Complications in Esophageal Surgery

Nina Nederlof

COMPLICATIONS IN ESOPHAGEAL SURGERY

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1

Introduction and outline of this thesis

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INTRODUCTION AND OUTLINE OF THIS THESIS

Esophageal carcinoma

In the last two decades, the incidence of esophageal cancer has risen. In 1990, 789 patients were diagnosed with esophageal cancer in the Netherlands, and in 2016 this number increased to 2540 patients. Mechanisms of tumor genesis in esophageal cancer are not completely understood. The disease has the highest incidence in parts of China, Korea and Japan, but also in South America.[1] The high incidence in this Eastern part of the world is mostly due to the frequent occurrence of squamous cell carcinoma. Tobacco and alcohol consumption are the primary cause of squamous cell carcinoma. The incidence is lower than in the Western world, where the predominantly adenocarcinoma has increased sharply since the 80s and 90s of last century.[2] The sharp rise in adenocarcinomas is parallel to the rise of obesity, and is possibly explained by the rise in incidence of gastro-intestinal reflux, leading to Barrett's dysplasia and eventually to adenocarcinoma. Evidence of a relation between diet, environment and esophageal carcinoma comes from a different incidence in various parts of the world.[3] Previously mentioned obesity increases intra-abdominal pressure and gastro-intestinal reflux, and adipose tissue itself influences tumor development.[4, 5]

Esophageal cancer is now number eight in the top ten most common malignancies in men (3.7% of men with cancer are diagnosed with esophageal cancer). In women, the percentage is 1.1%.[2] The male-female ratio in relation to incidence in the Netherlands increased to 3.5, and is one of the highest of all tumors.[6]

The five-year relative survival of patients with esophageal cancer in the Netherlands is comparable to the European average, and rose from 8% in 1988-1992 to 15% in 2003-2007.[2,6] In patients with adenocarcinoma of the (distal) esophagus who were operated with curative intent, five-year survival is between 37% and 51%, depending on stage, the surgical approach, (neo-)adjuvant therapy and unknown factors.[7]

Treatment

Esophagectomy with or without (neo-) adjuvant chemo (radiation) therapy is considered the preferred treatment for $cT_{1-4a}N_{0-3}M_0$ cancer of the esophagus and the gastro-esophageal junction. At presentation of the disease, most patients suffer from dysphagia and subsequently weight loss. Hence, within the light of a reasonable 5-year survival, long term relief of dysphagia is an important goal of the surgical procedure. This can be achieved by a safe operation and an optimal esophago-gastric anastomosis. Surgical technique and the poor blood circulation of the gastric tube are risk factors for anastomotic leakage or stricture.[8-12] Prevention of anastomotic leakage is also important for reducing associated morbidity, prevention of long term hospital admission and reducing mortality.[13-17] Prevention of late benign strictures is

important since this reduces food intake with subsequent weight loss and reduces health related quality of life.[13] Risk factors for anastomotic leakage include atherosclerosis[18,] a low preoperative[19] albumin level, radiotherapy and the use of steroids.[20]

Surgery

Surgery for cancer of the esophagus is considered to be one of the most extensive and traumatic oncological surgical procedures. Surgical resection and reconstruction not only involves a long operation time but also necessitates post-operative care in the intensive care unit, an extended in-hospital recovery with decreased quality of life and carries a significant risk of morbidity and mortality.

The effect of the extend of the operation, or the surgical approach (transhiatal versus transthoracic) is proven to be comparable in hospital mortality, overall survival and cancer-specific survival.[21] Transthoracic esophagectomy can result in a more extended lymph node resection, but shows no significantly difference in long-term survival, although one study suggests a trend in improved survival with a transthoracic approach.[22] Early survival is significantly higher for patients who underwent an transhiatal approach.[23] Benefits of transhiatal esophagectomy are shorter hospital admission and stay in the Intensive Care Unit. Complications, and more specific, pulmonary complications, do not differ between the two surgical approaches. Research on minimally invasive esophagectomy (MIE) has shown faster postoperative recovery and a marked decrease in pulmonary complications. The TIME[53] study was updated in February 2017 with three-year outcomes, and shows no differences in disease-free and overall 3-year survival between open and minimally invasive esophagectomy. Literature suggests that minimally invasive esophagectomy might reduce postoperative morbidity (especially pulmonary complications). The debate about oncological results remains, but this study[53] shows that the type of resected specimen and lymph nodes are comparable with the open series and disease-free and overall survival reported for minimally invasive surgery and open resection are comparable.

Chapter 2 consists of a systematic literature review focusing on anastomotic leakage, stricture rate and hospital mortality for cervical versus intrathoracic anastomoses and stapled versus hand-sewn anastomoses. In many centers, the end-to-end (ETE) cervical anastomosis has become the procedure of choice for esophageal reconstruction. In other parts of the gastrointestinal tract however, end-to-side (ETS) or side-to-side (STS) anastomosis proved superior to end-to-end anastomosis regarding post-operative leakage rate and stricture formation.[24] In **Chapter 3**, a randomized controlled trial is described comparing the rate of post-operative stricture formation after one year between a cervical single-layered hand-sewn ETE-anastomosis and a cervical single-layered hand-sewn ETS-anastomosis. Early postoperative complications, hospital stay and mortality were also evaluated.

Leakage of the anastomosis between the remnant esophagus and gastric tube after esophagectomy which occurs in approximately 5-25% of patients was the reason for a search for novel surgical techniques.[25-28] In 1998 Collard[29] et al. published a technique for creating a semi-mechanical anastomosis. Retrospective studies have suggested that this semi-mechanical side-to-side (SMA) anastomosis is associated with low anastomotic leak rates and low rates of anastomotic strictures. The aim of the randomized controlled trial in **Chapter 4** was to assess the leak and stricture rate of ETE compared to SMA technique. We hypothesized that SMA reduces the anastomotic leak rate and anastomotic stricture rate.

In **Chapter 5**, the outcome after colon interposition for restoration of the continuity of the upper gastrointestinal tract after esophagectomy is described. While health related quality of life after colon interposition is reported by some to have an equal outcome compared to gastric tube reconstruction, gastric tube interposition is still the standard technique for reconstruction after esophagectomy. At present, colon interposition is only used for reconstruction in patients with previous gastric resections, incomplete vascularization of the stomach and patients that need a esophagogastrectomy for malignant or benign disorders.[30-35] Studies describing the outcome after colonic interposition are scarce. Hence, the aim of this study was to assess morbidity and mortality including anastomotic leakage in a large series of patients from a single institution.

Leakage of the cervical esophagogastrostomy after esophagectomy with gastric tube reconstruction occurs in 5-25% of patients, is associated with significant morbidity and accounts for 25-50% of postoperative deaths.[36-38] In order to detect anastomotic leakage before clinical signs develop and the patients deteriorate, contrast swallow and/or endoscopy are often performed within the first week after surgery. However, it has been reported that contrast swallow studies have a low sensitivity and specificity, failing to contribute to clinical decision making. There is also a risk of aspiration leading to pulmonary complications. Upper gastrointestinal endoscopy has the advantage of direct visualization and quantification of dehiscence, necrosis or ulcers and it may be performed in patients who are sedated and intubated.[39-42] On the other hand, there is a possibility of iatrogenic injuries and of worsening the anastomotic dehiscence.[41] Therefore, in **Chapter 6**, we published a study which investigated the diagnostic and predictive value of systematically routine contrast swallow study and endoscopy in the postoperative management of patients with a cervical anastomosis after esophagectomy and gastric tube reconstruction (GTR) for esophageal carcinoma. We analyzed our data and hypothesized that routine diagnostic studies do not contribute to the early detection of anastomotic leakage.

Comprehensive Complication Index (CCI)

A major challenge in designing randomized controlled trials (RCTs) is the choice of objective, concise and clinically relevant endpoints. Mortality is not always the best primary endpoint in surgical studies given the sharp decline in mortality for most procedures in the past decades and hence large numbers of patients are needed. Morbidity is often poorly defined, which has led to inconsistent reporting and confusion in the literature.[43-48] Furthermore, most authors have reported only the most severe complications or only events judged to be relevant, but ignored complications of lesser magnitude as well as the total number of complications.[49] To address this issue, the Comprehensive Complication Index (CCI) was developed. It integrates all postoperative complications with their respective severities, on a scale ranging from 0 (no burden from complications) to 100 (death).[49] The CCI, summarizing the entire postoperative experience of the patient with respect to complications, is based on the widely established Clavien-Dindo classification.[50] Validations from four different perspectives showed that the CCI is a valid endpoint for postoperative overall morbidity. While the CCI is an attractive novel tool, which may serve as a primary or secondary endpoint in many types of studies, the external validity has not been tested in RCTs. Therefore, the aim of **Chapter 7** was to externally evaluate whether the CCI is more sensitive than traditional primary endpoints in detecting between-group differences.

The largest published randomized clinical trial on the value of neoadjuvant chemo radiotherapy (CROSS-trial)[51] shows a survival benefit for patients with nCRT followed by surgery. Importantly, there was no difference in the frequency of complications and postoperative mortality between the patients who were treated with neoadjuvant chemo radiotherapy followed by surgery and the patients who underwent surgery alone. While traditional endpoints showed no significant differences in incidence of postoperative complications within the CROSS trial, **Chapter 8** was designed to evaluate the overall effect of neoadjuvant chemo radiotherapy on the severity of postoperative complications, and the overall burden in patients of the CROSS trial. Therefore, the CCI between patients with esophageal or esophagogastric junction cancer who underwent chemo radiotherapy plus surgery versus patients who underwent surgery alone was compared.[52]

Chapter 9 summarizes all presented studies and in **Chapter 10** a Dutch summary is presented. In **Chapter 11**, all subjects are discussed more extendedly as well as future prospectives.

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PART 1

SURGICAL TECHNIQUES

2

The influence of surgical technique on postoperative outcome after esophagectomy for esophageal cancer; leakage of the anastomosis: a review of the literature

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ABSTRACT

Objective: To review the literature regarding the effect of the site of the esophagogastric anastomosis and the technique of the anastomosis after esophageal resection and gastric tube reconstruction.

Background data: Esophageal resection and reconstruction with a gastric tube plays an important role in the treatment of esophageal cancer. The technique and influence of technique on postoperative complications, especially leakage, remains subject of many research. This article reviews the current literature for the site of the anastomosis (cervical or intra-thoracic) and the technique for the esophago-gastric anastomosis (circular stapled, linear stapled or hand-sewn) and impact on anastomotic leakage after operation.

Methods and data sources: Comprehensive searches were carried out in Embase, MEDLINE OvidSP, Web of Science, Google Scholar, CENTRAL (the Cochrane Library 2013, issue 5). The search was performed for articles published until November 2016 relevant to leakage of the gastro-esophageal anastomosis after esophagectomy for esophageal cancer. Endpoints were anastomotic leakage, postoperative stricture rate, dysphagia, overall morbidity and in-hospital mortality.

Results: Of the 1341 studies identified, 61 studies were eligible for this review. After careful consideration, 25 studies remained after exclusion. The first three studies compare cervical anastomoses with intra-thoracic anastomoses, and show that both techniques are equally safe, with a trend ($p = 0.08$) towards more leakage in patients with a cervical anastomosis. Stapled (circular, linear, totally mechanic, semi-mechanic cervical, intra-thoracic) versus hand-sewn was the subject of the next 22 studies, and show that semi-mechanical anastomoses do not result in lower leakage rates (%) in comparison with a hand-sewn anastomosis. There are higher incidences reported in dysphagia and stricture rate ($p = < 0.01$), however.

Conclusion: Cervical and intra-thoracic anastomoses are equally safe, although there is a trend towards more leakage in the groups with patients with a cervical anastomosis. Comparison of a stapled (either circular, linear or semi-mechanical) anastomosis to a hand-sewn anastomosis does not minimize anastomotic leakage, but there are higher incidence of dysphagia and stricture rate reported in the circular stapled anastomosis. Overall morbidity and mortality are not statistically different between groups.

INTRODUCTION

Esophageal resection and reconstruction with a gastric tube plays an important role in the curative treatment of esophageal cancer. Unfortunately, surgical morbidity remains high. Retrospective studies report overall complication rates around 50%.[1, 2] Leakage of the esophagogastrostomy occurs in 5-25% of patients[1] and 30-40% patients need endoscopic dilatations for an anastomotic stricture.[3, 4] The anastomotic leak and stricture formation the anastomosis has a great impact on patients' quality of life.[5] Anastomotic complications may also lead to significant morbidity and even mortality. The diversity of anastomotic techniques described as well as the ongoing debate about the optimal location of the anastomosis (neck versus chest) indicates that there is not one superior technique.

Anastomotic leakage is likely to be caused by an inadequate perfusion of the gastric conduit. Arterial insufficiency or venous congestion due to absence of direct vascular branches from the gastro-epiploic arcade at the fundus of the stomach is thought to be the underlying phenomenon. Neoadjuvant (chemo)radiation, surgical technique and patient-related factors including generalized atherosclerosis, smoking, diabetes mellitus and use of steroids are other risk factors for anastomotic leakage.[6] In this review, we focus on two main aspects of anastomotic leakage and strictures being the location (cervical versus an intrathoracic) and the technique (stapled versus hand-sewn).

METHODS

All aspects of the Cochrane Handbook for Interventional Systematic Reviews were followed[7], and the manuscript was written according to the PRISMA statement.[8]

Comprehensive searches were carried out in Embase, MEDLINE OvidSP, Web of Science, Google Scholar, CENTRAL (the Cochrane Library 2013, issue 5). Search terms for each search-engine are provided as Supplementary methods. The search was performed in December 2016 for articles published until November 2016. Studies comparing two surgical techniques (cervical versus intra-thoracic anastomosis or hand-sewn versus stapled anastomosis) in patients who underwent esophagectomy for esophageal cancer and gastric tube reconstruction were included. The English language restriction was used.

Studies were evaluated by a single investigator. All abstracts were reviewed for relevance and reporting of selected endpoints, and if eligible, the full text was assessed and reviewed. Excluded were studies not yet published, case-reports, letters, editorials, case-series, animal studies, studies on children (< 18 years), or if the abstract revealed no relevance to the subject. For publications without abstract, the full text was acquired. The following data were

extracted from the studies and entered in a table: study design, number of patients, baseline characteristics, surgical characteristics, site of anastomosis (neck versus chest), type of anastomosis, technical details of the anastomosis and outcome measures. Outcome measures were anastomotic leakage, stricture, dysphagia and in-hospital mortality. Manual reference checks of included papers were performed to search for missing studies.

All studies were imported in to the GRADE tool[9], in which risk of bias (not serious/serious/very serious), inconsistency (not serious/serious/very serious), indirectness (not serious/serious/very serious), imprecision (not serious/serious/very serious), publication bias (undetected/strongly suspected), effect size (no/large/very large), plausible confounding (no/would reduce demonstrated effect/would suggest spurious effect) and dose response gradient (yes/no) were graded.

STATISTICAL ANALYSIS

There was no meta-analysis performed given the clinical heterogeneity of the studies with regard to surgical techniques, method and time of follow up, type of outcomes measures and definition of the outcomes. Values in tables represent the number of patients that had a complication with the percentages in brackets. The follow-up is presented as median values (months). When reported, odds ratio, relative risk and 95% confidence intervals, as well as p-values are presented in the tables.

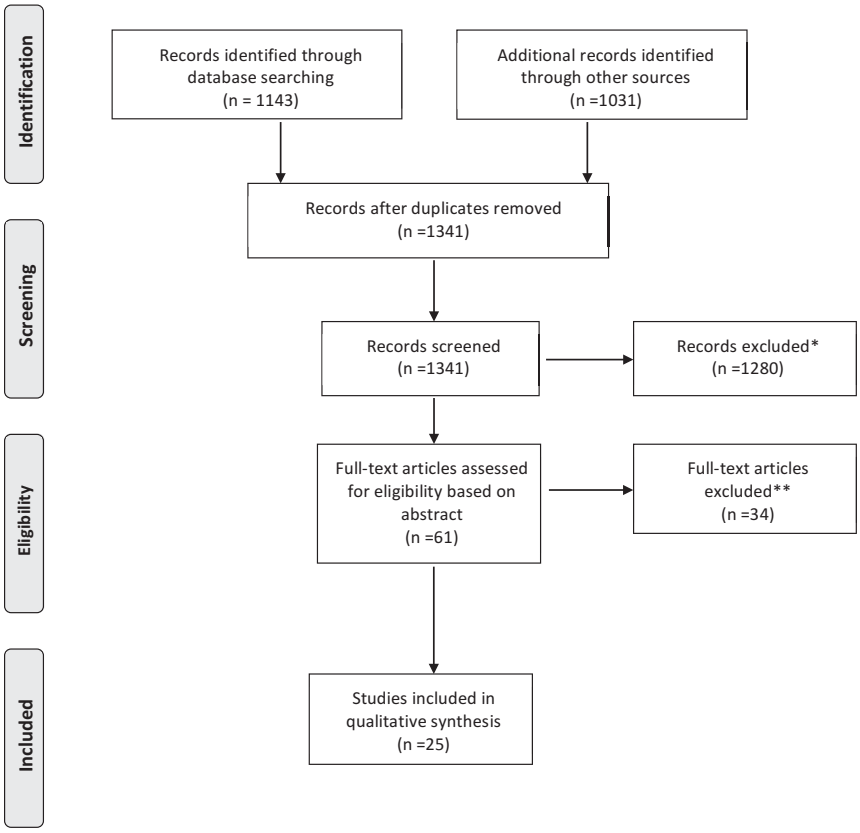
LIST OF ABBREVIATIONS

SMA	semi-mechanical anastomosis
HS	hand-sewn
CS	circular stapled
LS	linear stapled
NGT	narrow gastric tube
WS	whole stomach
TM	totally mechanic anastomosis
NS	not statistically significant
NR	not reported
ETE	end-to-end
ETS	end-to-side
SSS	stapled side-to-side

RESULTS

Figure 1 shows the inclusion and exclusion of studies, and results of the search strategy (supplementary file 1). After removal of the duplicates, 1341 studies remained (1143 found on Embase and 1132 found on MedLine Ovid SP, Web-of-Science, Cochrane Central and Google Scholar). Reasons for exclusion were: unavailable in full-text, studies on children or animals, no clinical study, studies reporting minimally invasive anastomotic techniques, patients who underwent damage control surgery (palliative surgery or surgery for complications), no esophagectomy performed, studies on vascular enhancement of the gastric tube and not on surgical techniques of the anastomosis itself.

Figure 1. Overview of search results; PRISMA flow chart



* Reasons for exclusion were: unavailable in full-text, studies on children or animals, histomorphological research, minimally invasive techniques, patient with damage control surgery (palliative), no esophagectomy performed, studies on vascular enhancement of the gastric tube.

** Reasons for exclusion full-text articles: studies on children or animals, histomorphological research, minimally invasive techniques, patient with damage control surgery (palliative), no esophagectomy performed, studies on vascular enhancement of the gastric tube.

Cervical versus intra-thoracic anastomosis

In Table 1, a summary of findings is presented of two cohort studies and one randomized trial comparing a cervical with an intra-thoracic anastomosis. The methodological quality of the two cohort studies is low given the fact that the decision on the site of the anastomosis was determined by the surgeon based on pre- or intraoperative evaluations (e.g. resection margin) and not by chance. The study by Shah[10] et al. includes patients from multiple centers. The authors tried to select a more homogenous study group by excluding patients who underwent esophagectomy for non-malignant diseases and patients with malignancies located in the upper or middle third of the esophagus. Hence, tumor location could not influence the choice for the site of the anastomosis. Another randomized controlled trial[11] included patients with benign and malignant esophageal disease. In contrast to the other studies, exclusion criteria were preoperative chemo radiation therapy or location of the tumor in the proximal intra-thoracic esophagus. The studies did no show a statistically significant difference in leak rate between a cervical or intra-thoracic anastomosis.[5, 10, 11]

Hand-sewn versus stapled anastomoses

A summary of studies comparing hand-sewn with stapled anastomosis is presented in Table 2.[2, 4, 12-24] The randomized controlled trials included in systematic reviews and meta-analyses are shown in Table 3.[23, 25-30] Stricture formation was statistically significant higher in patients that underwent a circular stapled anastomosis (in 6 of 15 studies). Consequently, the percentage of patients reporting dysphagia was higher after a circular stapled anastomosis. The randomized trials are further described in Table 4.[4, 14, 16-19, 22, 31] The studies are clinically heterogeneous regarding surgical techniques used and (definition of) endpoints. The reporting of most trials is not according to current standards (CONSORT)[8] and the surgical techniques used are mostly poorly described.

DISCUSSION

This review summarizes the studies on the association between surgical technique, location of anastomosis and anastomotic leakage, stricture, dysphagia and in-hospital mortality. Cohort studies, RCTs and meta-analyses were included and critically appraised.

The cohort studies suggest that the intra-thoracic anastomoses are associated with a higher risk of complications and postoperative death.[32] At the same time, leak rate for an intra-thoracic anastomosis are reported to be lower than for a cervical anastomosis. The three studies identified found no statistically significant difference in complication rates between intra-thoracic and cervical anastomosis. The main limitations of two studies were the incomplete

description of the operative techniques used and the decision for the type of anastomosis was based on the location of tumor.

The use of staplers is thought to be a method of reducing of esophagogastric leaks, but this remains controversial. The largest systematic review by Kim[26] et al. showed a leak rate of 4.7% in the SMA group versus 20% in the ETE/hand-sewn group. Others[21] have described an absolute difference of 17% in favor of totally mechanical anastomosis, but compared this anastomosis with a hand-sewn anastomosis or a semi-mechanical anastomosis. Therefore, the study does not reflect a clear comparison between hand-sewn and stapled anastomoses. Limitations of the reviews are that suture materials and surgical techniques vary considerably between studies, as shown in Table 4. There is no uniform technique for the creation of a stapled or hand-sewn anastomosis. Single-layered and double-layered hand-sewn anastomosis are included, and different kind of staplers (linear and circular). There was also a significant variation in reporting of mortality among studies; from 'early postoperative mortality' to in-hospital mortality or 30-day mortality. Some studies even reported 1 and 3-months mortality numbers. And there is variation in the application of neoadjuvant treatment regimes.

The eight RCTs described in this review differ in participants, definitions of complications and endpoints are not clear, blinding is not described and the method of randomization and allocation is not clearly described in detail. This hampers a formal comparison between studies as well as a meta-analysis of studies. There is a need for a large controlled trial with a clear definition of endpoints (leakage, stricture, morbidity and mortality). Follow-up time is very important for the assessment of late complications including stricture formation. In several studies, leakage was defined as abnormality on radiological tests, but recent studies showed that clinical features of leakage are at least as important as radiological findings, because of low sensitivity and specificity of contrast swallow studies.

The present review validates the published literature, using the GRADE tool and a checklist to check for heterogeneity. From the data presented in the present study, it can be concluded that there is no evidence for the superiority of a cervical or intra-thoracic anastomosis. Although, a circular stapled anastomosis does not show a significant lower leakage rate compared to a hand-sewn anastomosis, they are associated with a higher rate of strictures. The linear stapled anastomosis (Collard or Orringer) may decrease leakage and stricture formation in comparison with hand-sewn and circular anastomoses.

A valid comparison of the surgical techniques for the formation of a esophago-gastrostomy after esophagectomy is hampered by intra-study heterogeneity. A large randomized controlled trial, in which the operation techniques are clearly defined, and postoperative protocol for complications (and endpoints) is rigidly described, is still missing. Also, quality of life which is influenced by leakage and stricture formation as well other postoperative complications should be included as an endpoint.

Table 1. Cervical versus intra-thoracic anastomosis

Author	Study design	Follow up (months)	Grade quality	Site of the anastomosis	N	Technique	Leakage	Stricture	In-hospital mortality
Egberts[11]	Cohort study	24	++ low	Cervical	33	Technique NR	11 of 33 (33.3%)	NR	2 of 33 (6.7%)
			++ low	Intra-thoracic	72	Technique NR	13 of 72 (18.1%)	NR	5 of 72 (6.1%)
				p-value			p=0.083		p=0.866
Shah[10]	Cohort study	NR	++ low	Cervical	601	Technique NR	NR	NR	18 of 601 (3%)
			++ low	Intra-thoracic	308	Technique NR	NR	NR	13 of 308 (4%)
				p-value					NS
Walther[5]	Randomized controlled trial	12	++++ high	Cervical	41	Hand-sewn, single layer continuous	1 of 41 (2.4%)	NR	1 of 41 (2.4%)
			++++ high	Intra-thoracic	42	Circular stapled	0 of 42 (0%)	NR	1 of 42 (2.4%)
				p-value			p=NS	p=NR	p= NS

Table 2. Hand-sewn versus stapled anastomosis; randomized controlled trials and cohort studies

Author	Study design	Follow-up (months)	quality	Technique	N	Anastomotic site	Technique specifications	Leakage	Stricture	Dysphagia	In-hospital mortality
Craig[14]	Randomized controlled trial	NR	++++ high	Hand-sewn	50	Intra-thoracic	Single layer Interrupted	3 of 50 (6%)	14 of 49 (28%)	NR	1 of 50 (2%)
	n=100			Stapled circular	50	Intra-thoracic		4 of 50 (8%)	14 of 46 (30%)	NR	4 of 50 (8%)
								NS	NS	NR	p=0.17
Hsu[16]	Randomized controlled trial	24	++++ high	Hand-sewn	32		Double layered Interrupted	7 of 32 (22%)	4 of 28 (14%)	NR	4 of 32 (13%)
	n=63			Stapled circular	31	Cervical		8 of 31 (26%)	5 of 28 (18%)	NR	3 of 31 (10%)
								p=NS	p=NS	NR	p=NS
Laterza[17]	Randomized controlled trial	21	++++ high	Hand-sewn	21	Intra-thoracic	Double layered Interrupted	1 of 21 (4.7%)	2 of 20 (10%)	NR	2 of 21 (9.5%)
	n=41			Stapled circular	20	Intra-thoracic		4 of 20 (20%)	3 of 18 (16.7%)	NR	1 of 20 (4.7%)
								p=NR	p=NR	NR	p=NR
Law[4]	Randomized controlled trial	20	++++ high	Hand-sewn	61	Intra-thoracic	Single layered Continuous	1 of 61 (1.6%)	5 of 55 (9.1%)	NR	4 of 61 (6.6%)
	n=122			Stapled circular	61	Intra-thoracic		3 of 61 (4.9%)	20 of 55 (40%)	NR	6 of 61 (9.8%)
								p=NS	p=<0.001	NR	p=NR
Luechakiettisak[18]	Randomized controlled trial	NR	++++ high	Hand-sewn	59	Intra-thoracic	Single layered Continuous	4 of 59 (6.7%)	10 of 52 (19.2%)	NR	7 of 59 (11.8%)
	n=59			Stapled circular	58	Intra-thoracic		2 of 58 (3.4%)	19 of 52 (36.5%)	NR	6 of 58 (10.3%)
								p=0.69	p=0.08	NR	p=0.97
Valverde[22]	Randomized controlled trial	3	++++ high	Hand-sewn	74	Cervical and intra-thoracic	Single or double layered Interrupted and continuous	12 of 74 (16%)	8 of 63 (13%)	NR	5 of 74 (6.8%)
	n=154			Stapled circular	78	Cervical and intra-thoracic		12 of 78 (15%)	7 of 53 (11%)	NR	12 of 78 (13.6%)
								p=NS	p=NS	NR	p=NS

Table 2. Hand-sewn versus stapled anastomosis; randomized controlled trials and cohort studies (continued)

Author	Study design	Follow-up (months)	quality	Technique	N	Anastomotic site	Technique specifications	Leakage	Stricture	Dysphagia	In-hospital mortality
Okuyama[19]	Randomized controlled trial	12	++++ high	Hand-sewn	18	Cervical	Double layered Interrupted	3 of 18 (16.7%)	0 of 18 (0%)	NR	0 of 18 (0%)
	n=32			Stapled linear	14	Intra-thoracic	End-to-side	1 of 14 (7.6%)	2 of 14 (14.2%)	NR	0 of 14 (0%)
								p=NS	p=NS	NR	p=NS
Wang[23]	Randomized controlled trial	3	++++ high	Hand-sewn	52	Intra-thoracic	Single layered Interrupted	3 of 52 (5.8%)	5 of 52 (9.6%)	15 of 52 (29%)	NR
	n=160			Stapled linear	45	Intra-thoracic	SMA Collard, linear	0 of 45 (0%)	0 of 45 (0%)	5 of 45 (11%)	NR
								p=NR	p<0.001	p=0.028	NR
Casson[12]	Retrospective study	34	++ low	Hand-sewn	53	Cervical	Single or double layered	12 of 53 (22.6%)	9 of 53 (17%)	NR	NR
	n=91			Stapled linear	38	Cervical	Semi mechanical side-to-side	3 of 38 (7.9%)	3 of 25 (7%)	NR	NR
								p=0.08	p=NS	NR	NR
Mishra[2]	Retrospective cohort study	30	++ low	Hand-sewn	66	Cervical	End-to-side Interrupted Single layered	12 of 66 (18%)	10 of 62 (16.1%)	NR	4 of 66 (6%)
	n=153			Stapled linear	74	Cervical	Collard	12 of 74 (16%)	3 of 69 (4.3%)	NR	5 of 74 (6.7%)
								p=0.82	p=0.03	NR	p=0.98
Orringer[20]	Retrospective study	3	++ low	Hand-sewn	114	Cervical		16 of 112 (14%)	54 of 112 (48%)	NR	2 of 114 (1,8%)
	n=228			Stapled linear	114	Cervical	Side-to-side	3 of 111 (2.7%)	39 of 111 (35%)	NR	3 of 114 (2.6%)
								p<0.001	p=0.05	NR	p=NR
Collard[13]	Cohort study	2	++ low	Hand-sewn	24	Cervical	End-to-side Single layer	NR	NR	7 of 24 (29,2%)	NR
	n=40			Stapled linear	16	Cervical	Side-to-side Linear	NR	NR	0 of 16 (0%)	NR

Table 2. Hand-sewn versus stapled anastomosis; randomized controlled trials and cohort studies (continued)

Author	Study design	Follow-up (months)	quality	Technique	N	Anastomotic site	Technique specifications	Leakage	Stricture	Dysphagia	In-hospital mortality
Deng[15]								NR	NR	p=NR	NR
	Cohort study	3	++ low	Hand-sewn	8	Cervical	End-to-end Interrupted Single layer	NR	NR	4 of 8 (50%)	NR
Xu[24]	n=17			Stapled linear	9	NR	Orringer Side-to-side	NR	NR	2 of 9 (22%)	NR
								NR	NR	p=NR	NR
	Cohort study	3	++ low	Hand-sewn	59	Intra-thoracic		2 of 59 (3.4%)	5 of 54 (9.3%)	14 of 54 (28%)	NR
Santos[21]	clinical study			Stapled linear	166	Intra-thoracic	Collard	2 of 166 (1.2%)	3 of 162 (1.9%)	10 of 162 (6%)	NR
	n=293			Stapled circular	68	Intra-thoracic		1 of 68 (1.5%)	14 of 67 (20.9%)	20 of 67 (30%)	NR
								p= 0.72	p<0.001	p<0.001	NR
	Cohort study	24	++ low	Hand-sewn	41	Cervical	Double layered Interrupted	HS combined SMA: (23%)	HS + SMA: (45%)	HS + SMA:	HS + SMA: 2 of 56 (4%)
				Stapled linear	15	Cervical	Side to side Collard			Median 2-3 dilatations	
				Totally stapled	125		Totally mechanical (TM)	TM: (6%)	TM: (18%)	TM: (median 1-2 dilatations	2 of 125 (2%)
								P<0.001	P<0.001	P=<0.001	p=NS

Table 3. Hand-sewn versus stapled anastomosis; systematic reviews and meta-analysis

Author	Study design	Studies	Follow-up (months)	Quality (GRADE)	Technique	N	Anastomotic site	Technique specifications	Leakage	Stricture	Dysphagia	Mortality
Beitler[25]	Systematic review	Valverde, Law, Craig, West-Schotland	NR	++++ high	Hand-sewn	210	Unknown	NR	17 of 210 (8%)	26 of 167 (16%)	NR	NR
	(4RCT)				Stapled	216	Unknown	NR	20 of 216 (9%)	40 of 149 (27%)	NR	NR
	n=426								P<0.67	p<0.02	NR	P<0.08
Blackmon[30]	Meta-analysis; propensity matched n=449	1 center	25.2 ± 20.4	++++ high	Hand-sewn	23	Intra-thoracic	End-to-side Double layered Interrupted	1 of 23 (4.3%)	8 of 23 (34.8%)	13 of 23 (56.5%)	NR
					Stapled linear	23	Intra-thoracic	Linear	2 of 23 (8.7%)	2 of 23 (8.7%)	6 of 23 (26,1%)	NR
					Stapled circular	23	Intra-thoracic	Circular	1 of 23 (4.3%)	2 of 23 (8.7%)	5 of 23 (21,7%)	NR
									p=0.78	p=0.04	p=0.04	NR
Kim[26]	Systematic review n=710 8RCT's	Luechakiettisak, Okuyama, Hsu, Walther, Laterza, Law, Valverde, Craig	3-6 months	++++ high	Hand-sewn	356	Cervical and intra-thoracic	Single layer and two-layer	1.6-22%	0-27%	NR	HS: (0-13%)
					Stapled circular	354	Cervical and intrathoracic		0-26%	11-40%	NR	0-15%
									p= NR	p= NR	NR	p= NR

Table 3. Hand-sewn versus stapled anastomosis; systematic reviews and meta-analysis (continued)

Author	Study design	Studies	Follow-up (months)	Quality (GRADE)	Technique	N	Anastomotic site	Technique specifications	Leakage	Stricture	Dysphagia	Mortality
Liu[27]	Meta-analysis 15 RCT's n=2773	Fok, Valverde, Craig, Law, Laterza Okuyama, Luechakeittisak, Aquino, Zhang, Saluja, Wu, Cayi, Wang, Walther, Hsu	NR	++++ high	Hand-sewn	1143	NR	NR	88 of 1143 (7.7%)	NR	NR	28 of 1061 (2.6%)
					Stapled	1194	NR	NR	68 of 1194 (5.7%)	NR	NR	43 of 1011 (4.3%)
					Hand-sewn vs Stapled end-to-side	843	NR	NR	75 of 856 (8.8%) 104 of 843 (12.3%) RR=1.45 95%CI=1.11-1.91, p=<0.01)	NR	NR	
					Hand-sewn vs stapled side-to-side	126 vs 134	NR	NR	22 of 134 (16.4%) 7 of 126 (5.6%) RR=0.34 95%CI=1.16-0.76, p=<0.01)	NR	NR	SA: (4.3%)
									RR = 0.77	NR	NR	RR = 1.52
									95%CI: 0.57-1.04;	NR	NR	95%CI: 0.97-2.40;
									P = 0.09	NR	NR	P = 0.07
Markar[28]	Meta-analysis	Law, Hsu, Laterza, Valverde, Luechakiettisak,	6	++++ high	Hand-sewn	381	Cervical and intra-thoracic	NR	33 of 381 (8.7%)	68 of 381 (17.8%)	NR	35 of 381 (9,2%)
		Walther, Okuyama,			Stapled not specified	381	Cervical and intra-thoracic	Linear and circular stapled	35 of 381 (9.2%)	126 of 381 (33.1%)	NR	47 of 381 (12,3%
		Craig, George							pooled odds ratio = 1.06	pooled odds ratio = 1.76	NR	pooled odds ratio = 1.71
									95% CI = 0.62 to 1.80	95% CI=1.09 to 2.86	NR	95% CI=0.822 to 3.56

Table 3. Hand-sewn versus stapled anastomosis; systematic reviews and meta-analysis (continued)

Author	Study design	Studies	Follow-up (months)	Quality (GRADE)	Technique	N	Anastomotic site	Technique specifications	Leakage	Stricture	Dysphagia	Mortality
									P=0.83	P=0.02	NR	P=0.15
Urschel[29]	Meta-analysis	Craig, Valverde, Law, Laterza,	NR	++++ high	Hand-sewn	231		NR	17 of 231 (7.4%)	28 of 415 (6.7%)	NR	8 of 415 (1.9%)
	n=467	West-Schotland			Stapled circular	236		NR	24 of 236 (10.2%)	43 of 415 (10.4%)	NR	20 of 415 (4.8%)
									RR=0.79	RR=0.60	NR	RR=0.45
									95% CI: 0.44, 1.42	95% CI: 0.27, 1.33	NR	95% CI: 0.20, 1.00
									P=0.43	P=0.21	NR	P=0.05
Wang[31]	Systematic review and meta-analysis	WSHSG, Law, Laterza, Hsu, Luechakiettisak,	NR	++++ high	Hand-sewn	447		End-to-side and side-to-side	52 of 447 (11.6%)	45 of 330 (13.6%)	NR	15 of 275 (5%)
	n=870 9 RCT's	Aquina, Saluja, Cai, Yang			Stapled circular	423		End-to-side and side-to-side	38 of 423 (20.6%)	55 of 300 (18.3%)	NR	18 of 272 (6.6%)
									RR=1.30	RR=0.97	NR	RR=0.83
									95% CI 0.87–1.92	95% CI 0.47–1.99	NR	95% CI 0.43–1.58
									p=0.20	p=0.93	NR	p=0.57

Table 4. Descripton of randomized trials comparing stapled with hand-sewn anastomsis

Author	Technique stapled	Technique HS	Surgical technique	Definition leakage clearly described	Definition stricture clearly described	Population; selection criteria	Endpoints (outcome measures)	Blinding	Randomisation	Follow-up (months)	Lost to follow up/ length of follow-up	Location tumor reported	Chemo/radiation	Tumor stage
Craig[14]	ILS stapler (Ethicon, Inc, Somerville, NJ)	Interrupted 2.0 silk	One stage left-sided thoraco-laparotomy. End-to-end anasto-moses created below the level or the arotic arch. Wrapped with omental scarf.	Barium contrast 5 days postopera-tive. Diag-nosed on radiological findings.	Dysphagia required dilatation.	Lokalized dis-ease, no need for estensive resection of esophagus or stomach. Ex-cluded in case of systemtic metastatic disease	Anastomosis time, op-erative time, blood loss, leak rate, stricture rate, hospital admission	NR	Pre-operative, further not described.	NR	HS: 6.5 months, SA: 4.2 months	NR	NR	NR
Hsu[16]	ILS (Ethicon, Inc, Somerville, NJ) circular stapler with reinforce-ment stitches	Double layer of interrupted sutures.		(1) egress of saliva through the cervical drains, or (2) radiological leakage	10-mm diam-eter flexible endoscope could not be passed	Curatively resectable SCC of the tho-racic esophagus staged T1 – T3 and N0 – N1 on endosonogra-phy or CT	Perioperative morbid-ity and mortality, anastomotic leakage, and benign stric-ture rates	NR	After esoph-agectomy, not further described	24 (1-88 months)	Mean of 24 months (1-88 months)	Thoracic esophagus	55 of 81 patients, 63 remaining for surgery after CRTx	T1 – T3 and N0 – N1

Table 4. Descripton of randomized trials comparing stapled with hand-sewn anastomsis (continued)

Author	Technique stapled	Technique HS	Surgical technique	Definition leakage clearly described	Definition stricture clearly described	Population; selection criteria	Endpoints (outcome measures)	Blinding	Randomisation	Follow-up (months)	Lost to follow up/ length of follow-up	Location tumor reported	Chemo/radiation	Tumor stage
Laterza[17]	Two layers of staples were used. The stapler was introduced in all cases through a gastrotomy which was closed using a linear mechanical stapler	The hand-sewn anastomoses were done end-to-end in two layers, with interrupted 4/0 monofilament sutures that absorbed slowly.	Thoracotomy followed by laparotomy. Drains at site of anastomosis.	Leakage of methylene blue from the drains radiological leakage	NR	Thoracic oesophageal or cardiac malignancy, < 70 years, SCC esophageal or adenocarcinoma of the cardia.	NR	NR	Sealed envelope, during surgery	21	NR	thoracic oesophageal or cardiac	Preoperative chemoradiotherapy was given only to patients with squamous cell carcinoma	NR
Law[4]	Both the EEA (United States Surgical Corporation, Norwalk, CT) and ILS (Ethicon,Inc, Somerville, NJ) circular staplers were used	Single layer of continuous absorbable monofilament suture (4-0 Maxon, polyglycnate; Davis and Geck, Danbury, CT).	Lewis-Tanner esophagectomy.. pyloric drainage procedure, and the anastomosis was constructed at the apex of the right pleural cavity.	Diagnosed based on clinical as well as on radiologic evidence	on endoscopy, a 10-mm diameter flexible endoscope could not be passed	Squamous cell carcinoma of the thoracic esophagus	Perioperative morbidity and mortality, anastomotic leakage and recurrence, and benign stricture rate		Randomized at surgery after extirpation of the tumor. stratified according to esophageal size, sealed envelope method.	20	20 (2.2) hand sewn 19(2.2) stapled	Thoracic esophagus	NR	I, II, III

Table 4. Descripton of randomized trials comparing stapled with hand-sewn anastomsis (continued)

Author	Technique stapled	Technique HS	Surgical technique	Definition leakage clearly described	Definition stricture clearly described	Population; selection criteria	Endpoints (outcome measures)	Blinding	Randomisation	Follow-up (months)	Lost to follow up/ length of follow-up	Location tumor reported	Chemo/radiation	Tumor stage
Luechakiettisak[18]	Intraluminal staple (ILS Ethicon), circular stapler was used.	A single layer of continuous suture using absorbable multifilament (4:0 Vicryl).	Ivor-Lewis esophagectomy.	Assessed for anastomotic leakage by gastrografin contrast study performed on day 7th after surgery.	Diagnosis of benign anastomotic stricture was made by flexible endoscope if it was unable to pass the anastomosis	Squamous cell carcinoma of the thoracic esophagus	Perioperative morbidity and mortality, anastomotic leakage, benign anastomotic stricture rate, cardiopulmonary complication,	NR	Randomization after categorisation in two groups, large and small diameter.	NR	NR	Thoracic esophagus	NR	I, II, III
Valverde[22]	Any stapling device as long as there were two layers of staples	One (n=69) or two (n=5) layers with either interrupted (n=45), continuous (n=29), absorbable (n=71), or nonabsorbable (n=3) sutures	Thoracotomy was left to the choice of the surgeon. Proximal resection of the stomach was mandatory. Palliative (n = 38) Site anastomosis intrathoracic or cervical.	Egress through the drains (methylene blue), radiological leakage	Any long-standing narrowing of the intestinal lumen leading to dysphagia requiring dilatation	Patients with esophageal or cardial carcinoma located between the esophagogastric junction (included) and the upper border of the aortic arch.	Anastomotic leakage, cardiopulmonary complications and peroperative complications	NR	After resection and before anastomosis,	3	NR	esophageal or cardiac carcinoma located between the esophagogastric junction (included) and the upper border of the aortic arch.	Preoperative and postoperative radiation, chemotherapy, or both were allowed	NR

Table 4. Descripton of randomized trials comparing stapled with hand-sewn anastomsis (continued)

Author	Technique stapled	Technique HS	Surgical technique	Definition leakage clearly described	Definition stricture clearly described	Population; selection criteria	Endpoints (outcome measures)	Blinding	Randomisation	Follow-up (months)	Lost to follow up/ length of follow-up	Location tumor reported	Chemo/radiation	Tumor stage
Okuyama[19]	Right side of the chest. Circular stapling devices for end-to-side anastomosis on the anterior wall of the gastric tube.	Cervical, two layers, using interrupted sutures for the inner layer, and interrupted 4-0 silk sutures for the outer layer.	Right postero-laterial incision followed by laparotomy.	Routine contrast swallow.	Benign anastomotic stricture was defined as dysphagia requiring dilatation.	The presence of middle or lower thoracic esophageal cancer and no metastatic involvement of the lymph nodes of the neck or upper mediastinum.	NR	NR	selected randomly before surgery from instructions in a sealed envelope	12	NR	Middle or lower esophagus	adjuvant che-motherapy to patients with lymph node metastasis.	0, I, II, III, IV
Wang[23]	A circular stapler was used. The side-to-side esophagogas-trostomy was modified and applied in the SM group.	Inverted interrupted single-layer sutures at the poste-rior wall and subsequent everted interrupted single-layer sutures at the anterior wall	All the op-erations were performed through the fifth or sixth intercostal space via a left posterolateral thoracotomy. The esopha-geal lesion was explored and mobilized. A tubular stom-ach 4–6 cm in diameter was created.		incidence of an anastomotic stricture at 3 months after the operation Secondary outcomes were the dysphagia score and reflux score, as well as the anastomotic diameter.	Exclusion cri-teria: previous upper gastro-intestinal tract surgery, other esophagogas-tric diseases, history of preoperative chemo/radio-therapy for esophageal cancer	primary outcome measure was the anastomotic stricture rate at 3 months after surgery. The second-ary outcome measures were dysphagia score, reflux score, and anastomotic diameter	NR	NR	Follow-up was con-ducted 3 months after surgery	3, 1 LOTFU in SM group, 2 in HS group	NR	Is exclusion criteria	NR

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3

End-to-end versus end-to-side esophagogastrostomy after esophageal cancer resection; a prospective randomized study

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ABSTRACT

Objective: To compare a single-layered hand-sewn cervical end-to-side (ETS) anastomosis with end-to-end (ETE) anastomosis in a prospective randomized fashion.

Background: The preferred organ used for reconstruction after esophagectomy for cancer is the stomach. Previous studies attempted to define the optimal site of anastomosis and anastomotic techniques. However, anastomotic stricture formation and leakage still remain an important clinical problem.

Methods: From May 2005 to September 2007, 128 patients (64 in each group) were randomized between ETE- and ETS-anastomosis after esophagectomy for cancer with gastric tube reconstruction. Routine contrast swallow studies and endoscopy were performed. Anastomotic stricture within 1 year, requiring dilatation, was the primary endpoint. Secondary endpoints were anastomotic leak rate and mortality.

Results: Ninety-nine men and 29 women underwent esophagectomy and gastric tube reconstruction. Benign stenosis of the anastomosis, for which dilatation was required, occurred more often in the ETE group (40% vs. ETS 18%, $p < 0.01$) after 1 year of follow-up. The overall (clinical and radiological) anastomotic leak rate was lower in the ETE group (22% vs. ETS 41%, $p = 0.04$). Patients with an ETE-anastomosis suffered less often from pneumonia; 17% versus ETS 44%, $p = 0.002$ and had subsequently significantly shorter in-hospital stay (15 days vs. 22 days, $p = 0.02$). In-hospital mortality did not differ between both groups.

Conclusion: ETS-anastomosis is associated with a lower anastomotic stricture rate, compared to ETE-anastomosis. However, prevention of stricture formation was at high costs with increased anastomotic leakage and longer in-hospital stay. This study is registered with the Dutch Trial Registry and carries the ID number ONDI317772.

INTRODUCTION

Esophagectomy with or without chemo (radio) therapy is considered the best treatment for $T_{1-3}N_{0-1}M_{0-1a}$ cancer of the esophagus or gastro-esophageal junction. After esophagectomy, the actuarial 5-year survival ranges from 20% to 35%.[1–4] Therefore, in many patients, relief of complaints is an important goal of the surgical procedure and overall outcome is closely related to the success of the esophagogastric anastomosis. This success is also related to the relative ischemia to the tip of the gastric tube, which may be influenced by type of anastomosis. Ischemia can be a risk factor for leakage or stricture.[1,3,5–7] Prevention of late benign stricture is important because recurrence of dysphagia defeats one of the main aims of surgery, which is to restore normal swallowing function.[8] Prevention of early complications like anastomotic leakage is also important to decrease associated morbidity, in-hospital stay and mortality.[8–12]

In many centers, the end-to-end (ETE) cervical anastomosis has become the procedure of choice for esophageal reconstruction. In other parts of the gastrointestinal tract however, end-to-side (ETS) or side-to-side (STS) anastomosis proved superior to ETE-anastomosis regarding postoperative leakage rate and stricture formation.[13–17] To date no randomized study is performed to compare ETE-to ETS-anastomosis in the neck. The aim of this study is therefore to compare the rate of postoperative stricture formation after 1 year between a cervical single-layered hand-sewn ETE-anastomosis and a cervical single-layered hand-sewn ETS-anastomosis. Early postoperative complications, hospital stay and mortality were also evaluated.

PATIENTS AND METHODS

Between May 2005 and September 2007, 175 patients underwent an esophageal resection. Inclusion criteria for the study were age above 18 years and biopsy proven $T_{1-3}N_{0-2}M_{0-1a}$ cancer of the esophagus or esophago-gastric junction. Exclusion criteria were: previous gastric surgery, benign disease, other reconstruction than gastric tube reconstruction and unwillingness to participate in the trial. Randomization, by the sealed envelope method, took place during surgery at the moment of cervical anastomosis. Sealed envelopes were prepared and provided by the Department of Biostatistics. During the hospital stay, 9 patients died (2 in the ETE group and 7 in the ETS group) and could not be evaluated for the primary endpoint, stricture within 1 year. This study was approved by the Institutional Review Board and registered in the Dutch Trial Registry under number ONDI317772. Patients were consented before surgery.

Operative procedure

For tumors of the gastro-esophageal junction (Siewert II), transhiatal resection (THE) was performed. Tumors of the mid and distal esophagus (Siewert I) were resected by combined right transthoracic and transabdominal esophagectomy (TTE). All operations were supervised by 1 of the 2 specialized senior gastro-intestinal surgeons. After esophageal resection, gastric tube reconstruction without pyloroplasty was performed. The gastric tube was created by the aid of a linear stapling device, TLC 55 (Ethicon, Johnson & Johnson, Amersfoort, the Netherlands) or 60-mm GIA (Autosuture, Covidien, Zaltbommel, the Netherlands), making a 3-cm-wide tube along the greater curvature of the stomach. In both groups, the anastomosis was created in the neck with a single continuous layer of monofilament suture (PDS 3–0, Ethicon, Amersfoort, the Netherlands).

In the ETE group, as much as possible of the proximal end of the gastric tube was resected to improve vascular supply, but without the anastomosis reaching the upper mediastinum to prevent intrathoracic leakage.

In the ETS group, the anastomosis was created at the front wall of the stomach tube, about 5 cm from the distal end of the gastric tube. After completion of the ETS-anastomosis, the

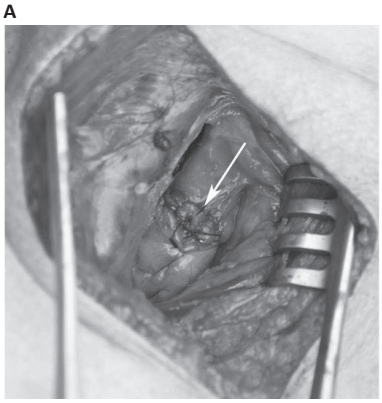

Figure 1a. Photograph of the ETE-anastomosis. Arrow points to the anastomosis. Head of the patient is top of the photograph.
Figure 1b. Schematic drawing of the ETE-anastomosis. Arrow points to the anastomosis. Head of the patient is top of the photograph.

proximal end of the gastric tube was removed by stapling at 2 cm from the anastomosis with the same linear stapler. The staple line was oversewn with an additional PDS 3–0 suture (Figures 1 and 2).

Post-operative period and follow-up

Postoperatively, patients were admitted to the intensive care unit for monitoring. The mean arterial blood pressure was kept above 80 mmHg with fenylefrine when needed. Patients were extubated the same day in the ICU. At day 6 after surgery a contrast swallow study was obtained and video-endoscopy was performed at day 7. Contrast swallow studies were performed using water-soluble contrast media. Normal oral intake was allowed after

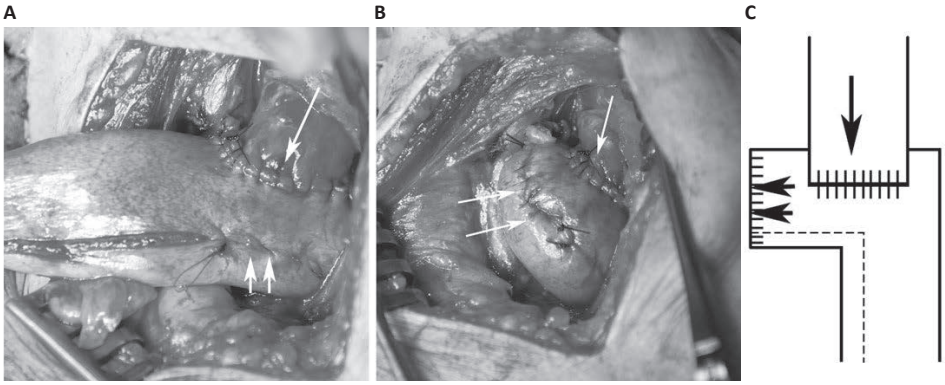

Figure 2a. Photograph of the ETS-anastomosis. Single arrow points to the anastomosis. Double arrows point to the suture line of the gastric tube. Head of the patient is top of the photograph. Picture is taken before stapling and oversewing the redundant tip of the gastric tube.

Figure 2b. Photograph of the ETS-anastomosis. Single arrow points to the anastomosis. Double arrows point to the suture line of the tip of the gastric tube. Head of the patient is top of the photograph.

Figure 2c. Schematic drawing of the ETS-anastomosis. Single arrow points to the anastomosis. Double arrows point to the suture line of the tip of the gastric tube. Head of the patient is top of the photograph.

confirmation of the integrity of the anastomosis on either investigation modalities. Routine postoperative follow-up included a 3- and 6-week outpatient clinic visit. Thereafter, patients were seen every 3 months in the first year after surgery and every 4 months in the second year.

Definition of post-operative complications

Postoperative complications were predefined and divided into anastomotic stricture, anastomotic leakage, and other surgical and nonsurgical complications.

'Anastomotic stricture' was defined as reported dysphagia with endoscopic proof of a stenosis through which an 8.8 mm endoscope could not be passed, in the absence of recurrent cancer.

Patients were asked every outpatient clinic visit about dysphagia and evaluated using the Mellow-Pinkas score (Table 1).[18] When grade II dysphagia or worse was reported (able to swallow only semisolid foods), an endoscopy was performed with Savary bougie dilatation over a guide wire when indicated to gradually reach 16–18 mm in diameter. In the case of suspect lesions, endoscopic biopsies were taken to rule out local recurrence. Severity of the stricture was graded by the number of dilatations needed to relieve dysphagia (mild: 1–2, severe: ≥ 3).[19]

'Anastomotic leakage' was defined liberally by any extravasation of water-soluble contrast during swallow study, visualization of anastomotic dehiscence or fistulae during endoscopy or visible loss of saliva through the cervical wound. Clinically relevant anastomotic leakage was

defined as any leakage, for which the cervical wound was drained, interventions were needed or that prolonged in-hospital stay. Anastomotic leaks were never treated with a stent.

Other predefined 'surgical complications' included ischemia or necrosis of the gastric tube, chylothorax, postoperative bleeding, wound infection, reoperation and vocal cord paralysis.

'Nonsurgical complications' included pneumonia, ARDS (adult respiratory distress syndrome), acute myocardial infarction, congestive heart failure, mediastinitis, sepsis, and urinary tract infection.

'Operative mortality' was defined as any death occurring within 30 days of surgery; 'in-hospital mortality' was defined as any death occurring during in-hospital stay.

Table 1. Mellow-Pinkas scoring system for grade of dysphagia

0	Able to eat normal diet/no dysphagia
1	Able to swallow some solid foods
2	Able to swallow only semi-solid foods
3	Able to swallow liquids only
4	Unable to swallow anything/total dysphagia

Statistical analysis

Postoperative anastomotic stenosis was the primary endpoint of the study. The number of patients included in the study was calculated on a stricture rate of 40% for ETE-anastomosis.[20,21] On the basis of previous studies[22] reporting significant lower incidence of anastomotic stenosis in ETS-anastomosis, a noninferiority principle was used with 1-sided testing. To detect a 50% reduction in stricture rate (to 20%), 64 patients per study arm were necessary, using 80% statistical power. Anastomotic leak and in-hospital mortality were chosen as secondary endpoints. All patients completed a follow-up period of 1 year or until death. Values are shown as means and standard error (SEM) or medians with their range, as appropriate. Groups were compared using nonparametrical Mann-Whitney-*U* test or Student's *T*- test, if normally distributed. For cross tabulations, Pearson's $\chi 2$-test with continuity correction or Fisher's exact test was used, as appropriate. All statistical analyses were performed on the statistical package SPSS 15.0 (SPSS Inc, Chicago, IL, USA). $p < 0.05$ was considered statistically significant.

RESULTS

Of the 175 patients who underwent esophagectomy in the study period, 47 patients were not included in this study, because they were not willing to participate (34), use of a colon interposition graft (4), laparoscopic procedure (2), or benign disease (7). Patient characteristics are listed in Table 2. More female patients and patients with squamous cell carcinoma were

Table 2. Basic patient characteristics and clinical data

	End-to-end (n=64)	**%**	**End-to-side (n=64)**	**%**	**p-value**
Age (yr) median [range]	60 [35-80]		63 [39-82]		0.11
Sex (M:F)	43:21		56:8		
Histology					0.04
- Squamous cell carcinoma	18	(28%)	9	(18%)	
- Adenocarcinoma with Barrett epithelium	10	(16%)	20	(33%)	
- Adenocarcinoma without Barrett epithelium	30	(47%)	32	(52%)	
- No malignancy left after neoadjuvant treatment	6	(9%)	3	(5%)	
Tumor site					0.79
- Esophagus	42	(67%)	43	(67%)	
- Gastro-esophageal junction	14	(22%)	16	(25%)	
- Gastric cardia	7	(11%)	5	(8%)	
Tumor Stage					0.65
- 0	6	(9%)	3	(5%)	
- I	4	(6%)	4	(6%)	
- IIA	12	(18%)	14	(22%)	
- IIB	3	(5%)	6	(9%)	
- III	16	(25%)	11	(17%)	
- IVA	18	(28%)	23	(36%)	
- IVB	5	(8%)	3	(5%)	
Radical resection (R0)	42	(66%)	49	(77%)	0.53
(Neo) adjuvant treatment	23	(36%)	21	(33%)	0.36
- Chemotherapy	11	(17%)	16	(25%)	
- Chemoradiation	12	(19%)	5	(8%)	
Co morbidity	40	(63%)	40	(63%)	1,0
- Cardiovascular	26	(41%)	18	(28%)	0.13
- Respiratory	5	(8%)	10	(16%)	0.32
- Diabetes Mellitus	2	(3%)	5	(8%)	0.44
Operating time (min) mean ± SEM	357 ± 12		363 ± 11		0.76
Surgical approach					0.34
- Transhiatal esophagectomy	41	(64%)	47	(73%)	
- Transthoracic esophagectomy	23	(36%)	17	(28%)	
Hospital stay (days) [median (range)]					
Intensive Care Unit	3 (1-48)		4 (1-47)		0.19
Hospital stay	15 (9-125)		22 (8-281)		0.02
Mortality					
- 30-day	0	(0%)	4	(6%)	0.13
- In-hospital	2	(3%)	7	(11%)	0.16

present in the ETE group. No relation between gender or histology and any of the outcome variables was found. The prevalence and doses of fenylefrine and other vasoactive drugs were equivalent in the 2 groups.

Anastomotic stenosis

Dysphagia grade II or worse occurred in 27 patients (44%) in the ETE group and in 12 patients in the ETS group (21%, p = 0.01). There were no differences between groups in time between surgery and onset of stricture (Table 3). At endoscopy a benign anastomotic stricture, for which (multiple sessions of) dilatation was indicated, was confirmed in 25 patients in the ETE group (40%) and in 10 patients in the ETS group (18%, p < 0.01). The remaining 4 patients had dysphagia due to partial dissolved suture material, obstructing the lumen (n = 2), reflux esophagitis (n = 1), and biopsy proven local recurrence (n = 1).

One-year actuarial stricture-free survival was 58% in the ETE group and 83% in the ETS group, p = 0.005 (Fig. 3). A mild stenosis occurred in 2 patients (3%) in the ETE group compared to 1 patient (2%) in the ETS group. Severe stenosis occurred in 23 patients (37%) in the ETE group and 9 patients (16%) in the ETS group, p = 0.01, Table 3. We found no differences

Figure 3. Stricture-free survival. Stricture-free survival was 58% in the ETE group and 83% in the ETS group, p = 0.005. Numbers are patients at risk.

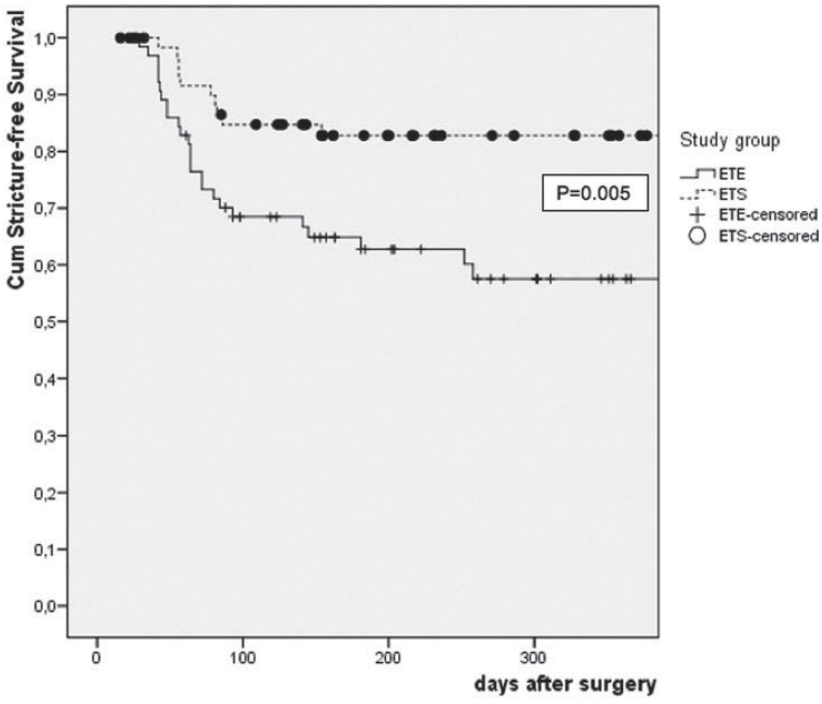

Table 3. Anastomotic stricture and leakage

Anastomotic stricture	End-to-end n=62	End-to-side n=57	p-value
- Dysphagia ≥ grade 2 (Mellow-Pinkas-score)	27 (44%)	12 (21%)	0.01
- Benign stricture	25 (40%)	10 (18%)	<0.01
- Onset of stricture (days) [median (range)]	64 [29-258]	68 [42-154]	0.71
- Severity of stricture (sessions needed)			0.01
o Mild stricture (1-2 sessions)	2 (3%)	1 (2%)	
o Severe stricture (≥ 3 sessions)	23 (37%)	9 (16%)	
Anastomotic leakage	N=64	N=64	
- Leakage (clinical and radiological)	14 (22%)	26 (41%)	0.04
- All clinical leakage	10 (16%)	21 (33%)	0.04

in the persistency of the stenosis between the groups. In the ETE group a median of 6 dilatation sessions were needed (range 1–19) and also 6 sessions were needed in the ETS group (range 2–20), p = 0.81. In total, 257 dilatations were performed in these 35 patients, without perforation or major bleeding.

Anastomotic leakage

In 14 patients in the ETE group (22%) clinically observed or radiological detected leakage occurred, compared to 26 patients in the ETS group (41%, p = 0.04). When only clinically relevant leaks are taken into consideration, still more patients in the ETS group were diagnosed with leakage; 10 patients in the ETE group (16%) compared to 21 patients in the ETS group (33%, p = 0.04; Table 3). An inversed relation between anastomotic leakage and stricture formation in our series was found: a stricture developed in 5 of the 40 patients who had leakage (13%), and in 30 of the 88 patients without anastomotic leakage (34%, p < 0.02). There was no difference between groups in this relation between anastomotic leakage and formation of strictures; 3 of the 14 patients with anastomotic leakage in the ETE group developed a stenosis (21%) compared to 2 of the 26 patients with leakage in the ETS group (8%, p = 0.32).

Evaluation of the anastomosis

At video-endoscopy, local ischemia was found in 10 of 60 patients in the ETE group (17%) and in 8 of 63 patients in the ETS group (13%, p = 0.71). A trend toward a higher rate of dehiscence of the anastomosis was found in the ETE group (8 patients, 13%), compared to 2 patients in the ETS group (3%; p = 0.05). There was no statistically significant difference in occurrence of ulcers (25% vs. 29%), necrosis (5% vs. 3%) or fistula formation (5% vs. 6%). At contrast-swallow study, leakage was noticed in 10 of 58 (17%) patients in the ETE group and 6 of 51 patients in the ETS group (12%, p = 0.6). Aspiration during contrast swallow study occurred in 16% of the patients in the ETE group and 21% of the patients in the ETS group (p = 0.51, Table 5).

Other postoperative complications

A trend toward more surgical site infections of the cervical wound and a higher reoperation rate was found in the ETS group (Table 4). Significantly more patients in the ETS group suffered from postoperative pneumonia: 11 patients in the ETE group (17%), compared to 28 patients in the ETS group (44%), p = 0.002). The localization of pneumonia was significantly different between the groups; in the ETE group right-sided pneumonia (site of cervical anastomosis) occurred in 10 of 11 patients (91%), in the ETS group this occurred in 12 of 28 patients (43%, p = 0.02). In both groups, pneumonia was strongly related to anastomotic leakage, as 21 of the 40 patients with anastomotic leakage developed pneumonia (53%), compared to 18 of 88 patients without leakage (20%), p < 0.001. We also found an overall relation between vocal cord paralysis and pneumonia. Of the 12 patients with vocal cord paralysis, 7 developed pneumonia (58%), compared to 32 patients of 116 without this complication (28%), p =0.04. There was, however, no difference in the number of patients with vocal cord paralysis between the two groups (Table 4). Pneumonia after aspiration of water-soluble contrast during swallow study occurred in 1 patient in the ETE group (2%) and in 6 patients in the ETS group (10%, p = 0.06). A trend toward more patients treated for mediastinal infection in the ETS group was found (Table 4).

Operative (30-day) mortality occurred in 0 patients (0%) in the ETE group, compared to 4 (6%) in the ETS group, p = 0.13. Overall in-hospital mortality showed no significant differences

Table 4. Postoperative complications

	End-to-end		End-to-side		p-value
Surgical complications					
- Re-operation	6	(9%)	15	(23%)	0.05
- Bleeding	2	(3%)	3	(5%)	1.0
- Cervical wound infection	5	(8%)	13	(20%)	0.07
- Pleura empyema	3	(5%)	1	(2%)	0.31
- Chylothorax	4	(6%)	1	(2%)	0.36
- Vocal cord paralysis	8	(13%)	4	(6%)	0.36
Non-surgical complications					
- Pneumonia	11	(17%)	28	(44%)	0.002
- ARDS	2	(3%)	3	(5%)	1.0
- Mediastinitis	3	(5%)	10	(16%)	0.08
- Congestive heart failure	2	(3%)	1	(2%)	1.0
- Atrial fibrillation	5	(8%)	5	(8%)	1.0
- Myocardial infarction	1	(2%)	2	(3%)	1.0
- Sepsis	3	(5%)	8	(13%)	0.21
- Delirium	3	(5%)	9	(14%)	0.07
- Urinary tract infection	2	(3%)	2	(3%)	1.0

Table 5. Findings at video-endoscopy and contrast swallow study

	End to end		End to side		p-value
Endoscopy	N=60		N=63		
- Ischemia	10	(17%)	8	(13%)	0.71
- Necrosis	3	(5%)	2	(3%)	0.68
- Ulcer	15	(25%)	18	(29%)	0.81
- Dehiscence	8	(13%)	2	(3%)	0.05
- Fistula	3	(5%)	4	(6%)	1.0
Contrast-swallow study	N=60		N=51		
- Leakage	10	(17%)	6	(12%)	0.60

between groups; 2 (3%) in the ETE group compared to 7 (11%) in the ETS group (p = 0.16, Table 2). One-year survival was 63% in the ETE group (median survival 315 days, 95% confidence interval 306–400 days) and 72% in the ETS group (median 366 days, 95% confidence interval 334–465 days), p = 0.63.

DISCUSSION

The frequent and still important problem of esophago-gastric anastomotic failure after esophagectomy, either stricture or leakage, has stimulated a variety of anastomotic methods.[10,23–32] The best technique to perform this anastomosis is still subject of debate.

In several studies, comparing different anastomotic techniques, the hand-sewn ETE-esophago-gastric anastomosis is regarded by many as the preferred technique, with 9–45% anastomotic stricture formation and 4–25% anastomotic leaks.[27–35] In other parts of the gastrointestinal tract however, ETS-or STS-anastomosis proved superior to ETE-anastomosis regarding postoperative leakage rate and stricture formation.[13–17]

The only two retrospective studies reporting hand-sewn cervical ETS-anastomosis after gastric tubulization are from Heitmiller et al.[22] and Anikin et al.[36] Anastomotic strictures occurred in 26% in the series of Heitmiller and numbers were not provided by Anikin.[36] This low incidence of stricture formation was in their experience accompanied by a very low incidence of anastomotic leaks (1% and 5% of the patients, respectively). These favorable results encouraged us to perform a randomized study between hand-sewn ETE-anastomosis and ETS-anastomosis in the neck.

In our study, anastomotic stricture formation was chosen over anastomotic leakage as primary endpoint of this study, because it defeats one of the main aims of surgery, which is to restore normal swallowing function. Dysphagia occurs in up to 66% of the patients in the earlypostoperative period[21,37] and negatively affects the quality of life after esophagectomy.[38] As dysphagia can be attributed to several anatomic and functional etiologies after

esophagectomy, difficulty in swallowing alone does not prove the presence of an anastomotic stricture. In a previous study however, endoscopic proof of narrowing was found in all patients complaining about newly onset dysphagia after surgery.[21] Also in this study we found endoscopic proof of stricture formation in the majority (90%) of the patients with dysphagia grade II or worse. However, not all patients with anastomotic narrowing—an intuitively objective outcome measure—complain about dysphagia. We believe that these patients with an asymptomatic stricture should not be treated as long as their quality of life is not impaired. We therefore considered dysphagia, associated with endoscopically proven anastomotic narrowing, as definition of anastomotic stricture, rather than to perform routine endoscopy at 1-year follow-up.

The rate of anastomotic strictures in the ETE group in our study (40%) is in line with the results reported in literature (20–45%),[21,23,26,33] whereas the 18% anastomotic stricture rate in the ETS group compares favorably to the results reported by Heitmiller et al. in their retrospective series (26%).[22] However, the rate of anastomotic strictures in our study seems higher, compared to the results of cervical semimechanical STS-anastomosis, reported by Collard et al. (6.3%),[39] but follow-up in that series was limited to 2 months, which is the median time to onset of stricture formation in our study. We found no significant differences between groups in the time to onset of stricture (first dilatation session) or the median number of dilatation sessions needed to relief symptoms, when stricture formation occurred. A stricture developed in 5 of the 40 patients (13%) who had leakage, and was similar in both groups. This number strongly differs from the results of Briel et al.,[19] who found that stricture formation occurred in half of the patients with leakage and established leakage as an independent risk factor for stricture formation. In our study, stents were never used for treatment of leakage, and therefore the difference in stricture formation between the two groups cannot be explained by this factor.

The rate of anastomotic leakage in our ETE group is high, but comparable to that reported in large series in literature (4–25%),[34,40–42] especially when only clinically relevant leaks are considered (16%). One of the technical reasons for the rather high leak rate in our study compared to other series could be the standard use of a 3-cm-wide gastric tube. This technique according to Marmuse[43] relies on the right and left gastroepiploic artery as the only arterial blood supply for the gastric tube with about 15% of the patients having a Koskas type II anatomy[44] lacking connections between these 2 arterial branches.[45,46] However, Tabira et al.[6] showed in their randomized study that a 3 cm narrow gastric tube has the same outcome after esophagectomy, compared to a subtotal stomach pull-up.

In the ETS group we found however an unexpectedly high rate of anastomotic leaks, with significantly more pulmonary complications and longer in-hospital stay. Interestingly, the increased anastomotic leaks in this group were not supported by differences in extravasation of contrast at the anastomotic site in the ETS group at routine contrast swallow. Video-

endoscopy even showed less partial anastomotic dehiscence in the ETS group, compared to the ETE group. This inverse relationship may be explained by the possibility that the increased anastomotic leakage does not result from the anastomosis itself, but rather from the blind ended most proximal end of the gastric tube.

Compared to an ETE-anastomosis, the ETS-anastomosis required more length of the gastric tube and the most ischemic proximal end is left in situ. Based on experimental work regarding the microcirculation in the gastric tube,[47] we considered it safer to remove the redundant tip and reinforce the staple line by oversewing it. In retrospect, oversewing the staple line may have introduced additional ischemia, leading to dehiscence of the suture and staple line. This may explain the increased leakage rate in the ETS group, whereas video-endoscopy showed intact esophago-gastric anastomoses in this group. This also may indicate why the increased leakage (of the tip) in this group was not accompanied by stricture formation (of the anastomosis), as is often reported after anastomotic leaks.

The observed increased need for reoperations and subsequent increased length of stay can be directly attributed to the increased anastomotic leakage in the ETS group. The relation between pneumonia and leakage is however more difficult to understand. One of the hypotheses may be that excessive leakage in the ETS group with mediastinal collection formation may provoke pneumonia, either by compression, or by pain, preventing adequate coughing. In our study, we found more right-sided pulmonary infiltrates in the ETE group (suitable with the anastomosis in the right neck); but in the ETS group infiltrates were both left and right-sided. Vocal cord paralysis is a risk factor for pneumonia in our series, but there was no difference in vocal cord paralysis between the two groups. Another explanation may be that in the ETS group with leakage more swallow studies were performed to follow-up the leak. Previous studies showed a relation between contrast swallows and (micro)aspiration. In our study, we found indeed a trend toward more aspiration during contrast swallow studies in the ETS group.

In conclusion, an ETS-cervical esophagogastric anastomosis in the neck is associated with a lower anastomotic stricture rate, compared to the ETE-technique. However, the ETS-technique is accompanied by an increased anastomotic leak rate and a longer in-hospital stay.

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4

A single blinded randomized controlled trial comparing semi-mechanical with hand-sewn cervical anastomosis after esophagectomy for cancer (SHARE-study)

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ABSTRACT

Objective: The aim of this study was to compare the leak rate between a hand-sewn end-to-end anastomosis (ETE) and a semi-mechanical anastomosis (SMA) after esophagectomy with gastric tube reconstruction.

Background data: The optimal surgical technique for the creation of an anastomosis in the neck after esophagectomy is unclear. No randomized controlled studies have been performed that compare a hand-sewn ETE-anastomosis with a SMA.

Methods: Patients with esophageal cancer who were planned for esophagectomy with gastric tube reconstruction and cervical anastomosis were eligible for participation after written informed consent. Patients were randomized in a 1:1 ratio to ETE- or SMA-anastomosis. The primary endpoint was anastomotic leak rate defined as external drainage of saliva from the site of the anastomosis or an intra-thoracic manifestation of a leak. Secondary endpoints included anastomotic stricture rate at one year follow up, number of dilations, dysphagia score, hospital stay, morbidity and mortality. Patients were blinded for the intervention.

Results: Between August 2011 and July 2014, 174 patients with esophageal cancer underwent esophagectomy. Some 93 patients were randomized to ETE (n=44) or SMA (n=49). Anastomotic leak occurred in 9 of 44 patients (20%) in the ETE group and 12 of 49 patients (24%) in the SMA group (absolute difference 4%, 95% CI -13% to +21%; p=0.804). There was no statistically significant difference in dysphagia at one year postoperatively (ETE 25% vs. SMA 20%; p=0.628), nor in median hospital stay (17 days in the ETE group, 13 days in the SMA group), morbidity (82% vs 73%, p=0.460) or mortality (0% vs 4%, p=0.175) between the groups.

Conclusion: There was no statistical significant difference in anastomotic leak rate between ETE and SMA cervical esophagogastrostomy.

Dutch Trial Registry number: NTR3029. No source of funding.

INTRODUCTION

Neoadjuvant chemotherapy or chemo radiation followed by esophagectomy is the treatment of choice for locally advanced esophageal cancer. Following esophagectomy, the continuity of the gastrointestinal tract is preferably restored with a gastric tube. Failure of the anastomosis[1, 2] between the remnant esophagus and the gastric tube occurs in 5-30%[1, 3, 4] of patients. Anastomotic leakage delays oral intake, prolongs hospital stay, is associated with a deterioration of health-related quality of life[5-7] and results in increased heath care costs.[8, 9] Anastomotic leakage is a risk factor for stenosis of the anastomosis[3, 10] and up to 40% of patients need endoscopically guided dilatations.[11, 12] Anastomotic leakage is also a risk factor for in-hospital mortality (3-6%).[1, 4, 13]

The optimal technique for creating a cervical anastomosis between the esophagus and gastric conduit is largely unknown due to a lack of randomized trials. As patients live longer, perioperative morbidity and late complications of surgery tend to become more important. A previous randomized controlled trial compared a cervical hand-sewn end-to-end anastomosis (ETE) to a cervical hand-sewn end-to-side (ETS) anastomosis. This study reported that an ETE-anastomosis was associated with a lower leak rate, but a higher rate of stenosis compared to an end-to-side anastomosis.[14] However, the reported leak rates were still high: 22% in the ETE group and 41% in the ETS group.

In 1998 Collard[17] et al. published a new technique for the cervical esophagogastrostomy. Retrospective studies have suggested that this semi-mechanical side-to-side anastomosis (SMA) is associated with low anastomotic leak rates and low rates of anastomotic strictures. The aim of this study was to assess the leak and stricture rate of the SMA technique. We hypothesized that the SMA reduces the anastomotic leak and stricture rate as compared to our standard ETE-anastomosis.

PATIENTS AND METHODS

Trial design

This was a single center, single blinded, parallel group with balanced randomization (1:1), clinical trial. The trial was registered at the Dutch trial registry (NTR3029). The study took place at the Department of Surgery, Erasmus MC, Rotterdam, the Netherlands. The Erasmus MC is an academic hospital and serves as a tertiary referral center for esophageal diseases. Ethical approval was obtained from the ethics committee of the Erasmus MC (trial number NL35746.078.11). After approval of the protocol on 11 August 2011, there were no changes or amendments made. The trial is reported according to the CONSORT 2010 guidelines.[15]

Patients

Eligible participants were patients aged ≥ 18 years with esophageal or junctional cancer and who were scheduled for a transhiatal or transthoracic esophagectomy with gastric tube reconstruction and a cervical anastomosis. Only patients who underwent surgery with curative intent (stage $cT_{1-4a}N_{0-2}M_0$) were eligible. Neoadjuvant treatment (chemotherapy or chemo radiation) was allowed.

Exclusion criteria were a planned intra-thoracic anastomosis, patient not available for follow up (up to 1 year postoperatively), cervical esophageal cancer (extending from upper esophageal sphincter to the sternal notch), American Society of Anesthesiologists (ASA) score of ≥ 4.

Patients were informed about the study in the outpatient clinic by one of the consultant surgeons 4-8 weeks before the operation. An information leaflet was handed out. The day before the operation, the patient was admitted to the hospital and the patient was asked to participate in the study. After written informed consent the patients were registered as trial participant.

Interventions

Three experienced esophageal surgeons (HWT, JJBvL, BPLW), proficient in both anastomotic techniques, participated in the study and performed the resection and reconstruction themselves or supervised the fellow.

A three stage transthoracic esophagectomy (McKeown) or transhiatal esophagectomy (Orringer) was performed depending on the patient's condition and location of the tumor[16]. A nasojejunal feeding tube or percutaneous jejunostomy was placed.

Surgical techniques

End-to-end anastomosis

The cervical esophagus was transected 4 to 5 cm below the upper esophageal sphincter, the esophageal was stripped and the resection specimen was retrieved. A 3-4 cm wide gastric tube was created and brought up to the neck via the prevertebral route. A hand-sewn, single layer running end-to-end esophagogastrostomy (ETE) was constructed with PDS 3/0 (Johnson & Johnson, New Brunswick, NJ, USA) as described before.[14] The anastomosis was performed as distal as possible on the gastric tube (towards the pylorus) and any redundant gastric tissue was resected. However, great care was taken to prevent any tension on the anastomosis. A photograph is shown in Figure 2.

Semi-mechanical anastomosis

The semi-mechanical anastomosis (SMA) was performed according to Collard et al. with some modifications.[17] After complete mobilization of the esophagus, the cervical esophagus was transected with a linear stapler (Covidien, Dublin, Ireland) 8-10 cm below the upper

esophageal sphincter via the neck incision. Once a 3-4 cm wide gastric tube was created and pulled up to the neck, five stay sutures with Ti-Cron 3/0 (Medtronic, Dublin, Ireland) kept the esophageal remnant and gastric tube in a parallel position to each other. A small incision was made in the gastric tube and the cervical esophagus. Another two stay sutures were placed between the esophagus and gastric tube via the enterotomy. The jaws of an Endostapler (Ethicon, USA) were placed across the two opposing walls with the anvil in the gastric lumen and the cartridge of staples in the esophageal lumen. The stapler was fired to allow forward displacement of the knife and the delivery of three rows of staples on each side. The stapler was removed and a V-shaped join was created. The anterior wall of the anastomosis was closed using a double-layer running suture technique. A photograph is shown in Figure 3.

Outcomes

The primary endpoint was anastomotic leakage within 30 days after the operation. This was defined as opening of the neck wound with subsequent drainage of saliva and/or ingested fluids through the wound site or intrathoracic manifestations of anastomotic leak including mediastinitis or abscess formation detected with radiologic imaging (CT scan with oral contrast) or endoscopy.

Secondary endpoints included anastomotic stricture within one year, defined as dysphagia with stenosis seen on endoscopy, number of dilations within one year and quality of life at one year follow-up.

Sample size

The reported leak rate for ETE in our center was 22%.[14] SMA is associated with a leak rate of 5%.[17] Hence, a 17% reduction in the leak rate in favor of SMA was anticipated. A sample size was calculated using an α of 0.05 (two-sided) and a power of 85%. Seventy-six patients had to be included per study arm. To correct for mortality within one year, the study arms were enlarged to 100 patients each. No formal interim analysis was planned.

Randomization

The Department of Biostatistics supervised the randomization process (by preparing the envelopes). A computer based hidden block size of 10 was used by the Department of Biostatistics. After the tumor was resected, the gastric tube constructed and pulled up to the neck, the lead surgeon decided if the patients could be randomized. Randomization took place in the operating room using sealed envelopes prepared by the Department of Biostatistics. Reasons for not randomizing patients were inability to construct ETE or SMA (when the esophageal remnant or gastric tube was too short), distant metastasis found during the operation, reconstruction with colon or a retrosternal or presternal route of the conduit. Stratification was performed for surgical approach (i.e. transhiatal or transthoracic approach).

Independent Data Monitoring and Safety Committee

An independent Data Safety and Monitoring Board (DSMB), consisting of two surgeons and a biostatistician, reviewed unblinded data for patient's safety. No interim analysis for efficacy or futility was planned. The DSMB monitored the (cumulative) incidence of serious adverse events every 3 months. Serious adverse events (SAEs) included anastomotic leakage requiring surgical re-intervention, any complication requiring prolonged hospital stay, any complication that results in death, re-admittance to the hospital, recurrence of disease or death. The DSMB could advise on the termination of the study. All SAEs were reported through the web portal ToetsingOnline to the accredited METC that approved the protocol, within 15 days after the sponsor was informed about a serious adverse event.

Statistical analysis

Analysis of data was according to intention to treat. Values are shown as means and standard deviation (SD) or medians with their range. Groups were compared using non-parametrical Mann-Whitney *U* test or Student's *T* test, if normally distributed. For cross tabulations, Pearson's Chi Square test with continuity correction or Fisher's exact test was used, as appropriate. All statistical analyses were performed on the statistical package SPSS 24.0 (SPSS Inc, Chicago, IL, USA). A p-value < 0.05 is considered statistically significant (two-sided). No futility analysis was performed because the reason to end the study prematurely was slow accrual.

Postoperative care

After the operation patients were transferred to the ICU; they were extubated in the operating room or within the following hour, if possible. ICU staff was unaware of the anastomotic technique. Patients were transferred to the surgical ward the day after surgery if they were not on inotropes and were hemodynamically and respiratory stable. At the ward a standardized care pathway was followed and a checklist with postoperative instructions was used by the attending surgeon, the nurse specialist or registrar. Patients were kept nil by mouth but ice chips were allowed according to the study protocol. Radiological examination of the anastomotic integrity was not performed routinely before oral intake was commenced on postoperative day 7. On postoperative day 8, thickened fluids were allowed (yoghurt/custard) and on day 9 semi-solids and soft foods were introduced until discharge. Enteral feeds were given by the nasojejunal feeding tube or the jejunostomy starting postoperative day 1. A dietician was involved in the assessment of caloric intake by the patients in the hospital and after discharge. It was the intention to discharge the patients without a need for additional enteral feeding via the feeding tube.

Follow up

Patients were seen in the outpatient clinic three weeks after discharge and every three months in the first year after surgery. The second year, patients were seen every 6 months and from year three onwards once a year. For the first year, the surgeon filled out a questionnaire

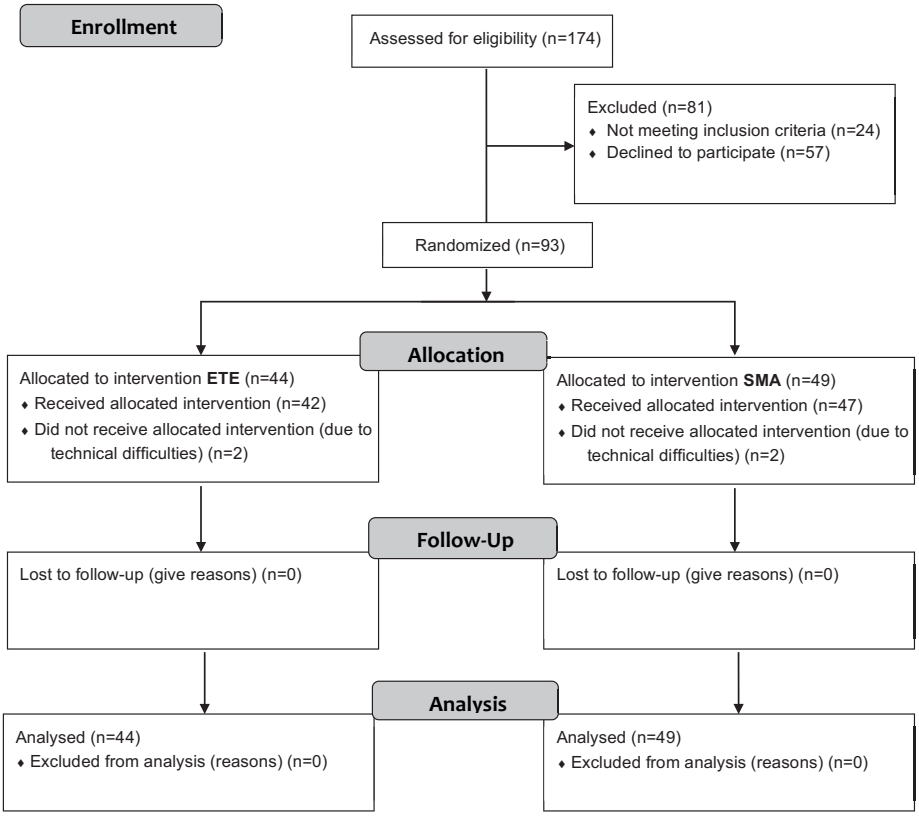
and case record forms regarding dysphagia and complications after interviewing the patient. Quality of life questionnaires (EORTC QLQ C-30 and OES-18) were answered preoperatively and at 3, 6, 9 and 12 months after surgery.

RESULTS

Patients

From August 2011 to July 2014, 174 patients with esophageal cancer underwent esophagectomy with gastric tube reconstruction for esophageal cancer. The CONSORT flow diagram is shown in Figure 1.

Figure 1. Overview of patient inclusion



Reasons for exclusion: no signed informed consent (n = 57), intra-thoracic anastomosis, no availability for follow up at 1 year (n = 2), upper thoracic/cervical esophageal cancer, American Society of Anesthesiologists score larger or equal to 4. Reasons not to randomize patients in the operating room were: technically not possible to perform SMA (n = 8), metastasis found during the operation (n = 5), no gastric tube created (n = 2), prevertebral route of the conduit (n = 1), reconstruction after previous resection (n = 6). All 4 patients who were randomized but did not receive the allocated anastomosis received either an ETE or ETS anastomosis.

Due to slow accrual and the publication of a similar trial[18], the DSMB recommended to stop the trial and report the outcomes. In total, 93 patients were randomized. The ETE group consisted of 44 patients and the SMA group of 29 patients. Patient characteristics are listed in Table 1. The mean (SD) age was 65 (8.30) years in the ETE group, and 64 (7.87) years in the SMA group. Neoadjuvant treatment (chemotherapy or chemo radiation) was given to 39 (89%) of patients in the ETE group and 46 (94%) patients in the SMA group.

Primary outcome

Anastomotic leakage occurred in 9 of 44 (20%) patients in the ETE group and in 12 of 49 (24%) patients in the SMA group (absolute difference 4%, 95% CI-13% to +21%; p=0.804) (Table 3). In one patient from the SMA group a reoperation was required because of a massive leak resulting in pneumohydrothorax. The gastric tube was resected and an esophagostomy in the

Table 1. Patient characteristics

	ETE* (n=44)	**SMA** (n=49)**
Age (yr) median [range]	65 [41-83]	64 [44-83]
Sex (M:F)	40:4	36:13
Histology		
- Squamous cell carcinoma	7 (16%)	18 (37%)
- Adenocarcinoma	36 (82%)	31 (63%)
- Undifferentiated	1 (3%)	0 (0%)
Tumor site		
- Esophagus	34 (77%)	38 (78%)
- Gastro-esophageal junction	10 (23%)	11 (22%)
Neo-adjuvant treatment		
- None	5 (11%)	3 (6%)
- Chemotherapy	6 (14%)	4 (8%)
- Chemoradiation	33 (75%)	42 (86%)
Comorbidity		
- Cardiovascular	26 (59%)	26 (53%)
- Respiratory	3 (7%)	6 (12%)
- Diabetes Mellitus	10 (23%)	8 (16%)
ASA		
- 1	4 (9%)	5 (10%)
- 2	32 (73%)	34 (69%)
- 3	8 (18%)	10 (21%)
- 4	0 (0%)	0 (0%)
- 5	0 (0%)	0 (0%)

* ETE denotes end-to-end

** SMA denotes semi-mechanical anastomosis

Table 2. Operative characteristics and pathology

	ETE (n=44)	SMA (n=49)
Mean operating time (min± sd)	398.9 (16.8)	389.9 (14.0)
Surgical approach		
- Transhiatal esophagectomy	18 (41%)	20 (41%)
- Transthoracic esophagectomy	26 (59%)	29 (59%)
Pathology		
Radicality of the operation		
- R0	41 (93%)	42 (86%)
- R1	3 (7%)	7 (14%)
- R2	0 (0%)	0 (0%)
Histology		
- Squamous cell carcinoma	3 (7%)	11 (22%)
- Adenocarcinoma	29 (66%)	28 (57%)
- No malignancy left after neoadjuvant treatment	11 (25%)	10 (20%)
- Lymphoepithelioma	1 (3%)	0 (0%)
Median (range) number of lymph nodes resected	19 (2-43)	18 (8-41)
pT-category		
- T0	11 (25%)	13 (27%)
- T1	8 (18%)	8 (16%)
- T2	11 (25%)	5 (10%)
- T3	14 (32%)	21 (43%)
- T4	0 (0%)	2 (4%)
pN-category		
- N0	26 (53%)	25 (51%)
- N1	13 (27%)	13 (27%)
- N2	4 (8%)	8 (16%)
- N3	1 (2%)	3 (6%)
pM-stage		
- M0	42 (95%)	49 (100%)
- M1	2 (5%)	0 (0%)
Disease stage		
- 0	10 (23%)	9 (18%)
- Ia	8 (18%)	7 (14%)
- Ib	5 (11%)	4 (8%)
- IIa	3 (7%)	6 (12%)
- IIb	6 (14%)	5 (10%)
- IIIa	8 (18%)	8 (16%)
- IIIb	3 (7%)	5 (10%)
- IIIc	1 (2%)	3 (6%)
- IV	0 (0%)	2 (4%)

Abbreviations used: ETE: End-to-end; SMA: semi-mechanical anastomosis

Table 3. Postoperative complications

	ETE (n=44)	SMA (n=49)	p-value
Any complication	36 (82%)	36 (73%)	0.460
Anastomosis related complications			
- Anastomotic leakage	9 (20%)	12 (24%)	0.804
- Reoperation required for leakage	0 (0%)	1 (2%)	1.000
Dysphagia	11 (25%)	10 (20%)	0.628
Stenosis of the anastomosis on endoscopy	11 (25%)	9 (18%)	0.460
Median (range) number of dilatations (1year)	6 [1-11]	3 [1-9]	0.276
Other complications			
- Postoperative bleeding#	3 (7%)	0 (0%)	0.249
- Chylothorax§	4 (9%)	3 (6%)	0.704
- Vocal cord paralysis	3 (7%)	5 (16%)	0.561
- Wound dehiscence (abdominal)	2 (5%)	1 (2%)	0.601
- Pneumonia†	14 (32%)	17 (35%)	0.828
- Mediastinitis	4 (9%)	5 (10%)	1.000
- Cardiac complication (other than AF) ‡	8 (18%)	8 (16%)	1.000
- Atrial fibrillation	6 (14%)	10 (20%)	0.423
- Sepsis	1 (2%)	2 (4%)	1.000
- Delirium	5 (11%)	1 (2%)	0.097
- Thrombosis~	1 (2%)	1 (2%)	1.000
Re-admission to ICU	3 (7%)	7 (14%)	0.324
Re-admission to hospital***	6 (14%)	13 (27%)	0.186

Abbreviations: ETE: end-to-end, SMA: semi-mechanical anastomosis, ICU: intensive care unit

Adverse events were graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events, version 4.0

^ Anastomotic leakage was defined as: opening of the neck wound with subsequent drainage of saliva and/or ingested fluids through the wound site or intrathoracic manifestations of anastomotic leak including mediastinitis or abscess formation detected with radiologic imaging (CT scan with oral contrast) or endoscopy

† Pneumonia (isolation of pathogen from sputum culture and a new or progressive infiltrate on chest radiograph), serious atelectasis (lobar collapse on chest radiograph)

Postoperative bleeding was defined as blood loss with the need of transfusion or intervention.

‡ Cardiac complications were arrhythmia (any change in rhythm on the electrocardiogram, requiring treatment), myocardial infarction (two or three of the following: previous myocardial infarction, electrocardiographic changes suggesting myocardial infarction, or enzyme changes suggesting myocardial infarction), cardiac decompensation and left ventricular failure (marked pulmonary edema on a chest radiograph).

~ Thrombosis was defined as the physical presentation of an acute deep venous thrombosis, confirmed by radiological exam or a pulmonary embolism, conformed by spiral computed tomography.

§ Chylothorax was recorded when elevated levels of triglycerides in intrathoracic fluid (>1 mmol per liter [89 mg per deciliter]) were found in combination with high fluid production of the drain. Mediastinitis was scored when reported by the local investigator.

***Reasons for re-admission: unable to maintain oral intake, pneumonia, wound infection

neck was created together with a feeding jejunostomy. In all other patients, leakage was managed conservatively by opening of the neck wound, antibiotics or percutaneous drainage of a mediastinal or pleural abscess. Operative characteristics and pathology are shown in Table 2.

Secondary and other outcomes

Dysphagia was reported by 11 patients (25%) in the ETE group and 10 patients (20%) in the SMA group (p=0.628). Most patients required dilatation for a benign anastomotic stricture as diagnosed on endoscopy. The median(range) number of dilatations within one year after surgery was 6(1-11) in the ETE group and 3 (1-9) in the SMA group (p=0.628).

Median(range) Intensive Care Unit stay was 3 (1-20) days for patients in the ETE group compared to 3 days (1-11 days) for patients in the SMA group. Median (range) hospital stay was 17 (10-95) days for patients in the ETE group compared to 15 days (5-78 days) for patients in the SMA group (p=0.261). In-hospital mortality for the ETE group was 0% versus 4% in the SMA group (p=0.175). One patient from the SMA group died within 30 days after the operation due to postoperative complications (2%). 90-day mortality was 0%in the ETE group versus 8% in the SMA group (p=0.118). The incidence of other postoperative complications was not statistically significant different between the groups (Table 3.)

Figure 2. Photograph of the ETE-anastomosis.

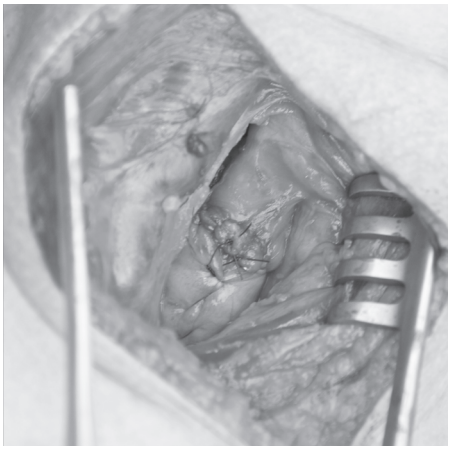
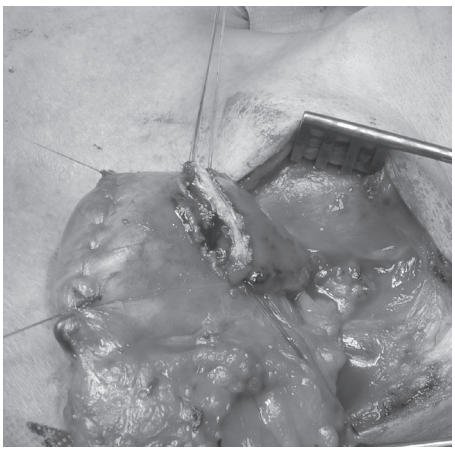


Figure 3. Photograph of the SMA-anastomosis



DISCUSSION

This study shows no statistically significant difference in anastomotic leak rate between a cervical ETE and SMA after esophagectomy with gastric tube reconstruction. The leak rate in this study of 20-24% is high, but comparable to a previous study from our group.[19] The present study could not confirm the hypothesis that SMA reduces the leak rate as reported by others[17, 20]. Before start of the study the experience of the surgical team with SMA was limited.

A senior surgeon from another surgical unit (Leuven, Belgium) who had a vast experience in SMA technique taught the study coordinator (BPLW) the details of the procedure. During the study period, all anastomoses were created or supervised by a staff surgeon. Despite this, the learning curve for SMA may not have been passed yet and minor but crucial details in the construction of SMA may have been missed. However, the leak rate did not change during the study period. One could argue though, that a longer pre-trial learning period should have been introduced to optimize the surgical technique before the start of the trial.

Other studies using the SMA technique show lower leak rates (between 4 and 16%).[21-24] The difference with the present study could be explained by the diligent way we scored the post-operative complications and the prospective study design. Also, the term 'semi-mechanical anastomosis' includes many different techniques that have similarities (usually side to side) but also differ in details (single versus double layered) between the studies that describe this technique. Hence, a comparison of the leak rate in our study with other studies is difficult. The leak rate of 20% in the ETE group is within the range reported in the literature.

This is not the first trial comparing a hand-sewn anastomosis with a (semi-)mechanical anastomosis. Again, the interpretation and clinical applicability of these studies and meta-analyses is difficult due to the different techniques used, varying definitions of leaks and strictures and different periods of follow up. Although previous studies have compared a hand-sewn end-to-side anastomosis with a circular stapled[25, 26] or linear stapled anastomosis.[17, 20-24, 27, 28] In 2005, Ercan et al.[22] published a cohort study of 274 patients and showed a benefit in post-operative morbidity for the SMA (modified Collard technique) anastomosis compared to the hand-sewn technique. Other studies reported a low leak rate of a V-shaped SMA (modified Collard, Collard, Orringer, linear stapled) (5%), and described it as a major refinement of the surgical technique[17, 20, 21, 24]. Meta-analyses[25, 27, 28], however, showed no statistically significant difference in anastomotic leakage or 3-month mortality between several techniques (circular stapled, linear stapled or hand-sewn). A systematic review, published in 2010 showed a lower stricture rate in the hand-sewn group, but also concluded that there is insufficient evidence to recommend one anastomotic technique over the other.[23] Another review showed an increased rate of postoperative anastomotic stricture, but shorter operating time for the stapled technique.[29]

Dysphagia, often defined as a need for dilatation, is between 4 and 63% for patients using the SMA technique and 16-88% in patients with a hand-sewn anastomosis at 1 year.[23, 30-32] The lower limit of the published percentages corresponds to studies with a short follow up (2-3 months postoperatively). The upper margin of patients with dysphagia is derived from studies with follow up until 12 months postoperatively and therefore is comparable to the present study. Our data show a trend towards a lower percentage of patients with dysphagia in the SMA group. The theoretical concept of SMA is to create a wide, triangular V-shaped connec-

tion between the gastric tube and esophagus and this might translate in reduced stricture of the anastomosis. The difference between the groups was not statistically significant however, which may be due to the smaller sample size than anticipated. However, the number of dilatations needed was less in the SMA group.

The major limitation of the present study is that it was decided to stop it prematurely because of slow accrual. Hence, the anticipated number of patients to be enrolled was not met and the study is underpowered to show a statistically significant difference (if any) in leak rate. The reasons for the slow accrual were changes in regional organization and referral of esophageal cancer patients and a shift towards more complex patients that were not eligible for participation in the study took place. Hence, the Data Safety Monitoring Board advised the steering committee of the study to end the study prematurely.

Although there was no significant difference in postoperative morbidity or mortality between the groups, the present study reports high complication rates after esophagectomy with gastric tube reconstruction. The prospective design of the study warrant detailed and timely reporting of all adverse events according to good clinical practice guidelines. Hence, the data reflect real practice and are in line with our nationwide prospective Dutch Upper GI Cancer Audit (DUCA).[33]

With an absolute difference of 4% and a 95% confidence interval of -13% to 21% for anastomotic leakage, absolute differences larger than 21% in favor of the SMA and of 13% in favor of ETE are unlikely. This study was underpowered to show statistically significant smaller differences in leak rates and it should be concluded that superiority or inferiority of any technique cannot be proven. A futility analysis can be done to calculate the chance for the trial to be successful if one would proceed with the study based on the numbers from an interim analysis. However, given the fact that the decision was taken to stop the trial due to slow accrual, a futility analysis is not useful for better interpretation of the data.

It is unlikely that a larger study will be initiated. At least in the Netherlands, most centers are moving towards an intra-thoracic anastomosis (Ivor Lewis esophagectomy) instead of the three stage McKeown with cervical anastomosis. A recently started Dutch RCT will answer the question whether leak rate, stenosis and quality of life are better in patients with an intrathoracic anastomosis compared to a cervical anastomosis (ICAN study, trial register NTR4333).

In conclusion, this study shows no significant differences in postoperative complications between a hand-sewn or semi-mechanic stapled anastomosis, but is underpowered due to premature ending of the study.

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5

Morbidity and mortality of colon interposition after esophagectomy

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ABSTRACT

Background: A segment of colon can be used for reconstruction of the digestive tract after esophagectomy. This retrospective study assessed the indications and outcome after colon interposition performed in a tertiary referral center.

Methods: All patients who underwent esophagectomy with colon interposition between 1976 and 2016 at the Erasmus MC University Medical Center Rotterdam were identified from an institutional database. Data on patients characteristics, operative details, morbidity and mortality were retrieved from the database and patients' charts.

Results: 126 patients were included. Indications for colon interposition were failed gastric tube reconstruction (n = 18), previous gastric surgery (n = 48), esophagectomy with total gastrectomy for cancer (n = 40), caustic injury (n = 6) and other reasons (n = 8). Postoperative in-hospital mortality was 18% (23 patients). Morbidity was 66%. The most prevalent complications were pneumonia in 40 patients (32%) and anastomotic leakage in 24 patients (19%).

Conclusion: The use of a colon conduit after esophagectomy is associated with a high mortality and morbidity but it is a viable option for reconstruction of the upper gastrointestinal tract.

INTRODUCTION

Esophagectomy has an important place in the curative treatment of esophageal cancer and may be indicated for benign disorders.[1,2] In the beginning of the previous century, the use of a segment of colon for reconstruction after esophagectomy was introduced. The technical details were first reported by Kelling[3] and Vulliet[4] in 1911.

Theoretical advantages of colon interposition are the abundant length and the reliable blood supply. Furthermore, in patients that undergo neoadjuvant (chemo)radiation therapy for esophageal cancer, the colon is not at risk for radiation-induced damage with a possible impact on perturbed anastomotic healing. However, colon interposition is associated with a high rate of postoperative complications including leakage, pneumonia and prolonged ileus.[5]

Although health-related quality of life after colon interposition is at least equal compared to gastric tube reconstruction, gastric tube interposition is nowadays considered the standard technique for reconstruction after esophagectomy. The stomach is often available and easily mobilized via a laparotomy or laparoscopy. Gastric tube reconstruction requires just a single anastomosis with the esophageal remnant. A disadvantage of using a gastric tube is gastro-duodenal reflux with possible aspiration or the re-development of Barrett's esophagus in the esophageal remnant.[6, 7]

At present, colon interposition is only used for reconstruction due to previous gastric resections, incomplete vascularization of the stomach and patients that need an esophagogastrectomy for malignant or benign disorders.[8-13] There have been few reports in the literature about the indications and outcome of patients after colon interposition. The aim of this study was to report the indications, operative details and morbidity and mortality of colon interposition over a 40-year period.

PATIENTS AND METHODS

All patients who underwent a colon interposition after esophagectomy between 1976 and 2016 were identified from a prospective institutional database. Preoperative, peroperative and postoperative data were collected by a data manager who reviewed all patients that were discharged from the hospital on a weekly basis. Demographic data included patient's age, gender and comorbidities. Tumor stage was determined after preoperative examinations that changed over the study period. In general, physical examination, standard laboratory tests and chest X-ray were performed in all patients. CT scan for staging esophageal cancer was introduced in 1980, later in time (since 1991) followed by endosonography. A colonoscopy was not routinely performed but indicated when colon neoplasms were suspected on clinical or radiological grounds. A CT-angiography to assess the vasculature of the colon was performed in individual cases prior to surgery.

Postoperative complications included surgical complications (anastomotic leakage, re-operation, colon necrosis, chyle leakage, bleeding, vocal cord palsy) as well as non-surgical complications (cardiac and pulmonary complications). Complications were retrieved from the patient's notes and entered in the database by the data manager. The attending surgeon at the time reviewed and evaluated all data entered in the database.

Surgical procedure

The surgical approach for esophagectomy included transhiatal, transthoracic and thoracoabdominal (left sided) resections. For preparation of the colon conduit, a laparotomy was performed. The greater omentum was dissected of the transverse colon. The right and left colon were fully mobilized. The adequacy of graft vascularity was assessed by temporary vascular occlusion. Pulsations of the marginal artery were palpated and the Doppler was used in some patients when there was doubt about the patency of the mesenteric vessels. Attention was also paid to the degree of venous distension. The choice for which segment of the colon (right, transverse or left) was used, was determined by the length and quality of the arterial and venous blood supply as well personal preference of the surgeon. The graft was brought up to the neck by the retrosternal, prevertebral or subcutaneous route. A single layer hand-sewn anastomosis was performed with the remnant esophagus. The segment of colon was distally anastomosed to either the remnant of the stomach or a Roux-and-Y reconstruction. Postoperative management included transfer to the Intensive Care Unit. No additional routine examinations were carried out apart from a swallow X-ray on day 7 postoperatively in most patients.

Statistical analysis

Values are shown as means and standard deviation (SD) or medians with their range, as appropriate. Groups were compared using non-parametrical Mann-Whitney-*U* test or Student's *T*-test, if normally distributed. For cross tabulations, Pearson's chi-squared test with continuity correction or Fisher's exact test was used, as appropriate. All statistical analyses were performed on the statistical package SPSS 20.0 (SPSS Inc, Chicago, Illinois, USA). A p-value < 0.05 was considered statistically significant.

RESULTS

Patients

In total, 126 patients underwent colon interposition for restoration of continuity after esophagectomy. There were 95 (75%) men and 31 (25%) women and the median (range) age was 61 yrs. (28-79). The indication for esophagectomy was malignant disease in 114 of 126 patients (90%; Table 1). A previous gastrectomy was the main reason for choosing a segment

of colon for reconstruction (48 of 126 patients) followed by esophagectomy with (sub)total gastrectomy for locally advanced malignant disease (40 of 126). In 18 patients, reconstruction with a gastric tube had failed due to necrosis of the conduit and colon interposition was necessary at a later stage after resection of the gastric conduit (Table 1).

Operative characteristics

In 72 of 126 patients (58%) the descending colon or transverse with part of the descending colon was used. In 66 of 126 patients (52%) in the prevertebral route was chosen to bring the colon segment up to the neck. For secondary reconstruction, the retrosternal or subcutaneous route was always used. Operative characteristics are shown in Table 2.

Morbidity and mortality

In 83 of 126 patients (66%), one or more complications occurred. Surgical complications were seen in 45 patients (36%). Reoperations were needed in 23 of 126 patients (18%). A reopera-

Table 1. Patient and tumor characteristics

	N=126
Gender (male: female)	95:31
Age (years) median, [range]	61 [28-79]
Comorbidity	
- Diabetes	6 (5%)
- COPD	15 (12%)
- Cardiovascular disease (atrial fibrillation, heart failure, infarct)	22 (18%)
- Medical history with malignant tumor	31 (25%)
Neoadjuvant therapy	
- None	54 (44%)
- Chemotherapy	15 (12%)
- Radiotherapy	51 (41%)
- Chemo radiation	4 (3%)
- Unknown	2 (2%)
Operation indication	
- Necrotic gastric tube	18 (15%)
- Intraoperatively stomach tube judged as inadequate due to ischemia	5 (4%)
- Previous (partial) gastrectomy	48 (39%)
- Tumor with invasion of esophagus and stomach	40 (32%)
- Caustic injury	6 (5%)
- Previous Whipple-procedure	1 (1%)
- Colon as first choice	2 (2%)
- Unknown	6 (5%)

tion for leakage was performed in 13 (10%) patients. Other reasons include chyle leak (2%), bleeding (4%), fascia dehiscence (5%), internal herniation (4%) and bowel perforation (2%).

Some 57 patients (45%) had non-surgical complications mainly pulmonary and cardiac complications.

In-hospital mortality was 18%. Four patients died as a result of anastomotic leakage, two patients because of progressive metastatic disease, seven patients of necrosis of the colon interposition and eight patients died of sepsis with underlying pulmonary complications. Two patients died because of a fistula between the colon conduit and trachea.

Between 1976 and 2001, 94 patients (75%) underwent a colon interposition, and in the last 15 years (2001-2016) 32 patients (25%). Morbidity and mortality was similar between the groups.

Table 2. Details of the operation

	N=126
Segment of colon used for reconstruction	
- Ascending colon	40 (33%)
- Transverse colon	11 (9%)
- Descending colon	40 (33%)
- Transverse and descending colon	35 (28%)
Surgical approach	
- Transthoracic	50 (40%)
- Transhiatal	75 (60%)
- Unknown	1 (1%)
Position of graft	
- An-isoperistaltic	27 (21%)
- Isoperistaltic	36 (29%)
- Unknown	63 (50%)
Anastomosis in the neck (esophago-colostomy)	
- End-to-End	74 (59%)
- End-to-Side	18 (14%)
- Unknown	34 (27%)
Drainage of colon conduit	
- Roux-Y reconstruction	90 (71%)
- Stomach remnant	33 (26%)
- Unknown	3 (3%)
Route of conduit	
- Retrosternal	44 (35%)
- Pre-vertebral	66 (52%)
- Subcutaneous	9 (7%)
- Unknown	7 (6%)

Table 3. Postoperative complications

Complication	No. of patients (%)
Any complication	83 (66%)
Leakage of the anastomosis	24 (19%)
Necrosis of colon interposition	8 (6%)
Chyle leakage	3 (3%)
Vocal cord palsy	11 (9%)
Fascia dehiscence	9 (7%)
Prolonged ileus	12 (10%)
Pneumonia	40 (32%)
Mediastinitis	9 (7%)
Cardiac complications (atrial fibrillation, heart failure, infarct)	21 (17%)
Sepsis	20 (16%)
Thrombo-embolic event	5 (4%)
Delirium	7 (6%)
In-hospital mortality	23 (18%)

Table 4. Overview of the literature

Author	No. of patients	Mortality	Morbidity	Anastomotic leak	Necrosis of conduit
Briel[21]	393	4.7%	NR	10.9%	9.2%
Cerfolio[20]	32	9.4%	24%	3.3%	9.4%
Curet-Scot[23]	53	3.8%	43%	9.4%	NR
DeMeester[7]	92	9%	15.2%	4%	7.6%
Doki[9]	28	NR	71%	46%	NR
Furst[24]	53	9.4%	60.3%	16%	1.6%
Hamai[25]	40	2.5%	45%	17.5%	5.0%
Thomas[26]	60	8.3%	65%	10%	NR
Wain[27]	52	4%	67%	5.8%	9.6%
Isolaura[28]	248	16%	37%	4%	3%
Fujita[29]	53	17	NR	22.6%	5.7%
Kolh[30]	38	2.5%	26%	0%	0%
Hagen[31]	72	5.6%	75%	12.5%	5.6%
DeMeester[6]	85	4.7%	NR	9.4%	NR
Davis[5]	42	16.7%	NR	14.3%	2.4%
Popovici[32]	347	4.6%	NR	6.9%	1.9%
Shirakawa[33]	51	0%	23.5%	7.8%	0%
Knezevic[12]	336	4.2%	26.5%	9.2%	2.4%
Motoyama[34]	34	0%	NR	9%	0%
Mine[35]	95	5.3%	64.2%	13%	0%
Klink[11]	43	16%	61%	30%	9%

DISCUSSION

This retrospective study shows that morbidity and mortality of colon interposition after esophagectomy is high: two-thirds of patients had one or more complication. The most common adverse events were pulmonary and cardiac complications. Although, the type complication was not completely specified in our database in the early years of registration, data from previous studies from our center indicate that pulmonary include pneumonia, atelectasis as well as persistent pleural effusion that needs drainage. The cardiac complications are mostly classified as dysrhythmias.[14, 15] In-hospital mortality was 18% and this is high compared to standard esophagectomy with gastric tube reconstruction. A recent audit from the Netherlands showed that postoperative mortality after esophagectomy (years 2011-2014) is around 4%.[16] The discrepancy may be explained by the poorer general health status of the patients in the present study. Some 40 patients had tumor invasion of the esophagus and stomach in such a way that esophagectomy and total gastrectomy was needed.

These patients may be more frail and suffer from malnutrition given the extensive tumor load. Other patients had previous abdominal operations (including failed gastric tube reconstruction) in the past that may have contributed to a poorer performance status and increased risk for complications. Patients age was equal compared to patients that undergo esophagectomy with successful gastric tube reconstruction.

Also, a time effect may be responsible for the high morbidity and mortality. However, mortality was 19% between the years 1976 and 2001 and 16% in the later time period. Over 40 years, several changes in surgical techniques have taken place including use of surgical devices that minimize blood loss, less liberal fluid administration and the use of enhanced recovery protocols after esophagectomy that may have contributed to better outcomes. However, these possible benefits do not translate in better outcomes in the present study. Minimally invasive surgery for esophageal cancer is associated with shorter hospital stay and less complications.[17] All patients in this cohort had a laparotomy for preparation of the conduit. This seems inevitable given the previous surgeries and intraoperative assessment of colon vascularization. Laparoscopic colon mobilization and colon segmental interposition in adults has not been published before but recently in children this approach was described.[18]

Table 4 shows morbidity and mortality rates reported by other studies. There is a wide variation in mortality (0-16%) and morbidity (15-71%) rates. Differences in definitions used as well as incomplete reporting due to the retrospective nature of the study may explain this. As shown by a Dutch prospective database on esophageal cancer resections, rates of complications are over 60% and this is higher than previous reports from single center studies that claim complication rates as low as 30 to 50% (16).

Several studies showed that a single dose of steroid preoperatively could reduce the complication rate in patients that undergo an esophagectomy. A meta-analysis however concluded

that well designed studies are still needed to substantiate the claimed benefit of steroid administration.[19] Whether preoperative angiography is required to plan surgical treatment remains debatable. Some authors are very much in favor because this may guide the surgeons to get the most optimal graft. We feel that this does not replace intraoperative thorough assessment of the colon vascularization. Full mobilization of the right and left colon and temporary clamping of the mesenteric vessels is still needed before a definite decision is made on the segment used for transposition to the neck. The rate of anastomotic leakage and colon conduit ischemia in our series was within the range of other studies.

Colon interposition is a challenging operation. Not only an esophago-colostomy is created but the colon is often anastomosed to a Roux-and-Y loop. Hence, several intestinal anastomoses are created which all are at risk for anastomotic leakage. Leakage occurred in 19% of our patients and is a risk factor for mortality. Although in some patients, anastomotic leaks can be treated with a conservative management, reoperation or reinterventions are needed, as was the case in 10% of our patients. Given the complexity and rare indication for colon interposition, the Dutch guidelines for the treatment of esophageal cancer support the centralization of the procedure in just a few hospitals in the Netherlands. This study supports this view given the still high morbidity and mortality rate.[5, 20, 21]

Limitations of this study are the long study period and the changes in surgical techniques and care for the patients over time. Also, neoadjuvant treatment for esophageal cancer is now standard of care in many countries and this may impact on complications.[22] Furthermore, the study patients are heterogeneous in terms of indication for surgery (benign and malignant disease) and despite the use of an institutional database this study is retrospective. However, the prospective database gave us the opportunity to report on rather detailed outcome measures assessed by a dedicated data manager. The present series is still the largest series reported in the literature so far.

In summary, colon interposition is accompanied by a substantial morbidity and mortality but in selected patients, the colon interposition remains the only option for restoration of continuity of the upper gastrointestinal tract after esophagectomy. Attempt to minimize surgical trauma, enhanced recovery of the patient and improvement of perioperative care may improve the outcome for these patients.

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6

Does routine endoscopy or contrast swallow study after esophagectomy and gastric tube reconstruction change patient management?

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ABSTRACT

Background: Anastomotic leakage is a severe complication after esophagectomy. The objective was to investigate the diagnostic and predictive value of routine contrast swallow study and endoscopy for the detection of anastomotic dehiscence in patients after esophagectomy.

Methods: All patients who underwent contrast swallow and/or endoscopy within 7 days after esophagectomy for cancer between January 2005 and December 2009 were selected from an institutional database.

Results: Some 173 patients underwent endoscopy and 184 patients underwent a contrast swallow study. The sensitivity of endoscopy for anastomotic leakage requiring intervention is 56%, specificity 41%, positive predictive value (PPV) 8% and negative predictive value (NPV) 95%. The sensitivity of contrast swallow study for detecting leakage requiring intervention in patients without signs of leakage was 16%, specificity 75%, PPV 11% and NPV 83%.

Conclusion: In patients without clinical suspicion of leakage, there is no benefit to perform routine examinations.

INTRODUCTION

Leakage of the cervical esophagogastrostomy after esophagectomy with gastric tube reconstruction occurs in 5-25% of patients, and is associated with significant morbidity and accounts for 25-50% of postoperative deaths.[1-3] Signs and symptoms of anastomotic leakage are fever, tachycardia and manifestations at the surgical site including redness, swelling and drainage of saliva and pus. Appropriate local drainage, intravenous antibiotics and enteric tube feeding or parental nutrition can manage the majority of anastomotic leakages conservatively. Sometimes, surgical or radiological intervention may be required. In order to detect anastomotic leakage before clinical signs develop and the patients deteriorate, contrast swallow and/or endoscopy are often performed within the first week after surgery. However, it has been reported that contrast swallow studies have a low sensitivity and specificity, failing to contribute to clinical decision making. There is also a risk of aspiration leading to pulmonary complications.[4-8] Upper gastrointestinal endoscopy (GI) has the advantage of direct visualization and quantification of dehiscence, necrosis or ulcers and it may be performed in patients who are sedated and intubated. [8-11] On the other hand, there is a fear of iatrogenic injuries and worsening of the anastomotic dehiscence.

The objective of this study is to investigate the diagnostic and predictive value of routine contrast swallow study and endoscopy in the postoperative management of patients with a cervical anastomosis after esophagectomy and gastric tube reconstruction (GTR) for esophageal carcinoma. Our hypothesis was that routine diagnostic studies do not contribute to the early detection of anastomotic leakage.

METHODS

In this retrospective cohort study, all patients who underwent esophagectomy with gastric tube reconstruction and a cervical anastomosis for esophageal cancer at the Erasmus University Medical Center Rotterdam between January 2005 and December 2009 were included. Patient's demographics, treatment characteristics were retrieved from a prospective, institutional database. This database includes age, sex, medical history, operative approach, site (neck or thorax) and type of anastomosis (end-to-end or end-to-side), and details on postoperative follow-up including complications and their treatment. As part of the postoperative protocol, patients were scheduled for a contrast swallow study and endoscopy 7 days postoperatively.

Surgical technique

For tumors at the gastro-esophageal junction, a transhiatal esophagectomy was preferred. Tumors of the mid and distal esophagus were resected by a right transthoracic approach.

All operations were supervised by one of two specialized senior gastro-intestinal surgeons. A gastric tube was created by the aid of a linear stapling device, TLC 55 (Ethicon, Johnson & Johnson, Amersfoort, The Netherlands) or 60 mm GIA (Autosuture, Covidien, Zaltbommel, The Netherlands), making a 3-4 cm wide tube along the greater curvature of the stomach. During the period the study was done the neck incision is routinely closed with subcuticular stitch. Drains were not routinely placed. The anastomosis was not reinforced with an omental flap or other vascularized tissues. The cervical anastomosis was created end-to-end (ETE) or end-to-side (ETS) with a running PDS 3/0 suture (Ethicon, Johnson & Johnson, Amersfoort, The Netherlands) depending on the preference of the surgeon or as part of a previously published randomized controlled trial.[12]

Postoperative management

Until anastomotic integrity was proven by contrast swallow or endoscopy patients were fed through a nasojejunal feeding tube with the distal tip situated and fixated in the jejunum and kept nil by mouth. As part of the standardized clinical pathway, a contrast swallow and/or an endoscopy before commencing oral intake were done. This was scheduled around postoperative day 7, but in some patients it was delayed due to logistical reasons. When endoscopy and/or contrast swallow confirmed integrity of the anastomosis, or in case of a minor anastomotic dehiscence (dehiscence of less than ¼ of the circumference) without signs of sepsis, oral feeding was gradually resumed, starting with sips of water on the 7th postoperative day.

Treatment of an anastomotic leakage depended on the presence of local and/or systemic manifestations of the leakage. In all patients the cervical wound was opened for drainage. In patients with a mediastinal abscess antibiotic treatment with percutaneous drainage was performed. In case of circular necrosis of the conduit, surgical treatment such as a revision of the anastomosis or takedown under general anesthesia was indicated.

Contrast swallow

Contrast swallow studies were performed using visipaque water-soluble contrast media (Visipaque™ Iodixanol, GE Healthcare). The patient was instructed to swallow 200 ml of contrast fluid while the attending radiographer made the X-rays from three different positions (anterior-posterior, lateral and 270 degrees). The radiologist reported on the findings of the study with the attending surgeon at the day of the examination. Some patients received prophylactic antibiotic treatment when aspiration occurred, based on clinical judgment.

Upper gastrointestinal endoscopy

A trained specialist according to the hospital's protocol performed endoscopy. If requested, patients were sedated. A gastrointestinal videoscope was introduced to assess the integrity and aspect of the esophagogastric anastomosis and gastric tube by the attending consultant gastroenterologist.

Definitions of anastomotic leakage

A clinical leak was defined according to Bruce et al.[13] by 'drainage of saliva or gastrointestinal content from the surgical join between the esophagus and gastric tube. Contents may emerge either through the wound or at the wound site, or may be collected near the anastomosis with or without systemic complications. Clinical leakage was defined as presence of luminal contents through the drain or wound site causing local inflammation, e.g. fever (temperature > 38.0°C) or leukocytosis (white cell count > 10,000/liter)'. Radiological leakage was defined as extra luminal contrast on contrast swallow study not due to aspiration, as judged by the attending radiologist. For endoscopy, leakage was defined as a partial or complete dehiscence of the esophagogastric anastomosis. Local necrosis, ischemia and ulcers without a visible dehiscence defined preliminary signs, and considered as an abnormal endoscopy. The gastroenterologist and radiologist were not aware about the results of the contrast swallow or endoscopy, whichever was done first.

The contrast swallow or endoscopy was considered true positive when the test showed anastomotic dehiscence and patients developed a clinical leak (Grade I-IV according to Clavien- Dindo). When normal oral intake was started and patients did not showed signs of a clinical or endoscopic leak, the modality was considered false positive. The study modality was considered false negative if, despite normal swallow and/or endoscopy, patients developed clinical signs of leakage. It was considered true negative when patients did not develop a clinical leak. Leakage originating from the blind end of the gastric tube in patients with an end-to-side anastomosis was also considered as anastomotic leakage. An intervention was defined as all surgical and radiological interventions for anastomotic leakage (Clavien-Dindo grade I or higher) including opening the neck wound at bedside.

Comprehensive Complication Index

Each postoperative event in each patient was assessed, and graded according to the Clavien-Dindo classification. The Comprehensive Complication Index (CCI) is calculated as the sum of all complications that are weighted for their severity by patients and physicians. The final formula yields a score from 0 (no complication) to 100 (death). It summarizes the entire postoperative experience of the patient with respect to complications.

Statistical analysis

Values are shown as means and standard deviation (SD) or as medians with their inter-quartile range, as appropriate. Groups were compared using non-parametrical Mann-Whitney *U* test or Student's *T*-test, if normally distributed. For cross tabulations, Pearson's Chi Square test with continuity correction was used. All statistical analyses were performed on the statistical package SPSS 20.0 (SPSS Inc, Chicago, Illinois, USA). A p-value < 0.05 was considered statistically significant. To rule out systematic differences between groups, a logistic regression method was used to compare groups regarding the prevalence of leakage as well as other

contributors, such as gender, neoadjuvant treatment, anastomosis, surgical approach and comorbidity and radical resection.

RESULTS

Between January 1st 2005 and December 31st 2009, 308 patients underwent esophagectomy with gastric tube reconstruction and a cervical anastomosis. Some 173 patients underwent upper endoscopy, 184 patients underwent a contrast swallow and 95 patients had both examinations done. The median (range) time between the operation and diagnostic test was 7 [6-12] days. Reasons for delay beyond postoperative day 7 of the contrast swallow or endoscopy were: leakage already clinically evident, patient on the ventilator in ICU, logistic reasons and patients were too sick to undergo an endoscopy or contrast swallow. The logistic regression test performed to compare equality between patient populations in the two groups had a log likelihood of 319,417, and as shown in Table 3, no statistical differences were found between groups.

Endoscopy

Clinical signs of anastomotic leakage were present in 23 of 173 patients (13%). In 14 of 23 patients (61%), anastomotic dehiscence, ischemia of the gastric tube, ulcers and/or necrosis was confirmed by endoscopy and 9 patients (64%) required a reoperation (take down of the anastomosis (n = 1) and revision of the anastomosis (n = 5), opening neck wound (n = 3). In 9 patients a normal anastomosis was seen by endoscopy. Of the 9 patients with a normal endoscopy, 5 patients required an intervention (revision of the anastomosis (n = 1), drainage of mediastinal abscess (n = 1), opening neck wound (n = 3)) (Figure 1).

In 63 of 150 patients (42%) without a suspicion for leakage, an abnormal endoscopy was reported and 10 patients (16%) developed a clinical leak requiring an intervention (revision (n = 2) or takedown of the anastomosis (n = 3), or opening neck wound (n = 5)) (Figure 1). In 87 patients endoscopy showed a normal anastomosis but 12 patients (14%) required an intervention at a later time point for a clinical leak (stent placement (n = 2), disconnection of the anastomosis (n = 1), revision of the anastomosis (n = 1), opening neck wound (n = 8))

The sensitivity of endoscopy for detecting leakage (requiring intervention) in patients without clinical leakage is 45%, specificity 41%, positive predictive value 16% and negative predictive value 86% (Table 1.).

Contrast swallow

In 15 patients, the contrast swallow study could not be evaluated due to aspiration during the study. Therefore, these 15 patients were excluded from the analysis. In 6 of 169 patients (4%) clinical leakage was present at time of the contrast swallow study and this was confirmed

Figure 1. Flowchart of patients; routine endoscopy

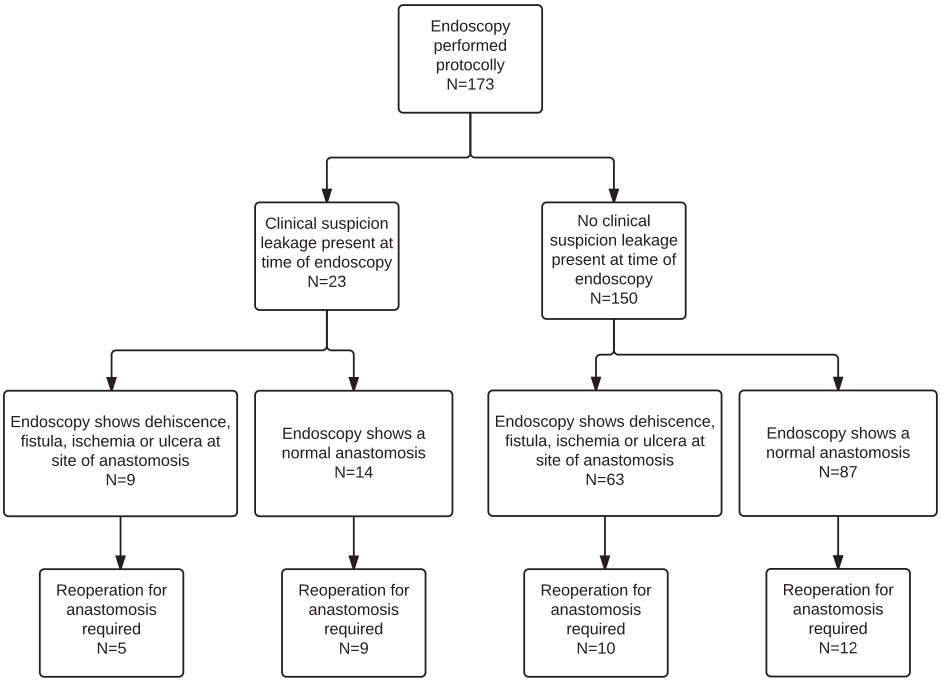

Table 1. Endoscopy

	Leakage +	**Leakage -**	
Endoscopy +	10 (7%)	53 (35%)	63 (42%)
Endoscopy-	12 (8%)	75 (50%)	87 (58%)
	22 (15%)	128 (85%)	150

with contrast swallow in 3 patients (Figure 2). Two patients required percutaneous CT-guided drainage of an abscess caused by anastomotic leakage.

In 37 of 163 patients (23%) without clinical leakage, radiological leakage was diagnosed by contrast swallow study. One of these patients required endoscopic stenting of the anastomosis. Some 127 patients (78%) had no leakage on contrast swallow study and 21 patients (17%) required an intervention (revision (n = 2) or takedown of the anastomosis (n = 2), opening neck wound (n = 17)).

The sensitivity of the contrast swallow study for detecting leakage requiring intervention in patients without signs of leakage was 16%, specificity 75%, PPV 11% and NPV 83% (Table 2).

Table 3 shows the incidence of tumor characteristics and postoperative complications divided into 'leakage' and 'no leakage' groups for endoscopy, Table 4 for contrast swallow study.

Figure 2. Flowchart of patients; routine contrast swallow study

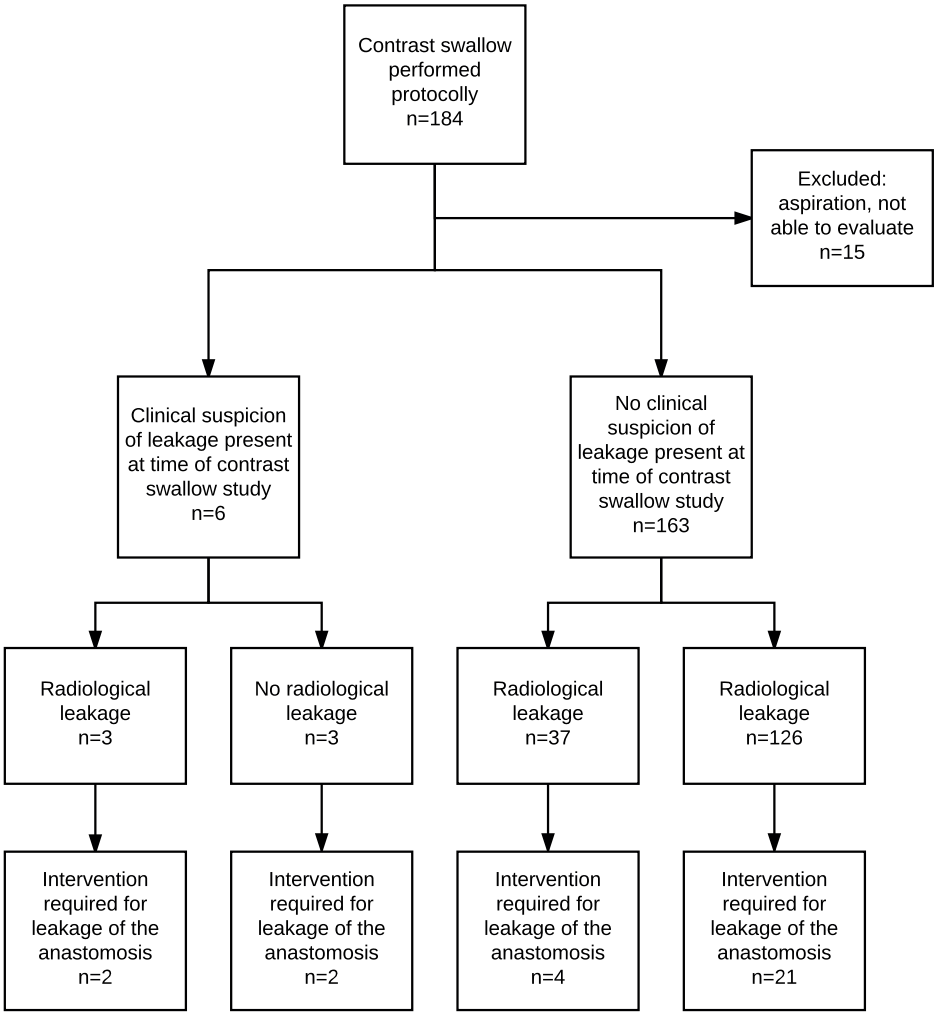

Table 2. Contrast swallow study

	Leakage +	**Leakage -**	
Contrast swallow +	4 (2%)	33 (20%)	37 (22%)
Contrast swallow-	21 (13%)	105 (64%)	132 (80%)
	25 (15%)	138 (85%)	163

Table 3. Endoscopy group; details (n = 173)

	Leakage (n=36)	No leakage (n=137)	p-value
Age (yr.) median [range]			
Sex (M:F)	29:7	104:33	0.66
Histology			0.65
- Squamous cell carcinoma	7 (19%)	32 (23%)	
- Adenocarcinoma	28 (77%)	104 (76%)	
- No malignancy after neoadjuvant treatment	1 (4%)	3 (1%)	
Tumor site			0.08
- Esophagus	33 (92%)	115 (85%)	
- Gastro-esophageal junction	0 (0%)	15 (11%)	
- Gastric cardia	3 (8%)	7 (4%)	
Tumor Stage			0.27
- 0	1 (4%)	4 (3%)	
- I	3 (9%)	11 (8%)	
- IIA	4 (11%)	35 (26%)	
- IIB	3 (9%)	10 (7%)	
- III	15 (42%)	38 (28%)	
- IVA	10 (25%)	36 (27%)	
- IVB	0 (0%)	2 (1%)	
Radical resection (pR0)	26 (72%)	104 (76%)	0.73
(Neo) adjuvant treatment	10 (27%)	43 (32%)	0.81
- Chemoradiation	3 (8%)	18 (13%)	
- Chemotherapy	7 (19%)	25 (18%)	
- None			
Comorbidity	17 (47%)	51 (38%)	0.82
- Cardiovascular	10 (27%)	25 (18%)	
- Respiratory	3 (9%)	13 (10%)	
- Diabetes Mellitus	1 (2%)	5 (4%)	
- Malignancy	3 (9%)	8 (6%)	
Surgical approach			0.46
- Transhiatal esophagectomy	20 (55%)	88 (65%)	
- Transthoracic esophagectomy	16 (45%)	49 (35%)	
Anastomosis			0.26
- End-to-end	14 (39%)	70 (53%)	
- End-to-side	22 (61%)	65 (47%)	
Complications	36 (100%)	102 (74%)	0.001
Mediastinitis	18 (50%)	17 (12%)	<0.001
Pneumonia	15 (42%)	49 (36%)	0.56
Delirium	11 (31%)	17 (12%)	0.012
Sepsis	8 (22%)	6 (4%)	0.002

Table 3. Endoscopy group; details (n = 173) (continued)

	Leakage (n=36)	No leakage (n=137)	p-value
Multiorgan failure	4 (11%)	3 (2%)	0.035
Vocal cord palsy	1 (3%)	17 (12%)	0.13
Bleeding	2 (6%)	5 (4%)	0.64
Chyle leakage	1 (3%)	7 (5%)	0.69
Respiratory insufficiency	12 (33%)	16 (12%)	0.003

CCI

All complications of surgery were graded using the Clavien-Dindo classification and the CCI was calculated for each patient.

In patients without clinical leakage, the median CCI for patients with an abnormal endoscopy was 22.6 (IQR 8.7-44.9) Patients with a normal endoscopy without clinical leakage have a median CCI of 20.9 (IQR 0-26.2) Independently, this difference was statistically significant (p = 0.004). In patients without clinical leakage, the median CCI for patients with an abnormal contrast swallow study was 20.9 (0-29.6) as compared to patients with a normal contrast swallow without clinical leakage CCI 8.7 (0-22.6) with p = 0.027.

DISCUSSION

The present study shows that patients without signs or symptoms suggestive of an anastomotic leakage do not benefit from a contrast swallow or upper endoscopy for identifying leaks that require operative or endoscopic interventions. Whilst endoscopy and contrast swallow do show abnormalities in 42 and 20% of patients, respectively, it does not lead to a change in (conservative) patient management. Hence, aggressive radiological or surgical treatment of patients with abnormal endoscopic findings or contrast swallow does not seem to be indicated. In only a few patients, interventions for anastomotic leakage are needed in due time.

On the other hand, if endoscopy or the contrast swallow study do not show any abnormalities, this does not fully exclude the development of anastomotic leakage and subsequent interventions are needed in 5 and 3% of patients respectively (false negative test). The CCI for asymptomatic patients differs significantly for patients without clinical signs of leakage. Even though this difference does not reflect in interventions, it is possible that small, subclinical leakages result in other complications; such as a mediastinitis or pneumonia. Furthermore, the CCI is known to be a very sensitive endpoint, as it takes all postoperative complications into account. Still, close surveillance and early recognition of a complication including anastomotic leaks are of utmost importance for best outcomes.

Table 4. Contrast swallow group, details (n = 184) (patients with aspiration during contrast swallow included (n = 15))

	Leakage (n=34)	No leakage (n=150)	p-value
Sex (M:F)	28:6	111:39	0.38
Histology			0.30
- Squamous cell carcinoma	2 (6%)	32 (21%)	
- Adenocarcinoma	31 (91%)	112 (51%)	
- No malignancy after neoadjuvant treatment	1 (3%)	6 (18%)	
Tumor site			0.043
- Esophagus	27 (79%)	114 (76%)	
- Gastro-esophageal junction	1 (3%)	24 (16%)	
- Gastric cardia	6 (18%)	12 (8%)	
Tumor Stage			0.12
- 0	1 (3%)	7 (5%)	
- I	4 (12%)	13 (13%)	
- IIA	1 (3%)	39 (26%)	
- IIB	5 (15%)	14 (9%)	
- III	12 (35%)	40 (27%)	
- IVA	11 (32%)	35 (23%)	
- IVB	0 (0%)	2 (1%)	
Radical resection (pR0)	22 (65%)	119 (81%)	0.097
(Neo) adjuvant treatment			0.30
- Chemoradiation	3 (9%)	28 (19%)	
- Chemotherapy	9 (26%)	29 (19%)	
- None	22 (65%)	93 (62%)	
Co morbidity			0.26
- Cardiovascular	8 (24%)	29 (19%)	
- Respiratory	1 (3%)	9 (6%)	
- Diabetes Mellitus	2 (6%)	4 (2%)	
- Malignancy	0 (0%)	10 (7%)	
Operating time (mean) SD and range			
Surgical approach			1.0
- Transhiatal esophagectomy	23 (%)	101 (%)	
- Transthoracic esophagectomy	11 (%)	49 (%)	
Anastomosis			0.87
- End-to-end	19 (%)	80 (57%)	
- End-to-side	15 (%)	69 (%)	
Complications	34 (100%)	95 (%)	<0.001
Mediastinitis	6 (18%)	5 (3%)	0.006
Pneumonia	6 (18%)	42 (28%)	0.28
Respiratory insufficiency	3 (9%)	4 (3%)	0.12

Table 4. Contrast swallow group, details (n = 184) (patients with aspiration during contrast swallow included (n = 15)) (continued)

	Leakage (n=34)	No leakage (n=150)	p-value
Delirium	3 (9%)	14 (9%)	1.0
Sepsis	1 (3%)	0 (0%)	0.19
Multiorgan failure	1 (3%)	1 (1%)	0.34
Vocal cord palsy	2 (6%)	17 (11%)	0.38
Bleeding	1 (3%)	3 (2%)	1.0
Chyle leakage	2 (6%)	5 (3%)	0.62

A contrast swallow is the most common routine examination after esophageal surgery. It has several benefits including the low costs and being a relatively safe first-line investigation with a high sensitivity and specificity when interpreted by an experienced radiologist.[14] However, the disadvantages of aqueous contrast are that it has a low radiographic density and a low mucosal adherence, thus limiting the ability to detect leaks, particularly in case of subtle ones. Boone et al. presented a low sensitivity and positive predictive value in their series of 207 patients, and also reported that 53% of patients already showed clinical signs of leakage. Doerfer et al. produced comparable results and no longer routinely perform a contrast swallow, and prefer a CT with contrast. Tonouchi also reviewed a large series (n=331) and found a low sensitivity of routine contrast swallow studies.[5-7] Indeed, in the present study contrast swallow was reported as normal in 3 patients with clinical suspicion of anastomotic leakage but CT-guided drainage of a mediastinal abscess was needed in 2 patients at a later point in time. In these patients CT scanning with oral contrast may be superior to a contrast swallow as it allows detection of peri-anastomotic and mediastinal fluid collections that may need surgical or radiological drainage. Endoscopy is likely to be more useful to assess the severity of anastomotic dehiscence in symptomatic patients. In may help selecting patients that need surgical revision of the anastomosis including resection of an ischemic segment of the gastric tube. These findings are also supported by Oezcelik[10], Maïsh[11], Schaible[8] and Page et al.[9], who presented their retrospective data and concluded that endoscopy is a safe and accurate method to detect early signs of leakage. However, 2 of 8 patients with a normal endoscopy developed a clinical leak that needed a surgical intervention and radiological drainage.

The present study supports the findings of a recent prospective trial that compared the accuracy of contrast swallow, CT with oral contrast and endoscopy for the identification of anastomotic leaks following esophagogastric surgery.[15] The authors concluded that routine tests of the anastomotic integrity are unnecessary and, when clinical suspicion is high for an anastomotic leak, CT scan is likely the first modality to perform. Our data supports also another study that has shown that flexible upper gastrointestinal endoscopy is more specific in comparison with a contrast swallow study. While it did not improve the identification of

clinical anastomotic leakage, it was beneficial to detect gastric necrosis or ulcers and guide management of these patients.

There are several limitations of the present study. Being of retrospective nature, clinical management of anastomotic leaks may have changed over time. Use of self-expandable stents may have led to a decrease of surgical and radiological interventions for anastomotic dehiscence. However, within the time period of the study, the surgical experience has not changed and also the care pathway has remained the same over time. In order to determine the accuracy of diagnostic tests for the assessment of anastomotic leakage, it is of great importance to define the study endpoint in a consistent and unambiguous matter. In the present study, the definition of Bruce et al.[13] was used. However, given the retrospective design of the study, misclassification cannot be ruled out. The Erasmus Medical Center is a high volume specialized center for upper GI-surgery and radiologists and gastroenterologists are well trained in the recognition and treatment of postoperative complications. Hence, our data are likely to be externally valid for other specialized centers.

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PART 2

COMPREHENSIVE COMPLICATION INDEX

7

The Comprehensive Complication Index (CCI): A novel and more sensitive endpoint for assessing outcome and reducing sample size in randomized controlled trials

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LIST OF ABBREVIATIONS

CCI	Comprehensive Complication Index
RCT	randomized controlled trial
LOS	length of hospital stay
ICU	intensive care unit
ETE	end-to-end
ETS	end-to-side
HP	Hartmann's Procedure
PA	primary anastomosis
SDC	Supplemental Digital Content
SD	standard deviation
CI	confidence interval
IQR	interquartile range

MINI-ABSTRACT

This study demonstrates superiority of the new Comprehensive Complication Index (CCI) over traditional endpoints in detecting between-group differences in randomized control trials. The CCI may therefore serve as preferred endpoint in future RCTs, and may help in designing RCTs with smaller sample sizes.

ABSTRACT

Objective: To test whether the newly developed Comprehensive Complication Index (CCI) is more sensitive than traditional endpoints for detecting between-group differences in randomized controlled trials (RCTs).

Background: A major challenge in RCTs is the choice of optimal endpoints to detect treatment effects. Mortality is no longer a sufficient marker in studies, and morbidity is often poorly defined. The CCI, integrating all complications including their severity in a linear scale ranging from 0 (no complication) to 100 (death), is a new tool, which may be more sensitive than other traditional endpoints to detect treatment effects on postoperative morbidity.

Methods: The CCI was tested in three published RCTs from European centers evaluating pancreas, esophageal or colon resections. To compare the sensitivity of the CCI with traditional morbidity endpoints, e.g. presence of any (yes/no) or only the most severe complications, all postoperative events were assessed, and the CCI calculated. Treatment effects and sample size calculations were compared using the CCI and traditional endpoints.

Results: While RCTs failed to show between-group differences using any or most severe complications, the CCI revealed significant differences between treatment groups in two RCTs; after pancreas ($p = 0.009$) and esophageal surgery ($p = 0.014$). The CCI in the RCT on colon resections confirmed the absence of between-group differences ($p = 0.39$). The required sample sizes in trials are up to nine-times lower for the CCI than for traditional morbidity endpoints.

Conclusions: This study demonstrates superiority of the CCI to traditional endpoints. The CCI may serve as an appealing endpoint for future RCTs and may reduce the sample size.

INTRODUCTION

A major challenge in designing randomized controlled trials (RCTs) is the choice for objective, concise and clinically relevant endpoints. Mortality is no longer an acceptable primary endpoint in surgical studies given the sharp decline in mortality for most procedures in the past decades. Morbidity is often poorly defined, which has led to inconsistent reporting and confusion in the literature.[1-7] Furthermore, most authors have reported only the most severe complications or only events judged to be relevant, but ignored complications of lesser magnitude as well as the total number of complications.[5] To address this issue, the Comprehensive Complication Index (CCI) was recently introduced. It integrates all postoperative complications with their respective severities, on a scale ranging from 0 (no burden from complications) to 100 (death).[8]

The CCI, summarizing the entire postoperative experience of the patient with respect to complications, is based on the widely established Clavien-Dindo classification.[3, 4, 8] Validations from four different perspectives showed that the CCI is a valid endpoint for postoperative overall morbidity. While the CCI is an attractive novel tool, which may serve as a primary or secondary endpoint in many types of studies, the external validity has not been tested in RCTs. Therefore, the aim of this study was to externally evaluate whether the CCI is more sensitive than traditional primary endpoints in detecting between-group differences.

METHODS

We externally validated the CCI[8] on recently published RCTs[9-11] that reported specific complications after different surgical procedures. The first step was to identify and contact a number of centers, which have conducted RCTs investigating specific and non-specific morbidity endpoints. We considered RCTs regardless of their conclusions in the original analysis, and focused on different types and complexity of general surgical procedures, different diseases, as well as countries. All RCTs with a proper study design according to the CONSORT guidelines were identified by a systematic literature search in peer-reviewed high impact journals in the last three years (2011-2013)[12-15] (Figure 2: flow diagram). After contacting several centers in general, cardiac and plastic surgery, we were granted full access to primary data and each patient record of three European trials[9-11] addressing different surgical interventions and diseases in compliance with our study design. The first trial focused on the rate of pancreatic fistulas after pancreatico-duodenectomy.[11] The second trial was evaluating the rate of anastomotic strictures after two different types of anastomosis following esophagectomy[9] and finally, the third trial focused on the rate of overall complications after colon resection for perforated diverticulitis.[10]

Primary data[9-11] were re-analyzed including calculation of the CCI in each patient. The CCI of the comparative groups in each trial was tested along traditional reported morbidity endpoints in the literature including the presence of any complication (yes/no) as well as the most severe complications (≥ grade IIIb according to the Clavien-Dindo classification[3]). The 1st author (KS) visited each centre to secure consistent and exhaustive re-evaluation of the data.

The multicenter RCT originating from France, published in 2011, was designed to test whether an external pancreatic duct stent might reduce the rate of pancreatic fistulas after pancreatico-duodenectomy.[11] A sample size calculation postulated a 10% reduction in the incidence of pancreatic fistulas in patients with pancreatic stents compared to those without drainage.[11] Assuming a power of 80% and an α-error of 0.05, the investigators enrolled 158 patients comparing 77 patients with, vs. 81 without insertion of an external stent drainage (Figure 1).[11] The results indicated that external stent drainage of the pancreatic duct significantly reduces the risk of pancreatic fistulas, as well as overall morbidity rates after pancreatico-duodenectomy.[11]

The second RCT,[9] performed in the Netherlands from 2005–2007, compared an end-to-end (ETE) with end-to-side (ETS) esophago-gastrostomy after esophageal cancer resection (Figure 1).[9] Their primary endpoint was the development of anastomotic stricture and need for dilatation within one year after surgery. They, therefore, performed a non-inferiority trial with one-sided testing assuming a 50% reduction in the rate of stenosis in patients with ETS-comparing to ETE-anastomosis. Assuming a power of 80% and an α-error of 0.05, 64 patients per group were required. The authors observed a lower incidence of anastomotic stricture in patients with ETS-anastomosis. They also concluded that ETS-anastomosis was associated with significantly more anastomotic leaks than ETE-anastomosis.[9] The authors, however, did not investigate the overall morbidity expressed as the presence of any complication, nor the most severe complication (≥ grade IIIb).

Finally, the third multicenter RCT focused on patients with perforated left-sided diverticulitis enrolled from four surgical centers in Switzerland (incl. the Department of Surgery at the University Hospital Zurich).[10] The study was designed to test whether the conventional Hartmann's procedure (HP: colonic resection with closure of the rectal stump and an end-colostomy) is comparable to a primary anastomosis (PA) with diverting ileostomy (Figure 1) using the rate of overall complications, regardless of the severity, as the main endpoint. Both strategies require a second operation, i.e. stoma reversal and in HP a re-establishment of the continuity of the colon. For the sample size calculation 25% reduction in the rate of overall complications was assumed with a power of 80% and an α-error of 0.05. This yielded an estimated group size of 68 patients. The planned interim analysis, enrolling 62 patients, lead to a discontinuation of the trial, as recommended by the data-monitoring board, due to significant differences in adequately powered relevant secondary endpoints. Thirty patients had been randomized for the HP and 32 for a primary anastomosis. While the overall complication rates for both resection and stoma reversal operations were comparable, severe complications (grades ≥ IIIb) were significantly reduced after reversal operations in the PA group.[10]

Figure 1. The three European randomized controlled trials[9-11]

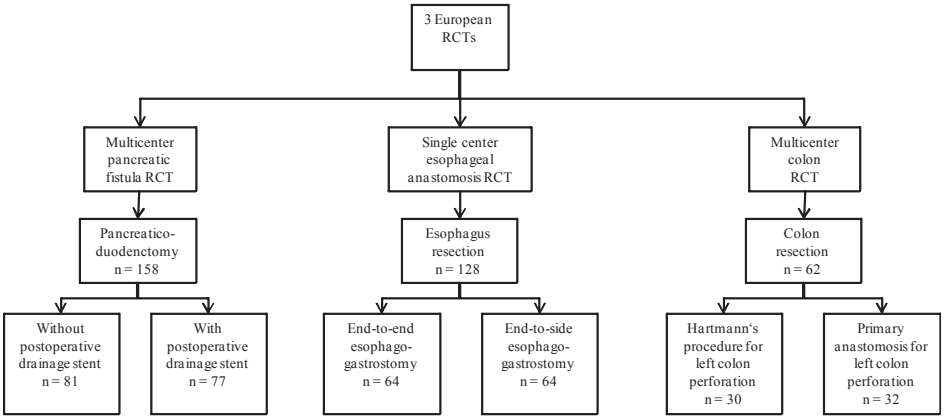
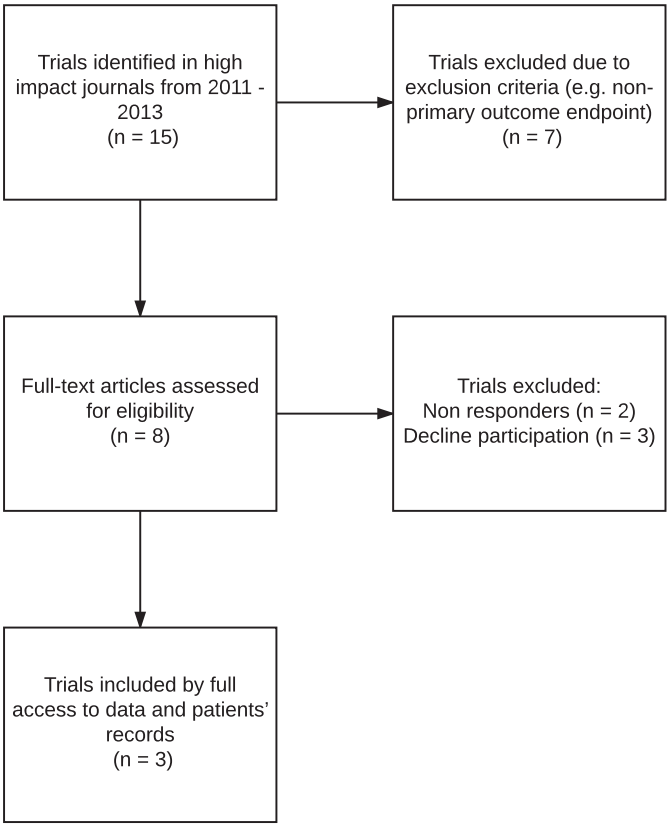


Figure 2. Flow diagram for the selection of trials for analysis.



From the 15 RCTs identified in high impact journals (New England Journal of Medicine, Lancet, JAMA, Annals of Surgery, British Journal of Surgery and British Journal of Medicine), seven were excluded because complications were not a primary endpoint. After assessment five trials could not be included because the authors did not respond or declined to participate.

Data collection & primary endpoint

We used the existing databases of these three RCTs, and calculated the CCI for each patient.[9-11] Each postoperative event in each patient was assessed on site, and graded according to the Clavien-Dindo classification, which is based on the treatment used to correct the postoperative complication.[3] For the development of the CCI, we used the established Clavien-Dindo classification system[3] for complications, adopting methods from operation-risk-index analysis in marketing research and developed a formula that considers any combination of complications.[16-18] The CCI was finally calculated as the sum of all complications that are weighted for their severity by patients and physicians.[8,19] The final formula yields a score from 0 (no complication) to 100 (death).[8] The CCI can easily be calculated online by free access at *www.assessurgery.com*.

Additionally, for each patient we assessed traditional morbidity endpoints: the total number of complications, the presence of any (yes/no), as well as the most severe (≥ grade IIIb[3]) complications. In the esophageal stricture trial we also calculated the CCI at discharge and a long-term CCI after one year following initial surgery in all patients. The longitudinal assessment of the overall morbidity using the CCI is novel allowing to present the cumulative effects of complication over time.

In-hospital-costs, the length of hospital (LOS) and ICU stays were also extracted from the respective original database. LOS and ICU stay were available in all three RCTs, whereas the in-hospital costs were only available in the multicenter colon RCT.

We additionally performed a sample size calculation to properly evaluate the sensitivity of the CCI as primary endpoint in trials. We assumed a difference of 10 points for the CCI, a relative risk reduction of 40% for the specific and traditional morbidity endpoints, a power of 80% and an α-error of 0.05. The difference of 10 points on the CCI scale is chosen because it reflects one grade difference in the established Clavien-Dindo classification. For the colon trial, we were not able to calculate a sample size because of premature termination of the initial trial, a two-step procedure and therefore unequal group sizes (n = 15 vs. n = 22) in the second surgery.

Eligibility criteria (SDC 2) and the paragraph about the statistical analysis (SDC 3) are reported in detail in the supplemental material online.[20-22] For all results, we reported point estimates, 95% confidence intervals (CI) and p-values (≤ 0.05 considered significant). We performed statistical analyses using STATA (version 11, Stata Corp., College Station, Texas).

RESULTS

As summarized in Figure 1, we re-analyzed 348 patients for which detailed characteristics were reported previously.[9-11]

Conventional morbidity endpoints versus CCI

In the pancreatic fistula trial, the overall burden of the postoperative morbidity represented by the median CCI after pancreatico-duodenectomy was significantly lower in patients with an external pancreatic stent, than in those without any drainage (0 (IQR 0-26.2) vs. 20.9 (IQR 0-29.6), p = 0.009) (Table 1). In contrast, there was no between-group difference considering the 'most severe complication' in patients with the external stent compared to those ones without stent (13% vs. 11%, 95% CI: 0.5 – 3.1, p = 0.72). The authors of this trial published a significant between-group difference in the rate of pancreatic fistulas (42% without stent vs. 26% with stent, p = 0.035).[11] These findings support the higher sensitivity of the CCI because the between-group difference for the CCI presented lower p-values (p = 0.009) as indirect comparison of effect sizes, than the differences for the specific complication 'pancreatic fistula' (p = 0.035), as well as for the 'most severe complication' (p = 0.72) in the same patient population.[20,21] The p-values for the CCI (p = 0.009) compared to those ones for the presence of any complications (p = 0.008) were similar in the same patient population (Table 1).

Table 1. Effects of stent vs. no stent on postsurgical morbidity using different measurements in patients with pancreatic fistula following pancreaticoduodenectomy[11]

	without stent n = 81	**with stent n = 77**	**unadjusted difference (95% CI, p-value)**
CCI	20.9 (0 – 29.6)	0 (0- 26.2)	-12.2 (-4.5 to-16.7, p=0.009)
CCI of the pancreatic fistula	0 (0 – 20.9)	0 (0 – 8.7)	-3.2 (-6.8 – 0.5, p=0.091)
Number of complications	1 (0 – 2)	0 (0 – 1)	-0.5 (-0.9 to-0.1, p=0.021)

	without stent n = 81	**with stent n = 77**	**unadjusted odds ratio (95% CI, p-value)**
Presence of any complication (%)	50 (61.7%)	32 (41.5%)	0.4 (0.2 – 0.8, p=0.008)
Severe complications ≥ IIIb* (%)	9 (11.1%)	10 (13.0%)	1.2 (0.5 – 3.1, p=0.72)
Pancreatic fistula (%)	34 (42%)	20 (26%)	0.5 (0.2 – 0.95, p=0.035)

CI = confidence interval, CCI = Comprehensive Complication Index; all results reported as median and interquartile range; * grading of complications according to the Clavien-Dindo classification system[3]

In the *esophageal anastomosis trial,* patients with an ETS anastomosis disclosed significantly higher CCI at discharge, than patients with an ETE-anastomosis (22.6 (IQR 0-41.2) vs. 10.5 (IQR 0-24.4), p = 0.014). In contrast, this trial failed to show any statistically significant between-group differences using traditional endpoints such as the presence of any or the most severe complications (≥ grade IIIb) (Table 2).

The original analysis of this trial reported a significantly higher rate of stricture in the anastomosis one year following the initial surgery (40% in ETE vs. 18% in ETS, p < 0.01).[9] The CCI directly after discharge was significantly different between both groups, mostly related to a significantly higher rate of anastomotic leaks in the ETS-anastomosis group (odds ratio 3.4

(95% CI 1.4 – 8.2, p = 0.04). After calculating the CCI at *one-year follow-up* (including stricture), however, the median CCI was similar between patients with ETE- and ETS-anastomosis (26.2 (20.9–40.6) vs. 26.2 (8.7-38.2), p = 0.75). This new finding suggests that there is no long-term difference (after one year) in the morbidity between both types of anastomoses. The CCI allows reporting of complications that occur during different time periods. After one-year follow-up the CCI (p = 0.75) balances the initially higher rate of anastomotic leaks in patients with ETS-anastomosis (p = 0.04) with the increasing rate of anastomotic strictures in patients with ETE-anastomosis (Table 2). Thus, although initially one patient group appears to have an advantage, long-term observations reverse this observation by considering late complications experienced by the other group of patients.

Table 2. Effects of end-to-end vs. end-to-side anastomosis on postsurgical morbidity using different measurements in patients with anastomotic stricture following esophagectomy[9]

	ETE n = 64	**ETS n = 64**	**unadjusted difference (95% CI, p-value)**
CCI at discharge	10.5 (0 – 24.4)	22.6 (0 – 41.2)	11.6 (2.4 – 20.8, p=0.014)
CCI after one year	26.2 (20.9 – 40.6)	26.2 (8.7 – 38.2)	-1.4 (-10.3 – 7.4, p=0.75)
Number of complications	1 (0 – 2)	1 (0 – 2.5)	0.5 (-0.1 – 1.1, p=0.08)

	ETE n = 64	**ETS n = 64**	**unadjusted odds ratio (95% CI, p-value)**
Presence of any complication (%)	42 (65.6%)	47 (73.4%)	1.5 (0.7 – 3.1, p=0.34)
Severe complications ≥ IIIb* (%)	11 (17.2%)	20 (31.3%)	2.2 (0.95 – 5.1, p=0.07)
Anastomotic stricture (%) after one year	20 (40%)	10 (18%)	0.3 (0.1 – 0.7, p=0.004)
Anastomotic leakage (%)	14 (22%)	26 (41%)	3.4 (1.4 – 8.2, p=0.04)

ETE = end-to-end esophagogastrostomy; ETS = end-to-side esophagogastrostomy; CI = confidence interval; CCI = Comprehensive Complication Index; all results were presented in median and interquartile range; * grading of complications according to the Clavien-Dindo classification system[3]

In the *multicenter colon trial*, there was no significant difference in the overall CCI, neither for the overall procedures nor in the respective steps (1st and 2nd operation). Nevertheless, the between-group difference of the CCI demonstrated a lower p-value than the differences in traditional morbidity endpoints that emphasize the higher sensitivity of the CCI over the traditional endpoints (Table 3).[20,21] This trial showed comparable between-group complication rates for both surgical steps. Comparing the outcome of the 1st operation between the groups, there was also no significant difference in the rate of severe complications (44% vs. 37%, p = 0.57; Table 3).

Table 3. Effects of the Hartmann's procedure vs. primary anastomosis on postsurgical morbidity using different measurements in patients with perforated diverticulitis[10]

	Hartmann's Procedure n = 30	**Primary Anastomosis n = 32**	**unadjusted difference (95% CI, p-value)**
CCI for both surgeries	40.3 ± 32.6	33.5 ± 28.3	6.8 (-8.7 – 22.3, p=0.39)
CCI after 1st surgery	37.3 ± 33.1	32.2 ± 28.4	5.1 (-10.5 – 20.7, p=0.52)
CCI after 2nd surgery	n = 15 12.4 ± 16.7	n = 22 5.2 ± 9.7	7.2(-1.7 – 16.0, p=0.11)

1st surgery	**Hartmann's Procedure n = 30**	**Primary Anastomosis n = 32**	**unadjusted odds ratio (95% CI, p-value)**
Any Morbidity (%)	24 (80%)	27 (84.4%)	0.74 (0.20 – 2.74; p=0.65)
Severe complications ≥ IIIb* (%)	11 (36.7%)	14 (43.8%)	0.74 (0.27 – 2.1, p=0.57)

2nd surgery	**Hartmann's Procedure n = 15**	**Primary Anastomosis n = 22**	**unadjusted odds ratio (95% CI, p-value)**
Any Morbidity (%)	6 (40%)	6 (27.3%)	1.78 (0.44 – 7.18, p=0.42)
Severe complications ≥IIIb* (%)	3 (20%)	0%	-

CCI = Comprehensive Complication Index; CI = confidence interval; all results reported as mean ± standard deviation. No statistical analysis was performed if ≤ 5 events in a group; * grading of complications according to the Clavien-Dindo classification system.[3]

The CCI and the sample size

For two trials a sample size calculation was performed for their specific endpoint, the CCI and traditional morbidity endpoints (any or most severe complications). The sample sizes are clearly lower for the CCI compared to the original and traditional endpoints as shown in Table 4. This illustrates the putative benefits of the CCI compared to complication endpoints such as any and more severe in minimizing the need for large sample sizes in the future. For example, in the *pancreatic fistula trial*, the required sample size would decrease from 695 patients/group to 76 patients per group when using the primary endpoint CCI vs. 'most severe complication'. Similar results were seen in the *esophageal anastomosis trial* (Table 4).

CCI associated to LOS, ICU stay, and in-hospital costs

The CCI was significantly associated to LOS and ICU stay in all three trials. We also evaluated the costs of complications in the colon trial. An increase in one point on the CCI scale created additional costs of CHF 883 (95% CI: 222 – 1543, p = 0.010) (about US $ 980, 95% CI: 247-1714). In other words, an increase of the CCI of 10 points on the scale increases the in-hospital costs to additional US $ 9800.

Table 4. Sample size calculation for surgical RCTs using different measurements for postsurgical morbidity

	Assumptions	Sample size
Pancreatic fistula trial[11]		
Pancreatic fistula[11]	40% relative risk reduction	149 patients/group
Presence of any complication (yes/no)	40% relative risk reduction	75 patients/group
Most severe complication ≥ IIIb*	40% relative risk reduction	695 patients/group
CCI	Δ 10 points, SD 22	76 patients/group
Esophageal anastomosis trial[9]		
Anastomotic stricture[9]	40% relative risk reduction	132 patients/group
Presence of any complication (yes/no)	40% relative risk reduction	76 patients/group
Most severe complication ≥ IIIb*	40% relative risk reduction	220 patients/group
CCI	Δ 10 points, SD 20	63 patients/group

Beta = 0.8; alpha = 0.05; Δ = difference in 10 points in the CCI scale; SD = standard deviation; RCT: randomized controlled trial; CCI = Comprehensive Complication Index; * grading of complications according to the Clavien-Dindo classification system.[3] Sample sizes were shown without considering loss of follow up.

DISCUSSION

This study demonstrates the superiority of the CCI over traditionally reported morbidity endpoints 'most severe complication' and specific complications by detecting between-group differences in three external trial populations. Another finding is the easy and new applicability to longitudinal assessment of complications over time, as illustrated in the analysis of the one-year CCI follow up in the esophageal anastomosis trial. Finally, the CCI is associated to LOS, length of ICU stay and in-hospital costs, which add clinical value to this morbidity index. The most relevant finding for the CCI is that the required sample sizes in trials are up to nine times lower for the CCI than for other endpoints.

Reporting outcomes of surgical or other invasive procedures using morbidity, as the primary endpoint, has been associated with serious limitations due to various definitions and different interpretation of postoperative events.[1, 2, 4, 5] Assessing the overall morbidity by the presence of any complication causes the problem of ignoring either the number of different complications occurring in a patient after surgery or, more importantly, the severity of complications. Recording only the most severe complication does not give weight to either any complication of lesser importance or the total number of complications, even though they affect the patient. As one of the first attempts in outcome standardization, in 1992, a classification system was proposed to grade the severity of complications according to the degree of treatment needed to correct the complications.[23] In 2004, this original classification was revised to generate the Clavien-Dindo classification based on the same principles, but eliminating criteria such as the length of stay and newly grading complications with readmis-

sion to ICU units due to organ dysfunction.[3, 6] The Clavien-Dindo classification gained wide acceptance, and became increasingly used in a variety of studies and registries.[24-28] However, with this system, each complication is graded separately. For ease of reporting, usually only the most severe complication was included, which does not represent the 'true' overall morbidity burden of surgical procedures.[5] The recently developed CCI is based on a formula used in the economy, which incorporates multiple factors influencing the globalization of a corporation decision. With this formula all complications, weighted by severity, are integrated in a linear scale. It facilitates reporting not only of the in-hospital morbidity, but also at various postoperative follow up, e.g. the 90-day morbidity or other time-span. Furthermore, the CCI is a primary outcome measure, which is calculated separately for each patient regardless of the population studied. Individual grade of complications or the CCI represent endpoints, and thus a risk-adjustment is necessary for proper interpretation in specific groups of patients. For example, a higher median CCI in a hospital compared to others might not mean better quality, particularly if the population of this specific center is at higher risk for surgery with high incidence of co-morbidities.

If future trials aim at focusing on the 'overall morbidity' and not on a specific complication related to the procedure under investigation, our current data strongly support the use of the CCI as a primary endpoint. It appears that the required sample size for superiority trials is impressively lower for the CCI than traditional endpoints, particularly the 'most severe complications' endpoint. Surgical trials often require large sample sizes to detect a between-group difference, which are only feasible in large and costly multicentre endeavour. Switching to the CCI may result in a dramatic reduction of the required sample size, so the feasibility of a trial increases, whereas costs decrease. In addition, the number of negative trials associated with a type II error may be reduced. It is obvious that there is a substantial number of false negative results in the surgical trial literature that are solely the result of insensitive endpoints.[29]

The strength of the current study is that the CCI was externally tested and was apparently more responsive than existing outcome endpoints. It may, therefore, serve as a standardized and easily applicable primary endpoint in surgical trials and other medical specialties. Furthermore, the CCI was performed on three different European patient populations enrolled for different surgical procedures and diseases supporting its broad use. Further strength in this report is the one-year CCI as a longitudinal measure of the overall morbidity over a certain time. The three trials all enrolled patients by randomization to control for confounding factors and bias.

There are also some limitations. Even though the CCI was externally tested on a broad spectrum of patients undergoing a variety of major abdominal surgical procedures, it might be still important to test the CCI in other medical fields such as interventional radiology, urology and

cardiology. A further limitation might be that the three trials were not powered for the CCI as primary endpoint. Nevertheless, this current study already showed in rather small patient populations significant between-group differences in the CCI whereas the differences in the frequencies of any and/or most severe complications were similar.

In conclusion, the CCI offers a novel sensitive endpoint for clinical trials that can be readily calculated (available at *www.assessurgery.com*). The CCI may also allow in future better information of patients, standardized reporting in outcome research including readily available assessment of morbidity at various time points, and increased comparability of quality of surgery across centers worldwide. Perhaps, one of the most attractive aspects of the CCI is the possibility to conduct conclusive trials with smaller sample sizes when focusing on the 'overall morbidity' as surgical outcome.

SUPPLEMENTAL DIGITAL CONTENT 1: ELIGIBILITY CRITERIA

Eligibility criteria were described in the published RCTs[9-11]. We did not exclude any patient of the existing databases. The trials were all approved by the local IRB and internationally registered at clinicaltrials.gov (NCT01068886, NCT01233713) and the Dutch Trial Registry (OND1317772).

SUPPLEMENTAL DIGITAL CONTENT 2: SAMPLE SIZE & STATISTICAL ANALYSIS

The sample size calculation in each trial was described in detail in the original articles.[9-11] We expressed the distribution of variables using means and standard deviation (SD) for normally distributed data, and medians and interquartile ranges for non-normally distributed data. We tested the data for normality with the Kolmogorow-Smirnov test and performed quantile-quantile plots of dependent variables. We compared the CCI and the total number of complications between the comparative groups in each RCTs using simple linear regression (without adjusting for confounders). With the same statistical method, we compared the in-hospital costs between the patient groups of the multicentre colon trial. Due to the randomization in all three trials, there was no imbalance in variables, so that a multivariable linear regression adjusting for potential confounders was deemed unnecessary. We performed univariate logistic regression analyses for conventional binary morbidity endpoints such as 'any complication' (yes/no) or 'most severe complication' (complications ≥ Clavien-Dindo grade IIIb). Testing the sensitivity by comparing p-values of the between-group differences allows an indirect comparisons of effect sizes among various defined endpoints (continuous vs. categorical) in the same patient population.[16, 17.] Comparing the effects of a treatment on different endpoints by p-values is only possible because the size of the population does not vary.[16, 17.] Linear regression was finally used to test the association of CCI to in-hospital costs, length of hospital (LOS) and ICU stay. For all results, we reported point estimates, 95% confidence intervals (CI) and p-values (≤ 0.05 considered significant). We performed the statistical analyses using the statistical program STATA (version 11, Stata Corp., College Station, Texas).

SUPPLEMENTAL DIGITAL CONTENT 3: CCI ASSOCIATED TO LOS, ICU STAY, AND IN-HOSPITAL COSTS

Recent studies suggest that the cost of complications may far exceed the costs of the original operation.[18] Hence, economic aspects of the procedure in combination with potential complications may be a decisive element in patient selection. In the multicenter pancreatic fistula

trial the CCI strongly associated with the LOS (unadjusted difference 0.26; 95% CI 0.18 – 0.35, $p < 0.001$). The CCI in the anastomosis study after esophagectomy is significantly associated with the LOS (0.47; 95% CI 0.27 – 0.67, $p < 0.001$), and with the length of ICU stay (0.19; 95% CI 0.14 – 0.23, $p < 0.001$). Similar results were observed for the association between the CCI and LOS (0.14; 95% CI 0.01 – 0.27, $p = 0.036$) and the length of ICU stay (0.07; 95% CI 0.02 – 0.11, $p = 0.005$) in the multicenter colon trial. Interestingly, this trial also shows a negative association between the CCI and the overall survival (-0.40, 95% CI:-0.57 to-0.22, $p < 0.001$). Finally, we evaluated the costs of the complications in the colon trial by normalizing them to the CCI. We found that an increase in one point on the CCI scale created additional costs of CHF 883 (95% CI: 222 – 1543, $p = 0.010$) (about US $ 980, 95% CI: 247-1714). In other words, an increase of the CCI of 10 points on the scale increases the in-hospital costs to additional US $ 9800.

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8

Using the Comprehensive Complication Index to assess the impact of neoadjuvant chemo radiotherapy on complication severity after esophagectomy for cancer

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ABSTRACT

Background: Neoadjuvant chemo radiotherapy (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. The aim of this study was to further evaluate the severity of complications in patients treated with nCRT followed by esophagectomy versus in patients who underwent esophagectomy alone using the Comprehensive Complication Index (CCI).

Study-design: All patients included in the CROSS trial, a randomized clinical trial on the value of nCRT followed by esophagectomy, were included. Complications were assessed and graded using the Clavien-Dindo classification. CCI was derived from these scores, using the CCI calculator available online (*www.assessurgery.com*). 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 ($p = 0.58$). 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.

Conclusion: Neoadjuvant chemo radiotherapy 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 is an esophagectomy with gastric tube reconstruction. Meta-analyses of randomized controlled trials comparing neoadjuvant chemo radiotherapy plus surgery to surgery alone[2-9] showed that multimodality treatment improves overall survival, but side-effects (e.g. radiofibrosis, 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 chemo radiotherapy (CROSS-trial)[8] also showed a survival benefit. Importantly, there was no difference in the frequency of complications and postoperative mortality between the patients who were treated with neoadjuvant chemo radiotherapy followed by surgery and the patients who underwent surgery alone.

In the past decades, not only the frequency but also the severity of postoperative complications has become an important quality measure in surgical studies. Also, patients' reported grading of complications gives 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 (CCI).[20, 23] CCI summarizes the frequency, severity and patient's 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] Therefore, it accounts for the whole burden of all complications. A recent study[20] showed that CCI is a sensitive method that is superior to traditional endpoints, because it summarizes the whole burden of postoperative complications to the patient with respect to complications. Whereas traditional endpoints showed no significant differences for incidence of postoperative complications within the CROSS trial, the current study was designed to evaluate the overall effect of neoadjuvant chemo radiotherapy on the severity of postoperative complications, and the overall burden in patients of the CROSS trial. Therefore, the CCI was compared between patients with esophageal or esophagogastric junction cancer who underwent chemo radiotherapy plus surgery versus patients who underwent surgery alone.

PATIENTS AND METHODS

Patients with esophageal cancer or cancer of the esophagogastric junction ($cT_{1-4a}N_{0-3}M_0$) 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 is a multicenter randomized controlled trial that compared overall survival for patients who were treated with neoadjuvant

chemo radiotherapy followed by esophagectomy and the 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.[26] was used: 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 hospital stay were assessed.

CCI

The CCI is a complication index introduced by Slankamenac et al.[23] in 2013 and is based on the Clavien-Dindo classification[22] (Table 4). In the development of the CCI, data on common postoperative complications were gathered and rated by both patients and physicians. By this method, each complication is validated and given a fixed number and also includes patient's perspective about the severity. After this, a score is calculated for each grade in the Clavien-Dindo classification. To calculate the CCI, all complications that a patient develops after surgery are summarized and computed through the operation risk index approach (commonly used in economics). This can be done easily and free of charges at 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 CCI. Based on results in earlier studies of patients who underwent esophageal cancer surgery in which specific complications have shown an increase in incidence, six subgroups were formed in this study. For example, some studies show influence of neoadjuvant treatment on pulmonary complications, due to the radiation field. In subgroup 2, patients with pulmonary complications are compared. Only patients with the specific complication were used to calculate the specific complication CCI.

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 CCI 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 (≥IIIb according to the Clavien-Dindo classification) were assessed.

Treatment

As previously described[24], patients randomized to neoadjuvant chemo radiotherapy underwent five weekly cycles of chemo radiotherapy (carboplatin/paclitaxel with 41.1 Gy concurrent radiotherapy) followed by surgery, preferably within 4-6 weeks of completion. Patients randomized to the surgery alone arm underwent esophagectomy as soon as possible.

Statistical analysis

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 case of a not-normally distributed variable, with the median and interquartile range. Normal distribution was calculated using the Kolmogorov-Smirnov test. Groups were compared using the non-parametric Mann-Whitney-*U* test. For cross tabulations, Pearson's chi-squared test with continuity correction was used. All statistical analyses were performed on the statistical package SPSS 22.0 (SPSS Inc., Chicago, Illinois, USA). A p-value < 0.05 two-sided was considered statistically significant.

RESULTS

Of the 368 patients randomized in the CROSS trial[8], 322 patients were included in the present study. An overview of inclusion and exclusion of patients in the present study is shown in Figure 1.

Patient's characteristics including age, sex, comorbidity and surgical approach were similar between both groups (Table 1). More R0 resections were performed in patients who received nCRT before esophagectomy (p < 0.001). In patients who were analyzed in the current study (n = 322), the combined treatment group 136 (85%) patients developed at least one complication versus 125 (78%) in the surgery alone group (p = 0.13) (Table 2).

Grade I complications were seen in 43% of patients after neoadjuvant chemo radiotherapy plus surgery versus 49% of patients after surgery alone (p = 0.37). There also was no statistically significant difference for grade II - grade V complications (Table 2).

Analyses in six subgroups showed that respiratory complications, i.e. pneumonia were the most common (30% vs. 21%, p = 0.32), followed by anastomotic leakage (23% vs. 30%, p = 0.13) and cardiac arrhythmias (20% vs. 12%, p = 0.29). Significantly more infections of the chest wound were found in patients with neoadjuvant treatment who underwent a transtho-

racic esophagectomy (0% vs. 6%, p = 0.007). The incidence of all other complications was not significantly different between the two groups.

There was no statistically significant difference in the CCI between both groups. Median CCI 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 = 0.58), Table 3.

In subgroup analyses of the specific complications, CCI for patients who underwent neoadjuvant chemo 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 = 0.78). The same was true for the other subgroups with patients who developed pulmonary or cardiac complications, thromboembolic event, chyle leakage or wound infection (Table 3).

Figure 1. Flowchart of patients.

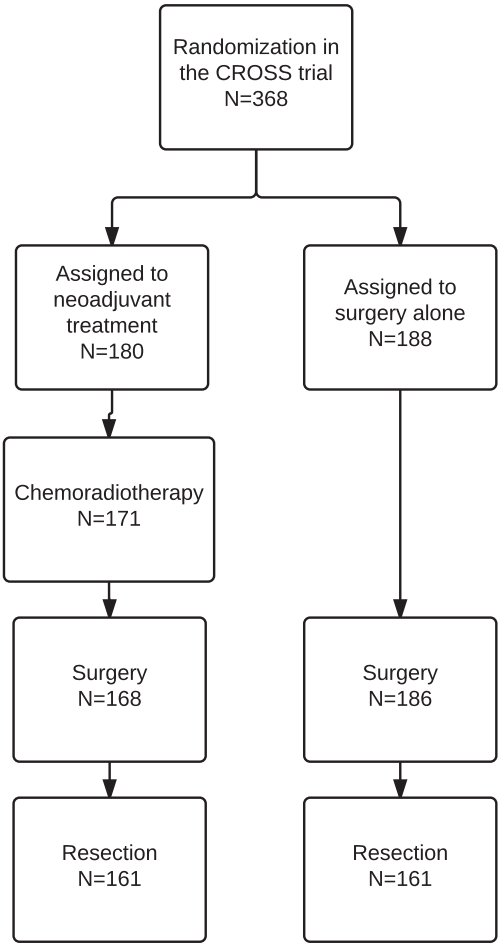

Table 1. Patient and tumor characteristics

	nCRT** and surgery (161)	Surgery alone (161)	p-value
Age (yr) median [range]	60 [37-76]	60 [36-76]	0.72
Sex (M:F)	129:34	123:38	0.41
WHO* Performance status±			
- 0	27	20	0.28
- 1	134	140	0.34
Co morbidity			
- Cardiovascular	45 (28%)	40 (25%)	0.48
- Respiratory	17 (11%)	19 (12%)	0.69
- Diabetes mellitus	14 (9%)	11 (7%)	0.55
Histology			
- Squamous cell carcinoma	37	37	1.0
- Adenocarcinoma	121	120	1.0
- Undifferentiated carcinoma	3	4	1.0
Tumor site			
- Proximal esophagus	2 (1%)	3 (2%)	1.0
- Mid esophagus	24 (15%)	16 (10%)	0.23
- Distal esophagus	112 (70%)	123 (76%)	0.20
- Gastro-esophageal junction	23 (14%)	17 (12%)	0.40
Mortality			
- 30-day	3 (2%)	4 (3%)	1.00
- In-hospital	5 (3%)	6 (4%)	0.99
Surgical approach			
- Transhiatal esophagectomy	72 (45%)	72 (45%)	1.0
Transthoracic esophagectomy	89 (55%)	87 (54%)	0.91
Resection with tumour free margins p(R0)	148 (92%)	111 (69%)	<0.001

Percentages may not add up to 100 because of rounding.

* WHO denotes World Health Organization.

** nCRT denotes Neoadjuvant Chemo radiotherapy

±. WHO performance status scores are on a scale of 0 to 5, with lower numbers indicating better performance status; 0 indicates fully active, and 1 unable to carry out heavy physical work.

DISCUSSION

The Dutch CROSS study showed an absolute 5-years survival benefit of 13% for patients who underwent neoadjuvant chemo radiotherapy followed by an esophagectomy for esophageal or esophagogastric cancer. Hence, neoadjuvant chemo radiotherapy is nowadays widely used in clinical practice. However, it is important to consider the possible harm of neoadjuvant chemo radiotherapy because trials frequently focus on the benefit of a treatment.[28-30] This may be caused by a lack of sensitive outcome parameters, by underreporting and by the

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

	nCRT** and surgery (161)	Surgery alone (161)	p-value
Any complication	136 (85%)	125 (78%)	0.13
Grade I complication	70 (43%)	79 (49%)	0.37
Grade II complication	90 (56%)	85 (53%)	0.65
Grade IIIa complication	58 (36%)	52 (32%)	0.56
Grade IIIb complication	25 (13%)	28 (15%)	0.76
Grade IVa complication	28 (15%)	33 (20%)	0.57
Grade IVb complication	3 (2%)	6 (3%)	0.50
Grade V complication	5 (3%)	6 (3%)	1.00
Subgroup 1; Anastomotic leakage ||	37 (23%)	49 (30%)	0.16
Subgroup 2; Pulmonary complications †	81 (50%)	82 (50%)	1.00
Subgroup 3; Cardiac complications ‡	34 (21%)	23 (14%)	0.57
Subgroup 4; Trombo-embolic events	6 (3%)	4 (2%)	1.00
Subgroup 5; Chyle leakage §	16 (10%)	11 (7%)	0.41
Subgroup 6; Wound infections	18 (11%)	21 (13%)	0.60
Anastomotic leakage	37 (23%)	49 (30%)	0.16
Leakage requiring surgical intervention	8 (4%)	6 (3%)	0.59
Pneumonia	49 (30%)	40 (21%)	0.32
Atelectasis	17 (11%)	22 (14%)	0.49
Empyema	14 (9%)	25 (16%)	0.09
Pneumothorax	10 (6%)	14 (9%)	0.52
Respiratory insufficiency	29 (15%)	33 (20%)	0.67
Re-intubation	33 (20%)	33 (20%)	1.00
Trombo-embolism	6 (3%)	4 (2%)	0.75
Cardiac arrhythmia	30 (20%)	22 (12%)	0.29
Myocardial infaction	0 (0%)	1 (1%)	1.00
Cardiac decompensation	4 (2%)	0 (0%)	0.13
Mediastinitis	6 (3%)	11 (7%)	0.32
Chylothorax	16 (10%)	11 (7%)	0.41
Vocal cord palsy	19 (12%)	12 (7%)	0.66
Wound infection neck	9 (6%)	6 (3%)	0.60
Wound infection thorax	0 (0%)	9 (6%)	0.007
Wound infection abdomen	9 (6%)	6 (3%)	0.60
Renal failure	4 (2%)	1 (1%)	0.37
Sepsis	7 (4%)	10 (6%)	0.62
Multi-organ failure	0 (0%)	4 (2%)	0.13
Re-admittance ICU	30 (19%)	27 (17%)	0.66

** nCRTS denotes Neoadjuvant Chemo radiotherapy

Adverse events were graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events, version 4.0

|| Anastomotic leakage was defined as: 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

† Pulmonary complications were pneumonia (isolation of pathogen from sputum culture and a new or progressive infiltrate on chest radiograph), serious atelectasis (lobar collapse on chest radiograph), pneumothorax (collection of air between the visceral and parietal pleural surfaces, requiring drainage), pleural effusion (collection of fluid between the visceral and parietal pleural surfaces, requiring drainage), pulmonary embolus (embolus detected on spiral CT or a ventilation–perfusion mismatch on a lung scintigram), and acute respiratory failure (partial pressure of arterial oxygen < 60 mm Hg while breathing ambient air).

‡ Cardiac complications were arrhythmia (any change in rhythm on the electrocardiogram, requiring treatment), myocardial infarction (two or three of the following: previous myocardial infarction, electrocardiographic changes suggesting myocardial infarction, or enzyme changes suggesting myocardial infarction), cardiac decompensation and left ventricular failure (marked pulmonary edema on a chest radiograph).

§ Chylothorax was recorded when elevated levels of triglycerides in intrathoracic fluid (> 1 mmol per liter [89 mg per deciliter]) were found. Mediastinitis was scored when reported by the local investigator.

strict inclusion criteria of trials that are frequently broadened after closure of the trial and the specifics of positive results. Also, sample sizes often are rather small masking the incidence of selectively rare but potentially serious complications. This study used the novel outcome measure for postoperative complicated course (CCI) to compare the additive impact of neoadjuvant chemo radiotherapy on the severity of complications in patients after esophagectomy, as the incidence of complications is already reported in the CROSS study. Our results show neither a significant difference in CCI between both groups nor in the incidence of specific common complications.

The benefit of neoadjuvant treatment has been a topic of many studies but the harm has been described less extensively. The Cochrane review, published in 2010[7] demonstrates that postoperative complications often are ill described or missing at all.[31] Herefore, in their meta-analysis no overall complication rate could be calculated. In a retrospective study published by Morita et al.[32] containing 686 patients, the total number of complications, as well as pulmonary complications and anastomotic leakage developed more frequently in patients with neoadjuvant treatment in comparison with patients without neoadjuvant treatment. Bosch et al.[16] confirmed an increase in cardiopulmonary complications in the neoadjuvant treatment group (pneumonia and cardiac arrhythmias). Merrit et al.[10], in a retrospective cohort study of 138 patients, showed no increase in postoperative morbidity and mortality, but concluded that major postoperative complications are rather due to surgical technique and preoperative morbidity rather than to neoadjuvant therapy. Furthermore, Kelley et al.[13] performed a prospective trial in 2004, showing no significantly higher complication rate in patients with preoperative chemo radiotherapy. In a study of 40 patients by Bagheri et al.[15], 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

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

	CRTx and surgery	Surgery alone	P-value
CCI (whole group; N=322)	26.22 [17.28- 42.43]	25.73 [8.66- 43.01]	0.58
CCI patients with anastomotic leakage (N=86)	8.66 [8.66 – 33.73]	8.66 [8.66 – 33.73]	0.78
CCI patients with pulmonary complications (N=163)	20.92 [20.92 – 42.43]	20.92 [20.92 – 42.43]	0.59
CCI patients with cardiac complications (N=57)	20.92 [20.92- 20.92]	20.92 [20.92- 20.92]	0.64
CCI patients with trombo-embolic events (N=10)	20.92 [20.92- 20.92]	20.92 [20.92- 20.92]	1.0
CCI patients with chyle leak (N=27)	8.66 [8.66 – 20.92]	14.79 [8.66 – 31.85]	0.65
CCI patients with wound infections (N=39)	8.66 [8.66 – 8.66]	8.66 [8.66 – 8.66]	0.93

The CCI for the whole group was computed on all patients. CCI of subgroups were calculated only in patients with the specific complication, to compare the severeness of the specific complications between groups. Values are shown as median with interquartile range and p-value.

* Anastomotic leakage was defined as: 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

‡ Pulmonary complications were pneumonia (isolation of pathogen from sputum culture and a new or progressive infiltrate on chest radiograph), serious atelectasis (lobar collapse on chest radiograph), pleural effusion (collection of fluid between the visceral and parietal pleural surfaces, requiring drainage) and acute respiratory failure (partial pressure of arterial oxygen < 60 mm Hg while breathing ambient air).

§ Cardiac complications were arrhythmia (any change in rhythm on the electrocardiogram, requiring treatment), myocardial infarction (two or three of the following: previous myocardial infarction, electrocardiographic changes suggesting myocardial infarction, or enzyme changes suggesting myocardial infarction), cardiac decompensation and left ventricular failure (marked pulmonary edema on a chest radiograph).

± Trombo-embolic events were defined as a deep venous thrombosis (shown on echo) or pulmonary embolus (embolus detected on spiral CT or a ventilation–perfusion mismatch on a lung scintigram)

** Chylothorax was recorded when elevated levels of triglycerides in intrathoracic fluid (> 1 mmol per liter [89 mg per deciliter]) were found. §§ Wound infections were defined as redness, inflammation, with extravasation of pus after drainage.

was no correlation found between neoadjuvant treatment and pulmonary complications. Several meta-analyses showed a decrease in mortality without any proof of a decrease in postoperative complications[4, 6, 9, 17] but most trials failed to produce information about postoperative complications. Greer et al.[5] found no difference in their meta-analysis and concluded that there was a need for large randomized trials.

With the recently developed sensitive Comprehensive Complication Index[20, 23], it is possible to take the severity of all complications in consideration; thus improving the accuracy of reporting the impact of all side effects combined. The CCI has been validated already in different surgical trials, showing its value. The CCI incorporates patients' opinion on a complication, as well as the physicians' opinion. It also takes into account low-grade complications, which are normally not considered as an endpoint but adds up to the patients' postoperative experience. Additionally, the CCI can be used to compare the severity of a specific complication (i.e. anastomotic leakage) between different patient groups (Table 3).

Table 4. Clavien-Dindo classification

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 antiemetics, antipyretics, 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	Requiring surgical, endoscopic or radiological intervention
IIIa	Intervention not under general anesthesia
IIIb	Intervention under general anesthesia
Grade IV	Life-threatening complication (including CNS complications) requiring IC/ICU management
IVa	Single organ dysfunction (including dialysis)
IVb	Multiorgan 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.

There are several limitations to the current study. As our study included patients from 7 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 application of the Clavien-Dindo classification. In the Netherlands, the transference to the Medium or Intensive Care Unit for more intensive monitoring of the 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 CCI. In the CROSS study, only the most severe complication counted. This study only reports early complications, within 30 days 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 study was powered to show a difference in overall survival, therefore the sample size of this study might be too small to show differences in rare complications. However, as described by Slankamenac et al.[20], when using the CCI as opposed to the original Clavien-Dindo classification as an endpoint, meaningful comparison can be obtained with smaller sample sizes.

The CCI 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 shows 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 CROSS trial is similar in the two groups; and the outcome of specific complications in the two groups is similar. Neoadjuvant chemo radiotherapy does not show a negative impact on the overall postoperative morbidity as expressed by the CCI compared with patients who underwent surgery alone for potentially curable esophageal or esophagogastric junctional cancer.

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9

Summary and conclusions

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SUMMARY AND CONCLUSIONS

This thesis discusses complications after esophageal surgery with special emphasis on surgical techniques in relation to outcome. **Part 1** described surgical techniques and postoperative imaging after esophagectomy and the creation of a esophagogastrostomy. Furthermore, postoperative complications and technical aspects of the esophago-gastric anastomosis and the use of a colon interposition for reconstruction is described. **Part 2** focusses on the use of the Comprehensive Complication Index (CCI) in surgical trials with special attention to anastomotic complications.

Part 1 Surgical techniques

Chapter 2 deals with postoperative complications after esophageal resection and gastric tube reconstruction including anastomotic leakage, anastomotic stricture, morbidity and mortality of different anastomotic techniques. Outcome after a stapled anastomosis was compared to a hand-sewn anastomosis and a cervical anastomosis was compared to an intra-thoracic anastomosis. The 25 reviewed articles show that cervical and intra-thoracic anastomosis are equal with regard to leakage and stricture rate, although there was a trend towards more leakage in the groups with patients with a cervical anastomosis. A stapled (either circular, linear or semi-mechanical) anastomosis or a hand-sewn anastomosis did not differ in anastomotic leakage, but there were higher incidences of dysphagia and strictures reported in the circular stapled anastomosis.

Previous studies attempted to define the optimal site of anastomosis and the optimal anastomotic techniques. However, anastomotic stricture formation and leakage still remains an important clinical problem. **Chapter 3** reports a randomized controlled trial comparing a single-layered hand-sewn cervical end-to-side (ETS) anastomosis with an end-to-end (ETE) anastomosis. From May 2005 to September 2007, 128 patients (64 in each group) were randomized between ETE- and ETS-anastomosis after esophagectomy for cancer with gastric tube reconstruction. Contrast swallow studies and endoscopy were routinely performed in all patients. Anastomotic stricture within one year requiring dilatation, was the primary endpoint. Secondary endpoints were anastomotic leak rate and mortality. 99 men and 29 women underwent esophagectomy and gastric tube reconstruction. Benign stenosis of the anastomosis, for which dilatation was required, occurred more often in the ETE group (40% vs. ETS 18%, $p < 0.01$) after one year of follow-up. The overall (clinical and radiological) anastomotic leak rate was lower in the ETE group (22% vs. ETS 41%, $p = 0.04$). Patients with an ETE-anastomosis suffered less often from pneumonia (17% vs. ETS 44%, $p = 0.002$) and had subsequently significantly shorter in-hospital stay (15 days vs. 22 days, $p = 0.02$). In-hospital mortality did not differ between both groups. In conclusion, the ETS-anastomosis was as-

sociated with a lower anastomotic stricture rate, compared to ETE-anastomosis. However, prevention of stricture formation was at high costs with increased anastomotic leakage and longer in-hospital stay.

In **Chapter 4** the leak rate of a hand-sewn end-to-end anastomosis (ETE) is compared with a semi-mechanical anastomosis (SMA) after esophagectomy with gastric tube reconstruction. No randomized controlled studies had been performed that compared a hand-sewn ETE-anastomosis with a SMA. Patients with esophageal cancer were scheduled for esophagectomy with gastric tube reconstruction and cervical anastomosis were eligible for participation. Patients were randomized to an ETE- or SMA-anastomosis. The primary endpoint was anastomotic leak rate. Secondary endpoints included anastomotic stricture at one year follow up, number of dilations, dysphagia score, hospital stay, morbidity and mortality. Patients were blinded for the type of anastomosis. Between August 2011 and July 2014, 174 patients with esophageal cancer underwent esophagectomy of whom 93 patients were randomized to ETE (n = 44) or SMA (n = 49) groups. Unfortunately, due to slow accrual and publication of a similar study, the study was stopped prematurely. Anastomotic leak occurred in 9 of 44 patients (20%) in the ETE group and 12 of 49 patients (24%) in the SMA group (p = 0.804) with a confidence interval of -13% to 21%. There was no statistically significant difference in dysphagia at one year postoperatively (ETE 25% vs. SMA 20%; p = 0.628). There was no difference in in-hospital stay, morbidity or mortality. Our study was stopped prematurely, with a confidence interval of-13 to 21% for leakage rate. Therefore, it is concluded that differences greater than 21% do not significantly differ. Smaller differences in leak rates cannot be proven equal or different.

Chapter 5 describes our 40-year experience with colon interpositions. All patients who underwent esophagectomy with a colon interposition between 1976 and 2016 in the Erasmus MC were identified from an institutional database. Data on patient's characteristics, operative details, morbidity and mortality were retrieved from the institutional database and patients' charts. 126 patients were included. Indications for colon interposition were failed gastric tube reconstruction (n = 18), previous gastric surgery (n = 48), esophagectomy with total gastrectomy for cancer (n = 40), caustic injury (n = 6) and other reasons (n = 8). Postoperative in-hospital mortality was 18% (23 patients). Morbidity was 66%. The most prevalent complications were pneumonia in 40 patients (32%) and anastomotic leakage in 24 patients (19%). The use of a colon conduit after esophagectomy is associated with a high mortality and morbidity but is a viable option for reconstruction of the upper gastrointestinal tract.

Chapter 6 investigates the diagnostic and predictive value of routine contrast swallow study and endoscopy for the detection of anastomotic dehiscence in patients after esophagectomy. All patients who underwent contrast swallow and/or endoscopy within 7 days after esophagectomy for cancer between January 2005 and December 2009 were selected from an insti-

tutional database. 173 patients underwent endoscopy and 184 patients underwent a contrast swallow study. The sensitivity of endoscopy for anastomotic leakage requiring intervention is 56%, specificity 41%, positive predictive value (PPV) 8% and negative predictive value (NPV) 95%. The sensitivity of contrast swallow study for detecting leakage requiring intervention in patients without signs of leakage was 16%, specificity 75%, PPV 11% and NPV 83%. In patients without clinical suspicion of leakage, there is no benefit to perform routine diagnostic tests.

Part 2 Comprehensive Complication Index

Whether the recently developed Comprehensive Complication Index (CCI) is more sensitive than traditional endpoints for detecting between-group differences in randomized controlled trials (RCTs), is described in **Chapter 7**. A major challenge in RCTs is the choice of optimal endpoints to measure treatment effects in an accurate and reliable way. The CCI, integrating all complications including their severity in a linear scale ranging from 0 (no complication) to 100 (death), is a new tool, which may be more sensitive than other traditional endpoints to detect treatment effects on postoperative morbidity. The CCI was tested in three published RCTs from European centres evaluating pancreas, esophageal or colon resections. To compare the sensitivity of the CCI with traditional morbidity endpoints, e.g. presence of any (yes/no) or only the most severe complications, all postoperative events were re-assessed, and the CCI calculated. Treatment effects and sample size calculations were compared using the CCI and traditional endpoints. While RCTs failed to show between-group differences using any or most severe complications, the CCI revealed significant differences between treatment groups in two RCTs after pancreas ($p = 0.009$) and esophageal surgery ($p = 0.014$). The CCI in the RCT on colon resections confirmed the absence of between-group differences ($p = 0.39$). The required sample sizes in trials are up to nine-times lower for the CCI than for traditional morbidity endpoints. This study demonstrated superiority of the CCI to traditional endpoints. The CCI may serve as an appealing endpoint for future RCTs and may reduce the sample size.

Chapter 8 concentrates on neoadjuvant chemo radiotherapy (nCRT) followed by surgery for patients with esophageal or junctional cancer. nCRT has become a standard of care. The aim of this study was to further evaluate the severity of complications in patients treated with nCRT followed by esophagectomy versus in patients who underwent esophagectomy alone using the comprehensive complication index (CCI). All patients included in the CROSS trial, a randomized clinical trial on the value of nCRT followed by esophagectomy, were included. Complications were assessed and graded using the Clavien-Dindo classification. The 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. 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 = 0.58). There was also no difference in the CCI between subgroups of patients with anastomotic leakage, pulmonary complications, cardiac complications, thromboembolic events, chyle leakage and wound infections. Neoadjuvant chemo radiotherapy according to the CROSS-regimen did not have a negative impact on postoperative complication severity expressed by the CCI compared to patients who underwent surgery alone for potentially curable esophageal or junctional cancer.

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Samenvatting en conclusies

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SAMENVATTING EN CONCLUSIES

In dit proefschrift worden de complicaties besproken van slokdarmchirurgie, en in het bijzonder de verschillende chirurgische technieken in relatie tot het ontstaan van postoperative complicaties. In **deel 1** worden chirurgische technieken en postoperatieve beeldvorming na slokdarmresectie beschreven, evenals postoperatieve complicaties met betrekking tot de anastomose en het gebruik van een coloninterponaat. **Deel 2** richt zich op het gebruik van de Comprehensive Complication Index (CCI) in chirurgische studies.

Deel 1 Chirurgische technieken

Hoofdstuk 2 beschrijft op systematische wijze de literatuur omtrent naadlekkage, strictuur van de anastomose, morbiditeit en mortaliteit van verschillende anastomosetechnieken. Gestaplede anastomoses werden vergeleken met handgelegde anastomoses, de locatie van de anastomose werd vergeleken (cervicaal versus intra-thoracaal), en het gebruik van een smalle buismaagreconstructie werd vergeleken met de gehele maag als interponaat. De 25 gereviewde artikelen tonen aan dat cervicale en intra-thoracale anastomoses even veilig zijn met betrekking tot lekkage en de vorming van strictuur, hoewel er een trend naar meer lekkage was in de groep patiënten met een cervicale anastomose. Een gestaplede anastomose (hetzij circulair, lineair of semi-mechanisch) en een handgelegde anastomose verschillen niet in het percentage naadlekkage, maar er was een hogere incidentie van dysfagie en strictuur bij de circulair gestapelde anastomose. **Hoofdstuk 3** bestaat uit een gerandomiseerde gecontroleerde trial met vergelijking van een met de hand gelegde, cervicale end-to-side (ETS) anastomose en een end-to-end (ETE) anastomose. In eerdere studies is geprobeerd om de optimale plaats van anastomose en anastomosetechniek te definiëren. Echter, lekkage en strictuur van de anastomose bleef een belangrijk klinisch probleem. Van mei 2005 tot september 2007 zijn 128 patiënten (64 in elke groep) gerandomiseerd tussen een ETE- en ETS-anastomose na slokdarmresectie voor slokdarmcarcinoom met buismaagreconstructie. Om de anastomose te beoordelen werden routinematig een slikfoto en gastroscopie uitgevoerd. Strictuur van de anastomose binnen een jaar, waarvoor dilatatie nodig was, was het primaire eindpunt. Secundaire eindpunten waren lekkage van de anastomose en mortaliteit. 99 mannen en 29 vrouwen ondergingen een slokdarmresectie met buismaagreconstructie. Benigne stenose van de anastomose, waarbij dilatatie nodig was, kwam vaker in de ETE-groep voor (40% vs. ETS 18%, $p < 0,01$) na één jaar follow-up. De totale (klinische en radiologische) lekkage van de anastomose was lager in de ETE-groep (22% vs. ETS 41%, $p = 0,04$). Patiënten met een ETE-anastomose ontwikkelden minder vaak een pneumonie; (17% vs. ETS 44%, $p = 0,002$) en hadden een significant korter ziekenhuisverblijf (15 dagen versus 22 dagen, $p = 0,02$). De ziekenhuismortaliteit verschilde niet tussen beide groepen. De ETS-anastomose werd geassocieerd met een lager percentage strictuur, vergeleken met ETE-anastomose.

Echter, het voorkomen van strictuur woog niet op tegen de verhoogde kans op naadlekkage en de langere opnameduur.

In **hoofdstuk 4** wordt een vergelijking gemaakt in de lekkage tussen een hand gelegde end-to-end anastomose (ETE) en een semi-mechanische anastomose (SMA) na resectie met maagsondereconstructie. Tot op de start van de studie waren geen gerandomiseerde gecontroleerde studies uitgevoerd waarin een handgelegde ETE-anastomose met een SMA werd vergeleken. Patiënten met slokdarmkanker die gepland werden voor een slokdarmresectie met buismaagreconstructie met cervicale anastomose kwamen, na schriftelijke toestemming, in aanmerking voor deelname. Patiënten werden gerandomiseerd in een 1:1 verhouding voor een ETE- of SMA-anastomose. Het primaire eindpunt was naadlekkage, gedefinieerd als uitvloed van speeksel of ingenomen vloeistoffen uit de halswond, of een intra-thoracale manifestatie van lekkage (abces of mediastinitis). Secundaire eindpunten omvatten: strictuur na een jaar follow-up, het aantal dilataties, de dysfagie-score, opnameduur, de morbiditeit en mortaliteit. Tussen augustus 2011 en juli 2014 ondergingen 174 patiënten met slokdarmkanker een slokdarmresectie met buismaagreconstructie, waarvan 93 patiënten gerandomiseerd werden voor een ETE (n = 44) of SMA (n = 49) anastomose. Vanwege lage inclusie-aantallen en publicaties van vergelijkbare studies werd de studie voortijdig gestaakt. Naadlekkage trad op bij 9 van 44 patiënten (20%) in de ETE-groep en 12 van 49 patiënten (24%) in de SMA-groep (p = 0,804) met een 95% betrouwbaarheidsinterval van -13% tot 21%. Er was geen statistisch significant verschil in dysfagie na een jaar na de operatie (ETE 25% vs. SMA 20%; p = 0,628).

Er was geen verschil in opnameduur in het ziekenhuis, ziekte of sterfte. Verschillen van meer dan 21% zijn niet aangetoond. Kleinere percentages kunnen echter vanwege het betrouwbaarheidsinterval niet significant worden aangetoond of uitgesloten.

Hoofdstuk 5 beschrijft onze 40-jarige ervaring met coloninterponaten. Een segment van de dikke darm kan worden gebruikt voor de reconstructie van het spijsverteringskanaal na resectie. Alle patiënten die tussen 1976 en 2016 in het Erasmus MC een slokdarmresectie ondergingen met een coloninterponaat werden geïdentificeerd uit een institutionele database. In totaal werden 126 patiënten geïncludeerd. Indicaties voor een coloninterponaat waren: gefaalde buismaagreconstructie (n = 18), eerdere maagchirurgie (n = 48), resectie met totale gastrectomie bij kanker (n = 40), caustisch letsel (n = 6) en andere redenen (n = 8). Postoperatieve sterfte in het ziekenhuis was 18% (23 patiënten). Morbiditeit was 66%. De meest voorkomende complicaties waren pneumonie (40 patiënten, 32%) en naadlekkage bij 24 patiënten (19%). Het gebruik van een coloninterponaat werd geassocieerd met een hoge mortaliteit en morbiditeit, maar is een acceptabele optie voor reconstructie van het bovenste maagdarmkanaal.

Hoofdstuk 6 onderzoekt de diagnostische en voorspellende waarde van routinematige slikfoto's en gastroscopie voor het aantonen van naadlekkage. Alle patiënten die een slikfoto en/of gastroscopie ondergingen binnen 7 dagen na een slokdarmresectie voor slokdarmkanker tussen januari 2005 en december 2009, werden geïdentificeerd uit de institutionele database. 173 patiënten ondergingen gastroscopie en 184 patiënten ondergingen een slikfoto. De sensitiviteit van gastroscopie voor naadlekkage is 56%, de specificiteit 41%, positief voorspellende waarde (PPV) 8% en negatief voorspellende waarde (NPV) 95%. De sensitiviteit van de slikfoto bij patiënten zonder tekenen van lekkage was 16%, specificiteit 75%, PPV 11% en de NPV 83%. Bij patiënten zonder klinisch vermoeden van lekkage is er geen voordeel voor routineonderzoek aangetoond.

Deel 2 Comprehensive Complication Index

Om te testen of de nieuw ontwikkelde Complicatie Index (CCI) gevoeliger is dan de traditionele eindpunten voor het detecteren van verschillen tussen de groepen in gerandomiseerde gecontroleerde studies (RCT's), werd de studie uit **Hoofdstuk 7** uitgevoerd. Een grote uitdaging van een RCT is de keuze van optimle eindpunten om behandelingseffecten aan te tonen. Mortaliteit is niet langer voldoende in studies, en morbiditeit wordt vaak slecht gedefinieerd. De CCI integreert van alle complicaties de ernst (op een lineaire schaal van 0 (geen complicatie) tot 100 (dood)) en is een nieuwe tool, die gevoeliger is dan andere traditionele eindpunten. De CCI werd getest in drie gepubliceerde RCT's van Europese centra. Om de gevoeligheid van de CCI te vergelijken met traditionele eindpunten (morbiditeit, aanwezigheid van een complicatie of alleen de meest ernstige complicaties) werden alle postoperatieve complicaties beoordeeld, en werd de CCI berekend. Behandelingseffecten en 'sample size'-berekeningen werden vergeleken met behulp van de CCI en traditionele eindpunten. Hoewel RCT's geen significante verschillen aantoonden in de aanwezigheid van een of de meest ernstige complicatie, toonde de CCI aan dat er significante verschillen tussen de behandelingsgroepen in twee RCT's waren: na pancreas- ($p = 0,009$) en slokdarmchirurgie ($p = 0,014$). De CCI in de RCT op dikkedarmresecties bevestigt dat er geen verschillen tussen de groepen aan te tonen waren ($p = 0,39$). De vereiste steekproefomvang in studies is tot negen keer lager voor de CCI dan bij traditionele morbiditeiteindpunten. Deze studie toonde de superioriteit van de CCI ten aanzien van de traditionele eindpunten. De CCI kan dienen als een aantrekkelijk eindpunt voor toekomstige RCT's en kan de steekproefgrootte verkleinen.

Hoofdstuk 8 concentreert zich op neoadjuvante chemo-radiotherapie (nCRT) gevolgd door chirurgie voor patiënten met slokdarmkanker. Het doel van deze studie was de ernst van complicaties bij patiënten die nCRT ondergingen gevolgd door resectie, versus patiënten die alleen resectie ondergingen, te vergelijken met behulp van de CCI. Alle patiënten uit de CROSS-studie werden geïncludeerd. Complicaties werden beoordeeld en ingedeeld met

behulp van de Clavien-Dindo classificatie. De CCI werd afgeleid van deze scores, met behulp van de CCI calculator die online beschikbaar is (*www.assessurgery.com*). De CCI van patiënten die nCRT ondergingen gevolgd door chirurgie werd vergeleken met de CCI van patiënten die alleen chirurgie ondergingen. In beide groepen werden 161 patiënten geïncludeerd. De mediaan (en interquartile range) van CCI patiënten met nCRT en chirurgie was 26,22 (17,28-42,43) versus 25,74 (8,66-43,01) bij patiënten die alleen chirurgie ondergingen (p = 0,58). Er was geen verschil in CCI tussen subgroepen van patiënten met een naadlekkage, pulmonale complicaties, cardiale complicaties, trombo-embolische complicaties, chyluslekkage en wondinfecties. Neoadjuvante chemo radiotherapie volgens CROSS-schema heeft geen invloed op postoperatieve complicaties en ernst van de complicaties, gemeten met de CCI.

11

General discussion and future perspectives

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GENERAL DISCUSSION AND FUTURE PERSPECTIVES

Anastomosis

The frequent and still important problem of esophago-gastric anastomotic failure after esophagectomy being leakage or stricture, has instigated the search for novel anastomotic techniques. The best technique to perform this anastomosis is still subject of debate. Recently, the data from the DUCA was presented; between 2011 and 2014, a total of 2786 patients with esophageal cancer were registered. Postoperative mortality remains stable (around 4%) for patients with esophageal cancer and leak rate is stable around 19%.[1]

To understand more about the failure of the anastomosis, it might be helpful to investigate the healing process of the anastomosis. Healing consists of three phases; at first inflammation (day 0-4), followed by proliferation (day 5-10) and finally remodeling (> day 10).[2,3] These three phases can be influenced by the suture materials, and some researchers hypothesize the possibility of the suture materials to be a cause of further inflammation, scar tissue and fibrosis, resulting in stricture. Healing is multifactorial, failing occurs if any phase is interrupted or shortened.[2] Studies suggest that inflammation, shock, hypo-perfusion, negative pressure inside the thoracic cavity, diabetes, steroid use and malnutrition have influence on healing of the anastomosis, as well as smoking and alcohol consumption.[4] For example, some studies show that a continuous suture in a hand-sewn anastomosis lead to better mucosal apposition and vascular bed preservation, and therefore less stricture than interrupted sutures.[5,6]

Comparing the hand-sewn technique with a circular stapler shows a shorter operation time, but an increase in stricture rate.[7-12] Hand-sewn versus linear stapled anastomoses show less operation time and a lower risk of postoperative stricture formation.[4, 13-16] Factors influencing anastomotic leakage also include adequate blood supply, degree of tension on the anastomosis and tight closure of the mucosal layer.[17]

To enhance adequate blood supply, the 'supercharged' anastomosis has been subject of research. In this technique, the anastomosis is provided with extra blood supply by adding a microvascular anastomosis (supercharging) at the distal end of the gastric tube. This has now become an established method of reconstruction, especially in Asia.[18-22] Studies remain small, and nonrandomized studies have been reported that show a superior outcome compared to a standard technique.

The use of fluorescence or intravenously injected indocyanine green (ICG) is known for enhancement of visualization of tissue microvasculature and blood supply[23-25] and has been adopted for assessment of blood flow in the esophageal conduit.[26] This technique, first described in cardiovascular and neurosurgery, is thought to assess whether the tip of the gastric tube has sufficient blood supply for healing of the anastomosis. The use of fluores-

cence angiography is not yet widely accepted, but it might help to prevent leakage in the future. So far, there is no randomized controlled trial in which results from peroperative use of indocyanine green is used to determine the site of the anastomosis, only prospective cohort studies.[27] Intraoperative assessment of intestinal perfusion provides us with an opportunity to insure sufficient blood supply to the anastomosis, and therefore, large randomized studies should be performed in which this technique is compared to the 'normal' assessment of the anastomotic site by the surgeon.

The use of an omentoplasty for wrapping around the anastomosis has been studied and in 2014, an update of the Cochrane review was published.[28] Three randomized trials show that it might provide additional benefit in decreasing the incidence of anastomotic leakage. Results are significantly better, but only in a subgroup of patients that underwent transhiatal resection. It also does not result in better long-term survival, as might be expected if postoperative morbidity is lowered. Other postoperative complications such as stricture are not improved by the omentoplasty. It could be argued that it might give some discomfort in the neck, as it bulges around the anastomosis. Further research in the form of large randomized trials with quality of life assessment is due.

Postoperative imaging

Diagnostic evaluation of the anastomosis consists in most centers of a contrast swallow study. It has several benefits including the low costs and being a relatively safe with a high sensitivity and specificity when interpreted by an experienced radiologist.[29] But aqueous contrast has a low radiographic density and a low mucosal adherence thus limiting the ability to detect small leaks. In chapter 6, the routine use of contrast swallow study and/or gastroscopy is not recommended. Recently, studies were published in which serial drain amylase is proven to detect anastomotic leak accurately. Amylase levels in drain fluid on day 4 showed to be more accurate for the detection of esophageal anastomotic leak than a contrast swallow study, and adds to the sensitivity of a CT.[30, 31] Other studies suggest the use of a CT-scan instead of a contrast swallow study or endoscopy. Possible advantages are a higher sensitivity and specificity, it is easier to perform in very ill patients and shows secondary findings as well (abscesses, pleural effusion, pneumothorax, pulmonary abnormalities).[32, 33]

The treatment of leakage can either be conservative, in most patients with a cervical anastomosis, by opening the cervical wound, nasogastric decompression, nil per mouth, parenteral feeding and medication (such as antibiotics). For intra-thoracic anastomoses, treatment is more often more aggressive including (re-)thoracotomy, thoracoscopy and percutaneous thoracic drainage. These measures are often needed because the impact of intra-thoracic leakage, with empyema, mediastinitis, and consequently (severe) sepsis and even mortality can occur if left untreated.

Colon interposition

Morbidity and mortality of colon interposition after esophagectomy is high: two-thirds of patients has one or more complications. A recent audit from the Netherlands showed that postoperative morbidity after esophagectomy is still high (around 60%) but mortality has decreased to 4%.[16] Over 40 years, several changes in surgical techniques have taken place including use of surgical techniques that minimize blood loss, less liberal fluid administration and the use of enhanced recovery protocols after esophagectomy.

To perform a colon interposition, the right colon (using the middle colic vessels as a pedicle) can be used, or the left colon (using the ascending branch of the left colic artery and the inferior mesenteric vein as a pedicle). In some patients, a pedicled jejunal graft is performed when the stomach is not available for reconstruction. Advantages of the jejunal graft include fewer anastomoses and vigorous peristalsis. Disadvantages include restricted graft length (because of the mesenteric arcade), no reservoir function and ischemia or congestion may occur in a long graft. The technique is challenging and often a supercharged technique has to be applied as well (microvascular anastomosis in the neck). The use of the colon provides a long graft, less reflux and a reservoir-like-capacity. On the other hand, the variation in mesenteric vessels is a risk factor for ischemia. It is also a formidable operation and there is a need for three or four anastomoses. Albeit very small, there is a small risk of carcinoma in the interposition. A comparison between right and left colon shows advantages of the right colon as a prevention of regurgitation by the Bauhin valve and a more a close match in diameter of esophagus and ileum which facilitates an end-to-end anastomotic technique. The left colon however, has a more reliable blood supply and adequate length for reconstruction but patients may suffer more from regurgitation.

In the near future, popularization of microvascular surgical techniques in the western world and use of combined colon-small bowel grafts in highly complex patients may further impact on the outcomes of esophageal reconstruction. Prospective comparisons of short-term outcomes as well as long-term quality of life are needed to identify the best reconstructive method.[34]

Comprehensive Complication Index

Reporting outcomes of surgical or other invasive procedures using morbidity as primary endpoint has been associated with serious limitations due to various definitions and different interpretation of postoperative events. Assessing the overall morbidity by the presence of any complication causes the problem of ignoring either the number of different complications occurring in a patient after surgery or, more importantly, the severity of complications. This thesis shows the superiority of the CCI over traditionally reported morbidity endpoints 'most severe complication' and specific complications by detecting between-group differences in three external trial populations.[35] Another finding is the easy and new applicability to longitudinal assessment of complications over time, as illustrated in the analysis of the one-year

CCI follow up in the esophageal anastomosis trial. The CCI is now widely used (> 200 trials) as a secondary, and primary endpoint. Several studies show the importance of an overall complication index, and in future research, the implementation of this sensitive tool will be further explored.

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APPENDICES

List of publications

Dankwoord

Curriculum Vitae

PhD portfolio

LIST OF PUBLICATIONS

1. End-to-end versus end-to-side esophagogastrostomy after esophageal cancer resection: a prospective randomized study
   Nederlof N, Tilanus HW, Tran TC, Hop WC, Wijnhoven BP, de Jonge J.
   Ann Surg. 2011 Aug;254(2):226-33.
   PMID: 21725230

2. Letter to the editor: Reply to Letter: "End-to-End Versus End-to-Side Esophagogastrostomy After Esophageal Cancer Resection: A Prospective Randomized Study".
   Nederlof N, Tilanus HW, Tran TC, Hop WC, Wijnhoven BP, de Jonge J.
   Ann Surg. 2014 Jan;259(1):e7.
   PMID: 23442777

3. The comprehensive complication index: a novel and more sensitive endpoint for assessing outcome and reducing sample size in randomized controlled trials.
   Nederlof N, Slankamenac K, Pessaux P, de Jonge J, Wijnhoven BP, Breitenstein S, Oberkofler CE, Graf R, Puhan MA, Clavien PA.
   Ann Surg. 2014 Nov;260(5):757-62; discussion 762-3. doi: 10.1097/SLA.0000000000000948.
   PMID: 25379846

4. Does Routine Endoscopy or Contrast Swallow Study After Esophagectomy and Gastric Tube Reconstruction Change Patient Management?
   Nederlof N, de Jonge J, de Vringer T, Tran TC, Spaander MC, Tilanus HW, Wijnhoven BP.
   J Gastrointest Surg. 2017 Feb;21(2):251-258. doi: 10.1007/s11605-016-3268-y.
   PMID: 2784426

5. Using the Comprehensive Complication Index to Assess the Impact of Neoadjuvant Chemoradiotherapy on Complication Severity After Esophagectomy for Cancer.
   Nederlof N, Slaman AE, van Hagen P, van der Gaast A, Slankamenac K, Gisbertz SS, van Lanschot JJ, Wijnhoven BP, van Berge Henegouwen MI; CROSS-Study Group.
   Ann Surg Oncol. 2016 Nov;23(12):3964-3971.
   PMID: 27301849

6. Morbidity and mortality of colon interposition after esophagectomy
   N. Nederlof, MD, T. de Vringer, BSc, B.P.L. Wijnhoven, MD, PhD, H.W. Tilanus, MD, PhD
   Submitted

7. The influence of surgical technique on postoperative outcome after esophagectomy for esophageal cancer; leakage of the anastomosis: a review of the literature
   N. Nederlof, MD, BSc, B.P.L. Wijnhoven, MD, PhD, H.W. Tilanus, MD, PhD
   Submitted

8. A single blinded randomized controlled trial comparing semi mechanical with hand sewn cervical anastomosis after esophagectomy for cancer (SHARE-study).
   Nina Nederlof, M.D., Hugo W. Tilanus, MD, PhD, Tahnee de Vringer, MSc, Jan J.B. van Lanschot, M.D., PhD, Sten P. Willemsen, MSc, Wim C.J. Hop, MSc, PhD, Bas P.L. Wijnhoven, MD, PhD.
   Submitted

DANKWOORD

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werd er ruimte gemaakt in het rooster. Leendert, Wijnand, Kirstin, Joost, Kim, Franny, Jeff, Inge, Annemarie. Dank.

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CURRICULUM VITAE

Nina Nederlof werd geboren op 7 mei 1985 te Zevenhuizen. Na haar eindexamen vwo aan het Coenecoop College in Waddinxveen begon zij in 2004 aan haar studie Geneeskunde aan de Erasmus Universiteit in Rotterdam. Tijdens haar studie begon zij met werkzaamheden op 8Noord; de Gastro-Intestinale Chirurgie, waar ook de eerste stappen in het wetenschappelijk onderzoek werden gezet. De laatste fase van haar coschappen liep zij op de afdeling Heelkunde in het Flevoziekenhuis in Almere en de afdeling Heelkunde in het IJsselland ziekenhuis in Capelle aan den IJssel. In 2012 behaalde zij haar artsexamen, waarna zij als arts-assistent eerst een jaar is gaan werken op de afdeling Heelkunde van het Erasmus MC en vervolgens nog twee jaar in het Maasstad Ziekenhuis in Rotterdam. Zij solliciteerde in 2015 voor de opleiding, en is op 1 juli 2015 gestart met de opleiding Heelkunde in het Ikazia ziekenhuis in Rotterdam. Het wetenschappelijk onderzoek wat zij tijdens haar studie Geneeskunde, werk als ANIOS en ook AIOS heeft verricht heeft uiteindelijk geleid tot de totstandkoming van dit proefschrift.

PHD PORTFOLIO / SUMMARY OF PHD TRAINING AND TEACHING

Name PhD student: Nina Nederlof Erasmus MC department: Surgery	PhD period: August 2011 – May 2017 Promotor: Prof. dr. H.W. Tilanus Copromotor: dr. B.P.L. Wijnhoven

1. PhD training

	Year	Workload (ECTS)
General Courses		
BROK ('Basiscursus Regelgeving Klinisch Onderzoek')	2011	1.0
NIHES cursus Statistical Methods and Data-analysis (CC02)	2011	3.0
Presentations (international conferences)		
Annual meeting ESA (European Surgical Association), Vienna (oral presentation)	2009	2.0
Annual meeting ESA (European Surgical Association), Athens (oral presentation)	2014	2.0
International Society for Diseases of the Esophagus, 19-21 September 2016, Singapore, Singapore Republic. (oral presentation)	2015	2.0
European Society for Diseases of the Esophagus (ESDE) (poster)	2016	2.0
Presentations (national conferences)		
Chirurgendagen NVvH (oral presentation, best abstract session)	2011	1.0
Chirurgendagen NVvH (oral presentation)	2014	1.0
Digestive Disease Days (oral presentation)	2017	1.0
Conferences:		
ESA	2014, 2017	2.0
Chirurgendagen NVvH	2011-2017	2.0

2. Teaching

	Year	Workload (ECTS)
Examination Basic Life Support	2012-2015	0.4
Supervising medical students	2013-2017	5.0