Institutionen för molekylär medicin och kirurgi

OESOPHAGEAL CANCER: SURGERY, SYMPTOMS AND SURVIVAL

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Maartje van der Schaaf

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To Mick: For his courage inspiration and endless determination.

ABSTRACT

This thesis aimed to identify factors that can improve survival and reduce persisting symptoms among surgically treated oesophageal cancer patients. In Sweden there are approximately 450 new cases of oesophageal cancer and 200 new cases of gastric cardia cancer diagnosed every year. Surgical tumour resection is the mainstay of curatively intended treatment for oesophageal cancer, often preceded by neoadjuvant chemo- or chemoradiotherapy. Despite improvements in treatment, the prognosis of patients with oesophageal cancer remains poor, and even after successful tumour resection most patients suffer from residual symptoms.

The included studies are based on two population-based, nationwide Swedish cohorts (**Studies I-IV**) and one Dutch (**Study V)**, hospital-based cohort. **Studies I-II** were based on a retrospective cohort of patients operated on between 1987-2010 and, **Studies III-IV** were based on a prospective cohort of patients who underwent surgery between 2001-2005. In **Study V** we used a prospective cohort of patients operated on between 1991-2010. Multivariable Cox regression was used to calculate hazard ratios (HR) with 95% confidence intervals (CI), adjusted for potential confounding factors.

Study I: Among 1044 patients the number of resected lymph nodes did not influence survival (HR 1.00, 95% CI 0.99-1.01). **Study II:** Among 1822 patients, the 200 (11%) patients who underwent reoperation had an increased risk of mortality (HR 1.27, 95% CI 1.05-1.53). **Study III:** Among 304 included patients, a cervical anastomosis (OR 0.86, 95% CI 0.33-2.23), creation of a fundoplication (OR 0.86, 95% CI 0.39-1.90) or performance of a pyloric drainage procedure (OR 1.49, 95% CI 0.86-2.58) did not influence patients' experience of reflux 6 months after oesophagectomy. **Study IV:** Among 277 patients followed up 6 months after surgery, those who suffered from an intrathoracic anastomotic leak were at increased risk of difficulties with eating (OR 4.05, 95% CI 1.47-11.16) and odynophagia OR 2.59, 95% CI 1.15-5.82), but not reflux or dysphagia. **Study V:** Among 922 patients, the 155 patients who had >10% preoperative weight loss, experienced an increased 5-year mortality (HR 1.34, 95% CI 1.02-1.74), but no increased risk of non- surgical or surgical complications.

LIST OF PUBLICATIONS

I. M. van der Schaaf, A. Johar, B. Wijnhoven, P. Lagergren, J. Lagergren.
No survival benefit from a more extensive lymph node removal during oesophageal cancer surgery in a population-based cohort study
Submitted manuscript

II. M. van der Schaaf, M. Derogar, A. Johar, M. Rutegård, J. Gossage, R. Mason, P. Lagergren, J. Lagergren.
Reoperation after oesophageal cancer surgery in relation to long-term survival
BMJ Open. 2014 Mar 20;4(3):e004648

III. M. van der Schaaf , A. Johar, J. Gossage, R. Mason, P. Lagergren, J. Lagergren.
Surgical Prevention of Reflux after Esophagectomy for Cancer
Annals of Surgical Oncology, October 2013;20(11): 3655-61

IV. M. van der Schaaf, P. Lagergren, J. Lagergren
Persisting symptoms after intrathoracic anastomotic leak following oesophagectomy for cancer
British Journal of Surgery, January 2012;99(1):95-9

V. M. van der Schaaf, H. Tilanus, J. van Lanschot, A. Johar, P. Lagergren, J. Lagergren, B. Wijnhoven
The influence of preoperative weight loss on postoperative course after oesophageal cancer resection
Journal of Cardiovascular and Thoracic Surgery, January 2014;147(1): 490-5

1 TABLE OF CONTENTS

2 LIST OF ABBREVIATIONS

AJCC	American Joint Committee on Cancer
ARDS	Adults Respiratory Distress Syndrome
BMI	Body Mass Index
CI	Confidence Interval
CT	Computer Tomography
EORTC	European Organisation for Research and Treatment of Cancer
EUS	Endoscopic Ultrasound
HR	Hazard Ratio
HRQOL	Health-related Quality of Life
OR	Odds Ratio
pTNM	Pathological TNM-stage
PET	Position Emission Tomography
SESS	Swedish Esophageal Cancer Surgery Study
SECC	Swedish Esophageal and Cardia Cancer
TNM	Tumour, Node, Metastasis
UICC	Union for International Cancer Control

3 INTRODUCTION

Oesophageal cancer is a rather uncommon type of cancer in the Western world, however it is the eight most common cancer and sixth leading cause of cancer death worldwide.[1] In Sweden approximately 450 patients are diagnosed with oesophageal cancer every year.[2]

Due to a late and subtle clinical presentation oesophageal cancer carries a poor prognosis, with a 5-year survival of approximately 10% in all patients and 30% among curatively treated patients in population-based studies.[3]

Surgical tumour resection is the most well-established curatively intended treatment. The introduction of neoadjuvant chemotherapy or chemoradiotherapy has improved the long-term survival somewhat, and has become the routine treatment for most resectable cancers, except for very early tumours, in many countries.[4, 5]

Oesophageal cancer resection entails an extensive surgery with a high risk of postoperative complications, including mortality and morbidity. Postoperative mortality has decreased to less than 5% in recent years,[6] but oesophageal resection still carries a substantial risk for postoperative complications, some of which require reoperation.[7-9] Furthermore, oesophagectomy introduces a wide range of physical disturbances of the alimentary tract,[10] and consequently patients often suffer from persisting symptoms long after the operation.[11-13]

Earlier studies have shown that oesophageal cancer resection has a long-standing negative effect on health-related quality of life (HRQOL).[13-16] The wellbeing of a patients is closely associated with their physical symptoms,[17, 18] therefore it is important to refine the surgical technique to prevent undesirable symptoms.

This thesis is based on five studies in which from different angles we aim to identify factors that can improve survival and reduce persisting symptoms among surgically treated oesophageal cancer patients.

4 BACKGROUND

4.1 *THE OESOPHAGUS*

Surgical anatomy

The oesophagus, also known as the “gullet” is a flattened, muscular tube that connects the pharynx to the stomach. The length from the upper- to the lower oesophageal sphincter is 18-26 cm. The oesophagus begins approximately 18 cm from the incisors at the pharyngoesophageal junction. It descends anteriorly to the vertebral column into the thoracic cavity, passes through the posterior mediastinum and enters the abdominal cavity through the hiatus in the diaphragm. There it extends through the gastroesophageal junction to terminate in the cardiac orifice of the stomach.

The oesophagus has three distinct anatomical regions: 1) the cervical oesophagus, extending from the pharyngoesophageal junction (vertebrae C5-C6) to the suprasternal notch (vertebrae T1), 2) the thoracic oesophagus, extending from the suprasternal notch (vertebrae T1) to the diaphragmatic hiatus (vertebrae T10), and 3) the abdominal oesophagus that extends from the diaphragmatic hiatus (vertebrae T10) to the orifice of the cardia of the stomach.

The oesophagus lies in close proximity to several delicate anatomical structures, which has important clinical implications. At the cervical level the oesophagus remains in close posterior relation to the trachea, and anterior relation to the vertebral column. In the thoracic cavity the oesophagus passes posterior to the trachea, tracheal bifurcation and, due to a slight left deviation, it lays in close proximity to the left main stem bronchus and the aortic arch. The lower part of the thoracic oesophagus lies close to the left atrium.

The oesophagus consists of several muscular layers. The internal layer consists of longitudinal fibres and the external layer of circular fibres. The circular layer provides sequential peristalsis, which facilitates transportation of food towards the stomach. Upper and lower sphincters prevent regurgitation of food from the stomach.

The vascularisation of the oesophagus is segmental and consists mainly of branches of arteries supplying other organs. The cervical oesophagus is supplied with blood through branches of the left and right, superior and inferior thyroid arteries. Paired oesophageal branches of the bronchial artery and unpaired branches that arise directly from the anterior wall of the thoracic aorta supply the thoracic oesophagus. The abdominal segment of the oesophagus is provided with blood via the left phrenic artery, a branch of the left gastric artery and with the fundal arteries derived from the splenic artery.[19-21] (Figure 1)

The venous draining system of the oesophagus consists of two distinct systems. The intrinsic system, located in the submucosa, is a parallel network of small draining veins following the entire length of the oesophagus and ultimately drains in the portal vein system. It forms a connection between the portal vein system and the vena cava. The extrinsic venous system, like the arterial vascularisation, is segmental. The blood from the upper oesophagus drains in the azygos and the hemiazygos veins, the blood from the mid and lower oesophagus drains into the left gastric or splenic vein and they drain into the portal vein system. [19,20] (Figure 2)

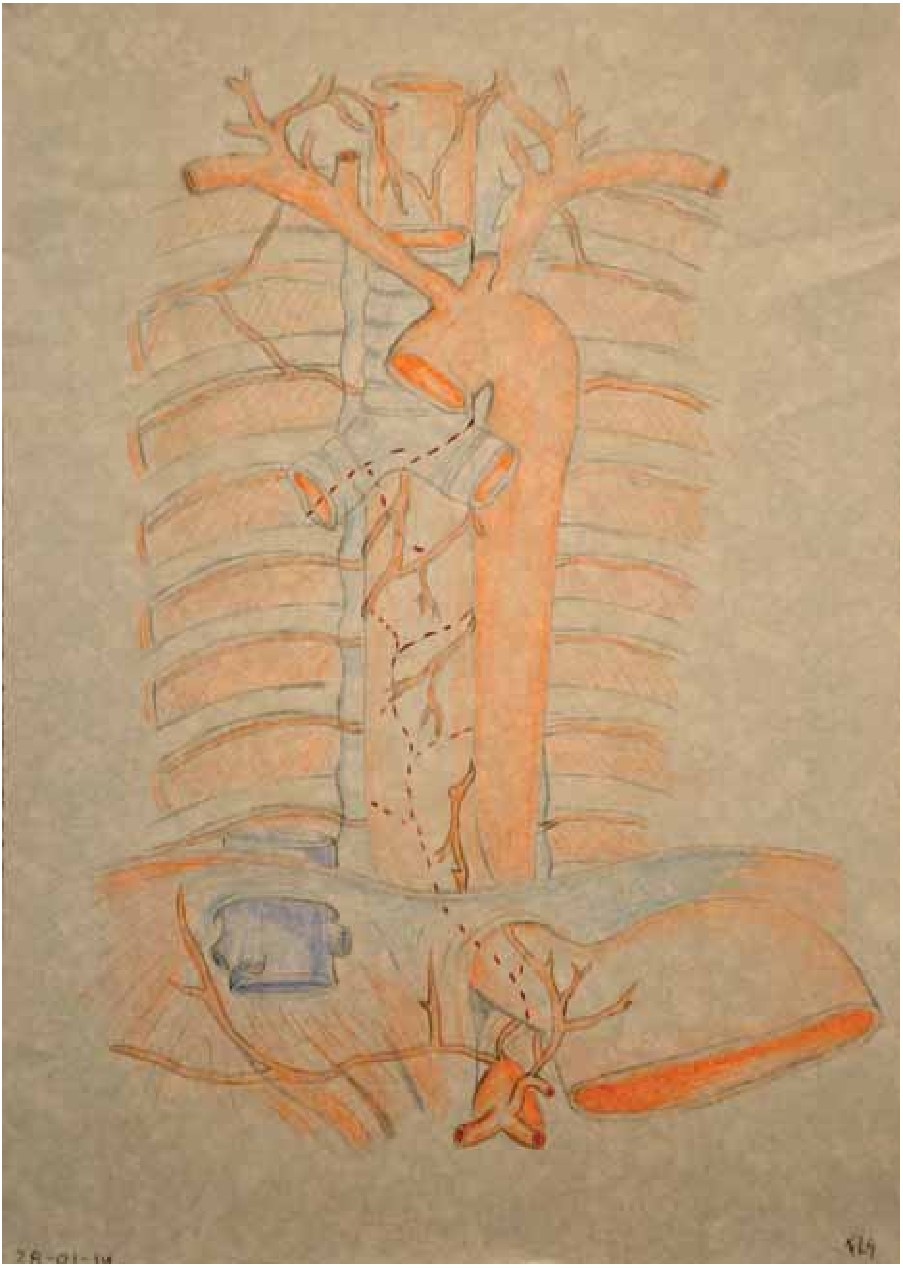

Figure 1. Regional anatomy of the oesophagus and its surrounding structures, arterial blood supply
Courtesy of *Fleur van der Schaaf*

Figure 2. Regional anatomy of the oesophagus and surrounding structures: venous drainage

Courtesy of *Fleur van der Schaaf*

The lymphatic drainage system of the oesophagus consists of lymphatic vessels and lymph nodes. The lymphatic vessels originate in the oesophageal tissue as a network of endothelial channels. Drainage of lymphatic fluid is segmental and differs in various anatomical regions of the oesophagus. Lymphatic fluid of the upper part of the oesophagus drains into the deep cervical lymph nodes and then into the thoracic duct. The lymphatic fluid of the middle segment drains into the superior and inferior mediastinal lymph nodes. The lower third drains into the lymphatic vessels that follow the left gastric artery and ultimately the gastric and celiac lymph nodes. The pattern of lymph flow can help predict potential tumour invasions and spreading patterns.[19] (Figure 3)

Similar to other internal organs, the oesophagus receives dual motor and sensory innervation via the sympathetic and parasympathetic division of the autonomic nervous system. The upper segment of the oesophagus is innervated by the glossopharyngeal nerve and the full length it is supplied by branches of the vagal nerve.[20] Additionally, it has its own intrinsic neural system composed of flat nerve networks in the muscular layers that form the myenteric and submucosal plexus. The ganglia between the longitudinal and circular layers form the Auerbach's plexus ganglia that lie in the submucosa form the Meissners plexus.[19,21]

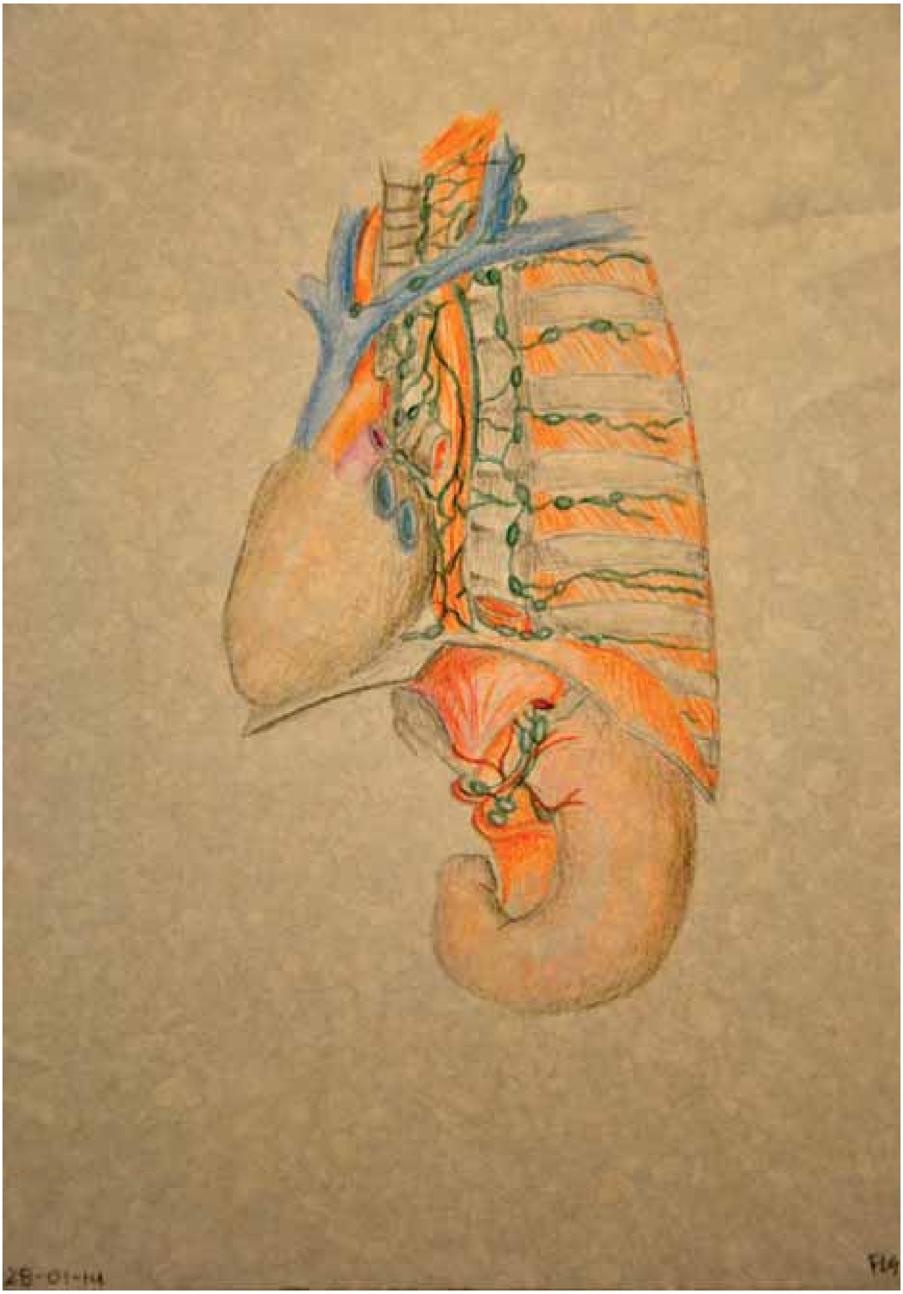

Figure 3. Regional anatomy of the oesophagus and its surrounding structures, lymphatic drainage
Courtesy of *Fleur van der Schaaf*

Histology

Microscopically, the oesophageal wall, like the rest of the alimentary tract, consists of four layers: the internal mucosa, submucosa, muscularis propria and advertitia. A non-keratinised squamous epithelium lines the entire length of the lumen of the oesophagus, however, at the gastroesophageal junction it may coexist with a gastric type columnar epithelium.[19-22] Unlike the rest of the gastrointestinal tract, the oesophagus has no serosa,[19, 23] which means that oesophageal cancer tends to spread more easily and surgical anastomoses of the oesophagus might be weaker than those of other organs.[23]

4.2 OESOPHAGEAL CANCER

Epidemiology

The two main histological types of oesophageal cancer, squamous cell carcinoma and adenocarcinoma, have a similarly poor prognosis but have otherwise distinct pathological features and epidemiological patterns. A characteristic of oesophageal cancer is the marked variation by geographical area, gender and ethnicity.[24] While the incidence of oesophageal squamous cell carcinoma is decreasing, the incidence of oesophageal adenocarcinoma is increasing worldwide.[25-28] In Europe alone nearly 46,000 patients were diagnosed with oesophageal cancer in 2012, and 39,000 patients died of the disease in the same year.[28] The lifetime risk of developing oesophageal carcinoma is 0.8% for men and 0.3% for women. The risk increases with age, and the mean age at diagnosis is 67 years.[29]

Variation in incidence of oesophageal cancer in different geographical areas is striking. In the so called ‘oesophageal cancer belt’, which encompasses Turkey, North-Eastern Iran, Kazakhstan, and Northern and Central China the incidence of squamous cell carcinoma is as high as 100 per 100,000 people yearly.[30, 31] The UK has the highest overall incidence of oesophageal adenocarcinoma for reasons yet unknown.[3, 26] Squamous cell carcinoma is still the most common type of oesophageal cancer worldwide. However, between 1975 and 2004 the incidence of adenocarcinoma among white men in the USA increased by 463%, leading to an overall incidence rate of oesophageal cancer

among white men of 8.34 per 100,000 patient years. The same trends are seen in the UK, other Western European countries and Australia.[3, 32, 33]
There is a striking male to female ratio difference in oesophageal adenocarcimona,[17, 18] which differs across geographical areas. In high-risk areas the differences seem to be smaller than in low risk areas where the ratio is as high as 9:1.[3, 32, 34, 35]

Pathology

Squamous cell carcinoma and adenocarcinoma have distinct pathological pathways and risk factors.
The main risk factors for oesophageal adenocarcinoma are gastro-oesophageal reflux,[33, 36-40] Barrett's oesophagus[3, 29, 41-43] and obesity.[37, 44-46] Patients reporting symptomatic reflux at least once a week have an almost eight times as high risk of developing adenocarcinoma than a control group. Patients reporting troublesome reflux during the night are at even greater risk of developing adenocarcinoma.[38] Barrett's oesophagus is another major risk factor for oesophageal adenocarcinoma.[29] It is defined by the metaplastic transformation of the normal squamous cell epithelium lining the oesophagus, to an intestinal type columnar epithelium,[42, 43] as was first described in 1950 by Norman Barrett.[47, 48] The transformation from the metaplastic Barrett's oesophagus to oesophageal adenocarcinoma is a multi-step process. It includes transformation from metaplasia or non-dysplastic disease to low-grade dysplasia, then to high-grade dysplasia and then to adenocarcinoma.[42] Barrett's oesophagus can be considered an acquired pre-malignant disease. Pathogenesis of the development of the pre-malignant stage to adenocarcinoma is still largely unknown. Barrett's oesophagus is strongly correlated with gastro-oesophageal reflux disease.[29, 41-43, 49] The risk of developing an oesophageal adenocarcinoma in a Barrett's oesophagus is up to 6 to 7 per 100,000 patient years,[43] although recent studies show a lower risk.[49] Central obesity, more than a high BMI alone, seems to play an independent role in the development of both Barrett's oesophagus and adenocarcinoma.[50, 51] People with central obesity have a higher level of insulin-like growth factor,

which stimulates cell proliferation, inhibits apoptosis and determines cell differentiation.[29, 51, 52] Additionally, obese people have a higher serum level of leptin, a hormone secreted by visceral fat that possibly promotes carcinogenesis. [29, 52-54]

Tobacco smoking is a modest risk factor for adenocarcinoma, though alcohol consumption does not seem to be a risk factor.[39, 46, 55] It has been suggested that infection with Helicobacter pylori bacteria has a protective effect against adenocarcinoma, possibly by a mechanism including gastric atrophy and reduced acid secretion.[56-58]

The principal risk factors for the development of squamous cell carcinoma are excessive tobacco smoking and alcohol intake.[33, 37, 59-62] A clear synergistic effect of combined tobacco smoking and alcohol consumption has been seen.[59] Other weaker risk factors that have been suggested include ingestion of hot beverages, consumption of fungus food, dietary deficiencies and infection with human papilloma virus (HPV).[63, 64]

Diagnosis and staging

Diagnosis and staging of oesophageal cancer is a multidisciplinary process.[65] Oesophageal cancer patients most often present with progressive dysphagia accompanied by weight loss and fatigue.[3, 33, 37] Less often oesophageal cancer presents as hoarseness, dyspnoea, coughing or pain, which all typically reflect an advanced disease.[3] On physical examination of the patient there are often no clinical signs of disease. Due to the elasticity of the oesophageal wall, symptoms of dysphagia might not occur until the tumour is in an advanced stage and obstructs the larger part of the lumen of the oesophagus. Due to this late presentation of oesophageal cancer, over 50% of patients have an unresectable disease by time of diagnosis.[37]

Oesophageal cancer is diagnosed by upper gastrointestinal endoscopy.[3, 33, 37, 65, 66] During this procedure biopsies are taken to histologically confirm the diagnosis which is most accurate when at least 6 biopsy samples are taken.[66] For further staging, endoscopic ultrasound (EUS) is performed to assess the depth of the tumour invasion and thus define the T-stage of the tumour.[66, 67] It also aids in detecting suspected locoregional lymph nodes through EUS-guided fine needle aspiration.[67, 68] A computer tomography (CT) of the abdomen and thorax is primarily used for the detection of any distant metastasis.[66, 68, 69] Positron emission tomography (PET) scans have also been shown to be valuable in this process.[33, 37, 66, 69, 70] The staging classification most often used is the tumour nodal metastasis (TNM) system developed by Pierre Denoix in the 1940's,[33, 71] and maintained by the International Union Against Cancer (UICC) and the American Joint Committee on Cancer (AJCC). The TNM system takes into account the depth of the tumour invasion (T), the involvement of lymph nodes (N), and presence of distant metastatic disease (M).[33] Accurate staging is of great importance since it dictates the prognosis and the choice of treatment.[3, 66, 67, 72]

Treatment

Surgical treatment

"*The aims of radical cancer surgery are: (a) to cure disease; while (b) rendering the patient's life useful and enjoyable, or at least bearable"- Ivor Lewis, 1946.*

Surgery of the oesophagus has been historically problematic due to the inaccessibility of the organ, lack of a serous coating and its proximity to structures where infection is especially dangerous and rapid.[73,74] This has considerably delayed the development of oesophageal cancer surgery in the past.[75,76] There are only a few reports on surgery of the oesophagus from ancient and classic periods. The first written observations of oesophageal anatomy and pathology stem from ancient Egypt, written on the "Smith Surgical Papyrus" found in 1862 by archaeologist Edwin Smith.[77] Many surgeons have had reservations about operating on the oesophagus in the past due to its tricky anatomical location. In 1877 a surgeon named Czerny performed the first successful resection of the cervical oesophagus.[76] Czerny was a pupil of Theodore Billroth, "the founding father of abdominal surgery".[78] Czerny successfully removed an annular tumour, just below the pharynx, through a local excision in the neck. The remnant pieces of the oesophagus were closed blindly and a cervical oesophagostomy was created for feeding purposes.[76]

General developments in medicine facilitated the development of oesophageal surgery, which resulted in the first successful transpleural oesophagectomy, performed by Torek in 1913.[74] He removed a mid-oesophageal tumour by an incision through the seventh intercostal space and the remnant upper stump of the oesophagus was tunnelled under the skin to make an oesophagostomy on the anterior chest wall. Continuity of the oesophagus was never restored during those years.

With the use of the Kocher manoeuvre to mobilise the duodenum, it was discovered in 1947 that the stomach could be placed in the thoracic cavity, facilitating oesophagogastrostomy and restoration of continuity of the gastrointestinal tract. The first successful resection with direct reconstruction, with oesophagogastric anastomosis, was described by Oshawa in Japan in 1933.[76] The British surgeon Ivor Lewis developed a method for resection of the middle third of the oesophagus, first described in the literature in 1946.[73] His two-stage right-sided thoracotomy technique with laparotomy to mobilise the oesophagus and stomach is still often used for tumours of the oesophagus or gastroesophageal junction.[73, 79] Historically, this procedure was performed with a week in between the thoracotomy and the laparotomy.[80]

The transhiatal oesophagectomy has been performed in many different ways by surgeons in the past,[81] but was brought attention again in 1978 by the American surgeons named Orringer and Sloan.[82, 83] The aim of the performance of a transhiatal, rather than a transthoracic oesophagectomy, was the avoidance of a combined thoracic and abdominal incision in debilitated patients, and avoidance of an intrathoracic anastomosis with the potential to leak and cause life-threatening mediastinitis.[84]

Despite the introduction of multimodal strategies in the treatment of oesophageal cancer, surgical tumour resection is still the cornerstone of oesophageal cancer treatment. There are a large number of surgical techniques currently used to remove the oesophagus of which the most used, transthoracic and transhiatal oesophagectomy will be described below.

Transthoracic oesophagectomy

The classic transthoracic Ivor Lewis oesophagectomy is a combined approach: a laparotomy and right-sided thoracotomy. The abdominal procedure often starts with a midline epigastric incision extending into the paraumbilical region. (Figure 4) This allows meticulous exploration of the abdomen to assess tumour extent and spread; in this stage the stomach is mobilised. The left gastric artery and vein are divided and the short gastric vessels are divided. The right gastric artery and mainly the gastro-epiploic arch are now the only contributors of blood supply to the gastric conduit. Lymphatic tissue along the celiac axis is often resected during the abdominal part of the oesophagectomy. A Kocher manoeuvre is sometimes performed to mobilise the duodenum, to facilitate the gastric pull-up and the stomach is used to create an oesophageal substitute, usually by making it into a gastric tube.

The thoracic part of the operation begins with a right-sided posterolateral thoracic incision, (Figure 4) which allows exposure of the oesophagus without interfering with the aortic arch. The oesophagus is mobilised while the azygos vein is divided. After this the oesophagus is dissected while mediastinal, perioesophageal and subcarinal lymph nodes are often removed. The oesophageal substitute is brought into the chest and connected to the remnant proximal oesophagus, often with an end-to-side anastomosis in the upper chest. (Figure 5)

A variation on the Ivor Lewis oesophagectomy is the 3-incision, or McKeown, oesophagectomy, where an additional right-sided cervical incision is made and the anastomosis is created in the neck instead of the upper chest. This technique is preferred for patients with tumours above the carina. The cervical incision allows wider resection margins for tumours of the upper third of the oesophagus.[85] This procedure usually starts with a thoracotomy rather than with a laparotomy to allow assessment of the thoracic resectability of the tumour. After that, the abdominal part with the gastric mobilisation is similar to the Ivor Lewis oesophagectomy. As a last step, a right cervical incision is made along the anterior border of the sternocleidomastoid muscle, to mobilise and resect the cervical part of the oesophagus. The resected oesophagus is removed through the abdominal incision and the oesophageal substitute is pulled up to the neck through the posterior mediastinum. Finally, a cervical end-to-end or end-to-side anastomosis is created.[19, 79]

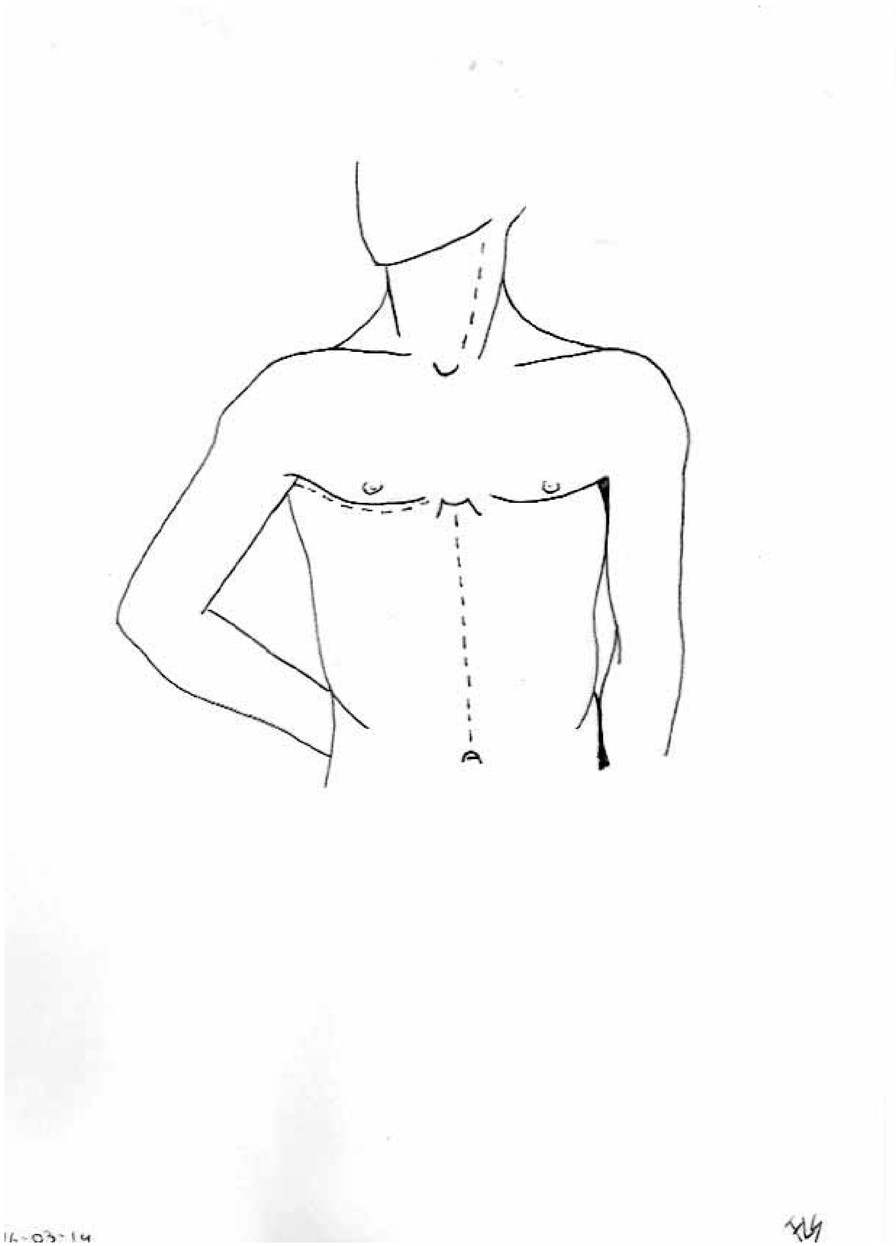

Figure 4. Schematic overview of the incisions (dotted lines) during transthoracic oesophagectomy and transhiatal oesophagectomy
Courtesy of Fleur van der Schaaf

Transhiatal oesophagectomy

During transhiatal oesophagectomy, the resection of the oesophagus is accomplished through incisions in the abdomen and in the neck. (Figure 4) The distal part of the oesophagus and the most proximal part are dissected under direct vision, but a part of the thoracic oesophagus is blindly mobilised. The operation begins in the same fashion as the transthoracic oesophagectomy, with an incision and exploration of the abdomen, exposure of the diaphragmatic hiatus, resection of the lymph nodes along the celiac axis and mobilisation of the stomach. The gastroepiploic arch is preserved while the left gastric artery and vein are divided. To widen the hiatus and obtain better visibility and accessibility, the diaphragm is usually incised anteriorly. The blunt dissection of the thoracic oesophagus is performed posteriorly along the aorta and spine followed by anterior dissection along the trachea and pericardium. The lateral aspects of the oesophagus are more complicated to dissect bluntly as they include small vessels and branches of the vagal nerve. A left cervical incision is made and dissection of the cervical oesophagus is performed. (Figure 4) Mobilisation of the upper thoracic oesophagus is performed by manual dissection by entering the mediastinum through the cervical incision and the lower oesophagus is mobilised from the abdominal side through the incision in the hiatus. The oesophagus is divided in the neck and gastric conduit or colon is brought to the neck after resection of the specimen containing the tumour. A side-to-side or end-to-side cervical anastomosis is created and the hiatal opening in the diaphragm is sometimes narrowed.[19, 79, 80]

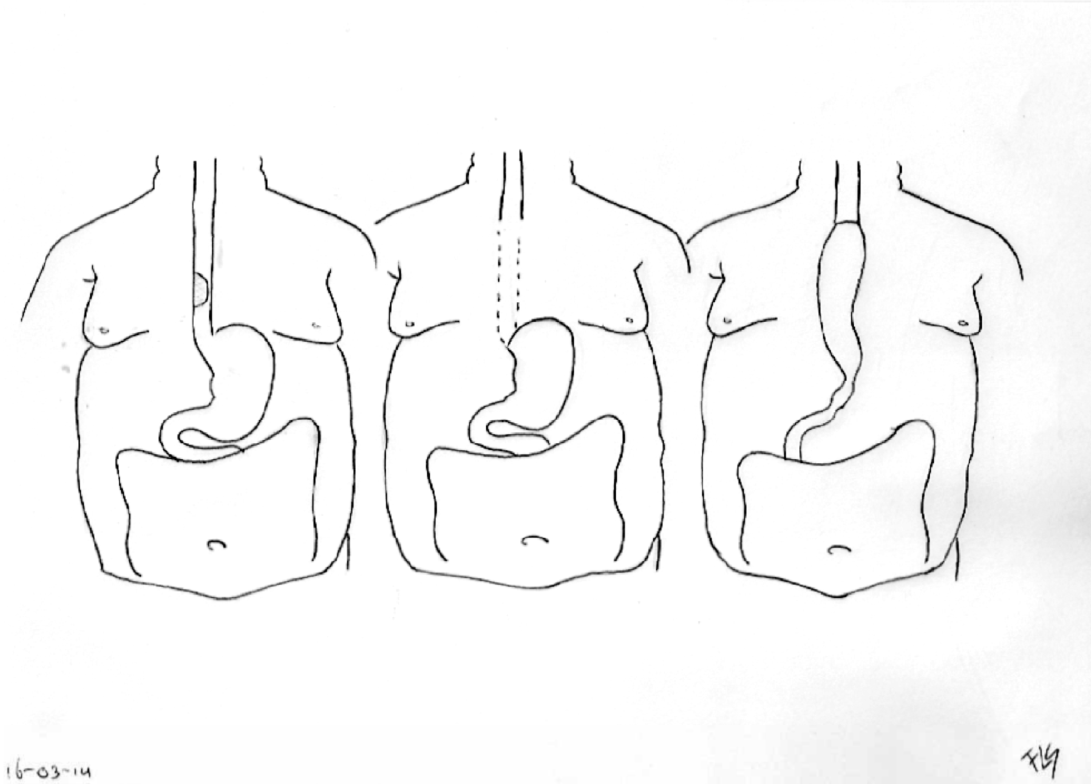

Figure 5. Gastric tube pull-up after oesophagectomy

Technical considerations

Choice of surgical approach

The choice of surgical approach depends on several factors: the location of the tumour, the desired extent of lymph node resection (see section "*Extent of lymph node dissection")* and comorbidity, the patient's habitus and also the surgeon's experience and preference.[79]

The transthoracic approach seems to be more common in patients with oesophageal tumours, while transhiatal might be more suitable for patients with gastroesophageal junction tumours or cardia tumours. [86]

Some retrospective studies have shown a higher risk of pulmonary complications after transthoracic oesophagectomy.[87] These results were confirmed in a recent randomised controlled trial;[88] the length of intensive care and hospital stay were longer in the transthoracic group. However, no studies have been able to show a significant survival difference in favour of any one of the two main approaches. One randomised controlled trial (RCT) showed a trend towards a better 5-year survival in favour of the transthoracic group, but this did not reach statistical significance.[89] Subgroup analyses of an updated version of the same RCT showed improved overall and disease free survival in patients with 1-8 positive lymph nodes in favour of the transthoracic approach, while this was not the case for patients without involved lymph nodes or those with more than 8 metastatic lymph nodes.[89] The use of one-lung ventilation during transthoracic oesophagectomy could cause excessive stress on both the ventilated and the unventilated lung and might induce post-ventilation injuries.[90] Consequently, for patients with comorbid lung disease, a transhiatal approach without thoracotomy might be safer. Preoperative respiratory dysfunction has been associated with an increased risk of pulmonary complications.[91] Since the risk of pulmonary complications is higher after transthoracic oesophagectomy, patients with preoperative pulmonary dysfunction might be better off undergoing a transhiatal oesophagectomy.

Minimally invasive oesophagectomy

During recent years several minimally invasive techniques have been developed for both transthoracic and transhiatal oesophagectomy. Surgeons

around the world more and more frequently use minimally invasive techniques and its development is ongoing.[68, 86] Other techniques, such as thoracoscopic and laparoscopic techniques are also used to perform oesophagectomy. Minimally invasive oesophagectomy has been shown to decrease blood loss during operation, and decrease the risk of some postoperative complications.[92] However, the rate of severe complications is similar to open techniques as is postoperative mortality.[93, 94] There is in particularly a higher risk of gastric tube necrosis with minimally invasive techniques that needs further investigation.[68] Oncological outcomes are still under investigation; no long-term follow-up studies are yet available. However, existing data indicate a similar survival after minimally invasive oesophagectomy and open oesophagectomy.[93, 94]
If minimally invasive oesophagectomy will be the standard treatment for oesophageal cancer patients in the near future remains to be seen as there are still several safety and long-term outcome issues that remain to be investigated. For example, the safety of thoracoscopic-assisted resection after radiotherapy is under debate.[94] Another problem is the learning curve;[95] to date no large high quality studies have been performed,[86] and further research is warranted before any recommendations can be made.

Extent of the lymph node dissection

The extent of the lymph node dissection has since long been a subject of debate. Nodal status is considered on of the most important prognostic factor after oesophageal cancer resection[96] and radical lymphadenectomy might therefore be important to improve survival.[97] The aim with a more extensive lymphadenectomy is improvement of the staging, the reduction of local recurrence and ensuring oncological completeness of the resection.[96, 98] It should be taken into consideration, however, that a more extensive lymphadenectomy increases the surgical trauma and the risk of complications.[98, 99] There is a delicate balance between optimal oncological treatment and the prevention of postoperative complications and early death. Current clinical guidelines typically recommend an extensive two-field lymphadenectomy, although the scientific evidence to support such a strategy is weak.[33, 68, 86, 100]

Multimodal treatment

Multimodal treatment for oesophageal cancer (e.g. chemo- or chemoradiotherapy) combined with surgery has long been a subject of debate,[5] and local clinical policy has often dictates the treatment regimen for oesophageal cancer patients.

Neoadjuvant treatment of oesophageal cancer aims to decrease the risk of recurrence and distant metastasis by eliminating micro metastasis and aiming to increase radical resectability.[101] In the past, mixed results have been published, some studies showing a survival advantage[102, 103] from neoadjuvant chemo or chemoradiotherapy and some studies showing no such advantage.[101, 104, 105] However, in recent years some high quality RCTs have shown that there is a significant survival benefit from multimodal treatment.[4, 5, 102, 106] It remains unclear whether patients benefit most from perioperative chemo-[107, 108] or chemoradiotherapy, however.[109, 110]

Complications

Despite the improvements in surgical technique, anaesthesia and postoperative care, oesophagectomy is still risky surgery with a reported mortality rate of 1.6-4.0% and morbidity rate of 29-45%. [111-115]

The majority of patients develop a medical complication rather than a surgical technical complication.[112] Pulmonary complications, in particular pneumonia, are the most frequently reported serious complications and one of the most frequent causes of postoperative death.[112, 115-117] The high incidence of postoperative pulmonary complications is caused by the combination of the two stages of the traditional Ivor Lewis oesophagectomy: thoracotomy and laparotomy. The tumour sub-site is an important factor for the development of pulmonary complications, with the highest risk in upper abdominal and thoracic procedures.[118] Other commonly reported medical complications are (often benign) cardiac arrhythmias, myocardial infarction, infections (urinary tract infections, infective diarrhoea) and neurological complications.[112, 114, 115, 117]

Intrathoracic anastomotic leaks are one of the most feared and severe surgical complications following oesophageal resection, responsible for 25-50% of postoperative deaths.[112, 119-121] The reported incidence of intrathoracic anastomotic leaks is between 3% and 12%.[119-124] The leak rate in cervical anastomosis is higher and can be up to 50%.[121, 125] The aetiology of anastomotic leaks is multi-factorial, but ischemia of the oesophageal substitute (conduit) and surgical technical errors seem to be the most important predisposing factors.[121, 126] Also, an important patient related factor that is associated with a higher risk for anastomotic leak is comorbidities that compromise vascularisation and blood.[125, 127] The severity of the anastomotic leak and its consequences are largely dependent on the location of the anastomosis and containment by the surrounding tissue.[128, 129] Leakage of gastro-intestinal contents into the thoracic cavity can have disastrous consequences, such as fulminant mediastinitis and septicaemia,[122] while leakage in the neck are less severe from this point of view.

Benign anastomotic strictures are common after oesophageal resection. There are several known risk factors for such a stricture; cervical anastomosis tends to cause strictures more often than intrathoracic anastomosis,[130] and another risk factor is anastomotic leak.[124, 131, 132] Anastomotic strictures might give rise to symptoms of dysphagia and trouble eating and can be quite debilitating for patients.[130, 132]

Prognosis

Cancer mortality in general has slowly but steadily decreased over the past decades, with the exception of pancreatic cancer and lung cancer in females.[133, 134]

Despite attempts to improve the diagnostic procedure, staging and treatment, the prognosis for oesophageal cancer patients remains poor.[3] However, over the last five decades the prognosis has improved to some extent. A population-based study with data from Sweden showed that 5-year survival for adenocarcinoma has improved from 4% in the early 1960’s to 10.5% in the late 1990’s. For squamous cell carcinoma, the 5-year survival increased from 3.8% to 7% during the same period.[135] Overall survival for both histological types 1, 3, and 5 years after surgery was 61.7%, 39.9% and 30.7%, respectively, in the late 1990’s to the early 2000’s compared to 46.5%, 24.1% and 19.7% in the late 1980's.[136] This improved survival compared to earlier decades could not be explained by differences in patient characteristics, and might be due to improved surgical treatment. Recent studies using mortality data from the Word Health Organisation (WHO) reported a continuing decline in mortality after oesophageal cancer diagnosis.[25, 137]

There are several known prognostic factors that influence survival in patients who have undergone surgical tumour resection. Several studies have shown that increasing age is a marker of worse prognosis.[135, 138, 139] Strong prognostic factors include tumour stage,[72, 140] tumour differentiation,[72, 141] lymph node status,[142-144] and surgeon and hospital volume.[145-149]

Health-related quality of life (HRQOL) and persisting symptoms

Health-related quality of life: The concept

Over the last 30 years, due to tremendous improvements in treatment and survival for most cancers, there has been increased concern about the cancer patient's wellbeing and psychosocial functioning. Quality of life has been referred to in many ways depending on the time and the circumstances. In the declaration of independence of the United States of America it is referred to as the "right to pursue happiness", and during the Great Depression in the 1930's it was material objects and wealth that determined quality of life. In the 1960's the social aspects of health and quality of life gained more acceptance. Quality of life became the pursuit of individual happiness and individual growth, rather than possessions or accomplishments.[150] However, this posed a challenge, since happiness and personal growth are not objective measures and it became difficult to reliably measure this new concept of quality of life. The idea emerged that quality of life was a multidimensional construct influenced by different aspects in a person's life such as social, emotional, physical and economic wellbeing.

Health-related quality of life has been described as encompassing those aspects of overall quality of life that clearly affect physical or psychological health. It refers to broad concepts of physical, psychological and social-wellbeing often assed in patients with different diseases.[151-153]

Health-related quality of life in cancer patients

Cancer has relatively recently gained the status of a manageable, chronic disease rather than one which is fatale. This has caused a delay in the development of the HRQOL constructs in these patients in the past.[150] For many years, survival was the single endpoint in much clinical cancer research.[154] However for patients, HRQOL is a very important outcome measure. Oesophageal cancer patients often suffer from severe symptoms and a decrease in HRQOL long after surgery.[13, 155, 156] The experience of symptoms in long-term survivors of oesophageal cancer surgery deserves attention since previous research shows that the surgery substantially influences symptom experience negatively in the short- and longer-term.[11, 156-159] Six months after surgery patients report a deterioration in role function, social function and several symptoms, including appetite loss, diarrhoea, dyspnoea, trouble eating, reflux, odynophagia, dry mouth, dysphagia, coughing and chest pain.[156, 160] There has been an advance in the development of HRQOL assessment tools and validated questionnaires that can reliably measure HRQOL are available.[156] There are both general cancer-specific questionnaires and site-specific questionnaires developed. HRQOL has become an accepted and increasingly acknowledged outcome, and is usually included in current clinical trials. In this thesis we chose to use the well-established cancer-specific questionnaire developed and validated by the European Organization for Research and Treatment of Cancer (EORTC), the QLQ-C30,[161-163] and the oesophageal cancer-specific module, the QLQ-OES18.[162] The QLQ-C30 is a cancer-specific core questionnaire that contains questions about symptoms that are common amongst cancer patients. The questionnaire consists of 30 questions which create 5 functional scales (emotional, physical, cognitive, social and role function), 1 global quality of life scale and 3 symptom scales (fatigue, nausea and vomiting, and pain). It also contains 6 single items common amongst cancer patients (dyspnoea, sleeping disorders, loss of appetite, diarrhoea, constipation and financial problems). The oesophageal cancer-specific questionnaire, the QLQ-OES18 assesses symptoms commonly reported by oesophageal cancer patients. The QLQ-OES18 consists of 18 questions which generate 4 symptom scales (dysphagia, eating difficulties, reflux and odynophagia) and 6 single items (dry mouth, trouble swallowing saliva, choking, taste, cough and speech difficulties).

Symptoms

The concept of symptom experience has been described as “the occurrence of sickness or disease and the patient’s response to the symptoms”, but to date no clear concept has been formulated.[164] Besides a reported decrease in general HRQOL and functioning, patients with oesophageal cancer often report persisting symptoms long after treatment has been completed.[10, 154] In this thesis we chose to assess symptoms often reported by oesophageal cancer patients rather than general HRQOL since the selected symptoms potentially influence all aspects of quality of life.[164] Symptoms were measured using the questionnaires mentioned in the section above and, hence, are subjective rather than objective measures.

Persisting symptoms

Oesophagectomy for oesophageal cancer is one of the most extensive surgical procedures used in humans. Besides the postoperative complications and long recovery, patients often suffer from persisting symptoms long after the operation.[11-13] Oesophagectomy introduces a wide range of physical disturbances of the alimentary tract.[10]

Gastro-oesophageal reflux of duodeno-gastric contents (reflux) is a common and troublesome problem whenever a gastric conduit replaces the resected oesophagus.[10, 165, 166] Symptoms of reflux have been reported by up to 60-80% of patients after oesophagectomy.[18, 167] Such postoperative reflux, especially when using a supine position, introduces a risk of aspiration pneumonia.[18] After such surgery, reflux might present as regurgitation, aspiration (pneumonia) or chronic cough rather than as heartburn, which is normally a cardinal symptom of reflux. Reflux is caused by disruption of several natural antireflux barriers, e.g. the lower oesophageal sphincter, the angle of His, and the diaphragmatic sling, and the creation of a positive intra-abdominal pressure.[18, 168] Post-oesophagectomy reflux can have disrupting consequences; it can cause reflux oesophagitis and Barrett's oesophagus of the oesophageal remnant, and aspiration.[169]

Some potential solutions to prevent reflux after oesophagectomy have been studied, but many of the results are conflicting. The role of the location of the anastomosis remains a subject of debate. It has been hypothesises that a cervical anastomosis might be less associated with reflux compared with an intrathoracic anastomosis, since a cervical anastomosis reduces the amount of stomach exposed to the positive intra-abdominal pressure.[18, 170] Some studies hypothesised that a cervical anastomosis is more likely to cause reflux and some studies argue that an anastomosis below the aortic (e.g. intrathoracic) arch is "refluxogenic" since a larger part of the remnant oesophagus is exposed to positive intra-abdominal pressure.[14] A suggested surgical solution is the creation of an "anti-reflux anastomosis" that might prevent reflux.[17, 18, 166]

Whether pyloric drainage reduces the risk of reflux after oesophagectomy is a matter of debate. Results from previous studies are contradictory,[171-174, 175] one study showed absence of reflux after the pyloric drainage procedure,[176] while others have shown an increase in bile reflux after pyloric drainage procedures.[172, 174] Proton-pump inhibitors are routinely prescribed after oesophagectomy and they might be the most potent solution to counteract postoperative reflux, however, few studies have been published on this subject.[177]

Delayed gastric emptying is another frequently reported problem. The necessary bilateral vagotomy during oesophagectomy typically causes dysmotility of the gastric remnant and the pylorus, causing gastric outlet dysfunction.[10, 171] These two phenomena might cause symptoms of delayed gastric emptying. Patients with delayed gastric emptying clinically present with nausea and vomiting, regurgitation, early satiety and post-prandial fullness.[10, 171] Besides troublesome symptoms, delayed gastric emptying may give rise to serious complications such as aspiration pneumonia, which can be fatal.[178]

There is currently no clear consensus regarding the best approach to prevent delayed gastric emptying and the results of previous studies have been contradicting.[167, 172, 174, 179]

Other, less frequent symptoms include dysphagia,[167] fatigue, diarrhoea[12], nausea and vomiting and loss of appetite.[11, 159]

5 AIMS OF THE STUDIES

5.1 OVERALL AIM OF THIS THESIS*:*

To identify factors that can improve survival and reduce persisting symptoms among surgically treated oesophageal cancer patients

5.2 SPECIFIC AIMS OF THE STUDIES IN THIS THESIS WERE:

- To assess how lymph node clearance (the number of lymph nodes resected, the number of metastatic lymph nodes and the lymph node ratio) influence survival of oesophageal cancer patients.
- To examine the impact of reoperation within 30 days of operation, on long-term survival after primary oesophageal cancer surgery.
- To clarify if an anti-reflux anastomosis, cervical anastomosis or pyloric drainage prevent reflux or dysphagia 6 months after oesophagectomy for cancer.
- To reveal whether intrathoracic anastomotic leak influences the development of symptoms after oesophagectomy for cancer.
- To investigate any influence of preoperative weight loss (>10%) on the postoperative course.

6 MATERIAL AND METHODS

6.1 DATA SOURCES

Studies I and II

"The Swedish Esophageal Cancer Surgery Study (SESS)"

This Swedish nationwide population-based retrospective cohort included patients who have undergone oesophageal cancer resection with curative intent in the period between 1987-2010. Patients eligible for inclusion were identified from the Swedish Cancer Register, a nationwide register with 98% coverage.[180, 181] Patients were identified from the Cancer Register using the diagnostic code for oesophageal cancer (150.0, 150.8, and 150.9) according to the 7th version of the International Classification of Diseases (ICD7). The oesophageal cancer patients who underwent tumour resection were identified from the Swedish Patient Registry, which has an excellent (99.6%) positive predictive value for oesophageal surgery.[182] Additionally, relevant medical records containing operation notes and histopathological reports of the studied patients were retrieved from all hospitals in Sweden where oesophageal cancer surgery had been performed. All medical records were carefully reviewed according to a predefined study form. Data regarding lymph node resection, neoadjuvant therapy, as well as tumour (TNM) stage, location, (surgical) radicality and histology were obtained from these records. Tumour stage was classified according to the 6th TNM classification of the Union Internationale Contre le Cancer (UICC), as some information that is necessary to stage according to the 7th edition of the TNM classification was not available when the cohort was initiated in 1987. The accuracy of the histopathological review was assessed by two researchers who independently reviewed 100 patient records, showing high accuracy (>90% concordance).[136] Information on patients' comorbidity and hospital admittance were collected from the Swedish Patient Registry.[182] By linking the oesophageal cancer surgery cohort to the highly complete and continuously updated Swedish Causes of Death Registry, data on death dates and causes of death were ascertained.[183] The linkage of data from all individual cohort members between registries and medical records were made possible by virtue of the Swedish 10-digit personal identity number, assigned to each Swedish resident upon birth or immigration.[184] Patients were followed-up until death or the end of the study period (31st of December 2012), whichever occurred first.

Studies III and IV

"The Swedish Esophageal and Cardia Cancer study (SECC)"

SECC is a prospective nationwide research cohort that includes 90% of all newly diagnosed patients with oesophageal or cardia cancer in Sweden, who underwent surgery between 2001 and 2005.[185] The establishment of SECC was facilitated by an earlier established collaboration with the nationwide Swedish network of hospitals and physicians involved in the diagnosis and treatment of oesophageal cancer patients.[38, 106, 114, 154] Patients in SECC were identified shortly after histopathological confirmation of the diagnosis, through collaboration with the pathology departments of the participating hospitals. A specialised project coordinator, who was a key contributor to the collection of the data and she (Eja Fridsta) received all the histopathological reports from the pathology departments and reminded physicians to include their oesophageal cancer patients in the study and send all clinically relevant information. She was also responsible for the assembly of all the files into the database. Before inclusion in the SECC study, informed consent was obtained from all patients. SECC contains details on tumour characteristics, surgical procedures and complications as well as HRQOL data. The clinical data was collected through medical records according to a predefined protocol, to ensure objectivity and uniformity. The almost complete national coverage and the detailed prospective data collection and objective review of each case ensured good validity.
The data collection additionally contains HRQOL assessments at three points: 6 months, 3 years and 5 years after surgery. Collection of 10-years post-surgery follow-up data is ongoing. In SECC the cancer-specific HRQOL questionnaire, the QLQ-C30 and the oesophageal cancer-specific questionnaire, the QLQ-OES18, were used to assess HRQOL. The project coordinator contacted and reminded patients to return the questionnaires.

Patients were followed up, regarding survival, until 5 years after surgery or until death, whichever occurred first.

Study V

"The Rotterdam Oesophageal Cancer database "

The Rotterdam Oesophageal Cancer database was established in 1978 by the Rotterdam Oesophageal Cancer Group. Included were patients diagnosed with invasive squamous cell carcinoma or adenocarcinoma of the oesophagus or gastroesophageal junction. Patients were treated at the Erasmus MC-University Medical Center in Rotterdam, the Netherlands. All included patients had undergone surgical tumour resection, with or without preoperative chemotherapy or chemoradiotherapy, from May 1, 1990 to October 29, 2010. Up until October 29, 2010 a total of 1271 patients were included. Information on patient demographics, clinical and pathologic characteristics, treatment, surgical procedure, and postoperative course was partly prospectively and partly retrospectively abstracted form medical records by a data manager.

Table 1. Overview study design and methods

	Studies I and II	**Studies III-IV**	**Study V**
Design	Cohort, retrospective	Cohort, prospective	Cohort, prospective and retrospective
Data source	Swedish Esophageal Surgery Study (SESS)	Swedish Esophageal and cardia cancer (SECC) study	Rotterdam Esophageal cancer Database
Cohort members	1044	615	1271
Inclusion period	1987-2010	2000-2005	1990-2010
Followed-up until	31 December 2012	31 December 2010	29 October 2010
Exposure	Lymph node clearance (Study I) Reoperation (Study II)	Anastomotic leak (Study III) “Anti-reflux procedures” (Study IV)	Preoperative weight loss
Outcome	Overall, long- and short-term survival	Oesophageal symptoms (Study III) Reflux and dysphagia (Study IV)	Survival and postoperative complications
Statistical methods	Cox-regressions (hazard ratios)	Logistic regressions (odds ratios)	Cox-regressions (hazard ratios), logistic regression (odds ratios)
Possible confounders	Age, sex, comorbidity, tumour stage, neoadjuvant treatment, surgeon volume and calendar period	Age, sex, tumour stage, histological type, comorbidity, complications (Study IV) neoadjuvant treatment (Study III), type of anastomosis (Study III)	Age, sex, tumour stage, comorbidity, neoadjuvant therapy

6.2 DESIGN AND METHODS

Study I

Using SESS, this study assed the influence of lymph node clearance i.e. the number of resected lymph nodes, number of metastatic lymph nodes and the ratio between metastatic and total resected lymph nodes on overall and disease-specific mortality. We hypothesised that a more extensive lymph node clearance would have a beneficial effect on the long-term survival in all T-stages, but mainly in higher T-stages, with a more beneficial survival associated with more lymph nodes resected, less metastatic lymph nodes and a lower ratio of metastatic and total number of resected lymph nodes.
The primary study outcome was overall all-cause mortality up to 5 years after surgery. Short-term (90-day), longer-term (90 days to 5 years) and disease-specific mortality were secondary outcomes. Short- and longer-term mortality were counted from the day of the operation up to 90 days after surgery, and from 90 days to 5 years after surgery, respectively. Patients who died within the first 90 days of surgery were censored from the long-term survival analyses because they most likely died from postoperative complications. Disease-specific mortality was assessed from the Swedish Causes of Death Register. When the code for oesophageal cancer was recorded as the cause of death the assumption was made that the patient had died of recurrent disease. We were not able to distinguish between local or distant recurrence.

Study II

Using SESS cohort the influence of any reoperation within 30 days after oesophagectomy for cancer on long-term survival was assessed. It was hypothesised that reoperation would negatively influence survival even after the initial postoperative period. The exposure was defined as any open or minimally invasive reoperation within 30 days of the initial oesophageal cancer resection. More specifically, reoperation was categorised as: 1) explorative laparotomy, 2) explorative thoracotomy, 3) reoperation for bleeding, 4) reoperation for anastomotic insufficiency and 5) reoperation for deep infection.

The outcomes were all-cause early and late mortality. “Early postoperative mortality” was defined as any death occurring within 90 days of the initial surgery, while “late mortality” was defined as any death between 90 days and 5 years of the primary resection.

Study III

Patients included in this study were identified from SECC and a study was conducted to test the hypothesis that reflux symptoms after oesophagectomy can be prevented surgically by creation of a cervical anastomosis, anti-reflux procedure around the anastomosis or a pyloric drainage procedure. The cervical anastomoses were conducted through a standard left-sided neck incision. The typical antireflux procedure was the creation of a full or partial wrap of the most proximal part of the gastric tube surrounding the anastomosis. The pyloric drainage procedure was a pyloromyotomy or a pyloroplasty.
The primary outcome was symptoms of reflux present at 6 months after oesophageal resection in patients reconstructed with a gastric tube. A secondary outcome was symptoms of dysphagia, which e.g. a cervical anastomosis might cause. To address time-related changes we also aimed to studied symptoms of reflux and dysphagia 3 years after surgery, although the statistical power might be insufficient. Both outcomes were measured using the QLQ-OES18.[162, 186] The scale assessing reflux symptoms in the QLQ-OES18 consists of two questions: 1) During the past week have you had any acid indigestion or heartburn and 2) During the past week have you had trouble with acid or bile getting into your mouth? These questions have been found to be of good quality to distinguish symptoms of reflux.[187] The dysphagia scale consists of three questions: 1) During the past week, could you eat solid foods, 2) During the past week could you eat liquidized or soft food, and 3) During the past week could you drink liquids.[162] These two scales have been shown to have good reliability and discriminative validity.[162]

Study IV

In this study the incidence of persisting symptoms after intrathoracic anastomotic leak following oesophagectomy for cancer was investigated using SECC.
It was hypothesised that intrathoracic anastomotic leak would make patients more susceptible to certain symptoms.
Anastomotic leak was defined as "intrathoracic anastomotic leak that was clinically evident and verified by radiological imaging; this included necrosis of the gastric conduit with clinically significant ischemia causing perforation or ulceration, or oesophago-tracheal fistula that was clinically evident and verified through radiological imaging". The leak had to have occurred within 30 days of surgery.
Five pre-defined outcome symptoms were: 1) difficulty eating, 2) odynophagia, 3) dysphagia, 4) trouble swallowing saliva and 5) reflux. These were measured using the QLQ-OES18.[162] The difficulty eating-scale consists of 4 questions: During the past week have you: 1) had trouble enjoying your meals, 2) felt full up too quickly, 3) had trouble with eating and 4) had trouble eating in front of others. The odynophagia scale consists of 3 questions: During the past week have you had 1) pain when you eat, 2) pain in your chest, and 3) pain in your stomach. The dysphagia scale consists of 3 questions: During the past week could you 1) swallow solid food, 2) eat liquidised food or soft food and 3) drink liquids. Trouble swallowing saliva is a single item in the QLQ-OES18: During the last week have you had trouble swallowing saliva. The reflux scale consists of two items: During the past week have you had 1) acid indigestion or heartburn and 2) trouble with acid or bile coming into your mouth. The patients were followed up for 6 months and 3 years after oesophageal cancer resection

Study V

To assess the influence of preoperative weight-loss on postoperative outcome, the comprehensive, hospital-based, Rotterdam Esophageal Cancer cohort was used. In this study we tested the hypotheses that oesophageal cancer patients with >10% preoperative weight loss would be at an increased risk of

postoperative complications, have a longer length of stay, and have a worse overall and disease-free survival. The exposure was defined as weight loss during the 3 months prior to diagnosis and categorised into “no or limited (≤10%)” or “severe (>10%) weight loss”.
The patients estimated their weight 3 months prior to their first visit, which was considered as the baseline weight. Patients were also weighed at their first visit to the outpatient clinic (actual weight). Percentage of weight loss in the 3 months prior to diagnosis was calculated by subtracting the baseline weight from the actual weight. The weight difference was thereafter divided by the baseline weight and multiplied by 100. There is no uniform consensus on the definition of malnutrition in relation to weight loss, but it has often been referred to as >5% in 3 months,[188] >10-15% weight loss within 6 months before surgery,[189] or >10% in the six months before surgery.[190] The choice of 10% weight loss as the cut-off was pre-defined and chosen based on earlier studies, where such weight loss has been found to be associated with increased risk of postoperative complications after major abdominal surgery.[190]
Study outcome was postoperative course, specified as postoperative complications, length of hospital stay and overall survival. Postoperative complications were categorised into: 1) early surgical complications, 2) early non-surgical complications, and 3) late surgical complications. Length of hospital stay was defined as the number of days in hospital since the date of the primary operation. Overall survival was calculated from the date of the oesophagectomy until death or end of follow-up, which was up to 5 years after the operation. Patients were seen in the outpatient clinic every 3rd month during the first year after the surgery, every 6th month the second year, and yearly thereafter until 5 years after the operation. Imaging was not routinely performed only in patients presenting with clinical signs of recurrence.

6.3 STATISTICAL METHODS

Survival: Studies I-II and V

For Studies I and II survival was calculated using Kaplan-Meier curves. Differences in survival between the survival curves of patients were evaluated using the log rank test. In a Cox proportional hazards model, hazard ratios (HR) with 95% confidence intervals (CI) of mortality were calculated. These analyses included adjustment for potential confounding factors in a multivariable model. Nine known prognostic factors for increased mortality after oesophagectomy were adjusted for. These factors included: 1) age, 2) sex, 3) comorbidity, 4) neoadjuvant therapy and 5) calendar period for both studies.

In Study I analyses were additionally adjusted for: 1) T-stage and 2) annual surgeon volume. In Study II analyses were additionally adjusted for: 1) tumour stage, 2) histological type of tumour and 3) surgical radicality.

Missing values on any of the covariates were handled using two strategies in the multivariable model: 1) missing data were grouped into a separate category or 2) patients with missing data were excluded.[191] Since the HR did not differ between these two strategies for missing data, only the results from strategy 1 are presented in the tables and text, since it better preserves the statistical power. Moreover, since HR were similar in the adjusted and unadjusted analyses, only the adjusted HR are presented.

In Study V, the odds of unintentional weight loss in relation to surgical and non-surgical complications were calculated using logistic regression, expressed as odds ratios (ORs) with 95% CI. In a multivariable model the OR of surgical and non-surgical complications in relation to unintentional weight loss was adjusted for potential confounding by: age, sex, tumour stage, comorbidity, and neoadjuvant chemo- and/or radiotherapy. Interactions between body mass index (BMI) and weight loss were tested in a Wald test. BMI was defined as weight prior to operation divided by the patient's height in metres, to the power of two (weight in kilogrammes / height in metres^2). Kaplan-Meier curves were used to illustrate hospital admission time and overall survival in the comparison groups, and the log rank test was used to analyse differences between the curves. In a Cox regression model HR with 95% CI regarding hospital admission time and overall survival were calculated. In a multivariable model the HR of differences in admission time and overall survival for the two weight-loss groups were adjusted for potential confounders (listed above).

Symptoms measurement: Studies III-IV

In Study III and IV symptoms were measured using the QLQ-OES18.[192] All questions have 4 response categories: 1) not at all, 2) a little, 3) quite a bit and 4) very much. Responses were further dichotomised into "no- or minor symptoms" versus "symptomatic". Patients who had at least one response of 3 (''quite a bit'') or 4 (''very much'') to any item within a scale were categorised as ''symptomatic.'' Otherwise patients were categorised as having ''no or minor symptoms in accordance with earlier studies.[160, 193] Odds of reporting the symptoms were estimated using logistic regression models and were expressed as OR with 95% CI. Analyses were adjusted for 1) sex, 2) age, 3) tumour stage, 4) histological type of the tumour and 5) comorbidity. Analyses in Study III were additionally adjusted for postoperative complications. Study IV additionally adjusted for neoadjuvant therapy.

In Study III the odds of reporting symptoms of reflux and dysphagia were measured, according to the above-mentioned methods, in relation to selected surgical techniques performed to reduce reflux symptoms (i.e. cervical anastomosis, anti-reflux procedure and pyloric drainage procedure). To address interactions between the different surgical procedures, the study exposures were redefined as follows in a separate analysis: 1) cervical anastomosis, 2) pyloric drainage procedure, 3) cervical anastomosis with pyloric drainage procedure, 4) antireflux procedure surrounding the anastomosis with pyloric drainage procedure, and 5) no additional procedure. Propensity-adjusted analyses were performed to adjust for selection bias and covariate confounding. Propensity scores were estimated by multinomial logistic regression model with the same covariates used in the full model. The multinomial logistic regression model was used to address the multi-group exposure. In the final step, the propensity score was used as the only covariate in multivariable logistic regression models for assessing risk of reflux and dysphagia (expressed as OR with 95% CI).

In Study IV the odds of relevant symptoms of eating difficulties, odynophagia, dysphagia, trouble swallowing saliva and reflux were calculated in relation to anastomotic leak.

7 RESULTS

7.1 STUDY I

During the study period, 1304 patients underwent resection for oesophageal cancer in Sweden. After applying exclusion criteria, 1044 patients were left for final analysis. Some characteristics of these study participants are presented in Table 2. The number of removed and examined lymph nodes ranged from 0 to 114 with a median of 7. The range of the number of metastatic lymph nodes was 0 to 22 with a median of 0. The median ratio between the number of metastatic and total resected nodes was 0.03 (range 0 to 1). Eighty-eight patients died within the first 90 days after surgery rendering a 90-day mortality rate of 8%. The overall absolute 5-year mortality was 81% (848 patients), and among those who died, 76% (795 patients) had a recorded tumour recurrence.

Table 2. Characteristics of the 1044 study patients included in Study I

Characteristics	Number of patients (%)
Age (years)	
≤ 64	471 (45.1)
65-75	415 (39.8)
>75	158 (15.1)
Sex	
Male	781 (74.8)
Female	263 (25.2)
Comorbidity	
0	516 (49.4)
1	339 (32.5)
≥2	189 (18.1)
Pathological T-stage	
Tis, T0, T1	376 (36.0)
T2	210 (20.1)
T3	373 (35.7)
T4	29 (2.8)
Missing data	56 (5.3)
Histological tumour type	
Squamous cell	552 (59.2)
Adenocarcinoma	437 (41.8)
Other	55 (5.3)
Neoadjuvant treatment	
No	629 (60.3)
Yes	349 (33.4)
Annual surgeon volume	
0-9	525 (50.3)
≥10	519 (49.7)
Calendar period	
1987-1992	193 (18.5)
1993-1998	238 (22.8)
1999-2004	267 (25.6)
2005-2010	346 (33.1)
Number of lymph nodes removed	
1-2nd quartile (0-6)	530 (50.8)
3rd quartile (7-15)	261 (25.0)
4th quartile (16-114)	253 (24.2)
Number of metastatic lymph nodes	
1-2nd quartile (0)	526 (50.4)
3rd quartile (1-3)	301 (28.8)
4th quartile (>3)	217 (20.8)
Ratio of metastatic and removed lymph nodes	
1-2nd quartile (0.00-0.03)	509 (50.1)
3rd quartile (0.04-0.38)	225 (25.1)
4th quartile (>0.38)	252 (24.8)

A higher number of lymph nodes removed did not decrease the overall mortality, disease-specific mortality or the short-term mortality. The linear regression analyses did not reveal an influence of a higher number of lymph nodes removed on overall 5-year mortality (HR 1.00, 95% CI 0.99-1.01). Patients in the third (7-11 nodes) and fourth (12-114 nodes) quartile of removed nodes did not have a decreased overall 5-year survival compared to those in the lowest two quartiles (≤6 nodes) (HR 1.17, 95% CI 0.94-1.45, and HR 1.13 and 95% CI 0.95-1.35, respectively). The T-stage specific results indicated an increased HR of mortality in the early T-stages (Tis-T1) (HR 1.61, 95% CI 1.17-2.23 in the third quartile and HR 1.37, 95% CI 0.95-2.00 in the fourth quartile), compared to later stages (T2-T3) (HR of 0.96, 95% CI 0.75-1.21 and HR 1.19, 95% CI 0.89-1.58, in the third and fourth quartile respectively). (Table 3, Figure 6) The disease-specific HR were similar to the overall HR. (Table 4)

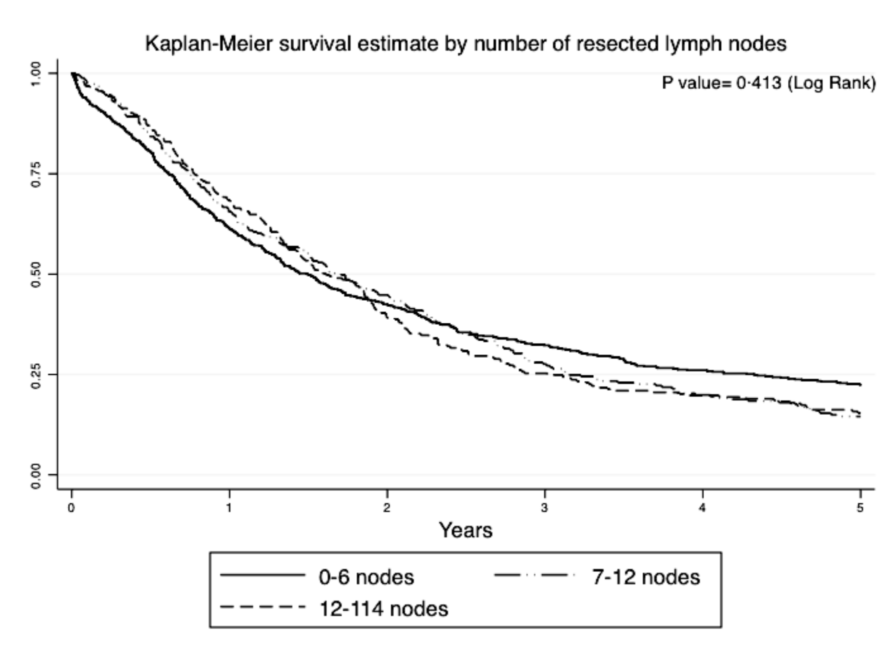

Figure 6. Survival estimates for the number of resected lymph nodes

An increasing number of metastatic lymph nodes had, as expected, a strong negative influence on the 5-year mortality (Table 5), but not on short-term mortality. The HR of overall 5-year mortality in the fourth quartile of metastatic lymph nodes (>3 metastatic nodes) was 2.74 (95% CI 2.26-3.39), compared to the lowest two quartiles (no metastatic nodes). The HR of overall 5-year mortality were slightly higher in lower compared to higher T-stages, but there were no statistically significant differences. (Table 3, Figure 7) HR of disease-specific mortality were similar to those of the overall mortality.

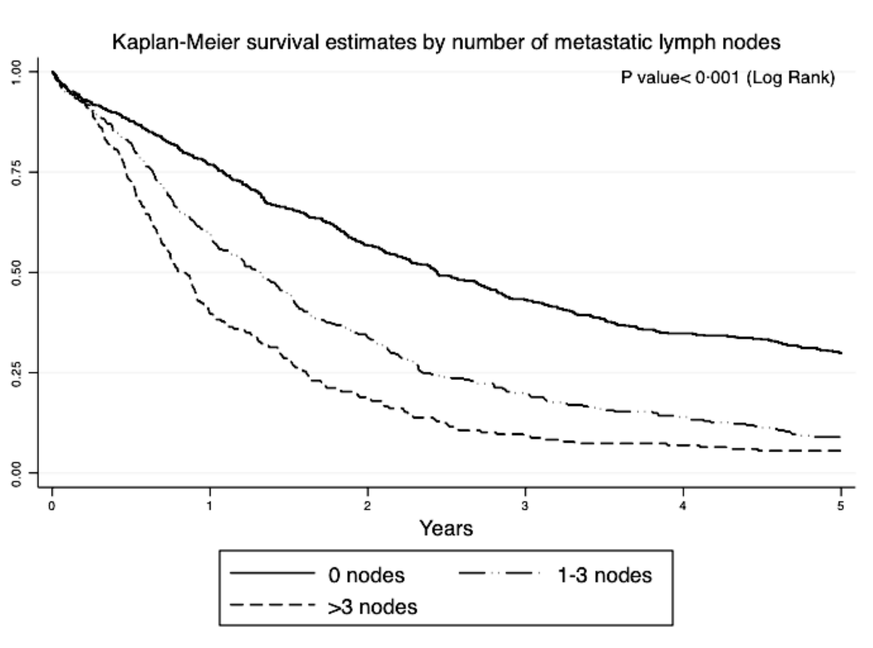

Figure 7. Survival estimates for the number of metastatic lymph nodes

As expected, a higher ratio between metastatic and total lymph nodes entailed a strongly increased overall 5-year HR of mortality, but not on mortality within 90 days of surgery. In the third quartile (ratio 0.04-0.38) the HR of mortality was 1.66 (95% CI 1.39-1-98) compared to the lowest two quartiles (ratio 0.0-0.03). In the fourth quartile (ratio >0.38) the HR of overall 5-year mortality was 3.19 (95% CI 2.65-3.84) compared to the lowest two quartiles. There were no differences in mortality between lymph node ratios in the specific T-stage analyses. (Table 3, Figure 8) The HR of disease-specific mortality were similar to those of the overall mortality.

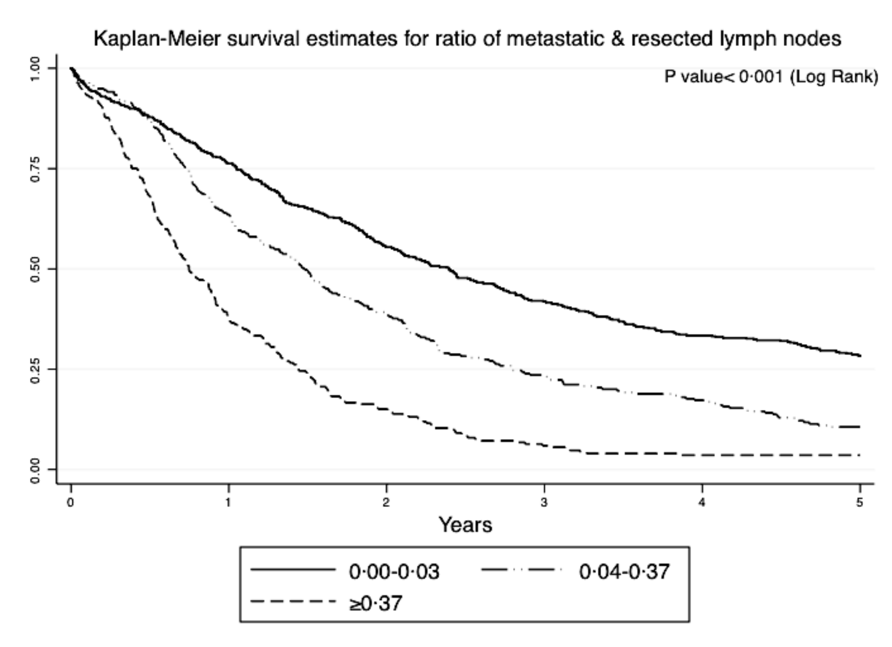

Figure 8. Survival estimates for the ratio between metastatic and resected lymph nodes

Table 3. Overall 5-year mortality presented as hazard ratios (HR) with 95% confidence interval (CI) in relation to number of resected lymph nodes, number of metastatic lymph nodes and ratio of metastatic and resected lymph nodes in 1044 patients operated for oesophageal cancer in 1987-2010 in Sweden

		All stages (Tis-T4)		
		Number	**HR***	**95% CI**
Resected lymph nodes		1044		
1st -2nd quartile	0-6	530	1.00	-
3rd quartile	7-15	261	1.13	0.95-1.35
4rd quartile	16-114	253	1.17	0.94-1.45
Metastatic lymph nodes		1044		
1st -2nd quartile	0	526	1.00	-
3rd quartile	1-3	301	1.91	1.62-2.25
4rd quartile	>3	217	2.74	2.26-3.39
Ratio of lymph nodes		1016		
1st -2nd quartile	0.0-0-03	509	1.00	-
3rd quartile	0.04-0.38	255	1.66	1.39-1.98
4rd quartile	>0.38	252	3.19	2.65-3.84

*Adjusted for potential confounding factors**:** Age, sex, comorbidity, neoadjuvant treatment, surgeon volume and calendar period.

Table 4. Overall 5-year disease-specific mortality, presented as hazard ratios (HR) with 95% confidence intervals (CI), in relation to number of removed lymph nodes, number of metastatic lymph nodes and lymph node ratio in 1044 patients operated for oesophageal cancer in 1987-2010 in Sweden.

		All tumour stages (Tis-T4)		
		Number	**HR***	**95% CI**
Resected lymph nodes				
1st -2nd quartile	0-6	459	1·00	-
3rd quartile	7-15	180	1·15	0·94-1·42
4rd quartile	16-114	156	1·19	0·90-1·57
Number of metastatic lymph nodes				
1st -2nd quartile	0	381	1·00	-
3rd quartile	1-3	233	2·22	1·81-2·70
4rd quartile	>3	181	2·82	2·25-3·53
Ratio lymph nodes				
1st -2nd quartile	0·0-0·03	361	1·00	-
3rd quartile	0·04-0·38	181	1·95	1·56-2·42
4rd quartile	>0·38	227	3·02	2·45-3·71

*Adjusted for potential confounding by: age, sex, comorbidity, neoadjuvant treatment, surgeon volume and calendar period

7.2 STUDY II

During the study period we identified 2195 patients who were eligible for inclusion in the study cohort. After exclusion of 373 patients (17%) where medical records were not available, 1822 (83%) patients remained for final analysis. Of these, 200 patients (11%) underwent a reoperation (in total 248 reoperations) within 30 days of the primary oesophageal resection. (Table 5) As shown in Table 6 there were no major differences in characteristics between the patients who did and did not undergo such reoperation.

Table 5. Categorisation of the 248 reoperations within 30 days after initial surgery in a cohort of 1822 patients undergoing oesophagectomy between 1987 and 2010 in Sweden, with follow-up until 28th February 2012.

Type of reoperation		Number (%)
Total number of reoperations		248 (100)
Explorative laparotomy		47 (19)
Explorative thoracotomy		11 (4)
Reoperation for bleeding		22 (9)
Reoperation for anastomotic insufficiency		43 (17)
	Laparotomy	3
	Thoracotomy	1
	Unknown/other	39
Reoperation for infection		8 (3)
Reoperation for wound revision		50 (20)
	Wound revision for bleeding	15
	Wound revision for infection	5
	Wound dehiscence	7
	Unknown	23
Other reoperations		75 (30)

Table 6. Characteristics of the 1822 patients included in Study II

Characteristic	Number of patients (%)	
	No reoperation	**Reoperation**
Total	1622 (89)	200 (11)
Sex		
Men	1211 (75)	151 (75)
Women	411 (25)	49 (25)
Age		
≤64	754 (46)	93 (47)
65-75	615 (38)	78 (39)
>75	253 (16)	29 (14)
Comorbidity*		
None	832 (51)	107 (54)
1	542 (34)	63 (31)
≥2	248 (15)	30 (15)
Stage‡		
0-I	339 (20)	41 (20)
II	532(33)	71 (35)
III	399 (25)	46 (23)
IV	127(8)	13 (7)
Missing†	225 (14)	29 (15)
Histology		
Adenocarcinoma	645 (40)	70 (35)
Squamous cell carcinoma	880 (54)	123 (62)
Missing†	97 (6)	7 (3)
Neoadjuvant therapy		
None	677 (42)	85 (43)
Radiotherapy	154 (9)	26 (13)
Chemoradiotherapy	302 (19)	35 (17)
Missing†	489 (30)	54 (27)
Radicality		
R0	1135 (69)	137 (68)
Not R0	251 (16)	30 (15)
Missing †	236 (15)	33 (17)
Hospital volume		
<9 per year	875 (54)	122 (61)
≥9 per year	747 (46)	78 (39)
Calendar period		
1987-1990	234 (14)	34 (17)
1991-1994	302 (19)	43 (22)
1995-1999	330 (20)	49 (25)
2000-2005	382(24)	37 (19)
2006-2010	374 (23)	37 (19)

Among the 208 patients (11%) who died within 90 days of surgery, 54 (26%) underwent reoperation. Reoperation was a risk factor for such short-term mortality even after adjustment for confounding factors (HR 3.05, 95% CI 2.22-4.17). Among the 1276 (79%) patients who died between 90 days and 5 years after surgery, 117 (10%) were reoperated upon. The log-rank test comparing the Kaplan-Meier survival curves of patients with and without reoperation between 90 days and 5 years after surgery revealed an increased mortality in the first group (p<0.0001). Additionally there was a 27% increased adjusted HR of mortality during the period 90 days to 5 years after surgery among reoperated patients (HR 1.27, 95% CI 1.05-1.53). (Table 7, Figure 9)

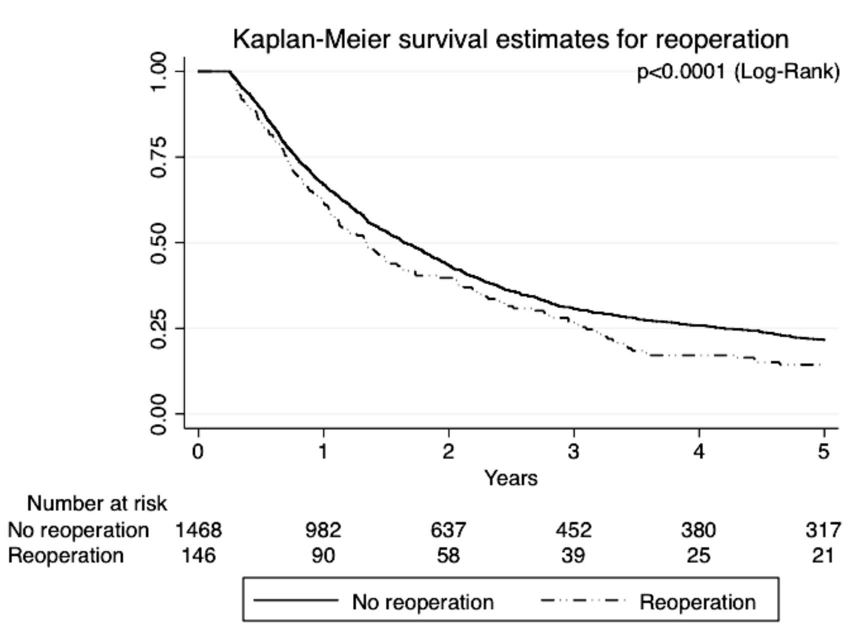

Figure 9. Survival estimates for patients who did and did not undergo a reoperation

In a subgroup analysis of the 3 most common types of reoperations, i.e. exploratory laparotomy, reoperation for anastomotic insufficiency and wound revision, the point HR were increased for each type of reoperation, (Table 4) and patients reoperated upon for anastomotic insufficiency in particular had an increased HR of mortality (adjusted HR 1.82, 95% CI 1.19-2.76). (Table 8)

Table 7. Hazard ratios (HR) with 95% confidence intervals (CI) of mortality after oesophagectomy with respect to occurrence of reoperation, based on 1822 patients undergoing oesophageal cancer surgery in 1987-2012 in Sweden

	Number of patients (%)	Number of events (%)‡	HR (95% CI)
All stages			
<90 days	1822 (100)	208 (11)	
Crude			3.17 (2.32-4.32)
Multivariable*,†			3.05 (2.22-4.17)
≥90 days – 5 years	1614 (89)	1276 (79)	
Crude			1.22 (1.02-1.47)
Multivariable*, †			1.27 (1.05-1.53)
>5 years	338 (19)	127 (37)	
Crude			0.51 (0.21-1.25)
Multivariable*,†			0.42 (0.17-1.07)

*Adjusted for sex, age, co-morbidities, tumour stage, histology, neoadjuvant therapy, radicality, hospital volume, and calendar period.

†Missing values of covariates were missing at random and considered as a separate group.

‡Event means death

Table 8. Hazard ratios (HR) with 95% confidence intervals (95% CI) of mortality between 90 days and 5-years in a subgroup analyses of the most common types of reoperations after oesophagectomy, based on 1822 patients undergoing oesophageal cancer surgery in 1987-2012 in Sweden

Type of reoperation	Number of patients (%)	HR (95% CI) *, †
Exploratory laparotomy	47 (19)	1.17 (0.82-1.67)
Reoperation for anastomotic insufficiency	43 (17)	1.82 (1.19-2.76)
Wound revision	50 (20)	1.32 (0.87-2.00)

*Adjusted for sex, age, co-morbidities, tumour stage, histology, neoadjuvant therapy, radicality, surgeon volume, and calendar period.

†Missing values of covariates were missing at random and considered as a separate group.

7.3 STUDY III

In total 616 patients were included in the entire SECC cohort. During the first 6 months after surgery 111 (18%) patients had died and another 103 (17%) were unable to participate at the 6-month postoperative outcome assessment. Among the remaining 402 patients, we excluded 37 (9%) patients with non-gastric substitute, 58 (13%) patients without an intrathoracic or cervical anastomosis, and 3 (1%) patients who did not answer the questions relevant for this study. Thus leaving 304 patients for final analyses. There were no major differences between the comparison groups regarding sex and age distribution, squamous cell carcinoma was overrepresented in patients with a cervical anastomosis, and there were more complications in the group with cervical anastomosis compared to those with intrathoracic anastomosis. (Table 9)

Table 9. Characteristics of 304 patients treated with oesophagectomy for cancer who were reconstructed with a gastric conduit. The comparison groups were patients with cervical or intrathoracic anastomosis, antireflux procedure or not, and pyloric drainage procedure or not.

	Surgical procedures					
	Intrathoracic anastomosis	**Cervical anastomosis**	**No antireflux procedure**	**Antireflux procedure**	**No pyloric drainage procedure**	**Pyloric drainage procedure**
Variable	**Number (%)**		**Number (%)**		**Number (%)**	
Total	274 (90)	30 (10)	262 (86)	42 (14)	120 (40)	184 (61)
Sex						
Male	226 (83)	25 (83)	211 (81)	40 (95)	100 (88)	151 (82)
Female	48 (18)	5 (17)	51 (19)	2 (5)	20 (17)	33 (18)
Age (years)						
<60	60 (22)	9 (30)	58 (22)	11 (26)	25(21)	44 (24)
60-74	162 (59)	13 (43)	153 (58)	22 (52)	74 (62)	101 (55)
>74	52 (19)	8 (27)	51 (20)	9 (21)	21 (18)	39 (21)
Histology						
Adenocarcinoma	204 (75)	10 (33)	180 (69)	34 (81)	81 (68)	133 (72)
Squamous cell carcinoma	70 (26)	20 (67)	82 (31)	8 (19)	39 (33)	51 (28)
Tumour stage						
0-II	135 (50)	17 (58)	132 (51)	20 (48)	57 (48)	95 (52)
III-IV	137 (50)	12 (41)	127 (49)	22 (52)	62 (52)	87 (48)
Comorbidity						
No	79 (29)	12 (40)	83 (32)	8 (19)	29 (24)	62 (34)
One or more	195 (71)	18 (60)	179 (68)	34 (81)	91 (76)	122 (66)
Complications						
No	227 (83)	19 (63)	211 (81)	35 (83)	96 (80)	150 (82)
Yes	48 (17)	11 (37)	51 (19)	7 (17)	24 (20)	34 (18)

Seven out of 30 (23%) patients with a cervical anastomosis and 75 out of 274 (27%) patients with an intrathoracic anastomosis experienced reflux symptoms 6 months postoperatively. There was no statistically significantly decreased OR of reflux symptoms when a cervical anastomosis was created, compared to an intrathoracic anastomosis (OR 0.86, 95% CI 0.32-2.23). (Table 10) Reflux symptoms were reported by 10 out of 42 (24%) of the patients with an antireflux anastomosis and 65 out of 232 (28%) of the patients with a conventional anastomosis, rendering no decreased risk of reflux symptoms in patients with an antireflux anastomosis compared to those without (OR 0.86, 95% CI 0.39-1.90). (Table 10) Reflux symptoms were reported by 54 out of 184 (29%) patients with a pyloric drainage procedure and by 28 out of 120 (23%) without any pyloric drainage procedure, and the adjusted OR of reflux symptoms was not decreased with pyloric drainage (OR 1.49, 95% CI 0.86-2.58). (Table 10) In the propensity-adjusted analysis no decrease in OR of reflux symptoms was found for any of the individual types or combinations of surgical procedure. (Table 3) Moreover, there was an increased OR of dysphagia (OR 10.34, 95% CI 1.19-89.91) with a cervical anastomosis, but no increased risk for dysphagia with any of the other surgical procedures. (Table 11)

Table 10. Odds ratios (OR) with 95% confidence intervals (CI) for reflux symptoms and dysphagia 6 months after oesophagectomy for cancer with gastric conduit for patients with cervical anastomosis compared to intrathoracic anastomosis, antireflux procedure compared to no antireflux procedure, and pyloric drainage compared to no pyloric drainage procedure.

	Surgical procedure					
	Intrathoracic anastomosis (N=274)	**Cervical anastomosis** (N=30)	**No antireflux procedure** (N=262)	**Antireflux procedure** (N=42)	**No pyloric drainage procedure** (N=120)	**Pyloric drainage procedure** (N=128)
Reflux						
Symptomatic Number (%)*	75 (27)	7 (23)	72 (28)	10 (24)	28 (23)	54 (29)
OR (95% CI)†	1.00	0.86 (0.32-2.23)	1.00	0.86 (0.39-1.90)	1.00	1.49 (0.86-2.58)
Dysphagia						
Symptomatic Number (%)*	19 (7)	3 (10)	21 (8)	1 (2)	29 (24)	12 (9)
OR (95% CI)†	1.00	1.85 (0.42-8.11)	1.00	0.30 (0.00-2.37)	1.00	1.71 (1.00-2.93)

* Patients are considered symptomatic if they score 3 ‘quite a bit’ or 4 ‘very much’ on any question within a scale. † Full adjustment model including adjustment for sex, age, tumour stage, histological type of tumour, complication and comorbidity

Table 11. Odds ratios (OR) adjusted for interaction and propensity-matched OR with 95% confidence intervals (CI) for reflux symptoms and dysphagia 6 months after oesophagectomy for cancer with gastric conduit for patients with cervical anastomosis compared to intrathoracic anastomosis, antireflux procedure compared to no antireflux procedure, and pyloric drainage compared to no pyloric drainage procedure.

Surgical procedure	No additional procedure (reference)	Cervical anastomosis	Cervical anastomosis with pyloric drainage procedure	Antireflux procedure with pyloric drainage procedure	Pyloric drainage procedure
Number	104	13	17	42	128
Reflux					
Symptomatic Number (%)*	26 (25)	2 (15)	5 (29)	10 (26)	39 (31)
OR (95% CI)†	1.0 (reference)	0.55 (0.11-2.77)	1.49 (0.43-5.05)	1.2 (0.5-2.7)	1.36 (0.74-2.50)
Propensity-adjusted OR (95% CI)§	1.0 (reference)	0.71 (0.12-4.07)	1.67 (0.46-6.07)	1.25 (0.45-3.45)	1.14 (0.60-2.17)
Dysphagia					
Symptomatic Number (%)*	6 (6)	2 (15)	1 (6)	1 (2)	12 (9)
OR (95% CI)†	1.0 (reference)	6.18 (0.82-46.24)	1.85 (0.15-21.66)	0.61 (0.06-5.66)	2.24 (0.73-6.86)
Propensity-adjusted OR (95% CI)§	1.0 (reference)	10.34 (1.19-89.91)	2.77 (0.26-29.45)	1.13 (0.10-12.08)	1.36 (0.40-4.55)

*Patients are considered symptomatic if they score 3 ‘quite a bit’ or 4 ‘ a lot’ on any question within a scale. † Multinomial analysis including adjustment for sex, age, tumour stage, histological type of tumour, complication and comorbidity § Propensity-

7.4 STUDY IV

Among 616 patients included in this study, 111 (18%) died before the six-month follow-up, and 103 (20%) declined or were too ill to participate. Among the remaining 402 patients, 125 were excluded because the anastomosis was not intrathoracic or they were not reconstructed with a gastric conduit. Some 277 patients (70% of eligible) remained in the final cohort. Of these, 29 (11%) had an anastomotic leak. At 3 years after surgery 103 patients remained. Some characteristics are presented in Table 12.

Compared to patients without an anastomotic leak, those with a leak had a 4-fold increased risk of difficulty eating (OR 4.05, 95% CI 1.47-11.16) and a more than 2-fold increased risk of odynophagia (OR 2.59, 95% CI 1.15-5.82) 6 months after surgery. Patients with an anastomotic leak had a two-fold increased point OR of trouble swallowing saliva, but this risk was not statistically significant (OR 1.98, 95% CI 0.58-6.67). There was no increased risk of dysphagia or reflux after intrathoracic anastomotic leak. (Table 13) At 3 years after surgery, the risk of eating difficulties remained increased with an OR of 5.78 (95% CI 1.03-32.39). The increased risk of odynophagia was persistent, however it was not statistically significant (OR 2.41, 95% CI 0.46-12.38). There was no increased risk for trouble swallowing, dysphagia or reflux 3 years after surgery.

Table 12. Patient details and tumour characteristics of a cohort including 277 patients who underwent oesophagectomy for cancer and were reconstructed with a gastric substitute and intrathoracic anastomosis.

Variable		6 months after surgery No anastomotic leak N (%)	Anastomotic leak N (%)
Total		248 (90)	29 (11)
Sex	Male	204 (82)	24 (83)
	Female	44 (18)	5 (17)
Age (in years)	<60	54 (22)	8 (28)
	60-69	91 (37)	12 (41)
	70-79	95 (38)	9 (31)
	>80	8 (3)	0 (0)
Comorbidity†	None	63 (23)	9 (31)
	One or more	214 (77)	20 (69)
Neoadjuvant treatment*	No	225 (91)	25 (86)
	Yes	23 (9)	4 (14)
Tumour histology	Adenocarcinoma	185 (74)	21 (72)
	Squamous cell carcinoma	71 (26)	8 (28)
Tumour stage	0-II	125 (51)	13 (45)
	III-IV	121 (49)	16 (55)
Type of anastomosis	Hand sewn	108 (44)	9 (31)
	Stapled	140 (57)	20 (69)

*****Neoadjuvant therapy was defined as one, or a combination of the following: chemotherapy or radiation. †Comorbidity is indicated by the presence of one of the following diseases: hypertension, angina pectoris, cardiac failure, chronic-obstructive pulmonary diseases, asthma, diabetes, tobacco smoking, renal disease, or liver disease.

Table 13. Risk of oesophageal symptoms after anastomotic leak, expressed as adjusted odds ratios (OR)* with 95% confidence intervals (CI).

		6 months after surgery	
Symptoms		**No anastomotic leak (Number=246)**	**Anastomotic leak (Number=29)**
Eating difficulties	Number (%)	131 (54)	23 (82)
	OR (95% CI)	1.0 (reference)	4.05 (1.47- 11.16)
	P- value		0.007
Odynophagia	Number (%)	80 (33)	16 (55)
	OR (95% CI)	1.0 (reference)	2.59 (1.15-5.82)
	P- value		0.021
Trouble swallowing	Number (%)	18 (7)	4 (14)
	OR (95% CI)	1.0 (reference)	1.98 (0.58-6.67)
	P-value		0.269
Dysphagia	Number (%)	17 (7)	2 (7)
	OR (95% CI)	1.0 (reference)	1.11 (0.22-5.42)
	P- value		0.894
Reflux	Number (%)	68 (28)	7 (25)
	OR (95% CI)	1.0 (reference)	0.92 (0.36-2.34)
	P- value		0.873

* The full model included adjustments for sex, age, tumour stage, tumour histology, comorbidity, neoadjuvant treatment, and type of anastomosis.

7.5 STUDY V

During the study period, 1271 patients with cancer of the oesophagus or gastro-oesophageal junction were considered for surgical resection in the Erasmus MC Rotterdam, the Netherlands. Exclusions were made for the following reasons: the primary plan (surgical tumour resection) was not pursued (235 [18%] patients), different histology (17 [1%] patients) and missing information on explanatory variables (67 [5%] patients). Of the 922 remaining patients (73%), 155 (17%) lost >10% of their usual weight in the 3 months prior to diagnosis and were thus classified as exposed. Patients with non-radical resections, i.e. R1 and R2 resections (336 [26%] patients) were excluded from the long-term survival analyses, but were included in the short-term outcome analyses e.g. length of hospital stay, postoperative mortality and early surgical-, non-surgical and long-term complications. Patient and tumour characteristics of exposed and non-exposed patients are shown in Table 14.

A total of 249 (27%) patients developed a surgical complication within 30 days of surgery. There was no increased risk of such early surgical complications comparing patients with and without weight loss (adjusted OR 0.83, 95% CI 0.54-1.24) (Table 15-16) and there was no increased risk of anastomotic leak (adjusted OR 0.87, 95% CI 0.46-1.64), wound infections (adjusted OR 95% 1.10, 95% CI 0.47-2.45) or necrosis of the substitute (adjusted OR 1.10 95% 0.34-13.20). (Table 15) Some 472 (51%) patients developed an early non-surgical complication. There was no increased risk of such complications when comparing the exposed with the non-exposed groups (adjusted OR 0.90, 95% CI 0.63-1.30). (Table 15-16) Late surgical complications were diagnosed in 327 (35%) patients. No increased risk was identified in patients with weight loss. (Table 16) The mean admission time was 22 days (standard deviation 20.9) and 20 days (standard deviation 15.3) for patients with and without weight loss, respectively. (Table 15)

Table 14. Characteristics of 922 patients who had undergone oesophageal cancer resection, with or without >10% weight loss during 3 months prior to diagnosis.

Variable	Number (%) Total	Weight loss ≤10%	Weight loss >10%
Total	922 (100)	767 (83)	155 (17)
Age			
Mean (SD)	63 (10)	62 (10)	60 (10)
Sex			
Male	712 (77)	609 (79)	103 (66)
Female	210 (23)	158 (21)	52 (34)
Body mass index*			
<25	419 (45)	324 (48)	95 (75)
25-29	285 (31)	260 (39)	25 (20)
≥30	95 (10)	88 (13)	7 (6)
Missing	89 (13)	73 (13)	16 (15)
Comorbidity[†]			
None	421 (46)	360 (47)	61 (40)
One or more	501 (54)	407 (53)	94 (61)
Neoadjuvant treatment			
No	721 (79)	601 (78)	120 (77)
Yes	201 (22)	166 (22)	35 (23)
Histology			
Squamous cell	263(25)	223 (29)	60 (37)
Adenocarcinoma	622 (69)	527 (69)	95 (61)
Adenocarcinoma in Barrett's epithelium	17 (2)	17 (2)	0 (0)
Tumour stage[‡]			
0-I	173 (19)	162 (21)	11 (7)
II	257 (28)	212 (28)	45 (29)
III	432(47)	342 (45)	90 (58)
IV	10 (1)	6 (1)	4 (30
Unknown	49 (7)	45 (7.8)	4 (4)
Surgical approach			
Transhiatal	722(79)	610 (80)	112 (73)
Transthoracic	169 (18)	135 (18)	34 (22)
Other[§]	28 (3)	20 (3)	8 (5)

Table 15. The postoperative course after oesophagectomy for cancer of 922 patients, with or without >10% weight loss during 3 months prior to diagnosis.

Variable		Number (%)		
		Total	Weight loss ≤10%	Weight loss >10%
Length of hospital stay (days)*	**Mean (SD)**	22 (21)	22 (21)	20 (15)
Postoperative mortality†	**Number**	71 (8)	55 (77)	16 (10)
Early surgical complications‡	**None**	674 (73)	556 (60)	118 (13)
	One or more	249 (27)	212 (23)	37(4)
Early non-surgical complications§	**None**	450 (49)	370 (40)	80 (9)
	One or more	473 (51)	398 (43.	75 (8)
Late surgical complications ‖	**None**	570 (63)	468 (53)	92 (10)
	One or more	327 (37)	267 (30)	60 (7)

*Admission time in days calculated from day of operation until discharge.

†Defined as: death within 90 days after surgery.

‡ Early surgical complications were defined as: complications occurring within 30 days of initial surgery, including anastomotic leak, recurrent laryngeal nerve paresis or paralysis, bleeding, (small) bowel obstruction, chyle leakage, leakage of the feeding tube, gastroparesis for >10 days after surgery, wound infection, or necrosis of the substitute for which a reoperation was required.

§ Defined as: ARDS (acute respiratory distress syndrome) thromboembolic events.

‖ Late surgical complications were defined as complications occurring after more than 30 days after initial surgery, including anastomotic stenosis (requiring dilatation or therapy), pyloric stenosis, intercostal neuralgia, ileus, weight loss or cachexia.

The Kaplan-Meier curve comparing admission time is shown in Figure 10. There was no difference in admission time for patients with and without weight loss (log-rank 0.6194). In the adjusted analysis, weight loss did not influence admission time (HR 1.06, 95% CI 0.85-1.33). (Table 17) The Kaplan-Meier curve comparing patients with and without weight loss regarding overall survival of up to 5 years after surgery showed a statistically significantly worse overall survival in patients with weight loss (p<0.0001). (Figure 11) After adjustment for potential confounders patients with weight loss had a slight increased mortality within 5 years after surgery (adjusted HR, 1.34, 95% CI 102-1.74. (Table 17)

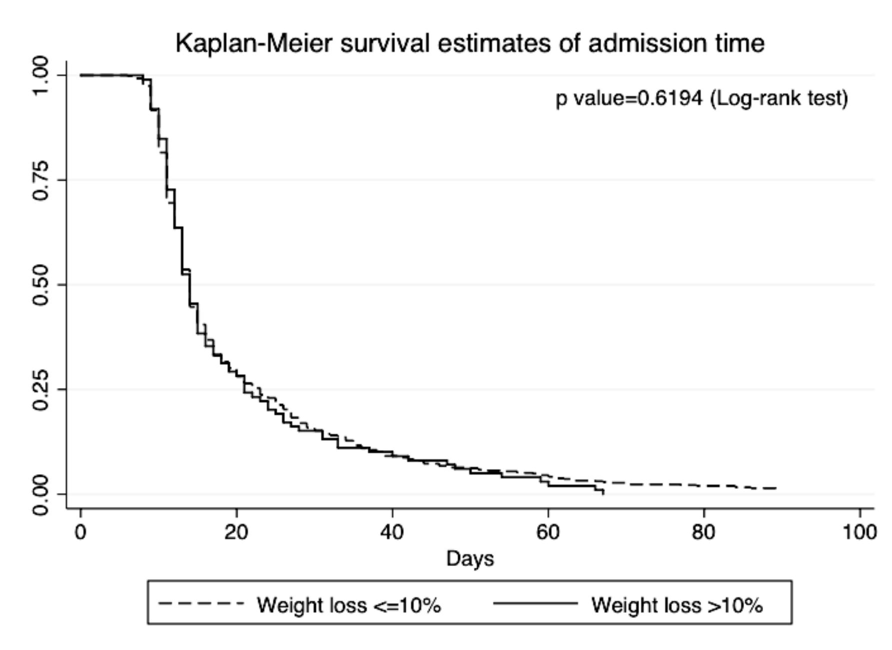

Figure 10. Admission time for patients with and without preoperative weight loss

Figure 11. Overall 5-year survival for patients with and without preoperative weight loss

Table 16. Risk of complications after oesophagectomy in association with weight loss, during 3 months prior to oesophageal cancer diagnosis, expressed as odds ratios (OR) and 95% confidence intervals (CI).

			Weight loss ≤10%	**Weight loss >10%**
		Number (%)	OR (95% CI)	OR (95% CI)
Early surgical complications*	All surgical complications	249 (27)	1.00 (reference)	0.83 (0.54-1.24)
	Anastomotic leak	89 (10)	1.00 (reference)	0.87 (0.46-1.64)
	Wound infection	41 (4)	1.00 (reference)	1.10 (0.47-2.45)
	Necrosis of the substitute	25 (3)	1.00 (reference)	1.10 (0.34-3.20)
	Other surgical†	108 (12)	1.00 (reference)	0.90 (0.52-1.61)
Early non-surgical complications	All non-surgical complications	472 (51)	1.00 (reference)	0.90 (0.63-1.30)
	Infectious‡	336 (36)	1.00 (reference)	1.20 (0.77-1.91)
	Non-infectious§	76 (8)	1.00 (reference)	0.47 (0.17-1.23)
Late surgical complications‖	All late surgical complications	327 (35)	1.00 (reference)	1.14 (0.79-1.66)
	Anastomotic stenosis	245 (27)	1.00 (reference)	1.10 (0.68-1.81)

* Early surgical complications were defined as: complications occurring within 30 days after initial surgery. † Defined as: anastomotic leak, recurrent laryngeal nerve paresis/paralysis, bleeding, (small) bowel obstruction, chyle leakage, leakage of the feeding tube, gastroparesis for >10 days of surgery, wound infection, or necrosis of the substitute for which a reoperation was required ‡ Defined as pneumonia, sepsis and urinary tract infection requiring treatment § Defined as: ARDS (acute respiratory distress syndrome) thromboembolic events, occurring within 30 days after initial surgery **||** Late surgical complications were defined as complications occurring after more than 30 days after initial surgery, including anastomotic stenosis (requiring dilatation or therapy), pyloric stenosis, intercostal neuralgia, ileus, weight loss or cachexia.

Table 17. Impact of preoperative weight loss of >10% prior to oesophageal cancer diagnosis on overall and disease-free survival and hospital admission time after esophagectomy, expressed as hazard ratios (HR) and 95% confidence intervals (CI).

	HR	95% CI	P-value
Overall 5-year survival*	1.34	1.02-1.74	0.03
Admission time	1.09	0.89-1.35	0.41

*Occurrence of an event means death

† Occurrence of an event means recurrence of disease

8 DISCUSSION AND METHODOLOGICAL CONSIDERATIONS

8.1 STUDIES I AND II

Both Studies I and II were conducted from the SESS cohort and therefore have similar strengths and flaws. A major strength is the population-based design. Virtually all patients who underwent oesophageal cancer resection in Sweden between 1987-2010 were included in this cohort rendering an unselected sample. Moreover, the large sample size provided sufficient power allowing detection of even moderate differences in outcome (mortality) between the exposure groups. Another strength is the possibility to adjust for several established prognostic factors, which reduces the risk of confounding, which is otherwise a threat to observational studies. However, residual confounding by the factors adjusted for or unknown factors cannot be entirely ruled out. The exposures and outcomes were predefined and assessed by means of strict criteria, which reduces the risk of chance findings and decreases the risk of systematic errors owing to misclassification. The retrospective design poses the largest problem, since such design introduces an increased risk of misclassification of exposures, outcomes and confounding factors. However, since the researchers involved in the collection of the clinical data had no link with the participating hospitals and were not involved in patient care, this risk should be minimal. Moreover, the great efforts to collect and review the medical data made the data collection nearly complete and very comprehensive. One of the other major sources of bias in follow-up studies is loss to follow-up, particularly in cohorts like the SESS cohort, with large sample sizes and long follow-up. But since each patient could be linked to the national registers through their personal identity numbers, there was virtually no loss to follow-up in this cohort.

8.2 STUDIES III AND IV

Studies III and IV were both conducted within SECC. This cohort, being a population-based, nationwide cohort has partly the same advantages and disadvantages as previously mentioned in Studies I and II. An additional advantage is the prospective design ensuring a higher accuracy and completeness of the data. However, in this cohort there is an additional type of bias: non-participation. Of the eligible patients 18% died before the first follow-up at 6 months. However, among the patients alive at follow-up the participation rate was sufficient; 17% of eligible patients were too sick to participate. This could potentially influence results since patients who were sicker and declined participation, are more likely to suffer from more severe symptoms. Another problem with symptoms assessment is the lack of baseline measures making it impossible to adjust for any preoperative symptoms. Finally, there was a lack of objective measures to verify reported symptoms, however for many symptoms the HRQOL-scales used have been proven sufficient, and for symptoms of reflux, subjective assessment is currently the Golden Standard.

8.3 STUDY V

This study was based on hospital-based data. Since it is a cohort with long follow-up, the same limitations apply as in the previous mentioned studies (I and II). An additional concern here is that the study is hospital-based, which might jeopardize the external validity or generalisability. Referral patterns might provide a selection problem. Due to the lack of national guidelines and treatment recommendations during most of the years the data was gathered, there were hospital policies that might be different from other hospitals.

9 INTERPRETATION OF FINDINGS AND IMPLEMENTATIONS

9.1 STUDY I

Contradictory to our hypothesis, a more extensive lymph node removal did not improve overall or disease-specific survival in this patient group. This result challenges current recommendations advocating at least two-field lymphadenectomy during oesophagectomy.[33, 68, 86, 100] The evidence supporting a more extensive lymphadenectomy (two-field or three-field lymphadenectomy) is limited and based on limited research. However, our results are in line with some well-designed studies that compared the extended lymphadenectomy via transthoracic oesophagectomy with “limited” lymphadenectomy by a transhiatal approach. One large RCT found no survival benefit from a more extensive lymphadenectomy, but instead a lower postoperative morbidity in the transhiatal group.[88, 89] Similarly, a recent large cohort study comparing transthoracic and transhiatal resection in 664 patients found no long-term overall survival differences between the two approaches.[194] Finally, a RCT comparing two-field with three-field lymphadenectomy found no difference in survival, while the complication rate was increased in the three-field lymphadenectomy group.[195] A RCT to more in detail assess the extent of lymphadenectomy during oesophagectomy is not ethically or practically feasible. Instead guidelines should rely on high quality studies based on population-based data like the current study. It might be time to reassess the extent of lymphadenectomy during oesophagectomy, a development well in line with the history of e.g. breast cancer surgery, which was much more extensive in the past.

9.2 STUDY II

This study suggests that reoperation after primary oesophageal resection decreases long-term survival. The finding of the prognostic role of reoperations after excluding the initial postoperative period is a finding that should encourage further research. It stresses the need for preventive measures to reduce the need for reoperation. The results of the subgroup analyses showed that patients undergoing reoperation for anastomotic insufficiency in particular had an increased risk of mortality. There is some evidence that anastomotic insufficiency entails direct tumour spread and seeding of remaining viable tumour cells in colon cancer patients.[196, 197] This might explain the higher mortality rate in patients with reoperation for anastomotic insufficiency. One biological mechanism that might explain the decreased long-term survival after reoperation is that the additional surgical injury reduces the protection against seeding of tumour cells, including activation of natural killer cells and other anti-carcinogenic factors.[198] Furthermore, it is possible that additional surgery triggers an elevated inflammatory response that might in turn stimulate growth of micro-tumours and induce tumour recurrence and death from recurrence.[199] Another potential mechanism considers certain complications. Blood transfusion has e.g. been linked with a worse long-term mortality and increased cancer recurrence in different types of cancer. [200-203] Unfortunately, we did not have information on blood transfusion in this study, but it can be assumed that patients returning to theatre are more likely to receive a blood transfusion, and speculatively, blood transfusion may be a mechanism that contributes to the main finding of this study.

9.3 STUDY III

This study indicated that a cervical anastomosis, antireflux anastomosis, and pyloric drainage during oesophagectomy do not prevent postoperative reflux symptoms after oesophageal cancer surgery. Therefore, such procedures might not be generally recommended merely for the purpose of counteracting postoperative reflux. Thus, the prevention of reflux symptoms after oesophagectomy remains a problem and till today there are no obvious surgical solutions to prevent this problem. This issue, that affects over half of the patients after oesophagectomy warrants further research. Potent anti-reflux medication is usually prescribed to counteract symptoms of reflux, which could counteract at least some of the problems.
of anastomotic leak.

9.4 STUDY IV

In this study, intrathoracic anastomotic leak seemed to increase the risk of eating difficulties and odynophagia 6 months after oesophageal cancer resection, and symptoms of eating difficulties persisted even 3 years after surgery. A possible mechanism is the increased formation of fibrotic scar tissue surrounding the gastric conduit and the proximal oesophagus due to inflammation of the mediastinum and surrounding tissue caused by a leak. Such fibrotic tissue might reduce the elasticity of the conduit.

These findings can be used to inform patients about the symptoms they might encounter after an intrathoracic anastomotic leak, and should be used to alert physicians and dieticians responsible for postoperative care to an increased risk of malnutrition in this group of patients. More efforts should be made to avoid anastomotic leak. Centralisation of services and referral to high-volume centres has, for example, been shown to improve outcomes after oesophageal cancer surgery and potentially offer a reduced risk of anastomotic leak.

9.5 STUDY V

Patients with oesophageal cancer who experience weight loss of >10% in the 3 months before diagnosis had no increased risk of postoperative complications or longer hospital stay in this study. However, they had an increased overall 5-year mortality after surgery. These results highlight the need for studies to test whether improving the nutritional status in malnourished patients with oesophageal cancer before oesophagectomy is beneficial from a prognostic viewpoint. Weight loss might continue after oesophagectomy.[204] This stresses the need to actively help oesophageal cancer patients, especially the ones treated with surgical tumour resection, to counteract malnutrition from the time of diagnosis. Weight loss before diagnosis might not be adjustable since patients are not under medical attention.

10 CONCLUSIONS

Study I - A more extensive lymph node resection does not seem to improve the 5-year survival after oesophagectomy for oesophageal cancer.

Study II - Reoperation might be associated with an increased mortality even after the initial 3 months following surgery for oesophageal cancer.

Study III- Cervical anastomosis, antireflux anastomosis, and pyloric drainage during oesophagectomy do not seem to prevent reflux symptoms following surgery for oesophageal cancer.

Study IV - Intrathoracic anastomotic leak is followed by an increased risk of eating difficulties and odynophagia 6 months after oesophagectomy.

Study V - Weight loss of >10% in the 3 months before diagnosis, might increase the overall 5-year mortality after surgery for oesophageal cancer.

11 FUTURE RESEARCH

The poor prognosis and persisting symptoms of oesophageal cancer patients after treatment with curative intent remains a concern. The implementation of multimodal therapy has somewhat improved long-term prognosis, however there is a lot of room for improvement. All too often the disease has already spread to the lymph nodes or other organs at time of diagnosis. This makes oesophageal cancer a systemic disease, warranting improvement in systemic treatment like chemotherapy or more targeted therapy. The latter is still highly experimental. Several studies have reported a complete pathological response in up to 25% of the patients in their study population. This leaves us wondering if there is a place for definitive chemoradiotherapy in the treatment plan of oesophageal cancer patients. It might be that certain patients benefit from definitive chemoradiotherapy while others benefit more from a complete resection. Research is needed to provide additional evidence and possible guidelines of what patients might benefit from such treatment.

Unfortunately all too often the disease is already metastasised at the time of diagnosis. One reason for this is the late and subtle presentation of symptoms. Currently there are no easy accessible methods for the early detection of oesophageal cancer. Patients with Barrett's oesophagus regularly undergo endoscopy; however the majority of oesophageal cancer patients have not been included in endoscopy surveillance programmes. The disease is too rare to implement a population screening for oesophageal cancer. However, high-risk patient groups could be defined and might be selected for screening for this cancer with regular intervals. This way we might catch more patients at an earlier tumour stage, and thus significantly improve the survival. Furthermore, with the development of minimally invasive and endoscopic techniques for early oesophageal cancer, the postoperative morbidity might be reduced, patient satisfaction might increase, and persisting symptoms might reduce.

Another hot topic within oesophageal cancer surgery is centralisation. Several studies have shown that patients operated on by high volume surgeons at high volume hospital have a lower risk of complications and better long-term survival compared with those who are not. In this thesis we showed a negative influence of reoperation on long-term survival. Reoperation often entails a serious postoperative complication, which in turn might be to some extent prevented by centralisation to high volume surgeons and hospitals.

Finally, but most controversially, we might have to challenge the current guidelines concerning lymphadenectomy. There is weak scientific evidence of the benefit of an extended lymphadenectomy and the results of this thesis challenge this. To reduce trauma and postoperative morbidity, a less extensive lymph node resection might be appropriate, since it does not seem to prolong survival. A lymphadenectomy that enables selective removal of metastatic nodes while leaving non-metastatic nodes would probably be ideal, but it might be difficult to readily identify metastatic nodes during surgery. Improvements in preoperative nodal staging would be beneficial in this respect, since it could guide surgeons to remove specific areas of metastatic nodes, but a better solution might be to identify biomarkers that can identify metastatic nodes and help tailor the nodal removal. Another possibility is to use sentinel node techniques, but the multidirectional spread and the high occurrence of skip metastasis argue against such approach. A sentinel node mapping procedure with ^{99m}technetium colloid has been proven efficient in early stage oesophageal cancer, but not in later stages. However, no large studies have been performed to investigate the feasibility of sentinel node mapping in more advanced cases of oesophageal cancer.

12 POPULAR SCIENTIFIC SUMMARY (ENGLISH)

12.1 BACKGROUND

Oesophageal cancer is a relatively rare disease in the Western world, but worldwide it is the 8th most common type of cancer, and the 6th most common cancer death. Yet, the number of new patients is increasing. The cause of this increase is partly unknown. In Sweden approximately 450 patients are diagnosed with oesophageal cancer yearly.

Most patients diagnosed with oesophageal cancer present to their doctor with complaints of unwanted weight loss, fatigue and trouble eating and swallowing. They often complain of food getting stuck in the oesophagus during their meals. Unfortunately, oesophageal cancer typically causes symptoms in an advanced stage. By the time the patients have developed these symptoms and go to their doctor, their oesophageal cancer is often already spread to lymph nodes or other organs. Therefore, the prognosis is poor. Generally only 5-15% of the patients survive for 5 years after diagnosis.

The most common and most established curatively intended treatment for cancer of the oesophagus includes surgery. Nowadays, most patients also receive chemotherapy or radiochemotherapy before their operation. During the operation the larger part of the oesophagus is removed to make sure that the tumour is removed as a whole with reasonable margins. The surgeon then creates a tube from the stomach, pulls it up through the diaphragm and chest and attaches it to the part of the oesophagus that is left after the tumour is removed; the surgical attachment is known as an anastomosis. This operation is extensive and complications are quite common. The recovery time after surgery is long and a lot of patients still have trouble with symptoms, like reflux, nausea and trouble eating, long after the operation is performed.

This thesis focuses on surgical techniques that might improve survival and decrease suffering among oesophageal cancer patients who undergo surgical treatment.

12.2 METHODS

This thesis is built of 5 studies (I-V)

For this thesis we used three data sources. In Studies I and II we used a large database (the Swedish Esophageal Cancer Surgery Study, or *SESS*) with patient information that was collected from all hospitals in Sweden operated on for oesophageal cancer between 1987 and 2010. The patients were identified from the nationwide Swedish Cancer Registry and the Swedish Patient Registry. Researchers from our group obtained the operation charts and pathology reports to collect information on the operation and tumour, respectively. All data were assembled afterwards in a large database.

In Studies III and IV we used the information of patients who were treated for oesophageal cancer between 2000 and 2005 (The Swedish Esophageal and Cardia Cancer or *SECC database*). A Swedish network of surgeons and other specialists involved in the care of oesophageal cancer patients made the collection of this data possible. Patients were identified shortly after they had been diagnosed with the cancer through collaboration with the pathology departments of the participating hospitals. The SECC database contains details on the tumour, surgical procedures and complications. Additionally, patients were asked to fill in a health-related quality of life (HRQOL) assessments at 6 months, 3 years and 5 years after their operation.

In Study V we used a database of patients from the Erasmus MC University Medical Center in Rotterdam, The Netherlands, including patients from 1978 and onwards. In this study we used only patients operated on for oesophageal cancer between 1990 and 2010. Information on patient demographics, clinical and pathologic information, and details of the received treatment, and postoperative course were obtained from medical records by a specialised data manager.

In Study I we investigated if it matters how many lymph nodes you remove from patients who are operated for oesophageal cancer. In Study II we addressed the question if oesophageal cancer patients who undergo a reoperation due to a complication within 30 days of surgery, have a shorter long-term survival compared with those who were not reoperated. In study III we tried to assess whether reflux after oesophageal cancer surgery can be prevented surgically by creating: 1) an anastomosis in the neck, 2) an anti-reflux anastomosis (in the chest) or 3) an incision in the outlet of the stomach (pyloromyotomy) to improve the emptying of the stomach. In study IV we compared certain symptoms after an oesophageal cancer surgery among patients with a leaking anastomosis in their chest with those who did not have a leaking anastomosis. In study V we assessed the postoperative course of patients with more than 10% weight loss in the 3 months before they were diagnosed with oesophageal cancer.

In Studies I, II and V we measured the risk of death of all causes within 5 years of surgery as well as death of patients who suffered from the disease again. The risk of death was calculated using a statistical method (called Cox proportional hazard method), including adjustment for influence of various factors that might confound any associations. In Studies III and IV the selected symptoms were measured using a self-administered questionnaires developed to assess common symptoms in cancer patients in general (the EORTC QLQ-C30) and a module assessing specific oesophageal cancer symptoms (the EORTC QLQ-OES18). We calculated the risk of symptoms (yes or no) when comparing the patients in the different groups. The risk of these symptoms was calculated using a statistical method (called logistic regression) and the relative risk was presented as odds ratios (OR) with 95%CI.

Results

Study I included 1044 patients. The main finding was that the number of lymph nodes that are removed during surgery did not influence survival. This is contradictory to current guidelines that advise removal as many lymph nodes as possible close to the oesophagus to improve survival.

Study II included 1.481 patients who underwent oesophageal cancer surgery between 1987 and 2010. In total 155 (11%) patients were reoperated within 30 days of their first operation due to a severe complication. Reoperated patients had a 27% higher risk of dying in the 5 years after surgery after excluding the initial 90 days of surgery and patients with a leaking anastomosis had the highest risk of such mortality (82% increased)

In Study III we included 274 patients. Thirty of those (10%) had an anastomosis in the neck, 42 (14%) had an anti-reflux anastomosis and 184 (64%) under went a pyloromyotomy. None of these techniques alleviate symptoms of reflux after oesophageal cancer operation.

We included 277 patients in Study IV. Of those patients 29 (10%) had suffered from a leaking anastomosis in the chest. We found that after such a leak patients had a 4-fold increased risk of developing trouble eating a more than 2-fold risk of pain when swallowing still 6 months after surgery. The difficulties eating were still present 3 years after surgery.

In Study V 922 patients were included during the period 1990-2010. Among these 155 (17%) lost more than 10% of their weight in the 3 months before they were diagnosed with oesophageal cancer. The patients who lost more than 10% of their weight did not have any increased risk of complications or any longer hospital stay than those who did not loose that much weight. However, they did have a 34% higher risk of mortality within the first 5 years after surgery.

12.3 CONCLUSIONS

Study I: A higher number of removed lymph nodes does not seem to lower the risk of death after surgery for oesophageal cancer. It might be justified to review the current guidelines that advise to remove a larger number of lymph nodes.

Study II: Patients who undergo a reoperation for a complication within the first 30 days of oesophageal cancer surgery have an increased risk of death in the first 5 years after surgery even after excluding the initial postoperative period. This risk is seemingly especially high in patients reoperated for a leaking anastomosis.

Study III: An anastomosis in the neck, an anti-reflux anastomosis, or a pyloromyotomy do not seem to decrease the risk of reflux symptoms 6 months after oesophageal cancer surgery.

Study IV: Patients suffering from a leaking anastomosis seem to have an increased risk of persisting symptoms of eating difficulties and pain while swallowing 6 months after surgery, and the eating difficulties seem to persist still after 3 years.

Study V: More than 10% weight loss in the 3 months before oesophageal cancer diagnosis is followed by an increased risk of death in the first 5 years after surgery, but does not influence the risk of symptoms or the length of the hospital stay.

13 POPULÄR VETENSKAPLIG SAMMANFATTNING (SVENSKA)

13.1 BAKGRUND

Matstrups- och magmuncancer är ovanliga sjukdomar i västernvärlden, men matstrupscancer är den åttonde mest vanliga form av cancer I världen.

I västernvärlden (USA, Europa, Australien och Ny Zealand) antalet patienter med matstrups- och magmuncancer ökar. Anledningen till ökat antal patienter är oklart. I Sverige blir ungefär 620 patienten diagnosticerad med matstrups-och magmuncancer varje år.

Patienter som blir diagnosticerat med matstrupscancer presenterar sig oftast med svälj svårigheter, trötthet och viktminskning. Dem klagar över mat som fastnar bakom bröstbenet efter dem har sväljt maten. Tyvärr get matstrupscancer symptom i ett sent skede och blir dem flesta diagnostiserad med sjukdomen när den redan har spridit ut sig till lymfkörtlar eller genom kroppen. På grund av detta är överlevnad av matstrupscancer patienter mycket dåligt, 5-15% lever 5 år efter diagnosen. Det mest vanliga och mest etablerade behandling för cancer är kirurgisk tumör resektion. Idag få patienterna oftast cellgift- eller strålbehandling eller en combination av dem två, innan operation. Operationen innebär ett ingrepp i båda bukhåla och brösthåla. Under operationen ta man bort tumören och en stor del av matstrupen för att säkerställa borttagning av hela tumören. Kirurgen som opererar patienten skapar en ny matstrupe från magsäcken och koppla den delen från matstrupen som är kvar till magsäcken (kopplingen heter anastomosen). Operationen är bland den mest avancerade och påfrestande ingrepp som genomförs och komplikationer är därför mycket vanligt efter ingreppet. Det är en anledning till att bara 31 % av patienter är vid liv 5 år efter operation. Återhämtningen efter operation är mycket lång och visse besvär som patienter har efter operation är kvarstående. Besvär patienter kan ha lång efter matstrupscancer kirurgi är bland annat reflux, illamående, kräkningar och ät-svårigheter.

Det här avhandling fokuserar på kirurgiska tekniker som kan förbättra överlevnad hos matstrupscancer patienter och kan förebygga kvarstående besvär. Målet med avhandlingen är att hitta den tekniken som är optimalt för överlevnad och som minskar kvarstående besvär.

13.2 METODER

Avhandlingen är uppbyggt kring fem delarbeten (I-V)

För delarbete **I** och **II** använder vi en stor databas (The Swedish Esophageal Cancer Surgery Study, eller *SESS)* med patient uppgifter insamlades in från alla sjukhus som opererade patienter för matstrupscancer, mellan 1987 och 2010. Patienterna blev identifierade med hjälp av länkningen mellan de nationellt heltäckande Cancerregistret och Patientregistret. Forskare från vår grupp samlade i operationsberättelsen, patient uppgifter och patologisvar och abstraherade så mycket detaljer som möjligt. Data samlades in i elektronisk i en stor databas.

I delarbete III och IV använder vi information av patienter som fick behandling för matstrupscancer mellan 2000 och 2005 (Swedish Esophageal and Cardia Cancer or *SECC* databas). Ett nätverk av Svenska läkare som är involverade i behandling av matstrupscancer patienter underlättade insamlingen av data. Patienterna identifierades efter diagnostisering i sammanarbeta med patologi avdelningen av dem deltagande sjukhus. SECC databasen innehåller detaljer om tumören, operation och komplikationer. Dessutom samlades information in om patienternas hälso-relaterade livskvalitet vid tre tillfällen (6 månader, 3 år och 5 år efter operationen).

I delarbete V använder vi en sjukhus baserad databas från Erasmus MC Universitets sjukhus is Rotterdam, Nederländerna. Läkarna har samlat i data från matstrupscancer patienter sedan 1978 och insamlingen är pågående. I detta delarbete använder vi patienter som blev opererade mellan 1990 och 2010. Information om patientkaraktäristika, kliniska och patologi uppgifter samt information om behandling, operation och postoperativa belopp abstraherades från patientjournaler.

I delarbete I undersökte vi påverkan av antalet borttagna lymfkörtlar på överlevnad i patienter som blev opererade för matstrupscancer kirurgi. Vår hypotes var att desto flera lymfkörtlar man ta bort, desto bättra överlevnaden.
I delarbete II försökte vi att svara på frågan om reoperation på grund av komplikationer, inom 30 dager efter matstrupscancer kirurgi, påverkar den långsiktiga överlevnaden jämfört med patienter som inte blev reopererade.
I delarbete III syftade vi att hitta en lösning till kvarstående reflux besvär efter matstrupscancer operation. Vi tittade på tre olika kirurgiska tekniker 1) en anastomos i halsen, jämfört med en anastomos i bröstet, 2) en antireflux anastomos, jämfört med en vanlig anastomos, och 3) ett litet snitt i magsäckens utgång som underlättar flöde från magsäcken till tarmen (snittet kallas for pyloromyotomi).
I delarbete IV tittade vi vilka symptom och besvär var kvarstående 6 månader efter operation, i patienter som hade haft en anastomos läckage i bröstkorgen. Vi tittade på reflux symptom, smärta när man sväljer, svårigheter att äta och svårt att svälja. Vi jämförde patienter som hade genomgott ett läckage med dem som inte hade det.
I delarbete V har vi jämfört det postoperativa beloppet av patienter som hade gott mer än 10 % ner i vikt i dem 3 månader innan diagnosen och dem som inte har gott mer än 10 % ner i vikt. Vi tittade på postoperativa komplikationer, överlevnad och vårdtid
I delarbete I, II och V har vi kalkylerad risken att dö av alla anledningen och död av tumör återfall i dem första 5 år efter operation. Risken att dö kalkylerades med statistiska metoden ”Cox proportional hazard”. Vi presenterar risken att dö som hazard ratios (HR) med konfidens intervaller (95 % CI) och procent (%). I delarbete III och IV har vi mättat dem utvalda symptom med en enkät som är utvecklad att mäta symptom som är vanliga hos cancer patienter (EORTC QLQ-C30) och en modul som mäter symptom som är vanliga i matstrupscancer patienter (EORTC QLQ-OES18). Enkäterna används ofta i olika sammanhang och är mycket tillförlitliga. En analys metod som heter logistic regression användes för att beräkna risk (OR) för symptom.

13.3 RESULTAT

Delarbete I inkluderade vi 1044 patienter. Resultaten visade att antalet borttagna lymfkörtlar inte påverkar överlevnad. Dem nuvarande riktlinjer råder att ta bort så många lymfkörtlar som möjligt för att förbättra överlevnaden. Men vår studie bekräftar inte detta. Patienter där flera lymfkörtlar var borttagna hade ingen lägre risk att dö, jämfört med dem där få lymfkörtlar har tagits bort. (HR 1.13, 95 % CI 0.95-1.01). Resultatet visade att dem som hade flera involverade lymfkörtlar (lymfkörtlar med metastas) hade en högre risk att dö av 275 % (HR 2.74, 95 % CI 2.26-3.39) inom 5 år efter operationen.
I delarbete II blev 1481 patienter inkluderade, som genomgick operation för matstrupscancer mellan 1987-2010. Totalt 155 (11 %) av patienterna blev reopererade inom 30 dagar efter första operation, på grund av alvarliga komplikationer. Dessa patienter hade ett 26 % ökad risk att dö nom 5 år jämfört med dem som inte blev reopererade. Patienter som blev reopererade på grund av ett anastomos läckage hade högsta risk att dö inom 5 år (82 %, HR 1.82, 95 % CI 1.19-2.76).
I delarbete III 274 patienter blev inkluderade. Trettio av dem (9.9%) hade en anastomos i halsen; fyrtiotvå hade en antireflux anastomos (13.8%) och etthundraåttiofyra hade genomgott en pyloromyotomi (64 %). Resultaten visade ingen skillnad i reflux symptoms, som 23-29% av patienterna rapporterade. Värken en hals anastomos, antireflux anastomos eller pyloromyotomy verkar skydda patienter mot reflux besvär efter operation.
Vi inkluderade 277 patienter i delarbete IV. Bland dessa patienter 29 (10 %) hade haft en anastomos läckage i bröstet. Resultat visade att dem som hade haft en anastomos läckage hade en fyra gånger ökad risk av kvarstående besvär med att äta (OR 4.1, 95 % CI 1.2-11.2) och en två gånger ökad risk att få svårt att svälja (OR 2.6, 95% CI 1.1-5.8) sex månader efter operationen. Svårigheter att äta var ett kvarståendet besvär, efter 3 år var risken för detta i patienter med anastomos läckage fortfarande ökad (OR 2.0, 95 % CI 1.0-32.4).
I delarbete V 922 patienter inkluderades under perioden 1990-2010. Bland dem 922, 155 (17 %) tappade fler än 10% av deras vikt under dem senaste 3 månader innan diagnosen. Vi såg att dem som hade tappad så mycket vigt hade

ingen ökad risk för postoperativa komplikationer (OR 0.83, 95 % CI 0.54-1.24) och vårdtid än dem som inte tappade så vikt (HR 1.06, 95 % CI 0.85-1.33). Dem hade dock en ökad risk mycket att dö inom dem första 5 år efter operationen (HR 1.34, 95 % CI 1.02-1.72)

13.4 SLUTSATSER

Delarbete I: Ett större antal borttagna lymfkörtlar minskar inte risken att dö inom 5 år efter matstrupscancer operation. Vi kan därför ifrågasätta gällande riktlinjer som råder att ta bort så många lymfkörtlar som möjligt. Som förväntat, ökar ett större antal involverade lymfkörtlar (dem med metastaser) risken att dö inom 5 år efter operation.

Delarbete II: Patienter som blev reopererade inom 30 dagar efter matstrupscancer operation hade en 27 % ökad risk att dö inom 5 år. Risken var i synnerhet ökar i patienter som blev reopererade för anastomos läckage (82 %).

Delarbete III: Värken en anastomos i halsen, en antireflux anastomos eller en pyloromyotomy skyddar mot reflux symptom 6 månader efter matstrupscancer operation.

Delarbete IV: Patienter som hade haft en anastomos läckage hade en ökad risk för att utveckla ät svårigheter och smärta när man sväljer 6 månader efter operation. Risken för att utveckla ät svårigheter är kvarstående 3 år efter operation.

Delarbete V: Mer än 10 % viktminskning i dem senaste 3 månader innan matstrupscancer diagnosen ökar inte risken för postoperativa komplikationer eller längre vård tid, men ökar dock risken att dö inom 5 år efter operation.

14 POPULAIR WETENSCHAPPELIJKE SAMENVATTING (NEDERLANDS)

14.1 ACHTERGROND

Slokdarmkanker en maagmondkanker zijn relatief zeldzame aandoeningen in de westerse wereld, maar wereldwijd staan ze op de achtste plek in de lijst van meest voorkomende vormen van kanker. In de westerse wereld (VS, Europa, Australië, Nieuw-Zeeland) stijgt het aantal patiënten dat wordt gediagnostiseerd met slokdarmkanker. De reden hiervoor is tot nog toe onduidelijk. In Zweden worden jaarlijks ongeveer 620 patiënten gediagnostiseerd met slokdarm- of maagmondkanker. De meeste patiënten melden zich bij hun arts met klachten van gewichtsverlies, vermoeidheid en problemen met slikken. Vaak klagen ze over eten dat achter het borstbeen blijft hangen. Helaas geeft slokdarmkanker pas laat klachten en worden de meeste patiënten gediagnostiseerd als de ziekte zich al naar de lymfeklieren of naar andere organen heeft uitgezaaid. Omdat patiënten pas zo laat gediagnostiseerd worden is de prognose vaak slecht: de kans op vijf jaar overleving ligt rond de 5-15% voor alle slokdarmkanker patiënten. Over het algemeen wordt slokdarmkanker behandeld met een chirurgische ingreep. Daarnaast krijgen de meeste patiënten vandaag de dag ook chemotherapie en bestraling voor de operatie. Tijdens de operatie worden de tumor en een groot deel van de slokdarm verwijderd, om er zeker van te zijn dat de tumor in zijn geheel verwijderd is. Van de maag creëert de chirurg vervolgens een buis die als vervangende slokdarm dient. Deze buis wordt opgetrokken naar het stuk slokdarm wat na verwijdering nog over is en hieraan bevestigd. Deze bevestiging heet een anastomose. De operatie voor slokdarmkanker is erg intensief en uitgebreid en het risico op complicaties na de operatie is niet gering. De herstelperiode is lang en patiënten hebben soms jaren na de operatie nog problemen met eten, misselijkheid, overgeven en zuurbranden.

In dit proefschrift richten wij ons op chirurgische technieken die de overleving van slokdarmkankerpatiënten kunnen optimaliseren en kunnen voorkomen dat patiënten lang na operatie nog problemen hebben. Ons doel is die technieken te vinden die de overlevingskans vergroten en de problemen verminderen, om deze patiënten een positievere toekomst te geven.

14.2 METHODEN

Dit proefschrift is opgebouwd uit vijf studies.

Voor deze studies hebben we drie verschillende bronnen van patiënten gebruikt. In studie I en II hebben we een grote, nationale, database gebruikt met uitgebreide informatie over patiënten die verzameld is uit alle ziekenhuizen in Zweden die betrokken waren bij de behandeling van slokdarmkankerpatiënten tussen 1987 en 2010 (the Swedish Esophageal Cancer Surgery Study, or *SESS*). De onderzoekers uit onze groep hebben de data verzameld uit operatieverslagen, patiëntendossiers en pathologieverslagen om zoveel mogelijk informatie te verzamelen over de patiënten, de tumor en de behandeling.

In studie III en IV hebben we een database gebruikt met patiënten die geopereerd zijn voor slokdarm kanker tussen 2001 en 2005 in heel Zweden (the Swedish Esophageal and Cardia Cancer or *SECC database*). Het netwerk van chirurgen en andere medische specialisten die betrokken zijn bij de behandeling van en zorg voor slokdarmkanker patiënte heeft de inzameling van deze data mogelijk gemaakt. Patiënten werden direct nadat ze de diagnose gekregen hadden en deze bevestigd was door de patholoog in de database opgenomen. In dit geval was het de patholoog die de patiënten informatie doorstuurde aan onze projectcoördinator. Daarnaast werd de patiënten gevraagd of ze een vragenlijst in wilde vullen over hun kwaliteit van leven en symptomen, dit werd op drie punten gedaan zes maanden, drie jaar en vijf jaar na hun operatie.

In studie V is een database gebruikt die in het Erasmus MC Universitair Medisch Centrum (EMC) in Rotterdam is opgezet. Alle patiënten vanaf 1978 en verder die behandeld zijn voor slokdarmkanker in het EMC zijn opgenomen in de database. In studie V zijn alleen patiënten inbegrepen die tussen 1990 en 2010 zijn geopereerd. Informatie over de patiënt, demografische gegevens, klinische data en details over de behandeling en de pathologie van de tumoren zijn uit de medische dossiers gehaald door een gespecialiseerd datamanager.

In studie I is gekeken naar het aantal lymfeklieren dat tijdens een operatie wordt verwijderd (lymfeklier resectie) en hoe dat aantal de overleving van de patiënt beïnvloedt. We hebben geprobeerd de vraag te beantwoorden of een uitgebreidere lymfeklier resectie de overleving verbetert in vergelijking met een minder uitgebreide lymfeklier resectie.

In studie II hebben we gekeken naar de patiënten die een heroperatie voor ernstige complicaties ondergingen binnen 30 dagen na de slokdarmkanker-operatie. We vergeleken hierbij de invloed van de heroperatie op de overleving van patiënten die opnieuw geopereerd zijn met die van patiënten die niet opnieuw geopereerd zijn.

In studie III hebben we geprobeerd een oplossing te vinden voor klachten van zuurbranden (reflux) na slokdarmoperatie door te kijken naar verschillende chirurgische ingrepen: 1) Een anastomose in de nek i.p.v. in de thorax, 2) een antireflux anastomose en 3) een snede in de maagportier (pyloromyotomy) wat het legen van de maag bevorderd.

In studie IV is gekeken naar aanhoudende klachten en symptomen zes maanden na operatie voor slokdarmkanker in patiënten die een lekkende anastomose hadden. We hebben de klachten en symptomen die deze patiënten met een lekkende anastomose hadden, vergeleken met patiënten die dit niet hebben doorgemaakt.

In studie V hebben we gekeken naar het postoperatieve beloop van patiënten met een gewichtsverlies van meer dan 10% in de drie maanden voor de vaststelling van de diagnose in vergelijking tot patiënten met minder of geen gewichtsverlies. Er is gekeken naar de overlevingskans, het risico op postoperatieve complicaties en het aantal opnamedagen.

In studie I, II en V is het risico op overlijden aan alle oorzaken, en het overlijden aan tumor recidief (terugkeer van de tumor) gedurende de vijf jaar na operatie berekend. Het risico op overlijden is berekend met een statistische methode “de Cox proportional hazard”. Het risico is berekend als hazard ratio (HR) met 95% confidence interval (95% CI) en percentages (%).

In studie III en IV zijn geselecteerde symptomen en klachten gemeten met behulp van een enquête dat ontwikkeld is om symptomen en klachten te meten die veel voorkomen onder kankerpatiënten (EORTC QLQ-C30) en een module die symptomen meet die veel voorkomen onder slokdarmkankerpatiënten (EORTC QLQ-OES18). Deze enquête en bijbehorende modules worden veel gebruikt in verschillende kankeronderzoek en geven een zeer betrouwbaar resultaat. Het risico op het ontwikkelen van symptomen (ja of nee) is berekend in de verschillende groepen. Het risico is berekend met een statistische methode, logistische regressie, en gepresenteerd als odds ratio (OR) met 95% confidence interval (95% CI).

14.3 RESULTATEN

In de eerste studie zijn 1044 patiënten opgenomen. De resultaten in studie I wezen er op dat een uitgebreidere lymfeklier resectie de overleving niet verbeterd. Huidige richtlijnen voor operatie adviseren een uitgebreidere lymfeklier resectie om de overleving te optimaliseren, ons onderzoek bevestigt dit niet. Wel zagen we dat patiënten met meerdere lymfeklieren met uitzaaiingen een hoger risico op overlijden hadden van 274% (HR 2.74, 95% CI 2.26-3.39) binnen vijf jaar.

In studie II zijn 1481 patiënten opgenomen, die geopereerd zijn voor slokdarmkanker tussen 1987 en 2010. In totaal zijn 155 (11%) van deze patiënten nogmaals geopereerd binnen 30 dagen na de eerste operatie omdat er ernstige complicaties optraden. Patiënten die een heroperatie hebben ondergaan, hadden een 26% hoger risico op overlijden in de vijf jaar na operatie. Patiënten die een lekkende anastomose hebben gehad, hadden een 82% verhoogd risico op overlijden (HR 1.82 95% CI 1.19-2.76

In studie III zijn 274 patiënten opgenomen. Dertig (9.9%) hadden een anastomose in de hals, tweeënveertig (13.8%) hadden een antireflux anastomose en bij 184 (64%) was er tijdens de operatie een pyloromyotomy verricht. Het risico op reflux-symptomen was in geen van de drie groepen verlaagd. De reflux-symptomen waren vermeld door 23-29% van de patiënten met een hals anastomose, antireflux anastomose of waarbij een pyloromyotomy is verricht.

In studie IV hebben we 277 patiënten opgenomen. Van deze patiënten hadden 29 (10%) een lekkende anastomose in de borstkas. We zagen dat patiënten met een lek een viervoudig verhoogd risico hadden op het ontwikkelen van eet problemen (OR 4.1, 95% CI 1.5.11.2) en een dubbel zo hoog risico op pijn tijdens het slikken (OR 2.6, 95% CI 1.1-5.8), gemeten zes maanden na de operatie. De problemen met eten waren na drie jaar nog steeds aanwezig (OR 2.0, 95% CI 1.0-32.4).

Van de 922 patiënten in studie V had 155 (17%) meer dan 10% gewichtsverlies in de drie maanden voor de diagnose. We zagen dat patiënten met meer dan 10% gewichtsverlies geen verhoogd risico op postoperatieve complicaties hadden (OR 0.83, 95% CI 0.54-1.24) en geen langere opnameduur hadden dan patiënten die geen of minder gewicht verloren hadden (HR 1.06, 95% CI 0.85-1.33). Daarentegen hadden patiënten met meer dan 10% gewichtsverlies wel een verhoogde kans op overlijden in de vijf jaar na operatie (HR, 1.34, 95% CI 102-1.74).

14.4 CONCLUSIES

Studie I: Een uitgebreidere lymfeklier resectie verbetert de overleving niet. Het is daarom misschien tijd om de geldende richtlijnen te herzien. Een hoger aantal lymfeklieren met uitzaaiingen verhoogde wel het risico op overlijden, zoals verwacht.

Studie II: Patiënten die na hun eerste operatie nogmaals geopereerd werden, hadden een verhoogde kans op overlijden van 27% in de eerste vijf jaar na operatie. Met name patiënten die nogmaals geopereerd zijn voor een lekkende anastomose hadden een verhoogd risico van 82%.

Studie III: Een anastomose in de hals, een antireflux anastomose of pyloromyotomy beschermen niet tegen symptomen van reflux zes maanden na een operatie voor slokdarmkanker.

Studie IV: Patiënten die een lekkage van de anastomose hadden doorgemaakt, hebben een verhoogd risico op aanhoudende klachten van problemen met eten en pijn tijdens het slikken.

Studie V: Gewichtsverlies van meer dan 10% verhoogd het risico op overlijden in de eerste vijf jaar na een operatie, maar niet het risico op postoperatieve complicaties of een langere opnameduur.

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