From DEPARTMENT OF MOLEDULAR MEDICINE AND SURGERY
Karolinska Institutet, Stockholm, Sweden

OESOPHAGEAL CANCER SURGERY - PREDICTORS OF HEALTH-RELATED QUALITY OF LIFE AND SURVIVAL

Maryam Derogar

Stockholm 2013

Published by Karolinska Institutet. Printed by [name of printer]
Photographer: Mirjam Messo

ISBN 978-91-7549-310-7

"Just living is not enough," said the butterfly,
"one must have sunshine, freedom and a little flower."

~Hans Christian Andersen

1 ABSTRACT

Oesophageal cancer is a devastating disease with a bleak prognosis. Only 25% of patients are eligible for surgery which is afflicted with 15% postoperative complications an overall 5-year survival of 30-50%. In the short term patients' health-related quality of life (HRQOL) is highly deteriorated and postoperative complications contribute to this impairment. This thesis aims at shedding light on the recovery of HRQOL in the longer term and indicators of HRQOL and survival.

Study I and II were based on a prospective nationwide cohort of oesophageal cancer patients operated on between 2001-2005 and followed up postoperatively with the HRQOL questionnaires EORTC QLQ-C30 and the oesophageal-specific module EORTC QLQ-OES18 and included 5-year survivors. **Study I** investigated postoperative HRQOL changes over time and compared to the general population. HRQOL outcomes seemed to recover; however, a subgroup of patients still suffered poor HRQOL in the longer term. **Study II** examined the effect of major postoperative complications on long-term HRQOL and found that the negative impact of these complications is long-standing.

Study III and IV were retrospective nationwide cohort studies of oesophageal cancer patients who underwent surgery between1987-2005. **Study III** investigated whether the experience of the hospital or surgeon with oesophageal cancer influenced prognosis. The amount of operations performed by the hospital was not associated with mortality in the short or long term. Patients who were operated on by a surgeon who had performed more such operations over time and operated frequently had the lowest short-term mortality. **Study IV** examined the determinants of splenic injury and unintended splenectomy during surgery and its influence on prognosis and severe infections. Experienced surgeons (described above) had less risk of both injuring the spleen and conducting unintended splenectomy. Accidental splenectomy was followed by an increased risk of overall mortality and of sepsis or meningitis.

In conclusion, for each HRQOL outcome some oesophageal cancer surgery survivors do not recover and postoperative complications exert a long-lasting negative effect in HRQOL. Patients operated on by experienced surgeons have an increased risk of survival and a decreased risk of splenic injury and accidental splenectomy. Accidental splenectomy confers an increased risk of mortality and severe infections.

2 LIST OF PUBLICATIONS

I. Derogar M, Lagergren P
Health-related quality of life among 5-year survivors of esophageal cancer surgery – a prospective population-based study.
Journal of Clinical Oncology 2012;30:413-8.

II. Derogar M, Orsini N, Sadr-Azodi O, Lagergren P
Influence of major postoperative complications on health-related quality of life among long-term survivors of esophageal cancer surgery.
Journal of Clinical Oncology 2012;30:1615-9.

III. Derogar M, Sadr-Azodi O, Lagergren P, Lagergren L.
Surgeon and hospital volume and survival after oesophageal cancer surgery.
Journal of Clinical Oncology 2013;31:551-7.

IV. Derogar M, Sadr-Azodi O, Lagergren P, Lagergren L.
Accidental splenectomy during esophageal cancer – risk factors and consequences.
Manuscript submitted.

The published papers (study I-III) have been reprinted with the kind permission of the American Society of Clinical Oncology.

3 TABLE OF CONTENTS

4 LIST OF ABBREVIATIONS

BO	Barrett's oesophagus
BMI	Body mass index
CI	Confidence interval
CT	Computerised tomography
EORTC	European Organisation for Research and Treatment of Cancer
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30
EORTC QLQ-OES18	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Oesophageal 18
GORD	Gastro-oesophageal reflux disease
EUS	Endoscopic ultrasound
HR	Hazard ratio
HRQOL	Health-related quality of life
ICD	International Classification of Diseases
MIO	Minimally invasive oesophagectomy
NSAID	Non-steroidal anti-inflammatory drugs
OAC	Oesophageal adenocarcinoma
OR	Odds ratio
OSCC	Oesophageal squamous cell carcinoma
PET	Positron emission tomography
SECC	Swedish Esophageal and Cardia Cancer Study
SESS	Swedish Esophageal Cancer Surgery Study
TNM	Tumour – node – metastasis (staging system)

5 INTRODUCTION

Oesophageal cancer is the sixth leading cause of cancer worldwide. In Sweden there are 400 cases of oesophageal cancer yearly and 200 cases of cancer of the oesophago-gastric junction. The two major histological types are squamous cell carcinoma and adenocarcinoma. In 2008, 480,000 new cases were diagnosed worldwide. The incidence of oesophageal adenocarcinoma is increasing to such a degree that it is considered epidemic in Western countries, including Sweden.

Since oesophageal cancer is typically asymptomatic in the beginning, the majority of patients present at a late stage when their chances of survival are dismal. Even for patients who are fit enough to undergo extensive surgery the prognosis is poor (only 30-50% of them survive 5 years after surgery) and they face a high risk of postoperative complications and strongly reduced health-related quality of life (HRQOL). The principal aim of this thesis was to address factors that may affect HRQOL and survival in patients who have undergone surgery for oesophageal cancer.

6 BACKGROUND

6.1 BRIEF HISTORY OF ESOPHAGEAL CANCER SURGERY

A landmark in oesophageal cancer surgery came in 1871, when the man who is regarded "the father of modern abdominal surgery", namely Theodor Billroth,[1] successfully resected the complete circumference of the cervical oesophagus in a dog. Six years later, Vincenz Czerny, a professor in Heidelberg and former assistant to Billroth performed such an operation on a human being.[2] This was before the introduction of blood transfusion, antibiotics, and intensive care. In 1913, Franz Torek performed the first successful transthoracic oesophageal resection in a 67-year-old woman with squamous cell carcinoma of the oesophagus.[3] He did a cervical oesophagectomy and reestablished continuity by means of an external rubber tube between the cervical fistula and a gastrostomy. The patient survived the operation and lived for another 17 years! The first oesophageal cancer surgery with reconstruction for intestinal continuity was performed by Oshawa, a Japanese surgeon from Kyoto, in 1933.[4] He did a thoracotomy to resect the oesophagus and connected the lower end of the oesophagus to the stomach.

Alwin von Ach, a German surgeon, did not succeed with intrathoracic oesophagectomies in dogs and concluded that this was due to respiratory failure and mediastinitis.[5] At about the same time as Torek did his first transthoracic oesophagectomy, von Ach performed a left subcostal incision for exploration of the abdomen and created a cervical oesophagostomy by making an incision in the subclavicular region, hence avoiding a thoracotomy. The transhiatal approach was continued by Wolfgang Denk, an Austrian surgeon who experimented on animals and cadavers.[5] The first successful transhiatal oesophagectomy on a human was performed by George Gray Turner in 1933 (for cancer of the thoracic oesophagus).[5] However, a transhiatal approach did not give the best visualisation of the oesophagus and was not used until 1978, when much progress had been made in anaesthesia and Marc B. Orringer reintroduced the technique.[5]

The main shortcomings of the left-sided transthoracic approach to the oesophagus were the challenging blunt dissection behind the aortic arch and postoperative complications, such as respiratory failure as a consequence of the incision in the diaphragm. In 1946, Ivor Lewis, a British surgeon, proposed a right-sided approach which took these issues into account.[2] He introduced a combination of two procedures, also called a two-incisional procedure, namely a laparotomy to allow for gastric mobilisation, followed by a right-sided thoracotomy for resection of the oesophagus and intrathoracic reconstruction 10-15 days later. The procedure evolved so that both incisions were made simultaneously, and is still a very common approach in oesophageal cancer surgery. In 1947, Tanner independently described the same procedure.[6] In 1976, McKeown suggested a three-incisional procedure that differed from the Ivor-Lewis procedure by completion of the operation with an incision and anastomosis in the neck[7] to avoid the severe consequences of an intrathoracic anastomotic leak.

6.2 ESOPHAGEAL CANCER

6.2.1 Incidence

The two main types of oesophageal cancer are squamous cell carcinoma and adenocarcinoma, which together account for over 90% of all oesophageal cancers. Squamous cell carcinoma is the dominant histological type worldwide. However, in Western countries, the incidence of oesophageal adenocarcinoma (OAC) has been increasing dramatically and surpassed that of oesophageal squamous cell carcinoma (OSCC),[8-11] such that oesophageal adenocarcinoma is now the fastest growing type of cancer in the United States.[12] This increase started abruptly, at different times in different populations, and can neither be adequately explained by a parallel increase in risk factors, e.g. obesity and gastro-oesophageal reflux disease (GORD), nor histological misclassification.[13] While some studies[14-16] suggest that the increase has reached a peak, two recent studies including the year 2008[13] and 2009[17] reported a continued increase globally and in the United States, respectively. In contrast, there has been a decline in the incidence of squamous cell carcinoma, partly explained by a decreased prevalence of its main risk factor, i.e. tobacco smoking.[18] This decrease was also seen in the high-risk areas of the oesophageal cancer belt, particularly in Shanghai,[19] but also in Lixin, China.[20] There are striking differences in the incidence of oesophageal cancer between the sexes. The 3:1 male predominance for OSCC has been explained by differences in exposure to its risk factors tobacco smoking and alcohol among men and women.[21] The reason for the high male to female ratio of up to 9:1 for the incidence of OAC remains an unsolved mystery.[13]

6.2.2 Risk factors and prevention

While older age, male sex, use of tobacco, and low dietary intake of fruit and vegetables are risk factors for both OAC and OSCC, each of these histological types has otherwise very different risk factor profiles that are determined by the prevalence of each risk factor within that specific geographical area.

6.2.2.1 Adenocarcinoma

GORD itself is a strong independent risk factor for OAC.[22] A recent meta-analysis of five population-based studies showed a five-fold increased risk in individuals with weekly symptoms of GORD compared with those without any symptoms and a seven-fold increase in those with daily symptoms.[23] ***Barrett's oesophagus (BO)*** is a strong risk factor for the development of OAC,[24] and is a consequence of mucosal lesions and chronic inflammation due to GORD.[25] Around 10% of patients with GORD develop BO.[26] In a recent Danish population-based study, the annual risk of OAC in a cohort of patients with BO was 0.12%.[27]

The association between ***body mass index (BMI)*** and OAC is stronger than that for any other cancer type and has a dose-dependent relation.[28] A recent meta-analysis and pooled analysis showed a 50-70% increased risk in those who were overweight compared to those with a normal BMI, a risk that increased to over 2-fold in obese and to nearly 5-fold in grossly obese individuals.[29, 30] Evidence is emerging that the association with obesity is mediated by abdominal adiposity rather than total body fat. The prevailing theory is that abdominal fat acts directly by increasing abdominal pressure and hence GORD.[31] However, since the association between obesity and OAC is independent of GORD[32] attention is now focused on the indirect carcinogenic effects of abdominal fat [33-39] and gene-adiposity interactions.[37, 40] Other risk factors are ***Caucasian race***,[41] ***achalasia***[42] and ***smoking***.[43] Increasing BMI seems to have an additive effect on the association between smoking and OAC.[43]

Helicobacter pylori infection confers an almost 50% reduced risk of OAC,[44] possibly by inducing gastric atrophy resulting in reduced secretion of gastric acid.[45, 46] Other factors associated with reduced risk of oesophageal cancer are ***low socioeconomic status***[47] and dietary factors, such as the intake of ***antioxidants***[48] and high intake of ***fruit and vegetables***.[49] ***Alcohol*** is not a risk factor for the development of OAC,[50, 51] but moderate intake of ***wine***[50, 51] or ***spirits***[51] might rather reduce this risk. In a meta-analysis, ***non-steroidal anti-inflammatory drugs (NSAIDs)*** and ***aspirin*** were shown to reduce the risk of OAC.[52] However, in a large recently published cohort study, no such association was reported.[53] Randomised clinical trials are warranted to assess the potential protective effect of NSAIDs and aspirin on the development of OAC.

Although ***familial*** clusters of both BO and OAC have been reported,[54] family history of digestive cancers has not been found in population-based studies.[55, 56] Dominating risk factors for oesophageal adenocarcinoma are non-genetic, implying that genetic factors are of limited importance in the development of this type of cancer.

6.2.2.2 Squamous cell carcinoma

The two main risk factors for OSCC in Western populations are ***tobacco smoking*** and high ***alcohol consumption***.[57] A dose-response relation has been shown for both and their combination increases the risk in a multiplicative manner.[57, 58] Mutations in alcohol metabolism enzymes are associated with an increased risk of OSCC.[59] ***Smokeless tobacco*** such as betel quid (a type of chewing tobacco) and snuff has also been suggested to increase the risk.[42, 60, 61]. Other risk factors for OSCC include ***low socioeconomic status***,[62] ***poor oral hygiene***,[63] repeated intake of ***high temperature drinks*** such as tea[64]**,** ***pickled vegetables,***[65] exposure to ***heavy metals,***[66, 67] ***achalasia,***[68, 69] ***caustic fluids,***[70] ***tylosis*** (a genetic disease leading to thickening of the skin)[71, 72] but not ***hereditary factors***.[55] Similar to OAC, high consumption of ***fruits*** and ***vegetables*** reduces the risk of OSCC.[73]

6.2.3 Diagnosis and staging

6.2.3.1 Clinical presentation and diagnosis

Oesophageal cancer typically causes no or only minor symptoms until the cancer has reached an advanced stage. The most common symptoms of oesophageal cancer are dysphagia and weight loss, followed by gastrointestinal reflux, odynophagia, and dyspnoea.[74] The primary diagnostic procedure in patients with suspected oesophageal cancer is flexible upper endoscopy, which enables assessment of tumour length and location relative to the gastro-oesophageal junction. Concurrently, biopsies are taken to confirm the diagnosis histologically and determine the tumour type and grade.

6.2.3.2 Staging

The treatment of the disease depends on the fitness of the patient and the extent and spread of the tumour. The latter is assessed according to the TNM classification system which takes into account the tumour depth (T), lymph node involvement (N), and distant metastasis (M), which are grouped into TNM stage I to IV. The currently used version of the TNM classification system, published in 2009, includes major revisions of both the T, N and M categories and groupings, along with introduction of other factors.[75] Staging is often initially performed with a computerised tomography (CT) of the thorax, abdomen, and pelvis to detect distant metastases. Combined positron emission tomography (PET)/CT increases the accuracy of detection of distant metastases over conventional CT-scan.[76] Endoscopic ultrasound (EUS) is useful in non-metastatic disease to assess the depth of tumour penetration in the oesophageal wall and regional lymph node involvement.[77] Combination of EUS with fine-needle biopsy substantially improves the sensitivity and specificity of the N stage. Staging laparoscopy and thoracoscopy may be more accurate than EUS or CT alone.[16] However, the data are limited and originate from highly specialised centres, which makes it difficult to generalise the results.[16]

6.2.4 Curative treatment

6.2.4.1 Prognosis

The overall 5-year survival in patients with oesophageal cancer has improved during recent decades, but is still lower than 15% in the Western world.[78] This figure has improved to 30%-50% after surgery with curative intent, partly due to better patient selection.[79, 80] Stage-specific overall 5-year survival for EAC and ESCC combined is 65% for stage I, 27% for stage II and 9% for stage III.[80]

6.2.4.2 Surgery

The cornerstone for the treatment of oesophageal cancer is resectional surgery. Only one of four patients is found suitable for surgery according to population-based studies.[79, 80]

6.2.4.2.1 Approach

There are two main approaches for oesophageal cancer surgery, both of which include an abdominal incision. The transthoracic procedure includes either an Ivor-Lewis resection with a right-sided thoracic incision and a high intrathoracic anastomosis or a McKeown incision with both a thoracic and a cervical incision with a cervical anastomosis. The transhiatal approach comprises a cervical incision with a cervical anastomosis. Dissection of the oesophagus and surrounding tissues is performed through the hiatus under direct vision up to the tracheal bifurcation in both procedures.

While the transthoracic approach allows continued visible dissection of the upper thorax, this part is performed with blunt dissection in the transhiatal approach. There is no consensus as to which approach is the optimal. Advocates of the transthoracic approach argue that it permits better clearance of the tumour and mediastinal lymph nodes translating into better oncological treatment. Although meta-analyses and randomised trials have not shown any survival benefit,[81-84] one large trial demonstrated lower pulmonary morbidity in the transhiatal group.[85] At present the selection is based on tumour location, patient's fitness and surgeon's preference. Nevertheless, the most common substitute for the oesophagus is the stomach (Figure 1), although the colon or jejunum may be used.

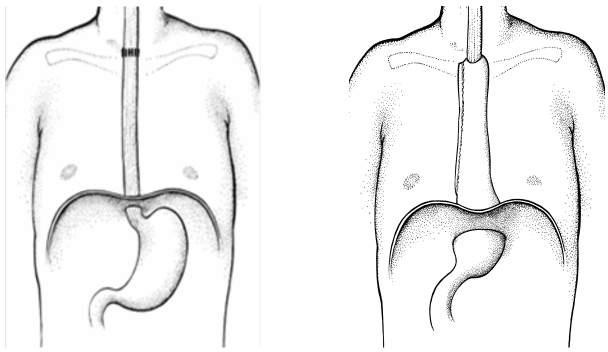

Figure 1. Schematic figures of the oesophagus and stomach (left picture) and replacement of the oesophagus with a gastric substitute (right picture).

6.2.4.2.2 Minimally invasive oesophagectomy

In an attempt to decrease morbidity associated with oesophagectomy, minimally invasive oesophagectomy (MIO) is increasingly used as an alternative to conventional open surgery. MIO incorporates various combinations of thoracoscopy, laparoscopy, hand-assisted laparoscopy, and conventional open laparotomy and thoracotomy. The only randomised controlled trial published to date comparing open oesophagectomy to MIO showed reduced blood loss, shorter in-hospital stay, and a reduced risk of pulmonary infections with MIO.[86] In addition, patients operated with MIO had better recovery of HRQOL, which has been shown also in non-randomised studies.[87-89] Nevertheless, the potential benefits of MIO for long-term recovery of HRQOL remain to be proven.

6.2.4.3 Lymphadenectomy

The lymphatic anatomy of the oesophagus includes a rich submucosal network of lymphatic vessels that drain longitudinally upwards or downwards along the entire length of the oesophagus.[90] For OAC that involves the submucosa, the frequency of lymph-node metastases exceeds 20%.[91] Controversy exists as to the prognostic value of the extent of lymphadenectomy, number of lymph nodes removed, and lymph node ratio (number of positive lymph nodes divided by the number of nodes sampled).[92] In the only randomised clinical trial that compared three-field (neck, thorax, and abdomen) and two-field lymphadenectomy (thorax and abdomen) neither technique conferred any significant survival benefit.[93] Several retrospective studies suggest that the number of lymph nodes retrieved is associated with long-term survival.[94] This could, however, be explained by stage migration, i.e. the reported survival benefit is a result of more accurate staging with a larger number of lymph nodes removed.

6.2.4.4 Neoadjuvant chemotherapy

The addition of oncological treatment, i.e. chemotherapy or radiotherapy alone or in combination, before or after esophagectomy has been a matter of debate. Recent RCTs and meta-analyses have shed new light on this topic. Controversy exists whether the addition of radiotherapy to chemotherapy is superior to chemotherapy only.

The largest trial on the role of preoperative chemotherapy versus surgery alone was published in the UK (MRC OE02 study) and showed an overall survival benefit of 16% in the chemotherapy arm (HR 0.84; 95% CI: 0.72-0.98).[95] A recent meta-analysis including 9 RCTs showed that chemotherapy is associated with a significant survival benefit (HR 0.87; 95% CI: 0.79-0.96). However, the benefit was limited to OAC (HR 0.83; 95% CI: 0.71-0.95).[96]

6.2.4.5 Neoadjuvant chemoradiotherapy

In the largest RCT from the Netherlands (CROSS study) 363 patients were randomised to either chemoradiotherapy followed by surgery or surgery alone.[97] While, there were no differences in mortality between the two groups and the preoperative chemoradiotherapy including Paclitaxel and Carboplatin was well tolerated, preoperative chemoradiotherapy conferred a survival benefit. Median survival was 49 months in the chemoradiotherapy with surgery group versus 24 months in the surgery group (HR 0.66; 95% CI: 0.50-0.87). The largest meta-analysis based on12 RCTs showed an all-cause mortality benefit of 22% for chemoradiotherapy (HR 0.78; 95% CI: 0.70-0.88) comparing chemoradiotherapy with surgery to surgery alone and this benefit was evident for both OAC and OSCC.[96] However, this study could not demonstrate an advantage of chemoradiotherapy over chemotherapy alone, which should be clarified in future studies.[96]

6.2.4.6 Postoperative adjuvant treatment

A recent meta-analysis including both RCTs and nonrandomised studies of patients with thoracic OSCC showed a 3-year overall survival benefit in the postoperative chemotherapy group in patients with stage III-IV, but not for earlier stages. Furthermore, postoperative chemotherapy prevented relapse within one year in all patients combined and within five years in patients with positive lymph node.[98]

6.3 PROVIDER VOLUME AND PROGNOSIS

The first article on the relationship between hospital volume and outcome for various surgical procedures was published by Luft et al in 1979.[99] Since then a plethora of studies have been published on this issue, of which several showed a benefit regarding short-term survival for high-risk surgeries including oesophagectomy for cancer.[100-103] Studies addressing the association between hospital volume and long-term survival were small and showed contradictory results.[104-110] Furthermore, previous studies had some methodological concerns deserving attention. None of the studies showing an inverse association mutually adjusted for surgeon volume, leaving the question whether hospital volume or surgeon volume contributes to better outcome. Moreover, the studies either did not exclude postoperative death in the analysis of overall survival or lacked a robust adjustment for case-mix and hospital clustering.

In terms of surgeon volume and long-term mortality, the few available studies showed inconsistent results.[103, 104, 110, 111] and had some methodological limitations including lack of stage and hospital volume and did not exclude postoperative death in the analysis.

Regarding hospital and surgeon volume and short-term mortality only one study addressed the relative influence of hospital and surgeon volume showing that short-term mortality was largely accounted for by surgeon volume.[103]

6.4 SPLENIC INJURY AND ACCIDENTAL SPLENECTOMY

The proximity of the oesophagus and the stomach, the most frequently used substitute, to adjacent organs poses a risk of iatrogenic injury during oesophageal cancer surgery. Splenic injury is a well-known complication which can occur due to traction, retractors or other instruments. Anatomically, the lower pole and hilum of the spleen are attached to the greater omentum by peritoneal bands[112] posing a risk of splenic injury during downward and medial traction of the stomach during preparation of the gastric conduit.

In a small study including 14 patients undergoing splenectomy during oesophageal surgery unintended splenectomy was associated with increased short-term mortality.[113] Ensuing studies investigated the role of unintended splenectomy in the short and long-term did not show such association.[114-116] However, these studies were hampered by their small size (range 6-34) impeding robust analysis[113, 114, 116] or did not perform multivariable analysis.[115]

Knowledge of the predictors of splenic injury and accidental splenectomy could provide ways to avoid such injuries. The few patients in the available studies (maximum 14 patients) did not allow for multivariable analysis.[116, 117]

6.5 HEALTH-RELATED QUALITY OF LIFE

Quality of life is a phrase used in many disciplines e.g. politics, sociology, and politics with different meaning depending on the context. Health-related quality of life (HRQOL) is limited to the quality of life related to a disease or its treatment.[118] There is no generally accepted definition of HRQOL. However, most definitions agree that HRQOL is a multidimensional concept including at least four dimensions: physical function, emotional function, social function, and symptoms.[118] This view on health as a multidimensional concept rather than absence of pathology was introduced over half of a century ago, when the World Health Organization defined health as "a state of complete physical, mental and social well-being, and not merely the absence of disease or infirmity".[119]

Importantly, HRQOL is a subjective experience and can only be reported by the patient. There is poor correlation between patients' and health professionals' evaluation of patients' problems.[120, 121] Further emphasizing the subjective nature of HRQOL, the U.S. Food and Drug Administration (FDA) recently coined the phrase patient-reported outcome (PRO), which 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'.[122]

6.5.1 HRQOL assessment

A plethora of HRQOL questionnaires are available.[123] These can broadly be categorized into generic, disease-specific, and aspect-specific. Generic HRQOL-questionnaires are designed to be relevant to anyone, allowing comparison of data across studies, and patients may be compared against the general population. The most widely used is the Medical Outcomes Study-36 item short form (SF-36). Disease-specific HRQOL-questionnaires cover issues that are relevant to certain groups of diseases or specific diseases, e.g. the EORTC QLQ-C30 which is intended for cancer patients and can be complemented with a module for a specific cancer site. Aspect-specific questionnaires may include e.g. the Hospital Anxiety and Depression Scale (HADS) and the McGill Pain Questionnaire (MPQ).

6.5.2 Conceptual model

Several models of HRQOL have been presented, of which the model presented by Wilson and Cleary in 1995 is the most frequently used in published HRQOL studies.[124] This model integrates biological and psychosocial aspects of health outcomes by linking traditional clinical variables to measures of HRQOL.[125] Five core domains are depicted in the scheme, including biological and physiological factors, symptom status, functional status, general health, perceptions, and overall QOL. The model also links individual and environmental characteristics to each of the five domains, although these components were not discussed in the original text.

6.5.3 HRQOL in oesophageal cancer patients

Studies have consistently shown a deleterious effect of oesophageal cancer surgery on HRQOL outcomes at short-term (6 months postoperatively) as compared to baseline levels and the general population.[126-136] However, studies on the recovery of HRQOL outcomes after the initial 6 months postoperatively have been more contradictory. While some studies suggest a recovery of most HRQOL outcomes within 5 years of surgery,[126, 127, 131, 133, 137-140] other studies report a continued deterioration.[133, 141, 142] Oesophageal cancer patients typically report more problems with fatigue, diarrhoea, appetite loss, and nausea and vomiting as assessed with the EORTC QLQ-C30 questionnaire. Comparisons of the results of the studies are challenging due to the heterogeneity of the populations, methodological approaches and questionnaires, which was affirmed in a recent meta-analysis.[143]

Several determinants of HRQOL outcomes have been identified. Among patient-related factors, age, sex, and comorbidity have been shown to influence various HRQOL outcomes.[128, 139, 144] For example younger age has been associated with poorer emotional function[128]. In addition, tumour-related factors such as stage,[145] type[133, 144] and location[144] may also affect HRQOL. Some surgical factors including surgical approach,[131, 136, 146] location of anastomosis[139, 146, 147] and route of construction[148] have been shown to predict survival.

Operative complications have been shown to have a diverse effect on HRQOL outcomes 6 months postoperatively. Each of reoperation, anastomosis leakage, infections, or respiratory insufficiency affected physical and role function negatively, while infections and cardiac complications negatively affected global quality of life.[149] The occurrence of technical surgical complications negatively affected global quality of life, physical and role function, dyspnoea, fatigue, nausea or vomiting, and coughing.[150] In a single-centre study, anastomotic leak was shown to have a negative effect on physical function in patients who survived at least 2 years postoperatively.[151]

7 AIMS OF THE STUDIES

The main aim of this thesis was to extend the knowledge on factors that may affect HRQOL and survival in patients who have undergone surgery for oesophageal cancer.

Specific aims were:

- To clarify patterns of HRQOL in long-term survivors of oesophageal cancer surgery.
- To evaluate the influence of major postoperative complications on HRQOL after oesophageal cancer surgery.
- To assess the impact of hospital and surgeon volume on long-term survival after oesophageal cancer surgery.
- To identify predictors of splenic injury and evaluate the influence of accidental splenectomy on survival and severe infectious diseases after oesophageal cancer surgery.

8 SUBJECTS AND METHODS

8.1 OVERVIEW

Table 1. Overview of material and methods used in study I-IV.

	Study I	Study II	Study III	Study IV
Design	Prospective population-based cohort study		Retrospective population-based cohort study	
Data sources	Swedish Esophageal and Cardia Cancer Study (SECC), Reference population study (RP)		Swedish Esophageal Cancer Surgery Study (SESS), Swedish Causes of Death Registry, Swedish Cancer Registry, Swedish Patient Registry	
Cohort	All Swedish residents undergoing oesophagectomy for oesophageal or cardia cancer and surviving 5 years.		All Swedish residents undergoing oesophagectomy for oesophageal cancer.	
Inclusion period	2 April 2001-31 Dec 2005		1 Jan 1987- 31 Dec 2005	1 Jan 1987- 31 Dec 2010
Follow-up	2 April, 2001-31 Dec, 2010		1 Jan 1987- 28 Feb 2011	1 Jan 1987- 24 Feb 2012
Exposure	Oesophageal cancer surgery	Major postoperative complications	Hospital and surgeon volume	**a)** See a) in confounders **b)** Accidental splenectomy
Outcome	HRQOL assessed with the EORTC QLQ-C30 and the EORTC QLQ-OES18		Short and long-term mortality	**a)** Splenic injury and accidental splenectomy **b)** Short and long-term mortality and severe infection
Confounders	Age, sex, comorbidity	Time, age, sex, comorbidity, tumour histology, tumour stage, surgical approach	Age, sex, comorbidity, tumour stage, tumour histology, neoadjuvant therapy, and calendar period, volume, clustering	**a)** Sex, age, tumour stage, previous surgery, neoadjuvant therapy, radicality, surgeon volume and calendar period **b)** In a) and comorbidity, tumour histology, reoperation
Main statistical methods	Student's t-test, Linear regression	Linear mixed-effects models	Multivariable parametric survival	Logistic regression, Cox regression

8.2 DATA SOURCES

The studies included in this thesis are based on three national Swedish databases gathered by our research group during several years: the Reference Population (RP) Study, the Swedish Esophageal and Cardia Cancer (SECC) Study, and the Swedish Esophageal Cancer Surgery Study (SESS).

8.2.1 The Swedish Esophageal and Cardia Cancer Study (SECC)

SECC is a nationwide Swedish prospectively collected cohort of nearly all patients (90%) undergoing oesophageal or gastro-oesophageal junction cancer surgery from 2001 through 2005, including repeated assessments of HRQOL.[22] The organisation behind SECC was extensive, involving 174 hospital departments (97% of all those in Sweden) caring for oesophageal cancer patients (general surgery, thoracic surgery, otorhinolaryngology, oncology, and pathology) along with collaboration with the six Swedish regional tumour registries. The network was centrally administered and a project administrator was rapidly notified of new cases and ensured the collection of all data. A study protocol with predefined definitions and categorisations was completed by scrutiny of hospital and pathology charts before and after surgery by the study researchers. Data were collected on characteristics of the patient and the tumour, treatment, complications, HRQOL, and mortality. The HRQOL questionnaires EORTC QLQ-C30 and EORTC QLQ-OES18 were sent to patients at 6 months, 3 and 5 years after surgery.

8.2.2 The Reference Population Study (RP)

The RP study was a national cross-sectional survey of Swedish adults in the general population in year 2008, with a focus on assessment of HRQOL outcomes of relevance for patients with oesophageal cancer. The sampling and collection of data was conducted by Statistics Sweden. A random sample of individuals aged 40-79 years was frequency-matched on age and sex to new cases of upper oesophagogastric cancers in 2006 as reported in the Swedish Cancer Registry. The HRQOL questionnaires EORTC QLQ-C3 and EORTC QLQ-OES18 were sent to each selected individual. The questionnaires were completed by 4910 (70.5%) out of 6969 eligible participants.[152]

8.2.3 The Swedish Esophageal Cancer Surgery Study (SESS)

SESS is a retrospective nationwide cohort of patients undergoing surgery for oesophageal cancer (not gastro-oesophageal junction cancer) in Sweden from 1987 and onwards. Patients who had a diagnosis of oesophageal cancer were identified from the Swedish Cancer Registry and were linked with patients who underwent surgery for oesophageal cancer during the period according to the Swedish Patient Registry. Hospital and histopathology charts for the eligible patients were retrieved from all hospitals and these charts were manually reviewed according to predefined protocols. Clinical data were collected, mainly on tumour and treatment characteristics.

8.3 ADDITIONAL DATA SOURCES

8.3.1 The Swedish Cancer Registry

The Swedish Cancer Registry was established in 1958 and since then all Sweden's health-care providers, whether public or private, have been required to report new cancer cases to the registry. Cancer diagnoses based on clinical, morphological, or laboratory examination are registered, while diagnoses based on autopsies are reported but not registered. All cancer diagnoses are registered according to the International Classification of Diseases (ICD). The overall completeness of the registration of oesophageal cancer was 98% in this registry, and the histopathological confirmation of these tumours was complete (100%).[153]

8.3.2 The Swedish Patient Registry

The Swedish Patient Registry was initiated in 1964 with the purpose of collecting information on in-patient care in Sweden. From 1987 all hospitals have been mandated to participate in the registry, allowing calculation of a nationwide completeness rate ever since. The registry contains patient-related, geographical and administrative data, along with surgical procedures (coded according to the Swedish Classification of Operations and Major Procedures) and up to six discharge diagnoses coded according to the Swedish version of the ninth revision of the International Classification of Diseases (IC-8) between 1987 and 1996 and the tenth revision (ICD-10) between 1997 and 2006. The completeness for oesophageal cancer surgery was 99.6% in our validation study of this registry.[154]

8.3.3 The Swedish Causes of Death Registry

The Swedish Causes of Death Registry comprises data on all deaths among Swedish residents, whether occurring in Sweden or abroad, from 1952 and onwards. The contributing and underlying causes of death and date of death are reported in a death certificate by a physician according to most recent version of ICD. The registry covers more than 99% of all deaths in Sweden since 1952.[155]

8.4 HRQOL QUESTIONNAIRES

8.4.1 EORTC QLQ-C30

The EORTC QLQ-C30 (version 3.0)[156] is a core questionnaire, developed by the European Organisation for Research and Treatment of Cancer (EORTC), that assesses how patients with cancer have perceived their HRQOL during the past week. It contains 30 items distributed over 5 functional scales (physical, role, cognitive, emotional, and social), 3 symptom scales (fatigue, pain, and nausea or vomiting), and 1 global health-status/quality of life scale. This questionnaire also contains 6 single items addressing further cancer symptoms (dyspnoea, appetite loss, insomnia, constipation, and diarrhoea) and the financial impact of the disease. Each item has 4 response alternatives: 1) “Not at all”, 2) “A little”, 3) “Quite a bit”, and 4) “Very much”, except the global health-status/quality of life scale, which has the response alternatives based on a marking on a categorical scale ranging between 1) “Very poor” and 7) “Excellent”. The QLQ-C30 has been tested and shown good validity and reliability[156-160].

8.4.2 EORTC QLQ-OES18

The EORTC QLQ-OES18 is a disease-specific module that supplements the QLQ-C30 questionnaire with oesophageal cancer symptoms.[161] The EORTC QLQ-OES18 comprises 4 symptoms scales (eating, reflux, oesophageal pain, and dysphagia) and 6 single items (cough, dry mouth, taste, choking, speech, and trouble swallowing saliva). It has the same 4 response alternatives as in the core questionnaire presented above. The EORTC QLQ-OES18 has been tested and shown high validity and for most scales high reliability.[161] However, the reliability for reflux and oesophageal pain was poor.[161] A recent study showed that the sensitivity, specificity and positive and negative predictive values of reflux in the QLQ-OES18 were poor compared to those in a more extensive reflux questionnaire, suggesting approaches to improve this scale.[162]

8.5 STUDY DESIGN

8.5.1 Study I

Based on data from SECC, this prospective cohort study assessed the changes in HRQOL 6 months, 3 years, and 5 years after surgery among 5-year survivors of oesophageal cancer who underwent resectional surgery between 2001 and 2005.

8.5.2 Study II

This was a prospective cohort study on the association between major postoperative complications and long-term changes in HRQOL among patients who underwent surgery between 2001 and 2005 using SECC data.

8.5.3 Study III

This retrospective cohort study investigated the role of annual hospital and annual and cumulative surgeon volume in long-term mortality after oesophageal cancer surgery among patients who underwent surgery in 1987 and 2005. This study used data from SESS.

8.5.4 Study IV

Using SESS data, this retrospective cohort study of patients who underwent oesophageal cancer surgery in 1987 and 2010 investigated: a) potential predictors of splenic injury and accidental splenectomy; b) factors affecting progression to splenectomy in case of splenic injury; c) the role of accidental splenectomy in mortality; and d) the influence of accidental splenectomy on the occurrence of severe infections.

8.6 EXPOSURES

8.6.1 Study I

The exposure in this study was ***oesophageal cancer surgery***.

8.6.2 Study II

The exposure was ***major postoperative complications*** that occurred within 30 days after oesophageal cancer surgery (categorised into yes or no) and included postoperative bleeding, anastomotic leakage, intra-abdominal or intrathoracic abscesses, renal failure, pulmonary embolism, myocardial infarction or stroke, and respiratory failure. All these complications were pre-defined according to criteria given in the study protocol.

8.6.3 Study III

The exposure ***annual hospital volume*** of oesophageal cancer surgery was calculated as the number of oesophagectomies performed for each hospital and year during the period 1987 through 2005. Thus, the annual volume could vary for a given hospital. The volume was categorised in quartiles of annual hospital volume. Since many hospitals in Sweden perform few oesophagectomies per year, the two lowest quartiles were combined, resulting in three categories: quartile 1 and 2 (≤50%), quartile 3 (51-75%), and quartile 4 (>75%). This was done to avoid comparison of volume categories with extremely low volumes.

The exposure ***surgeon volume*** of oesophageal cancer surgery was evaluated as both annual and cumulative surgeon volume. An algorithm was developed to assign the operation to the most experienced surgeon whenever more than one surgeon took part in the resection. First, the primary surgeon's chronological number of surgeries was calculated for each year over the study period. Thereafter, the surgeon with the highest chronological number of surgeries at the index operation was considered responsible for the surgery. Annual surgeon volume was then calculated as the number of times the surgeon had been responsible for an operation at the index operation, while cumulative surgeon volume was calculated as the chronological number of operations the surgeon had been responsible for at the time of the index operation during the entire inclusion period, 1987-2005. Annual and cumulative surgeon volume were then divided into quartiles. The majority of the surgeons had low annual and cumulative volume. Therefore, the two lowest quartiles were combined, resulting in three categories: quartile 1 and 2 (≤50%), quartile 3 (51-75%), and quartile 4 (>75%).

Combination of hospital and surgeon volume and ***annual and cumulative surgeon volume***, were assessed by subdividing these volumes into above median and below or equal to the median.

8.6.4 Study IV

Splenic injury was defined as splenic subcapsular haematoma or unintended laceration of the splenic capsule, parenchyma, or hilar vessels, and included patients who did and did not undergo splenectomy because of such injury. ***Accidental splenectomy*** was defined as unintended splenic injury necessitating splenectomy, regardless of whether any attempt was made to preserve the spleen. Splenic injury and accidental splenectomy were the study outcomes in the part of the study addressing the predictors of these events, while accidental splenectomy was the study exposure in the part of the study that addressed their consequences (mortality and infections). Patients who had previously undergone splenectomy and those who underwent planned splenectomy for better tumour clearance were excluded from the study.

8.7 OUTCOMES

8.7.1 Study I and II

In study I and II, the outcome was change in ***HRQOL*** comparing the levels at 3 and 5 years with the HRQOL at 6 months after oesophageal cancer surgery. Depending on the change in mean score for each item, HRQOL was categorised as having improved, remained stable, or deteriorated. Improvement was defined as an increase of at least 10 mean scores within the categories function and global quality of life and a decrease of at least 10 mean scores within the symptom categories. Correspondingly, deterioration was defined as a decrease of at least 10 mean scores for function and global quality of life and an increase of at least 10 mean scores for symptoms. For some patients the mean scores in the first assessment were so high or low that it was not possible for them to attain a difference in 10 mean scores. In those cases, any difference in the better direction was considered an improvement, while any change to the worse direction was considered deterioration, regardless of mean scores change. HRQOL outcomes that were not classified as either improved or deteriorated were considered stable.

8.7.2 Study III and IV

The outcome overall ***mortality*** included any deaths (all causes) occurring after the surgery, independent of the cause of death. Short-term mortality was defined as any death within three months of surgery, while longer-term mortality was defined as any death occurring later than three months after surgery.

8.7.3 Study IV

As described above, occurrence of ***splenic injury*** or ***accidental splenectomy*** were outcomes in the part of study assessing predictors for these intraoperative complications. These outcomes were defined above.

Severe infections defined as bacterial sepsis or meningitis after surgery were assessed from the Swedish Patient Registry, defined by the ICD codes representing these diseases.

8.8 STATISTICAL ANALYSES

All statistical analyses were performed using Stata, version 11.2 (StataCorp, TX, USA).

8.8.1 Study I

Mean scores were calculated for each HRQOL outcome at 6 months, 3 years, and 5 years, and depicted in a graph with the corresponding HRQOL values of the corresponding background population. A paired *t* test was used to determine whether there was a statistically significant change between HRQOL assessments at 6 months and 5 years after surgery. The changes in HRQOL outcomes were categorised as improvement, stable, or deterioration as described above.

Multivariable linear regression was used to compare HRQOL outcome mean scores at 5 years for the patients assigned to each category of change in HRQOL (i.e., improved, stable, deteriorated) with the scores of the corresponding background population. The analyses were adjusted for age (continuous variable), sex, and comorbidity (categorised as yes if any comorbidity; otherwise no). The comorbidities included hypertension, angina, heart failure, chronic obstructive pulmonary disease, diabetes, and kidney disease.

8.8.2 Study II

Multivariable linear mixed-effects models were used to assess differences in mean scores for each HRQOL outcome in patients with or without major postoperative complications. Adjustments were made for time, age (<60 or ≥ 60 years), sex, comorbidity (none, one, or >one), histologic tumour type (squamous cell carcinoma or adenocarcinoma), tumour stage (0 to II, III to IV, or missing), and surgical approach (transthoracic, transhiatal, or cervical). The following conditions were included among the predefined comorbidities: hypertension, angina, heart failure, chronic obstructive pulmonary disease, diabetes, and kidney disease. Moreover, a group-by-time interaction term was added to the multivariable model of each HRQOL aspect and examined with the Wald test. A compound symmetry correlation was assumed among repeated measures of all longitudinal analyses. A significant interaction indicated that the mean score difference between the two groups was not the same for all time points.

For HRQOL aspects with a significant interaction at *P* <.1, the mean score difference between the two groups was compared at each follow-up (6 months and 3 and 5 years). This was done to determine at which point or points in time the groups differed. Otherwise, the interaction term was removed from the model before testing the main effect of major postoperative complications over the three time points.

8.8.3 Study III

Multivariable parametric survival analysis was used to calculate hazard ratios (HRs) and 95% confidence intervals (CIs).[163]. Gompertz survival distribution resulted in the lowest Akaike information criteria score (i.e. best model fit) and was therefore used.[164] To account for the effect of clustering of patients within hospitals and surgeons, a shared frailty term with gamma distribution was added to the models.[163] The multivariable models were adjusted for seven known prognostic factors: age (categorised into: <65, 65-75, or >75 years), sex, revised Charlson comorbidity index (0, 1, or ≥2), tumour stage at the time of surgery (0-I, II, III, IV, or missing), histological type of tumour (adenocarcinoma, squamous carcinoma, or missing or undefined), neoadjuvant therapy (yes, no, or missing), and calendar period (year 1987-1990, 1991-1995, 1996-2000, or 2001-2005). To disentangle any influence of surgeon and hospital volume and take into account surgeon and hospital clustering, a total of four models were analysed. Model 1 was adjusted for all seven confounders presented above. Model 2 was further mutually adjusted for volume variables (surgeon volume when the effect of hospital volume was assessed and vice versa). Model 3 was adjusted for all seven confounders, volume variables, and hospital clustering. Model 4 was adjusted for all seven confounders, volume variables, and surgeon clustering. Finally, the effect of variations in hospital and surgeon volume with calendar time was analysed by stratification into the inclusion periods 1987 to 1995 or 1996 to 2005.

8.8.4 Study IV

Multivariable logistic regression models were used to calculate ORs with 95% CIs for the role of eight predefined predictors on the development of splenic injury or accidental splenectomy. The predictors were sex, age (<65, 65-75, or >75 years), tumour stage (0-I, II, III, IV, or missing), previous upper abdominal surgery (yes or no), neoadjuvant therapy (none, chemotherapy, radiotherapy, chemoradiotherapy, or missing), radicality (R0 or R1/R2), calendar period (years 1987-1990, 1991-1995, 1996-2000, 2001-2005, or 2006-2010), and surgeon volume (evaluated as the combination of annual volume and cumulative experience, categorised into four groups: ≤median volume and ≤median experience, >median volume and ≤median experience, ≤median volume and >median experience, or >median volume and >median experience). The median annual surgeon volume was 4 surgeries and the median cumulative experience was 15 surgeries.

One analysis was restricted only to patients with splenic injury to assess the association between surgeon volume, surgeon experience, and calendar period in relation to risk of accidental splenectomy among patients with splenic injury.

The influence of accidental splenectomy on survival or severe infection (sepsis or meningitis) was evaluated using multivariable Cox regression analyses, and the results are presented as HR with 95% CI. Person-years were calculated from the date of surgery until the date of death or date of infection, or end of study period (28 February 2012), whichever occurred first. The multivariable model adjusted for 10 potential confounding factors: sex, age, tumour stage, neoadjuvant therapy, radicality, calendar period, and surgeon volume, which were all categorised as presented above, together with three additional variables: comorbidity (using a revised Charlson Comorbidity Index, categorised into three groups: 0, 1, or ≥2), histological type of tumour (adenocarcinoma, squamous carcinoma, or missing or undefined), and reoperation after the primary resection (yes or no). All categories were defined prior to any analysis. To account for the effect of clustering of patients within surgeons, a shared frailty term with Gamma distribution was also added to the models.[163] Finally, sub-analysis was performed for mortality after excluding the first two weeks after surgery to reduce potential effects of early postoperative complications.

8.9 ETHICAL CONSIDERATIONS

Informed consent was obtained from each patient before inclusion in the SECC. The SESS was approved by the Regional Ethical Review Board in Stockholm. Results were presented at the group level which prevents identification of the participants. Medical charts were available to the researchers only.

9 RESULTS

Some characteristics of patients and characteristics are shown in Table 2.

Table 2. Overview of patient and tumour characteristics in study I-IV.

	Study			
	I	**II**	**III**	**IV**
Number of patients	117	141	1335	1679
Sex, number (%)				
Male	93 (79)	112 (80)	983 (74)	1255 (75)
Female	24 (21)	29 (21)	352 (26)	424 (22)
Median age, years (range)	63 (31-84)	64 (31-84)	66 (18-86)	65 (18-88)
Comorbidity, number (%)				
No	38 (32)	51 (36)	887 (66)	1044 (62)
Yes	79 (68)	90 (64)	448 (34)	635 (5)
Tumour stage, number (%)				
0-II	89 (76)	108 (77)	671 (50)	920 (55)
III-IV	27 (23)	31 (22)	437 (33)	533 (32)
Missing	1 (1)	2 (1)	227 (17)	226 (13)
Tumour histology, number (%)				
Adenocarcinoma	80 (68)	99 (70)	486 (36)	666 (40)
Squamous carcinoma	29 (25)	34	797	938 (56)
High-grade dysplasia	8 (7)	8 (6)	34 (3)	48 (3)
Missing	0 (0)	0 (0)	18 (1)	27 (2)

9.1 STUDY I

In total 117 (76%) patients responded to all three HRQOL assessments and were included in this study. Among a random sample of 6,969 Swedish adults representing the corresponding background population 4,910 (70.5%) responded. Regarding HRQOL, two aspects changed over time: appetite loss and diarrhoea became less troublesome between 6 months and 5 years. The differences in mean scores for these HRQOL aspects were both clinically relevant and statistically significant. For each HRQOL aspect the majority of patients were either stable or improved from 6 months to 5 years after surgery. Nevertheless, for each aspect the situation had deteriorated for 10% to 40% of the patients. The aspects of HRQOL that had most frequently deteriorated were dysphagia and reflux. The results for some HRQOL aspects are shown in Figure 2.

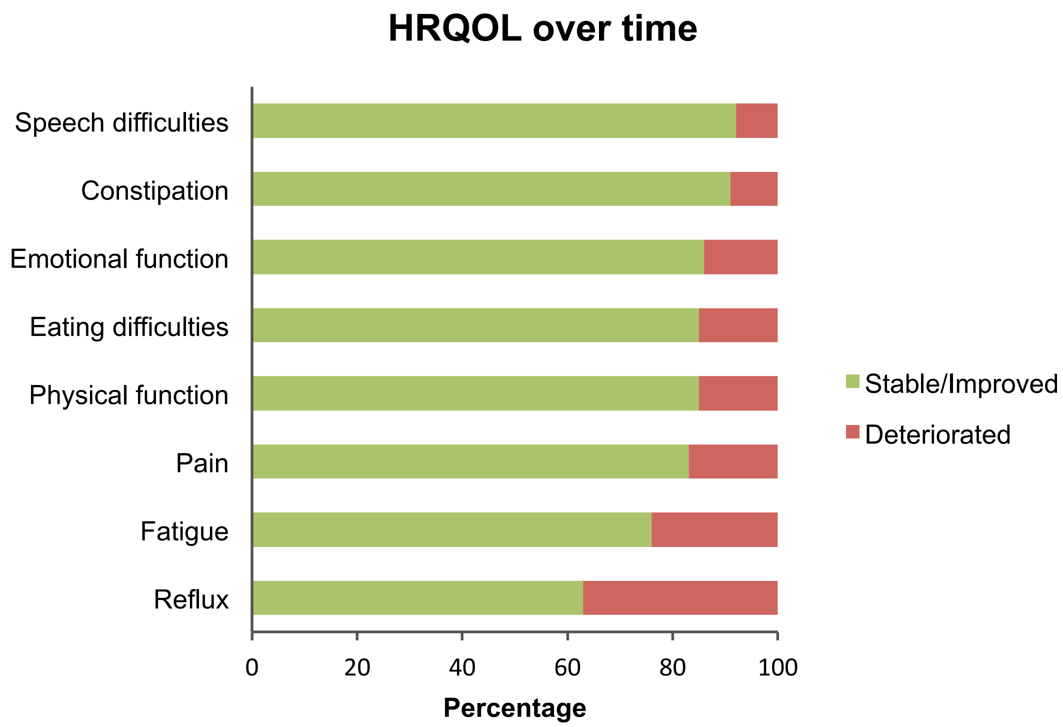

Figure 2. Percentage of patients whose HRQOL had deteriorated and improved/remained stable between 6 months and 5 years after surgery. Each aspect of HRQOL is shown separately.

For most HRQOL outcomes, patients whose condition improved or remained stable over time reached the level of the general population, whereas patients whose condition deteriorated had worse results for all HRQOL outcomes. Patients had more problems with diarrhoea and eating difficulties than the general population irrespective of how HRQOL changed over time. Figure 3 illustrates the mean score for physical function and eating difficulties of the general population and patients at the three assessment points according to deterioration or improvement.

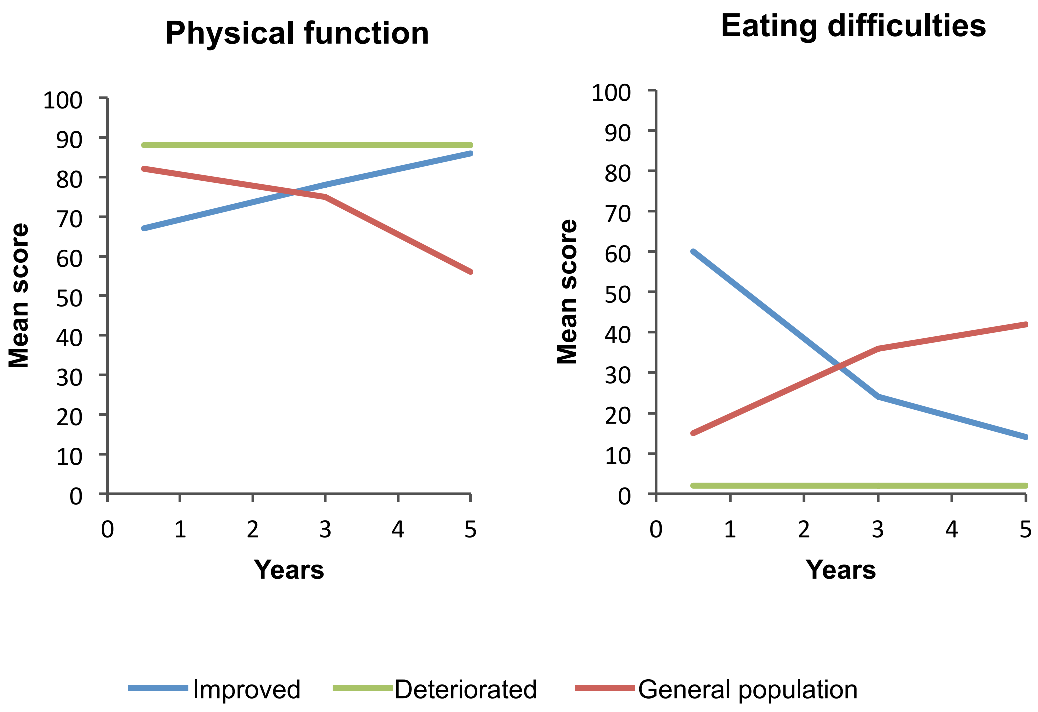

Figure 3. Physcial function and eating difficulties in the general population and patients, showing how HRQOL changed over time.

9.1.1 Study II

In all, 141 (92%) patients responded to the 5-year questionnaire and were included. A total of 46 patients (33%) sustained at least one major postoperative complication, mainly respiratory failure, pneumonia, anastomotic leakage, or sepsis. Patients with at least one major postoperative complication reported more problems with appetite loss, dyspnoea, fatigue, and eating restrictions over the three assessment points (6 months, 3 years and 5 years) than patients without major postoperative complications. These differences were large enough to be clinically relevant. However, the difference in loss of appetite was not statistically significant. For some HRQOL outcomes the differences in the mean scores varied according to assessment point. For example, patients with major postoperative complications had clinically relevant and statistically significantly more problems with choking 6 months after surgery and with reflux 5 years after surgery. Figure 4 illustrates means scores over time for some HRQOL aspect in patients with and without major postoperative complications.

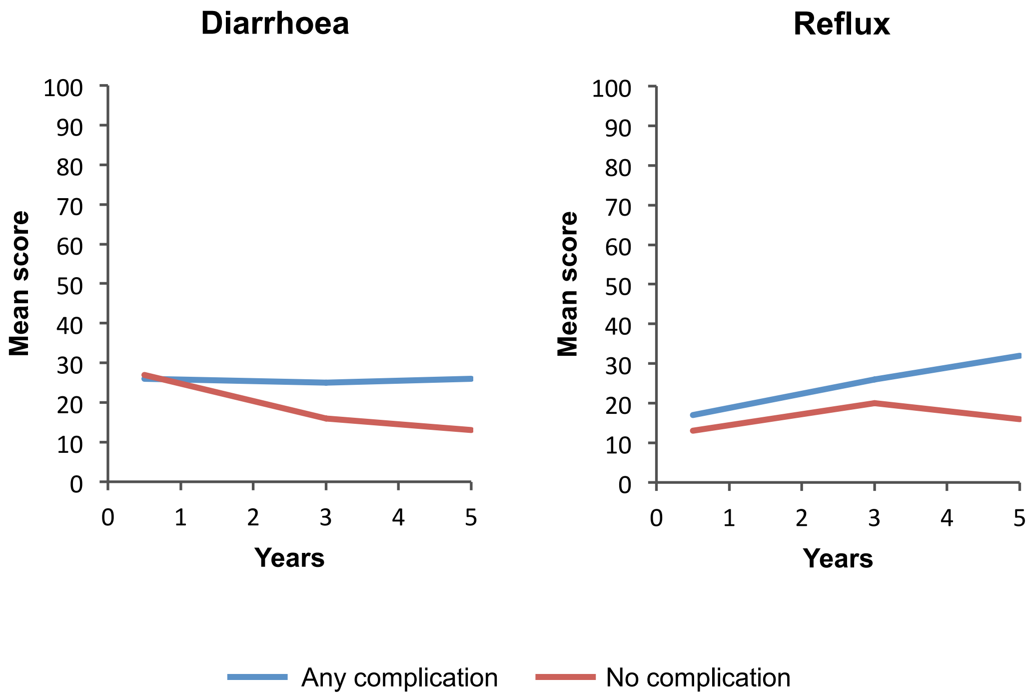

Figure 4. Diarrhoea and reflux over time in patients with and without major postoperative complications.

9.1.2 Study III

In all, 1,411 patients underwent surgery for oesophageal cancer in Sweden in 1987-2005. Surgical charts were retrieved for 1,335 (94.6%) patients, who constituted the study cohort. Among 46 hospitals and 122 surgeons contributing with these oesophagectomies 46, 6, and 2 hospitals and 122, 23, and 6 surgeons were included in quartile 1-2, quartile 3, and quartile 4, respectively.(Figure 5)

There was no association between annual hospital volume and long-term mortality (i.e., mortality between 3 months and 5 years after surgery).

There was a 23% decreased risk of mortality in the long term among patients who underwent surgery by surgeons in quartile 3 compared with quartile 1 to 2 after adjustment for confounders and hospital volume (HR 0.77; 95% CI: 0.65-0.92). This association remained after taking hospital and surgeon clustering into account. A similar pattern was found when comparing quartile 4 with quartile 1 to 2, but this association was not statistically significant (HR 0.84; 95% CI: 0.66-1.07). Cumulative surgeon volume was not associated with mortality in any of the analyses.

There was a 22% lower risk of longer term mortality when both annual and cumulative surgeon volume were above the median versus below the median, after adjustment for hospital volume (HR 0.78; 95% CI: 0.65-0.92), an association that remained also after adjustment for hospital and surgeon clustering.

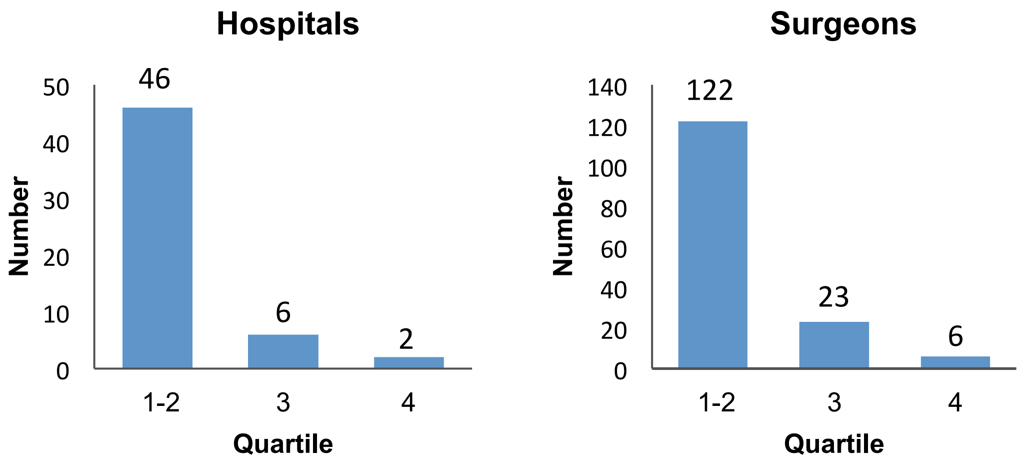

Figure 5. Number of hospitals and surgeons performing oesophagectomies between 1987-2005 in Sweden by patient quartiles. (The total does not equal the total number of hospitals and surgeons since their annual volume could vary from year to year).

9.1.3 Study IV

In total, 1,785 patients underwent surgery for oesophageal cancer in Sweden in 1987 to 2010. After exclusion of 9 (0.5%) patients who were splenectomised prior to oesophageal cancer surgery, 40 (2.3%) patients who underwent intended splenectomy, and 57 (3.2%) patients with missing surgical charts, 1,679 (94.1%) resected patients constituted the final study cohort. Splenic injury was found in 264 (15.7%) patients, of whom 120 patients (45.5%) underwent splenectomy, corresponding to 7.1% patients accidentally splenectomised in the study cohort. A total of 73 (4.4%) patients developed bacterial sepsis or meningitis during the follow-up.

Patients operated on by surgeons in the highest volume category had a lower risk of splenic injury and accidental splenectomy compared to those operated on by surgeons in the lowest volume category (OR 0.59; 95% CI: 0.43-0.82 for splenic injury and OR 0.42; 95% CI: 0.26-0.68 for accidental splenectomy; Table 3). Among patients with splenic injury, progression to splenectomy was 69% less common in patients operated on by surgeons in the highest volume category compared to those operated on by surgeons in the lowest volume category (OR 0.31; 95 CI: 0.15-0.66). The risk of accidental splenectomy decreased in more recent years, and among patients with splenic injury, a smaller proportion progressed to splenectomy in more recent years.

Table 3. Predictors of splenic injury (including accidental splenectomy) and accidental splenectomy in 1,679 patients who underwent oesophageal cancer surgery between 1987 and 2010 in Sweden, expressed as adjusted odds ratios (OR) with 95% confidence intervals (CI).

	Splenic injury Number=264		**Accidental splenectomy** Number=120	
	OR*	**95% CI**	**OR***	**95% CI**
Tumour stage				
0-I	1.00	Reference	1.00	Reference
II	1.23	0.83 – 1.82	1.55	0.83 – 2.90
III	1.36	0.88 – 2.10	1.56	0.79 – 3.11
IV	1.05	0.57 – 1.94	1.04	0.58 – 7.86
Previous upper abdominal surgery				
No	1.00	Reference	1.00	Reference
Yes	0.99	0.72 – 1.36	0.82	0.51 – 1.33
Surgeon volume and experience†				
Volume ≤median, experience ≤median	1.00	Reference	1.00	Reference
Volume ≤median, experience >median	0.98	0.64 – 1.50	0.65	0.34 – 1.24
Volume >median, experience ≤median	1.07	0.71 – 1.62	0.55	0.29 – 1.03
Volume >median, experience >median	0.58	0.41 – 0.80	0.41	0.25 – 0.66

* Sex, age, tumour stage, previous surgery, neoadjuvant therapy, radicality, surgeon volume and calendar period

†Median surgeon volume = 4 surgeries; median surgeon experience = 15 surgeries.

Accidental splenectomy was followed by an increased risk of crude overall mortality (HR 1.63; 95 CI: 1.35-1.98; Figure 6). However, this result attenuated after adjustment for confounders (HR 1.29; 95% CI: 1.03-1.61). After stratification for time, there was a 61% increased risk of mortality within the first 3 months after surgery after accounting for confounders (HR 1.61; 95% CI: 1.09-2.38), which remained after the first two weeks of surgery were excluded (HR 1.61; 95% CI: 0.99-2.59). No such association was found at longer term (>3 months after surgery) (HR 1.18; 95% CI: 0.93-1.50).

There was an increased overall risk of sepsis or meningitis after accidental splenectomy (HR 2.79, 95% CI: 1.35-5.79). This risk was evident at longer-term (HR 3.97; 95% CI: 1.99-7.93) but not such association was found at short-term (HR 0.64; 95% CI: 0.04-9.73).

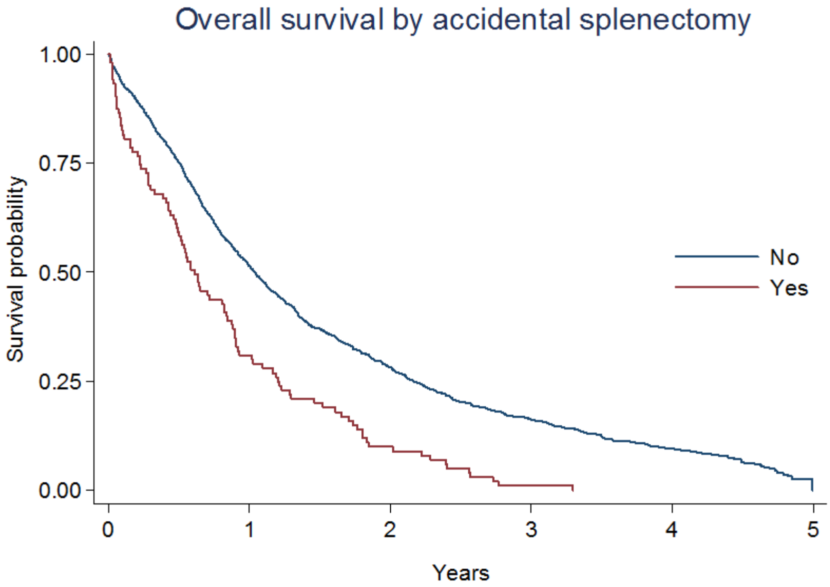

Figure 6. Kaplan-Meier survival curves after oesophagectomy among patients with and without accidental splenectomy.

10 METHODOLOGICAL CONSIDERATIONS

10.1 STUDY DESIGN

Clinical research can be either experimental or observational (nonexperimental). The ideal situation in a study is when participants in the different groups are identical in all factors except the factor under study. As such, the experimental design where individuals are assigned randomly to the groups has been considered the gold standard. However, no study design is free of bias and some argue that the hierarchical level of evidence should be based on the internal validity of the study and not its design. Nonetheless, since random allocation may be unethical (as it would be in study III), infeasible (as in study II and IV), or impractical (study I), observational studies are designed in an attempt to simulate experimental studies. The main types are cohort studies, case-control studies, cross-sectional studies and ecologic studies. All four studies in this thesis are designed as cohort studies.

In a cohort study, individuals are grouped according to the exposure (exposed and unexposed) and followed over time for occurrence of the outcome, for example HRQOL or mortality. Cohort studies are termed prospective, when the outcome occurs after the assembly and exposure of individuals, or retrospective, when the outcome occurs prior to the assembly of individuals and their exposure. Study I and II were prospective since the information on patients and exposure (oesophageal cancer surgery and postoperative complications) was collected prior to information on the outcome (HRQOL). Study III and IV were retrospective since the information on patients and exposure (surgeon and hospital volume and splenic factors) was collected after the occurrence of the outcome (mortality, splenic factors and severe infection). An advantage of a cohort design is decreased risk of selection bias; the major disadvantage is the risk of loss to follow-up, leading to missing data.

10.2 VALIDITY

Clinical research with each of its steps (study design, execution, and analysis) is a process that aims to measure the parameter under study with as little error as possible. Errors are classified as random or systematic (also named bias). A study without random error is perfectly valid and a study without systematic error is perfectly precise. Validity is categorized into internal validity, the extent to which the data measures what it is intended to measure, and external validity, the degree to which the results can be extrapolated to other settings.

There are many types of bias and these are broadly categorized as ***selection bias***, ***information bias*** and ***confounding***.

10.3 SELECTION BIAS

Selection bias commonly results from non-random sampling of controls in a case-control study. In such a setting, the association between exposure and outcome does not represent the true association in the population from which the controls were sampled. Although more rarely, selection bias can occur in cohort studies. In extreme cases, when non-participation is high, the characteristics of the participating cohort, often healthier than the average population, might result in false associations between the exposure and the outcome.[165] Such selection bias can be reduced by aiming to include every single patient in a specific geographic area. In study I and II almost all patients (90%) undergoing oesophageal cancer surgery in Sweden during the inclusion period were covered and non-participation was due to administrative difficulties or reluctance of five hospitals to participate. Study III and IV were based on the Swedish Cancer Register which has been shown to have a high completeness for oesophageal cancer. However, some operation charts (5.4% and 3.2% in study III and IV, respectively) were not retrieved for patients undergoing oesophageal cancer surgery during the inclusion period, introducing selection bias. Selection bias could occur in cohort studies if loss to follow-up is different between exposed and non-exposed cohort members.[166] In study I and II 20% of the patients did not answer the questionnaire at 6 months. However, this was mainly due to administrative issues and is thus unlikely to be related to the exposure or the outcome.

10.4 INFORMATION BIAS

Information bias, also called misclassification, arises when the information collected on the exposure or outcome or both, is incorrect among the included individuals. Information bias is called differential when the misclassification differs between the groups under study and non-differential when the misclassification does not differ between the groups. While non-differential misclassification will tend to lead to bias towards the null, differential misclassification can lead to bias in either direction.

When one uses registry data, incorrect coding of the diagnosis codes might result in measurement error. Therefore, the validity of the diagnosis codes should be ascertained when using registries as a source of data in epidemiologic studies. As long as the measurement error misclassification occurs at the same rate among the groups being compared, such misclassification will be regarded as non-differential.

In this thesis, baseline information was collected prospectively in study I and II. Information from hospital charts was collected using a predefined protocol. The study coordinator and the researchers involved made sure that the information collected was correct and complete, which should reduce such misclassification. Nonetheless, some non-differential misclassification is likely, since reporting of certain information, e.g. comorbidity, to the medical record depends on the practitioner at each hospital. In study III and IV, certain variables were assessed through the Swedish Patient Registry. In both studies, comorbidity was retrieved from the registry and could have been subject to non-differential misclassification. Information on the outcome in study IV (severe infections) was retrieved through the registry. The recording of the codes used might have differed between different hospitals, introducing non-differential misclassification. Furthermore, the codes used might not have included all events, since other, less specific codes might have been used. Finally, since the Swedish Patient Registry does not provide information about care in outpatient clinics, it is likely that information on comorbidities was not complete and therefore misclassified. However, it is unlikely that such misclassification was dependent on the outcome, i.e. postoperative death or development of severe infections.

10.5 CONFOUNDING

Confounding occurs when a third factor, which is associated with both exposure and the outcome without being an intermediate step in the exposure-outcome association, spuriously influences the risk estimates. If the effect of such confounders is not accounted for, the observed association will be incorrect. In the studies included in this thesis, we had access to information on all the main established factors that affect outcome after oesophageal cancer surgery at both short and long-term. However, we cannot rule out that there might be some residual confounding by different life-style factors, such as body mass index or smoking.

10.6 PRECISION

Precision denotes the amount of random error in a study, i.e. higher random error equals lower precision. Random error can be reduced by increasing the study sample and is presented with confidence interval (CI) and p-value. Assuming the absence of systematic errors, a 95% confidence interval indicates that replication of the particular study would provide a point estimate included in the CI 95% of the time. Under the same assumption, the P-value is the probability of seeing the observed difference, or greater, just by chance if the null hypothesis is true. The null hypothesis could be rejected when it is true, i.e. type I error, or not rejected when it is false, i.e. type II error.

The studies included in this thesis had to answer the study hypothesis with good precision (limited risk of type II error). The role of incorrect chance findings (type I error) in the thesis work were minimized by using clear predefined hypotheses, having large cohorts and using only clinically relevant factors in the multivariable analyses, thus counteracting multiple testing.

10.7 HRQOL ASSESSMENTS

10.7.1 Interpretation

The p-value is both related to the effect size and the size of the study. Therefore, with a large sample the p-value might be significant even when the magnitude of the difference is small. A significant p-value does not automatically signify clinical importance.

Minimal clinically important difference (MCID) was initially defined as “the smallest difference in score in the domain of interest which patients perceive as beneficial and which would mandate, in the absence of troublesome side effects and excessive costs, a change in the patient’s management”.[167] Two typical methods used for assessment of MCID are the distribution-based approach, which is based on statistical distribution of the results, and the anchor-based approach, which uses an external criterion, e.g. patients or clinicians. The MCID of 10 points in mean scores used in study I and II was based on two landmark studies by Osoba and King published in the late 1990s.[168, 169] Both studies included patients with different cancer types and suggested a clinical significance for a 10 point mean score difference for the HRQOL aspects in the EORTC QLQ-C30. Two recently large studies, also including patients with different cancer types, assessed MCID for each HRQOL aspect pertaining to comparisons between groups of patients and in patients over time, respectively. The MCID was shown to vary among HRQOL aspects and for improved and deteriorated HRQOL in both of these studies.[170, 171]

10.7.2 Response shift

Response shift is a change in the meaning of an individual's self-evaluation and can occur whenever any self-reported measure is assessed over time. The term was coined in research concerning educational training interventions and organizational change.[172, 173] The original definition included recalibration and reconceptualization, but Sprangers and Schwartz added reprioritizing.[174] Recalibration is a change in the internal standard of measurement (for example after experiencing a kidney stone a patient's rating the pain in his/her bruised knee might change from 6/10 to 3/10).[175] Reconceptualization is a redefinition of the target constructs (for example a patient with a newly acquired disability defines the term independence as being able to use assistive devices rather than being completely autonomous).[175] Reprioritization is a change in the values (for example a person who initially valued physical function more than family interaction might change this order after a health scare).[176]

In their theoretical model, Sprangers and Schwartz present how response shift affects HRQOL outcomes as a consequence of change in an individual's health status. The model starts with the change in health status (catalyst) which prompts an adaptation through behavioural, cognitive, or affective processes (mechanism). These processes interact with characteristics of the individual such as personality or gender and may lead to response shift and in turn change in perceived HRQOL.

The "then test" is the most widely used method to assess response shift.[177] To date, no study has investigated response shift in patients with oesophageal cancer. The direction and magnitude of response shift remains to be determined.[178]

11 GENERAL DISCUSSION

11.1 STUDY I – HRQOL RECOVERY AT LONG-TERM

For most patients, HRQOL remained stable or improved over time after surgery for oesophageal cancer, and their HRQOL became comparable to that of the background population. However, for each aspect of HRQOL, a subgroup of patients did not recover. The reason for this finding is unknown.

Reflux is caused by changes in the anatomy of the gastro-oesophageal junction during oesophageal cancer surgery, including decrease or loss of function of the lower oesophageal sphincter.[179] While preventive surgical procedures, such as fundoplication during the oesophageal cancer resection, have been used to decrease the risk of reflux, a recent study did not show any benefit of antireflux procedures.[180] A recent trial reported that patients given narrow gastric tube reconstruction experienced less trouble with reflux at one year after the operation than patients given whole stomach reconstruction.[181]

Fatigue is a common problem for cancer survivors. Physiological and psychological mechanisms, e.g. altered immune system,[182] have been identified. Genetic factors, such as cytokine polymorphisms, might also contribute to differences in HRQOL outcomes.[183] Comorbidities, such as anaemia, could also contribute to fatigue symptoms.[184]

11.2 STUDY II – POSTOPERATIVE COMPLICATIONS AND HRQOL

Major postoperative complications had a long-lasting effect on some HRQOL outcomes in this thesis. Dyspnoea, eating restrictions, and fatigue were worse over all three assessment points in patients with postoperative complications. It is noteworthy that postoperative complications, while exerting an apparent physiological change during a short time, continue to influence HRQOL outcomes at longer term. However, there are some possible explanations. Response shift might have occurred as a result of the complication and its consequences. Moreover, postoperative complications might alter physiological functions including cytokine levels which, depending on the polymorphisms described above, have differential effects on HRQOL outcomes. For example, polymorphism in IL-6 and IL-1B was shown to be associated with dyspnoea in lung cancer survivors.[185] Eating difficulties might be caused by anastomotic strictures.

Patients with major postoperative complications had more problems with choking six months after surgery; however the difference in mean score between those with and without major postoperative complications attenuated over time, suggesting recovery. Another possible explanation could be response shift.

Still five years postoperatively, patients with major postoperative complications reported more problems with reflux and sleep disturbance. Reflux has been shown to be associated with sleep problems,[186] although the direction of this association is complex and not fully understood.[187]

11.3 STUDY III – PROVIDER VOLUME AND MORTALITY

Study III showed a positive association between the surgeons' annual volume and cumulative experience on the patients' long-term survival.

To the author's knowledge, the influence of cumulative surgeon volume on mortality has not been assessed previously. Annual volume reflects how often the surgeon performed this operation, whereas cumulative volume indicates the amount of experience the surgeon has with this operation, i.e. the total number of operations performed for oesophageal cancer. Since oesophageal cancer surgery usually involves more than one surgeon, the most senior surgeon was deemed responsible for the operation. Intuitively, the more operations the surgeon performs, the more skills he/she acquires, along with improvement in "surgical judgment". In the same vein, acquired skills should be practiced if they are to be maintained. Nonetheless, in general, the definition of surgical expertise is poorly defined.[188]

There is no commonly accepted cut-off for surgeon or hospital volume. The cut-offs in study III were determined a priori and based on quartiles of oesophageal cancer surgeries. Since the lowest quartiles included very few operations, the two lowest quartiles were merged. This was done to avoid comparison of very low-volume surgeons or hospitals with high-volume surgeons or hospitals. Other cut-offs have been used in our group previously.[107, 189] While the cut-offs could be considered very low compared to the thresholds proposed by the Leapfrog group, they are comparable to other volume studies from the United States and the United Kingdom.[103, 110]

It could be argued that surgeon specialty has an effect on outcome. However, studies from the United States show contradictory findings regarding the association between thoracic surgeons and mortality in oesophageal cancer surgery due to different definitions and methodology.[190, 191] Nevertheless, results from other countries may not be generalizable to Europe, including Sweden, since oesophageal cancer surgery is performed by upper gastrointestinal surgeons specialized in oesophageal cancer rather than by thoracic surgeons.

High hospital volume seemed to decrease the risk of short-term mortality. However, this association was better explained by hospital clustering rather than volume per se, i.e. some other factors shared by the patients at high-volume hospitals explain the association. Indeed, it has been suggested that high hospital volume for a given procedure is a consequence of other factors, e.g. well-functioning intensive care units,[192] nurse staffing,[193] complication rates and rescue from complications,[194] and high volume of other surgical procedures.[195]

A debatable issue in the discussion of hospital volume is referral bias. In this study, referral bias is unlikely due to the organisation of the Swedish healthcare system. The system is publicly funded. Sweden is divided into 21 county councils, each subdivided into a number of different districts with primary healthcare centres and local hospitals. The country is also divided into six medical regions, each one connected to a large referral hospital. Patients undergoing surgery are referred to the hospital in their medical region and not to any specific surgeon.

11.4 STUDY IV – SPLENIC INJURY DURING OESOPHAGECTOMY

Study IV showed that higher surgeon volume and experience is associated with lower risk of splenic injury and accidental splenectomy. These results further support the finding in study III, indicating that high surgeon volume is associated with better outcomes. In case of splenic injury, high-volume surgeons were less likely to conduct a splenectomy on an injured spleen, but instead try to repair it. This decision requires both competence and judgment, since the surgeon must find a suitable balance between repairing an injured spleen and risk of re-bleeding. Although most injuries were minor, as judged from the operation journals, and should be managed conservatively according to the guidelines, less experienced surgeons might be more hesitant about taking measures to preserve the spleen, knowing that re-bleeding is a potential complication.

The finding that accidental splenectomy increases the risk of mortality might be explained by tumour recurrences. However, the role of the spleen in cancer is complex and bidirectional.[196] Another explanation could be mortality due to increased risk of severe infections, but there was no association between accidental splenectomy and severe infections in the short-term. However, this could be explained by a higher rate of death in the shorter term. Moreover, other codes might have been used in case of severe infections before microbiological confirmation, e.g. systemic inflammatory response syndrome.

Accidental splenectomy was associated with an increased risk of severe infections in the longer term. Splenectomized patients have a life-long increased risk of severe infections, particularly caused by encapsulated bacteria since successful removal of these bacteria is dependent on the production of immunoglobulin M antibodies by the splenic marginal B cells.[197]

12 CONCLUSIONS

- While HRQOL outcomes in most 5-year survivors of oesophageal cancer surgery recover to levels comparable to those of the general population, a clinically important subgroup of patients (15%) have long-lasting impairments in some HRQOL outcomes.

- Major postoperative complications have a long-lasting negative influence on some HRQOL outcomes.

- Long-term mortality is lower in patients with oesophageal cancer who are operated on by oesophageal cancer surgeons who have high yearly and cumulative volume.

- Patients operated on by surgeons with more experience of oesophageal cancer have a reduced risk of splenic injury and unintended splenectomy.

- Accidental splenectomy during oesophageal cancer surgery is associated with an increased risk of mortality and severe infections.

13 FUTURE RESEARCH

HRQOL research among oesophageal cancer patients is in its early infancy and there is much more to be developed. Further investigations need to be done to explain why a subgroup of patients does not recover for each HRQOL aspect. This may be explained by differences in psychosocial characteristics of the patients such as personality and coping strategies, health-seeking behaviour, and social support. Another potential explanation is various molecular and genetic factors such as CRP and single-nucleotide polymorphisms. There is a need to capture response shift, particularly when assessing HRQOL over time. Knowledge on its extent and direction would make it possible to correct for its effect. Last but not least, more work is needed to include HRQOL measurement as a routine procedure in clinical practice. Some previously acknowledged barriers, e.g. economy and time, might be overcome by computer assisted HRQOL assessments.

Future research on the volume and outcome relationship should investigate the underlying factors responsible for the survival benefit among patients operated on in high-volume hospitals. One such factor could be hospital level, which will be addressed in future studies. We are also planning a study to assess the influence of BMI and weight loss on short and long-term survival after oesophageal cancer surgery. Finally, an interesting topic is whether education of surgeons in clinical research could improve surgical quality.[198]

14 POPULÄRVETENSKAPLIG SAMMANFATTNING (SUMMARY IN SWEDISH)

14.1 BAKGRUND

Matstrupscancer är en svår cancerform som drabbar 400 personer i Sverige varje år (600 per år om cancer i övergången mellan matstrupe och magsäck räknas med). Globalt är sjukdomen den 8:e vanligaste cancerformen och den 6:e vanligaste orsaken till cancerdöd. I USA och Europa har antalet personer som insjuknar i körtelscellscancer (en av de två vanligaste cancertyperna i matstrupen) ökat kraftigt. Hos de flesta patienterna upptäcks sjukdomen i ett sent skede, eftersom tumörer i matstrupen kan växa sig stora utan att orsaka några symtom. De vanligaste symptomen är tilltagande svårigheter att svälja och viktnedgång. Hörnstenen i behandlingen är ett omfattande kirurgiskt ingrepp med stor risk för komplikationer efter operationen och nedsatt livskvalitet (t.ex. sämre global livskvalitet, försämrad fysisk funktion och mer besvär med sura uppstötningar och diarré). Av det fåtal patienter som lämpar sig för operation överlever mindre än hälften 5 år efter operationen. Det övergripande syftet med denna avhandling var att kartlägga om livskvaliteten återhämtar sig över tid efter operation för matstrupscancer, och finna faktorer som långsiktigt påverkar överlevnad och livskvalitet efter operationen.

14.2 METODER OCH RESULTAT

Syfte med **Studie I** var att kartlägga om livskvaliteten återhämtar sig hos patienter som överlevt 5 år efter matstrupscanceroperation. Data baserades på en omfattande svensk studie av nästan alla patienter som opererats för denna sjukdom mellan åren 2001 och 2005. Information om patienten, tumören och operationen insamlades kontinuerligt i samband med diagnos och behandling. Patienterna följdes upp med välbeprövade livskvalitetsenkäter 6 månader, 3 år och 5 år efter operation. Huvudenkäten, QLQ-C30, mätte generella livskvalitetsaspekter och symtom som är vanligt förekommande hos cancerpatienter i allmänhet, medan modulen QLQ-OES18 mätte symtom som är vanligt förekommande hos patienter med matstrupscancer. För att få ett referensmått på olika livskvalitetsaspekter fick ett slumpmässigt urval av den svenska befolkningen svara på samma enkäter som patienterna. Patienternas hälsa över tid kategoriserades som förbättrad, oförändrad eller försämrad. Analyserna tog hänsyn till ålder, kön och annan sjuklighet.

Huvudresultatet var att de flesta patienters globala livskvalitet, funktioner och symtom på lång sikt återgick i nivå med den svenska befolkningens. För varje livskvalitetsaspekt fanns en liten grupp patienter (ca 15%) som försämrades påtagligt över tid. Dessa hade betydligt sämre global livskvalitet, mer nedsatt fysisk och kognitiv funktion och mer besvär av symtom som halsbränna och andningssvårigheter än den svenska befolkningen.

Studie II undersökte om allvarliga komplikationer efter operation för matstrupscancer, t.ex. akut andningssvikt eller blodförgiftning, påverkar livskvaliteten på lång sikt efter operationen. Studien baserades på samma datakälla som i studie I. Analyserna tog hänsyn till ålder vid operation, kön, annan sjuklighet, typ av kirurgiskt ingrepp, tumörtyp och tumörstadium. Totalt drabbades 46 (33 %) patienter av minst en allvarlig komplikation. Dessa patienter rapporterade mer symtom på trötthet, halsbränna, sömnbesvär, andningssvårigheter och ätsvårigheter än patienter som inte drabbades av en allvarlig komplikation. Skillnaden mellan grupperna fanns sex månader efter operation och kvarstod vid femårsuppföljningen.

Studie III belyste om sjukhusets eller kirurgens erfarenhet av operation för matstrupscancer spelar roll för överlevnad på lång sikt efter operationen. Studien baserades på en nationell kirurgisk studie där patienter som opererats för matstrupscancer mellan 1987 och 2005 ingick och följdes upp till år 2011. Journaler för diagnos och operation insamlades från alla sjukhus och granskades med avseende på tumör- och behandlingsrelaterade faktorer. Analyserna tog hänsyn till alla etablerade prognostiska faktorer. Studiens huvudresultat var att patienter som opererades av kirurger som inte bara opererat många patienter utan också opererade ofta hade 22% lägre dödlighet på lång sikt jämfört med patienter som opererades av kirurger som opererat få patienter och opererade sällan. Däremot hade det årliga antalet operationer som utförts på ett sjukhus ingen oberoende betydelse för överlevnaden på lång sikt efter att hänsyn tagits till bl.a. kirurgens årliga operationsvolym.

Studie IV analyserade faktorer som skulle kunna påverka risken för mjältskada och vilka faktorer som kräver att mjälten tas bort i samband med operation för matstrupscancer. Vidare studerades risken för död och allvarliga infektioner efter borttagande av mjälten. Studien baserades på en utökad version av databasen i studie III och utgick från alla patienter som opererats i Sverige mellan 1987 till 2010 med uppföljning till 2012. Analyserna justerades för viktiga störfaktorer. Huvudresultatet var att kirurger som opererat många patienter och opererade ofta hade 42% mindre risk för mjältskador och 59% mindre risk för att mjälten avlägsnas i samband med operation för matstrupscancer. Patienter vars mjälte togs bort hade 30% ökad risk för död efter operationen och 3 gånger ökad risk för att drabbas av allvarliga infektioner.

14.3 DISKUSSION

De två första studierna visar att en undergrupp av patienter som överlever operation för matstrupscancer har fortsatt sämre livskvalitets ur olika aspekter än den svenska befolkningen och allvarliga komplikationer efter operationen bidrar till mer symtom även på lång sikt. Dessa resultat visar att patienter som opererats för matstrupscancer är i behov av en långvarig uppföljning för att hitta uppkomna problem och initiera riktade insatser.

De två sista studierna visar att patienter som opererades av erfarna kirurger har lägre dödlighet och mindre risk för mjältskada och borttagning av mjälten, vilket i sig ger ökad dödlighet och risk för infektioner. Studierna talar för att operation av matstrupscancer bör koncentreras till färre kirurger som får operera fler patienter.

15 ACKNOWLEDGMENTS

I wish to express my sincere gratitude to all those who have contributed to this thesis. A special thanks to all patients who have participated in the studies.

My sincere gratitude goes to:

Pernilla Lagergren, my main supervisor, for introducing me to clinical research and for your support, optimism and encouragement all the way! Thank you for always being open to new ideas and keeping up my interest in research!

Jesper Lagergren, my co-supervisor and head of the group, for your speediness in e-mails and support no matter of the day of the week or the time of day. Thank you for accepting me to one of the most outstanding research groups at Karolinska Institutet and for creating a highly stimulating and exceptionally well-organized research unit!

Brigitta Omazic, my mentor, for supervising me during my research project as a medical student. Thank you for fruitful discussions during the lunches and coffee breaks. You have been a true mentor to me!

Co-authors in studies within and outside this thesis for valuable comments and support. Special thanks to **Nicola Orsini** and **Asif Johar**, for your statistical expertise and fruitful discussions in the second and third study, respectively.

Margrete Gellervik, secretary and project administrator, for all your help with administrative matters and for the lovely songs for the doctoral students after their dissertation!

Ulrika Eriksson, information officer and research secretary, for expeditious help with everything from our network folders to copyright issues and for nice laughs in the corridor!

John Blomberg, consultant surgeon, for being so friendly and letting me participate in a spleen-preserving operation for my third study.

Eja Fridsta, co-ordinator of SECC. Thank you for your fast help with questions regarding the data collection.

Lizzy Leigh, for valuable and prompt editing of the included manuscripts.

Janet Holmén. Thank you for agreeing to edit this thesis at short notice. I am very grateful for your valuable comments!

All administrative personnel at MMK. Special thanks to **Jan-Erik Kaarre** and **Lennart Helleday**, IT support, for expeditious help even on Good Friday.

Former and current doctoral students in UGIR: **Anna Lindam, Carl Kilander, Emma Sverdén, Hedvig Löfdahl, Ioannis Rouvelas, Jenny Oddsberg, John Blomberg, Lena Martin, Maartje van der Schaaf, Mats Lindblad, Magdalena Plecka Östlund, Richard Shore , Therese Djärv, Tomas Sjöberg Bexelius, Wenjing Tao, Ylva Hellstadius, Yulan Lin;** and former and current researchers in the group.

To all **colleagues at the Karolinska University Hospital** in Solna for a friendly atmosphere and after-works so far during my research-internship.

All my **friends**. Thank you for being there for me when I needed it the most!

Mirjam Messo. You are the definition of great friendship. I look forward to sharing our future life moments! You will always be my Moussali Moussali!

My family, in Iran for having us visit during summer vacations when we were children!

My parents, for all your support and ecouragement! Thank you for always believing in me and being open-minded!

Leila Derogar, my sister, for all memorable moments during our childhood. Thank you for reminding me of the values in life and persuading me to visit Stockholm, if only for a day!

Mohssen Sadr-Azodi, for all the support during this journey. Thank you for all the laughs, dancing moments in the middle of my studies and for assuring me that you would help me distribute my articles if needed! I did not know that meat balls can be prepared in so many different ways! I look forward to future moments! Thank you!

Omid, my best friend! Thank you for all the stimulating discussions from research to everything else in life. I look forward to sharing the rest of my life with you!

Slutligen vill jag också tacka Karolinska Institutet för en mycket fin utbildning.

16 REFERENCES

1. Busman DC. Theodor Billroth 1829 - 1894. Acta Chir Belg 2006; 106: 743-752.
2. Hurt R. Surgical treatment of carcinoma of the oesophagus. Thorax 1991; 46: 528-535.
3. Dubecz A, Schwartz SI. Franz John A. Torek. Ann Thorac Surg 2008; 85: 1497-1499.
4. Heitmiller RF. The left thoracoabdominal incision. Ann Thorac Surg 1988; 46: 250-253.
5. Dubecz A, Kun L, Stadlhuber RJ et al. The origins of an operation: a brief history of transhiatal esophagectomy. Ann Surg 2009; 249: 535-540.
6. Tanner NC. The present position of carcinoma of the oesophagus. Postgrad Med J 1947; 23: 109-139.
7. McKeown KC. Total three-stage oesophagectomy for cancer of the oesophagus. Br J Surg 1976; 63: 259-262.
8. Cook MB, Chow WH, Devesa SS. Oesophageal cancer incidence in the United States by race, sex, and histologic type, 1977-2005. Br J Cancer 2009; 101: 855-859.
9. Schmassmann A, Oldendorf MG, Gebbers JO. Changing incidence of gastric and oesophageal cancer subtypes in central Switzerland between 1982 and 2007. Eur J Epidemiol 2009; 24: 603-609.
10. Steevens J, Botterweck AA, Dirx MJ et al. Trends in incidence of oesophageal and stomach cancer subtypes in Europe. Eur J Gastroenterol Hepatol 2010; 22: 669-678.
11. Bosetti C, Levi F, Ferlay J et al. Trends in oesophageal cancer incidence and mortality in Europe. Int J Cancer 2008; 122: 1118-1129.
12. Pera M, Manterola C, Vidal O, Grande L. Epidemiology of esophageal adenocarcinoma. J Surg Oncol 2005; 92: 151-159.
13. Edgren G, Adami HO, Weiderpass E, Nyren O. A global assessment of the oesophageal adenocarcinoma epidemic. Gut 2013.
14. Thrift AP, Whiteman DC. The incidence of esophageal adenocarcinoma continues to rise: analysis of period and birth cohort effects on recent trends. Ann Oncol 2012; 23: 3155-3162.
15. Lagergren J, Mattsson F. No further increase in the incidence of esophageal adenocarcinoma in Sweden. Int J Cancer 2011; 129: 513-516.
16. Chang L, Stefanidis D, Richardson WS et al. The role of staging laparoscopy for intraabdominal cancers: an evidence-based review. Surg Endosc 2009; 23: 231-241.
17. Hur C, Miller M, Kong CY et al. Trends in esophageal adenocarcinoma incidence and mortality. Cancer 2013; 119: 1149-1158.
18. Brown LM, Devesa SS. Epidemiologic trends in esophageal and gastric cancer in the United States. Surg Oncol Clin N Am 2002; 11: 235-256.
19. Zheng W, Jin F, Devesa SS et al. Declining incidence is greater for esophageal than gastric cancer in Shanghai, People's Republic of China. Br J Cancer 1993; 68: 978-982.
20. Lu JB, Yang WX, Liu JM et al. Trends in morbidity and mortality for oesophageal cancer in Linxian County, 1959-1983. Int J Cancer 1985; 36: 643-645.
21. Muir CS, McKinney PA. Cancer of the oesophagus: a global overview. Eur J Cancer Prev 1992; 1: 259-264.

22. Lagergren J, Bergstrom R, Lindgren A, Nyren O. Symptomatic gastroesophageal reflux as a risk factor for esophageal adenocarcinoma. N Engl J Med 1999; 340: 825-831.
23. Rubenstein JH, Taylor JB. Meta-analysis: the association of oesophageal adenocarcinoma with symptoms of gastro-oesophageal reflux. Aliment Pharmacol Ther 2010; 32: 1222-1227.
24. Spechler SJ. Barrett esophagus and risk of esophageal cancer: a clinical review. JAMA 2013; 310: 627-636.
25. Milind R, Attwood SE. Natural history of Barrett's esophagus. World J Gastroenterol 2012; 18: 3483-3491.
26. Kulig M, Nocon M, Vieth M et al. Risk factors of gastroesophageal reflux disease: methodology and first epidemiological results of the ProGERD study. J Clin Epidemiol 2004; 57: 580-589.
27. Hvid-Jensen F, Pedersen L, Drewes AM et al. Incidence of adenocarcinoma among patients with Barrett's esophagus. N Engl J Med 2011; 365: 1375-1383.
28. Lagergren J. Influence of obesity on the risk of esophageal disorders. Nat Rev Gastroenterol Hepatol 2011; 8: 340-347.
29. Hoyo C, Cook MB, Kamangar F et al. Body mass index in relation to oesophageal and oesophagogastric junction adenocarcinomas: a pooled analysis from the International BEACON Consortium. Int J Epidemiol 2012; 41: 1706-1718.
30. Turati F, Tramacere I, La Vecchia C, Negri E. A meta-analysis of body mass index and esophageal and gastric cardia adenocarcinoma. Ann Oncol 2013; 24: 609-617.
31. La Vecchia C, Negri E, Lagiou P, Trichopoulos D. Oesophageal adenocarcinoma: a paradigm of mechanical carcinogenesis? Int J Cancer 2002; 102: 269-270.
32. Lagergren J, Mattsson F, Nyren O. Gastroesophageal Reflux Does Not Alter Effects of Body Mass Index on Risk of Esophageal Adenocarcinoma. Clin Gastroenterol Hepatol 2013.
33. Howard JM, Beddy P, Ennis D et al. Associations between leptin and adiponectin receptor upregulation, visceral obesity and tumour stage in oesophageal and junctional adenocarcinoma. Br J Surg 2010; 97: 1020-1027.
34. Ogunwobi OO, Beales IL. Leptin stimulates the proliferation of human oesophageal adenocarcinoma cells via HB-EGF and Tgfalpha mediated transactivation of the epidermal growth factor receptor. Br J Biomed Sci 2008; 65: 121-127.
35. Brochu-Gaudreau K, Rehfeldt C, Blouin R et al. Adiponectin action from head to toe. Endocrine 2010; 37: 11-32.
36. Doyle SL, Donohoe CL, Finn SP et al. IGF-1 and its receptor in esophageal cancer: association with adenocarcinoma and visceral obesity. Am J Gastroenterol 2012; 107: 196-204.
37. McElholm AR, McKnight AJ, Patterson CC et al. A population-based study of IGF axis polymorphisms and the esophageal inflammation, metaplasia, adenocarcinoma sequence. Gastroenterology 2010; 139: 204-212 e203.
38. Singh S, Sharma AN, Murad MH et al. Central Adiposity is Associated with Increased Risk of Esophageal Inflammation, Metaplasia, and Adenocarcinoma: a Systematic Review and Meta-Analysis. Clin Gastroenterol Hepatol 2013.

39. Donohoe CL, Doyle SL, McGarrigle S et al. Role of the insulin-like growth factor 1 axis and visceral adiposity in oesophageal adenocarcinoma. Br J Surg 2012; 99: 387-396.
40. MacDonald K, Porter GA, Guernsey DL et al. A polymorphic variant of the insulin-like growth factor type I receptor gene modifies risk of obesity for esophageal adenocarcinoma. Cancer Epidemiol 2009; 33: 37-40.
41. Bollschweiler E, Wolfgarten E, Gutschow C, Holscher AH. Demographic variations in the rising incidence of esophageal adenocarcinoma in white males. Cancer 2001; 92: 549-555.
42. Zendehdel K, Nyren O, Luo J et al. Risk of gastroesophageal cancer among smokers and users of Scandinavian moist snuff. Int J Cancer 2008; 122: 1095-1099.
43. Whiteman DC, Sadeghi S, Pandeya N et al. Combined effects of obesity, acid reflux and smoking on the risk of adenocarcinomas of the oesophagus. Gut 2008; 57: 173-180.
44. Ye W, Held M, Lagergren J et al. Helicobacter pylori infection and gastric atrophy: risk of adenocarcinoma and squamous-cell carcinoma of the esophagus and adenocarcinoma of the gastric cardia. J Natl Cancer Inst 2004; 96: 388-396.
45. Islami F, Sheikhattari P, Ren JS, Kamangar F. Gastric atrophy and risk of oesophageal cancer and gastric cardia adenocarcinoma--a systematic review and meta-analysis. Ann Oncol 2011; 22: 754-760.
46. Anderson LA, Murphy SJ, Johnston BT et al. Relationship between Helicobacter pylori infection and gastric atrophy and the stages of the oesophageal inflammation, metaplasia, adenocarcinoma sequence: results from the FINBAR case-control study. Gut 2008; 57: 734-739.
47. Powell J, McConkey CC, Gillison EW, Spychal RT. Continuing rising trend in oesophageal adenocarcinoma. Int J Cancer 2002; 102: 422-427.
48. Terry P, Lagergren J, Ye W et al. Antioxidants and cancers of the esophagus and gastric cardia. Int J Cancer 2000; 87: 750-754.
49. Terry P, Lagergren J, Hansen H et al. Fruit and vegetable consumption in the prevention of oesophageal and cardia cancers. Eur J Cancer Prev 2001; 10: 365-369.
50. Anderson LA, Cantwell MM, Watson RG et al. The association between alcohol and reflux esophagitis, Barrett's esophagus, and esophageal adenocarcinoma. Gastroenterology 2009; 136: 799-805.
51. Pandeya N, Williams G, Green AC et al. Alcohol consumption and the risks of adenocarcinoma and squamous cell carcinoma of the esophagus. Gastroenterology 2009; 136: 1215-1224, e1211-1212.
52. Corley DA, Kerlikowske K, Verma R, Buffler P. Protective association of aspirin/NSAIDs and esophageal cancer: a systematic review and meta-analysis. Gastroenterology 2003; 124: 47-56.
53. Abnet CC, Freedman ND, Kamangar F et al. Non-steroidal anti-inflammatory drugs and risk of gastric and oesophageal adenocarcinomas: results from a cohort study and a meta-analysis. Br J Cancer 2009; 100: 551-557.
54. Chak A, Lee T, Kinnard MF et al. Familial aggregation of Barrett's oesophagus, oesophageal adenocarcinoma, and oesophagogastric junctional adenocarcinoma in Caucasian adults. Gut 2002; 51: 323-328.
55. Lagergren J, Ye W, Lindgren A, Nyren O. Heredity and risk of cancer of the esophagus and gastric cardia. Cancer Epidemiol Biomarkers Prev 2000; 9: 757-760.

56. Dhillon PK, Farrow DC, Vaughan TL et al. Family history of cancer and risk of esophageal and gastric cancers in the United States. Int J Cancer 2001; 93: 148-152.
57. Brown LM, Hoover R, Silverman D et al. Excess incidence of squamous cell esophageal cancer among US Black men: role of social class and other risk factors. Am J Epidemiol 2001; 153: 114-122.
58. Baan R, Straif K, Grosse Y et al. Carcinogenicity of alcoholic beverages. Lancet Oncol 2007; 8: 292-293.
59. Yang SJ, Wang HY, Li XQ et al. Genetic polymorphisms of ADH2 and ALDH2 association with esophageal cancer risk in southwest China. World J Gastroenterol 2007; 13: 5760-5764.
60. Akhtar S, Sheikh AA, Qureshi HU. Chewing areca nut, betel quid, oral snuff, cigarette smoking and the risk of oesophageal squamous-cell carcinoma in South Asians: a multicentre case-control study. Eur J Cancer 2012; 48: 655-661.
61. Lagergren J, Bergstrom R, Lindgren A, Nyren O. The role of tobacco, snuff and alcohol use in the aetiology of cancer of the oesophagus and gastric cardia. Int J Cancer 2000; 85: 340-346.
62. Gammon MD, Schoenberg JB, Ahsan H et al. Tobacco, alcohol, and socioeconomic status and adenocarcinomas of the esophagus and gastric cardia. J Natl Cancer Inst 1997; 89: 1277-1284.
63. Abnet CC, Qiao YL, Mark SD et al. Prospective study of tooth loss and incident esophageal and gastric cancers in China. Cancer Causes Control 2001; 12: 847-854.
64. Islami F, Pourshams A, Nasrollahzadeh D et al. Tea drinking habits and oesophageal cancer in a high risk area in northern Iran: population based case-control study. BMJ 2009; 338: b929.
65. Islami F, Ren JS, Taylor PR, Kamangar F. Pickled vegetables and the risk of oesophageal cancer: a meta-analysis. Br J Cancer 2009; 101: 1641-1647.
66. Wang M, Song H, Chen WQ et al. Cancer mortality in a Chinese population surrounding a multi-metal sulphide mine in Guangdong province: an ecologic study. BMC Public Health 2011; 11: 319.
67. Gatto NM, Kelsh MA, Mai DH et al. Occupational exposure to hexavalent chromium and cancers of the gastrointestinal tract: a meta-analysis. Cancer Epidemiol 2010; 34: 388-399.
68. Sandler RS, Nyren O, Ekbom A et al. The risk of esophageal cancer in patients with achalasia. A population-based study. JAMA 1995; 274: 1359-1362.
69. Leeuwenburgh I, Scholten P, Alderliesten J et al. Long-term esophageal cancer risk in patients with primary achalasia: a prospective study. Am J Gastroenterol 2010; 105: 2144-2149.
70. Csikos M, Horvath O, Petri A et al. Late malignant transformation of chronic corrosive oesophageal strictures. Langenbecks Arch Chir 1985; 365: 231-238.
71. Ellis A, Field JK, Field EA et al. Tylosis associated with carcinoma of the oesophagus and oral leukoplakia in a large Liverpool family--a review of six generations. Eur J Cancer B Oral Oncol 1994; 30B: 102-112.
72. Risk JM, Mills HS, Garde J et al. The tylosis esophageal cancer (TOC) locus: more than just a familial cancer gene. Dis Esophagus 1999; 12: 173-176.
73. Boeing H, Dietrich T, Hoffmann K et al. Intake of fruits and vegetables and risk of cancer of the upper aero-digestive tract: the prospective EPIC-study. Cancer Causes Control 2006; 17: 957-969.

74. Daly JM, Fry WA, Little AG et al. Esophageal cancer: results of an American College of Surgeons Patient Care Evaluation Study. J Am Coll Surg 2000; 190: 562-572; discussion 572-563.
75. Strong VE, D'Amico TA, Kleinberg L, Ajani J. Impact of the 7th Edition AJCC staging classification on the NCCN clinical practice guidelines in oncology for gastric and esophageal cancers. J Natl Compr Canc Netw 2013; 11: 60-66.
76. Bruzzi JF, Munden RF, Truong MT et al. PET/CT of esophageal cancer: its role in clinical management. Radiographics 2007; 27: 1635-1652.
77. Puli SR, Reddy JB, Bechtold ML et al. Staging accuracy of esophageal cancer by endoscopic ultrasound: a meta-analysis and systematic review. World J Gastroenterol 2008; 14: 1479-1490.
78. Ferlay J, Shin HR, Bray F et al. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. Int J Cancer 2010; 127: 2893-2917.
79. Coupland VH, Lagergren J, Luchtenborg M et al. Hospital volume, proportion resected and mortality from oesophageal and gastric cancer: a population-based study in England, 2004-2008. Gut 2013; 62: 961-966.
80. Rutegard M, Charonis K, Lu Y et al. Population-based esophageal cancer survival after resection without neoadjuvant therapy: an update. Surgery 2012; 152: 903-910.
81. Hulscher JB, Tijssen JG, Obertop H, van Lanschot JJ. Transthoracic versus transhiatal resection for carcinoma of the esophagus: a meta-analysis. Ann Thorac Surg 2001; 72: 306-313.
82. Chu KM, Law SY, Fok M, Wong J. A prospective randomized comparison of transhiatal and transthoracic resection for lower-third esophageal carcinoma. Am J Surg 1997; 174: 320-324.
83. Goldminc M, Maddern G, Le Prise E et al. Oesophagectomy by a transhiatal approach or thoracotomy: a prospective randomized trial. Br J Surg 1993; 80: 367-370.
84. Hulscher JB, van Sandick JW, de Boer AG et al. Extended transthoracic resection compared with limited transhiatal resection for adenocarcinoma of the esophagus. N Engl J Med 2002; 347: 1662-1669.
85. Omloo JM, Lagarde SM, Hulscher JB et al. Extended transthoracic resection compared with limited transhiatal resection for adenocarcinoma of the mid/distal esophagus: five-year survival of a randomized clinical trial. Ann Surg 2007; 246: 992-1000; discussion 1000-1001.
86. Biere SS, van Berge Henegouwen MI, Maas KW et al. Minimally invasive versus open oesophagectomy for patients with oesophageal cancer: a multicentre, open-label, randomised controlled trial. Lancet 2012; 379: 1887-1892.
87. Parameswaran R, Blazeby JM, Hughes R et al. Health-related quality of life after minimally invasive oesophagectomy. Br J Surg 2010; 97: 525-531.
88. Nafteux P, Moons J, Coosemans W et al. Minimally invasive oesophagectomy: a valuable alternative to open oesophagectomy for the treatment of early oesophageal and gastro-oesophageal junction carcinoma. Eur J Cardiothorac Surg 2011; 40: 1455-1463; discussion 1463-1454.
89. Parameswaran R, Titcomb DR, Blencowe NS et al. Assessment and comparison of recovery after open and minimally invasive esophagectomy for cancer: an exploratory study in two centers. Ann Surg Oncol 2013; 20: 1970-1977.
90. Rice TW. Commentary: Esophageal carcinoma confined to the wall--the need for immediate definitive therapy. J Thorac Cardiovasc Surg 1999; 117: 26-27.
91. Leers JM, DeMeester SR, Oezcelik A et al. The prevalence of lymph node metastases in patients with T1 esophageal adenocarcinoma a retrospective review of esophagectomy specimens. Ann Surg 2011; 253: 271-278.

92. Hiranyatheb P, Osugi H. Radical lymphadenectomy in esophageal cancer: from the past to the present. Dis Esophagus 2013.
93. Nishihira T, Hirayama K, Mori S. A prospective randomized trial of extended cervical and superior mediastinal lymphadenectomy for carcinoma of the thoracic esophagus. Am J Surg 1998; 175: 47-51.
94. Tong D, Law S. Extended Lymphadenectomy in Esophageal Cancer is Crucial. World J Surg 2013; 37: 1751-1756.
95. Allum WH, Stenning SP, Bancewicz J et al. Long-term results of a randomized trial of surgery with or without preoperative chemotherapy in esophageal cancer. J Clin Oncol 2009; 27: 5062-5067.
96. Sjoquist KM, Burmeister BH, Smithers BM et al. Survival after neoadjuvant chemotherapy or chemoradiotherapy for resectable oesophageal carcinoma: an updated meta-analysis. Lancet Oncol 2011; 12: 681-692.
97. van Hagen P, Hulshof MC, van Lanschot JJ et al. Preoperative chemoradiotherapy for esophageal or junctional cancer. N Engl J Med 2012; 366: 2074-2084.
98. Zhang SS, Yang H, Xie X et al. Adjuvant chemotherapy versus surgery alone for esophageal squamous cell carcinoma: a meta-analysis of randomized controlled trials and nonrandomized studies. Dis Esophagus 2013.
99. Luft HS, Bunker JP, Enthoven AC. Should operations be regionalized? The empirical relation between surgical volume and mortality. N Engl J Med 1979; 301: 1364-1369.
100. Birkmeyer JD, Siewers AE, Finlayson EV et al. Hospital volume and surgical mortality in the United States. N Engl J Med 2002; 346: 1128-1137.
101. Begg CB, Cramer LD, Hoskins WJ, Brennan MF. Impact of hospital volume on operative mortality for major cancer surgery. JAMA 1998; 280: 1747-1751.
102. Finlayson EV, Goodney PP, Birkmeyer JD. Hospital volume and operative mortality in cancer surgery: a national study. Arch Surg 2003; 138: 721-725; discussion 726.
103. Birkmeyer JD, Stukel TA, Siewers AE et al. Surgeon volume and operative mortality in the United States. N Engl J Med 2003; 349: 2117-2127.
104. Bachmann MO, Alderson D, Edwards D et al. Cohort study in South and West England of the influence of specialization on the management and outcome of patients with oesophageal and gastric cancers. Br J Surg 2002; 89: 914-922.
105. Simunovic M, Rempel E, Theriault ME et al. Influence of hospital characteristics on operative death and survival of patients after major cancer surgery in Ontario. Can J Surg 2006; 49: 251-258.
106. Birkmeyer JD, Sun Y, Wong SL, Stukel TA. Hospital volume and late survival after cancer surgery. Ann Surg 2007; 245: 777-783.
107. Rouvelas I, Lindblad M, Zeng W et al. Impact of hospital volume on long-term survival after esophageal cancer surgery. Arch Surg 2007; 142: 113-117; discussion 118.
108. van de Poll-Franse LV, Lemmens VE, Roukema JA et al. Impact of concentration of oesophageal and gastric cardia cancer surgery on long-term population-based survival. Br J Surg 2011; 98: 956-963.
109. Dikken JL, Dassen AE, Lemmens VE et al. Effect of hospital volume on postoperative mortality and survival after oesophageal and gastric cancer surgery in the Netherlands between 1989 and 2009. Eur J Cancer 2012; 48: 1004-1013.
110. Gillison EW, Powell J, McConkey CC, Spychal RT. Surgical workload and outcome after resection for carcinoma of the oesophagus and cardia. Br J Surg 2002; 89: 344-348.

111. Sundelof M, Lagergren J, Ye W. Surgical factors influencing outcomes in patients resected for cancer of the esophagus or gastric cardia. World J Surg 2008; 32: 2357-2365.
112. Lord MD, Gourevitch A. The Peritoneal Anatomy of the Spleen, with Special Reference to the Operation of Partial Gastrectomy. Br J Surg 1965; 52: 202-204.
113. Kyriazanos ID, Tachibana M, Yoshimura H et al. Impact of splenectomy on the early outcome after oesophagectomy for squamous cell carcinoma of the oesophagus. Eur J Surg Oncol 2002; 28: 113-119.
114. Gockel I, Kneist W, Junginger T. Influence of splenectomy on perioperative morbidity and long-term survival after esophagectomy in patients with esophageal carcinoma. Dis Esophagus 2005; 18: 311-315.
115. Black E, Niamat J, Boddu S et al. Unplanned splenectomy during oesophagectomy does not affect survival. Eur J Cardiothorac Surg 2006; 29: 244-247.
116. Aminian A, Mirsharifi R, Karimian F et al. Influence of splenectomy on morbidity of esophageal cancer surgery. Scand J Surg 2010; 99: 9-13.
117. Dowdall JF, McAnena OJ. Linear stapling of the short gastric vessels reduces blood loss and splenectomy at oesophageal and gastric surgery. Surg Endosc 2006; 20: 770-772.
118. Fayers P, Machin D. Quality of life: The assessment, analysis and interpretation of patient-reported outcomes. John Wiley & Sons Ltd 2007.
119. Preamble to the Constitution of the World Health Organization as adopted by the International Health Conference, New York, Official Records of the World Health Organization, no. 2, page 100. 1948.
120. Sneeuw KC, Sprangers MA, Aaronson NK. The role of health care providers and significant others in evaluating the quality of life of patients with chronic disease. J Clin Epidemiol 2002; 55: 1130-1143.
121. Blazeby JM, Williams MH, Alderson D, Farndon JR. Observer variation in assessment of quality of life in patients with oesophageal cancer. Br J Surg 1995; 82: 1200-1203.
122. US Department of Health and Human Services Food and Drug Administration. Guidance for Industry. Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims. In. 2009.
123. Blazeby JM, Alderson D, Farndon JR. Quality of life in patients with oesophageal cancer. Recent Results Cancer Res 2000; 155: 193-204.
124. Bakas T, McLennon SM, Carpenter JS et al. Systematic review of health-related quality of life models. Health Qual Life Outcomes 2012; 10: 134.
125. Wilson IB, Cleary PD. Linking clinical variables with health-related quality of life. A conceptual model of patient outcomes. JAMA 1995; 273: 59-65.
126. Lagergren P, Avery KN, Hughes R et al. Health-related quality of life among patients cured by surgery for esophageal cancer. Cancer 2007; 110: 686-693.
127. Avery KN, Metcalfe C, Barham CP et al. Quality of life during potentially curative treatment for locally advanced oesophageal cancer. Br J Surg 2007; 94: 1369-1376.
128. Viklund P, Wengstrom Y, Rouvelas I et al. Quality of life and persisting symptoms after oesophageal cancer surgery. Eur J Cancer 2006; 42: 1407-1414.
129. Fang FM, Tsai WL, Chiu HC et al. Quality of life as a survival predictor for esophageal squamous cell carcinoma treated with radiotherapy. Int J Radiat Oncol Biol Phys 2004; 58: 1394-1404.

130. Healy LA, Ryan AM, Moore J et al. Health-related quality of life assessment at presentation may predict complications and early relapse in patients with localized cancer of the esophagus. Dis Esophagus 2008; 21: 522-528.
131. de Boer AG, van Lanschot JJ, van Sandick JW et al. Quality of life after transhiatal compared with extended transthoracic resection for adenocarcinoma of the esophagus. J Clin Oncol 2004; 22: 4202-4208.
132. Blazeby JM, Farndon JR, Donovan J, Alderson D. A prospective longitudinal study examining the quality of life of patients with esophageal carcinoma. Cancer 2000; 88: 1781-1787.
133. Gockel I, Gonner U, Domeyer M et al. Long-term survivors of esophageal cancer: disease-specific quality of life, general health and complications. J Surg Oncol 2010; 102: 516-522.
134. Reynolds JV, McLaughlin R, Moore J et al. Prospective evaluation of quality of life in patients with localized oesophageal cancer treated by multimodality therapy or surgery alone. Br J Surg 2006; 93: 1084-1090.
135. Blazeby JM, Sanford E, Falk SJ et al. Health-related quality of life during neoadjuvant treatment and surgery for localized esophageal carcinoma. Cancer 2005; 103: 1791-1799.
136. Barbour AP, Lagergren P, Hughes R et al. Health-related quality of life among patients with adenocarcinoma of the gastro-oesophageal junction treated by gastrectomy or oesophagectomy. Br J Surg 2008; 95: 80-84.
137. Moraca RJ, Low DE. Outcomes and health-related quality of life after esophagectomy for high-grade dysplasia and intramucosal cancer. Arch Surg 2006; 141: 545-549; discussion 549-551.
138. De Boer AG, Genovesi PI, Sprangers MA et al. Quality of life in long-term survivors after curative transhiatal oesophagectomy for oesophageal carcinoma. Br J Surg 2000; 87: 1716-1721.
139. McLarty AJ, Deschamps C, Trastek VF et al. Esophageal resection for cancer of the esophagus: long-term function and quality of life. Ann Thorac Surg 1997; 63: 1568-1572.
140. Deschamps C, Nichols FC, 3rd, Cassivi SD et al. Long-term function and quality of life after esophageal resection for cancer and Barrett's. Surg Clin North Am 2005; 85: 649-656, xi.
141. Djarv T, Lagergren J, Blazeby JM, Lagergren P. Long-term health-related quality of life following surgery for oesophageal cancer. Br J Surg 2008; 95: 1121-1126.
142. Donohoe CL, McGillycuddy E, Reynolds JV. Long-term health-related quality of life for disease-free esophageal cancer patients. World J Surg 2011; 35: 1853-1860.
143. Scarpa M, Saadeh LM, Fasolo A et al. Health-related quality of life in patients with oesophageal cancer: analysis at different steps of the treatment pathway. J Gastrointest Surg 2013; 17: 421-433.
144. Djarv T, Blazeby JM, Lagergren P. Predictors of postoperative quality of life after esophagectomy for cancer. J Clin Oncol 2009; 27: 1963-1968.
145. McKernan M, McMillan DC, Anderson JR et al. The relationship between quality of life (EORTC QLQ-C30) and survival in patients with gastro-oesophageal cancer. Br J Cancer 2008; 98: 888-893.
146. Parameswaran R, McNair A, Avery KN et al. The role of health-related quality of life outcomes in clinical decision making in surgery for esophageal cancer: a systematic review. Ann Surg Oncol 2008; 15: 2372-2379.

147. Schmidt CE, Bestmann B, Kuchler T et al. Quality of life associated with surgery for esophageal cancer: differences between collar and intrathoracic anastomoses. World J Surg 2004; 28: 355-360.
148. Wang H, Tan L, Feng M et al. Comparison of the short-term health-related quality of life in patients with esophageal cancer with different routes of gastric tube reconstruction after minimally invasive esophagectomy. Qual Life Res 2011; 20: 179-189.
149. Viklund P, Lindblad M, Lagergren J. Influence of surgery-related factors on quality of life after esophageal or cardia cancer resection. World J Surg 2005; 29: 841-848.
150. Rutegard M, Lagergren J, Rouvelas I et al. Population-based study of surgical factors in relation to health-related quality of life after oesophageal cancer resection. Br J Surg 2008; 95: 592-601.
151. Headrick JR, Nichols FC, 3rd, Miller DL et al. High-grade esophageal dysplasia: long-term survival and quality of life after esophagectomy. Ann Thorac Surg 2002; 73: 1697-1702; discussion 1702-1693.
152. Derogar M, van der Schaaf M, Lagergren P. Reference values for the EORTC QLQ-C30 quality of life questionnaire in a random sample of the Swedish population. Acta Oncol 2012; 51: 10-16.
153. Lindblad M, Ye W, Lindgren A, Lagergren J. Disparities in the classification of esophageal and cardia adenocarcinomas and their influence on reported incidence rates. Ann Surg 2006; 243: 479-485.
154. Ljung R, Ruck C, Mattsson F et al. Selective serotonin reuptake inhibitors and the risk of acute pancreatitis: a Swedish population-based case-control study. J Clin Psychopharmacol 2012; 32: 336-340.
155. The Swedish National Board of Health and Welfare: Swedish Causes of Death Register - Bortfall och kvalitet i dödsorsaksregistret. . In.
156. Aaronson NK, Ahmedzai S, Bergman B et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst 1993; 85: 365-376.
157. Osoba D, Zee B, Pater J et al. Psychometric properties and responsiveness of the EORTC quality of Life Questionnaire (QLQ-C30) in patients with breast, ovarian and lung cancer. Qual Life Res 1994; 3: 353-364.
158. Ringdal K, Ringdal GI, Kaasa S et al. Assessing the consistency of psychometric properties of the HRQoL scales within the EORTC QLQ-C30 across populations by means of the Mokken Scaling Model. Qual Life Res 1999; 8: 25-43.
159. Groenvold M, Klee MC, Sprangers MA, Aaronson NK. Validation of the EORTC QLQ-C30 quality of life questionnaire through combined qualitative and quantitative assessment of patient-observer agreement. J Clin Epidemiol 1997; 50: 441-450.
160. Hjermstad MJ, Fossa SD, Bjordal K, Kaasa S. Test/retest study of the European Organization for Research and Treatment of Cancer Core Quality-of-Life Questionnaire. J Clin Oncol 1995; 13: 1249-1254.
161. Blazeby JM, Conroy T, Hammerlid E et al. Clinical and psychometric validation of an EORTC questionnaire module, the EORTC QLQ-OES18, to assess quality of life in patients with oesophageal cancer. Eur J Cancer 2003; 39: 1384-1394.
162. Lagergren P, Johar AM, Lagergren J. Validation of the reflux scale in the European Organisation for Research and Treatment of Cancer QLQ-OES18. Eur J Cancer 2013; 49: 1097-1103.

163. Gutierrez R. Parametric frailty and shared frailty survival models. Stata J 2002; 2: 22-44.
164. Akaike H. A new look at the statistical model identification. IEEE Trans Automatic Control 1974; 19: 716–723.
165. Hernan MA, Hernandez-Diaz S, Robins JM. A structural approach to selection bias. Epidemiology 2004; 15: 615-625.
166. Kristman V, Manno M, Cote P. Loss to follow-up in cohort studies: how much is too much? Eur J Epidemiol 2004; 19: 751-760.
167. Jaeschke R, Guyatt G, Meade M. Evidence-based practice: what it is, why we need it. Adv Wound Care 1998; 11: 214-218.
168. Osoba D, Rodrigues G, Myles J et al. Interpreting the significance of changes in health-related quality-of-life scores. J Clin Oncol 1998; 16: 139-144.
169. King MT. The interpretation of scores from the EORTC quality of life questionnaire QLQ-C30. Qual Life Res 1996; 5: 555-567.
170. Cocks K, King MT, Velikova G et al. Evidence-based guidelines for determination of sample size and interpretation of the European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30. J Clin Oncol 2011; 29: 89-96.
171. Cocks K, King MT, Velikova G et al. Evidence-based guidelines for interpreting change scores for the European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30. Eur J Cancer 2012; 48: 1713-1721.
172. Golembiewski RT, Munzenrider RF. Burnout as an indicator of gamma change, I: Methodological perspectives on a crucial surrogacy. J Health Hum Resour Adm 1988; 11: 218-248.
173. Howard G, Dailey P. Response shift bias: a source of contamination of self-report measures. Journal of Applied Psychology 1979; 64.
174. Sprangers MA, Schwartz CE. Integrating response shift into health-related quality of life research: a theoretical model. Soc Sci Med 1999; 48: 1507-1515.
175. Howard JS, Mattacola CG, Howell DM, Lattermann C. Response shift theory: an application for health-related quality of life in rehabilitation research and practice. J Allied Health 2011; 40: 31-38.
176. Barclay-Goddard R, Epstein JD, Mayo NE. Response shift: a brief overview and proposed research priorities. Qual Life Res 2009; 18: 335-346.
177. Hamidou Z, Dabakuyo TS, Bonnetain F. Impact of response shift on longitudinal quality-of-life assessment in cancer clinical trials. Expert Rev Pharmacoecon Outcomes Res 2011; 11: 549-559.
178. Schwartz CE, Bode R, Repucci N et al. The clinical significance of adaptation to changing health: a meta-analysis of response shift. Qual Life Res 2006; 15: 1533-1550.
179. Aly A, Jamieson GG. Reflux after oesophagectomy. Br J Surg 2004; 91: 137-141.
180. van der Schaaf M, Johar A, Lagergren P et al. Surgical Prevention of Reflux after Esophagectomy for Cancer. Ann Surg Oncol 2013.
181. Zhang M, Wu QC, Li Q et al. Comparison of the Health-related Quality of Life in Patients with Narrow Gastric Tube and Whole Stomach Reconstruction after Oncologic Esophagectomy: A Prospective Randomized Study. Scand J Surg 2013; 102: 77-82.
182. Bower JE, Ganz PA, Aziz N et al. T-cell homeostasis in breast cancer survivors with persistent fatigue. J Natl Cancer Inst 2003; 95: 1165-1168.

183. Reyes-Gibby CC, Wu X, Spitz M et al. Molecular epidemiology, cancer-related symptoms, and cytokines pathway. Lancet Oncol 2008; 9: 777-785.
184. Mitchell SA. Cancer-related fatigue: state of the science. PM R 2010; 2: 364-383.
185. Rausch SM, Clark MM, Patten C et al. Relationship between cytokine gene single nucleotide polymorphisms and symptom burden and quality of life in lung cancer survivors. Cancer 2010; 116: 4103-4113.
186. Lindam A, Jansson C, Nordenstedt H et al. A population-based study of gastroesophageal reflux disease and sleep problems in elderly twins. PLoS One 2012; 7: e48602.
187. Dent J, Holloway RH, Eastwood PR. Systematic review: relationships between sleep and gastro-oesophageal reflux. Aliment Pharmacol Ther 2013; 38: 657-673.
188. Alderson D. Developing expertise in surgery. Med Teach 2010; 32: 830-836.
189. Rouvelas I, Jia C, Viklund P et al. Surgeon volume and postoperative mortality after oesophagectomy for cancer. Eur J Surg Oncol 2007; 33: 162-168.
190. Dimick JB, Goodney PP, Orringer MB, Birkmeyer JD. Specialty training and mortality after esophageal cancer resection. Ann Thorac Surg 2005; 80: 282-286.
191. Gopaldas RR, Bhamidipati CM, Dao TK, Markley JG. Impact of surgeon demographics and technique on outcomes after esophageal resections: a nationwide study. Ann Thorac Surg 2013; 95: 1064-1069.
192. Levy MM, Rapoport J, Lemeshow S et al. Association between critical care physician management and patient mortality in the intensive care unit. Ann Intern Med 2008; 148: 801-809.
193. Kanai-Pak M, Aiken LH, Sloane DM, Poghosyan L. Poor work environments and nurse inexperience are associated with burnout, job dissatisfaction and quality deficits in Japanese hospitals. J Clin Nurs 2008; 17: 3324-3329.
194. Almoudaris AM, Mamidanna R, Bottle A et al. Failure to rescue patients after reintervention in gastroesophageal cancer surgery in England. JAMA Surg 2013; 148: 272-276.
195. Allareddy V, Allareddy V, Konety BR. Specificity of procedure volume and in-hospital mortality association. Ann Surg 2007; 246: 135-139.
196. Prehn RT. The paradoxical effects of splenectomy on tumor growth. Theor Biol Med Model 2006; 3: 23.
197. Di Sabatino A, Carsetti R, Corazza GR. Post-splenectomy and hyposplenic states. Lancet 2011; 378: 86-97.
198. Soreide K, Alderson D, Bergenfelz A et al. Strategies to improve clinical research in surgery through international collaboration. Lancet 2013; 382: 1140-1151.