OESOPHAGEAL CANCER
-THE ROLE OF CO-MORBIDITIES

Lovisa Backemar

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av
Lovisa Backemar
ABSTRACT

The overall aim of this thesis was to produce information which can be used to improve clinical decision-making in order to optimise treatment and improve the well-being of patients with oesophageal cancer following surgery. Oesophageal cancer is a devastating disease with poor prognosis. The most established curatively intended treatment involves major surgery, often in combination with neoadjuvant therapy, and comes with a high risk of morbidity and limited chance of long-term survival.

The clinical decision process of determining which patients would benefit from surgery is critically important. Several factors are considered when evaluating whether a patient is suitable for surgery or not, but the main factors are tumour stage, general fitness and co-morbidity. The focus of this thesis focus was to assess how co-morbidities in general, and specific co-morbidities in particular, influence mortality, morbidity and health related quality of life (HRQOL) after surgery for oesophageal cancer. A subjective outcome such as HRQOL is of great importance in this patient group which adds an extra dimension to more objective outcomes in determining the outcome of the treatment.

The four studies included in the thesis were cohort studies from Sweden and England. Studies I and III were based on a prospective cohort including patients operated on between 2001 and 2005 in Sweden, and study II was based on a retrospective cohort of patients who underwent surgery between 1987 and 2010 in Sweden. Study IV used a prospective cohort of patients who underwent oesophagectomy at St Thomas’ Hospital London between 2011 and 2014/2015.

In studies I and II, co-morbidity was examined in relation to mortality after oesophageal cancer surgery. There was an increased risk of mortality among patients with a Charlson co-morbidity index score ≥2 and among patients with a history of myocardial infarction and congestive heart failure. Study III assessed co-morbidity in relation to morbidity after surgery. Patients with ≥1 co-morbidities or cardiac disease had an increased risk of severe post-operative complications. In study IV, co-morbidity was assessed in relation to HRQOL. Before surgery, patients with co-morbidities had worse HRQOL for several aspects, while at 6 months following surgery, patients had deteriorated in most HRQOL aspect regardless of co-morbidity status, except for the fact that patients with several co-morbidities had worse physical function, fatigue and more trouble with coughing compared to those with fewer co-morbidities.

In conclusion, this thesis provides additional information on how co-morbidities affect outcomes following surgery for oesophageal cancer and could help to improve clinical decision-making for these patients.
LIST OF PUBLICATIONS

This thesis is based on the following papers, which will be referred to by their Roman numerals (I-IV)

   The role of diabetes and other co-morbidities on survival after esophageal cancer surgery in a population-based study

II. Backemar L, Lagergren P, Johar A, Lagergren J.
   Impact of co-morbidity on mortality after oesophageal cancer surgery
   *The British journal of surgery* 2015;102(9): 1097-1105

    Comorbidities and Risk of Complications After Surgery for Esophageal Cancer: A Nationwide Cohort Study in Sweden

   Co-morbidity and recovery of health related quality of life after oesophageal cancer surgery
   *Manuscript*

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CONTENTS

1 INTRODUCTION..............................................................................................................................................1

2 BACKGROUND..................................................................................................................................................2

2.1 The Oesophagus ..............................................................................................................................................2

2.2 Oesophageal Cancer ......................................................................................................................................4

2.2.1 Pathogenesis ..............................................................................................................................................4

2.2.2 Incidence ....................................................................................................................................................4

2.2.3 From Diagnosis to Surgery .........................................................................................................................6

2.3 Prognosis - Morbidity and Mortality ............................................................................................................12

2.4 Co-morbidities .............................................................................................................................................14

2.5 Health Related Quality of Life - HRQOL .......................................................................................................17

3 AIMS ..............................................................................................................................................................25

4 MATERIALS AND METHODS ..........................................................................................................................26

4.1 Data Sources .................................................................................................................................................27

4.1.1 The Swedish Esophageal and Cardia Cancer register (SECC) .............................................................27

4.1.2 The Swedish Esophageal Cancer Surgery Study (SESS) .................................................................27

4.1.3 Guy's & St Thomas' Gastric and Oesophageal Tissue and Data Bank, London ........................................29

4.2 Study Design ................................................................................................................................................29

4.2.1 Study I .....................................................................................................................................................29

4.2.2 Study II ...................................................................................................................................................30

4.2.3 Study III ..................................................................................................................................................31

4.2.4 Study IV ..................................................................................................................................................31

5 RESULTS .........................................................................................................................................................33

5.1 Study I and III ..............................................................................................................................................34

5.2 Study II ......................................................................................................................................................38

5.3 Study IV ......................................................................................................................................................41

6 DISCUSSION ....................................................................................................................................................46

6.1 Methodological Considerations ..................................................................................................................46

6.2 Findings and explanations ............................................................................................................................52

6.2.1 Study I .....................................................................................................................................................52

6.2.2 Study II ...................................................................................................................................................53

6.2.3 Study III ..................................................................................................................................................53

6.2.4 Study IV ..................................................................................................................................................54

7 CONCLUSIONS ............................................................................................................................................56

8 IMPLICATIONS AND FUTURE RESEARCH ................................................................................................57

9 POPULÄRVETENSKAPLIG SAMMANFATTNING ..........................................................................................58

10 TILLKÄNNAGIVANDEN ................................................................................................................................61

11 REFERENCES ...............................................................................................................................................63

12 STUDIES I-IV ...............................................................................................................................................79
**LIST OF ABBREVIATIONS**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>AJCC</td>
<td>American Joint Committee on Cancer</td>
</tr>
<tr>
<td>ASA</td>
<td>American Society of Anaesthesiologists Classification</td>
</tr>
<tr>
<td>BMI</td>
<td>Body Mass Index</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence interval</td>
</tr>
<tr>
<td>COPD</td>
<td>Chronic obstructive pulmonary disorder</td>
</tr>
<tr>
<td>CT</td>
<td>Computed tomography (radiology)</td>
</tr>
<tr>
<td>EORTC</td>
<td>The European Organisation for Research and Treatment of Cancer</td>
</tr>
<tr>
<td>EUS</td>
<td>Endoscopic ultrasound</td>
</tr>
<tr>
<td>FACT-G</td>
<td>Functional Assessment of Cancer Therapy</td>
</tr>
<tr>
<td>HADS</td>
<td>Hospital Anxiety and Depression Scale</td>
</tr>
<tr>
<td>HR</td>
<td>Hazard ratio</td>
</tr>
<tr>
<td>HRQOL</td>
<td>Health related quality of life</td>
</tr>
<tr>
<td>ICD-7</td>
<td>International Classification of Diseases version 7</td>
</tr>
<tr>
<td>MDM</td>
<td>Multidisciplinary meetings</td>
</tr>
<tr>
<td>MFI</td>
<td>Multidimensional Fatigue Inventory</td>
</tr>
<tr>
<td>MPQ</td>
<td>McGill Pain Questionaire</td>
</tr>
<tr>
<td>OR</td>
<td>Odds ratio</td>
</tr>
<tr>
<td>PET-CT</td>
<td>Positron emissions tomography computed tomography</td>
</tr>
<tr>
<td>QLQ-C30</td>
<td>Quality of Life Questionnaire – Core 30 The General Cancer Core Questionnaire</td>
</tr>
<tr>
<td>QLQ-OG25</td>
<td>Quality of Life Questionnaire – Oesophago-Gastric 25 The Oesophago-gastric Specific Questionnaire</td>
</tr>
<tr>
<td>SECC</td>
<td>Swedish Esophageal and Cardia Cancer register</td>
</tr>
<tr>
<td>SEIQoL</td>
<td>Schedule for individual evaluation of quality of life</td>
</tr>
<tr>
<td>SESS</td>
<td>The Swedish Esophageal Cancer Surgery Study</td>
</tr>
<tr>
<td>SF-36</td>
<td>The Short Form (36) Health Survey</td>
</tr>
<tr>
<td>TNM</td>
<td>Tumour-node-metastasis (TNM) classification</td>
</tr>
<tr>
<td>UICC</td>
<td>Union for International Cancer Control</td>
</tr>
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<td>WHO</td>
<td>The World Health Organisation</td>
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</table>
1 INTRODUCTION

Each year, approximately 430 new cases of oesophageal cancer and 200 new cases of gastro-oesophageal junctional cancer are diagnosed in Sweden.\textsuperscript{1} It is a relatively uncommon disease from a European perspective but globally there are 482,300 new cases of oesophageal cancer yearly which corresponds to the 8\textsuperscript{th} most common cancer, and it is the 6\textsuperscript{th} most common cause of death by cancer worldwide.\textsuperscript{2}

Since oesophageal cancer is typically asymptomatic at its onset, many patients present at a late stage when their chances of survival are limited. Due to this late and subtle presentation, its aggressive growth and rapid spread, oesophageal cancer has a poor prognosis with an overall 5-year survival of only 10\% in the Western world.\textsuperscript{3} The most established curatively intended treatment involves major surgery, and during recent years, often in combination with neoadjuvant therapy, which increases the 5-year survival to approximately 30\%\textsuperscript{,4,5} to 50\%.\textsuperscript{4,5} The surgery is extensive and typically requires access to both the abdomen and the thorax, and sometimes also a neck dissection. Even though early mortality and complications after surgery have decreased during recent years, probably mainly due to centralisation of procedures,\textsuperscript{6} development of surgical techniques, and improvements in perioperative care\textsuperscript{7}, the short-term postoperative mortality rate is still as high as 3-14\%\textsuperscript{8,9,10} and the complication rates range from 26\% to 64\%.\textsuperscript{3,11-14} Oesophageal cancer surgery has also been seen to have a substantial negative impact on the patient’s health related quality of life (HRQOL),\textsuperscript{15,16} and patients who do not recover their HRQOL within 6 months of surgery have a higher risk of mortality than those who do recover.\textsuperscript{17}

Several factors are considered when evaluating whether or not a patient is suitable for surgery, but the main factors are tumour stage, overall fitness and co-morbidity. As a result, surgery is undertaken in only 20-35\% of patients,\textsuperscript{18} while the remaining 65-75\% of patients are offered palliative treatment.\textsuperscript{19,20} Nevertheless, about two-thirds of all operated patients have at least one co-morbidity prior to surgery.\textsuperscript{21} Therefore, it is very important to understand how co-morbidities in general, and specific co-morbidities in particular, influence postoperative mortality, morbidity and patients’ HRQOL after surgery.

This thesis is based on four original papers focusing on how co-morbidity affects mortality, morbidity and HRQOL after oesophageal cancer surgery. In clinical practice, the occurrence of co-morbidity strongly influences the choice of therapy. The crucial choice is between curatively intended surgery and palliation. Surgery is often considered to be best used in fit patients, ideally without co-morbidities, but the scientific evidence to support such strategy is very limited. This thesis has the intention to increase the knowledge-base and help guide clinical decision-making so that treatment can be better tailored for each patient. As a result, this will hopefully increase survival and improve the well-being of surgically treated oesophageal cancer patients.
2 BACKGROUND

2.1 THE OESOPHAGUS

Figure 1. Regional anatomy of the oesophagus and its surrounding organs.

Painted by: Lovisa Backemar
Anatomy and Histology
The oesophagus is a muscular tube connecting the pharynx to the stomach by the gastro-oesophageal junction (Figure 1). With a length of 18-26 cm it stretches from the same level as the cricoid cartilage in the neck, descends between the trachea and spine while passing behind the tracheal bifurcation, the aortic arch and then close to the left atrium of the heart before entering the diaphragm hiatus into the abdomen. This well protected location and the closeness to vital organs may both delay the detection of the tumour and increase the risk of and complicate surgery.

The histology of the oesophagus is similar to the entire gastrointestinal system, composed of four layers: the internal mucosa, the submucosa, the muscularis propria, and the adventitia (Figure 2). Unlike the rest of the gastrointestinal track, however, the oesophagus lacks serosal coating, which facilitates tumour spreading and challenges the repair when a surgical anastomosis is created.

The internal mucosa consists of smooth muscles and squamous epithelium in the oesophagus. The muscularis propria consists of an external longitudinal layer and an internal circular layer by which peristaltic movement facilitates the transportation of food towards the stomach. In the upper part, it consists of voluntary controlled striated muscles, with involuntary controlled smooth muscle fibres in the lower part. While food passes, the normally collapsed oesophagus can stretch up to a couple of centimetres. This capacity allows a tumour to grow large before presenting any symptoms. Most distally, the muscle fibres form a thickening which constitutes the lower oesophageal sphincter (LES), preventing regurgitation of food and gastric acid from the stomach.22

Figure 2. Histology of the oesophagus.
2.2 OESOPHAGEAL CANCER

Oesophageal cancer can have many types of histological origin but over 90% of cases are squamous cell carcinoma or adenocarcinoma, which are the focus of this thesis. They have similar prognosis and treatment, but differ in risk factors and incidence patterns, with distinct variations by geographical area, ethnicity and gender.

2.2.1 Pathogenesis

Squamous cell carcinoma is far more frequent in the middle to upper oesophagus while adenocarcinomas are predominantly found in the lower part of the oesophagus or at the gastro-oesophageal junction. The pathogenesis of oesophageal cancer is not yet fully understood and there are different molecular mechanisms for the two histological types. For adenocarcinoma, it is suggested that repeated mucosal injury caused by gastro-oesophageal reflux causes metaplasia in which the normal lining of the oesophagus, the stratified squamous epithelium, is replaced by abnormal columnar epithelium. This condition is also known as Barrett’s oesophagus. This metaplasia is considered a premalignant condition which predisposes to dysplasia and finally adenocarcinoma. However, this development is a multistep process and requires several genetic errors, and the risk of developing adenocarcinoma among patients with Barrett’s is only 0.6% per year or less. The pathological pathway of squamous cell carcinoma is not as well documented as for adenocarcinoma. However, it predominantly develops from chronic irritation of the oesophageal squamous epithelium, caused by the exposure of risk factors, e.g. tobacco smoking, alcohol or certain dietary habits (including hot drinks). As for adenocarcinoma, the fulminant squamous cell carcinoma develops through a series of molecular changes from dysplasia to invasive carcinoma.

2.2.2 Incidence

Each year, an estimated 456,000 new oesophageal cancer cases are diagnosed each year, including 45,900 in Europe, 8,332 in the UK, and 430 in Sweden. There are distinctive differences in incidence between geographical areas and around 80% of the cases worldwide do not occur in the Western world. In those regions squamous cell carcinoma is dominant, which is why this is also the most common histological type worldwide. The incidence is particularly high in the so called “oesophageal cancer belt” including Turkey, North-Eastern Iran, Kazakhstan and Northern and Central China, where incidence rates are as high as 100 per 100,000 person years. The incidence of squamous cell carcinoma is stable or decreasing in the industrialised world, while the incidence of adenocarcinoma, on the contrary, has increased during the past few decades without signs of stabilising. In fact in many countries, the incidence has risen more rapidly than any other cancer, and adenocarcinoma is now the most common histological type of oesophageal cancer in most parts of the Western world (Figure 3). The highest incidence of adenocarcinoma is seen in
the UK, where the crude incidence rate is 18 new oesophageal cancer cases for every 100,000 males per year, and 9 for every 100,000 females per year.\textsuperscript{34} In Sweden those numbers are approximately one third of the UK incidence, 6.7 per 100,000 males per year and 2.2 per 100,000 females per year.\textsuperscript{1} This geographical difference between squamous cell carcinoma and adenocarcinoma might be due to differences in the prevalence of risk factors. There is a sex variation in incidence. For squamous cell carcinoma, there is a 3:1 male predominance but for adenocarcinoma there is a striking 7:1 ratio. The sex variation for squamous cell carcinoma is explained by differences in exposures to known risk factors, but the 7:1 male predominance for adenocarcinoma remains unexplained.\textsuperscript{35-38}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure3}
\caption{Age-standardised incidence of oesophageal cancer per 100,000, stratified by sex from 1970-2013.\textsuperscript{39}}
\end{figure}

\textbf{Risk Factors}

The two main risk factors for squamous cell carcinoma are tobacco smoking and high alcohol consumption.\textsuperscript{40} A combination of those accounts for an even higher risk and may cause up to 90\% of the squamous cell carcinomas in the Western world.\textsuperscript{3} Additionally, squamous cell carcinoma has been associated with low intake of fruits and vegetables\textsuperscript{41} and low socioeconomic status.\textsuperscript{3, 42} There are also other risk factors that have been debated such as such as achalasia, hot beverages and caustic injury, which could all potentially chronically irritate the squamous epithelium and cause carcinoma.

Established risk factors for adenocarcinoma are gastro-oesophageal reflux,\textsuperscript{3, 43-46} Barrett’s oesophagus,\textsuperscript{18, 27, 28, 47} and obesity.\textsuperscript{3, 36, 48} It has also been established that tobacco smoking is a
modest risk factor for adenocarcinoma, but high alcohol consumption does not seem to increase that risk. Infection with the bacterium Helicobacter pylori has been seen to decrease the risk of adenocarcinoma, hypothetically because of the gastric atrophy and reduction in acid secretion that counteracts acidic reflux.

**Gastro-oesophageal Junctional Cancer**

Gastro-oesophageal junctional cancer or cardia cancer is the presence of adenocarcinomas whose centres are situated 5 cm above to 5 cm below the oesophago-gastric junction, which is where the oesophagus meets the stomach. However, there is indecision in the literature as to how to exactly define the location of the oesophago-gastric junction and gastro-oesophageal junctional cancers. There are many similarities between oesophageal adenocarcinomas and gastro-oesophageal junctional cancers, which is why they may be classified as one group of tumours. From the latest edition (7th edition) of the Union for International Cancer Control (UICC)/American Joint Committee on Cancer (AJCC) TNM staging system, gastro-oesophageal junctional cancers are also staged as oesophageal cancers. Location wise, these tumours have a further sub-classification called the Siewert classification: Type I, midpoint of adenocarcinoma between 1 cm and 5 cm above the junction; Type II, adenocarcinoma midpoint between 1 cm above and 2 cm below the junction and Type III, adenocarcinoma midpoint between 2 cm and 5 cm below the junction. Risk factors for gastro-oesophageal junctional cancer are the same as for adenocarcinoma of the oesophagus, i.e. gastro-oesophageal reflux, Barrett’s oesophagus and obesity. 

### 2.2.3 From Diagnosis to Surgery

The process of diagnosis, staging and treatment of oesophageal cancer is done in a multidisciplinary setting involving physicians specialised in for example oncology, radiology, pathology and surgery, as well as nurses and dietitians.

**Symptoms**

There are no typical early symptoms of oesophageal cancer, instead patients most often present with difficulty in swallowing solid food (dysphagia) as a result of luminal obstruction. These problems first occur when there is tumour growth of more than 2/3 of the lumen, i.e. when the tumour has been growing for a while and has had time to systemically spread. Upcoming symptoms are weight loss which is partly due to the dysphagia, heartburn and pain when swallowing (odynophagia). Further, as the tumour may metastasise or overgrow the nearby nerves or organs, symptoms such as dyspnoea, cough, hoarseness or retrosternal, back or right upper abdominal pain may be present reflecting a more advanced disease. With the late presentation of the first symptoms, the tumour can grow unrecognisably and over 50% of patients already have a non resectable disease by the time of diagnosis. The above described symptoms are oesophageal cancer specific, but in addition, general cancer symptoms might be present, such as fatigue.
Diagnosis and Staging

Patients with oesophageal cancer will not show any distinct abnormalities in a thorough clinical examination or in lab tests. If, however, there is a suspicion of oesophageal cancer, the investigation should be thorough and prioritised so that a decision on treatment could be based upon that. When it comes to deciding an individual’s treatment, co-morbidity status and tumour stage play the most important role. To stage the disease, the tumour-node-metastasis (TNM) classification is used.\textsuperscript{52} T defines how deep the tumour has grown in the oesophageal wall (Figure 4), N is the extent of lymph node involvement and M represents the occurrence of distant metastasis. Depending on these parameters, the oesophageal and gastric oesophageal junctional cancer can be categorised into stages ranging from 0 to IVB.\textsuperscript{52} (Table 1).

The foundation of the whole investigation is thorough anamnesis, including the assessment of dysphagia, weight loss, pain, vomiting or reflux. It is also important to examine the patient’s physical fitness, including co-morbidities, since that is taken into account when the treatment decision is made.\textsuperscript{18} Physical examination includes heart- and lung auscultation, palpation of lymph nodes and the abdomen. If an enlarged liver or enlarged sub-clavicular lymph nodes are found, it might be sign of a metastatic disease.\textsuperscript{3} A standard set of investigations include gastroscopy with biopsies in order to confirm and evaluate the tumour (T), and a computed tomography (CT) with intravenous contrast of the thorax and abdomen for evaluation of the tumour growth (T), enlarged lymph nodes (N), and if there is evidence of distance metastasis (M).\textsuperscript{3, 56} However, the CT cannot detect the different layers of the oesophageal wall, so the ability to determine T-stadium is limited. Endoscopic ultrasound (EUS) has the ability to distinguish between the layers and with this technique, fine needle aspiration of lymph nodes could also be performed in order to further investigate the N-stage.\textsuperscript{3, 56} If the CT does not detect any distant metastasis, one should consider a positron emissions tomography CT (PET-CT), which has been shown to have good sensitivity detecting distant metastasis.\textsuperscript{57} Laparoscopic staging can also be performed in some unclear cases.

![Figure 4. Histology and tumour (T)](image-url)
Table 1. The American Joint Committee on Cancer (AJCC) 7th edition staging system for oesophageal cancer and gastric oesophageal junctional cancer

<table>
<thead>
<tr>
<th>Primary tumour (T)</th>
<th>T</th>
<th>N</th>
<th>M</th>
<th>G</th>
</tr>
</thead>
<tbody>
<tr>
<td>TX</td>
<td>Primary tumour cannot be assessed</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T0</td>
<td>No evidence of primary tumour</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tis</td>
<td>High grade dysplasia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1</td>
<td>Tumour invades lamina propria or submucosa</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T2</td>
<td>Tumour invades muscularis propria</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T3</td>
<td>Tumour invades adventitia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T4a</td>
<td>Tumour invades adjacent structures such as pleura, pericardium, diaphragm and is resectable</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T4b</td>
<td>Tumour invades adjacent structures such as aorta, vertebra, trachea and is non resectable</td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

| Regional lymph nodes (N)                        |        |        |        |        |
| (Any peri-oesophageal lymph nodes from cervical or celiac nodes) |        |        |        |        |
| NXR                                            | Regional lymph nodes cannot be assessed |        |        |        |
| N0                                             | No regional lymph nodes metastasis   |        |        |        |
| N1                                             | 1 to 2 positive regional lymph nodes |        |        |        |
| N2                                             | 3 to 6 positive regional lymph nodes |        |        |        |
| N3                                             | ≥7 positive regional lymph nodes     |        |        |        |

| Distance metastasis (M)                         |        |        |        |        |
| MX                                             | Distant metastasis cannot be assessed |        |        |        |
| M0                                             | No distant metastasis                |        |        |        |
| M1                                             | Distant metastasis                   |        |        |        |

| Histologic grade (G)                           |        |        |        |        |
| G1                                             | Well differentiated                   |        |        |        |
| G2                                             | Moderately differentiated             |        |        |        |
| G3                                             | Poorly differentiated                 |        |        |        |
| G4                                             | Undifferentiated                      |        |        |        |

| Cancer location                                |        |        |        |        |
| Upper                                          | 20 to 25 cm from incisors             |        |        |        |
| Middle                                         | >25 to 30 cm from incisors            |        |        |        |
| Lower                                          | >30 to 40 cm from incisors            |        |        |        |
Choice of Treatment
Today, several factors are considered when evaluating the treatment regime for each individual patient. An important tool in this decision is the multidisciplinary meetings (MDM) which may involve a variety of different specialists including surgeons, oncologists, gastroenterologists, radiologists, pathologists, dieticians and specialist nurses. The decision of treatment is based upon the stage of the oesophageal cancer, general fitness, co-morbidities and the patient’s preferences.58 Today, in curatively intended treatment, surgery is the cornerstone often in combination with neoadjuvant chemotherapy or chemo-radiotherapy.56 The 5-year survival after curatively intended surgery is 30% to 50%4,5 compared to an overall survival of 10%.3 However, about 65-80% of all patients with oesophageal cancer are not considered eligible for surgery.18,20 Except for advanced tumour stage, the main reason for exclusion from surgery is unfitness, which is often due to co-morbidities.18,20,59 However, exclusion of patients due to co-morbidity is supported by scientific evidence to only a limited degree.20

Palliative Treatment
Since the majority of the oesophageal cancer patients are not suitable for surgery or curative treatment,3 palliative treatment plays an important role. Additionally, recurrence after curative treatment is quite common60-63 and there is no efficient second-line treatment, so palliative treatment is also important for patients with recurrent disease. It aims to keep symptoms like dysphagia under control, preserve HRQOL and if possible, prolong survival.64,65

Pre-operative Care
It is important to consider patients’ co-morbidities and optimise the fitness status of patients with co-morbidity before initiation of treatment in order to avoid complications and maintain a good HRQOL. The goals for pre-operative care are to optimise the nutritional status and counteract symptoms, e.g. dysphagia, pain and anxiety.56 The incidence of malnutrition among oesophageal cancer patients is around 60%66 which in turn increases the risk of complications.67

Before surgery, the anaesthesiologist makes an evaluation of the patient’s physical status in order to see if he/she is suitable for surgery. One tool is the American Society of Anaesthesiologists (ASA) classification which is a readily available and widely accepted system used prior to surgical procedures to assess the physical fitness of the patient based on their co-morbidities.68,69

Neo-adjuvant Treatment
Previously, adding neoadjuvant treatment, i.e. preoperative chemotherapy and/or radiotherapy to the surgical treatment, was a topic of dispute. For a long time, surgery was a single modality treatment for cure, but today neoadjuvant therapy is a part of the treatment regime in most patients who are eligible for curatively intended treatment.56 Chemotherapy
treats micro-metastasis as well as the main tumour and makes the tumour more radiosensitive. Radiotherapy could further suppress the main tumour and loco-regional recurrences. A large randomised clinical trial from the Netherlands found a clear survival advantage of neoadjuvant chemo-radiotherapy compared to surgery alone for patients eligible for resection. Additionally, a meta-analysis of 17 trials addressing survival after neoadjuvant therapy plus surgery and surgery alone showed that the overall mortality was lower after preoperative chemo-radiotherapy or chemotherapy. A direct comparison of preoperative chemo-radiotherapy with preoperative chemotherapy revealed a tendency of better survival in the chemo-radiotherapy group, but there was no statistically significant difference.

The Operation
Oesophageal cancer surgery is an extensive procedure associated with high morbidity and mortality but it also offers a chance of cure. The main approaches for oesophageal cancer surgery are transthoracic and transhiatal, with transthoracic dominant in Sweden, the UK and many other countries.

The transthoracic approach is either done as an Ivor-Lewis or McKeown resection. Both start with an abdominal incision giving access to dissect the stomach and lower oesophagus as well as dissect nodal tissue. With the classic Ivor-Lewis resection the thorax is entered through a right sided posterolateral thoracotomy at the fifth intercostal space. This gives access to further dissect the middle and upper oesophagus. By approaching from the right side, interference with the aortic arch is avoided. However, some surgeons prefer a left sided approach for the dissection of bulky distal tumours. Either way, during the thoracic entrance, one lung is deflated in order to get a good access to the operation field. The McKeown resection also involves a further third incision, a left sided cervical incision, which is preferable for patients where the tumour is located proximally.

Figure 5. Schematic picture of the replacement of the oesophagus with a gastric substitute.

The transhiatal approach involves incisions in the abdomen and neck. Dissection of the oesophagus is then made partly blindly through the hiatus of the diaphragm. The purpose is to decrease the surgical trauma by avoiding the thoracic entrance. However, there is no evidence of which approach has better outcomes. Neither randomised controlled trials nor
meta-analyses have shown any difference in survival rate. However, the frequency of pulmonary complications is lower for patients operated with the transhiatal approach. Still, the selection of the surgical approach is based mainly on the surgeon’s preference, location of the tumour and fitness of the patient. Regarding the fitness of the patients and co-morbidities, it is mostly pulmonary disease that might affect the choice of surgical approach since the transhiatal approach might in that case be safer.

After resecting the tumour and thus a large part of the oesophagus, the stomach, or sometimes the jejunum or colon, functions as a substitute (Figure 5). The anastomosis between the remaining oesophagus and the substitute is located in the upper thorax for the Ivor-Lewis approach and in the neck for the McKeown and transhiatal approach.

If distant metastasis is found during the surgery, the procedure is aborted, a so called “open and close surgery” with patients going on to a palliative treatment pathway instead.

Minimally Invasive Oesophagectomy
Minimally invasive oesophagectomy is either done as Ivor Lewis or McKeown but involves laparoscopy or thoracoscopy, sometimes in combination with conventional open laparotomy or thoracotomy. This technique is used more and more in an attempt to decrease postoperative morbidity and improve recovery. Studies comparing the minimally invasive technique with open surgery are sparse, but it has been shown that minimally invasive oesophagectomy reduces blood loss and decreases morbidity. Still, the rate of more severe complications and survival rate are similar. However, to date there are no studies on long-term outcomes.

Postoperatively
The postoperative treatment of patients after oesophagectomy is mainly based on well-tried experience rather than evidence based guidelines since the literature is sparse. After surgery, the patient usually stays in the intensive care unit before being transferred to a surgical ward. Postoperative treatment involves securing good nutritional status and mobilising the patient. Postoperative adjuvant therapy has been debated and still its role remains unclear. Thus there is no definite recommendation that can be made but today adjuvant therapy is not a part of the treatment regime in Sweden. In the UK, the approach is a bit different. Adjuvant therapy may be given to patients who have positive margins and are estimated to have a high risk of local recurrence. Additionally, patients also need to be fit enough after the surgery within an appropriate time frame, which is strongly influenced by the high postoperative morbidity rate.

In the longer term, the follow-up is focused on nutritional status and HRQOL. The recommendations are regular physician check-ups at the surgical open clinic up to two years after surgery. Thereafter, patients go to their general practitioner.
2.3 PROGNOSIS - MORBIDITY AND MORTALITY

Mortality
As previously stated, the prognosis for oesophageal cancer patients is poor. However, the prognosis has slowly improved over the last few decades. Between 2000-2004 and 2005-2009, oesophageal cancer mortality decreased among European men by 7% from 5.34 to 4.99 per 100,000, and the prediction is that those numbers will continue to improve (Figure 6). But despite the improvement, the survival rate is still lower than 15%. In Sweden, there is also an improvement of survival among operated patients. The 5-year survival between 1997 and 2000 was 30.7% compared to 19.7% between 1987-1991, but the survival did not improve in 2001-2005. The strongest prognostic factor is tumour stage, the 5-year survival is 65% for stage I, 27% for stage II and 9% for stage III. Other prognostic factors are older age, higher hospital volume and surgeon volume.

Figure 6. Trends in age-standardised mortality rates per 100 000 men for oesophageal cancer in the European Union (EU) as a whole and selected European countries from 1980 to 2011, and predicted rates for 2015. 85 Copyright© Oxford University Press, Annals of Oncology. All rights reserved.
Postoperative Morbidity
Because of the magnitude and complexity of the surgery, oesophagectomy is also associated with a 26-64% risk of potentially lethal complications.\textsuperscript{3,11-14} One distinguishes between surgical complications depending on surgical issues and medical complications which are due mostly to the patient’s physical status. In more recent years, a system to grade the severity of complications after surgery has been used, called Clavien-Dindo classification.\textsuperscript{89} This is based on a five grade scale from Grade I (any deviation from the normal postoperative path not requiring any pharmacological or surgical treatment), Grade II (requiring pharmaceuticals including blood transfusion and total parenteral nutrition), Grade III (requiring surgical intervention), Grade IV (life-threatening complication requiring intensive care), to Grade V (death).\textsuperscript{89}

Surgical Complications
There is a wide range of surgical complication rates depending on the study, probably because of different definitions and cut-offs, but also because of patient selection. Surgical complications include post-operative bleeding, anastomotic insufficiency, injury to the thoracic duct, intra-abdominal or intrathoracic abscess, wound rupture, wound infection, necrosis of the substitute, ileus, and anastomotic stricture. The most feared complication is anastomotic leak, which has a prevalence of 4-14%,\textsuperscript{11,13,14} and 9% in a Swedish study.\textsuperscript{90} Such a leak is associated with a 25-50% risk of postoperative death.\textsuperscript{91-94} It is more common with anastomotic leak in cervical anastomosis and has been shown to appear in up to 50% of these patients.\textsuperscript{94,95} However, a leak in the cervical region is considerably less severe than in the thoracic cavity because when gastrointestinal contents contaminate the surroundings it may lead to mediastinitis and sepsis.\textsuperscript{96} The aetiology of anastomotic leak is multifactorial, but technical surgical errors and ischemia of the substitute seem to play a major role.\textsuperscript{94,97} Additionally, certain co-morbidities have been shown to increase the risk of anastomotic leak, including hypertension, congestive heart failure, and renal insufficiency.\textsuperscript{95,98} For all of these co-morbidities there is an increased risk of impaired micro-vascularisation affecting the healing of the anastomosis.

Medical Complications
Medical complications are more common than surgical complications,\textsuperscript{90} and include pneumonia, deep venous thrombosis, pulmonary embolism, respiratory insufficiency, sepsis, myocardial infarction, atrial fibrillation, cerebrovascular infarction, renal insufficiency and liver insufficiency. Atrial arrhythmia (14-23%),\textsuperscript{11,14} pulmonary complications (10-21%)\textsuperscript{11-14} and respiratory failure (6-18%)\textsuperscript{11-14} are the most common and may lead to postoperative deaths.\textsuperscript{91,99} Co-morbidities also play a role in medical complications where patients with cardiac disease are at a higher risk of atrial fibrillation.\textsuperscript{100,101} Surgery site also seems to play an important role where there is evidence that surgery involving the upper abdomen and thoracic cavity is associated with a higher risk of pulmonary complications.\textsuperscript{102}
Recurrence
Despite the curatively intended surgery, recurrence is common and within one year, 28-71% of the patients have developed recurrence depending on the study. The length of survival after suffering recurrence is usually only a few months.

2.4 CO-MORBIDITIES
The concept of one patient having more than one disease is referred to as co-morbidity. In this thesis, since all participating patients have oesophageal cancer, any other disease represents co-morbidity. The incidence of several of the major chronic diseases, e.g. diabetes, cardiac disease and cancer, increases with age, and as a result, having multiple co-morbidities is more common in the elderly population. Different co-morbidities may have variable impact on the patient, but it has been shown that the presence of co-morbidities has a negative impact on HRQOL in general. Patients who are diagnosed with oesophageal cancer are often elderly and about two-thirds of all oesophageal cancer patients have at least one co-morbidity prior to surgery. As a result, this is an important aspect to take into consideration in the clinical decision-making. As previously described, it is clear that co-morbidity status could play an important role in patient selection for surgery and that it affects the outcome of the treatment as it is a predictor of early postoperative mortality and other severe complications. Further, there is also evidence that co-morbidities affect short-term HRQOL after oesophageal cancer surgery, and that pre-existing co-morbidities lead to poorer HRQOL in 5 year survivors. In this thesis, ASA, the Charlson co-morbidity index and individual co-morbidities such as diabetes, hypertension, obesity, cardiac disease and pulmonary disease were analysed. In the following section these will be described in more detail.

The Charlson Co-morbidity Index
The Charlson co-morbidity index was developed in 1987 in order to have a systematic way of predicting long-term mortality on the basis of co-morbidities. The index was developed by reviewing 559 patients’ co-morbidities and assessing these co-morbidities in conjunction with 1-year all-cause mortality. The mortality rates for the different scores were 0=12%, 1-2=26% and 3-4=52%. The index was then validated, i.e. tested for its ability to predict risk of death from co-morbidities, in 685 breast cancer patients during a 10-year follow-up. Mortality rates for deaths from the co-morbidity were then 0=8%, 1=25%, 2=48% and ≥3=59%. In conclusion, they found it to be a simple, readily applicable and valid method of estimating risk of mortality among patients with co-morbidities. The index has since been validated in several patient groups, including cancer and critically ill patients. When using the Charlson co-morbidity index in this thesis, a slight modification was made by excluding oesophageal cancer, gastric cancer and metastatic cancer since oesophageal cancer could be misclassified as gastric cancer before surgery and metastatic cancer could include oesophageal cancer. There is also an age-adjusted Charlson co-morbidity index which takes age into account. (Table 2)
Table 2. Scoring system for the Charlson co-morbidity index.\textsuperscript{108}

<table>
<thead>
<tr>
<th>Condition</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myocardial Infarction</td>
<td>1</td>
</tr>
<tr>
<td>Congestive Heart Failure</td>
<td>1</td>
</tr>
<tr>
<td>Peripheral Vascular Disease</td>
<td>1</td>
</tr>
<tr>
<td>Cerebrovascular Disease</td>
<td>1</td>
</tr>
<tr>
<td>Dementia</td>
<td>1</td>
</tr>
<tr>
<td>Chronic Pulmonary Disease</td>
<td>1</td>
</tr>
<tr>
<td>Connective Tissue Disease</td>
<td>1</td>
</tr>
<tr>
<td>Peptic Ulcer Disease</td>
<td>1</td>
</tr>
<tr>
<td>Liver disease mild</td>
<td>1</td>
</tr>
<tr>
<td>Diabetes, uncomplicated</td>
<td>1</td>
</tr>
<tr>
<td>Diabetes, end-organ damage</td>
<td>2</td>
</tr>
<tr>
<td>Chronic Kidney Disease</td>
<td>2</td>
</tr>
<tr>
<td>Hemiplegia</td>
<td>2</td>
</tr>
<tr>
<td>Leukaemia</td>
<td>2</td>
</tr>
<tr>
<td>Malignant Lymphoma</td>
<td>2</td>
</tr>
<tr>
<td>Solid Tumour</td>
<td>2</td>
</tr>
<tr>
<td>Liver Disease, moderate to severe</td>
<td>3</td>
</tr>
<tr>
<td>Solid Tumour and Metastasis</td>
<td>6</td>
</tr>
<tr>
<td>AIDS</td>
<td>6</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Age</th>
<th>Score</th>
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</thead>
<tbody>
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<td>&lt;50 years</td>
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<tr>
<td>50-59 years</td>
<td>1</td>
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<td>60-69 years</td>
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</tr>
<tr>
<td>70-79 years</td>
<td>3</td>
</tr>
<tr>
<td>80-89 years</td>
<td>4</td>
</tr>
<tr>
<td>90-99 years</td>
<td>5</td>
</tr>
</tbody>
</table>

ASA Classification
The ASA classification is a readily available and widely accepted system used prior to surgical procedures to assess the physical fitness of the patient based on their co-morbidities. It was first introduced in 1941 and has developed into a six-category physical status system:\textsuperscript{68, 69} ASA I) a healthy patient; ASA II) a patient with mild systemic disease (e.g. well-controlled diabetes mellitus or hypertension, mild lung disease); ASA III) a patient with severe systemic disease (e.g. poorly controlled diabetes mellitus, chronic obstructive pulmonary disorder (COPD), morbid obesity or history of myocardial infarction; ASA IV) a patient with severe systemic disease that is a constant threat to life (e.g. ongoing cardiac ischemia or severe valve dysfunction or sepsis); ASA V) a moribund patient who is not expected to survive without the operation; and ASA VI) a declared brain-dead patient whose organs are being removed for donor purposes.\textsuperscript{112} It is a partly subjective assessment, made by the anaesthesiologist prior to surgery, but it is a well-established system which has been shown to be a reliable way to classify pre-operative physical status.\textsuperscript{113, 114}

Co-morbidities and Risk of Oesophageal Cancer
It is already well established that obesity is a risk factor of oesophageal adenocarcinoma. However, since obesity is also one of the main criteria in the metabolic syndrome, it has been hypothesised that there may be an association between oesophageal cancer and the metabolic syndrome.\textsuperscript{115} The metabolic syndrome is defined by the presence of three out of the following five components: abdominal obesity, elevated triglycerides, low high-density lipoprotein cholesterol, hypertension and diabetes.\textsuperscript{116} Each of these increases the risk of cardiovascular disease, but as a combination the risk is even higher. The prevalence of the
metabolic syndrome in Europe is around 25%, and as well as increasing the risk of cardiovascular disease, it has also been shown to increase the risk of certain types of cancer. However, no study has shown an association between metabolic syndrome and oesophageal cancer. There is one study showing a two-fold increased risk of oesophageal carcinoma among patients with hypertension but the mechanism remains unclear.

**Obesity**
The definition of obesity is excess of fat accumulated under the skin and around internal organs. The World Health Organisation (WHO) defines obesity as a body mass index (BMI) ≥30. Since 1980, the prevalence of obesity has doubled and today 13% of the world’s population is obese. Obesity is caused by an imbalance between energy intake and energy consumption and the prevalence increases because of lifestyle factors. The condition increases the risk of cardiovascular disease, diabetes mellitus, musculoskeletal disorders and several types of cancer (e.g. oesophageal, endometrial, breast and colon). Obesity is also a part of the metabolic syndrome.

**Diabetes**
There are two major types of diabetes mellitus, type 1 and type 2, with a prevalence of 3-5% in Western society, where type 2 accounts for 80-90% of all cases. Type 2 is also the most common chronic metabolic disease, with a global prevalence of 366 million people, which is expected to rise to 552 million by 2030. This striking rise is due to the ageing population, decreased physical activity and increased obesity. Diabetes mellitus is a metabolic disease defined by fasting serum glucose levels ≥6.1mmol/l, this is either caused by lack of insulin (type 1) or insulin resistance (type 2), leading to chronic hyperglycaemia which causes microvascular harm and may damage circulation to the kidneys, eyes and nerves. Poor control of glucose levels is a major risk factor for coronary heart disease. Type 2 diabetes mellitus is included in the metabolic syndrome.

**Cardiac Disease**
Cardiac disease represents conditions that affect the heart, including arrhythmias, congenital heart diseases, cardiomyopathy and vascular disease. Cardiovascular disease is the most common cardiac disease in Europe. It accounts for 4 million deaths (48% of all deaths), hence it is the most common cause of death. Cardiovascular disease is a chronic condition defined as atherosclerosis in the arteries leading to thickening of the arterial wall and the eventual triggering of thrombus formation which may lead to an acute blockage of the artery. This causes myocardial infarction or stroke depending on where the thrombosis is blocking. There are seven identified risk factors: abnormal blood lipids, smoking, hypertension, diabetes, abdominal obesity, poor psychosocial conditions and poor physical activity.
Hypertension

Hypertension is defined as elevated blood pressure, above 140mmHg at systole and above 90mmHg at diastole. The pressure is increased because of greater resistance in the blood vessels. Hypertension is very common and the prevalence increases with age, resulting in a lifetime prevalence of almost 90%. Apart from age, risk factors for developing hypertension are hereditary factors, obesity, physical activity, smoking and alcohol drinking. Hypertension is the most established risk factor for cardiovascular disease and if left untreated, there is a dramatically increased risk of stroke or myocardial infarction. However, it has also been shown that if hypertension is controlled either by pharmaceuticals or by changing life style factors, the risk of cardiovascular disease or mortality decreases substantially.

Hypertension is also a part of the metabolic syndrome.

Pulmonary Disease

The most common chronic pulmonary diseases are asthma and chronic obstructive pulmonary disorder (COPD). Asthma has a prevalence of 6.5% in Sweden, and ranges between 2% and 15% in the world depending on the country. Symptoms of asthma are recurrent breathing problems such as breathlessness and chest tightness, coughing and wheezing. These symptoms are caused by airway obstruction related to airway inflammation which is a response to an allergenic or non-allergenic trigger factor. Asthma may be treated, reversed and well controlled by inhalation of β2-stimulators and glucocorticoids. COPD is mainly caused by tobacco smoking and has a prevalence of between 2.2% and 8.5%. COPD presents with an airflow limitation that is not fully reversible and is usually progressive. Additionally, it often presents with chronic hypoxia. As with asthma symptoms such as breathlessness and chest tightness, coughing and wheezing are common due to the obstruction to the airways. Additionally, exacerbations may occur, which often require additional bronchial expanding medicines and antibiotics.

2.5 HEALTH RELATED QUALITY OF LIFE - HRQOL

The constitution of the World Health Organisation defined health in 1948 as: “A state of complete physical, mental and social well-being and not merely the absence of disease or infirmity”. This view of health as a multidimensional concept, i.e. not only as absence of a disease, has been adapted into the definitions of HRQOL. However, there are no generally agreed upon definitions of HRQOL. In medical research, most agree that HRQOL is the effect of a medical condition or therapy on the patient’s function, and that it is a multidimensional concept concerning the patient’s negative and positive perception of at least four dimensions: physical function, emotional function, social function and symptoms.

The healthcare providers’ and the patients’ opinion of whether or not this goal of the treatment is achieved can differ. Thus, HRQOL is an important measure along with the traditional measures, e.g. survival, tumour response and postoperative complications, in order to capture patients’ subjective burden of illness. By doing this, it may answer the question of cost versus benefit for different treatment alternatives. It has been shown that HRQOL
measures in surgical oncology may help clinical decision-making since it has provided data as a basis for informed consent, i.e. information for the patient. HRQOL may provide a tool for the decision between curative and palliative treatments, which may be of extra importance for oesophageal cancer patients, especially as there is a poor postoperative prognosis and most treatments have severe adverse side-effects.

Patient Reported Outcomes
Patient reported outcomes is defined as “a measurement based on a report that comes directly from the patient about the status of a patient’s health condition without amendment or interpretation of the patient’s response by a clinician or anyone else”. This is an umbrella term for the overall concept that includes HRQOL as an important part.

HRQOL as a Conceptual Model
There are several models attempting to characterise HRQOL conceptually, of which the model introduced in 1995 by Wilson and Cleary is the most frequently used. This model links traditional clinical variables with HRQOL measures thus emphasising that HRQOL is depended on more than physical health. It is also dependent on environmental factors and includes symptoms, functional status and overall health perception. It is comprised of five core domains: biological and psychosocial variables, symptom status (e.g. cognitive and physical symptoms), functional status, general health perception and overall quality of life.

Measurement of HRQOL
HRQOL can be measured through interviews or questionnaires, either computer based or printed. They are preferably completed by the patient but if necessary with help from someone else. The measurements may be grouped as:

- Generic – independent of illness and measures broad aspects of HRQOL, for example the Medical Outcomes the Short Form (36) Health Survey (SF-36), and the Schedule for Individual Evaluation of Quality of Life (SEIQoL)
- Disease-specific – more focus on specific diseases and the issues they entail, for example the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 and the Functional Assessment of Cancer Therapy (FACT-G)
- Aspect-specific – independent of illness but focus on certain aspects, for example the Hospital Anxiety and Depression Scale (HADS), the McGill Pain Questionaire (MPQ) and the Multidimensional Fatigue Inventory (MFI)

When choosing an instrument for a study it is important to take the purpose of the trial into account. Additionally it is important to consider a few initial questions: which aspects you want to evaluate, generic, disease, single symptoms or treatment? Is HRQOL the primary or secondary endpoint? What does the study population look like in terms of education level, age, language and cultural variations? It needs to be a questionnaire that suits the study population. You would also need to take practical issues into account, such as how long it
takes to fill in the questionnaire, how frequently or how many times you want to measure and how missing data should be handled in order to plan for the resources needed.\textsuperscript{148} The questionnaires also have to be validated and need to have good psychometric properties. There are some fundamental concepts in psychometrics that needs to be evaluated for a questionnaire:

1. Validity – Does the instrument adequately measure what it is intended to measure? This can be evaluated through comparison with another instruments or between scales within the same instrument.\textsuperscript{136} Validity also includes floor and ceiling effects. An instrument is considered as having a floor or ceiling effect if >15\% of the responders answer the lowest or highest score.\textsuperscript{149}

2. Reliability - Does the instrument measure what it is supposed to measure in a reliable manner? This may be divided into: 1) External reliability, i.e. are the results the same when repeatedly measured? This can be evaluated through test-retest when using the instrument at two time points and comparing the results. 2) Internal reliability, i.e. is the measure consistent with itself. This can be tested through split half reliability which involves splitting half the questions onto a unidimensional scale and comparing them with each other, or with Chronbachs $\alpha$ which is a measure of how the items relate to each other and how much error there is between the items. It is the mean of all split-half combinations.

3. Sensitivity – Does the instrument capture as many cases as possible of what it is intending to measure?

4. Specificity – Does the instrument capture as few cases as possible of what it is intending to not measure?

5. Responsiveness – How sensitive to change is the instrument? Is it possible to detect differences in HRQOL between patients or in the same patients over time?

**Response Shift**

When HRQOL is measured at several time points in patients who have experienced a major event such as a cancer diagnosis and major cancer surgery, it might be difficult to know who to compare the data with. Patients might have recalibrated their own personal scale based on personal experiences. This has been described as a response shift. A response shift is the adaption of sensitivity of HRQOL that can occur as a result of change in personal values (reprioritisation), internal standards (recalibration), or meaning in the definition of HRQOL (reconceptualisation), which may affect the outcomes of the study. A response shift that leads to a meaningful improvement in HRQOL is not the same as a meaningful decrease in HRQOL, thus resulting in a risk of under- or over-reporting of changes.\textsuperscript{150}
The European Organisation for Research and Treatment of Cancer (EORTC)
The EORTC in an international organisation that was founded in Belgium 1962 by oncologists working in the main cancer research institutes of the European Union countries and Switzerland. Their aims are to develop, conduct, coordinate, and stimulate translational and clinical cancer research in Europe and by that, improve the management of cancer and related problems by increasing survival but also patient quality of life.\textsuperscript{151} In 1980, a quality of life research group was initiated within EORTC with the main aim of developing reliable instruments for measuring the quality of life of cancer patients.\textsuperscript{152} In this thesis, one cancer-specific instrument, the EORTC QLQ-C30, and one oesophago-gastric-specific instrument, the EORTC QLQ-OG25 were used.

The General Cancer Core Questionnaire – QLQ-C30
The EORTC QLQ-C30 version 3\textsuperscript{153} is a multidimensional instrument including 30 items corresponding to 9 multi-item scales and 6 single items:

- Global quality of life scale
- Functional scales
  - physical function
  - role function
  - cognitive function
  - emotional function
  - social function
- Symptom scales
  - fatigue
  - pain
  - nausea and vomiting
- Single items
  - dyspnoea
  - appetite loss
  - insomnia
  - constipation
  - diarrhoea
  - financial impact

Several studies have investigated the psychometric properties for the QLQ-C30 concluding that it is a well-functioning HRQOL measurement for cancer patients.\textsuperscript{153-157} The initial version of the QLQ-C30, version 1.0, was originally tested psychometrically before and during treatment, including chemotherapy, on 305 lung cancer patients from 13 different countries, showing that QLQ-C30 was a reliable and valid measure for HRQOL. Cronbach’s $\alpha$ were >0.70 in all subscales except for role function, it had good clinical validity through known-group comparison and satisfactory inter-scale correlations.\textsuperscript{153} The latest version 3.0 which was also used in this thesis was tested among 622 head and neck cancer patients from
12 different countries. It showed as good psychometric properties as the previous study but the improved physical function scale showed better reliability than the previous version.\textsuperscript{157}

**The Oesophago-Gastric Specific Questionnaire – QLQ-OG25**

The QLQ-OG25 was developed in 2007 as a recommended supplement to the EORTC QLQ-C30 when assessing HRQOL in patients with oesophageal, junctional or gastric cancer.\textsuperscript{158}

The QLQ-OG25 comprises 25 items distributed on 6 multi-item scales and 10 single items:

- **Scales**
  - dysphagia
  - eating restrictions
  - reflux
  - odynophagia
  - pain
  - anxiety

- **Single items**
  - eating with others
  - dry mouth
  - trouble with taste
  - body image
  - trouble swallowing saliva
  - choked when swallowing
  - trouble with coughing
  - trouble talking
  - weight loss
  - hair loss

The QLQ-OG25 was developed as a combination of the already existing oesophageal cancer specific QLQ-OES18, and the stomach cancer specific QLQ-STO22 questionnaires. These two questionnaires plus an additional seven modified items were administered to 300 patients with oesophageal-, junctional- or gastric cancer. Through interviews and multi-trait scaling analysis, the new questionnaire was formed. The validation of the QLQ-OG25 showed good reliability with Cronbach’s $\alpha$ between 0.67 and 0.87. The clinical validity was also satisfactory, being able to distinguish between patients with different tumour sites and disease stages. Additionally, the scales of the QLQ-OG25 did not strongly correlate with scales of the QLQ-C30, indicating that it measures different aspects of HRQOL and that it is a good complement for use by oesophageal cancer patients.\textsuperscript{158}

**Interpretation of Results**

For both the EORTC QLQ-C30 and the QLQ-OG25, items are scored on a 4-point Likert-type scale with respond alternatives: 1) not at all, 2) a little, 3) quite a bit and 4) very much. The items corresponding to the global quality of life scale are scored on a 7-point scale ranging from 1) very poor to 7) excellent. Responses are transformed to a 0-100 point scale.
according to the EORTC Scoring Manual. High scores on the global QOL and function scales correspond to better HRQOL, while high scores on symptom scales and single items reflect worse symptoms and poorer HRQOL.

Since a HRQOL measure is a score of a patient’s subjective impression of health, it is important to know how to interpret the results. In a large sample, a minor difference in HRQOL score may be detected and be statistically significant but this change might not be noticeable for the individual patient. Thus, not all HRQOL effects are clinically relevant but there are two general approaches to interpreting the minimal clinically important difference, the anchor-based method and the distribution-based method. In the anchor based method, comparisons are made between HRQOL scores with already known measures correlated to HRQOL such as clinical changes. This is the recommended method and most appropriate to use in order to establish clinical relevance. However, if reference data are absent, the distribution approach may be used when the comparison is based on a statistical distribution of the results instead. There are two milestone studies that have evaluated clinically relevant cut-offs for the QLQ-C30 which are used in this thesis. Osoba et al. included breast- and lung cancer patients measuring HRQOL with the EORTC QLQ-C30 at two time points, before and after treatment with chemotherapy. At the second time point, the patients were also asked how their global QOL, physical function and emotional function had changed since last time they filled in the questionnaire. On a 0-100 scale, they concluded that patients with mean score changes of 5-10 reported a “little” change, a change of 10-20 corresponded to a “moderate” change and more than 20 corresponded to a “large” change. King et al. conducted a retrospective study using data from 14 published studies and grouped patients according to different clinical status, e.g. performance status, weight loss, toxicity or severity of disease. Change in clinical status was then compared with HRQOL scores and the authors could conclude that a difference of 10 points in the mean score may represent symptom control in a clinical setting.

HRQOL in Oesophageal Cancer Patients
The extensive nature of the surgery for oesophageal cancer has shown to greatly reduce the patients’ HRQOL, which is a crucial aspect of survivorship in these patients. Longer-term studies have found no improvement in HRQOL from 6 months to 5 years after surgery. In more detail, one study that assessed HRQOL 6 months after oesophageal cancer surgery in Sweden showed that patients reported deteriorated HRQOL in role and social function and more problems with fatigue, appetite loss, diarrhoea, dyspnoea, cough, reflux, odynophagia, and dysphagia than the general population. When the same patients were followed up until 3 years after surgery, those HRQOL impairments carried on to a large extent. Several studies have shown similar long-term results. Interestingly, after continuing follow-up for 5 years post-operatively, patients who improved or were stable reported HRQOL comparable to the background population for most measures. However, patients who deteriorated over time reported clinically and statistically significantly much worse scores for all functions (range -23 to -45) and symptoms (range 25 to 59). Thus, within
5 years the majority of the patients had recovered their HRQOL to a level comparable with the general population with a few exceptions of expected persistent symptoms. However, 8-37% of patients deteriorated dramatically in HRQOL despite cure. To this date there is not yet any explanation for why some patients continue to deteriorate in their HRQOL.

Further, complications after surgery have been seen to affect HRQOL both in the short- and long term. Patients experiencing postoperative reoperation, anastomosis leakage, infections or respiratory insufficiency see an effect on their physical and role function while infections or cardiac complications affect global quality of life negatively. Remarkably, this impact of complication seems to continue long term after surgery where dyspnoea, fatigue, eating difficulties, sleeping problems and reflux are among the deteriorated aspects after post-surgical complications.

There is evidence that co-morbidities might affect short-term HRQOL after oesophageal cancer surgery and that pre-existing co-morbidities are associated with poorer HRQOL among 5-year survivors. Patients with co-morbidities before surgery have poorer measures of global QOL, dyspnoea and fatigue 5 years after surgery compared to patients that were healthy before surgery.

Minimally invasive surgery is becoming more and more common, and it has been hypothesised that patients recover their HRQOL better after such surgery compared to an open procedure. In one study of 222 patients, there were no differences between pre-operative scores and postoperative scores after a mean of 19 months of follow-up, suggesting that patients recover faster after minimally invasive surgery. However, the general SF-36 was used as the HRQOL instrument which is not oesophageal cancer specific and might not detect particular symptoms. In another study comparing open transthoracic oesophagectomy, open transhiatal oesophagectomy and minimally invasive thoracoscopic and laparoscopic surgery, there was no difference in HRQOL between the different surgical approaches.

Neoadjuvant therapy has been seen to have a negative impact of HRQOL during therapy, but patients usually recover before surgery and such therapy does not seem to influence HRQOL postoperatively. However, it has been shown that neoadjuvant therapy increases the risk of malnutrition after surgery which in turn affects HRQOL.

Predictors of Poor HRQOL after Surgery
It is important to identify predictors of HRQOL after surgery in order to work prophylactically. One study including 355 patients observed exactly this issue and identified several factors predictive of worse HRQOL after oesophageal cancer surgery. Having one or more co-morbidities, squamous cell carcinoma, a tumour stage of III or IV and a more proximal tumour all independently showed an increased risk of deteriorated HRQOL post-surgery.
HRQOL measured before surgery has also been shown to be a prognostic factor for survival after oesophageal cancer surgery. Good physical function, role function and global quality of life has been seen to improve survival, while increased problems with fatigue, appetite loss, dyspnoea and pain have been seen to increase mortality. Maybe those patients need extra support in order to be able to deal with the extensive surgery.\textsuperscript{17, 180, 181} For postoperative scores of HRQOL, deterioration in physical function, role function and global quality of life increased the risk of mortality with 50-60\%. More trouble with fatigue, pain, dyspnoea, appetite loss and dysphagia and odynophagia increased the risk of mortality by 30-70\%.\textsuperscript{182} There are also symptom clusters that have been identified as prognostic factors. Presence of the symptom cluster “reflux/cough” (including dry mouth, problem with taste, coughing and reflux) and “eating difficulties” (including appetite loss, dysphagia, eating difficulties, and nausea/vomiting) showed an increased risk of mortality by approximately 40\%.\textsuperscript{183}
3 AIMS

The overall aim of this thesis is to improve clinical decision-making in order to optimise treatment and improve the well-being of patients with oesophageal cancer.

To be able to accomplish the overall aim, this thesis focuses on clarifying how co-morbidities influence outcomes after oesophageal cancer surgery by addressing the following specific aims:

I. To clarify the influence of diabetes and other co-morbidities on survival.

II. To identify how different co-morbidities affect survival.

III. To reveal the influence of co-morbidity on postoperative complications.

IV. To elucidate the influence of co-morbidity on HRQOL before surgery and on short-term (6 months) recovery of postoperative HRQOL.
4 MATERIALS AND METHODS

Table 3. Overview of materials and methods used in studies I-IV.

<table>
<thead>
<tr>
<th>Study I</th>
<th>Study III</th>
<th>Study II</th>
<th>Study IV</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Design</strong></td>
<td>Prospective population-based cohort study</td>
<td>Retrospective population-based cohort study</td>
<td>Prospective single-centre cohort study</td>
</tr>
<tr>
<td><strong>Data Source</strong></td>
<td>Swedish Esophageal and Cardia Cancer Study (SECC)</td>
<td>Swedish Esophageal Cancer Surgery Study (SESS)</td>
<td>Guy's &amp; St Thomas' Gastric and Oesophageal Tissue and Data Bank, London</td>
</tr>
<tr>
<td><strong>Cohort</strong></td>
<td>Swedish residents undergoing curatively intended oesophagectomy for oesophageal or cardia cancer</td>
<td>Swedish residents undergoing curatively intended oesophagectomy for oesophageal cancer</td>
<td>Patients undergoing curatively intended oesophagectomy for oesophageal cancer at Guy's &amp; St Thomas' Hospital, London</td>
</tr>
<tr>
<td><strong>Follow-up</strong></td>
<td>Until December 2011</td>
<td>Until 30 days after surgery</td>
<td>Until February 2012</td>
</tr>
<tr>
<td><strong>Exposure</strong></td>
<td>Co-morbidity count and individual co-morbidities</td>
<td>Co-morbidities and Charlson co-morbidity index</td>
<td>Charlson co-morbidity index and individual co-morbidities</td>
</tr>
<tr>
<td><strong>Outcome</strong></td>
<td>Short- and long-term mortality</td>
<td>Postoperative complications</td>
<td>Short- and long-term mortality</td>
</tr>
<tr>
<td><strong>Statistical method</strong></td>
<td>Cox regression</td>
<td>Logistic regression</td>
<td>Cox regression</td>
</tr>
<tr>
<td><strong>Confounders</strong></td>
<td>Age, sex, tumour stage, tumour histology, type of surgery, complications and other co-morbidities</td>
<td>Age, sex, tumour stage, tumour histology, neoadjuvant therapy, type of surgery, annual hospital volume, other co-morbidities, complications</td>
<td>Age, sex, tumour stage, tumour histology, neoadjuvant treatment, operation type, complications, tobacco smoking, other co-morbidities</td>
</tr>
</tbody>
</table>
4.1 DATA SOURCES

4.1.1 The Swedish Esophageal and Cardia Cancer register (SECC)

Studies I and III were based on a nationwide clinical data collection from patients who underwent surgery for oesophageal or junctional cancer with a curative intent in Sweden during April 2001 to December 2005. This database is entitled the Swedish Esophageal and Cardia Cancer study (SECC) and is based on a network of hospitals in Sweden where 174 (97%) out of 179 eligible hospitals participated. The SECC included 616 patients or 90% of all oesophageal or gastro-oesophageal junctional cancer patients in Sweden who underwent surgical resection. The 10% non-participation rate was mainly explained by a few non-participating hospitals, but also due to missing data from consenting patients. Additionally, due to missing data on tumour stage in 6 patients and missing histology in 1 patient, the final analyses in studies I and III were performed on 609 (99%) patients.

Background and Data Collection

The SECC was coordinated by a central project administrator who received histopathology reports as soon as an oesophageal cancer diagnosis was confirmed, leading to a reminder to the treating physician to include the patient. Informed consent was obtained from each patient prior to the inclusion. Additionally, data were checked against the Swedish Cancer Register in order to ensure completeness.

Detailed clinical data, including data on co-morbidity and postoperative complications, were retrieved through prospective manual review of medical records based on a comprehensive pre-defined study protocol, and thus not self-reported by clinicians treating the patients. The study protocol was developed by experienced researchers and experienced oesophageal cancer surgeons.

Survival data were obtained by linkages to the Register of the Total Population. Additionally, the SECC was linked to the Swedish Patient Register in order to obtain additional information on the patients during follow-up, including co-morbidities.

Validity

Close to full national coverage, detailed prospective manual data collection according to a pre-defined study protocol and the fact that data were collected by personnel not involved in treating the patient are aspects that suggest good validity. Further, quality was ensured by the project administrator constantly checking quality and ensuring complete medical record retrieval from every patient.

4.1.2 The Swedish Esophageal Cancer Surgery Study (SESS)

The SESS is a nationwide database of patients who underwent oesophageal cancer surgery with a curative intent between 1987 and 2010 in Sweden and includes 1822 patients. Patients
were identified and data were collected using registers and reviews of operation charts and pathology reports. The assessment of medical records and register data was possible through the unique 10-digit personal identity number assigned to each Swedish resident upon birth or immigration.

**Data Collection**

Patients included in the cohort were identified by linking the Swedish Cancer Register for oesophageal cancer diagnosis (International Classification of Diseases version 7 (ICD-7) and the Swedish Patient Register for oesophageal resections. All cancer diagnosis codes in the Cancer Register were translated to ICD-7 codes. Only tumours of the main histological types, i.e. adenocarcinoma and squamous cell carcinoma were included. The Swedish Cancer Register was established in 1958 and it is compulsory by law for every health care provider (both clinicians and pathologists) to report all newly detected cancers. A validation study from our group showed that the Swedish Cancer Register is 98% complete regarding the reporting of oesophageal cancer. The Swedish Patient Register contains ICD codes for diagnoses, including co-morbidities, and surgical procedures on all in-hospital care in Sweden since 1987, hence this date was chosen as the starting date for this study. Regarding diagnosis codes, the 8th version of the ICD (ICD-8) was used before 1987, ICD-9 was used between 1987 and 1996, and ICD-10 has been used since 1997. All hospitals are obligated by law to report all inpatient care. The drop-out rate has been estimated at <1% and the overall positive predictive value of recorded diagnoses has been estimated at 85-95%. Between 1987 and 1996, the 6th edition of the Swedish Classification Operations was used to define oesophageal resection: 2820, 2821, 2822 and 2829, and from 1997 another system, the Swedish Classification of Operations and Major Procedures, was used: JCC00, JCC10, JCC11, JCC20, JCC30, JCC96 and JCC97. A validation study of oesophageal cancer surgery in 1987-2005 from our group showed a positive predictive value of 99.6% of the operations recorded in the Swedish Patient Register compared to operation charts. Histopathology reports and operation charts were retrieved and evaluated to assess tumour stage, location of the tumour, histology of the tumour, and surgical approach for each included patient. The Swedish Register of the Total Population and the Swedish Causes of Death Register were used to assess date of mortality and causes of death, respectively. The Population Register is 100% complete and accurate and continuously updated regarding dates of death. All physicians have been obligated to report causes of death to the Cause of Death Register since 1961, and the completeness is over 99%. Validation Close to full coverage, detailed manual data collection according to a pre-defined study protocol and the fact that data were collected by personnel not involved in treatment of the patient are aspects that suggest good validity. All investigators were kept blinded to the patients’ length of survival, since the date of mortality was linked to the data after medical charts had been reviewed. The assessment of clinical data was validated in a random sample of 100 records, which showed >90% correctness between three independent researchers.
regarding stage, location, and histology of the tumour, as well as the surgical approach. Throughout all updates of this cohort, the same study protocol has been used, thus ensuring uniformity throughout the long study period.

4.1.3 Guy's & St Thomas' Gastric and Oesophageal Tissue and Data Bank, London

This is a comprehensive and prospective cohort study of patients recruited at the Academic Health Science Centre, entitled King’s Health Partners in London, United Kingdom, following a diagnosis of oesophageal cancer. Patients selected for curatively intended surgery were identified by a project coordinator and invited to participate upon admission to the upper gastrointestinal inpatient ward. At this point, informed consent was obtained. Detailed information about patients’ characteristics, treatment, risk factors and pre-defined comorbidities were collected prospectively based on a pre-defined study protocol. The EORTC QLQ-C30 and the oesophago-gastric module EORTC QLQ-OG25 were used for assessing HRQOL pre-surgery and 6 months postoperatively. This data collection is a result of a close collaboration between our group (Surgical Care Sciences and Upper Gastro Intestinal Surgery) and the Section of Gastrointestinal Cancer at King’s College London and St. Thomas’ Hospital (which is included in the King’s Health Partners). Data collection was initiated in November 2011, and is on-going.

Validity

Detailed prospective manual data collection according to a pre-defined study protocol and the fact that data were collected by personnel not involved in treatment of patient are aspects that suggest good validity. Further, quality was ensured by the project administrator constantly checking quality and ensuring complete medical record retrieval from every patient.

4.2 STUDY DESIGN

4.2.1 Study I

Design: This was a nationwide, Swedish population-based prospective cohort study of patients diagnosed with oesophageal or gastro-oesophageal junctional cancer who underwent curative oesophageal resection from 2nd April, 2001 to 31st December, 2005, including 609 patients with follow-up until death or the end of the study period (31st May, 2011).

Study exposures: The main co-morbidity being evaluated was diabetes. Secondary exposures were: a) cardiovascular disease, b) hypertension, c) pulmonary disease, and d) any other predefined co-morbidity. In addition, patients were classified as having: a) none, b) 1, or c) ≥2 co-morbidities.

Study outcome: The outcome was mortality. Patients were followed up through linkage to the Swedish Register of the Total Population.
**Statistical analysis:** To determine the risk of mortality in patients with and without diabetes and other co-morbidities, a multivariable Cox proportional hazard regression model was used to provide adjusted hazard ratios (HRs) with 95% confidence intervals (CIs). The potential confounding factors included in the multivariable model were age (categorised into 3 groups: <60, 60-74, or ≥75 years), sex (male or female), tumour stage (0-I, II, or III-IV), tumour histology (adenocarcinoma or squamous cell carcinoma), type of surgery (oesophageal resection, cardia resection, extended total gastrectomy, or total gastrectomy and oesophageal resection), number of post-operative complications (0, 1, or ≥2), and other co-morbidities.

**4.2.2 Study II**

**Design:** This was a Swedish nationwide retrospective cohort study including almost all patients operated for oesophageal cancer between 1987 and 2010. A total of 1822 patients where included. Patients were followed up until end of 2012.

**Study exposure:** Co-morbidity was categorised according to the Charlson co-morbidity index. Individual co-morbidities were also analysed but then grouped into 11 co-morbidity groups: 1) myocardial infarction, 2) congestive heart failure, 3) peripheral vascular disease, 4) cerebrovascular disease, 5) chronic pulmonary disease, 6) connective tissue disease, 7) peptic ulcer disease, 8) diabetes (uncomplicated and with end-organ damage), 9) other cancer (leukaemia, malignant lymphoma and solid tumours excluding oesophageal and gastric cancer), 10) liver disease (mild to severe), and 11) others (dementia, chronic kidney disease, hemiplegia and acquired immunodeficiency syndrome [AIDS]).

**Study outcome:** The main outcome was all-cause mortality and the secondary outcome was both short- and long-term disease-specific mortality.

**Statistical analysis:** Mortality analysis was conducted using a Cox proportional hazard regression model, which provided HRs with 95% CIs in order to assess differences in mortality between patients with and without co-morbidity. Adjustments were made for potential confounding by all 7 established prognostic factors: 1) age (categorised into 4 groups: <55, 55-65, 66-75, or >75 years), 2) sex (male or female), 3) tumour stage (0-I, II, III or IV), 4) tumour histology (adenocarcinoma or squamous cell carcinoma), 5) neoadjuvant therapy (yes or no), 6) surgical volume (a cumulative volume of <6 operations, 6-15 operations, 16-46 operations, or >46 operations), and 7) calendar period of surgery (1987-1990, 1991-1994, 1995-1999, 2000-2004, or 2005-2010). Stratified analyses were conducted for calendar time of surgery and histological type of cancer. Missing values were used as separate categories in the Cox regression model since a sensitivity analysis comparing these models with models excluding all missing data showed similar results.
4.2.3  Study III

**Design:** This was a nationwide, Swedish population-based prospective cohort study of patients diagnosed with oesophageal or gastro-oesophageal junctional cancer who underwent curative oesophageal resection from 2nd April, 2001 to 31st December, 2005 including 609 patients with follow-up until 30-days post-surgery.

**Study exposure:** The Charlson co-morbidity index\textsuperscript{108} and pre-defined co-morbidity present before surgery and categorised into 4 main groups: 1) cardiac disease (angina or heart failure), 2) hypertension, 3) pulmonary disease (chronic obstructive pulmonary disease or asthma), and 4) diabetes.

**Study outcome:** Pre-defined complications occurring within 30 days of surgery. The complications were categorised into three main groups: 1) surgical (post-operative bleeding, anastomotic insufficiency, damage to the thoracic duct, intra-abdominal or intrathoracic abscess, wound rupture, wound infection, necrosis of the substitute, ileus, or anastomotic stricture), 2) medical (pneumonia, deep venous thrombosis, pulmonary embolism, respiratory insufficiency, sepsis, myocardial infarction, atrial fibrillation, cerebrovascular infarction, renal insufficiency, or liver, and 3) any complications (all complications included in the two groups above, plus death within 30 days of surgery, divided into two groups: [a] none or [b] at least one).

**Statistical analysis:** A multivariable logistic regression model was used to provide odds ratios (ORs) with 95% CIs adjusted for potential confounding by the following variables: 1) age (continuous variable), 2) sex (male or female), 3) tumour stage (0-I, II, or III-IV), 4) tumour histology (adenocarcinoma or squamous cell carcinoma), 5) neo-adjuvant therapy (yes or no), 6) type of surgery (oesophageal resection, cardia resection, extended total gastrectomy, or total gastrectomy and oesophageal resection), 7) annual hospital volume of oesophagectomy (based on previous studies: >9, 4-9, or <4), 8) co-morbidity (any of the other predefined groups of co-morbidities), and 9) complications (in the analysis of medical and surgical complications). We also performed analyses restricted to two sub-groups of patients: 1) those who underwent transthoracic surgery, and 2) those with data available on BMI. Additionally, to assess linear trends for the Charlson co-morbidity index score and risk of complications, a likelihood ratio test was performed.

4.2.4  Study IV

**Design:** This prospective single centre cohort study included patients with oesophageal cancer undergoing curatively intended oesophagectomy at St Thomas’ Hospital, London between November 2011 and February 2015 for baseline and between November 2011 and August 2014 for 6-month analysis. Follow-up was 6 months postoperatively. There were 134 patients assessed before surgery and at 6 months after surgery, data for 78 patients were available at the time of data collection.
**Study exposure:** number of co-morbidities divided into 4 groups: 1) no co-morbidity, 2) 1 co-morbidity, 3) 2 co-morbidities or 4) ≥3 co-morbidities), ASA classification\(^{68,69}\) divided into 2 ASA groups: ASA I-II and ASA III-IV and specific co-morbidities: 1) cardiac disease (including angina, previous myocardial infarction and heart failure), 2) hypertension (requiring medication), 3) diabetes, 4) pulmonary disease (chronic obstructive pulmonary disease and asthma), and 5) obesity (body mass index ≥30 just before surgery).

**Study outcomes:** HRQOL at baseline and recovery of HRQOL 6 months postoperatively were assessed using the EORTC QLQ-C30\(^{153}\) and the QLQ-OG25.\(^{158}\) The selected aspects were global quality of life, physical function, emotional function, social function, fatigue, pain and dyspnoea from the QLQ-C30, and reflux, anxiety and trouble with coughing from the QLQ-OG25.

**Statistical analysis:** Responses were transformed linearly to a 0-100 point scale according to the EORTC Scoring Manual and missing responses were handled accordingly.\(^{159}\) Linear regression models were used to assess co-morbidity in relation to mean score differences (MDs) with 95% CIs for the selected HRQOL scales and items. Additionally, at 6 months, mean scores for patients with different numbers of co-morbidities, as well as between the ASA classifications, were compared. Adjustments were made for age (<65 or ≥65 years), sex (male or female), tumour stage (0-II or III-IV), tumour histology (squamous cell carcinoma or adenocarcinoma), neoadjuvant treatment (yes or no), operation type (transhiatal oesophagectomy, thoraco-abdominal oesophagectomy or laparoscopic oesophagectomy), postoperative complications (yes or no regarding predefined complications occurring within 30 days of surgery), tobacco smoking (non-smoker or current smoker) and other co-morbidities (all co-morbidities except the one being analysed were included). Missing values were considered as separate categories in the linear regression model since a sensitivity analysis comparing these models with models excluding all missing data showed similar results.
5 RESULTS

Table 4. Selected characteristics of the participants of studies I-IV

<table>
<thead>
<tr>
<th></th>
<th>Number of patients (%)</th>
<th>I and III</th>
<th>II</th>
<th>IV</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td>609 (100)</td>
<td>1822 (100)</td>
<td>134 (100)</td>
</tr>
<tr>
<td><strong>Mean age</strong></td>
<td></td>
<td>66</td>
<td>65</td>
<td>64</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td></td>
<td>490 (80)</td>
<td>1362 (75)</td>
<td>106 (79)</td>
</tr>
<tr>
<td>Female</td>
<td></td>
<td>119 (20)</td>
<td>460 (25)</td>
<td>28 (21)</td>
</tr>
<tr>
<td><strong>Tumour stage</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-II</td>
<td></td>
<td>293 (48)</td>
<td>983 (54)</td>
<td>43 (32)</td>
</tr>
<tr>
<td>III-IV</td>
<td></td>
<td>316 (52)</td>
<td>585 (32)</td>
<td>91 (68)</td>
</tr>
<tr>
<td>Missing</td>
<td></td>
<td>254 (4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Tumour histology</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td></td>
<td>460 (76)</td>
<td>715 (39)</td>
<td>121 (90)</td>
</tr>
<tr>
<td>Squamous-cell carcinoma</td>
<td></td>
<td>149 (24)</td>
<td>1003 (55)</td>
<td>13 (10)</td>
</tr>
<tr>
<td>Missing</td>
<td></td>
<td>104 (6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Neoadjuvant therapy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td></td>
<td>30 (5)</td>
<td>576 (32)</td>
<td>116 (87)</td>
</tr>
<tr>
<td>No</td>
<td></td>
<td>579 (95)</td>
<td>1165 (64)</td>
<td>18 (13)</td>
</tr>
<tr>
<td>Missing</td>
<td></td>
<td>81 (4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Postoperative complications</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td></td>
<td>294 (48)</td>
<td></td>
<td>48 (36)</td>
</tr>
<tr>
<td>No</td>
<td></td>
<td>315 (52)</td>
<td>Not assessed</td>
<td>68 (51)</td>
</tr>
<tr>
<td>Missing</td>
<td></td>
<td></td>
<td></td>
<td>18 (13)</td>
</tr>
</tbody>
</table>
5.1 STUDY I AND III

Patient Characteristics
At least one co-morbidity was identified in 370 (61%) of the study participants. Older patients had co-morbidity and complications more frequently, while the distribution of sex, tumour stage, tumour histology, operation type, and annual hospital volume was similar among patients with and without co-morbidity or complications. Anastomotic insufficiency was the most frequent surgical complication (n=52; 9%), while the most common medical complication was respiratory insufficiency (n=99; 16%), defined as requiring intubation and ventilation.

Study I
Co-morbidity and Risk of Mortality
The 30-day mortality rate was 3% (n=18). The Kaplan-Meier curve did not reveal any major differences in mortality in patients with and without any co-morbidity or for patients with diabetes (Figure 7). Of the 492 patients (81%) who died during the follow-up, 310 (63%) had at least one co-morbidity, of whom 53 (11%) had diabetes. The overall mortality rate (up to 11 years after surgery) among patients with co-morbidities ranged from 79% to 84% (Table 5). No statistically significantly increased risk of mortality was found in patients with one co-morbidity or at least two co-morbidities, compared to those without any co-morbidity. Diabetes, cardiovascular disease, hypertension and pulmonary disease did not increase the postoperative risk of mortality (Table 5).

Figure 7. Kaplan-Meier survival curve of patients with no co-morbidity (number=239) and those with diabetes (number=67).
Table 5. Risk of mortality after curatively intended surgery for oesophageal cancer among 609 patients with and without diabetes and other co-morbidities. Results presented as hazard ratios (HRs) with 95% confidence intervals (CIs).

<table>
<thead>
<tr>
<th>Co-morbidity</th>
<th>Mortality Number (%)</th>
<th>HR (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>492 (81)</td>
<td></td>
</tr>
<tr>
<td>No co-morbidity</td>
<td>182 (76)</td>
<td>1 (reference)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>53 (79)</td>
<td>0.81 (0.60-1.09)</td>
</tr>
<tr>
<td>Diabetes and cardiovascular disease</td>
<td>10 (71)</td>
<td>0.55 (0.28-1.05)</td>
</tr>
<tr>
<td>Diabetes and hypertension</td>
<td>22 (79)</td>
<td>0.72 (0.46-1.12)</td>
</tr>
<tr>
<td>Diabetes and pulmonary disease</td>
<td>4 (67)</td>
<td>0.64 (0.24-1.73)</td>
</tr>
<tr>
<td>Diabetes and any co-morbidity #</td>
<td>39 (78)</td>
<td>0.94 (0.66-1.34)</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>74 (80)</td>
<td>0.87 (0.67-1.13)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>113 (82)</td>
<td>0.83 (0.67-1.04)</td>
</tr>
<tr>
<td>Pulmonary disease</td>
<td>65 (82)</td>
<td>0.91 (0.69-1.19)</td>
</tr>
<tr>
<td>One co-morbidity #</td>
<td>176 (83)</td>
<td>1.15 (0.93-1.43)</td>
</tr>
<tr>
<td>Two or more co-morbidities #</td>
<td>134 (85)</td>
<td>1.05 (0.83-1.33)</td>
</tr>
</tbody>
</table>

*Adjusted for age, sex, tumour stage, histological type, type of operation, postoperative complications and other co-morbidities.

# Co-morbidity including cardiovascular disease, hypertension, pulmonary disease, diabetes, liver failure, kidney failure, other cancers and other significant diseases.

Study III

Co-morbidity and Risk of Complications

Compared to patients without pre-defined co-morbidity, patients with cardiac disease were at a nearly 2-fold increased risk of having any of the pre-defined complications, while no such associations were found among patients with hypertension, pulmonary disease, diabetes, or obesity (Table X). There was an increased risk of any complication among patients with a Charlson score of 1 and a Charlson score ≥2. A trend test showed that an increased Charlson co-morbidity score was associated with a statistically significantly increased risk of complications.

Co-morbidity and Risk of Surgical Complications

Patients with hypertension had an 80% increased risk of surgical complications. Also, patients with a Charlson score ≥2 indicated an increased risk of surgical complications. A Charlson score of 1 and other specific co-morbidities (cardiac, pulmonary, diabetes, and obesity) were not associated with any statistically significantly increased ORs of mortality.
Co-morbidity and Risk of Medical Complications
Patients with a Charlson score ≥2 showed an increased risk of medical complications. A Charlson score of 1 indicated slightly elevated risk of medical complications, while none of the studied individual co-morbidities was associated with any statistically significantly increased risk of pre-defined complications (Table 6).
Table 6. Risk of complications within 30 days of curatively intended surgery for oesophageal cancer among 609 patients with and without co-morbidities, expressed as odds ratios (ORs) with 95% confidence intervals (CIs).

<table>
<thead>
<tr>
<th>Co-morbidity</th>
<th>Total</th>
<th>All complications</th>
<th>Surgical complications</th>
<th>Medical complications</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number (%)</td>
<td>Number (%)</td>
<td>Number (%) OR (95% CI)*</td>
<td>Number (%) OR (95% CI)*</td>
</tr>
<tr>
<td></td>
<td>No (%)</td>
<td>Yes (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>239 (39)</td>
<td>151 (63)</td>
<td>88 (37) 1</td>
<td>38 (16) 1</td>
</tr>
<tr>
<td>Cardiac</td>
<td>92 (15)</td>
<td>39 (42)</td>
<td>53 (58) 1.81 (1.13-2.90)</td>
<td>23 (25) 1.30 (0.74-2.31)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>137 (22)</td>
<td>75 (55)</td>
<td>62 (45) 0.99 (0.67-1.49)</td>
<td>36 (26) 1.81 (1.11-2.95)</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>79 (13)</td>
<td>39 (49)</td>
<td>40 (51) 1.29 (0.79-2.12)</td>
<td>17 (22) 1.18 (0.64-2.18)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>67 (11)</td>
<td>39 (58)</td>
<td>28 (42) 0.82 (0.48-1.41)</td>
<td>17 (25) 1.45 (0.75-2.77)</td>
</tr>
<tr>
<td>Charlson score 0</td>
<td>322 (53)</td>
<td>204 (64)</td>
<td>117 (36) 1</td>
<td>51 (16) 1</td>
</tr>
<tr>
<td>Charlson score 1</td>
<td>149 (24)</td>
<td>79 (53)</td>
<td>70 (47) 1.45 (0.97-2.17)</td>
<td>29 (19) 1.21 (0.71-2.06)</td>
</tr>
<tr>
<td>Charlson score ≥2</td>
<td>139 (23)</td>
<td>56 (40)</td>
<td>83 (60) 2.44 (1.60-3.72)</td>
<td>37 (27) 1.70 (1.01-2.86)</td>
</tr>
<tr>
<td>Obesity *</td>
<td>66 (17)</td>
<td>37(56)</td>
<td>29 (44) 1.34 (0.76-2.38)</td>
<td>15 (23) 1.31 (0.64-2.71)</td>
</tr>
</tbody>
</table>

*Adjusted for age, sex, tumour stage, histological type, neo-adjuvant therapy, type of operation, hospital volume, other post-operative complications and other co-morbidities.

# BMI >30. Analysis on 382 patients with data available on height and weight.
5.2 STUDY II

Patient Characteristics
Patients aged less than 65 years had a lower proportion of co-morbidities and the proportion of patients with co-morbidity increased with calendar time period. Groups were similar regarding tumour stage, histology, treatment with neoadjuvant therapy and surgeon volume. A total of 756 patients (42%) had a Charlson score of at least 1 at baseline.

There were 1474 deaths (81%) in the cohort during the entire study period. 1176 patients (80% of all deaths) died from a documented oesophageal cancer recurrence, and the vast majority of these disease-specific deaths (954; 81%) occurred between 91 days and 5 years after surgery. The 90-day mortality rate was 11% (208 patients).

Co-morbidity and Risk of Mortality
Patients with a Charlson score ≥2 had a 24% increased risk of overall mortality (Table 7). Among specific groups of co-morbidity, statistically significantly increased HRs for overall mortality were seen for patients with a history of myocardial infarction and congestive heart failure. Myocardial infarction was also associated with increased 90-day postoperative mortality. Patients with peripheral vascular disease, cerebrovascular disease, chronic pulmonary disease, connective tissue disease, peptic ulcer disease, diabetes, liver disease or other cancers did not have statistically significantly increased HRs for all-cause mortality, independent of the time of death (Table 7). The HRs for disease-specific mortality were generally similar to those for all-cause mortality, but the positive associations were slightly attenuated.
Table 7. Co-morbidities and risk of all-cause mortality after curatively intended surgery for oesophageal cancer in 1822 patients. Relative risks are estimated as hazard ratios (HRs) with 95% confidence intervals (CIs).

<table>
<thead>
<tr>
<th>Co-morbidity</th>
<th>Number (%)</th>
<th>91 days - 5 years</th>
<th>≤90-days</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>Charlson score 1</td>
<td>381 (22)</td>
<td>0.96 (0.83-1.12)</td>
<td>1.13 (0.77-1.68)</td>
<td>1.04 (0.91-1.18)</td>
</tr>
<tr>
<td>Charlson score ≥2</td>
<td>150 (8)</td>
<td>1.13 (0.96-1.32)</td>
<td>1.18 (0.77-1.61)</td>
<td>1.24 (1.08-1.42)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>88 (5)</td>
<td>1.05 (0.83-1.33)</td>
<td>1.87 (1.10-3.17)</td>
<td>1.23 (1.01-1.49)</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>61 (3)</td>
<td>1.16 (0.87-1.54)</td>
<td>1.28 (0.70-2.36)</td>
<td>1.31 (1.04-1.67)</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>109 (6)</td>
<td>1.15 (0.89-1.60)</td>
<td>1.24 (0.58-2.63)</td>
<td>1.18 (0.88-1.59)</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>109 (6)</td>
<td>1.08 (0.85-1.38)</td>
<td>1.03 (0.54-1.96)</td>
<td>1.06 (0.85-1.49)</td>
</tr>
<tr>
<td>Chronic pulmonary disease</td>
<td>189 (10)</td>
<td>0.86 (0.69-1.06)</td>
<td>0.98 (0.60-1.59)</td>
<td>0.93 (0.78-1.11)</td>
</tr>
<tr>
<td>Connective tissue disease</td>
<td>44 (2)</td>
<td>1.02 (0.69-1.50)</td>
<td>1.01 (0.39-2.62)</td>
<td>1.06 (0.76-1.49)</td>
</tr>
<tr>
<td>Peptic ulcer disease</td>
<td>88 (5)</td>
<td>0.90 (0.68-1.19)</td>
<td>0.60 (0.29-1.23)</td>
<td>0.88 (0.69-1.12)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>134 (7)</td>
<td>1.05 (0.83-1.33)</td>
<td>0.98 (0.53-1.84)</td>
<td>1.12 (0.91-1.38)</td>
</tr>
<tr>
<td>Liver disease</td>
<td>41 (2)</td>
<td>1.02 (0.68-1.51)</td>
<td>0.97 (0.43-2.16)</td>
<td>1.20 (0.86-1.66)</td>
</tr>
<tr>
<td>Other cancers</td>
<td>192 (11)</td>
<td>1.11 (0.91-1.35)</td>
<td>0.70 (0.41-1.19)</td>
<td>1.14 (0.96-1.35)</td>
</tr>
</tbody>
</table>

* Adjusted for age, sex, tumour stage, tumour histology, neoadjuvant therapy, surgeon volume and calendar period of surgery.

1 Charlson score 1 or ≥2 versus Charlson score 0.
2 Presence of specific co-morbidity versus absence.

Co-morbidity and Risk of Death by Calendar Period
A Charlson score ≥2 was associated with an increased risk of overall all-cause mortality during 1987–1999, but not in 2000–2010 (Table 8). Among patients with a history of myocardial infarction, the HR was also higher during the earlier period, whereas it was higher among patients with congestive heart failure during the later period. Otherwise, the results were generally similar between the time intervals.
Table 8. Co-morbidities and risk of all-cause mortality after curatively intended surgery for oesophageal cancer in 1822 patients, stratified by calendar periods. Relative risks are estimated as hazard ratios (HRs) with 95% confidence intervals (CIs).

<table>
<thead>
<tr>
<th>Co-morbidity</th>
<th>Overall mortality</th>
<th>1987-1999 n=992</th>
<th>HR (95% CI)*</th>
<th>2000-2010 n=830</th>
<th>HR (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Charlson score 1</td>
<td>381 (22)</td>
<td>1.09 (0.92-1.30)</td>
<td>0.96 (0.78-1.19)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Charlson score ≥2</td>
<td>150 (8)</td>
<td>1.28 (1.06-1.53)</td>
<td>1.12 (0.99-1.49)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>88 (5)</td>
<td>1.38 (1.04-1.83)</td>
<td>1.17 (0.89-1.55)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>61 (3)</td>
<td>1.29 (0.91-1.84)</td>
<td>1.44 (1.04-2.01)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>109 (6)</td>
<td>1.15 (0.77-1.71)</td>
<td>1.16 (0.75-1.80)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>109 (6)</td>
<td>1.06 (0.78-1.44)</td>
<td>1.03 (0.75-1.41)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic pulmonary disease</td>
<td>189 (10)</td>
<td>1.08 (0.84-1.39)</td>
<td>0.84 (0.65-1.10)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Connective tissue disease</td>
<td>44 (2)</td>
<td>1.02 (0.67-1.56)</td>
<td>1.18 (0.67-2.08)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peptic ulcer disease</td>
<td>88 (5)</td>
<td>0.80 (0.58-1.09)</td>
<td>0.95 (0.63-1.42)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>134 (7)</td>
<td>1.10 (0.80-1.53)</td>
<td>1.09 (0.83-1.44)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liver disease</td>
<td>41 (2)</td>
<td>1.00 (0.62-1.63)</td>
<td>1.36 (0.85-2.18)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other cancers</td>
<td>192 (11)</td>
<td>1.17 (0.93-1.47)</td>
<td>1.10 (0.84-1.43)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Adjusted for age, sex, tumour stage, tumour histology, neoadjuvant therapy, surgeon volume and calendar period of surgery.
1 Charlson score 1 or ≥2 versus Charlson score 0.
2 Presence of specific co-morbidity versus absence.

Co-morbidity and Risk of Death by Tumour Histology
Patients with squamous cell carcinoma with a Charlson score of ≥2 had a greater risk of overall all-cause mortality than patients with adenocarcinoma (Table 9). The increased HRs following a diagnosis of myocardial infarction were similar for the two histological tumour types. Congestive heart failure was a slightly stronger risk factor for mortality in patients with adenocarcinoma than among those with squamous cell carcinoma. Patients with squamous cell carcinoma also had increased overall all-cause mortality if they had had a diagnosis of cerebrovascular disease or other cancers, which was not found for adenocarcinoma. The disease-specific mortality results were similar to the all-cause mortality results.
Table 9. Co-morbidities and risk of all-cause mortality after curatively intended surgery for oesophageal cancer in 1822 patients, stratified for tumour histology. Relative risks are estimated as hazard ratios (HRs) with 95% confidence intervals (CIs).

<table>
<thead>
<tr>
<th></th>
<th>Overall</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Adenocarcinoma n=715</td>
<td>Squamous cell carcinoma n=1003</td>
</tr>
<tr>
<td></td>
<td>Number</td>
<td>HR (95% CI)*</td>
<td>HR (95% CI)*</td>
</tr>
<tr>
<td>Charlson score 1^1</td>
<td>381</td>
<td>1.06 (0.85-1.32)</td>
<td>1.05 (0.88-1.25)</td>
</tr>
<tr>
<td>Charlson score ≥2^1</td>
<td>150</td>
<td>1.14 (0.91-1.41)</td>
<td>1.37 (1.14-1.65)</td>
</tr>
<tr>
<td>Myocardial infarction^2</td>
<td>88</td>
<td>1.28 (0.96-1.73)</td>
<td>1.30 (0.99-1.73)</td>
</tr>
<tr>
<td>Congestive heart failure^2</td>
<td>61</td>
<td>1.43 (1.01-2.02)</td>
<td>1.12 (0.79-1.60)</td>
</tr>
<tr>
<td>Peripheral vascular disease^2</td>
<td>109</td>
<td>1.58 (0.95-2.65)</td>
<td>1.02 (0.70-1.49)</td>
</tr>
<tr>
<td>Cerebrovascular disease^2</td>
<td>109</td>
<td>0.82 (0.60-1.14)</td>
<td>1.35 (1.00-1.83)</td>
</tr>
<tr>
<td>Chronic pulmonary disease^2</td>
<td>189</td>
<td>1.04 (0.78-1.38)</td>
<td>0.89 (0.70-1.14)</td>
</tr>
<tr>
<td>Connective tissue disease^2</td>
<td>44</td>
<td>1.40 (0.86-2.28)</td>
<td>0.74 (0.44-1.23)</td>
</tr>
<tr>
<td>Peptic ulcer disease^2</td>
<td>88</td>
<td>0.78 (0.52-1.17)</td>
<td>0.91 (0.66-1.25)</td>
</tr>
<tr>
<td>Diabetes^2</td>
<td>134</td>
<td>1.06 (0.81-1.40)</td>
<td>1.24 (0.87-1.77)</td>
</tr>
<tr>
<td>Liver disease^2</td>
<td>41</td>
<td>1.10 (0.60-1.99)</td>
<td>1.41 (0.92-2.16)</td>
</tr>
<tr>
<td>Other cancers^2</td>
<td>192</td>
<td>0.99 (0.74-1.33)</td>
<td>1.36 (1.09-1.71)</td>
</tr>
</tbody>
</table>

* Adjusted for age, sex, tumour stage, tumour histology, neoadjuvant therapy, surgeon volume and calendar period of surgery.
^1 Charlson score 1 or ≥2 versus Charlson score 0.
^2 Presence of specific co-morbidity versus absence.

5.3 STUDY IV

Patient Characteristics

Most characteristics were equally common among patients with different numbers of co-morbidities, except that patients aged ≥65 had more co-morbidities.

Pre-surgical HRQOL

Patients with ≥3 co-morbidities had clinically and statistically significantly worse global quality of life, worse physical function and more fatigue compared to patients without co-morbidity. This was also seen in patients with an ASA score of III-IV with the addition of worse social function and more pain compared to patients with an ASA score of I-II (Table 10). For specific co-morbidities, patients with cardiac co-morbidities reported clinically and statistically significantly worse global quality of life and experienced more dyspnoea. Patients with pulmonary co-morbidities experienced more trouble with coughing. Patients
with diabetes, hypertension and obesity did not report deteriorated HRQOL in any of the aspects, except for social function among diabetic patients (Table 11).

**HRQOL from Pre-surgery to 6 months Postoperatively**

At 6 months after surgery, all patients deteriorated in several aspects of their HRQOL (Table 12). For global quality of life, both patients with and without co-morbidity, deteriorated between before and 6 months after surgery. Patients with co-morbidities had worse global quality of life before surgery (i.e., had lower scores at baseline), and there was no difference in mean scores 6 months after surgery between the patients with and without co-morbidities. For pain and reflux, both the no co-morbidity group and the co-morbidity groups had clinically and statistically significant deterioration between before and 6 months after surgery, but mean scores at 6 months were similar, yet starting from different preoperative levels. For physical function, patients with no co-morbidity, 2 co-morbidities and ≥3 co-morbidities all deteriorated. Patients with ≥3 co-morbidities also had clinically significantly worse mean scores at 6 months compared to patients with no co-morbidity. For trouble with coughing, patients with 2 and ≥3 co-morbidities deteriorated and the mean scores 6 months after surgery were statistically significantly worse compared to patients with no co-morbidity and 1 co-morbidity.

Patients with ASA I-II had similar deterioration in most HRQOL aspects as those with ASA III-IV. For example, for global quality of life, both groups had lower scores and they experienced similar mean scores at 6 months after surgery. For physical function, social function and fatigue both groups deteriorated, but the patients with an ASA score of III-IV had either statistically or clinically significantly worse mean scores 6 months after surgery than those with an ASA score of I-II.
Table 10. Co-morbidities, ASA (American Society of Anaesthesiologists physical status classification) and HRQOL before surgery for oesophageal cancer in 134 study patients, presented as adjusted* mean score differences (MDs) with 95% confidence intervals (CIs).

<table>
<thead>
<tr>
<th></th>
<th>1 co-morbidity MD§ (95% CI)</th>
<th>2 co-morbidities MD§ (95% CI)</th>
<th>≥3 co-morbidities MD§ (95% CI)</th>
<th>ASA III-IV MD# (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>QLQ-C30</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Global quality of life</td>
<td>-12 (-21, -2)</td>
<td>-9 (-19, 1)</td>
<td>-16 (-28, -4)</td>
<td>-11 (-20, -3)</td>
</tr>
<tr>
<td>Physical function</td>
<td>-12 (-20, -4)</td>
<td>-3 (-11, 5)</td>
<td>-13 (-23, -3)</td>
<td>-17 (-23, -11)</td>
</tr>
<tr>
<td>Emotional function</td>
<td>-3 (-13, 7)</td>
<td>6 (-5, 16)</td>
<td>-3 (-15, 9)</td>
<td>-7 (-15, 1)</td>
</tr>
<tr>
<td>Social function</td>
<td>-12 (-24, 1)</td>
<td>-2 (-15, -11)</td>
<td>-8 (-23, 7)</td>
<td>-14 (-24, -3)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>18 (8, 28)</td>
<td>10 (0, 20)</td>
<td>20 (8, 32)</td>
<td>16 (8, 24)</td>
</tr>
<tr>
<td>Pain</td>
<td>9 (-2, 19)</td>
<td>7 (-4, 18)</td>
<td>8 (-5, 21)</td>
<td>14 (6, 23)</td>
</tr>
<tr>
<td>Dyspnoea</td>
<td>15 (4, 25)</td>
<td>1 (-10, 12)</td>
<td>11 (-2, 25)</td>
<td>9 (-1, 18)</td>
</tr>
<tr>
<td>QLQ-OG25</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reflux</td>
<td>4 (-5, 13)</td>
<td>7 (-3, 16)</td>
<td>1 (-10, 13)</td>
<td>7 (-1, 15)</td>
</tr>
<tr>
<td>Anxiety</td>
<td>-7 (-20, 6)</td>
<td>-11 (-24, 3)</td>
<td>9 (-7, 25)</td>
<td>-1 (-13, 10)</td>
</tr>
<tr>
<td>Trouble with coughing</td>
<td>1 (-8, 11)</td>
<td>-2 (-12, 8)</td>
<td>2 (-10, 14)</td>
<td>3 (-6, 11)</td>
</tr>
</tbody>
</table>

*Adjusted for age, sex, tumour stage, histology of the tumour, neoadjuvant treatment, operation type, postoperative complications, smoking and other comorbidities (including all co-morbidities except the one being analysed).

§ No co-morbidity was used as the reference category.

# ASA score I-II was used as the reference category.
Table 11. Specific co-morbidities and HRQOL before surgery for oesophageal cancer in 134 study patients, presented as adjusted* mean score differences (MDs) with 95% confidence intervals (CIs).

<table>
<thead>
<tr>
<th></th>
<th>Cardiac disease MD§ (95% CI)</th>
<th>Hypertension MD§ (95% CI)</th>
<th>Pulmonary disease MD§ (95% CI)</th>
<th>Diabetes MD§ (95% CI)</th>
<th>Obesity MD§ (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>QLQ-C30</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Global quality of life</td>
<td>-14 (-26, -2)</td>
<td>1 (-7, 10)</td>
<td>-9 (-20, 3)</td>
<td>-2 (-14, 9)</td>
<td>3 (-6, 12)</td>
</tr>
<tr>
<td>Physical function</td>
<td>-8 (-18, 1)</td>
<td>0 (-7, 7)</td>
<td>-2 (-12, 7)</td>
<td>0 (-10, 9)</td>
<td>2 (-5, 10)</td>
</tr>
<tr>
<td>Emotional function</td>
<td>-9 (-21, 3)</td>
<td>-3 (-12, 6)</td>
<td>7 (-5, 19)</td>
<td>2 (-9, 14)</td>
<td>7 (-3, 16)</td>
</tr>
<tr>
<td>Social function</td>
<td>-12 (-26, 3)</td>
<td>-1 (-12, 9)</td>
<td>-4 (-19, 10)</td>
<td>13 (-1, 27)</td>
<td>4 (-8, 15)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>12 (0, 24)</td>
<td>4 (-5, 13)</td>
<td>5 (-7, 17)</td>
<td>-4 (-15, 8)</td>
<td>0 (-9, 10)</td>
</tr>
<tr>
<td>Pain</td>
<td>10 (-3, 23)</td>
<td>2 (-8, 11)</td>
<td>-3 (-15, 9)</td>
<td>-4 (-17, 8)</td>
<td>-4 (-13, 6)</td>
</tr>
<tr>
<td>Dyspnoea</td>
<td>17 (5, 29)</td>
<td>0 (-9, 9)</td>
<td>11 (-2, 23)</td>
<td>-8 (-20, 4)</td>
<td>-7 (-17, 2)</td>
</tr>
<tr>
<td><strong>QLQ-OG25</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reflux</td>
<td>10 (-1, 21)</td>
<td>-3 (-11, 5)</td>
<td>5 (-5, 16)</td>
<td>2 (-9, 13)</td>
<td>-5 (-13, 4)</td>
</tr>
<tr>
<td>Anxiety</td>
<td>15 (0, 31)</td>
<td>-3 (-14, 9)</td>
<td>5 (-10, 21)</td>
<td>0 (-15, 15)</td>
<td>-8 (-20, 5)</td>
</tr>
<tr>
<td>Trouble with coughing</td>
<td>-4 (-15, 7)</td>
<td>-5 (-14, 3)</td>
<td>12 (0, 23)</td>
<td>1 (-10, 12)</td>
<td>0 (-9, 9)</td>
</tr>
</tbody>
</table>

*Adjusted for age, sex, tumour stage, histology of the tumour, neoadjuvant treatment, operation type, postoperative complications, smoking and other comorbidities (including all co-morbidities except the one being analysed).

§ Not having that specific co-morbidity was used as the reference category.
Table 12. Co-morbidities and the difference in HRQOL between pre-surgical scores and scores 6 months after surgery, as well as mean scores at 6 months after surgery for oesophageal cancer in 78 study patients, presented as adjusted mean score differences (MDs) with 95% confidence intervals (CIs) and mean scores.

<table>
<thead>
<tr>
<th></th>
<th>No co-morbidity</th>
<th>1 co-morbidity</th>
<th>2 co-morbidities</th>
<th>≥3 co-morbidities</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>6 months after</td>
<td>6 months after</td>
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<td></td>
<td>versus before</td>
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<td></td>
<td>surgery</td>
<td>surgery</td>
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<tr>
<td></td>
<td>MD (95% CI)</td>
<td>Mean scores</td>
<td>Mean scores</td>
<td>Mean scores</td>
</tr>
<tr>
<td>QLQ-C30</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Global quality of life</td>
<td>-23 (-39, -8)</td>
<td>53</td>
<td>-9 (-24, 7)</td>
<td>-13 (-28, 2)</td>
</tr>
<tr>
<td>Physical function</td>
<td>-20 (-32, -6)</td>
<td>69</td>
<td>-11 (-25, 3)</td>
<td>-26 (-38, -13)</td>
</tr>
<tr>
<td>Emotional function</td>
<td>-1 (-15, 13)</td>
<td>63</td>
<td>5 (-10, 19)</td>
<td>-6 (-20, 14)</td>
</tr>
<tr>
<td>Social function</td>
<td>-18 (-38, 2)</td>
<td>54</td>
<td>-14 (-34, 6)</td>
<td>-27 (-45, -9)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>30 (14, 45)</td>
<td>44</td>
<td>12 (-4, 28)</td>
<td>28 (14, 42)</td>
</tr>
<tr>
<td>Pain</td>
<td>30 (12, 48)</td>
<td>38</td>
<td>28 (9, 47)</td>
<td>21 (4, 38)</td>
</tr>
<tr>
<td>Dyspnoea</td>
<td>13 (-3, 29)</td>
<td>24</td>
<td>3 (-14, 21)</td>
<td>14 (-2, 29)</td>
</tr>
<tr>
<td>QLQ-OG25</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reflux</td>
<td>32 (12, 53)</td>
<td>45</td>
<td>36 (16, 57)</td>
<td>35 (16, 54)</td>
</tr>
<tr>
<td>Anxiety</td>
<td>-6 (-24, 13)</td>
<td>72</td>
<td>-2 (-21, 17)</td>
<td>-5 (23, 12)</td>
</tr>
<tr>
<td>Trouble with coughing</td>
<td>1 (-16, 18)</td>
<td>19</td>
<td>2 (-16, 19)</td>
<td>24 (8, 41)</td>
</tr>
</tbody>
</table>

* Adjusted for age, sex, tumour stage, histology of the tumour, neoadjuvant treatment, operation type, postoperative complications and smoking.

* p<0.05 compared to means score of patients with no-co-morbidities.

*² Clinically significant (score difference ≥10) compared to means score of patients with no-co-morbidities.
6 DISCUSSION

6.1 METHODOLOGICAL CONSIDERATIONS

In this thesis, modern epidemiological methods were used in order to evaluate the effect of co-morbidities on mortality, complications and HRQOL after oesophageal cancer surgery. Historically, epidemiology has been the methodology to study occurrence of disease, but today it has developed into the concept of “the distribution and determinants of disease in the human population.”

Study Design

The two main types of epidemiological studies in clinical research are experimental and observational. Experimental studies, typically randomised control trials, are considered as generating the most reliable results since that is as close to an ideal situation as possible. Participants in the different groups are in theory identical in all factors except the one studied. Thus, randomisation is a way to remove confounding. Aspects such as blinding, completeness of follow-up, similarities of outcomes and clinical characteristics are important. There is always some sort of bias in each study design and some argue that it should be the validity of the study that matters and not the study design per se. Nonetheless, randomisation would be impossible in the studies in this thesis, since you cannot give patients co-morbidities. For the same reason, randomisation might also be unethical and therefore observational studies are designed as much as possible to simulate experimental studies. The most common types of observational studies are cohort studies, case-control studies, cross-sectional studies and ecological studies. All four studies in this thesis are cohort studies, which usually have higher “methodological status” than other observational studies. A cohort often consists of a group of people who share a common experience or condition which for this thesis is oesophageal cancer surgery. In a cohort study, the individuals are grouped according to exposure status and followed for occurrence of the outcome, e.g. co-morbidities (exposure) and mortality (outcome). Advantages of the cohort study design include the ability to take temporality into account (that the exposure comes before the outcome) and thus reduce the risk of selection bias and information bias (e.g. recall bias). Disadvantages include that it might be highly costly and difficult to track cohort members for follow-up, which also might lead to missing data and bias accordingly. A cohort study may also be either prospective or retrospective. The definitions of these differ and some mean that cohort studies by definition are prospective. However, it refers to the timing of the initiation of the study in relation to the outcome. A cohort study is prospective if the study was initiated before the outcome has occurred as in studies I, III and IV, while a study is retrospective if the outcome has already occurred when the study was initiated, as in study II. With the retrospective design, risk of selection bias increases but in study II, the information of the exposure (co-morbidities) could not have influenced the outcome (mortality).
Validity
In clinical research each step, including study design, execution and analysis, is a step towards an end product which will always be an estimate of the truth, even though the aim is to have as little error as possible. Errors are classified as either random or systematic. Systematic errors are also called bias. An estimate free from systematic error is considered valid.\textsuperscript{191} Validity is further broken down into internal and external validity. Internal validity corresponds to how well the study effects measure what it was intended to measure. Biases may lead to an over- or underestimation of the results and thus reduce the internal validity. There are numerous types of biases, but the main groups are selection bias, information bias and confounding. External validity defines to what degree the results could be applied outside the study population, i.e. the generalisability. A study free from random errors is considered perfectly reliable which refers to consistency or dependability, i.e. precision of the measurement. Random errors are unknown or unpredictable but in many cases they may sum up to zero and not affect the result. \textsuperscript{191}

Selection Bias
Selection bias might occur if there is a non-random sampling when including participants in a study. Various factors might influence the study participation. If there is a selection bias, the associations between exposure and outcome may be different from the true association in the population. Since the true association is usually unknown, the level of selection bias is assumed rather than proven.\textsuperscript{191} Selection bias is correlated to participation rate. If non-participation is high, the risk of selection is increased. Participating patients might e.g. be healthier than the average population which might result in false associations between exposure and outcome. Additionally, when there are single centre or hospital-based studies, as with most literature on oesophageal cancer surgery, local traditions might interfere the selection of patients for surgery making the result not representative of other populations.

Studies I-III in this thesis included virtually all patients undergoing surgery for oesophageal cancer in a defined population (all Swedish residents) within a defined geographical area (Sweden) and are therefore population-based in design. In theory, a population-based design eliminates concerns about selection bias since there is no such selection if participation is complete. The participation rates in studies I and III were high (90%) and non-participation was mainly due to administrative problems, rather than patients not wanting to participate. Such reason is not likely to generate selection bias. Study II had almost full completeness (98%).\textsuperscript{184} However, the retrospective design might increase the risk of selection bias since researchers might already be aware of the outcome. However, the data were collected by researchers with no involvement with the hospitals or patients, which reduces such risks. In study IV, a single-centre cohort was used so there is a risk of selection bias caused by different selection of patients than other centres. However, The Upper Gastro Intestinal unit at St Thomas' Hospital in London, United Kingdom is a highly research oriented group following evidence based guidelines just as other centres do. Additionally, they discuss patients with hospitals all over London during their MDM-meetings. These two factors
reduce the risk of selection bias. The drop-out rate is also a concern. At 6 months post-operatively, 77% of the included patients remained. Unfortunately, there is no data indicating whether the patients had died or chosen not to participate. However the 6-month mortality rate is around 20% after oesophagectomy\textsuperscript{21, 192}, which should explain some of the non-participation. It is not as easy to follow patients in the UK as in Sweden since patients can be identified through the personal identity number whereas in the UK, they cannot. Yet, the high rate of non-responders at 6-month follow-up increases the risk of selection bias. However, in a drop out analysis, responders and non-responders were similar regarding characteristics and as a result, strong selection bias seems unlikely.

**Information Bias**

Information bias, also known as misclassification, can occur when information collected about or from study subjects is incorrect. It can be differential when the misclassification is different between the comparison groups studied, or non-differential when the misclassification does not differ between the groups. Non-differential misclassification tends to dilute any associations toward null. This is mainly a major problem in studies showing no associations, since the lack of associations can be due to dilution of risk estimates. Differential misclassification might lead to biased risk estimates in either direction.

In general when using register data, incorrect coding of the diagnosis might lead to misclassification. It is therefore important to know the validity of the diagnosis codes in the registers when used for research.

In studies I, III and IV, information was collected prospectively and the project administrator and the researchers involved in collecting the data made sure the information was correct, and it was collected according to a pre-defined study protocol ensuring uniformity and completeness. However, co-morbidities were reported by clinicians in medical charts and it is up to the clinician to decide which co-morbidities to report. For study II, the retrospective design introduces a risk of misclassification but the data were collected from the medical records and the data collection was done according to a pre-defined study form, and exposures and outcomes were predefined and followed well-validated strategies, which reduces the risk of misclassification. Some of the data for study II were collected from registers, including co-morbidities (exposure) and mortality (outcome), which introduces a risk of misclassification. The overall positive predictive value in the Swedish Patient Register from which co-morbidities were collected, of recorded diagnoses has been estimated at 85-95\% depending on diagnosis\textsuperscript{185} and mortality data were accurate by virtue of the Population Register. However, the Patient Register does not give information about outpatient care before the year 2001 and therefore some co-morbidities might be missing, thus introducing a risk of misclassification. However, such misclassification should be random and would only dilute risk estimates and not explain the positive associations in the study.
The lack of information on the severity of the studied co-morbidities is a weakness in all of the studies. For all studies there might be a selection bias due to the selection of patients going through surgery. Patients selected for surgery, despite them having co-morbidities, may e.g. have a better performance status than patients suffering from these co-morbidities who were not selected. This might affect the generalisability of the results since the patients selected for surgery might be different from all oesophageal cancer patients. However, the impact of this was reduced by different strategies in the different studies. Patients selected for surgery, despite having co-morbidities, may have had a better performance status than those with these co-morbidities who were not selected. In study I, patients with both diabetes and cardiovascular or pulmonary disease were analysed since this indicated more advanced diabetes. In studies II and III, the Charlson co-morbidity index was used which has been developed to take the severity of co-morbidity into account by giving higher scores to more severe diseases, and the index has been tested and well validated to accomplish this. In study IV, the ASA classification was used together with number of co-morbidities and individual co-morbidities. The ASA classification is developed to take the severity of the co-morbidity into account by giving higher scores to more severe diseases, which has been well validated to classify pre-operative co-morbidity status.

Confounding
To take confounding into account is of great importance in observational research. A confounder is a third factor that influences the association between an exposure and an outcome that is associated with both the exposure and the outcome without being an intermediate step between them. If a confounder is not controlled for, the associations will be incorrect. There are different methods of how to control for potential confounders. In this thesis, stratification was partly used in study II and multivariable regression was used to adjust for potential confounders in all studies. Because of the comprehensive and good quality of the data, confounding could be managed very well in the statistical analyses. However, despite adjusting for confounders there is always a risk of residual confounding, e.g. by rough categorisation, threshold effects, and unknown confounders.

Precision
The level of precision defines whether a measurement yields consistent results when repeated. It is associated with the concept of random error that, if present, leads to measurable values being inconsistent when repeated. In statistical analysis, the precision of risk estimates is reflected as confidence intervals or p-values. If a level of confidence is set at 95% (which is typically used), the correct result should be included in the CI 95% of the times if the study were to be replicated numerous of times. The closely related p-value represents the probability of observing a result equal to or stronger than what was actually observed, assuming that the hypothesis under consideration, the null hypothesis, is true. The null hypothesis is the statement assuming that there is no association between an exposure and outcome. So a very small p-value (e.g. 0.0001) indicates that there is little likelihood that there is no association between an exposure and outcome. The null hypothesis could be
rejected even though it is true, known as type I error, or not rejected even though it is false, known as type II error. Precision, e.g. narrower CIs and lower p-values, is improved along with increasing sample size.

**Type I error**

A type I error occurs when an association between the exposure and outcome is statistically significant even though no such association exists. The probability of a type I error is the level of significance, also known as significance, i.e. alpha $\alpha$, meaning that if you choose to have $\alpha=0.05$, you accept a 5% risk of encountering a type I error. In studies where several analyses are conducted, 1 risk estimate out of 20 will be false even though it is statistically significant.

To reduce the risk of such type I error in this thesis, predefining the exposure and outcome as well as restricting the number of hypotheses were performed. For example, in study IV only some of the HRQOL aspects were analysed instead of all. In study II, the number of tests was quite large, however the main positive finding that a Charlson score $\geq 2$ increased risk of mortality was seen among several analysis and therefore is unlikely to be due to chance. Additionally, the exposures and outcomes were predefined and followed well-validated strategies.

**Type II error**

A type II error occurs when there is no statistically significant association even though there is a true association. The power is the ability to appropriately reject the null hypothesis and is often set as 80%, meaning a 20% chance of making a type II error, i.e. accept that one test out of five will not detect an association that is true. Risk of type II errors is reduced by a larger sample size, high quality exposure and outcome data and good study design.

In studies I, II and IV there was a limited sample size, which increases the risk of type II error. Many of the results were negative, especially in study I, but power but power calculation were satisfactory so other explanations might be more likely. In study II, a larger cohort was used in order to increase sample size and power.

**Generalisability**

Generalisability is the same as external validity mentioned above. It defines how well results from the individual study can be transferred to other populations and settings. Studies I-III are population-based, and should therefore have good generalisability, at least for other Western countries where demographics, tumour histology, diagnostics and treatment are similar. Further, studies I and III included patients undergoing surgery between 2001 and 2005 when the standard treatment of today, neoadjuvant therapy, was used less often. It might therefore be argued that the study is outdated, which might affect the generalisability of the study to current practice. Yet, since it studied surgery alone as the exposure, this did not likely affect the conclusions. Additionally, the surgical approaches and the short-term surgical outcomes during the study period are similar to current clinical practice in Sweden and therefore
applicable to patients of today.\textsuperscript{56} In study II, the very long study period might reduce generalisability; hence stratification by year of surgery was used.

Study IV took place at a single centre in London, UK, but as mentioned before it is a highly research oriented hospital following evidence-based guidelines and should thus be equivalent to the rest of the UK and the Western world. Therefore, generalisability should be good, at least in comparison with other larger centres.

**HRQOL Measures**

In study IV, HRQOL was the outcome and the EORTC QLQ-C30 and the QLQ-OG25 were used. These two were chosen because they have good psychometric properties.\textsuperscript{153, 157, 158} Since HRQOL was the primary outcome it was important that they measured disease-specific issues. The questionnaires have also been widely used, which facilitates interpretation and comparison of the study results.

The EORTC questionnaires have 4 response alternatives which are transformed into categorical ordinal data. In study IV, the responses were linearly transformed to a score ranging from 0-100 in accordance with the EORTC Scoring Manual.\textsuperscript{159} The transformation is based upon the well-established Likert method, meaning that items in each scale are simply summed. Thus, when single items are transformed they retain the categorical data form and there is still an order between the values, i.e. 0, 33, 67 or 100 points. Because single items can be only a limited number of scores, subtractions of individual scores from different time points as done in study IV might be questionable. Instead we could have looked for a binary outcome, deterioration or not, to avoid this issue. For the multi-item scales, this will not be a problem since the transformed result could have several different values. However, the scales face the problem that each item is weighted the same, which might not be true for the patients. Also, the distance between answer alternatives is regarded equal. However, it has been shown that the linear scoring system is robust and the EORTC states that “there are no grounds to believe that the EORTC items are sufficiently non-linear to warrant any correction before using them in summated scales”.\textsuperscript{159}

Even though scores might be sufficiently linear for statistical analysis, they are rarely linear in nature. For example, when comparing scores of the physical function scale with percentages of patients able to walk a block, mean scores of 40, 50, 60 and 70 correspond to 32\%, 50\%, 80\% and 90\%. As observed, changes of 10 in physical function are not the same for patients having a score of 40 and a patient having a score of 70.\textsuperscript{197} It has also been seen that patients experience deteriorations and improvements differently. Patients tend to be more sensitive to an improvement than the opposite.\textsuperscript{198} When looking at means for the cohort, the distribution of the results is not taken into consideration. In study IV, this means that a mean score difference of 5 between pre-surgery and post-surgery might mean that half of the patients have a clinically significant difference of 10 while half did not change at all. However, we presented interval estimates by 95\% CI of the HRQOL scores to give information on how the group differed according to exposure.
The baseline assessment of HRQOL in surgical oncology or pre-surgical assessment, as was done in study IV, might be influenced by the cancer diagnosis. To what extent this affects the scores may be very variable but a true baseline, i.e. before diagnosis is impossible to receive. There are studies that have used the background population as a proxy for baseline data in order to obtain “disease-free” baseline values. However, it will not be the same cohort that will be followed from baseline and onwards.

Most patients have recovered in terms of their acute symptoms 6 months after oesophagectomy.\textsuperscript{143, 199, 200} Therefore, assessing HRQOL 6 months after surgery and not earlier might omit the acute symptoms, but since HRQOL remains deteriorated in some aspects it is still important to have a 6-month assessment. Additionally, some data suggests that it takes up to a year to recover.\textsuperscript{170} Measuring at an earlier time point might have given a different result but 6-month follow-up was chosen in order to avoid tumour recurrence affecting the HRQOL measures, as tumour recurrence more often occurs later.\textsuperscript{201} It is also important not to measure too often, as patients might remember their answers from the previous assessment and therefore respond differently than otherwise.

\section*{6.2 FINDINGS AND EXPLANATIONS}

\subsection*{6.2.1 Study I}

Study I indicated that patients with diabetes or the co-morbidities cardiovascular disease, hypertension, and pulmonary disease are not at an increased risk of mortality after surgery for oesophageal cancer compared to patients without any co-morbidity.

Methodological strengths and weaknesses have been discussed above. Strengths include the study design and weaknesses include lack of information on the severity of co-morbidities and the limited statistical power.

In contrast to the results of this study, two previous studies have found that diabetes is associated with an increased risk of 30-day mortality after oesophageal resection, however these studies had no data on long-term survival.\textsuperscript{12, 202} For longer follow-up, there are also studies that suggest an increased risk of mortality among diabetic patients,\textsuperscript{203, 204} but one was not statistically significant\textsuperscript{203} and the other was a single-centre study.\textsuperscript{204} The few studies that have investigated co-morbidities other than diabetes in relation to long-term survival after oesophageal cancer surgery have indicated a worse prognosis in patients with co-morbidities in general.\textsuperscript{205, 206} The disparity between these studies and study I might be explained by the different methods used to define co-morbidities. The finding of a similar prognosis in patients with and without the studied co-morbidities who undergo surgical treatment for oesophageal cancer indicates a possible underuse of surgery for patients with co-morbidity. It has been
found that patients with co-morbid conditions are less likely to receive surgical treatment than patients with less co-morbidity, which might not always be justified.  

6.2.2 Study II

The main finding of study II was that patients with oesophageal cancer and a Charlson co-morbidity score of ≥2 or a history of myocardial infarction or congestive heart failure had an increased risk of mortality following surgery for oesophageal cancer.

Strengths include the study design. The main weaknesses are misclassification, retrospective design, and lack of information on the severity of co-morbidities.

Increased risk of mortality in patients with a Charlson score ≥2 was in line with some other investigations. However, the results were different from the results in study I where there were no associations between co-morbidities and mortality. This might be due to the lack of power and thus a type II error in study I, or how information of co-morbidities was collected. Moreover, study I also included patients with gastroesophageal junctional cancer.

A history of myocardial infarction or congestive heart failure was associated with increased mortality. Similarly, a single-centre study found increased disease-specific 5-year mortality among patients with ischaemic heart disease, hypertension and myocardial infarction.

Patients with oesophageal squamous cell carcinoma who had a history of another cancer were at increased risk of death after surgery, whereas those with adenocarcinoma were not. Tobacco smoking might be an explanation for this increased mortality. Similarly, the increased mortality among patients with squamous cell carcinoma and a Charlson score ≥2, compared with patients with adenocarcinoma, might be explained by lifestyle factors (tobacco smoking, alcohol abuse, and lower socioeconomic status) that are stronger risk factors for squamous cell cancer than for adenocarcinoma.

6.2.3 Study III

Study III indicates that the presence of angina or heart failure and a higher Charlson score increase the risk of early complications after oesophageal cancer surgery. Hypertension, pulmonary disease, diabetes and obesity did not consistently or independently increase the risk of complications, except for an increased risk of surgical complications among patients with hypertension.

The major strength is the population-based study design and weaknesses include lack of information on the severity of co-morbidities and risk of type II error.
Only a few other large studies have addressed the role of co-morbidities in relation to the risk of complications after oesophageal cancer surgery. Studies have showed an increased risk of complications among patients with several co-morbidities, particularly cardiac disease, diabetes and hypertension.\textsuperscript{207, 208} The results from previous studies together with the results of study III suggest that cardiac co-morbidity substantially increases the risk of postoperative complications after oesophageal cancer resection.\textsuperscript{207, 208} Several studies have found that cardiac disease is associated with an increased risk of complications after oesophageal cancer surgery.\textsuperscript{208, 209} Also, patients with cardiac disease are at a higher risk of atrial fibrillation, which is a common complication after oesophagectomy.\textsuperscript{100, 101}

Study III indicates that patients with hypertension might have an increased risk of surgical complications, but not of medical complications. These results might partly be explained by the influence of lifestyle factors linked to hypertension, e.g. obesity and tobacco smoking. However, the adjustment for BMI did not change the results, and tobacco smoking could not be adjusted for. Yet, an association between hypertension and postoperative complications after oesophagectomy, including surgical complications, has been reported previously, and those results were adjusted for tobacco smoking.\textsuperscript{208} Additionally, another study reported an increased risk of anastomotic leak, the most common surgical complication, for patients with hypertension.\textsuperscript{98} The increased risk might be explained by affected micro-vascularisation involved in the healing of the anastomosis.

This study provides no evidence of an association between diabetes and complications following oesophagectomy, while previous studies addressing this relationship have provided conflicting results.\textsuperscript{12, 205, 208, 210} One explanation for the diverging results might be that the value of tight glucose control in order to avoid diabetic-linked complications has been taken more seriously during the last decade compared to earlier.\textsuperscript{211, 212} Two of the studies showing an increased risk of complications after oesophagectomy among patients with diabetes included patients with oesophageal cancer before new guidelines for glucose control were introduced,\textsuperscript{12, 210} suggesting that patients in those studies did not have as well-controlled and managed diabetes as the patients in the present study.

### 6.2.4 Study IV

This study showed that oesophageal cancer patients with more co-morbidities and higher ASA scores experience worse HRQOL before surgery, particularly those with cardiac or pulmonary disease. However, most patients deteriorate in HRQOL to a similar extent regardless of co-morbidity status and ASA score. Patients with 2 or \(\geq 3\) co-morbidities had worse HRQOL in physical function, fatigue and trouble with coughing 6 months after surgery and patients with ASA III-IV had worse mean scores in physical function, social function and fatigue than patients with ASA I-II. Regarding specific co-morbidities, cardiac disease predisposes patients to worse global quality of life and dyspnoea, and pulmonary disease
predisposes patients to more trouble with coughing pre-surgery, while hypertension, diabetes and obesity do not.

The study design has both advantages and weaknesses due to the single centre setting. The hypothesis-driven selection of outcomes was a strength. Weaknesses of the study include the high rate of non-responders at 6-month follow-up, the limited sample size, and lack of detailed information on the severity of co-morbidities.

There is evidence that co-morbidities in general affect HRQOL in the short term after oesophageal cancer surgery, and in the long term it has been shown that one or more pre-operative co-morbidities worsens the global QOL and causes more problems with fatigue and dyspnoea. There are also studies investigating the effect of co-morbidities on HRQOL using the SF-36 questionnaire in other diagnoses, concluding that common chronic co-morbidities have a negative impact on HRQOL in general. One other study used the EORTC QLQ-C30 and concluded that HRQOL worsened significantly if cancer survivors suffered from hypertension and diabetes. Those patients reported lower HRQOL in most aspects compared to patients without cancer diagnosis. Thus, there are conflicting results compared to study IV regarding recovery after surgery. The studies that used the SF-36 might differ since the SF-36 is a generic questionnaire and measures different aspects of HRQOL than the EORTC.
7 CONCLUSIONS

Mortality and Morbidity
This thesis indicates a worse prognosis in patients with pre-existing co-morbidities who have a Charlson ≥2 regarding mortality, and patients with a Charlson score ≥1 are at an increased risk of postoperative complications after oesophageal cancer surgery.

Individual co-morbidities:

Increased risk of mortality and post-operative complications:

- Cardiac disease

No increased risk of mortality or complications:

- Chronic pulmonary disease
- Diabetes

No increased risk of mortality:

- Peripheral vascular disease
- Cerebrovascular disease
- Connective tissue disease
- Peptic ulcer disease
- Liver disease.

No increased risk of complications:

- Obesity

HRQOL
Patients with co-morbidities, higher ASA score, cardiac disease or pulmonary disease experience worse HRQOL in some aspects before surgery. However, co-morbidities might not severely influence the recovery of HRQOL.
8 IMPLICATIONS AND FUTURE RESEARCH

The main aim of this thesis, to help improve clinical decision-making in order to optimise treatment and improve the well-being of patients with oesophageal cancer, can be achieved by the results from this thesis together with future research. There have been studies indicating an underuse of surgery for oesophageal cancer patients, with co-morbidities as one potential reason. Patients with oesophageal cancer and a Charlson co-morbidity score $\geq 1$ or a history of cardiac disease might need more evaluation and intervention before undergoing oesophagectomy, or may not benefit from surgery at all. An increased risk of surgical complications among patients with hypertension cannot be dismissed, but requires further investigation. Additionally, co-morbidities do not seem to severely influence the recovery of HRQOL after surgery. The knowledge of how co-morbidities affect surgical outcomes may help throughout the whole treatment process and better tailor the treatment for these patients and improve their well-being. Importantly, oesophageal cancer patients with other co-morbidities should not be excluded from oesophagectomy merely on the basis of the presence of these co-morbidities.

With this said, further investigations need to be carried out in order to rule out the effect of co-morbidities on surgical outcomes. This thesis alone is far from the sufficient evidence needed to develop clinical guidelines for patients with co-morbidities, but it is one step towards the aim.
9 POPULÄRVETENSKAPLIG SAMMANFATTNING

Den här avhandlingen undersöker hur överlevnad, antalet komplikationer och livskvaliteten påverkas efter operation för matstrupscancer hos patienter som även har andra sjukdomar. Det är viktigt att veta detta för att kunna välja rätt behandling till varje individ så att resultatet blir så bra som möjligt och inte orsakar onödigt lidande för patienten. Målet med den här avhandlingen är att optimera beslutfattandet av behandlingen för att kunna optimera behandlingen och förbättra välbefinnandet hos matstrupscancerpatienter.

Bakgrund


De första symptomen på matstrupscancer är sväljningsvårigheter och viktnedgång. Eftersom matstrupen är mycket töjbar kommer symptomen sent och ofta har cancern då redan hunnit sprida sig. Detta bidrar till en dålig prognos med en 5-årsöverlevnad på 10-15%. Om patienter behandlas med operation ökar överlevnadschanserna till 30-50% efter 5 år. Operationen är mycket omfattande och inkluderar operation i buken, bröstkorgen och ibland även halsen. Man tar då bort matstrupen med tumör och gör om magsäcken till en ny matstrupe. En så stor operation innebär stora risker för komplikationer (26% till 65% får komplikationer) och även korttidsdöd (3% till 14% dör av operationen). Man har även sett att patientens livskvalitet påverkas negativt av operationen på grund av till exempel problem att äta och trötthet.

När man ska besluta om en patient lämpar sig för operation eller inte tar man hänsyn till många faktorer, men de två huvudsakliga är tumörstadiet, det vill säga hur stor tumören är och hur omfattande den har växt, samt om patienten har några andra sjukdomar, så kallade komorbiditeter. Andra sjukdomar kan till exempel vara hjärtsjukdomar, lungsjukdomar eller diabetes. Att patienterhar andra sjuksommar är en av orsakerna till att bara 25-35% av alla patienter opereras med matstrupscancer och endast denna grupp ges därmed en ökad chans till överlevnad. Resterande patienter får symptomlindrande behandling men blir inte av med sin livshotande sjukdom. Ungefär två tredjedelar av alla patienter har minst en annan sjukdom innan operation och många blir idag exkludera från operation utan att det finns vetenskapliga bevis för vilka som bör exkluderas. Det är därför viktigt att veta hur andra sjukdomar påverkar utgången av operation för att kunna välja rätt och kanske fler patienter...
till operation. Målet är att så många som möjligt överlever samtidigt som de bibehåller sin livskvalitet.

Den här avhandlingen är baserad på fyra olika studier som undersöker hur andra sjukdomar påverkar överlevnad, komplikationer och hälsorelaterad livskvalitet efter matstrupscanceroperation.

**Metoder och resultat**


**Sammanfattning**

10 TILLKÄNNAGIVANDE

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