, or cardia undergoing esophagectomy were included. Exclusion

criteria were: acute surgery, salvage procedures, perioperative metastases. Groups were analyzed according to the year of esophagectomy: 1993–1997, 1998–2002, 2003–2007, 2008–2012, and 2013–2017. Missing data were retrospectively collected from patients' medical files and otherwise excluded by pairwise deletion. The local institutional review board waived requirements for informed consent.

Staging

Staging occurred routinely by gastroscopy with biopsies, endoscopic ultrasound, and CT scans of neck, thorax, and abdomen. Since 2011, PET/CT was used to detect metastases after neoadjuvant chemoradiotherapy. Tumors were classified according to the 4th–8th American Joint Committee on Cancer (AJCC) prior to neoadjuvant treatment.¹⁰ Truncal node positivity was scored as N+M0.

Oncologic treatment

Neoadjuvant chemoradiotherapy has been implemented as standard treatment for cT0–1N+ and cT2–4aNO–3MO carcinomas since 2010.^{6,11} This consisted of radiotherapy (41.4 Gy, daily fractions of 1.8 Gy) and 5 cycles of concomitant intravenous carboplatin (AUC-2) and paclitaxel (50 mg/m²). Adapted schemes were administered during trials or as perioperative chemotherapy for cardiac tumors.^{12–14}

Surgery

Minimally invasive esophagectomy was implemented in 2009. Intrathoracic anastomoses were introduced by thoracotomy in 2007, followed by thoracoscopy in 2013. Cervical anastomoses were created after transhiatal or 3-stage transthoracic esophagectomy during the entire study period. Routine postoperative ICU admissions occurred in the first half of the study. With application of the Enhanced Recovery after Surgery program (ERAS) since 2009, ICU admission was only required for patients with ASA \geq 3 or postoperative complications. Outpatient clinics were visited 2 and 6 weeks after surgery, every 3 months in the first year, and every 6 months thereafter until 5 years postoperatively. Follow-up imaging was performed on indication.¹¹

Study outcomes and definitions

The primary outcome was 5-year overall survival. Secondary outcomes were morbidity, mortality, reinterventions, reoperations, ICU readmissions, hospital and ICU length of stay (LOS), R0 resections, and lymph node yield. The Clavien–Dindo classification was applied for assessing complication severity and to define reinterventions.¹⁵ Anastomotic leakage was defined according to the definition of the Esophageal Cancer Consensus Group (ECCG).¹⁶

Statistical methods

Baseline characteristics were compared using Chi square tests and one-way ANOVA or Kruskal–Wallis tests. Survival outcomes were compared using Kaplan–Meier with log-rank tests for trends. Chi square tests for trends and Jonckheere–Terpstra tests were used to evaluate trends.¹⁷ The Jonckheere–Terpstra test is a one-tailed, non-parametric test to assess linear trends in medians of groups. It is comparable to the Kruskal–Wallis test, but incorporates orderly arrangement of parameters. Year-on-year analyses were performed between 2013 and 2017. $P < .05$ was considered to be significant. Outcomes were adjusted for confounders. SPSS Statistics 26.0.0.1 (2019, Armonk, NY: IBM Corp.) was used for all statistical analyses. Latest follow-up data were extracted on 25 August 2021.

RESULTS

After applying inclusion criteria, 1612 patients were analyzed (Fig. 1). Mean age was 63 years (95% CI 63–65) and increased from 62 (95% CI 61–63) to 64 years (95% CI 63–65) over 25 years ($P = .012$, Table 1). Mean body mass index increased from 24.5 (95% CI 23.9–25.0) to 26.0 kg/m² (95% CI 25.5–26.4, $P < .001$). Adenocarcinoma was the most common tumor type (71.8%), gradually increasing over time (from 60.3 to 78.9%, $P < .001$).

Use of neoadjuvant chemoradiotherapy increased significantly over 25 years, up to 88.9% of patients in 2017 ($P < .001$, Fig. 2a). Before 2012, >90% of patients had a cervical anastomosis (Fig. 2b). Minimally invasive McKeown esophagectomy was the most common procedure in 2011–2012 (43.8 and 67.2%, respectively). Ivor Lewis esophagectomy became more popular after 2013, constituting 93.1% of all procedures in 2017. Reasons for colonic interpositions were as follows: previous gastrectomy or pancreaticoduodenectomy, extended tumor invasion, and severe radiation effects.

Figure 1. Flow chart

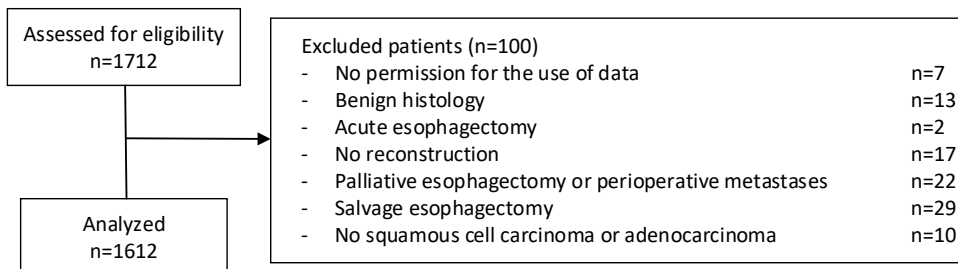


Table 1. Baseline characteristics

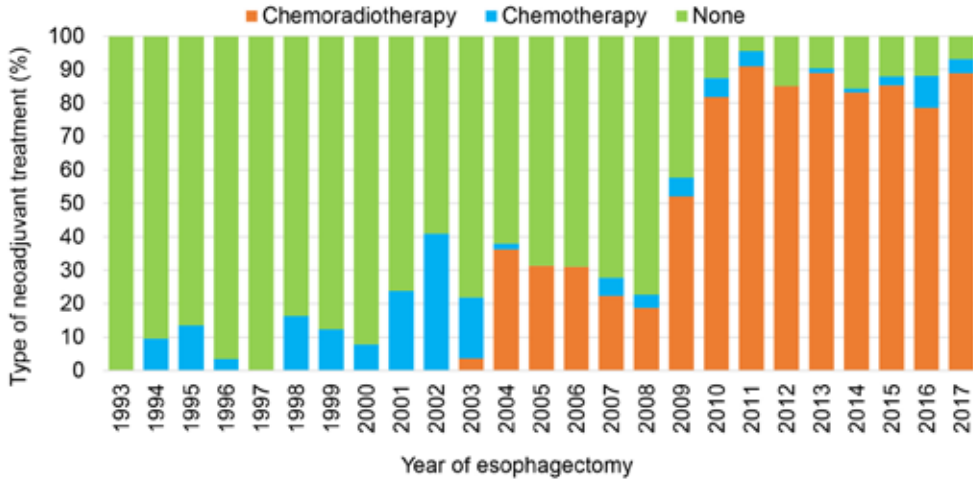
	1993-1997 (n=257)	1998-2002 (n=255)	2003-2007 (n=327)	2008-2012 (n=393)	2013-2017 (n=380)	Total (n=1612)	P value
Sex (male)	189 (73.5)	192 (75.3)	248 (75.8)	311 (79.1)	290 (76.3)	1230 (76.3)	.56
Age (years)	62 (10)	63 (10)	62 (10)	64 (9)	64 (8)	63 (10)	.012
BMI (kg/m ²) ^a	24.5 (3.9)	24.5 (3.9)	25.8 (4.0)	25.6 (3.9)	26.0 (4.4)	25.4 (4.1)	<.001
ASA classification ^b							.49
1	99 (38.7)	85 (33.3)	100 (30.6)	136 (34.7)	141 (37.1)	561 (34.8)	
2	111 (43.4)	129 (50.6)	161 (49.2)	177 (45.2)	177 (46.6)	755 (46.9)	
3	46 (18.0)	41 (16.1)	66 (20.2)	78 (19.9)	62 (16.3)	293 (18.2)	
4	0	0	0	1 (0.3)	0	1 (0.1)	
Tumor site							<.001
Proximal esophagus	6 (2.3)	2 (0.8)	3 (0.9)	0	5 (1.3)	16 (1.0)	
Mid esophagus	44 (17.1)	38 (14.9)	58 (17.7)	60 (15.3)	42 (11.1)	242 (15.0)	
Distal esophagus	136 (52.9)	164 (64.3)	185 (56.6)	248 (63.1)	265 (69.7)	998 (61.9)	
Gastroesophageal junction	44 (17.1)	49 (19.2)	68 (20.8)	70 (17.8)	51 (13.4)	282 (17.5)	
Cardia	27 (10.5)	2 (0.8)	13 (4.0)	15 (3.8)	17 (4.5)	74 (4.6)	
Histology							<.001
Adenocarcinoma	155 (60.3)	174 (68.2)	235 (71.9)	294 (74.8)	300 (78.9)	1158 (71.8)	
Squamous cell carcinoma	102 (39.7)	81 (31.8)	92 (28.1)	99 (25.2)	80 (21.1)	454 (28.2)	
T-stadium							.004
T1	27 (10.5)	20 (7.8)	26 (8.0)	39 (9.9)	32 (8.4)	144 (8.9)	
T2	25 (9.7)	32 (12.5)	36 (11.0)	48 (12.2)	75 (19.7)	216 (13.4)	
T3	195 (75.9)	199 (78.0)	258 (78.9)	303 (77.1)	262 (68.9)	1217 (75.5)	
T4	10 (3.9)	4 (1.6)	7 (2.1)	3 (0.8)	11 (2.9)	35 (2.2)	
Neoadjuvant treatment							<.001
None	243 (94.6)	206 (80.8)	229 (70.0)	114 (29.0)	43 (11.3)	835 (51.8)	
Chemotherapy	14 (5.4)	49 (19.2)	15 (4.6)	16 (4.1)	15 (3.9)	109 (6.8)	
Chemoradiotherapy	0	0	83 (25.4)	263 (66.9)	322 (84.7)	668 (41.4)	

Approach	257 (100)	255 (100)	327 (100)	259 (65.9)	9 (2.4)	1107 (68.7)	<.001
Open	0	0	0	122 (31.0)	355 (93.4)	477 (29.6)	
Total minimally invasive	0	0	0	1 (0.3)	7 (1.8)	8 (0.5)	
Hybrid (open thorax)	0	0	0	11 (2.8)	9 (2.4)	20 (1.2)	
Hybrid (open abdomen)	0	0	0				
Esophagectomy	172 (66.9)	179 (70.2)	158 (48.3)	134 (34.1)	42 (11.1)	685 (42.5)	<.001
Transhiatal esophagectomy	86 (33.1)	76 (29.8)	169 (51.7)	259 (65.9)	338 (88.9)	927 (57.5)	
Transthoracic esophagectomy	257 (100)	254 (99.6)	311 (93.1)	366 (93.1)	126 (33.2)	1314 (81.5)	<.001
Anastomosis	0	1 (0.4)	27 (4.9)	27 (6.9)	254 (66.8)	298 (18.5)	
Cervical	0	0	0	0	0	0	
Intrathoracic	242 (94.2)	250 (98.0)	324 (99.1)	388 (98.7)	374 (98.4)	1578 (97.9)	.001
Reconstruction	15 (5.8)	5 (2.0)	3 (0.9)	4 (1.0)	6 (1.6)	33 (2.0)	
Gastric conduit	0	0	0	1 (0.3)	0	1 (0.1)	
Colon interposition	0	0	0	0	0	0	
Esophagejejunostomy	0	0	0	0	0	0	

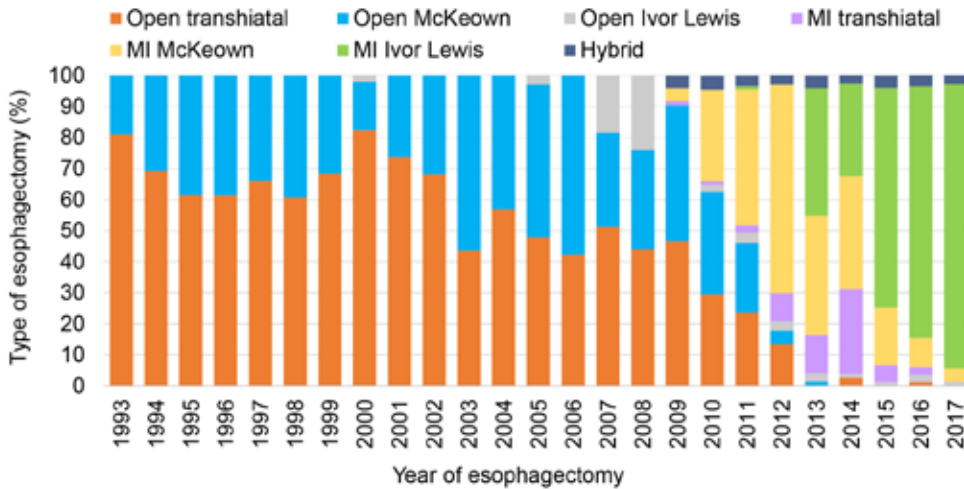
Continuous data are presented in mean (SD). Data of 58 patients (3.6%)^a and 2 patients (0.1%)^b were missing.

Figure 2

a) Type of neoadjuvant treatment per year



b) Type of esophagectomy per year (MI minimally invasive)



Survival over 25 years

Median follow-up for surviving patients (462/1612) was 84.0 months (IQR 60.1–125.4). The median overall survival was 37.8 months (95% CI 33.2–42.4). This improved steadily from 26.0 (95% CI 21.2–30.8) to 51.5 months (95% CI 38.3–64.7) over 25 years ($P < .001$, Fig. 3 and 4). The 5-year overall survival increased from 32.5% to 47.7% ($P < .001$). This improved from 30.3% to 45.5% for adenocarcinomas ($P < .001$), and from 35.8% to 55.8% for squamous cell carcinomas ($P = .003$, Fig. 5). For R0 resections, the 5-year overall survival increased from 38.7% to 48.8% ($n=1452$, $P = .007$). R0 resections have increased from 80.6% to 97.1% over 25 years.

Figure 3. Kaplan Meier curve for all patients

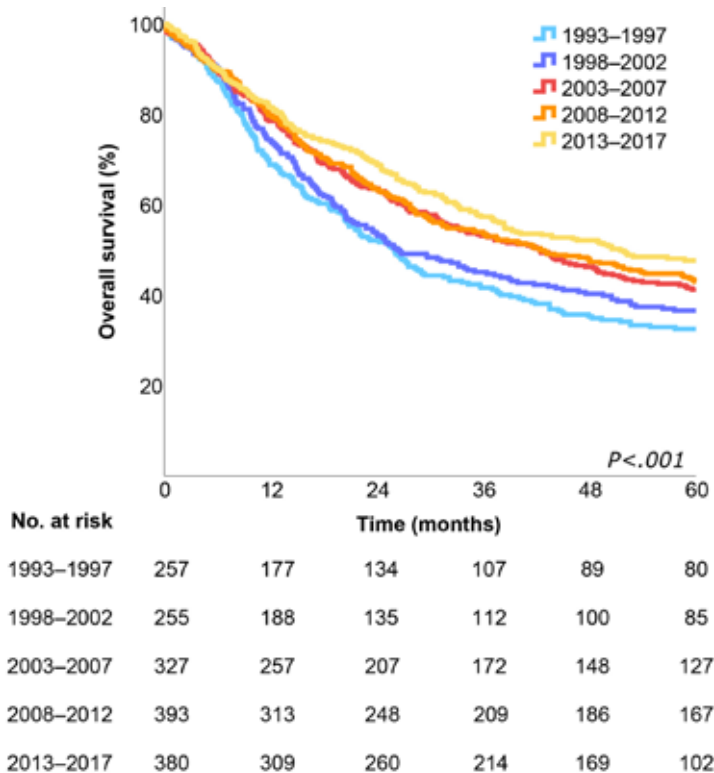


Figure 4. Major changes in the treatment of esophageal cancer and overall survival (MI minimally invasive, ERAS Enhanced Recovery After Surgery program, nCT neoadjuvant chemotherapy, nCRT neoadjuvant chemoradiotherapy, THE transhiatal esophagectomy)

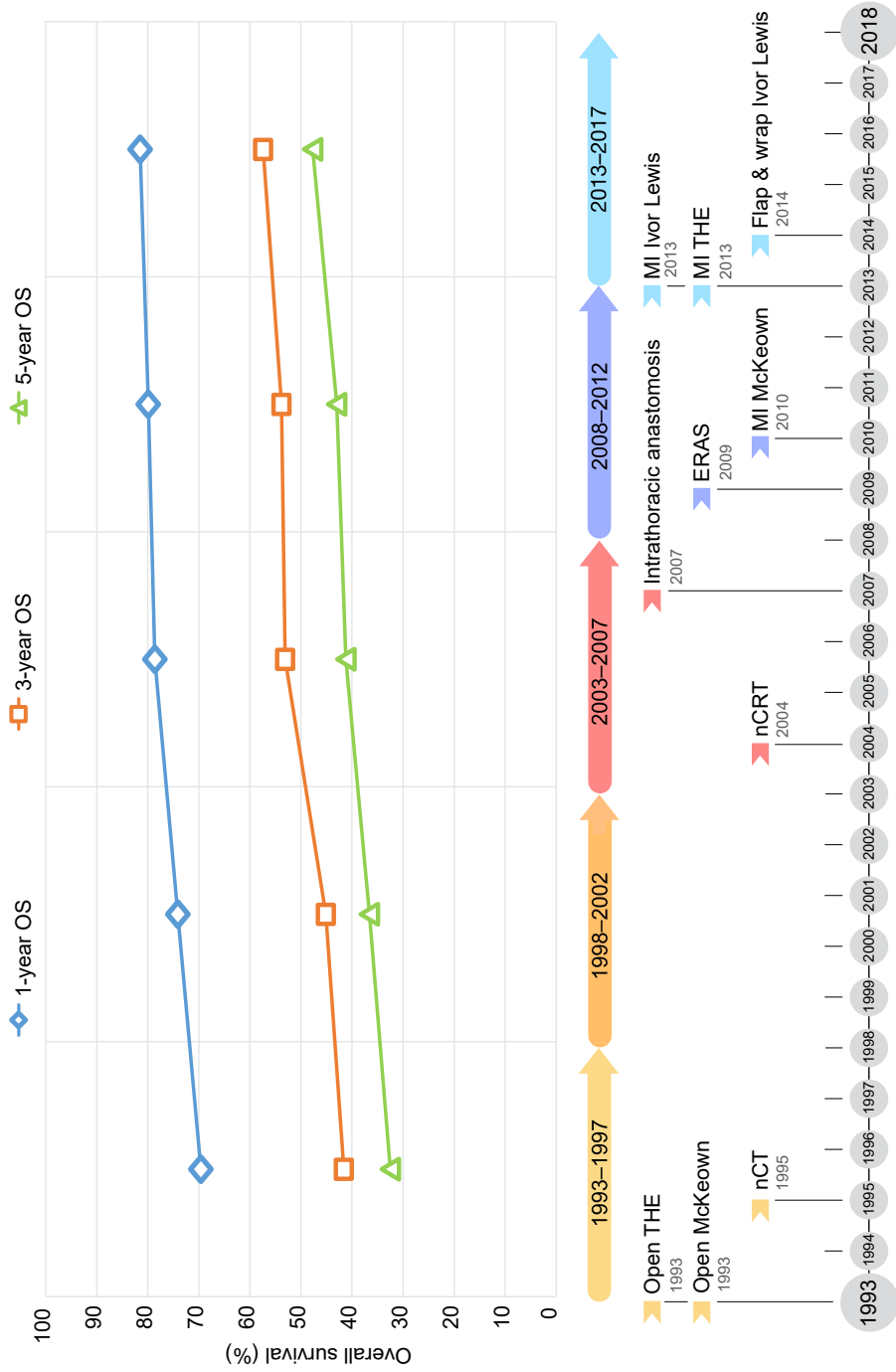
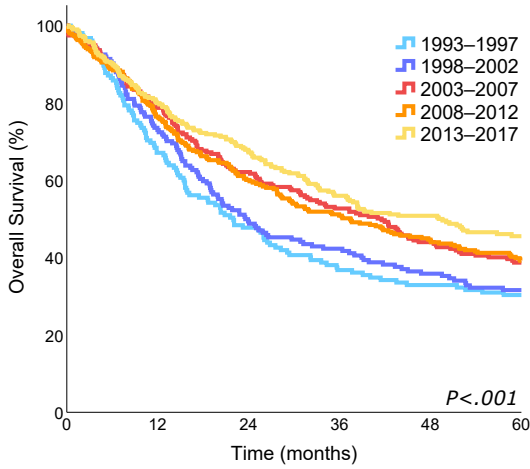


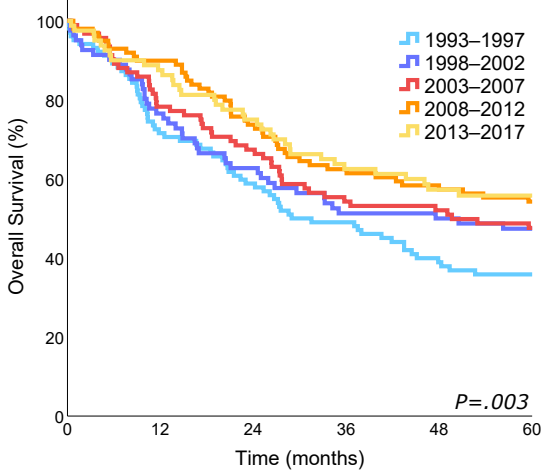
Figure 5

a) Patients with adenocarcinoma (n=1158)



No. at risk						
1993-1997	155	104	74	57	51	45
1998-2002	174	127	85	72	61	49
2003-2007	235	185	145	123	101	85
2008-2012	294	224	176	148	130	114
2013-2017	300	239	200	164	128	80

b) Patients with squamous cell carcinoma (n=454)



No. at risk						
1993-1997	102	73	60	50	38	35
1998-2002	81	61	50	40	39	36
2003-2007	92	72	62	49	47	42
2008-2012	99	89	72	61	56	53
2013-2017	80	70	60	50	41	22

Table 2. Short-term outcomes after esophagectomy between 1993 and 2017

	1993-1997 (n=257)	1998-2002 (n=255)	2003-2007 (n=327)	2008-2012 (n=393)	2013-2017 (n=380)	P value
RO resections ^a	203 (80.6)	214 (83.9)	296 (90.5)	371 (94.4)	368 (97.1)	<.001
Resected lymph nodes ^b	15 (8-23)	16 (9-22)	20 (13-28)	22 (17-29)	30 (22-39)	<.001
Morbidity	156 (60.7)	158 (62.0)	224 (68.5)	234 (59.5)	226 (59.5)	.42
Reinterventions ^c	59 (23.0)	57 (22.4)	69 (21.1)	83 (21.2)	110 (28.9)	.11
Reoperations	26 (10.1)	26 (10.2)	47 (14.4)	49 (12.5)	37 (9.7)	.96
ICU readmissions	60 (23.3)	54 (21.2)	73 (22.3)	88 (22.4)	76 (20.0)	.44
Reintubations	41 (16.0)	41 (16.1)	56 (17.1)	59 (15.0)	48 (12.6)	.19
Hospital length of stay	16 (14-24)	16 (13-24)	16 (12-25)	12 (9-19)	11 (8-18)	<.001
ICU length of stay	3 (2-7)	2 (1-5)	1 (1-4)	1 (1-3)	0 (0-2)	<.001
Mortality						
30-day	8 (3.1)	7 (2.7)	7 (2.1)	10 (2.5)	5 (1.3)	.16
In-hospital	10 (3.9)	9 (3.5)	10 (3.1)	16 (4.1)	5 (1.3)	.12
90-day	11 (4.3)	14 (5.5)	15 (4.6)	20 (5.1)	15 (3.9)	.74

Continuous data are presented in medians (interquartile range). Data of 6 patients (0.4%)^a, 12 patients (0.7%)^b and 1 patient (0.1%)^c were missing.

Table 3. Short-term outcomes after esophagectomy between 2013 and 2017 (n=380)

	2013 (n=72)	2014 (n=77)	2015 (n=75)	2016 (n=84)	2017 (n=72)	P value
RO resections ^a	70 (98.6)	74 (96.1)	74 (98.7)	80 (95.2)	70 (97.2)	.55
Resected lymph nodes	22 (18-28)	30 (20-42)	32 (24-42)	33 (26-41)	36 (28-43)	<.001
Overall morbidity	45 (62.5)	48 (62.3)	38 (50.7)	50 (59.5)	45 (62.5)	.87
Anastomotic leakage	19 (26.4)	21 (27.3)	11 (14.7)	5 (6.0)	7 (9.7)	<.001
Pneumonia	16 (22.2)	8 (10.4)	9 (12.0)	9 (10.7)	10 (13.9)	.20
Chyle leakage	4 (5.6)	7 (9.1)	4 (5.3)	12 (14.3)	10 (13.9)	.043
Vocal cord injury	2 (2.8)	1 (1.3)	2 (2.7)	2 (2.4)	1 (1.4)	.77
Reinterventions	23 (31.9)	25 (32.5)	21 (28.0)	24 (28.6)	17 (23.6)	.22
Reoperations	14 (19.4)	6 (7.8)	3 (4.0)	3 (3.6)	11 (15.3)	.23
ICU readmissions	22 (30.6)	17 (22.1)	11 (14.7)	13 (15.5)	13 (18.1)	.031
Reintubations	17 (23.6)	9 (11.7)	8 (10.7)	7 (8.3)	7 (9.7)	.011
Hospital length of stay	12 (8-19)	13 (9-22)	10 (9-15)	10 (8-7)	11 (8-21)	.06
ICU length of stay	1 (1-5)	1 (0-4)	0 (0-1)	0 (0-1)	0 (0-1)	<.001
Mortality						
30-day	2 (2.8)	1 (1.3)	1 (1.3)	1 (1.2)	0	.19
In-hospital	3 (4.2)	1 (1.3)	2 (2.7)	0	0	.022
90-day	6 (8.3)	5 (6.5)	1 (1.3)	3 (3.6)	0	.007

Continuous data are presented in medians (IQR). ^aRO resection could not be confirmed in 1 patient (Rx).

Short-term outcomes between 1993 and 2017

Resected lymph nodes increased from a median of 15 (IQR 8–23) to 30 per patient (IQR 22–39, $P < .001$, Table 2). Morbidity, mortality, reinterventions, reoperations, and ICU readmissions did not change over time. Nevertheless, median hospital and ICU length of stay decreased from 16 (IQR 14–24) to 11 days (IQR 8–18) and from 3 (IQR 2–7) to 0 days (IQR 0–2), respectively ($P < .001$).

Short-term outcomes between 2013 and 2017

Year-on-year comparisons between 2013 and 2017 revealed significantly increased median numbers of resected lymph nodes over the latest 5 years, from 22 (IQR 18–28) in 2013 to 36 (IQR 28–43) in 2017 ($P < .001$, Table 3). No differences were observed for RO resections within this period ($P = .55$). In-hospital and 90-day mortality decreased from 4.2% and 8.3% in 2013 to 0% for both parameters in 2017 ($P < .050$). Most anastomotic leakage occurred in 2013 and 2014 (respectively 26.4 and 27.3%). Each year after 2014, this decreased gradually towards 9.7% in 2017 ($P < .001$).

DISCUSSION

This study is based on a prospectively maintained database of a tertiary referral center, investigating more than 1600 patients undergoing esophagectomy for cancer over 25 years. It shows improvement of the 5-year overall survival from approximately 30% to 50%. In addition, the study reveals increased use of neoadjuvant chemoradiotherapy and transthoracic resections. Hospital and ICU length of stay shortened, whilst morbidity remained constant. Eventually, anastomotic leakage rates fell to less than 10% with no mortality in 2016 and 2017. The strength of the study is that consecutive patients were prospectively included in the database over a large study period. It uses Jonckheere–Terpstra tests for trend analyses instead of the Kruskal–Wallis test, by which the direction of the difference in medians was incorporated.¹⁷ By setting the inclusion period up to January 2018, a minimum potential follow-up of 44 months was guaranteed in all groups. Although this is also a limitation since not all patients could complete 5-year follow-up, it was taken into account that most recurrences occur within two years after surgery.^{6,12,13} What exact policy change was responsible for the results is complex to define and was certainly multifactorial as outcomes were evaluated over 25 years. In order to gain insight into the influence of the changing policies, findings are discussed separately.

Survival

The overall survival in the last 5 years of this study (52 months) was comparable to the study of Griffin and colleagues, which investigated patients between 1989–2018.¹⁸ Their latest cohort showed a median overall survival of 56 months and 5-year overall survival of less than 50% (2014–2018). Other studies investigating outcomes over a longer period showed lower 5-year overall survival rates (13–36%), but most studies were conducted before 2014 and included non-surgically-treated or metastatic patients.^{7,8,19}

PET/CT

Imaging was one of the factors that possibly contributed to survival improvement. For example, the addition of PET/CT to esophageal cancer treatment for detection of metastases before and after neoadjuvant chemoradiotherapy. Accuracy of PET/CT has been investigated at this center between 2011 and 2013.³ PET/CT detected metastases in 11% of patients after neoadjuvant chemoradiotherapy, who were consequently excluded from complex, non-curative esophagectomy. Since PET/CT after neoadjuvant chemoradiotherapy became standard of care, it has contributed to accurate patient selection for curative esophagectomy and probably resulted in survival improvement after esophagectomy.

Neoadjuvant chemoradiotherapy

A factor that probably contributed the most to the survival improvement was neoadjuvant chemoradiotherapy. The 5-year overall survival of this study was consistent with that of the neoadjuvant chemoradiotherapy group in the CROSS trial.⁶ Talsma and colleagues have already suggested a predictive value for improved 2-year overall survival in patients after neoadjuvant chemoradiotherapy and esophagectomy between 1999 and 2000.⁹ Recently, the Dutch Comprehensive Cancer Registry showed greatest survival increase in neoadjuvant chemoradiotherapy patients over 25 years.⁷ However, less than 43% of their patients were neoadjuvantly treated with chemoradiation, whilst this was more than 80% in the latest group of this study. Besides, survival improvement of this study already existed prior to, and well after implementation of neoadjuvant chemoradiotherapy, corresponding to observations in other studies.^{7,9,18} Therefore, the value of neoadjuvant chemoradiotherapy to survival improvement is strengthened, but survival improvement cannot be attributed to chemoradiotherapy alone.

R0 resections

An upward trend towards more R0 resections in later years was found in the study, to $\geq 95\%$ after 2013. The literature has shown that survival after esophageal cancer is strongly associated with more R0 resections.²⁰ Although neoadjuvant chemoradiotherapy may also have influenced R0 resections, increasing numbers of R0 resections were already manifest in the era prior to chemoradiation. It is plausible that other factors, e.g., improved staging and T4b tumor exclusion from curative esophagectomy, additionally contributed to more R0 resections and survival.

Lymph node yield

This study showed parallel improvement of lymph node yield and survival rates, which continued well after the implementation period of neoadjuvant chemoradiotherapy. Since the choice for transthoracic esophagectomy is often made because of the avoidance of blunt dissection and the possibility of extended lymphadenectomy, rising numbers of transthoracic esophageal resections likely contributed to the increase in resected lymph nodes over the past 25 years. A recent systematic review also demonstrated the independent relation of extended lymphadenectomy with survival improvement, even if patients underwent neoadjuvant treatment.²¹ Although that review was limited by follow-up periods of the included studies (15–94 months), most of these studies included transthoracic resections.

Minimally invasive surgery

Superiority of minimally invasive esophagectomy on survival as compared to open procedures has not yet been proven. One systematic review suggested beneficial effects of minimally invasive esophagectomy on 5-year mortality, but adjustment of confounding factors was limited and many retrospective studies were included.²² Thus, conclusions about the impact of minimally invasive surgery on survival of esophageal cancer patients should be drawn cautiously.

Short-term outcomes

The introduction of ERAS and minimally invasive surgery in 2009 could have contributed to shortened hospital and ICU length of stay with constant morbidity in this study. Previous research of this center has demonstrated significant shorter length of stay in patients following ERAS after open esophagectomy (2009–2010) without affecting other outcomes.²³ This was supported by studies investigating esophagectomy, but also by other gastrointestinal procedures.^{24,25} The randomized controlled TIME trial, in which more than 50% of participants underwent esophagectomy at this center, showed that minimally invasive esophagectomy caused shorter hospital length of stay.²⁶ However, an external validation study cautiously suggested that the influence of high expertise levels of participating centers should be incorporated in the interpretation of the TIME trial results.²⁷

Preventing anastomotic leakage after esophagectomy is an important goal and became crucial since the literature showed that anastomotic leakage and morbidity predict worse long-term outcomes.^{28,29} Most anastomotic leakages were found in 2013 and 2014 at this center, which may be caused by simultaneous introduction of several new surgical techniques at the time (e.g., minimally invasive surgery, intrathoracic anastomosis). According to Claassen and colleagues, surgical learning curves for minimally invasive esophagectomy based on anastomotic leakages consist of 50 to 120 cases.³⁰ With approximately 90 cases per year and minimally invasive Ivor Lewis esophagectomy introduced in February 2013, it could have attributed to the peak incidence of anastomotic leakage. Since significantly fewer anastomotic leakages and no mortality were observed after 2014 (following introduction of the 'flap and wrap' reconstruction), this may result in better survival outcomes for these patients.

CONCLUSIONS

The study has shown improved short- and long-term outcomes in a large patient group undergoing esophagectomy for cancer at a tertiary referral center over 25 years. Likely contributors include neoadjuvant chemoradiotherapy, transthoracic minimally invasive esophagectomy, extended lymphadenectomy, R0 resections, and reduction of anastomotic leakages. Future survival improvements are expected due to further treatment developments, such as personalized neoadjuvant and adjuvant therapies. Subsequently, further surgical advancements will decrease morbidity and mortality, and thus improve survival after esophagectomy for cancer.

References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin.* 2018;68(6):394-424. DOI:10.3322/caac.21492
2. Arnold M, Ferlay J, Van Berge Henegouwen MI, Soerjomataram I. Global burden of esophageal and gastric cancer by histology and subsite in 2018. *Gut.* 2020;69(9):1564-1571. DOI:10.1136/gut-jnl-2020-321600
3. Anderegg MCJ, De Groof EJ, Gisbertz SS, et al. 18F-FDG PET-CT after neoadjuvant chemoradiotherapy in esophageal cancer patients to optimize surgical decision making. *PLoS One.* 2015;10(11):1-14. DOI:10.1371/journal.pone.0133690
4. Sturm EC, Zahnd WE, Mellinger JD, Ganai S. Survival implications of increased utilization of local excision for cT1N0 esophageal cancer. *Ann Surg.* 2019;270(2):295-301. DOI:10.1097/sla.0000000000002782
5. Tonison JJ, Fischer SG, Viehrig M, et al. Radiation pneumonitis after intensity-modulated radiotherapy for esophageal cancer: Institutional data and a systematic review. *SCI Rep.* 2019;9(1):4-11. DOI:10.1038/s41598-018-38414-5
6. Shapiro J, van Lanschot JJB, Hulshof MCCM, et al. Neoadjuvant chemoradiotherapy plus surgery versus surgery alone for esophageal or junctional cancer (CROSS): Long-term results of a randomized controlled trial. *Lancet Oncol.* 2015;16(9):1090-1098. DOI: 10.1016/S1470-2045(15)00040-6.
7. van Putten M, de Vos-Geelen J, Nieuwenhuijzen GAP, et al. Long-term survival improvement in esophageal cancer in the Netherlands. *Eur J Cancer.* 2018;94:138-147. DOI:10.1016/j.ejca.2018.02.025
8. Law S, Kwong DLW, Kwok KF, et al. Improvement in treatment results and long-term survival of patients with esophageal cancer: Impact of chemoradiation and change in treatment strategy. *Ann Surg.* 2003;238(3):339-348. DOI:10.1097/01.sla.0000086545.45918.ee
9. Talsma AK, Damhuis RAM, Steyerberg EW, Rosman C, Van Lanschot JJB, Wijnhoven BPL. Determinants of improved survival after esophagectomy for cancer. *Br J Surg.* 2015;102(6):668-675. DOI:10.1002/bjs.9792
10. Rice TW, Blackstone EH, Rusch VW. 7th edition of the AJCC Cancer Staging Manual: esophagus and esophagogastric junction. *Ann Surg Oncol.* 2010;17(7):1721-1724. DOI:10.1245/s10434-010-1024-1
11. Vereniging van Maag-Darm-Leverartsen. Dutch guideline for esophageal cancer, version 3.1. *Oncoline.* https://richtlijndatabase.nl/richtlijn/oesofaguscarcinoom/oesofaguscarcinoom_-_startpagina.html. Published 2015.
12. van den Ende T, de Clercq NC, van Berge Henegouwen MI, et al. A phase II feasibility trial of neoadjuvant chemoradiotherapy combined with atezolizumab for resectable esophageal adenocarcinoma: The PERFECT trial. *J Clin Oncol.* 2019;37:4045-4045. DOI:10.1200/jco.2019.37.15_suppl.4045
13. Stroes CI, Schokker S, Creemers A, et al. Phase II feasibility and biomarker study of neoadjuvant trastuzumab and pertuzumab with chemoradiotherapy for resectable human epidermal growth factor receptor 2-positive esophageal adenocarcinoma: Trap study. *J Clin Oncol.* 2020;38(5):462-471. DOI:10.1200/JCO.19.01814
14. Stroes CI, Schokker S, Molenaar RJ, et al. A phase II study demonstrates no feasibility of adjuvant treatment with six cycles of s-1 and oxaliplatin in resectable esophageal adenocarcinoma, with *ercc1* as biomarker for response to sox. *Cancers (Basel).* 2021;13(4):1-15. DOI:10.3390/cancers13040839
15. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: A new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg.* 2004;240(2):205-213. DOI:10.1097/01.sla.0000133083.54934.ae
16. Low D, Alderson D, Ceconello I, et al. International consensus on standardization of data collection for complications associated with esophagectomy: Esophagectomy Complications Consensus Group (ECCG). *Ann Surg.* 2015;262(2):286-294. DOI: 10.1097/SLA.0000000000001098
17. Field A. Testing for trends: the Jonckheere-Terpstra test. In: *Discovering statistics using SPSS.* 3rd ed. Sage Publications; 2009:568-572.
18. Griffin SM, Jones R, Kamarajah SK, et al. Evolution of esophagectomy for cancer over 30 years: Changes in presentation, management and outcomes. *Ann Surg Oncol.* 2020. DOI:10.1245/s10434-020-09200-3

19. De Vos-Geelen J, Geurts SME, Valkenburg-Van Iersel LBJ, et al. Trends in treatment and overall survival among patients with proximal esophageal cancer. *World J Gastroenterol.* 2019;25(47):6835-6846. DOI:10.3748/wjg.v25.i47.6835
20. Evans R, Bundred JR, Kaur P, Hodson J, Griffiths EA. Meta-analysis of the influence of a positive circumferential resection margin in esophageal cancer. *BJS open.* 2019;3(5):595-605. DOI:10.1002/bjs.50183
21. Visser E, Markar SR, Ruurda JP, Hanna GB, van Hillegersberg R. Prognostic value of lymph node yield on overall survival in esophageal cancer patients: A systematic review and meta-analysis. *Ann Surg.* 2019;269(2):261-268. DOI:10.1097/SLA.0000000000002824
22. Gottlieb-Vedi E, Kauppila JH, Malietzis G, Nilsson M, Markar SR, Lagergren J. Long-term survival in esophageal cancer after minimally invasive compared to open esophagectomy. *Ann Surg.* 2019;270(6):1005-1017. DOI:10.1097/SLA.0000000000003252
23. Blom RLGM, Van Heijl M, Bemelman WA, et al. Initial experiences of an enhanced recovery protocol in esophageal surgery. *World J Surg.* 2013;37(10):2372-2378. DOI:10.1007/s00268-013-2135-1
24. Nicholson A, Lowe MC, Parker J, Lewis SR, Alderson P, Smith AF. Systematic review and meta-analysis of enhanced recovery programs in surgical patients. *Br J Surg.* 2014;101(3):172-188. DOI:10.1002/bjs.9394
25. Findlay JM, Gillies RS, Millo J, Sgromo B, Marshall REK, Maynard ND. Enhanced recovery for esophagectomy: A systematic review and evidence-based guidelines. *Ann Surg.* 2014;259(3):413-431. DOI:10.1097/SLA.0000000000000349
26. Biere SSAYAY, Van Berge Henegouwen MI, Maas KW, et al. Minimally invasive versus open esophagectomy for patients with esophageal cancer: A multicenter, open-label, randomized controlled trial. *Lancet.* 2012;379(9829):1887-1892. DOI:10.1016/S0140-6736(12)60516-9
27. Markar SR, Ni M, Gisbertz SS, et al. Implementation of minimally invasive esophagectomy from a randomized controlled trial setting to national practice. *J Clin Oncol.* 2020;38(19):2130-2139. DOI:10.1200/JCO.19.02483
28. Fransen LFC, Berkelmans GHK, Asti E, et al. The effect of postoperative complications after minimally invasive esophagectomy on long-term survival. *Ann Surg.* 2020; Publish Ah(Xx):12-15. DOI:10.1097/sla.0000000000003772
29. Van Der Werf LR, Wijnhoven BPL, Fransen LFC, et al. A national cohort study evaluating the association between short-term outcomes and long-term survival after esophageal and gastric cancer surgery. *Ann Surg.* 2019;270(5). DOI:10.1097/SLA.00000000000003520
30. Claassen L, van Workum F, Rosman C. Learning curve and postoperative outcomes of minimally invasive esophagectomy. *J Thorac Dis.* 2019;11:S777-S785. DOI:10.21037/jtd.2018.12.54



SUMMARY

Optimal classification and management of complications
after curative esophagectomy for cancer

In the era of neoadjuvant chemoradiotherapy
and minimally invasive surgery



The scientific research of this thesis contributes to the evaluation of the recent trends within the curative surgical treatment of esophageal cancer and their effects on postoperative complications. Many changes in the surgical treatment of esophageal cancer focus on the prevention of severe postoperative complications after curative esophagectomy. To pursue this as accurate and efficient as possible, insight in these complications and possible predictive factors is paramount. Ensuring transparent complication registration contributes to this. Therefore, **Part I** of this thesis investigates methods pursuing accurate complication registration and severity classifications to assess the burden of complications on patients. In **Part II**, incidences of specific complications and other postoperative outcomes after esophageal cancer surgery are compared between several surgical techniques. Predictive factors are analyzed, including neoadjuvant therapy, location of anastomosis and surgical approach. Finally, the thesis describes changes that are related to patients' characteristics, curative treatments, short-term outcomes and survival of patients who underwent esophagectomy over the past 25 years.

Part I. Evaluation of different methods for the registration of postoperative complications

In **Chapter 2** of this thesis, a detailed description is given for the development of the trigger tool as a method to simplify the registration of complications for residents and staff members at the surgical department. The trigger tool selects patients with an increased risk of complications during their admission in the hospital after which their medical files are searched for additional complications. The second part in this chapter shows that the sensitivity of the trigger tool is equal to that of the weekly complication meeting, in which multiple residents and staff members of the department are present. By using this trigger tool, the administrative workload of the clinicians can be reduced. Additional cost-effectiveness investigation is needed to compare the cost-efficacy of the trigger tool with that of a weekly complication meeting, but it can be expected that costs will be lower when the trigger tool is used.

Severity classification systems for complications are explored in **Chapter 3** and **4**. **Chapter 3** describes stronger relationships between the most recently developed classification system, the Comprehensive Complication Index and traditional outcome parameters than when the Clavien–Dindo classification is applied. Hence, it can be concluded that the Comprehensive Complication Index provides a more detailed representation of the severity of complications in patients after esophagectomy than the Clavien–Dindo classification. If more national and international studies will use the Comprehensive Complication Index, subtle differences in postoperative outcomes between different surgical

techniques could become apparent, which will lead to possible treatment improvements. In the study of **Chapter 4**, the Comprehensive Complication Index confirms that neoadjuvant chemoradiation prior to esophagectomy for cancer does not affect the severity of postoperative complications as compared to the severity of complications in patients who have not been treated with chemotherapy and radiation prior to esophagectomy.

Part II.

The influence of surgical techniques on complications after esophagectomy

By means of a propensity-score matched analysis, **Chapter 5** shows that the incidence of severe anastomotic leakage (ECCG type>2) and 90-day mortality after minimally invasive transthoracic esophagectomy is lower in patients with an intrathoracic anastomosis than with cervical anastomosis. In **Chapter 6**, patients with anastomotic leakage after esophagectomy are investigated in detail. Although a low incidence of serious anastomotic leakage after an Ivor Lewis esophagectomy is found (12.4%), the anastomotic leakages after transhiatal or a McKeown procedure seem relatively less severe.

To protect the intrathoracic anastomosis against (severe) anastomotic leakage, the gastric conduit can be stitched to the pleural flap, followed by covering the anastomosis by the pleural flap and a wrap of the omentum. This reduces the tensile forces on the anastomosis, protects the anastomosis against the surrounding negative intrathoracic pressure and creates a barrier for infections to spread in the thoracic cavity. These techniques are collectively referred to as the 'flap and wrap' reconstruction. After the introduction of the 'flap and wrap' reconstruction in **Chapter 7**, the incidence of anastomotic leakage after Ivor Lewis esophagectomy is 7.5%. Furthermore, anastomotic leakages that arise after this reconstruction lead to less severe postoperative courses than when the reconstruction created by the standard Ivor Lewis esophagectomy. The 'flap and wrap' reconstruction is a safe technique that can be used to reduce and limit the severity of anastomotic leakage in patients who are fit enough to undergo transthoracic esophagectomy.

The proficiency-gain curve of the Ivor Lewis esophagectomy in this chapter shows a steep slope in the beginning of the curve, which is consistent with gaining proficiency for a very complex surgical technique. Assessing the proficiency-gain curve for a new surgical technique contributes significantly to an accurate interpretation of research results. Therefore, the proficiency-gain curve should be included in any scientific research about new surgical techniques in order to perform a fair and transparent comparison of the outcomes. This also has important implications for putting a new technique into practice in a na-

tional setting.

In **Chapter 8**, the incidence, risk factors, diagnosis, treatment and burden of a symptomatic diaphragmatic hernia after esophagectomy are described. The incidence is 2.5% of all esophageal resections in this series. Symptomatic diaphragmatic hernia is often underexposed and can occur at a later stage after an esophageal resection. The research presented in this chapter shows that the minimally invasive Ivor Lewis procedure is a risk factor for the occurrence of this complication, with an incidence of 9.5% of symptomatic diaphragmatic hernias after Ivor Lewis esophagectomy. Recurrences after treatment occur relatively often, i.e., in 19.0% of patients. Awareness about the importance of rapid diagnosis and treatment of symptomatic diaphragmatic hernias after esophagectomy is of great value in order to limit possible severe consequences.

The last chapter of this thesis shows that there has been a great evolution in the treatment of esophageal cancer over the past 25 years (**Chapter 9**). Nowadays, patients' characteristics are different from those of the early 1990s. The mean age and body mass index at time of esophagectomy of patients are higher, and the proportion of patients with adenocarcinoma as compared to squamous cell carcinoma has increased. The study also shows that more than 90% of all patients are currently treated with neoadjuvant chemoradiotherapy followed by a minimally invasive Ivor Lewis esophagectomy. The improving postoperative outcomes within the last 5 years of the study are probably caused by the most recent improvements of surgical techniques and optimization of perioperative protocols. The main finding of this chapter is the improvement of the 5-year overall survival from 30% in the early 1990s to 50% for patients undergoing esophagectomy in most recent years. This chapter in particular underlines the value of evaluation of outcomes over a longer period of time and conducting high-quality research into diagnostics, treatments and complication registration in large groups of patients.

GENERAL DISCUSSION AND FUTURE PERSPECTIVES



GENERAL DISCUSSION

This thesis focuses on improving complication registration and classification after surgery and investigates the incidence of complications after esophageal cancer surgery in an era where neoadjuvant chemoradiotherapy, minimally invasive surgery and Ivor Lewis esophagectomy are used as part of the curative treatment of patients with cancer of the esophagus or gastroesophageal junction. The contents of this thesis describe differences between several complication registration methods regarding the accuracy of the incidence and the burden of complications. The second part of the thesis investigates whether the incidence and severity of complications after esophagectomy are influenced by recent changes in the treatment of esophageal cancer, with particular focus on minimally invasive transthoracic esophageal resections and anastomotic leakages. Finally, it gives insight in the changes of short- and long-term outcomes over the past 25 years, in which the short-term results of the last 5 years are described in more detail. To interpret the study results of all chapters together, discussions and future perspectives are described with consideration of the thesis' limitations.

Registration of complications

Awareness of postoperative complications by clinicians and researchers has increased over the last years and prevention of these complications has become one of the most important goals in surgery.¹ Since complication rates are set as quality indicators for hospitals, a form of complication registration became mandatory in many countries.^{2,3} In practice, surgical departments deliver data with information about the occurred complications after surgery to national audits.³⁻⁵ However, methods of complication registration are often not standardized in (inter-)national practice and the accuracy of these methods has rarely been investigated. Inadequate complication registration leads to a distorted picture of outcomes after surgery and may limit the quality of scientific research and improvements based on this inadequate registration.⁶ The goal for researchers and staff members is to decrease the complication rate after surgery. In order to achieve this, qualitative and accurate data with information about these complications is paramount. Many surgical departments use a regular verbal inventory meeting with attending residents and surgical staff for the detection of complications. However, this method is very time consuming and studies show that the sensitivity varies between 63–85%.^{7,8} **Chapter 2** shows that time efforts of surgical residents and staff can be reduced by a trigger tool. In addition, the use of trigger tools can be an important step for clinicians since unwanted administrative workload and increasing working hours are predictive factors in developing burnout amongst healthcare professionals,

especially amongst surgical residents.⁹ Time efforts can consequently be transferred to other individuals, such as database managers. Furthermore, institutional health care costs may be reduced since multiple surgeons have to attend in case of a verbal inventory meeting and the hour loan of surgeons is generally higher than that of a database manager. In accordance with literature, the thesis shows that detection of patients at risk of postoperative complications by a trigger tool combined with screening of medical records at a surgical department of a tertiary referral center seems to be at least as reliable as a verbal inventory meeting (**Chapter 2**).¹⁰ Trigger tools seem to be applicable in daily practice of other medical specialties and peripheral hospitals, depending on its purpose. For example, they can be used for identifying critically ill patients at risk of adverse events at the Intensive Care Unit or patients at risk of severe adverse drug events after protocol-based therapy (e.g. chemoradiotherapy).^{11,12} The use of trigger tools in scientific research may eventually result in more patient-tailored treatment.

Since mortality rates after surgery have decreased over the last decades, the attention on severity of complications has increased over time. In an attempt to compare the burden of complications between surgical patients, several complication classifications have been developed over the last years.¹³⁻¹⁵ The Clavien–Dindo classification is most commonly used, but does not incorporate the burden of all complications together during the admission period of

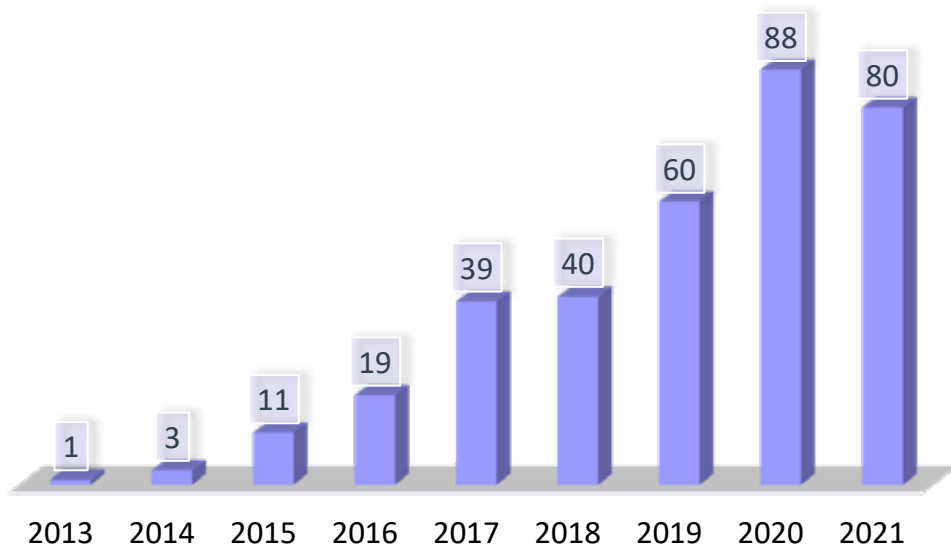


Figure 1. The absolute number of scientific reports by year using "Comprehensive Complication Index" in title or abstract on <https://pubmed.ncbi.nlm.nih.gov> (Latest data retrieved on: 12 September 2021)

patients. This thesis observed that the Comprehensive Complication Index is more accurate than the Clavien–Dindo classification in grading the severity of complications (**Chapter 3**), which is in line with other study results amongst other surgical specialties.^{15–17} Due to these good results of the Comprehensive Complication Index in validation studies, the number of studies using the Comprehensive Complication Index as a primary or secondary outcome representing complication severity has increased significantly, which indicates its relevance (Fig. 1).

Additionally, the Comprehensive Complication Index can play a role in improving the detection rate of complications by trigger tools.¹⁸ Since missed complications are most frequently of lower severity (**Chapter 2**), trigger tools can highlight patients at risk of (multiple) less severe complications using a maximum cut-off value of the Comprehensive Complication Index. Another benefit of the Comprehensive Complication Index is that it incorporates patient-related factors in contrast to the Clavien–Dindo classification. The detection of minor complications by the combination of the maximum cut-off value of the Comprehensive Complication Index and the trigger tool may eventually lead to higher quality of life of patients after applying relatively small protocol adjustments in hospitals. However, this Comprehensive Complication Index-based trigger tool has to be validated first and automated Comprehensive Complication Index calculation has to be implemented in electronic hospital databases. In addition, the Comprehensive Complication Index can be used as a more accurate outcome parameter to identify risk factors for severe complications. Based on this risk assessment, surgeons may choose for another surgical technique for certain patients, optimize these patients using strict preventive measures prior to surgery (e.g., physiotherapy), and adapted intraoperative and postoperative protocols. If severe complications are prevented by these protocols, hospitals will face reduced healthcare costs and quality parameters may be improved. Ultimately, patients' health-related quality of life and survival may be increased.

The influence of different esophagectomy techniques on complications

The curative treatment of esophageal cancer patients has changed tremendously over the past decades, which has resulted in improved postoperative and survival outcomes. Between 2009 and 2015, many surgical cancer centers added neoadjuvant chemoradiotherapy to the standard curative treatment of esophageal cancer. The preferred surgical technique has changed from open transhiatal and McKeown esophagectomy towards minimally invasive Ivor Lewis esophagectomy in many centers in the Netherlands, but also in some international centers (**Chapter 4, 7 and 9**).^{19,20} Recent studies have shown

that the occurrence of complications after esophagectomy impairs long-term quality of life and survival of patients with esophageal cancer independently of neoadjuvant therapies.^{5,21} Neoadjuvant chemoradiotherapy has been reported to cause radiation effects when administered to the proximal esophagus or the stomach that is used for the gastric conduit. However, a correlation between chemoradiotherapy and morbidity or severity of complications after esophagectomy was not shown in the study within this thesis that investigated patient groups of the CROSS trial using the Clavien–Dindo classification and the Comprehensive Complication Index (**Chapter 4**).^{22,23} This might be caused by the fact that the CROSS trial was powered on the survival outcome of the patients, not on the severity of complications after esophagectomy or morbidity in general.

Since surgeons aim for curation of patients with esophageal cancer with preservation of the best possible quality of life, it is paramount to protect patients against (severe) complications as much as possible by choosing the right surgical technique. This thesis has shown that the incidence and severity of complications vary with different esophagectomy techniques, which strengthens the importance of (inter)national guidelines for surgical techniques in the treatment of esophageal cancer (**Part II**). Regarding one of the most common complications—*anastomotic leakage*, Ivor Lewis esophagectomy seems to be associated with a lower incidence and ECCG type ≥ 2 *anastomotic leakages* than transhiatal and McKeown esophagectomy (**Chapter 5–7**). These results are comparable to other national and international research studies.^{24,25} However, a more detailed observation of *anastomotic leakage* patients alone showed that amongst all *anastomotic leakages*, the occurred *anastomotic leakage* was likely to be more severe when Ivor Lewis esophagectomy was performed than after transhiatal and McKeown esophagectomy (**Chapter 6–7**). An explanation for this fact may be found in the low overall incidence of *anastomotic leakage* after Ivor Lewis esophagectomy as compared to the other two techniques. Since Ivor Lewis esophagectomy contains a shorter gastric conduit than McKeown and transhiatal esophagectomy, blood perfusion to the anastomosis is better preserved and traction on the anastomosis is limited, resulting in a better quality of the anastomosis. Nevertheless, infections caused by intrathoracic *anastomotic leakages* logically have a higher probability to spread throughout the thorax than those caused by cervical *anastomotic leakages*. Besides, intrathoracic *anastomotic leakages* are associated with a higher reoperation rate, which results generally in higher severity scores. Cervical *anastomotic leakages* can (naturally) drain through the neck wound, which probably leads to faster healing from this complication and thus, a lower severity. However, if the leakage descends into the mediastinum after McKeown esophagectomy it can be

severe and difficult to treat, and may even cause tracheoesophageal fistulas with extensive radiation-associated necrosis since these patients usually have an extended radiation field.

The thesis describes a possible solution for the higher severity of anastomotic leakage after Ivor Lewis esophagectomy. Although the protective value of the greater omentum against anastomotic leakages has not been found in lower gastrointestinal surgery, literature and results of this thesis suggest that using the greater omentum in combination with the pleural flap may improve the incidence and severity of anastomotic leakages after Ivor Lewis esophagectomy (**Chapter 7**).²⁶ This can be explained by the two steps in creating the 'flap and wrap' reconstruction. First, tensile forces on the anastomosis are limited as much as possible by stitching the conduit to the pleural flap. Secondly, the greater omentum is wrapped around the anastomosis. Hereby, the pleural flap and the omentum create a protection mechanism against the negative pressure of the thoracic cavity, and function as a mechanical barrier for spread of the infection throughout the thorax. It is hypothesized that alleged revascularization and immunological functions of the greater omentum also play an important role in the prevention of severe anastomotic leakages.²⁷ Although this thesis investigates patients during the proficiency-gain curve of Ivor Lewis esophagectomy, the addition of the 'flap and wrap' reconstruction led to fewer anastomotic leakages and lower severity scores than when the 'flap and wrap' reconstruction was not performed. Therefore, these anastomotic leakages may be treated by less invasive procedures, such as the use of endoscopic vacuum therapy.²⁸

The final chapter of the thesis gives insight in several major changes within the curative surgical treatment of esophageal cancer over the last 25 years. The use of neoadjuvant chemoradiotherapy and minimally invasive Ivor Lewis esophagectomy have significantly increased to approximately 89% and 93% (resp.) at this large tertiary referral center. In addition to the changes in treatment, patient characteristics have also changed in recent years, i.e. increased body mass index, age at time of surgery and the proportion of adenocarcinomas. The cumulative effect of all changes together within the curative surgical treatment of esophageal cancer has resulted in a substantial increase of the 5-year overall survival from approximately 30% in the early nineties to 50% in the latest years (**Chapter 9**). Although results of the final chapter are based on a single center, it has included more than 1600 patients and comparable survival improvements have been described in other national and international research studies investigating patients who underwent esophagectomy for cancer over a longer time period.²⁹⁻³¹ The fact that morbidity rates have not

decreased over the last 25 years might be caused by higher age and body mass index of patients at time of esophagectomy and increased awareness of complications amongst surgeons, which consequently resulted in an improved registration of complication by surgical departments over recent years.

FUTURE PERSPECTIVES

In **Part I**, this thesis proposed the use of a trigger tool and the Comprehensive Complication Index as accurate methods for improving the registration of complications and severity. In the analysis of the trigger tool, this was the first study that provided a golden standard containing two patient groups with and without complications of equal size. Consequently, sensitivity between the trigger tool and the commonly used verbal complication meeting could be compared. However, the trigger tool in this chapter was assessed in only one general surgical department, so generalizability remains speculated. Although other trigger tools—such as the Global Trigger Tool—also show promising results, further investigations evaluating the trigger tool used in this thesis specifically should be performed to assess its generalizability in other hospitals and surgical specialties.¹⁰ Additionally, the exact time-efforts amongst clinicians and healthcare costs should be compared between use of the verbal complication meeting and the trigger tool in a separated cost-effectiveness study of good quality. Future systems that can potentially improve the registration of complications and simultaneously decrease the administrative burden of employees are machine learning and artificial intelligence. These elements can use natural language processing in free-text reports that surgeons and surgical residents use in clinical daily practice to highlight patients at risk or even register complications in separate databases.³²

Regarding the Comprehensive Complication Index as a severity classification method for postoperative complications, its calculation is more time consuming than the Clavien–Dindo classification. Ideally, the registration and calculation of the Comprehensive Complication Index needs to be simplified and implemented in the hospitals' electronic system before researchers will use it regularly in very large patient groups of multicenter (randomized) studies. However, registration of each complication after esophagectomy is already mandatory in many countries so if surgical departments will keep tracking complications and their severity on a daily basis, time-efforts can be reduced. A national online complication registration database with access to the hospital's own data can avoid repeated administration of outcomes into different (research) databases.⁴

Regarding associations between surgical techniques and the incidence and severity of complications, it seems that Ivor Lewis esophagectomy is the best approach to reduce the incidence of anastomotic leakages and other postoperative outcomes in patients with esophageal or gastroesophageal junction carcinomas as compared to transhiatal and McKeown esophagectomy (**Part II**). Anastomotic leakages seem to be more severe if they occur after Ivor Lewis esophagectomy, and this severity can be reduced by the addition of the 'flap and wrap' reconstruction. However, the effect of this reconstruction has only been investigated in a single center during a learning-curve period. This is confirmed by the proficiency-gain curve in **Chapter 7**, but the exact proportion of patients who experienced learning-associated morbidity was not calculated in this thesis. Since learning-associated morbidity can influence several outcomes after surgery, future studies should incorporate this to perform transparent comparisons between new surgical techniques.³³ The influence of other anastomosis techniques, such as the stapling or suture technique (end-to-side versus side-to-side), could also have been assessed, but were not investigated in the chapters of this thesis.³⁴ In this assessment, different models in the multivariate analyses should preferably be used in future studies in order to, for example, distinguish patient-related factors from surgical variables.

A remaining difference was found regarding the type of tumor between the patient groups in despite of propensity-scored matching and correction for confounders. This is a small reflection of the great diversity of patients undergoing different esophagectomy techniques. As can be expected, patients with esophageal cancer are selected for certain procedures by several patient and tumor parameters, such as the location of the tumor, the extent of the radiation field, patient condition and comorbidities. Hence, results of the chapters reflect a general population of esophageal cancer patients and do not optimize patient groups before performing statistical investigations. Finally, the cumulative effect of all diagnostic and treatment changes over 25 years have shown an improved 5-year overall survival for patients with esophageal cancer from approximately 30% to 50%, but assessment of contributing factors could not be performed due to the (mostly smaller) protocol changes that were not registered in the prospective database of that study.

Overall conclusions

Qualitative research investigating registration methods for postoperative complications is a topic that needs more attention in the surgical field. Using a trigger tool combined with medical record screening seems to be an accurate method in the detection of surgical complications with beneficial effects in terms of time-effort and administration workload for surgical residents and

staff members. Regarding the registration and classification of the severity of complications, the Comprehensive Complication Index is a more detailed method than the Clavien–Dindo classification to reflect on the burden of complications in surgical patients. The Comprehensive Complication Index can therefore be used in scientific studies comparing different surgical techniques, but could also be promising as a risk assessment method in other medical fields.

Many improvements were established in the curative treatment of esophageal cancer over the last years. This resulted in a change of patient characteristics, tumor type, substantially increased use of neoadjuvant chemoradiotherapy and transthoracic esophagectomy, and improved clinical and survival outcomes in patients after esophagectomy for cancer. Within this field, minimally invasive Ivor Lewis esophagectomy in combination with the ‘flap and wrap’ reconstruction is a promising technique that decreases anastomotic leakage rates and reduces their severity. However, not every patient is eligible for a transthoracic resection with intrathoracic anastomosis due to the patient’s condition, comorbidities, tumor location and/or radiation fields. For those patients, surgeons can choose for transhiatal or McKeown esophagectomy. In all perspectives, patients and healthcare workers should be aware of the possible serious post-operative outcomes after esophagectomy.

References

1. Veen EJ, Janssen-Heijnen MLG, Leenen LPH, Roukema JA. The registration of complications in surgery: A learning curve. *World J Surg.* 2005;29(3):402-409. DOI:10.1007/s00268-004-7358-8
2. Inspectie Gezondheidszorg en Jeugd. Basisset medisch specialistische zorg kwaliteitsindicatoren 2021 - Voor ziekenhuizen en particuliere klinieken.;2021.
3. Peerboom D, De Coster J, Vanhaecht K, et al. quality indicators in vascular surgery: toward a national consensus on 20 quality indicators in Belgium. *Ann Vasc Surg.* 2021;71(August 2020):237-248. DOI:10.1016/j.avsg.2020.07.037
4. Cromwell D, Wahedally H, Park MH, et al. National Esophago-Gastric Cancer Audit. *Healthc Qual Improv Partnersh.* 2019;(December):30.
5. Van Der Werf LR, Wijnhoven BPL, Franssen LFC, et al. A national cohort study evaluating the association between short-term outcomes and long-term survival after esophageal and gastric cancer surgery. *Ann Surg.* 2019;270(5). DOI:10.1097/SLA.0000000000003520
6. Duclos A, Chollet F, Pascal L, et al. Effect of monitoring surgical outcomes using control charts to reduce major adverse events in patients: Cluster randomised trial. *BMJ.* 2020;371:1-10. DOI:10.1136/bmj.m3840
7. Marang-Van De Mheen PJ, Van Hanegem N, Kievit J. Effectiveness of routine reporting to identify minor and serious adverse outcomes in surgical patients. *Qual Saf Heal Care.* 2005;14(5):378-382. DOI:10.1136/qshc.2004.013250
8. Ubbink DT, Visser A, Gouma DJ, Goslings JC. Registration of surgical adverse outcomes: A reliability study in a university hospital. *BMJ Open.* 2012;2(3):1-6. DOI:10.1136/bmjopen-2012-000891
9. Pulcrano M, Evans SRT, Sosin M. Quality of life and burnout rates across surgical specialties: A systematic review. *JAMA Surg.* 2016;151(10):970-978. DOI:10.1001/jamasurg.2016.1647
10. Klein DO, Renneberg RJMW, Koopmans RP, Prins MH. A systematic review of methods for medical record analysis to detect adverse events in hospitalized patients. *J Patient Saf.* 2021;17(8):1234-1240. DOI:10.1097/pts.0000000000000670
11. Aikawa G, Sakuramoto H, Ouchi A, et al. Development of the Japanese version of the Intensive Care Unit Trigger Tool to detect adverse events in critically ill patients. *Acute Med Surg.* 2021;8(1):6-9. DOI:10.1002/ams2.672
12. Menat U, Desai CK, Panchal JR, Shah AN. An evaluation of trigger tool method for adverse drug reaction monitoring at a tertiary care teaching hospital. *Perspect Clin Res.* 2021;12(1):33-39. DOI:10.4103/picr.PICR_30_19
13. Low DE, Alderson D, Ceconello I, et al. International consensus on standardization of data collection for complications associated with esophagectomy: Esophagectomy Complications Consensus Group (ECCG). *Ann Surg.* 2015;262(2):286-294. DOI:10.1097/SLA.0000000000001098
14. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: A new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg.* 2004;240(2):205-213. DOI:10.1097/01.sla.0000133083.54934.ae
15. Slankamenac K, Graf R, Barkun J, Puhon MA, Clavien PA. The comprehensive complication index: A novel continuous scale to measure surgical morbidity. *Ann Surg.* 2013;258(1):1-7. DOI:10.1097/SLA.0b013e318296c732
16. Kowalewski KF, Müller D, Mühlbauer J, et al. The comprehensive complication index (CCI): proposal of a new reporting standard for complications in major urological surgery. *World J Urol.* 2021;39(5):1631-1639. DOI:10.1007/s00345-020-03356-z
17. Tirota F, Parente A, Richardson T, et al. Comparison of Comprehensive Complication Index and Clavien-Dindo classification in patients with retroperitoneal sarcoma. *J Surg Oncol.* 2021;(April). DOI:10.1002/jso.26612
18. Slankamenac K, Nederlof N, Pessaux P, et al. The Comprehensive Complication Index: a novel and more sensitive endpoint for assessing outcome and reducing sample size in randomized controlled trials. *Ann Surg.* 2014;260(5):757-763. DOI: 10.1097/SLA.000000000000094
19. Haverkamp L, Seesing MFJJ, Ruurda JP, et al. Worldwide trends in surgical techniques in the treatment of esophageal and gastroesophageal junction cancer. *Dis Esophagus.* 2017;30(1):1-7. DOI:10.1111/dote.12480

20. Reynolds J V, Donlon N, Elliott JA, et al. Comparison of esophagectomy outcomes between a national center, a national audit collaborative, and an international database using the Esophageal Complications Consensus Group (ECCG) standardized definitions. *Dis Esophagus*. 2020;34(1):1-9. DOI:10.1093/dote/daaa060
21. Jezerskyte E, Saadeh LM, Hagens ERC, et al. Long-term health-related quality of life after McKeown and Ivor Lewis esophagectomy for esophageal carcinoma. *Dis Esophagus*. 2020;33(11):1-9. DOI:10.1093/dote/daaa022
22. Koëter M, Kathiravetpillai N, Gooszen JA, et al. Influence of the extent and dose of radiation on complications after neoadjuvant chemoradiation and subsequent esophagectomy with gastric tube reconstruction with a cervical anastomosis. *Int J Radiat Oncol Biol Phys*. 2017;97(4):813-821. DOI:10.1016/j.ijrobp.2016.11.054
23. Vande Walle C, Ceelen WP, Boterberg T, et al. Anastomotic complications after Ivor Lewis esophagectomy in patients treated with neoadjuvant chemoradiation are related to radiation dose to the gastric fundus. *Int J Radiat Oncol Biol Phys*. 2012;82(3):e513-e519. DOI:10.1016/j.ijrobp.2011.05.071
24. Van Workum F, Verstegen MHP, Klarenbeek BR, et al. Intrathoracic vs cervical anastomosis after totally or hybrid minimally invasive esophagectomy for esophageal cancer: A randomized clinical trial. *JAMA Surg*. 2021;156(7):601-610. DOI:10.1001/jamasurg.2021.1555
25. Sabra MJ, Alwatari YA, Wolfe LG, et al. Ivor Lewis vs Mckeown esophagectomy: analysis of operative outcomes from the ACS NSQIP database. *Gen Thorac Cardiovasc Surg*. 2020;68(4):370-379. DOI:10.1007/s11748-020-01290-w
26. Grigor EJM, Kaaki S, Fergusson DA, Maziak DE, Seely AJE. Interventions to prevent anastomotic leak after esophageal surgery: a systematic review and meta-analysis. *BMC Surg*. 2021;21(1):42. DOI:10.1186/s12893-020-01026-w
27. Wang AW, Prieto JM, Cauvi DM, Bickler SW, De Maio A. The greater omentum - a vibrant and enigmatic immunologic organ involved in injury and infection resolution. *Shock*. 2020;53(4):384-390. DOI:10.1097/SHK.0000000000001428
28. Tavares G, Tustumi F, Tristão LS, Bernardo WM. Endoscopic vacuum therapy for anastomotic leak in esophagectomy and total gastrectomy: A systematic review and meta-analysis. *Dis Esophagus*. 2021;34(5):1-11. DOI:10.1093/dote/daaa132
29. van Hagen P, Hulshof MCCM, van Lanschot JJB, et al. Preoperative chemoradiotherapy for esophageal or junctional cancer. *N Engl J Med*. 2012;366(22):2074-2084. DOI:10.1056/nejmoa1112088
30. Griffin SM, Jones R, Kamarajah SK, et al. Evolution of esophagectomy for cancer over 30 years: changes in presentation, management and outcomes. *Ann Surg Oncol*. 2020;28(6):3011-3022. DOI:10.1245/s10434-020-09200-3
31. Cavallin F, Scarpa M, Cagol M, et al. Esophageal cancer clinical presentation: trends in the last 3 decades in a large Italian series. *Ann Surg*. 2018;267(1):99-104. DOI:10.1097/SLA.0000000000002048
32. Young IJB, Luz S, Lone N. A systematic review of natural language processing for classification tasks in the field of incident reporting and adverse event analysis. *Int J Med Inform*. 2019;132(September):103971. DOI:10.1016/j.ijmedinf.2019.103971
33. Van Workum F, Stenstra MHBC, Berkelmans GHK, et al. Learning curve and associated morbidity of minimally invasive esophagectomy: a retrospective multicenter study. *Ann Surg*. 2019;269(1):88-94. DOI:10.1097/SLA.0000000000002469
34. Schröder W, Raptis DA, Schmidt HM, et al. Anastomotic techniques and associated morbidity in total minimally invasive transthoracic esophagectomy: results from the EsoBenchmark database. *Ann Surg*. 2019;270(5):1. DOI:10.1097/SLA.0000000000003538

APPENDICES



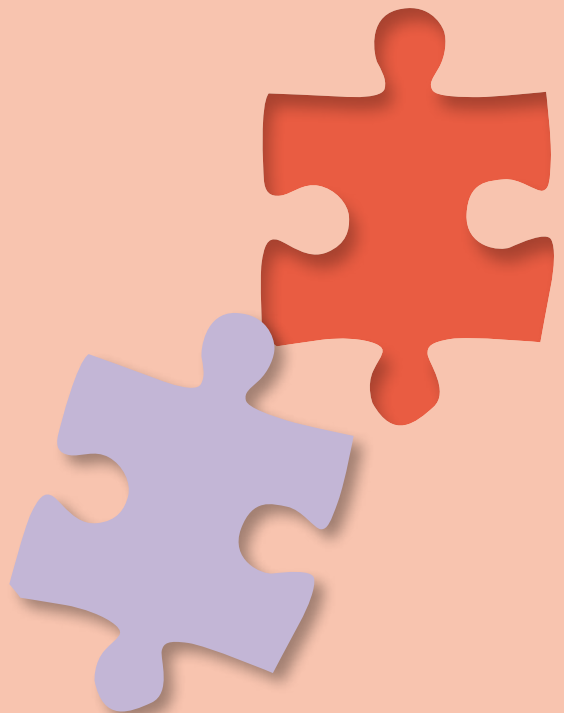


SAMENVATTING

(Summary in Dutch)

**De optimale classificatie en behandeling
van complicaties na een curatieve slokdarmresectie
bij patiënten met slokdarmkanker**

In het tijdperk van minimaal invasieve chirurgie
en voorbehandeling met chemotherapie en bestraling



Het wetenschappelijke onderzoek in dit proefschrift draagt bij aan de evaluatie van de recente ontwikkelingen binnen de curatieve, chirurgische behandeling van slokdarmkanker en het effect hiervan op postoperatieve complicaties. Veel aanpassingen in de chirurgische behandeling van slokdarmkanker zijn erop gericht om ernstige postoperatieve complicaties na een slokdarmresectie te voorkomen. Om dit zo nauwkeurig en efficiënt mogelijk na te kunnen streven, is inzicht in deze complicaties en de beïnvloedende factoren hierop van groot belang. Het waarborgen van een transparante complicatieregistratie draagt hieraan bij. Om dit te kunnen doen onderzoekt **Deel I** van dit proefschrift enkele methoden ten behoeve van een zo nauwkeurige mogelijke registratie van complicaties en de classificatie voor de impact van complicaties op patiënten. In **Deel II** worden de incidentie van specifieke complicaties en postoperatieve uitkomsten na verschillende operatietechnieken binnen de slokdarmchirurgie met elkaar vergeleken. Hierbij worden factoren die van invloed zijn geanalyseerd, waaronder neoadjuvante chemoradiatie, de intrathoracale anastomose en de minimaal invasieve chirurgische benadering van een slokdarmresectie. In het laatste deel van het proefschrift worden veranderingen belicht die betrekking hebben op patiëntkarakteristieken, curatieve behandelingen, korte termijn uitkomsten en overleving van patiënten die een slokdarmresectie ondergingen in de afgelopen 25 jaar.

Deel I. Evaluatie van verschillende methoden voor het registreren van postoperatieve complicaties

In **Hoofdstuk 2** van dit proefschrift wordt een gedetailleerde beschrijving gegeven voor het ontwikkelen van een trigger tool als methode om de registratie van complicaties te vereenvoudigen voor arts-assistenten en stafleden van een chirurgische afdeling. De *trigger tool* selecteert patiënten met een verhoogd risico op het ontstaan van complicaties tijdens opname op een chirurgische afdeling, waarna de medische gegevens van deze patiënten worden doorzocht op additionele complicaties. Het vergelijkende deel van dit onderzoek laat zien dat de sensitiviteit van de *trigger tool* gelijk is aan die van de wekelijkse complicatiebespreking, waarbij meerdere arts-assistenten en stafleden van de afdeling aanwezig zijn. Door gebruik te maken van de *trigger tool* kan de administratieve werkdruk van de klinische werknemers verlaagd worden. Aanvullend kosten-effectiviteitsonderzoek is nodig om de *trigger tool* af te zetten tegen die van een wekelijkse complicatiebespreking, maar lagere kosten voor ziekenhuizen bij gebruik van de *trigger tool* worden hierbij voorspeld.

Classificatiesystemen voor de ernst van complicaties worden onderzocht in **Hoofdstuk 3** en **4**. **Hoofdstuk 3** beschrijft sterkere relaties tussen de ernst van postoperatieve complicaties en traditionele uitkomstparameters wanneer het

meest recent ontwikkelde classificatiesysteem (de *Comprehensive Complication Index*) wordt gebruikt dan wanneer de Clavien–Dindo classificatie wordt toegepast. Door middel van deze uitkomsten kan worden geconcludeerd dat de *Comprehensive Complication Index* een gedetailleerdere weergave geeft van de ernst van postoperatieve complicaties bij patiënten na een slokdarmresectie dan de Clavien–Dindo score. Indien steeds meer nationale en internationale studies de *Comprehensive Complication Index* zullen gaan gebruiken zullen subtiele uitkomstverschillen tussen chirurgische technieken zichtbaar worden. Dit zal uiteindelijk leiden tot een verbetering van de patiëntenzorg.

In het onderzoek van **Hoofdstuk 4** wordt door middel van de *Comprehensive Complication Index* bevestigd dat neoadjuvante chemoradiatie voorafgaand aan een oncologische slokdarmresectie geen invloed heeft op de ernst van postoperatieve complicaties in vergelijking met postoperatieve complicaties in patiënten die niet zijn voorbehandeld met chemotherapie en bestraling.

Deel III. De invloed van chirurgische technieken op complicaties na een slokdarmresectie

Hoofdstuk 5 toont door middel van een propensity-score matched analyse aan dat de incidentie van ernstige naadlekkages en 90-dagen mortaliteit na een minimaal invasieve transthoracale slokdarmresectie lager is wanneer er een intrathoracale anastomose is aangelegd dan wanneer er een cervicale anastomose wordt gecreëerd. In **Hoofdstuk 6** wordt er dieper ingegaan op patiënten met naadlekkages na een slokdarmresectie. Hoewel de absolute incidentie van ernstige naadlekkages na een Ivor Lewis slokdarmresectie lager is (12,4%) dan na een McKeown slokdarmresectie (23,3%), laten uitkomsten van dit onderzoek zien dat naadlekkages die ontstaan na een transhiatale of een McKeown slokdarmresectie relatief minder ernstig verlopen. Om de intrathoracale anastomose tegen (ernstige) naadlekkages te beschermen kan de buismaag aan de pleuraflap gehecht worden, waarbij de anastomose bedekt wordt door de pleuraflap en vervolgens het omentum er omheen gedrapeerd wordt. Hierdoor wordt de trekkracht op de anastomose verminderd, de anastomose beschermd tegen de omgevende negatieve intrathoracale druk en wordt er een barrière gecreëerd tegen verspreiding van infecties door de thorax. Deze technieken worden samen de 'flap en wrap' reconstructie genoemd. **Hoofdstuk 7** laat zien dat na deze 'flap en wrap' reconstructie de incidentie van naadlekkages na een transthoracale slokdarmresectie 7,3% bedraagt. Daarnaast leiden de naadlekkages die toch ontstaan na aanleg van een 'flap en wrap' reconstructie tot een minder ernstig verloop dan wanneer de reconstructie zonder deze techniek wordt aangelegd in de thorax. De 'flap en wrap' reconstructie is een veilige techniek die na het bereiken van de plateaufase in de chirurgische

leercurve naadlekkages lijkt te verminderen en de ernst hiervan te beperken bij patiënten die fit genoeg zijn om een transthoracale slokdarmresectie te ondergaan. De leercurve van de Ivor Lewis slokdarmresectie laat een steile helling zien aan het begin van de curve, dat past bij het verkrijgen van vaardigheid voor een zeer complexe chirurgische techniek. Het weergeven van een leercurve voor een nieuwe chirurgische techniek draagt in belangrijke mate bij aan de interpretatie van studieresultaten. Evaluatie van de leercurve van een nieuwe chirurgische techniek dient bij elk wetenschappelijk onderzoek betrokken te worden om zo een eerlijke en transparante vergelijking te kunnen maken van de uitkomsten. Dit heeft tevens belangrijke implicaties voor het in praktijk brengen van een nieuwe techniek in een landelijke setting.

In **Hoofdstuk 8** worden de incidentie, risicofactoren, diagnostiek, behandeling en gevolgen van een symptomatische hernia diafragmatica na een slokdarmresectie beschreven. Dit is een minder vaak voorkomende (2,5% van alle slokdarmresecties in deze serie) en onderbelichte complicatie die ook in een latere fase na een slokdarmresectie kan optreden. Het onderzoek uit dit hoofdstuk toont aan dat de minimaal invasieve Ivor Lewis procedure een risicofactor is voor het ontstaan van deze complicatie, met een incidentie van 9,5%. Recidieven van symptomatische hernia diafragmatica na een eerdere behandeling ontstaan relatief vaak, in 19,0% van de patiënten. Bewustwording voor het belang van snelle diagnostiek en behandeling van een symptomatische hernia diafragmatica na een slokdarmresectie is vereist om de mogelijke ernstige gevolgen te kunnen beperken.

Het laatste hoofdstuk van dit proefschrift laat zien dat er veel veranderd is in de behandeling van slokdarmkanker over de afgelopen 25 jaar (**Hoofdstuk 9**). Het belangrijkste resultaat van dit onderzoek is een stijging van de algemene 5-jaars overleving van 30% in het begin van de jaren '90 naar 50% voor patiënten die een slokdarmresectie ondergingen in de afgelopen jaren. Daarnaast is te zien dat de patiënt karakteristieken in de huidige tijd anders zijn dan die van patiënten uit het begin van de jaren '90. De gemiddelde leeftijd en body mass index van de huidige patiënten zijn hoger, en het aandeel patiënten met een adenocarcinoom ten opzichte van het plaveiselcelcarcinoom is gestegen. Ook wordt bevestigd dat meer dan 90% van alle patiënten tegenwoordig wordt behandeld met neoadjuvante chemoradiotherapie gevolgd door een minimaal invasieve Ivor Lewis slokdarmresectie. Doordat bewustwording van complicaties heeft geleid tot een betere complicatieregistratie en thans tot mogelijkheden om chirurgische technieken te verbeteren, is in dit hoofdstuk te zien dat postoperatieve uitkomsten ook in de laatste 5 jaar van het onderzoek verbeterden. Met name in dit laatste hoofdstuk wordt de waarde van het uitvoeren van kwalitatief goed onderzoek naar diagnostiek, behandelingen en complicatieregistratie in grote groepen patiënten onderstreept.

DISCLOSURE STATEMENT

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PHD PORTFOLIO

Name PhD student: Annelijn Slaman
PhD period: July 2015–September 2021
Name PhD supervisor: Prof. dr. M.I. van Berge Henegouwen

1. PhD training

Courses	Year	Workload (hours/ECTS)
Practical biostatistics	2016	1.1
Zoeken voor een CAT	2016	0.1
Pubmed basics	2016	0.1
Advanced topics of biostatistics	2018	2.1

Seminars, workshops and master classes	Year	Workload (hours/ECTS)
Monthly journal club	2017-2018	2.0
Regionale refereeravonden regio Amsterdam	2015-2019	1.0
Lokale refereeravonden OLVG	2018-2019	1.0
Gut club Amsterdam	2014-2016	1.0

Presentations	Year	Workload (hours/ECTS)
Trigger tool versus verbal inventory to detect surgical complications - Weekly research meeting AMC	2014	0.5
A quantified scoring system for postoperative complication severity compared to the Clavien–Dindo classification - Najaarsvergadering Nederlandse vereniging voor Heelkunde, Veldhoven	2014	0.5

Presentations	Year	Workload (hours/ECTS)
Ivor Lewis or McKeown versus Orringer esophagectomy for cancer of the distal esophagus or gastro-esophageal junction (IVORY trial) - Gut club Amsterdam	2014	0.5
The role of preoperative use of statins in treatment for patients with a carcinoma of the esophagus - Voorjaarsvergadering Nederlandse vereniging voor Heelkunde, Veldhoven (poster)	2014	0.5
The relevance of the location of the involved lymph nodes including the coeliac trunk region in patients with a tumor of the distal esophagus or gastrointestinal junction - Voorjaarsvergadering Nederlandse vereniging voor Heelkunde, Veldhoven (poster)	2014	0.5
Improved anastomotic leakage rates in patients following Ivor Lewis esophagectomy with omental wrap and pleural flap - European Congress of the International Society for Diseases of the Esophagus, Stockholm, Sweden	2014	0.5
- World Congress of the International Society for Diseases of the Esophagus, Singapore, Singapore Republic (poster)	2016	0.5
- Digestive Disease Days, Vereniging voor Gastroenterologie, Veldhoven	2016	0.5
- Afdeling Chirurgie Rode Kruis Ziekenhuis, Beverwijk	2016	0.5
- Afdeling Chirurgie Waterland Ziekenhuis, Purmerend	2017	0.5
Using the Comprehensive Complication Index to assess the impact of neoadjuvant chemoradiotherapy on postoperative complications after esophagectomy for cancer - World Congress of the International Society for Diseases of the Esophagus, Singapore, Singapore Republic	2016	0.5

Presentations	Year	Workload (hours/ECTS)
Outcomes of salvage surgery in patients with recurrent esophageal cancer after definitive chemoradiotherapy		
- World Congress of the International Society for Diseases of the Esophagus, Singapore, Singapore Republic (Poster)	2016	0.5
- Voorjaarsvergadering, Nederlandse vereniging voor Gastroenterologie	2018	0.5
Long-term quality of life after esophagectomy: do postoperative complications matter?		
- United European Gastroenterology week (Poster)	2016	0.5
Symptomatic diaphragmatic hernia following esophagectomy		
- World Congress of the International Society for Diseases of the Esophagus, Singapore, Singapore Republic (Poster)	2016	0.5
Esophageal cancer patients' management: Cross-cultural differences between Dutch and Italian patients in perceived quality of provided oncological information		
- Digestive Disease Week, San Diego, California, USA (poster)	2016	0.5
- World Congress of the International Society for Diseases of the Esophagus, Singapore, Singapore Republic	2016	0.5
Long-term survivor after esophagectomy: cross-cultural differences between Dutch and Italian patients in referred quality of life.		
- World Congress of the International Society for Diseases of the Esophagus, Singapore, Singapore Republic (Poster)	2016	0.5
Surgical management of esophageal sarcoma: A multicenter European experience		
- World Congress of the International Society for Diseases of the Esophagus, Vienna, Austria	2018	0.5

Presentations	Year	Workload (hours/ECTS)
Prospective evaluation of 18F-FDG PET/CT after neoadjuvant chemoradiotherapy for detecting lymph node metastases near the celiac trunk in patients with esophageal cancer		
- World Congress of the International Society for Diseases of the Esophagus, Vienna, Austria (Poster)	2018	0.5
- Voorjaarsvergadering, Nederlandse vereniging voor Heelkunde, Veldhoven	2018	0.5
Surgical management of tracheoesophageal fistulas in patients with esophageal cancer		
- World Congress of the International Society for Diseases of the Esophagus, Vienna, Austria (Poster)	2018	0.5
Improved survival after esophagectomy for esophageal or gastroesophageal cancer in the last 25 years		
- World Congress of the International Society for Diseases of the Esophagus, Vienna, Austria	2018	0.5
- Regionale refereeravond regio Amsterdam, Amsterdam	2018	0.5

(Inter)national conferences	Year	Workload (hours/ECTS)
Voorjaarsvergadering Nederlandse vereniging voor Heelkunde, Veldhoven	2014	0.25
	2015	0.25
	2016	0.25
	2018	0.25
Digestive Disease Days, Nederlandse vereniging voor Gastroenterologie, Veldhoven	2016	0.25
	2018	0.25
European Congress of the Society for Diseases of the Esophagus, Stockholm, Sweden	2015	0.5
International Congress of the Society for Diseases of the Esophagus, Singapore, Singapore Republic	2016	0.5
International Congress of the Society for Diseases of the Esophagus, Vienna, Austria	2018	0.5

2. Teaching

Lecturing	Year	Workload (hours/ECTS)
Surgical principles to nurses at a surgical department of a general hospital: gastrointestinal, trauma and vascular surgery	2018	1.0
Surgical principles to medical students at a surgical department of a general hospital: gastrointestinal, trauma and vascular surgery	2019-2020	1.0
Gastrointestinal and thoracic anatomy on computed tomography to students of the bachelor's degree program of Medicine	2020-2021	1.0
General principles of surgery as preparation for rotations of students of the master's degree program of Medicine	2020-2021	1.0

Tutoring, mentoring	Year	Workload (hours/ECTS)
Mees de Jong, bachelorthesis, department of surgery	2017	1.0
Jasper de Groen, masterthesis, department of surgery	2018	0.5

Other	Year	Workload (hours/ECTS)
Basis kwalificatie onderwijs	2020–present	2.0

3. Parameters of esteem

Grants	Year
Slokdarm- en maagkankerfonds	2017

Awards and prizes	Year
Student Award by the Dutch Society of Gastroenterology (NVGE) for the most qualified research project performed by a student	2016

LIST OF PUBLICATIONS

This thesis

- A quantified scoring system for postoperative complication severity compared to the Clavien-Dindo classification. AE Slaman, SM Lagarde, SS Gisbertz, MI van Berge Henegouwen. *Dig Surg*. 2015;32(5):361-366. DOI: 10.1159/000433608
- Trigger tool versus verbal inventory to detect surgical complications. A Visser, AE Slaman, CM van Leijen, DJ Gouma, JC Goslings, DT Ubbink. *Langenbeck's Arch Surg*. 2015; DOI:10.1007/s00423-015-1337-4.
- Using the Comprehensive Complication Index to assess the Impact of neoadjuvant chemoradiotherapy on complication severity after esophagectomy for cancer. AE Slaman, N Nederlof, P van Hagen, A van der Gaast, K Slankamenac, SS Gisbertz, JJB van Lanschot, BPL Wijnhoven, MI van Berge Henegouwen and CROSS-Study Group. *Ann Surg Oncol* (2016) 23:3964-3971. DOI: 10.1245/s10434-016-5291-3
- Propensity-score matched analysis comparing minimally invasive Ivor-Lewis versus minimally invasive McKeown esophagectomy. F van Workum, AE Slaman, MI van Berge Henegouwen, SS Gisbertz, EA Kouwenhoven, MJ van Det, FJH van den Wildenberg, F Polat, MDP Luyer, GAP Nieuwenhuijzen, C Rosman. *Ann Surg* 2020;271:128-13. DOI 10.1097/SLA.0000000000002982
- Outcomes of patients with anastomotic leakage after transhiatal, McKeown or Ivor Lewis esophagectomy: A nationwide cohort study. MHP Verstegen, AE Slaman, BR Klarenbeek, MI van Berge Henegouwen, SS Gisbertz, C Rosman, F van Workum. *World J Surg* 2021;45(11):3341-3349. DOI: 10.1007/s00268-021-06250-w
- Improved anastomotic leakage rates after the 'flap and wrap' reconstruction in Ivor Lewis esophagectomy for cancer. AE Slaman, WJ Eshuis, MI van Berge Henegouwen, SS Gisbertz. Submitted in September 2021
- Symptomatic diaphragmatic hernia following Esophagectomy. AE Slaman, JAH Gooszen, SS Gisbertz, MI van Berge Henegouwen. *Ann Surg Oncol* (2016) 23:3964-3971. DOI: 10.1245/s10434-016-5291-3
- Improved clinical outcomes and survival after esophagectomy for cancer over 25 years. AE Slaman, G Pirozzolo, WJ Eshuis, JJGHM Bergman, MCCM Hulshof, HWM van Laarhoven, SL Meijer, SS Gisbertz, MI van Berge Henegouwen. Submitted (August 2021).

Other publications

- Postoperative outcomes of minimally invasive gastrectomy versus open gastrectomy during the early introduction of minimally invasive gastrectomy in the Netherlands. A population-based cohort study. HJF Brenkman, SS Gisbertz, AE Slaman, L Goense, JP Ruurda, MI van Berge Henegouwen, R van Hillegersberg, Dutch Upper Gastrointestinal Cancer Audit (DUCA) group. *Ann Surg* 2017; 266:831-838. DOI:10.1097/SLA.0000000000002391
- Minimally invasive approach of gastro-esophageal junction tumors. In: Minimally invasive abdominal surgery. Cuesta MA (editor). 1st ed. London: Springer; 2017. DOI:10.1007/978-3-319-54301-7
- A propensity score matched analysis of open versus minimally invasive transthoracic esophagectomy in the Netherlands. MFJ Seesing, SS Gisbertz, L Goense, R van Hillegersberg, HM Kroon, SM Lagarde, JP Ruurda, AE Slaman, MI van Berge Henegouwen, BPL Wijnhoven. *Ann Surg.* 2017; 266(5):839-846. DOI:10.1097/SLA.0000000000002393
- Surgical management of esophageal sarcoma: a multicenter European experience. D Mege, L Depypere, G Piessen, AE Slaman, BPL Wijnhoven, A Hölscher, M Nilsson, MI van Berge Henegouwen, JJB van Lanschot, W Schröder, PA Thomas, P Nafteux, XBD D'Journo. *Dis Esophagus.* 2018; 1;31(3). DOI: 10.1093/dote/dox146
- Esophageal cancer patient's information management: Cross-cultural differences between Dutch and Italian patients in perceived quality of provided oncological information. LM Saadeh, AE Slaman, E Pinto, SS Gisbertz, F Cavallin, E Jezerskyte, R Alfieri, L Noteboom, Maria Cristina Bellissimo, M Cagol, G Pirozzolo, C Castoro, M Scarpa, MI van Berge Henegouwen. *J Thorac Dis* 2018; 10(8):5123-5130. DOI: 10.21037/jtd.2018.07.117
- Learning curve and associated morbidity of minimally invasive esophagectomy: A retrospective multicenter study. F van Workum, MHBC Stenstra, GHK Berkelmans, AE Slaman, MI van Berge Henegouwen, SS Gisbertz, FJH van den Wildenberg, F Polat, T Irino, M Nilsson, GAP Nieuwenhuijzen, MD Luyer, EM Adang, G Hannink, MM Rovers, C Rosman. *Ann Surg* 2019; 269:88-94. DOI:10.1097/SLA.0000000000002469
- Cardiorespiratory comorbidity and postoperative complications following esophagectomy: a European multicenter cohort study. F Klevebro, JA Elliot, AE Slaman, BD Vermeulen, S Kamiya, C Rosman, SS Gisbertz, PR Boshier, JV Reynolds, I Rouvelas, GB Hanna, MI van Berge Henegouwen, SR Markar. *Ann Surgical Oncol* (2019) 26, 2864-2873. DOI:10.1245/s10434-019-07478-6
- Neoadjuvant radio-chemotherapy for esophageal cancer: a multicenter European study comparing paclitaxel/carboplatin, 5-FU/cisplatin and FOLFOX. P Alleman, S Mantziari, M Winiker, AD Wagner, MI van Berge Henegouwen, SS Gisbertz, AE Slaman, R van Hillegersberg, JP Ruurda, H Brenkman, M Nilsson, K Satoshi, G Piesen, D Collet, C Gronnier, N Carrere, A Marinho, N Demartines, M Schafer. *Gastrointestinal Tumours, non-colorectal.* ESMO Abstract 2018. DOI: 10.1093/annonc/mdy282.014

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CURRICULUM VITAE AUCTORIS

Annelijn Elisabeth Slaman was born in Heemskerk on 14 October 1988. She started the Bachelor's degree program of Medicine in 2009. After one year of studying, she moved to Amsterdam. In her third year of the bachelor study she applied for a part-time job as a database manager for postoperative complications at the Department of Surgery of the Academic Medical Center Amsterdam. This gave her the opportunity to get involved in writing scientific research. Awaiting the start of her clinical internships as part of the Master's degree program of Medicine she started the current PhD program with the focus on multiple aspects of complications after esophageal cancer under supervision of Prof. dr. M.I. van Berge Henegouwen and Dr. S.S. Gisbertz. During this program she got the opportunity to travel through Australia for three months, carrying her laptop in her backpack to be able to revise the submitted manuscripts if necessary from wherever she was Down Under.



After she came back to the Netherlands in 2015, she started her Master's degree program and continued with her PhD research simultaneously. This PhD program resulted in many presentations at national and international conferences. From here she was able to combine traveling, meeting new people and the scientific research in esophageal cancer. It was within this period that she won the student award for the most qualified research project performed by a student awarded by the Dutch Society for Gastroenterology. In 2017, Annelijn finished her Master's degree program after completing a medical internship at the Emergency Department of the Prince of Wales Hospital NSW, in Sydney, Australia. She continued with her PhD program and worked as a surgical resident not in training at the Onze Lieve Vrouwe Gasthuis in Amsterdam until the end of 2019. Since February 2020 Annelijn works as a radiology resident at the Leiden University Medical Center, where she combines her interest in diagnostic imaging, anatomy and education of medical students. Recently, she has moved to the lovely city of Leiden. Annelijn is a very social person that loves to combine working with traveling and socializing with colleagues and friends. She is already considering new projects to start after finishing her PhD program. Next to her job, she loves visiting the Dutch beach and cooking for friends and family.

