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

IMPROVING SURGICAL THERAPY FOR OESOPHAGEAL CANCER

Sheraz Rehan Markar

Karolinska Institutet

Stockholm 2018

Published by Karolinska Institutet.

ISBN 978-91-7831-122-4
Printed by E-Print AB 2017

Improving surgical therapy for oesophageal cancer

THESIS FOR DOCTORAL DEGREE (Ph.D.)

By

Sheraz Rehan Markar

Principal Supervisor:
Professor Jesper Lagergren
Karolinska Institutet, Stockholm, Sweden
Department of Molecular medicine and Surgery

Co-supervisor(s):
Professor Mark I. van Berge Henegouwen
Academic Medical Center, Amsterdam,
The Netherlands
Department of Surgery

Professor Christophe Mariette (deceased)
University Hospital Claude Huriez, Lille, France
Department of Digestive and Oncological Surgery

Opponent:
Professor Lorenzo Ferri
McGill University, Montreal
Department of Surgery

Examination Board (alphabetic order):
Professor Kamila Czene
Karolinska Institutet, Stockholm, Sweden
Department of Medical Epidemiology and Biostatistics

Associate Professor Jakob Hedberg
Uppsala University, Uppsala, Sweden
Department of Surgical Sciences

Adjunct Professor Jan Johansson
Lund University, Lund, Sweden
Department of Clinical Sciences

ABSTRACT

Despite advances in multimodality treatment, surgery remains the mainstay of curative treatment for oesophageal cancer. However short- and long-term mortality from oesophagectomy for oesophageal cancer still shows large variations nationally and internationally.

This thesis addresses three themes concerning oesophageal cancer surgery. The first theme focuses on technical challenges, learning in surgery and the influence of surgeon age on outcomes from oesophagectomy. **Study I** utilised a large French multi-centre database (FREGAT), and showed in contrast to previous smaller single-centre studies, salvage oesophagectomy after definitive chemoradiotherapy can offer acceptable short- and long-term outcomes in selected patients at experienced oesophageal cancer centres. **Study II** used a national Swedish dataset (SESS) and demonstrated that the period during which surgeons gain proficiency in performing oesophagectomy for cancer is associated with substantial adverse effects upon short- and long-term mortality at a national level. The length of the proficiency gain period was longer for long-term mortality than for short-term mortality, implying a change in surgeon focus during the initial stages of their independent practice. **Study III** also used the SESS and was able to show the optimal surgeon age in performing oesophagectomy in Sweden is between 51 and 56 years. Outside of this age period, increases in short- and long-term mortality are noted, as surgeons are still gaining experience or maybe experiencing decline in their technical abilities.

The second theme, sought to evaluate the effect of hospital factors, which may affect outcome from oesophagectomy for cancer. **Study IV** used SESS once more, and showed surgery performed in university hospitals has no improvements in long-term mortality from oesophagectomy after adjustment for surgeon volume and other confounders.

The third theme of this thesis considered the effect of complications during treatment for oesophageal cancer upon long-term prognosis. **Study V** used FREGAT and demonstrated severe oesophageal anastomotic leak following oesophagectomy for cancer, adversely impacts cancer prognosis with a decrease in overall and disease-free survival and an increasing in overall, loco-regional and mixed cancer recurrence.

In conclusion, the studies conducted within this thesis have shown the safety of new therapeutic surgical strategies for oesophageal cancer, the importance of surgeon proficiency gain and surgeon age in prognosis, the lack of significance of university hospital status, and the adverse long-term prognostic effects of severe oesophageal anastomotic leak.

LIST OF SCIENTIFIC PAPERS

I. **Markar SR,** Gronnier C, Duhamel A, Pasquer A, Thereaux J, du Rieu MC, Lefevre JH, Turner K, Luc G, Mariette C, on behalf of the FREGAT working group –FRENCH-AFC.
Salvage Surgery after Chemoradiotherapy in the Management of Esophageal Cancer: Is it a viable therapeutic option?
Journal of Clinical Oncology 2015; 33: 3866–73.

II. **Markar SR,** Mackenzie H, Lagergren P, Hanna GB, Lagergren J.
Surgical Proficiency Gain and Survival after Esophagectomy for Cancer.
Journal of Clinical Oncology 2016; 34: 1528–36.

III. **Markar SR,** Mackenzie H, Lagergren P, Lagergren J.
Surgeon Age in Relation to Prognosis after Esophageal Cancer Resection.
Annals of Surgery 2017[Epub ahead of print].

IV. **Markar SR,** Wahlin K, Lagergren P, Lagergren J.
University hospital status and prognosis following surgery for esophageal cancer.
European Journal of Surgical Oncology 2016; 42: 1191–5.

V. **Markar SR,** Gronnier C, Duhamel A, Mabrut JY, Bail JP, Carrere N, Lefevre JH, Brigand C, Vaillant JC, Adham M, Msika S, Demartines N, Nakadi IE, Meunier B, Collet D, Mariette C, on behalf of the FREGAT working group –FRENCH-AFC.
The Impact of Severe Anastomotic Leak on Long-term Survival and Cancer Recurrence after Surgical Resection for Esophageal Malignancy.
Annals of Surgery 2015; 262: 972–80.

CONTENTS

1 INTRODUCTION 1
2 BACKGROUND 3
2.1. Oesophageal cancer 3
2.2. Surgical treatment of oesophageal cancer 4
2.3. Multimodality treatment of oesophageal cancer 4
2.4. Salvage oesophagectomy 5
2.5. Proficiency-gain curve 5
2.6. Surgeon age 6
2.7. Hospital and service structure related factors 6
2.8. Complications during treatment of oesophageal cancer 6
3 AIMS OF THE STUDIES 9
4 MATERIALS AND METHODS 11
4.1. Overview 11
4.2. Data sources 12
4.3. Data sources included in SESS 13
4.4. Study design 14
4.5. Exposures 15
4.6. Outcomes 15
4.7. Statistical analysis 16
4.8. Ethical considerations 18
5 RESULTS 21
5.1. Study I 21
5.2. Study II 22
5.3. Study III 24
5.4. Study IV 24
5.5. Study V 25
6 METHODOLOGICAL CONSIDERATIONS 27
6.1. Study design 27
6.2. Validity 27
6.3. Selection bias 28
6.4. Information bias 28
6.5. Confounding 29
6.6. Precision 29
7 GENERAL DISCUSSION 30
7.1. Study I 30
7.2. Study II 30
7.3. Study III 31
7.4. Study IV 32
7.5. Study V 32
8 CONCLUSIONS 34
9 FUTURE RESEARCH 35

10 ACKNOWLEDGEMENTS 36
11 REFERENCES 38

LIST OF ABBREVIATIONS

ASA	American Society of Anaesthesiology
CI	Confidence Interval
dCRT	Definitive Chemoradiotherapy
FREGAT	French esophagogastric database
GORD	Gastro-Oesophageal Reflux Disease
HR	Hazard Ratio
NCRS	Neoadjuvant Chemoradiotherapy and Surgery
OA	Oesophageal adenocarcinoma
OR	Odds Ratio
OSCC	Oesophageal Squamous Cell Carcinoma
SESS	Swedish Esophageal Cancer Surgery Study

1 INTRODUCTION

Oesophageal cancer is in the top five most rapidly rising cancers in the Western World and in Europe has an age-standardized incidence rate of 4.7 per 100,000 individuals. In its early stages oesophageal cancer grows slowly and often presents with non-specific upper gastrointestinal symptoms. As a result the majority of patients present with advanced disease and have a poor survival. The minority of patients with less advanced disease are considered for curative treatment with surgical resection with or without neoadjuvant chemotherapy or combined chemoradiotherapy.

Recent randomized controlled trials have focused on the addition of neoadjuvant therapy to surgery to improve long-term survival, or in some cases primary (definite) treatment with chemoradiotherapy. However, surgery remains the mainstay of curative treatment for oesophageal cancer, despite this is a highly invasive procedure with considerable treatment-related mortality and morbidity. The principal aim of this thesis was to evaluate treatment, surgeon and hospital related factors along-with postoperative complications that may affect survival in patients undergoing surgery for oesophageal cancer.

2 BACKGROUND

2.1. Oesophageal cancer

The incidence of oesophageal cancer is increasing annually; representing 7% of all gastrointestinal malignancies internationally [1–3]. In 2012 the number of new cases of oesophageal cancer across Europe was 45,900 with an age-standardized incidence rate of 4.7 per 100,000 individuals [4]. Oesophageal cancer is broadly defined into two main histological subtypes, squamous cell carcinoma and adenocarcinoma. In Far Eastern countries the most common subtype is oesophageal squamous cell carcinoma (OSCC), and given the high incidence in these countries, OSCC remains the most common histological subtype worldwide [5]. Risk factors for OSCC include tobacco smoking, overconsumption of alcohol, achalasia, drinking very hot liquids, low dietary intake of fruit and vegetables and receiving radiation to upper chest and abdomen. During the recent four decades there has been a rapid rise in the incidence of oesophageal adenocarcinoma (OA) in the Western world. This tumour is associated with gastro-oesophageal reflux disease (GORD), increased body mass index, low dietary intake of fruit and vegetables and tobacco smoking, while infection with Helicobacter pylori is inversely associated with this tumour [6,7]. The pathogenesis of OA is typically initiated by long-standing acidic insult caused by GORD to the lower oesophagus, which causes a metaplastic change in the epithelium from squamous cell to a glandular-type specialised columnar epithelium, entitled Barrett's oesophagus. The ongoing acidic insult to the lower oesophagus can further cause dysplastic change in these metaplastic cells and eventually progression to invasive OA [8–10]. Therefore these two histological subtypes differ in their location with typically OSCC affecting any part of the oesophagus and OA affecting almost exclusively the lower part of the oesophagus [11,12]. Early diagnosis of oesophageal cancer allows treatment at an earlier stage of disease, which has been shown to translate into a substantial improvement in five-year survival (up 80%) [13]. However often the disease presents in a non-specific fashion with more specific symptoms (dysphagia and weight loss) only occurring at more advanced cancer stages and carrying a much poorer prognosis [14]. The overall European pooled relative 1-year and 5-year survival rates for oesophageal cancer from the EUROCARE-4 study have previously been shown to be approximately 33.4% (95%CI 32.9–33.9%) and 9.8% (95%CI 9.4–10.1%) respectively [15], illustrating this diagnostic issue. In the current era, most patients with oesophageal cancer are diagnosed first after cardinal symptoms are evident and only one third of patients, mainly those without distant metastasis and with reasonably good fitness, are considered eligible for curative treatment [16].

2.2. Surgical treatment of oesophageal cancer

Oesophagectomy for cancer often involves thoracotomy and laparotomy with resection of most of the oesophagus, formation of a gastric conduit (made into a tube), which is then translocated to the thorax or neck for anastomosis. This is a highly morbid procedure, which carries a 30-day mortality rate ranging from 2% to 8% in the current era [17] and high rates (40-60%) of postoperative complications and substantial impact upon patients' functional status and health-related quality of life [18–20]. In more recent years, some surgeons have employed minimally invasive techniques to oesophagectomy and demonstrated reduced pulmonary morbidity within a randomised trial setting [21], and reduced mortality at a national level [22].

2.3. Multimodality treatment of oesophageal cancer

Multimodality treatment has become the standard of care in Western centres for locally advanced oesophageal cancer. Two neoadjuvant approaches have been adopted. The first is neoadjuvant chemoradiotherapy, based in recent years on the regimen evaluated in a large and influential randomised clinical trial from the Netherlands (CROSS), which resulted in a 5-year survival advantage of 14% in comparison to surgery alone [23,24]. An alternative option is perioperative or preoperative chemotherapy using the protocol from two other well-designed randomised clinical trials (MAGIC and OEO2), which showed respectively 5-year survival improvements of 13% and 6% compared to surgery alone [25,26]. The maximum benefit in the CROSS-trial was observed in OSCC, with highly significant benefit compared to surgery alone (hazard ratio [HR] 0.48; 95% confidence interval [CI] 0.28–0.83; p=0.009). In OA, the benefit was more modest (HR=0.73; 95%CI 0.55–0.98; p=0.037). However, the benefit of neoadjuvant chemoradiotherapy was consistent across subgroups, without any significant interactions identified [23,24]. Two other smaller randomised clinical trials comprising 119 and 75 patients with OA did not show any significant difference in survival between neoadjuvant chemoradiotherapy plus surgery and neoadjuvant chemotherapy plus surgery [27,28]. The recently reported NeoRES trial in a mixed cohort of 181 patients with OA or OSSC, showed pathological benefits without any changes in survival associated with the addition of radiotherapy to neoadjuvant chemotherapy [29]. Taken together, the current weight of evidence suggests a prognostic benefit to the utilisation of neoadjuvant chemoradiotherapy for OSCC, however any prognostic difference between neoadjuvant chemoradiotherapy and chemotherapy for OA remains to be established and is the subject of ongoing trials.

2.4. Salvage oesophagectomy

Current National Comprehensive Cancer Network (NCCN) and French guidelines state definitive chemoradiotherapy (dCRT) without surgery is an alternative to neoadjuvant chemoradiotherapy and resectional surgery (NCRS) for locally advanced OSCC [30]. Previous randomised controlled trials have demonstrated equivalence in 2-year survival for patients with OSCC treated by NCRS and those treated with dCRT [31,32]. However local recurrence rates are high (40–75%) following dCRT [33–35]. These groups of patients with persistent or recurrent disease are selectively considered for salvage oesophagectomy. Use of dCRT can adversely impact patient performance status [36,37], and together with the effects of high radiation doses upon thoracic tissue places as well as radiation effects on cardiac and pulmonary function, this can make salvage oesophagectomy a considerable challenge. In a meta-analysis of 8 retrospective studies comprising 254 patients suggested salvage oesophagectomy was associated with increased mortality, anastomotic leak, pulmonary complications and length of hospital stay when compared to NCRS [38]. However with the total number of patients in the salvage oesophagectomy group ranging from 14 to 65 for the studies included, it may be suggested this analysis was based upon small series of patients from historical studies, and there is a need for a prospective randomised controlled trial.

2.5. Proficiency-gain curve

A critical challenge in the introduction of complex surgical techniques is the proficiency-gain curve while surgeons gain experience in performing new procedures. A review of 23 published studies suggested that the proficiency-gain curve for laparoscopic colorectal surgery is approximately 88 to 152 cases, when considering complications, operative time, blood loss and length of hospital stay [39]. Similarly, a proficiency-gain curve has been observed in oesophageal and gastric cancer surgery [40,41]. While significant improvement is expected with new techniques, learning at the expense of patient safety and prognosis remains a major clinical and ethical consideration. The majority of studies regarding proficiency-gain curves originate from individual surgeons or single institutions, which do not reflect the real clinical environment for the uptake of new techniques at a population level. I have previously co-authored a study on the national proficiency-gain curve in the United Kingdom in minimal access surgery that described measurable effects upon short-term clinical outcomes following oesophageal and colorectal cancer resections as surgeons gain proficiency [42].

2.6. Surgeon age

Oesophagectomy is a technically demanding and time-consuming procedure with higher rates of mortality and morbidity than most other surgical procedures [43,44]. The physical and psychological abilities required for oesophagectomy may change with increasing surgeon age. Government regulatory bodies often specify the retirement age threshold with a primary emphasis on balancing the workforce, and thus physicians in medical and surgical specialties have a similar retirement age, despite the high technical demands for complex surgery [45,46]. As individual surgeons age their risk-taking behaviour and levels of confidence might change, which may be reflected in surgical practice [47,48]. Yet, there is very limited evidence of the role of surgeon age on patient outcomes from surgery. One previous publication suggested that older surgeon age may negatively influence in-hospital mortality from selected procedures, including pancreatectomy, coronary artery bypass grafting, and carotid endarterectomy [49]. No previous study has examined the influence of surgeon age upon long-term prognosis following any type of cancer surgery, and oesophagectomy may be of particular relevance in this respect.

2.7. Hospital and service structure related factors

In recent years there has been steady improvement in outcome parameters including postoperative mortality following oesophagectomy for oesophageal cancer [50–52]. The reasons for this improvement are multi-factorial but include better patient selection, preoperative optimisation, centralisation of services, advances in surgical technique and improvements in perioperative care [17,53]. The centralisation of oesophageal cancer surgical services to high volume centres with the appropriate infrastructure to manage these complex patients and deliver a consistently high level of care has been shown to reduce oesophagectomy associated morbidity and mortality [43,44,54]. Thus the volume-outcome effect in the setting of oesophagectomy is well established and has influenced policy and outcome through centralisation in many countries worldwide. However more specific factors of these high volume centres that may be responsible for the improvement in outcomes have only been evaluated to a limited extent previously.

2.8. Complications during treatment of oesophageal cancer

Complications following oesophagectomy for cancer have been suggested to have an adverse prognostic impact upon disease recurrence and thus long-term survival. A study of

531 patients with a focus on technical complications suggested that of all technical complications, anastomotic leak had the largest impact on long-term survival [55]. Conversely an analysis of 567 patients, 47 of whom developed an anastomotic leak, found no effect on long-term survival (median 22.0 vs. 24.4 months) [56]. Meta-analysis of large datasets from the colorectal cancer surgery literature have suggested that anastomotic leak following resection had a negative prognostic impact on local recurrence and reduced long-term cancer specific survival, with no effect on distant recurrence [57]. Previously authors have suggested that for colorectal surgery, colorectal cancer cells are detectable in the bowel lumen and on the suture or staple lines during resection, with in vitro and animal models demonstrating these cells retain their metastatic potential [58,59]. Leakage of enteric contents sets up a pro-inflammatory environment with the release of a variety of acute phase reactants and cytokines stimulating local recurrence and poorer survival [58,59]. Therefore there is a scientific rationale for the adverse impact of anastomotic leak on survival from oesophagectomy, although there remain conflicting published results. As the utilisation of neoadjuvant therapy has become an increasingly common component of the multi-modality management of patients with oesophageal cancer, it becomes more important to consider the potential adverse effects of neoadjuvant regimes. Some researchers have suggested an increase in the incidence of anastomotic leak after neoadjuvant chemoradiotherapy, possibly due to the ischaemic effects of radiotherapy upon the microcirculation of the gastric conduit [60, 61].

3 AIMS OF THE STUDIES

The main aim of this thesis was to extend the body of knowledge on treatment, surgeon and hospital related factors along-with postoperative complications that may affect survival in patients undergoing surgery for oesophageal cancer.

Specific aims were:

• To assess the impact of salvage oesophagectomy after definitive chemoradiotherapy on clinical outcomes.

• To identify the presence and length of oesophagectomy proficiency gain curves in terms of short- and long-term mortality for oesophageal cancer.

• To evaluate the effect of surgeon age upon short- and long-term mortality from oesophagectomy for cancer.

• To consider how management in a university hospital affects prognosis following surgery for oesophageal cancer.

• To determine the impact of severe oesophageal anastomotic leak upon long-term survival and loco-regional cancer recurrence.

4 MATERIALS AND METHODS

4.1 OVERVIEW

Table 1. Over of the material and methods used in studies I–V.

	Study I	**Study II**	**Study III**	**Study IV**	**Study V**
Design	Population-based cohort study				
Data sources	French esophagogastric (FREGAT) database	Swedish Esophageal Cancer Surgery Study (SESS), including data from the Swedish Cause of Death Registry, Cancer Registry, Patient Registry and medical records.			French esophagogastric (FREGAT) database
Cohort	Patients undergoing oesophagectomy for oesophageal cancer in 30 French-speaking university hospitals	Swedish residents undergoing oesophagectomy for oesophageal cancer			Patients undergoing oesophagectomy for oesophageal cancer in 30 French-speaking university hospitals
Inclusion period	1st Jan 2000 to 31st Dec 2010	1st Jan 1987 to 31st Dec 2010			1st Jan 2000 to 31st December 2010
Follow-up	1st Jan 2000 to 15th Jul 2013	1st Jan 1987 to 31st Nov 2014			1st Jan 2000 to 15th Jul 2013
Exposure	Salvage oesophagectomy	Proficiency gain curve	Surgeon age	University hospital	Anastomotic leak
Outcome	3-year overall and disease-free survival	90-day and 5-year all-cause and disease-specific mortality			Long-term survival and recurrence
Confounders	Age, sex, ASA, tumour stage,	Age, sex, medical comorbidities tumour stage, histology, neoadjuvant			Age, sex, ASA, tumour stage,

	histology and location, hospital volume, surgical technique	therapy, surgeon volume (IV), calendar period (IV)		histology and location, hospital volume, surgical technique, neoadjuvant therapy
Main statistical methods	Propensity score matching, Logistic and Cox regression	Risk adjusted cumulative sum analysis	Cox regression	Logistic and Cox regression

4.2. DATA SOURCES

The studies included in this thesis are based upon two large databases gathered by research groups over several years: (i) French esophagogastric (FREGAT) database and (ii) Swedish Esophageal Cancer Surgery Study (SESS).

4.2.1. French esophagogastric (FREGAT) database

The FREGAT database includes data from 2944 consecutive patients (aged 18 years or older) undergoing surgical resection for oesophageal cancer (including Siewert type I and II junctional tumours) with a curative intent in 30 French-speaking European centres between 2000 and 2010. Data were retrospectively collected through a dedicated website (http://www.chirurgie-viscerale.org), with an independent monitoring team auditing data capture to minimise missing data and to ensure concordance, and inclusion of consecutive patients. Data collected included patient demographic factors, preoperative and surgical treatments, postoperative outcomes, histopathological results and long-term oncological outcomes. Missing or inconsistent data were obtained from email exchanges or telephone calls with the treating centre.

4.2.2. Swedish Esophageal Cancer Surgery Study (SESS).

The Swedish Esophageal Cancer Surgery Study (SESS) is a retrospective cohort of almost all patients in Sweden receiving surgery for primary oesophageal cancer from 1987 to 2010, with follow-up until 31st November 2014. Patients with a diagnosis of oesophageal cancer were identified from the Swedish Cancer Registry. These patients were then linked with the Swedish Patient Registry to identify those who underwent surgery for oesophageal cancer during the study period. The Swedish personal identity number, assigned to each

Swedish resident at birth or immigration was used to link data between registries and in the identification of individual medical records. Hospital and histopathology records for eligible patients were retrieved from all Swedish hospitals where oesophageal cancer surgery was performed and these records were manually reviewed according to predefined protocols to ensure uniformity. Clinical data on tumour and treatment characteristics were collected through a nationwide Swedish clinical network established in the 1990s. Data concerning neoadjuvant therapy, names of surgeons, date of surgery, pathological tumour stage, and histological subtype were obtained from review of individual patient medical records. Information about death and causes of death was available from the Swedish Cause of death Registry.

4.3. DATA SOURCES INCLUDED IN SESS

4.3.1. The Swedish Cancer Registry

The Swedish Cancer Registry was established in 1958, with all Swedish healthcare providers (both public and private) required to report new cancer cases to the registry. Cancer diagnoses based on clinical, morphological, or histopathological examination are registered according to the International Classification of Diseases seventh edition, for oesophageal cancer (150.0, 150.8 and 150.9). Diagnoses based on autopsies are reported but not registered. The Swedish Cancer Registry has 98% nationwide coverage of oesophageal cancer cases in Sweden, and histopathological confirmation of these tumours has been shown to be 100% complete [62, 63].

4.3.2. The Swedish Patient Registry

The Swedish Patient Registry was initiated in 1964 for the collection of data regarding in-hospital care of patients in Sweden. From 1987, participation in the registry was mandatory for all Swedish hospitals, allowing calculation of a nationwide completeness rate ever since. Patients with oesophageal cancer who received oesophagectomy were identified from this registry, which has an excellent positive identification rate (99.6%) for oesophageal surgery [63]. This registry also provided data regarding patient medical comorbidities and reoperations.

4.3.3. The Swedish Causes of Death Registry

Since 1952, this registry has provided data on all deaths of Swedish residents, whether in Sweden or abroad. The contributing cause(s) of death using the most recent version of ICD, and date of death are reported in a death certificate issued by the treating physician. The

registry covers more than 99% of all deaths in Sweden since 1952 [64].

4.4. STUDY DESIGN

4.4.1. Study I

This retrospective cohort study investigated the impact of salvage oesophagectomy following definitive chemoradiotherapy upon short and long-term clinical outcomes compared with neoadjuvant chemoradiotherapy and planned surgery (NCRS) for patients who underwent surgery between 2000 and 2010, with follow-up until 15th July 2013, from the FREGAT database. A subset comparison of short and long-term clinical outcomes for patients within the salvage oesophagectomy group receiving treatment for persistent or recurrent oesophageal cancers was also conducted.

4.4.2. Study II

Using the SESS dataset, this population-based cohort study investigated the length and clinical implications of the proficiency gain curve for surgeons performing open oesophagectomy for oesophageal cancer from 1987 to 2010, with follow-up until November 2014, in terms of short- and long-term mortality within Sweden.

4.4.3. Study III

This population-based cohort study utilised the SESS dataset to investigate the effect of surgeon age upon short and long-term mortality from oesophagectomy for oesophageal cancer from 1987 to 2010, with follow-up until 31st May 2016, within Sweden.

4.4.4. Study IV

A population-based cohort study design was used to evaluate the effect of surgery performed in university hospitals upon short and long-term mortality from oesophagectomy for oesophageal cancer from 1987 to 2010, with follow-up until November 2014, within Sweden. The study used data from the SESS dataset.

4.4.5. Study V

The FREGAT database was used to investigate the impact of severe oesophageal anastomotic leak upon long-term survival and tumour recurrence following oesophagectomy performed between 2000 and 2010, with follow-up until 15th July 2013, for oesophageal cancer. The association between patient, tumour and treatment-related factors, and severe oesophageal anastomotic leak was also evaluated within this study.

4.5. EXPOSURES

4.5.1. Study I

The exposure in this study was salvage oesophagectomy defined as removal of the oesophagus for persistent or recurrent disease within the tumour or loco-regional lymph nodes after definitive chemoradiotherapy.

4.5.2. Study II

The exposure was period of surgeon proficiency gain in performing open oesophagectomy for oesophageal cancer.

4.5.3. Study III

The exposure in this study was the age of the surgeon at the time of oesophagectomy for each patient. This age was calculated from the date of birth of each surgeon and the date of each operation.

4.5.4. Study IV

The exposure investigated was oesophagectomy performed in any of the six Swedish university hospitals compared to non-university hospitals.

4.5.5. Study V

The exposure in this study was severe oesophageal anastomotic leak. This was defined as a symptomatic (mediastinal abscess, mediastinitis or digestive content in the chest drain) disruption of the intrathoracic anastomosis, classified as grade III or IV according to the Clavien-Dindo classification [65].

4.6. OUTCOMES

4.6.1. Study I

The outcomes evaluated in this study included in-hospital mortality and morbidity, 3-year overall and disease-free survival and overall, mixed and loco-regional cancer recurrence. In-hospital morbidity was sub-classified and analysed as anastomotic leak, conduit necrosis, surgical site infection, chylothorax, postoperative haemorrhage, gastroparesis, pulmonary, cardiovascular, thromboembolic and neurologic with severity graded according to the Clavien-Dindo classification [65].

4.6.2. Study II

The main outcomes studied were 30-day, 90-day, 1-year, 3-year and 5-year all-cause and disease-specific mortality, all calculated from the date of surgery. Additional outcomes evaluated included lymph node harvest, resection margin status and incidence of reoperation.

4.6.3. Study III

The outcomes analysed in this study were all-cause 90-day and 5-year mortality and disease-specific 5-year mortality, all calculated from the date of surgery.

4.6.4. Study IV

Similarly the outcomes analysed in this study were all-cause 90-day and 5-year mortality and disease-specific 5-year mortality, all calculated from the date of surgery.

4.6.5. Study V

The main outcomes of this study were overall and disease-free survival, along-with overall, local, distant and mixed tumour recurrence. The secondary outcomes of the study were the identification of preoperative and intraoperative factors associated with severe oesophageal anastomotic leak.

4.7. STATISTICAL ANALYSIS

4.7.1. Study I

For crude analyses, Mann-Whitney U test was used for intergroup comparisons of continuous variables, chi-squared or Fisher's exact tests were used to compare categorical data, and overall and disease-free survivals were estimated by the Kaplan-Meier method. A propensity score was calculated to develop well-balanced groups and reduce any effects of potential confounding factors in short- and long-term outcomes analysis. A multivariable logistic regression model was used to estimate the propensity score, with the study groups as the dependent variables and all potential confounders as covariates. Confounders included in this model were surgery after 2006 (yes or no), age 60 years or more (yes or no), male sex (yes or no), ASA score (1, 2, 3 or 4), centre volume ≥80 (yes or no), tumour location (upper, middle or lower), clinical TNM stage (I, II, III or IV), surgical technique (Ivor Lewis, three stage or transhiatal oesophagectomy), and tumour histology (squamous cell carcinoma or adenocarcinoma). Patients in the salvage oesophagectomy group were matched in a 1:1 ratio with patients from the NCRS group according to the propensity score

using the global optimum method. Short and long-term outcomes between the matched groups were compared using logistic regression or Cox-regression models using the robust sandwich estimate for the matched sets. These models allowed the generation of odds ratios (ORs) and HRs as effect-size measures with 95% CIs. The comparison within the salvage oesophagectomy group of persistent and recurrent oesophageal cancer cases had a very small sample size and therefore the propensity score was used to adjust the analysis rather than a formal matching process. Adjustment was performed using multivariable logistic regression or Cox regression models include the propensity score as a covariate within the model.

4.7.2. Study II

The primary method of analysis used in this study was Risk Adjusted Cumulative Sum (RA-CUSUM) curves [66] to evaluate changes in mortality associated with increase case number or proficiency gain. Logistic regression models were used to create risk prediction models for the binary outcomes (mortality, reoperation and resection margin), and calculate the predicted probability of each outcome for individual cases. Potential confounding factors included in the models were age (continuous variable), sex (male or female), tumour histological subtype (adenocarcinoma or squamous cell carcinoma), pathological stage (stage I, II, III or IV), use of neoadjuvant therapy (yes or no), and individual pre-operative co-morbidities (yes or no). RA-CUSUM curves plot the cumulative difference between the observed and expected outcome. This was calculated using the CUSUM equation $Si=Si-1+(\Sigma i- \Sigma R)$; $S0=0$: Si is the cumulative sum, Σ i the sum of events at procedure number i, and ΣR the sum of expected events at procedure number i. On the basis of this equation the curve increases if the observed exceeds the expected outcome and vice versa. The change-points in the curve were identified as the maximal deflection of the curve from 0. Mann-Whitney U test was used for continuous variables and chi-squared test was used for categorical data to compare outcomes before and after the change-point.

4.7.3. Study III

Similarly to study II, RA-CUSUM was used as the primary method of analysis to evaluate changes in mortality associated with operating surgeon age. Again similarly confounding factors were included in the logistic regression model to generate the expected probability of mortality, age (continuous variable), sex (male or female), comorbidity (Charlson comorbidity score 0, 1 or ≥2), pathological tumour stage (0 or I, II, III or IV), tumour histology (adenocarcinoma or squamous cell carcinoma), and use of neoadjuvant therapy

(yes or no). Surgeon age was seen to strongly correlate with surgeon volume and year of surgery so these were included in subsequent Cox regression analyses. As before change-points in surgeon age affecting mortality were identified by RA-CUSUM curve analysis. These were then analysed in relation to the mortality outcomes also using a multivariable Cox-proportional hazards model, providing HRs with 95%CIs. Co-variates included in this model were the six factors above and cumulative surgeon volume of esophagectomies during study period (≤16 or >16) and calendar period of surgery (year 1987–1994, 1995–2002 or 2003–2010).

4.7.4. Study IV

Unadjusted Kaplan Meier survival analysis was conducted to visualise the effect of university hospital status on crude all-cause and disease-specific mortality within 5 years of surgery. University hospital status was analysed in relation to mortality using a multivariable Cox-proportional hazards model, providing HRs with 95% CIs, adjusted for eight potential confounding factors. Two Cox regression models were created with adjustment for the factors below: Model (a); age (continuous), sex (male or female), tumour stage (0-I, II or III-IV), Charlson co-morbidity index (0, 1 >1), neoadjuvant therapy (yes or no), histological subtype (adenocarcinoma or squamous cell carcinoma), surgeon volume (<6, 7 – 16 or 17 – 46), and calendar period (1987 – 1994, 1995 – 2002 or 2003 – 2010). Model (b); age (continuous), sex (male or female), tumour stage (0-I, II or III-IV), Charlson co-morbidity index (0, 1 or >1), neoadjuvant therapy (yes or no), histological subtype (adenocarcinoma or squamous cell carcinoma), and calendar period (1987 – 1994, 1995 – 2002 or 2003 – 2010).

4.7.5. Study V

Patients were categorised into those who developed a severe oesophageal anastomotic leak and those that did not. Crude analysis comprised Mann-Whitney U test used for intergroup comparisons of continuous variables, chi-squared or Fisher's exact tests used to compare categorical data, and overall and disease-free survivals were estimated by the Kaplan-Meier method. The factors associated with survival were analysed by Cox proportional hazard regression analysis using a stepwise procedure. Binary logistic regression modelling was used to identify factors associated with tumour recurrence.

4.8. ETHICAL CONSIDERATIONS

All studies conducted as part of this research were from either the SESS in Sweden

database or the FREGAT database in France. In each study all patients are anonymised. All data were retrieved and stored on safe servers at the Karolinska Institutet, University Hospital Lille or Imperial College London, and the risk for data leakage is negligible.

One further ethical concern specific to the Swedish cohort study (SESS) is that patients are not explicitly asked to be included. All individuals residing in Sweden are included in registries regarding birth and death, hospital attendances, diagnoses and operations. Therefore the data from Sweden included with the studies I have described were retrieved without the consent of the individual patient. However given the anonymisation of these data and the benefits of this type of research, which allow patients to be followed up for a long time, providing sufficient sample sizes to study rare subsets and treatment algorithms for oesophageal cancer, it is ethically acceptable to conduct this type of research. The FREGAT dataset was collected with all patients consented to allow their information to be included within the database and used for this exact purpose of research, and therefore no additional ethical concerns are raised from this dataset.

5 RESULTS

5.1. Study I

Propensity matched analysis matched 308 patients undergoing salvage oesophagectomy following definitive chemoradiotherapy with 308 undergoing planned oesophagectomy following neoadjuvant chemoradiotherapy. There were no significant differences between the groups in the incidence of in-hospital mortality (OR=0.719, 95%CI 0.414-1.25) or morbidity (OR=1.117, 95%CI 0.818-1.525), with the exception of anastomotic leak (OR=1.732, 95%CI 1.110-2.703) and surgical site infection (OR=1.614, 95%CI 1.058-2.461). There were no significant differences between groups in 3-year overall (Figure 1) or disease free survival, or overall, loco-regional, distant or mixed cancer recurrence. Within the salvage oesophagectomy group, when compared to patients with recurrent disease, those with persistent disease showed reduced 3-year overall and disease-free survival and increased overall, loco-regional, distant mixed tumour recurrence (Table 1).

3-year outcome	**Persistent cancer (%)**	**Recurrent cancer (%)**	**P value**
Survival			
Overall	39.1	56.2	0.086
Disease-free	35.4	51.6	0.09
Tumour recurrence			
Overall	51.1	39.4	0.136
Loco-regional	20.6	13.9	0.233
Distant	26.5	18.7	0.64
Mixed	15.5	6.9	0.339

Table 1: Comparison of 3-year outcomes for patients undergoing salvage oesophagectomy for persistent or recurrent oesophageal cancer.

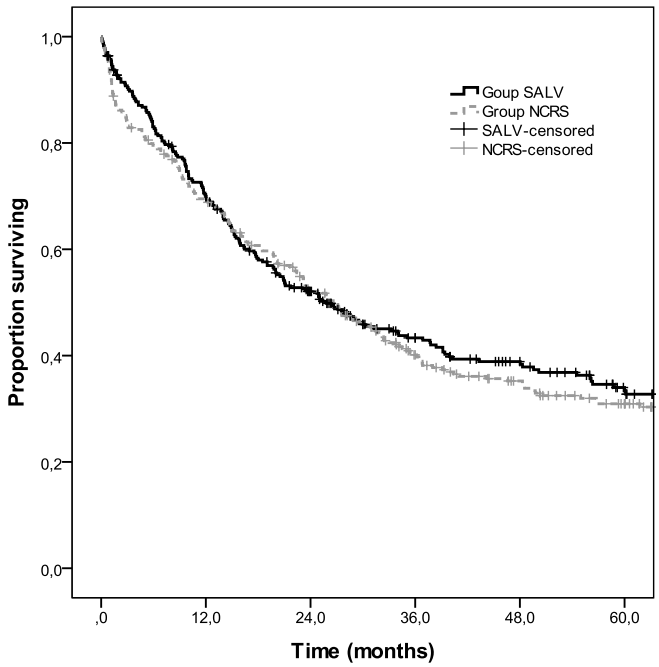

Figure 1: Comparison of overall survival in propensity matched salvage oesophagectomy following definitive chemoradiotherapy and the neoadjuvant chemoradiotherapy followed by planned oesophagectomy groups.

5.2. Study II

This study included 1820 patients with oesophageal cancer who received oesophagectomy performed by a 139 surgeons. RA-CUSUM analysis of 30-day and 90-day all-cause mortality showed change-points in the proficiency gain curves at 15 and 22 cases, respectively, after which, 30-day all-cause mortality decreased from 7.9% to 3.1% (P<0.001) (Figure 2) and 90-day all-cause mortality decreased from 7.3% to 5.2% (P=0.079). RA-CUSUM analysis of 3-year and 5-year all-cause mortality showed change-points in the proficiency gain curves at 35 and 59 cases, respectively, after which, 3-year all-cause mortality decreased from 47.4% to 41.5% (P=0.039), and 5-year all-cause mortality decreased from 31.4% to 19.1% (P=0.006) (Figure 3). Analyses of tumour involvement in the resection margin (R1/2) and reoperation showed change-points at 17 and 55 cases, respectively, with lymph node harvest showing no plateau of the proficiency gain curve, but increasing in a continuous fashion with increasing experience.

Figure 2: Proficiency gain curve for 30-day all-cause mortality from oesophagectomy for cancer with a significant change-point at 15 cases with a reduction from 7.9% to 3.1% (P<0.0001).

Figure 3: Proficiency gain curve for 5-year all-cause mortality from oesophagectomy for cancer with a significant change-point at 59 cases with a reduction from 31.4% to 19.1% (P=0.006).

5.3. Study III

From the source cohort of 1820 patients, 59 were excluded as surgeon's age was not available for these patients, leaving 1761 patients included in the final analysis, operated on by 139 surgeons. RA-CUSUM analysis of 5-year all-cause mortality showed significant change-points associated with surgeon age at 52 years (downward deflection) and 56 years (upward deflection) (Figure 4). Comparison with surgeon age between 52 and 55 years (reference category), surgeon age ≤51 years (adjusted HR=1.71, 95%CI 1.01–2.90) and surgeon age ≥56 years (adjusted HR=2.38, 95%CI 1.38–4.13), were associated with increased 90-day mortality. Similarly, when compared with surgeon age between 52 and 55 years (reference category), surgeon age ≤51 years (adjusted HR=1.21, 95%CI 1.02–1.43) and surgeon age ≥56 years (adjusted HR=1.29, 95%CI 1.08–1.55), were associated with increased 5-year all-cause mortality.

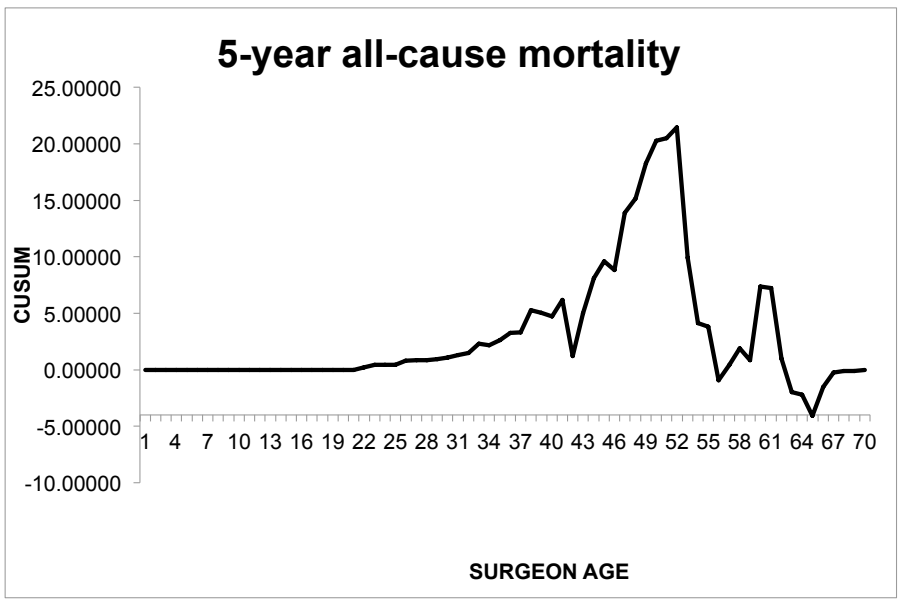

Figure 4. RA-CUSUM curve for 5-year all-cause mortality, showing change-points at surgeon ages of 52 (downward deflection) and 56 years (upward deflection).

5.4. Study IV

In total 1820 patients who underwent surgery for oesophageal cancer between 1987 and 2010 in Sweden were included in the study. From Kaplan-Meier survival analysis, university hospital status did not affect all-cause 90-day (P=0.115), all-cause 5-year (P=0.460) (Figure 5) or disease-specific 5-year mortality (P=0.419). Multivariable regression analysis indicated improved all-cause 90-day mortality within university hospitals, but the 18% reduction in the

point estimate was not statistically significant (HR=0.82, 95% CI 0.61–1.10). However multivariable analysis also showed surgery within university hospitals did not improve long-term mortality; the all-cause 5-year (HR=0.94, 95% CI 0.83–1.05) and disease-specific 5-year mortality (HR=1.00, 95% CI 0.88–1.14).

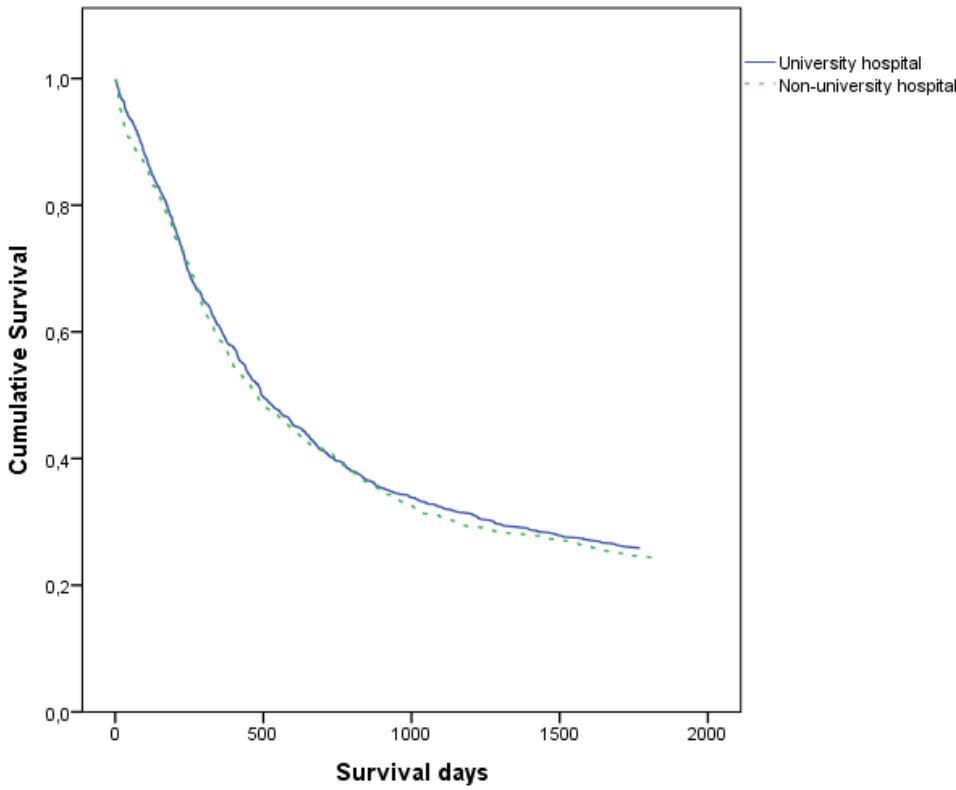

Figure 5: Kaplan-Meier survival curve for the effect of surgery for oesophageal cancer within university hospitals upon all-cause 5-year survival.

5.5. Study V

From the FREGAT database, 2439 patients received surgical resection for oesophageal cancer and were included in the present study. Of these 208 patients (8.5%) developed a clinically significant severe oesophageal anastomotic leak grade III or IV. Factors associated with an increased incidence of severe oesophageal anastomotic leak included low volume centre (OR=1.92, 95%CI 1.28 to 2.88), cervical location of the anastomosis (OR=1.69, 95%CI 1.14 to 2.5), upper third tumour location (OR=1.77, 95%CI 1.12 to 2.81) and ASA score III or IV (OR=1.63, 95%CI 1.03 to 2.59). Severe oesophageal anastomotic leak was associated with reduced overall survival (HR=1.28, 95%CI 1.04 to 1.59) (Figure 6). Severe oesophageal anastomotic leak was also associated with significant increases in overall

(OR=1.35, 95%CI 1.15 to 1.73), loco-regional (OR=1.56, 95%CI 1.05 to 2.24), and mixed tumour recurrence (OR=1.81, 95%CI 1.2 to 2.71).

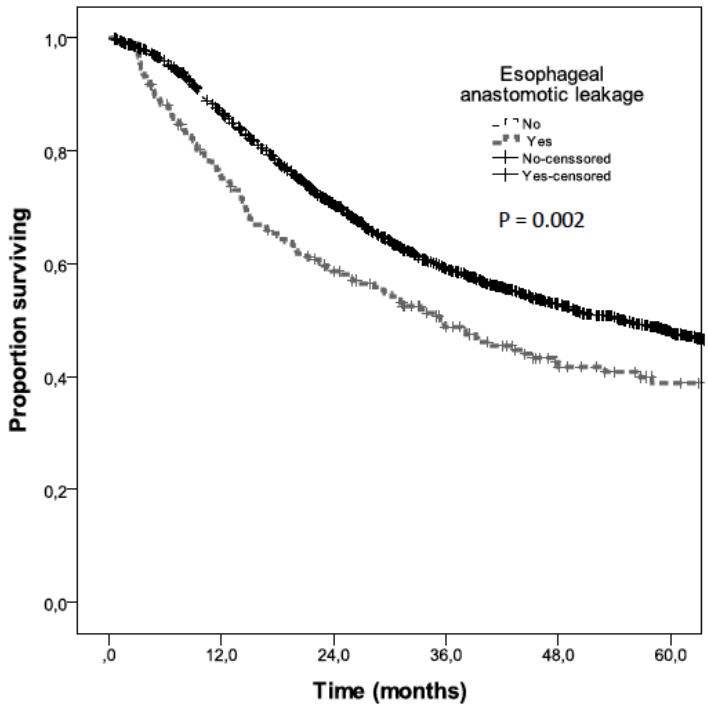

Figure 6: The overall survival curves in the severe oesophageal anastomotic leak group (n=208) and the absence of severe oesophageal anastomotic leak (n=2231).

6 METHODOLOGICAL CONSIDERATIONS

6.1. STUDY DESIGN

Clinically-based research is either experimental or observation in design. Experimental clinical research is most commonly as a randomized controlled trial study design. The main advantage of this design is the equal distribution of known and unknown confounding factors between groups (if they are large enough), ensuring the only exposure differing between the groups is the intervention under investigation. However within a surgical or oncology setting, strict inclusion criteria employed with the study design, reduces the external validity of the study findings to the population of interest at a national or international level. Furthermore randomisation can be unethical (as in Study V) or unfeasible (as in Studies II, III and IV), for many research questions, thus alternative study designs are required. Observational studies when conducted in large national datasets often reflect the true effect size of the exposure under investigation, and may be more representative of 'real life clinical practice' than a randomised controlled trial. The most common types of observational studies are the cohort and case-control design. All five studies in this thesis are large cohort studies, which are less prone to recall bias compared to case-control studies.

In a cohort study, individual patients are classified according to the presence or absence of the exposure under investigation (exposed and unexposed), and are followed up within the study over a period of time to identify the occurrence of the outcome for example mortality. The studies included in this thesis can be regarded retrospective as the outcome occurred prior to the assembly of patients and classification of their exposure. Main advantages of large population-based cohort studies with high participation rates (Studies II, III and IV) are the low risk of selection bias and good external validity of the results gained. The disadvantage of a cohort study design is the risk of loss to follow-up and missing data, which was minimized in the FREGAT (Study I and V) through robust clinical follow-up and in SESS (Studies II, III and IV) through careful medical chart review and linkages to nationwide complete registries.

6.2. VALIDITY

Validity is often classified into internal validity, the extent to which the data measures what it is intended to measure (unbiased), and external validity, the degree to which results can be extrapolated to other settings (generalizability). The studies conducted within this thesis do have high internal validity as the datasets utilised are well validated, with robust methods of data capture, and the analyses conducted carefully designed to evaluate the primary research

question in each case. The external validity of the findings from these studies is unknown until they are replicated in other large national datasets. Study II and III concerning surgical proficiency gain and surgeon age could be both considered controversial studies because of the exposures under study and the results, and further research is required to establish the external validity of these findings. Sweden does have a unique healthcare structure and only in more recent years has centralised oesophageal cancer surgical services. Therefore it would be important to perform studies examining the research questions in studies II and III also in countries with a centralised oesophageal cancer service, such as the United Kingdom, as this may provide further validity to these findings in future practice in Sweden.

6.3. SELECTION BIAS

Selection bias is less commonly observed in population-based cohort studies with high participation rates, robust inclusion methodology, active data verification at source and strategies to minimise missing data. Studies II, III and IV were based on SESS, which is a well validated database, capturing 98% of all oesophageal cancer patients treated surgically in Sweden. Studies I and V used the FREGAT dataset, which similarly has very robust methods of data collection and strategies to minimise missing data. However the FREGAT dataset only includes patients managed at highly experienced French-speaking European Oesophageal Cancer Centres, and thus the results from these studies may not have external validity if the results are extrapolated to the entire France. Furthermore in Study I patients undergoing salvage oesophagectomy are by definition a selected group of patients, and thus as stated in the manuscript, the results of this study can only be applied in high volume centres with strict patient selection.

6.4. INFORMATION BIAS

Information bias is essentially misclassification or miscoding of data related to the exposure or outcome related to the individuals under investigation within the study. It may be differential (non-random) when the misclassification systematically differs between the study groups and this may lead to bias of the outcome in either direction from the misclassification. Information bias may also be non-differential (random) when the misclassification does not differ between the groups, leading the attenuation of potential associations and thus bias towards the null.

For both the FREGAT and SESS datasets, information from hospital medical records was collected using a detailed predefined protocol. For both datasets, researchers involved ensured that the data collected were correct and complete, in order to reduce misclassification

and information bias. However it must be acknowledged that within hospitals coding of medical comorbidities and complications including their severity may be subject to biases of individual inputting the data. In SESS, more than one researcher has reviewed the most important variables to reduce misclassification. In more recent years, consensus groups have sought to define complications following oesophagectomy to reduce this aspect of information bias in future oesophageal cancer surgery studies [67, 68].

6.5. CONFOUNDING

Confounding factors are factors that are associated with both the exposure and the outcome and may influence the findings of the study, without being part of the direct causal pathway between exposure and outcome. In the studies conducted in this thesis, all known established confounding factors that may influence the outcomes studied were adjusted for in the analysis to counteract confounding. However as stated in the limitations paragraph of all the studies, unmeasured potential confounding, e.g. by obesity, smoking or other lifestyle factors could have introduced residual unmeasured confounding, which cannot be ruled out in observational studies. Importantly though, given the size of the datasets used in these studies, the influence of these unmeasured confounding factors is likely to be equally distributed between the exposure groups and thus unlikely to be a primary factor influencing the outcomes.

6.6. PRECISION

Precision describes the degree of random error within a study. The size of random error can be reduced by increasing the sample size and often narrows the confidence interval for the effect size. The hazard or odds ratio results in the studies in this thesis were presented with 95% confidence intervals, which indicate that replication of the study would generate a point estimate included within the confidence interval 95% of the time. The P values provided in several of the studies, describe the probability of the result being due to chance, which was set at 0.05 to assign statistical significance to the results, accepting 5% of the results may be secondary to chance. In this situation the null hypothesis could be rejected when it is true (type I error), or not rejected when it is false (type II error).

The P value to assign statistical significance to the studies in this thesis was set at 0.05, suggesting the results had to show good precision (reducing the risk of type II error). Several mechanisms reduced the chance of type II error within the studies; (i) clearly predefined hypotheses, (ii) large national or regional cohorts and (iii) the use of clinically relevant factors in multivariable analyses to limit the effects of multiple testing.

7 GENERAL DISCUSSION

7.1. STUDY I

This study showed short- and long-term mortality and cancer recurrences, were similar between patients undergoing salvage oesophagectomy after definitive chemoradiotherapy compared with planned oesophagectomy after neoadjuvant chemoradiotherapy. Importantly surgery in high volume centres and following a lower total radiation dose, were associated with a reduced postoperative mortality and morbidity rate in the salvage oesophagectomy group.

The results from this cohort study contradict a meta-analysis I previously published [38], which is likely due to two main reasons. Firstly in this cohort study, approximately 80% of patients underwent salvage oesophagectomy at experienced centres, and benefited from discussion within multidisciplinary team meetings ensuring appropriate patient selection and standardised postoperative protocols to optimise recovery [69]. Secondly, the mediation radiation dose in this cohort study in patients receiving definitive chemoradiotherapy was 50Gy, much lower than those in the majority of studies included in the meta-analysis [38].

Patients with no tumour response following definitive chemoradiotherapy had a reduced overall and disease-free survival compared with those with recurrent disease. This may suggest that tumours that persisted following definitive chemoradiotherapy have an underlying more aggressive pathology. Therefore clearly the early identification of patients not responding to multi-modality therapy is a priority area for ongoing research with several research groups focusing on the use of positron emission tomography to identify the metabolic activity of the tumour [70,71], or contrast enhanced MRI or repeat endoscopic ultrasound with biopsies.

7.2. STUDY II

Study II identified that gaining proficiency in performing resection of oesophageal cancer is associated with measurable changes in short- and long-term mortality. The length of the proficiency-gain curve was limited for short-term mortality but greater for long-term mortality.

The shorter length of proficiency-gain curve regarding short-term survival demonstrated in the present study parallels previous publications concerning open oesophagectomy from single centres [72] and a national study of minimally invasive oesophagectomy in England

[42]. Even though this period of proficiency gain was short, 15 cases for 30-day all-cause mortality, there was substantial reduction in 30-day mortality, relative risk reduction of 61%. Similarly the longer period of proficiency gain for 5-year all-cause mortality (59 cases), was associated with substantial effects on patient mortality, with a relative risk reduction of 39%. The differences in the length of proficiency gain curve for short- and long-term mortality, within this study may be explained by the psychological primary concern of the independently practicing surgeon. Initially the focus is on short-term outcomes, ensuring a low anastomotic leak rate and short-term mortality, however in the longer-term once the short-term outcomes are acceptable they begin to focus on the oncological quality of their resection, improving cancer outcomes for their patients.

Surgical learning at the expense of patient mortality is morally unacceptable, and must be addressed at a national level before surgeons practice established procedures independently or introduce new techniques adding to their proficiency gain curve. Structured based training programs with competency based assessments, and a long period of mentorship during the early stages of independent practice may reduce any adverse effects of surgical proficiency gain to patients [73,74,75].

7.3. STUDY III

Study III indicated the importance of surgeon age as a prognostic factor short and long-term mortality from oesophagectomy for oesophageal cancer. The “optimal” surgeon age in Sweden for oesophageal cancer surgeons from the present study is between 52 and 56 years. Before this age, surgeons are gaining surgical proficiency, paralleling the results of Study II [76]. After this age, there is a decline in surgical performance as illustrated by an increase in short- and long-term mortality.

Oesophageal cancer surgery is a highly psychologically and technically demanding procedure, with long periods of intense concentration and high level physical performance required. An analogy may be drawn with other technical professions such as athletes or musicians, who have a short time period of optimal performance, when the individual has sufficient expertise and is at the peak of their technical abilities to maximise their level of performance.

Clearly there is wide range in how individual surgeons age, and in their physical and psychological abilities at different ages, therefore compulsory retirement ages, or relying on individual surgeons to recognise any change in their abilities is unfair. Individual competency-based assessments with human reliability analysis [77, 78, 79] may be able to identify changes in operative performance before patient harm occurs.

7.4. STUDY IV

Study IV demonstrated a negative finding, and disproved the hypothesis that oesophagectomy performed within university hospital settings reduced the risk of long-term mortality after adjustment for surgeon volume (and other potential confounders). An important limitation of this study was that the majority of cases performed by higher volume surgeons were performed in university hospitals, highlighting that in clinical practice these two variables are closely linked.

This study demonstrates the importance of surgeon volume in the long-term outcome of patients undergoing oesophageal cancer surgery, paralleling previous studies [80, 81]. The key principles of high quality oesophageal cancer surgery with strong prognostic influence, more commonly employed by high volume surgeons, include minimizing blood loss, reducing complications and reducing positive resection margin incidence [80, 81, 82]. In the SESS dataset, university hospital status and surgeon volume were closely linked, and given the pattern of centralisation of high-risk surgery such as oesophagectomy, this is likely to be the case internationally. University hospitals may in the future provide an ideal environment for surgeons to be trained in the key principles of high quality oesophageal cancer surgery before embarking upon independent practice [83].

7.5. STUDY V

The most important findings from Study V, were that severe oesophageal anastomotic leak after oesophagectomy is associated with decreased overall and disease-specific survivals and an increase in overall, loco-regional, and mixed cancer recurrences. Important factors associated with severe oesophageal anastomotic leak included low hospital volume, cervical anastomosis, upper third tumour location and ASA grade III or IV.

Previous smaller studies have been inconsistent in their findings concerning the prognostic influence of anastomotic leak following oesophagectomy [84–88]. However the present study is the largest in the area, and identifies a strong association between severe oesophageal anastomotic leak and decreased prognosis, which parallels previous research from colorectal cancer surgery [89]. The mechanism of increased loco-regional recurrence following severe oesophageal anastomotic leak may parallel that seen for colorectal leak, with the leakage of enteric contents creating a pro-inflammatory environment. The release of acute phase reactants and cytokines, IL-32, TNF-alpha, IL-6 and IL-1beta, may promote tumour proliferation following the spillage of viable tumour cells from anastomotic lines following leak [90, 91, 92].

Tumour and patient factors associated with severe oesophageal anastomotic leak really identified established risk factors, which may compromise the gastric micro-circulation promoting anastomotic leak. The best established of these is the cervical location to the anastomosis, which commonly places the anastomosis and gastric circulation on a stretch and thus has been suggested to lead to increased incidence of anastomotic leak [93]. The association of low hospital volume with increased severe oesophageal anastomotic leak provides further evidence of the prognostic importance of hospital volume in high risk cancer surgery, and the need for centralisation of oesophagectomy to high volume centres [94, 95].

8 CONCLUSIONS

- Salvage oesophagectomy after definitive chemoradiotherapy can offer acceptable short- and long-term outcomes in selected patients at experienced oesophageal cancer centres.
- The period during which surgeons gain proficiency in performing oesophagectomy for cancer is associated with substantial adverse effects upon short- and long-term mortality.
- The optimal surgeon age in performing oesophagectomy in Sweden is between 51 and 56 years. Outside of this age period, increases in short- and long-term mortality are noted, as surgeons are still gaining experience or maybe experiencing decline in their technical abilities.
- Surgery performed in university hospitals has no independent improvements in long-term mortality from oesophagectomy after adjustment for surgeon volume and other measured confounders.
- Severe oesophageal anastomotic leak following oesophagectomy for cancer, adversely impacts cancer prognosis with a decrease in overall and disease-free survival and an increasing in overall, loco-regional and mixed cancer recurrence.

9 FUTURE RESEARCH

Strategies for organ preservation using combined oncological-targeted therapies in the management of oesophageal cancer may be the next step for clinical researchers. A large multi-centre randomised controlled trial comparing two strategies for locally advanced oesophageal cancer is needed; (i) definitive chemoradiotherapy with salvage oesophagectomy for persistent or recurrent disease vs. (ii) neoadjuvant chemoradiotherapy and planned oesophagectomy. Given the radio-sensitivity of oesophageal squamous cell carcinoma, a study focused on this histological subtype would be of great interest.

Studies II and III have suggested that specific surgeon related factors such as a proficiency gain and surgeon age, can adversely impact patient mortality from oesophagectomy. Future research is needed to create standardised competency based assessments for oesophagectomy with sufficient sensitivity to identify changes in a surgeon's proficiency or technical ability before patient harm is observed. Importantly the period of proficiency gain required for the adequate performance of a new surgical technique may require careful investigation before that technique is investigated in a randomised trial setting. Competency based assessments may also serve as a test to allow surgeon entry into randomised controlled trials to prevent poor outcomes from the new interventional arm associated with the surgical proficiency gain period.

The importance of university hospital status on long-term outcome from oesophagectomy does require further investigation with a dataset where university hospital status and surgeon volume are less closely linked. A further area of investigation may include university hospitals with active participation in randomised controlled trials, testing the hypothesis that active trial participation can raise the clinical outcomes of an individual hospital through exposure to novel therapies and close patient monitoring.

The mechanism through which oesophageal anastomotic leak increases loco-regional recurrence and decreases long-term survival is an important area for future research. This may be a result of the proinflammatory environment with upregulation of cytokines stimulating tumour growth, or this may also involve an interaction with the host microbiome given the leakage of enteric comments. The complex interplay between the patient microbiome, oesophageal cancer and postoperative complications with immune effects is an extremely interesting area for future research.

10 ACKNOWLEDGEMENTS

I would like to express my sincere gratitude to everyone who has contributed to this thesis, most importantly the patients and surgeons, who participated in these studies.

Jesper Lagergren, my primary supervisor, has been a constant source of support during my PhD studies. Every conversation we have had has been extremely educational for me, and I have greatly enjoyed working with someone who shares my passion for clinical research and motivation for maintaining the pace of work. I am incredibly grateful to you personally for investing the time and effort in this PhD and for welcoming me into your incredible research group, which provides the benchmark for European research in our field.

Christophe Mariette, my co-supervisor, who sadly passed away during my PhD studies, and who I sincerely miss. The opportunity to work with, learn from and be mentored by you is something I will always cherish. You may have moved on but the principles you lived by every day will never be forgotten by me.

Mark Van Berge Henegouwen, my co-supervisor and friend, has always been a great colleague to discuss ideas for research, and was the first person to step in and continue to support me when Christophe passed away. As always Mark I am very grateful, and we will continue to collaborate for many years I hope.

Hanna Johans, deserves special mention, as without Hanna's constant help and organisation this PhD would not have been possible. I am and always will be extremely grateful for all you have done for me during my PhD studies at Karolinska.

Hugh Mackenzie, my close colleague who I have worked with for many years now. I am always grateful for your hard work in helping with our studies and for putting up with my many late night calls to push the projects through.

Pernilla Lagergren, co-author of three of the studies, and who has been incredibly welcoming to me during my time in Sweden. Always a friendly smile and kind word, or an extremely insightful comment to help raise the quality of the research we are doing.

I would also like to thank all the other staff and PhD students in the Upper Gastrointestinal Surgery and Surgical Care Science research groups, who have been so welcoming and kind to me during my visits to Stockholm. I hope to be able to return this kindness if you visit London.

Magnus Nilsson and Fredrik Klevebro, who always met me during my visits to Karolinska to take me for a beer, these evenings were some of my best times in Stockholm, and definitely were always looked forward during my visits.

My family, including my parents, Ayesha, Loren, Chiara and Sabina, have always kept me grounded and supported me in everything I have done. To my parents specifically any success I have had in my life is only a reflection of the sacrifices you made to help me during my childhood.

Most importantly I would like to thank my wife, **Marta**, for constantly supporting me even when I decide to do things like a second PhD! **Marta** is and always will be my best friend, the person I depend on always, and my inspiration in everything I do.

11 REFERENCES

1. Powell J, McConkey CC. The rising trend in oesophageal adenocarcinoma and gastric cardia. Eur J Cancer Prev 1992; 1: 265 – 269
2. Blot WJ, Devesa SS, Kneller RW, et al. Rising incidence of adenocarcinoma of the esophagus and gastric cardia. JAMA 1991; 265: 1287 – 1289
3. Siegel R, Naishadham D, Jemal A. Cancer statistics 2012. CA Cancer J Clin 2012; 62: 10 – 29
4. Ferlay J, Steliarova-Foucher E, Lortet-Tieulent J, et al. Cancer incidence and mortality patterns in Europe: Estimates from 40 countries in 2012. Eur J Cancer 2013; 49: 1374 – 1403
5. Kamangar F, Dores GM, Anderson WF. Patterns of cancer incidence, mortality, and prevalence across five continents: defining priorities to reduce cancer disparities in different geographic regions of the World. J Clin Oncol 2006; 24: 2137 – 2150.
6. Lagergren J, Bergstrom R, Lindgren A, et al. Symptomatic gastroesophageal reflux as a risk factor for esophageal adenocarcinoma. N Engl J Med 1999; 340: 825 – 831.
7. Lagergren J, Bergstrom R, Nyren O. Association between body mass and adenocarcinoma of the esophagus and gastric cardia. Ann Intern Med 1999; 130: 883 – 890.
8. Rubio CA, Lagergren J. Histological features pertinent to local tumour progression in Barrett's adenocarcinoma. Anticancer Res 2003; 23: 3015 – 3018.
9. Visrodia K, Singh S, Krishnamoorthi R, et al. Systematic review with meta-analysis: prevalent vs. incident oesophageal adenocarcinoma and high-grade dysplasia in Barrett's oesophagus. Aliment Pharmacol Ther 2016; 44: 775 – 784.
10. Genome-wide association studies in oesophageal adenocarcinoma and Barrett's oesophagus: a large-scale meta-analysis. Lancet Oncol 2016; [Epub ahead of print].
11. Feller A, Fehr M, Bordoni A, et al. Trends in incidence of oesophageal and gastric cancer according to morphology and anatomical location, in Switzerland 1982–2011. Swiss Med Wkly 2015; 145:w14245.
12. Davies AR, Sandhu H, Pillai A, et al. Surgical resection strategy and the influence of radicality on outcomes in oesophageal cancer. Br J Surg 2014; 101: 511 – 517.
13. Noguchi Y, Imada T, Matsumoto A, et al. Radical surgery for gastric cancer. A review of the Japanese experience. Cancer. 1989; 64: 2053–2062 .

14. Shawihdi M, Thompson E, Kapoor N, et al. Variation in gastroscopy rate in English general practice and outcome for oesophagogastric cancer: retrospective analysis of Hospital Episode Statistics. Gut 2014; 63: 250 – 261.
15. Gavin AT, Francisci S, Foschi R, et al. Oesophageal cancer survival in Europe: A EUROCARE-4 Study. Cancer Epidemiology 2012; 36: 505 – 512.
16. UK National Oesophago-Gastric Cancer audit. http://www.hqip.org.uk/resources/national-oesophago-gastric-cancer-audit-2016/ [last accessed 10th October 2016].
17. Markar SR, Karthikesalingam A, Thrumurthy S, et al. Volume-outcome relationship in surgery for esophageal malignancy: systematic review and meta-analysis 2000 – 2011. J Gastrointest Surg 2012; 16: 1055 – 1063.
18. Derogar M, Orsini N, Sadr-Azodi O, et al. Influence of major postoperative complications on health-related quality of life among long-term survivors of esophageal cancer surgery. J Clin Oncol 2012; 30: 1615 – 1619.
19. 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.
20. Blazeby JM, Metcalfe C, Nicklin J, et al. Association between quality of life scores and short-term outcome after surgery for cancer of the oesophagus or gastric cardia. Br J Surg 2005; 92: 1502 – 1507.
21. 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.
22. Messager M, Pasquer A, Duhamel A, et al. Laparoscopic gastric mobilization reduces postoperative mortality after esophageal cancer surgery: a French Nationwide Study. Ann Surg 2015; 262: 817 – 822.
23. 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
24. Shapiro J, van Lanschot JJ, Hulshof MC, et al. Neoadjuvant chemoradiotherapy plus surgery versus surgery alone for oesophageal or junctional cancer (CROSS): long-term results of a randomised controlled trial. Lancet Oncol 2015; 16: 1090 – 1098.
25. Cunningham D, Allum WH, Stenning SP, et al. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. N Engl J Med 2006; 355: 11 – 20
26. 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.
27. Burmeister BH, Thomas JM, Burmeister EA, et al. Is concurrent radiation therapy required in patients receiving preoperative chemotherapy for adenocarcinoma of the oesophagus? A randomized phase II trial. Eur J Cancer 2011; 47: 354 – 360.
28. Stahl M, Walz MK, Stuschke M, et al. Phase III comparison of preoperative chemotherapy compared with chemoradiotherapy in patients with locally advanced adenocarcinoma of the esophagogastric junction. J Clin Oncol 2009; 27: 851 – 856.
29. Klevebro F, Alexandersson von Dobeln G, Wang N, et al. A randomized clinical trial of neoadjuvant chemotherapy versus chemoradiotherapy for cancer of the oesophagus or gastro-oesophageal junction. Ann Oncol 2016; 27: 660 – 667.
30. Ajani JA, Bentrem DJ, Besh S, et al. Esophageal and esophago-gastric junction cancers (excluding the proximal 5cm of the stomach). NCCN Clinical practice Guidelines in Oncology (NCCN Guidelines ®) version 2. 2012
31. Teoh AY, Chiu PW, Yeong WK, et al. Long-term survival outcomes after definitive chemoradiation versus surgery in patients with resectable squamous carcinoma of the esophagus: results from a randomized controlled trial. Ann Oncol 2013; 24: 165 – 171
32. Bedenne L, Michel P, Bouche O, et al. Chemoradiation followed by surgery compared with chemoradiation alone in squamous cancer of the esophagus: FFCD 9102. J Clin Oncol 2007; 25: 1160 – 1168
33. Wakui R, Yamashita H, Okuma K, et al. Esophageal cancer: definitive chemoradiotherapy for elderly patients. Dis Esophagus 2010; 23: 572 – 579
34. Cooper JS, Guo MD, Herskovic A, et al. Chemoradiotherapy of locally advanced esophageal cancer: long-term follow-up of a prospective randomized trials (RTOG 85 – 01). Radiation Therapy Oncology Group. JAMA 1999; 281: 1623 – 1627
35. Minsky BD, Pajak TF, Ginsberg RJ et al. INT 0123 (Radiation Therapy Oncology Group 94 – 05) phase III trial of combined modality therapy for esophageal cancer: high-dose versus standard dose radiation therapy. J Clin Oncol 2002; 20: 1167 – 1174.
36. Takeuchi S, Ohtsu A, Doi T, et al. A retrospective study of definitive chemoradiotherapy for elderly patients with esophageal cancer. Am J Clin Oncol 2007; 30: 607 – 611
37. Gardner-Thorpe J, Hardwick RH, Dwerryhouse SJ. Salvage oesophagectomy after local failure of definitive chemoradiotherapy. Br J Surg 2007; 94: 1059 – 1066
38. Markar SR, Karthikesalingam A, Penna M, Low DE. Assessment of short-term clinical outcomes following salvage esophagectomy for the treatment of esophageal malignancy: systematic review and pooled analysis. Ann Surg Oncol 2014; 21: 922 – 931

39. Miskovic D, Ni M, Wyles SM, et al. Learning curve and case selection in laparoscopic colorectal surgery: systematic review and international multicenter analysis of 4852 cases. Dis Colon Rectum 2012; 55: 1300–10.
40. Tapias LF, Morse CR. Minimally invasive Ivor Lewis esophagectomy: description of a learning curve. J Am Coll Surg 2014; 218: 1130–40.
41. Zhou D, Quan Z, Wang J, et al. Laparoscopic-assisted versus open distal gastrectomy with D2 lymph node resection for advanced gastric cancer: effect of learning curve on short-term outcomes, a meta-analysis. J Laparoendosc Adv Surg Tech A. 2014; 24: 139–50.
42. Mackenzie H, Markar SR, Askari A, et al. National proficiency-gain curves for minimally invasive gastrointestinal cancer surgery. Br J Surg. 2016; 103: 88 – 96.
43. Birkmeyer D, Siewers AE, Finlayson EV, et al. Hospital volume and surgical mortality in the United States. N Engl J Med 2002; 346: 1128 – 1137.
44. Finks JF, Osborne NH, Birkmeyer JD. Trends in hospital volume and operative mortality for high-risk surgery. N Engl J Med 2011; 364: 2128 – 2137.
45. Schenarts PJ, Cemaj S. The aging surgeon: implications for the workforce, the surgeon, and the patient. Surg Clin North Am 2016; 96: 129 – 138.
46. Bhatt NR, Morris M, O'Neil A, et al. When should surgeons retire? Br J Surg 2016; 103: 35 – 42.
47. Ruteledge RB, Smittenaar P, Zeidman P, et al. Risk taking for potential reward decreases across the lifespan. Curr Biol 2016; 26: 1634 – 1639.
48. Josef AK, Richter D, Samanez-Larkin GR, et al. Stability and change in risk-taking propensity across the adult life span. J Pers Soc Psychol 2016; 111: 430 – 450.
49. Waljee JF, Greenfield LJ, Dimick JD, et al. Surgeon age and operative mortality in the United States. Ann Surg 2006; 244: 353 – 362.
50. Young JA, Shimi SA, Waugh L, et al. Improved short term surgical outcome in Scotland for oesophageal cancer. Eur J Surg Oncol 2013; 39: 131 – 135.
51. Cen P, Banki F, Cheng L, et al. Changes in age, stage distribution, and survival of patients with esophageal adenocarcinoma over three decades in the United States. Ann Surg Oncol 2012; 19: 1685 – 1691.
52. Da Costa WL Jr, Coimbra FJ, Ribeiro HS, et al. Total gastrectomy for gastric cancer: an analysis of postoperative and long-term outcomes through time: results of 413 consecutive cases in a single center. Ann Surg Oncol 2015; 22: 750 – 757.
53. Kim W, Kim HH, Han SU, et al; Koren Laparo-endoscopic Gastrointestinal Surgery Study (KLASS) Group. Ann Surg 2016; 263: 28 – 35.

54. Munasinghe A, Markar SR, Mamidanna R, et al. Is it time to centralize high-risk cancer care in the United States? Comparison of outcomes of esophagectomy between England and the United States. Ann Surg 2015; 262: 79 – 85.
55. Rizk NP, Bach PB, Schrag D, et al. The Impact of Complications on Outcomes after Resection for Esophageal and Gastroesophageal Junction Carcinoma. J Am Coll Surg 2004; 198: 42 – 50
56. Rutegard M, Lagergren P, Rouvelas I, et al. Surgical complications and long-term survival after esophagectomy for cancer in a nationwide Swedish cohort study. Eur J Surg Oncol 2012; 38: 555 – 561
57. Mirnezami A, Mirnezami R, Chandrakumaran K, et al. Increased local recurrence and reduced survival from colorectal cancer following anastomotic leak: systematic review and meta-analysis. Ann Surg 2011; 253: 890 – 899
58. Symes MO, Fermor B, Umpleby HC, et al. Cells exfoliated from colorectal cancers can proliferate in immune deprived mice. Br J Cancer 1984; 50: 423 – 425
59. Fermor B, Umpleby HC, Lever JV, et al. Proliferative and metastatic potential of exfoliated colorectal cancer cells. J Natl Cancer Inst 1986; 76: 347 – 349
60. Juloori A, Tucker SL, Komaki R, et al. Influence of preoperative radiation field on postoperative leak rates in esophageal cancer patients after trimodality therapy. J Thorac Oncol 2014; 9: 534 – 540.
61. Robb WB, Messager M, Gronnier C, et al. High-grade toxicity to neoadjuvant treatment for upper gastrointestinal carcinomas: what is the impact of perioperative and oncologic outcomes? Ann Surg Oncol 2015; 22: 3632 – 3639.
62. Barlow L, Westergren K, Holmberg L, et al. The completeness of the Swedish Cancer Register: A sample survey for year 1998. Acta Oncol 2009; 48: 27 – 33.
63. Lindbald M, Ye W, Lindgren A, et al. Disparities in the classification of esophageal and cardia adenocarcinomas and their influence on reported incidence rates. Ann Surg 2006; 243: 479 – 485.
64. The Swedish National Board of Health and Welfare: Swedish Causes of Death Register – Bortfall och kvalitet I dodsorsaksregistret. In.
65. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg 2004; 240: 205 – 213.
66. Grigg OA, Farewell VT, Spiegelhalter DJ. Use of risk-adjusted CUSUM and RSPRT charts for monitoring in medical contexts. *Stat Methods Med Res.* 2003; **12**: 147-170.

67. Low DE, Alderson D, Cecconello I, et al. International consensus on standardization of data collection for complications associated with esophagectomy: esophagectomy complications consensus group (ECCG). Ann Surg 2015; 262: 286 – 294.
68. Low DE, Kuppusamy MK, Alderson D, et al. Benchmarking complications associated with esophagectomy. Ann Surg 2017; [Epub ahead of print].
69. Markar SR, Naik R, Malietzis G, et al. Component analysis of enhanced recovery pathways for esophagectomy. Dis Esophagus 2017; 30: 1 – 10.
70. Lordick F, Ott K, Krause BJ, et al. PET to assess early metabolic response and to guide treatment of adenocarcinoma of the oesophagogastric junction: the MUNICON phase II trial. Lancet Oncol 2007; 8: 797 – 805.
71. Findlay JM, Bradley KM, Wang LM, et al. Predicting pathologic response of esophageal cancer to neoadjuvant chemotherapy: The implications of metabolic nodal response for personalized therapy. J Nucl Med 2017; 58: 266 – 275.
72. Sutton DN, Wayman J, Griffin SM. Learning curve for oesophageal cancer surgery. Br J Surg 1998; 85: 1399 – 1402.
73. Mackenzie H, Cuming T, Miskovic D, et al. Design, delivery, and validation of a trainer curriculum for the national laparoscopic colorectal training program in England. Ann Surg 2015; 261: 149 – 156.
74. Mackenzie H, Ni M, Miskovic D, et al. Clinical validity of consultant technical skills assessment in the English National Training Programme for Laparoscopic Colorectal Surgery. Br J Surg 2015; 102: 991 – 997.
75. Coleman MG, Hanna GB, Kennedy R. The National Training Programme for Laparoscopic Colorectal Surgery in England: A new training paradigm. Colorectal Dis 2011; 13: 614 – 616.
76. Markar SR, Mackenzie H, Lagergren P, et al. Surgical proficiency gain and survival after esophagectomy for cancer. J Clin Oncol 2016; 34: 1528 – 1536.
77. Miskovic D, Ni M, Wyles SM, et al. Observational clinical human reliability analysis (OCHRA) for competency assessment in laparoscopic colorectal surgery at the specialist level. Surg Endosc 2012; 26: 796 – 803.
78. Ahmed AR, Miskovic D, Vijayaseelan T, et al. Root cause analysis of internal hernia and Roux limb compression after laparoscopic Roux-en-Y gastric bypass using observation clinical human reliability assessment. Surg Obes Relat Dis 2012; 8: 158 – 163.
79. Talebpou M, Alijani A, Hanna GB. Proficiency-gain curve for an advanced laparoscopic procedure defined by observation clinical human reliability assessment (OCHRA). Surg Endosc 2009; 23: 869 – 875.

80. Derogar M, Sadr-Azodi O, Johar A, et al. Hospital and surgeon volume in relation to survival after esophageal cancer surgery in a population-based study. J Clin Oncol 2013; 31: 551 – 557.
81. Brusselaers N, Mattsson F, Lagergren J. Hospital and surgeon volume in relation to long-term survival after oesophagectomy: systematic review and meta-analysis. Gut 2014; 63: 1393 – 1400.
82. 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.
83. Phillips AW, Dent B, Navidi M, et al. Trainee involvement in Ivor Lewis Esophagectomy does not negatively impact outcomes. Ann Surg 2018; 267: 94 – 98.
84. Escofet X, Manjunath A, Twine C, et al. Prevalence and outcome of esophagogastric anastomotic leak after esophagectomy in a UK regional cancer network. Dis Esophagus 2010; 23: 112 – 116.
85. Hi MW, Smithers BM, Gotley DC, et al. Impact of postoperative morbidity on long-term survival after oesophagectomy. Br J Surg 2013; 100: 95 – 104.
86. Takeuchi H, Saikawa Y, Oyama T, et al. Factors influencing the long-term survival in patients with esophageal cancer who underwent esophagectomy after chemoradiotherapy. World J Surg 2010; 34: 277 – 284.
87. Xia BT, Rosato EL, Chojnacki KA, et al. Major peroperative morbidity does not affect long-term survival in patients undergoing esophagectomy for cancer of the esophagus or gastroesophageal junction. World J Surg 2013; 37: 408 – 415.
88. Rutegard M, Lagergren P, Rouvelas I, et al. Surgical complications and long-term survival after esophagectomy for cancer in a nationwide Swedish cohort study. Eur J Surg Oncol 2012; 38: 555 – 561.
89. Mirnezami A, Mirnezami R, Chandrakumaran K, et al. Increase local recurrence and reduced survival from colorectal cancer following anastomotic leak: systematic review and meta-analysis. Ann Surg 2011; 253: 890 – 899.
90. Yousif NG, Al-Amran FG, Hadi N, et al. Expression of IL-32 modulates NF-kB and p38 MAP kinase pathways in human esophageal cancer. Cytokine 2013; 61: 223 – 227
91. Chen MF, Lu MS, Chen PT, et al. Role of interleukin 1 beta in esophageal squamous cell carcinoma. J Mol Med (Berl) 2012; 90: 89 – 100
92. Ito H, Kaneka, Makino R, et al. Interleukin-1 beta gene in esophageal, gastric and colorectal carcinoma. Oncol Rep 2007; 18: 473 – 481

93. Markar SR, Arya S, Karthikesalingam A, Hanna GB. Technical factors that affect anastomotic integrity following esophagectomy: systematic review and meta-analysis. Ann Surg Oncol 2013; 20: 4271 – 4281
94. Anderson O, Ni Z, Moller H et al. Hospital volume and survival in oesophagectomy and gastrectomy for cancer. Eur J Cancer 2011; 47: 2408 – 2414
95. Birkmeyer JD, Sun Y, Wong SL, et al. Hospital volume and later survival after cancer surgery. Ann Surg 2007; 245: 777 – 783