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IMPROVED SURGICAL TREATMENT OF OESOPHAGEAL CANCER

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Cover illustration: Surgical resection of oesophageal cancer and creation of gastric conduit.
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Improved surgical treatment of oesophageal cancer

THESIS FOR DOCTORAL DEGREE (Ph.D.)

By

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In loving memory of my father.

Här går nya vägar.
Låt oss vandra fromma.
Kom, låt oss söka
någon ny och vacker blomma.

Kasta det vi äger!
Allting nått och färdigt
livlöst oss tynger,
dröm och sång och dåd ej värdigt.

Liv är det som väntar,
det man ej kan veta…
Kom, låt oss glömma!
Låt oss nytt och fagert leta!

Nya vägar. Ur diktsamlingen ”Gömda Land”. Karin Boye 1924.

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ABSTRACT

Oesophageal cancer is the 7th most common cancer globally and the 5-year survival is poor (below 20%). Curative treatment usually involves surgical resection of the tumour (oesophagectomy), with or without neoadjuvant chemo(radio)therapy. The aim of the thesis was to identify surgery-related factors of importance for improved long-term survival in oesophageal cancer.

Study I was a nationwide Swedish cohort study of patients who underwent oesophagectomy for oesophageal cancer between 1987 and 2010, with follow-up until 2016. The study included 1,384 patients who had undergone surgery by any of 36 surgeons. Risk adjusted cumulative sum analysis was used to create proficiency gain curves for "lower volume surgeons" (<4 cases per year) and "higher volume surgeons" (≥4 cases per year), as well as "younger surgeons" (<45 years) and "older surgeons" (≥45 years) regarding all-cause 1 to 5-year mortality (main outcome). The results were adjusted for confounders. "Higher volume surgeons" reached proficiency at 14 cases compared to 31 cases for "lower volume surgeons". "Younger surgeons" reached proficiency at 13 cases compared to 48 cases for "older surgeons".

Study II was a systematic review and meta-analysis comparing long-term survival after minimally invasive oesophagectomy (MIO) with open oesophagectomy (OO) for oesophageal cancer in studies published up until 2018. Based on 55 relevant studies and 14,592 patients (7,358 MIO and 7,234 OO), random effects meta-analysis was used to produce hazard ratios (HR) with 95% confidence intervals (CI) for all-cause 5-year mortality (main outcome) with adjustment for confounders. MIO was associated with 18% lower risk of all-cause 5-year mortality compared to OO (HR 0.82, 95% CI 0.76-0.88).

Study III was a population-based cohort study including almost all patients operated for oesophageal cancer in Sweden from 2011 until 2015 and in Finland from 2010 until 2016, with follow-up throughout 2019. Multivariable Cox regression was used to produce HRs with 95% CIs comparing MIO (n=459) with OO (n=771) for the main outcome all-cause 5-year mortality. The results were adjusted for confounders. MIO was associated with 18% lower risk of all-cause 5-year mortality compared to OO (HR 0.82, 95% CI 0.67-1.00 [P=0.048]).

Study IV was a population-based cohort study including almost all patients who underwent surgery for oesophageal cancer from 2000 until 2015 in Sweden and from 2000 until 2016 in Finland, with follow-up throughout 2019. The 2,306 included patients were divided into deciles (10 about equal size group) by the level of lymphadenectomy during oesophagectomy. Multivariable Cox regression was used to produce HRs with 95% CIs for the main outcome all-cause 5-year mortality with adjustment for confounders. Compared to the 1st decile (0-3 nodes) the lowest risk for all-cause 5-year mortality was found in decile 8 (25-30 nodes). Upon stratification, this survival benefit was especially apparent for T3/T4 tumours and for patients who did not receive neoadjuvant therapy.

In conclusion, this thesis indicates that intense training in oesophagectomy of younger surgeons, use of minimally invasive oesophagectomy and moderate extent of lymphadenectomy improve long-term survival in patients who undergo surgery for oesophageal cancer.

LIST OF SCIENTIFIC PAPERS

I. Gottlieb-Vedi E, Mackenzie H, van Workum F, Rosman C, Lagergren P, Markar S, Lagergren J. **Surgeon volume and surgeon age in relation to proficiency gain curves for prognosis following surgery for esophageal cancer.** ***Ann Surg Oncol.*** 2019 Feb;26(2):497-505.

II. Gottlieb-Vedi E, Kauppila JH, Malietzis G, Nilsson M, Markar SR, Lagergren J. **Long-term survival in esophageal cancer after minimally invasive compared to open esophagectomy: a systematic review and meta-analysis.** ***Ann Surg.*** 2019 Dec;270(6):1005-1017.

III. Gottlieb-Vedi E, Kauppila JH, Mattsson F, Lindblad M, Nilsson M, Lagergren P, Rouvelas I, FINEGO group, Lagergren J. **Long-term survival in esophageal cancer after minimally invasive esophagectomy compared to open esophagectomy.** ***Ann Surg.*** 2021 Jan 20. Online ahead of print.

IV. Gottlieb-Vedi E, Kauppila J, Mattsson F, Hedberg J, Johansson J, Edholm D, Lagergren P, Nilsson M, FINEGO group, Lagergren J. **Extent of lymphadenectomy and long-term survival in oesophageal cancer.** ***Ann Surg.*** 2021 Jun 25. Online ahead of print.

LIST OF ABBREVIATIONS

5-FU	Fluorouracil
AJCC	American Joint Committee on Cancer
CCRBT	Cochrane Collaborations Risk of Bias Tool
CI	Confidence interval
cTNM	Clinical tumor stage group
GOJ	Gastro oesophageal junction
Gy	Gray
HR	Hazard ratio
LISA	Longitudinal Integration database for Health insurance and Labor market studies
M-stage	Distant metastasis stage
MIO	Minimally invasive oesophagectomy
N-stage	Regional lymph node stage
NREV	Swedish National Register for Esophageal and Gastric cancer
OAC	Oesophageal adenocarcinoma
OO	Open oesophagectomy
OSCC	Oesophageal squamous cell carcinoma
pTNM	Pathological tumour stage group
RA-CUSUM	Risk adjusted cumulative sum
RCT	Randomized controlled trial
T-stage	Primary tumour stage
ypTNM	Postneoadjuvant pathological tumour stage group

INTRODUCTION

Oesophageal cancer is the 6th most common cause of cancer deaths globally.[1] The main curative treatment is surgical resection of the oesophagus (oesophagectomy), usually in combination with chemo(radio)therapy.[2] However, even after curatively intended treatment, survival within 5 years of treatment is below 50%.[3]

This thesis aimed to answer clinically relevant research questions that may lead to improved long-term survival in patients with oesophageal cancer undergoing curative treatment. The thesis is based on four studies. Study I explored proficiency gain curves for different categories of surgeon age and annual operation volume. Study II and III compared the long-term survival after minimally invasive surgery compared to open surgery, in a systematic review and meta-analysis and in a cohort study, respectively. Study IV assessed if long-term survival changes across different levels of lymphadenectomy.

LITERATURE REVIEW

THE OESOPHAGUS

The oesophagus is an elastic muscular tube, approximately 25 cm in length.[4] Its function is to transport food and liquids from the pharynx to the stomach.[5] Along its course it passes organs and structures such as the common carotid arteries, trachea, lungs, heart, aorta, liver and spine (Figure 1).[4] The oesophageal wall consists of 4 distinctive layers (counted from the lumen and outwards; Figure 2): mucosa, submucosa, muscularis externa and adventitia. The mucosa is further sub-divided into the epithelium, lamina propria and muscularis mucosa. The native epithelium, facing the lumen of the oesophagus, is made up by nonkeratinized stratified squamous epithelium, which ends at the junction between the oesophagus and the stomach, the gastro oesophageal junction (GOJ), where it is replaced by columnar epithelium.[5] The division into layers is relevant in a clinical setting for tumour staging (Figure 2).[6]

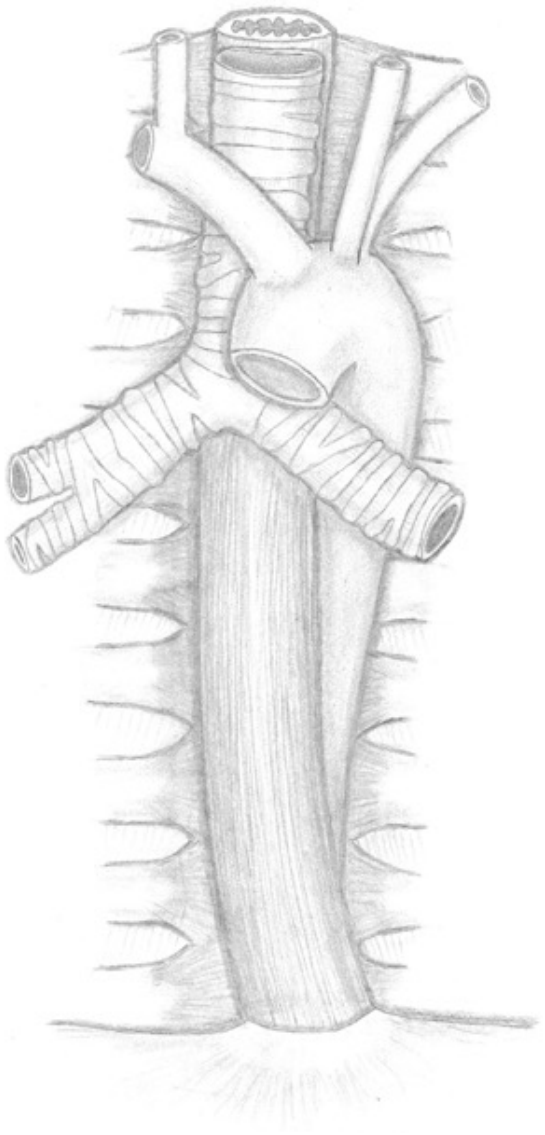

Figure 1. The oesophagus and its relation to the common carotid arteries, trachea, aorta, spine and diaphragm. Illustration by the author.

OESOPHAGEAL CANCER

In 2020 there were 604,100 incident cases and 544,076 deaths of oesophageal cancer globally.[1] This ranks it as the 7th most common cancer and the 6th most common cancer death.[7] The survival has improved over the past decades, but despite advances in diagnostics and treatment the overall 5-year survival is still below 20%.[8, 9]

There are two main histological subtypes of oesophageal cancer, namely oesophageal squamous cell carcinoma (OSCC) and oesophageal adenocarcinoma (OAC).[10] Globally, 87% of all cases are OSCC.[11] The most important risk factors for OSCC are tobacco smoking and high consumption of alcohol,[12] whereas consumption of fruits and vegetables is protective.[13] OSCC affects men more often than women, with a male to female ratio of 2.7:1.[11] The highest incidence rates are found in Asia, foremost Eastern and South-East Asia (53% of global cases in China alone), and sub-Saharan Africa.[11] In these high-endemic areas, consumption of very hot beverages,[14] poor nutritional status and lack of proper sanitation are other important risk factors.[15] OSCC can develop if the epithelium receives physical or chemical damage, leading to inflammation, hyperplasia and dysplasia through DNA damage.[16] A global trend among men is a decrease in incidence during the last decades, whereas the trend for women varies across countries, and increased incidence rates have been observed in for example the Netherlands and Norway.[17]

Whereas OSCC can form anywhere along the length of the oesophagus, OAC typically forms in the distal part where metaplastic columnar cell mucosa (Barrett's oesophagus) can occur in response to long-standing gastro oesophageal reflux disease (described below).[10] The most important risk factor for OAC is therefore gastro oesophageal reflux disease, followed by obesity.[18, 19] Although not as important as for OSCC, tobacco smoking is also a risk factor.[18, 20] Consumption of fruits and vegetables has a protective effect,[18] whereas consumption of meat and saturated fat seems to increase the risk.[21] Colonization of the bacteria Helicobacter pylori of the stomach is associated with decreased risk of OAC, but not OSCC.[22] Opposite to OSCC, incidence rates of OAC have increased substantially in many parts of the world during the last four decades, by as much as 3.5-8.1% annually in some countries since the 1970s.[23] This increase correlates with an increased prevalence of gastro oesophageal reflux disease and obesity and a decreased prevalence of Helicobacter pylori infecton.[2] The highest incidence rates are found in North America, Northern and Western Europe and Oceania.[11] Compared to OSCC, OAC is more evenly spread around the world, but the highest proportions are found in Northern and Western Europe (22.8%).[11] Among individual countries, the incidence is highest in the United Kingdom and the Netherlands,[11] where OAC is by far the most common histology of oesophageal cancer.[24] As with OSCC, OAC is more common among men, but the male to female ratio of 4.4:1 is stronger.[11] OAC develops as long lasting reflux of acid and bile from the stomach causes a physiological response of metaplasia (Barrett's oesophagus) in which the squamous cell epithelium of the oesophagus transforms into columnar epithelium as a way of adaptation, thus pushing the GEJ more proximally.[10] Finally, Barrett's oesophagus transforms into OAC through low and high grade dysplasia, through mechanisms which are not completely understood, with an annual risk in the range of 0.12 to 0.60%.[10]

Staging

Staging of oesophageal cancer serves as a basis for deciding on treatment as well as being a prognostic indicator. Classification is based on the depth of growth of the primary tumour (T-stage), number of regional lymph node metastasis (N-stage) and distant metastasis (M-stage), jointly described as the TNM-system. Each stage can either be clinical (information based on imaging methods before treatment is initiated) or pathological (information based on pathological examination of resected specimen). Currently the 8th edition of the American Joint Committee on Cancer (AJCC) staging manual is used. T-stage is categorised as T0 (no evidence of primary tumour), Tis (high grade dysplasia), T1 (invasion of lamina propria or muscularis mucosa [T1a], or submucosa [T1b]), T2 (invasion of muscularis propria), T3 (invasion of adventitia), T4 (invasion of pleura, pericardium, azygos vein, diaphragm or peritoneum [T4a], or invasion of other adjacent structures, e.g. the aorta or trachea [T4b]) or TX (tumour cannot be assessed) (Figure 2). N-stage is categorized as N0 (0 regional lymph node metastases), N1 (1-2 regional lymph node metastases), N2 (3-6 regional lymph node metastases), N3 (≥7 regional lymph node metastases) or NX (regional lymph node metastasis cannot be assessed). M-stage is categorized as M0 (no distant metastasis), M1 (distant metastasis) or MX (distant metastasis cannot be assessed). T-stage, N-stage and M-stage are further grouped in a clinical stage group (cTNM) or in a pathological stage group (pTNM). cTNM is used for deciding treatment routes, but has inaccuracies due to limitations of the imaging methods compared to histopathological examination, wherefore it does not predict survival as well as pTNM. On the other hand, pTNM is problematic as it is affected by neoadjuvant therapy administered prior to surgery. For this reason, a separate system exists for the latter group (ypTNM). However, survival differs between corresponding stages of pTNM and ypTNM, especially for early stages where survival is worse for ypTNM. Tumour stage groups according to cTNM, pTNM and ypTNM are all classified as I-IV, with higher stages corresponding to more advanced disease.[6]

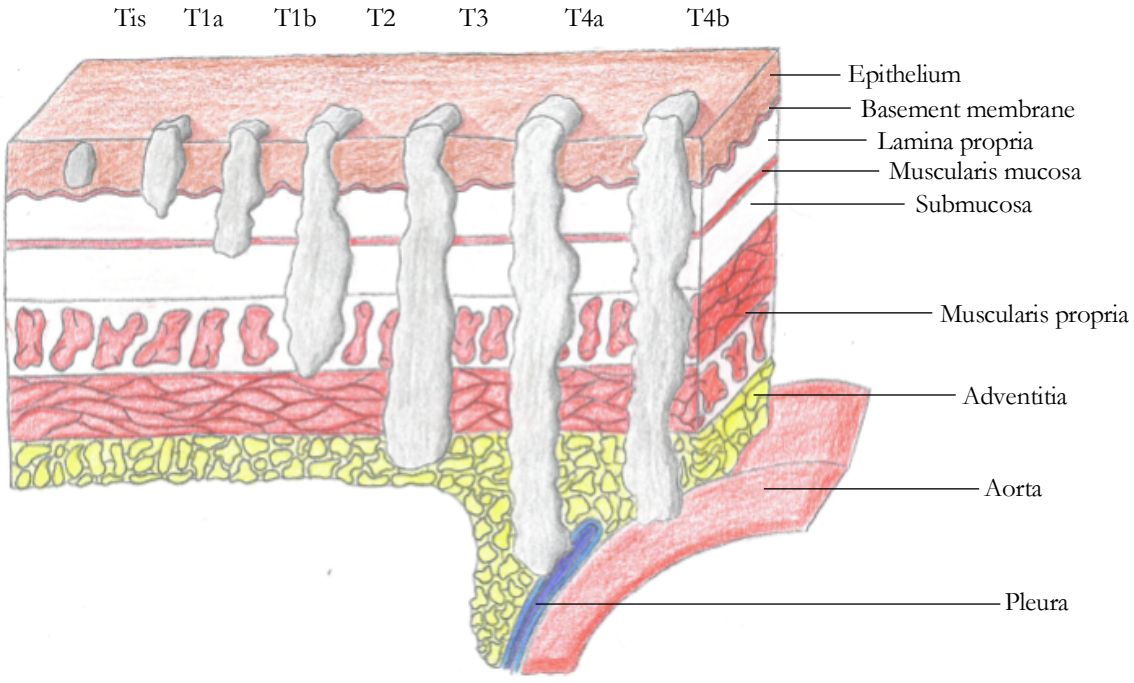

Figure 2. Layers of the oesophageal wall and T-stages. Illustration by the author.

Curative treatment options

Early stage OAC and OSCC (cT1-T2, cN0, cM0) is effectively treated by resection. According to updated guidelines of the European Society for Medical Oncology (unpublished), endoscopic resection is the first treatment of choice in general for cT1 tumours. Further treatment with surgical resection (oesophagectomy) and lymphadenectomy might be conducted if there is tumour involvement of the deep resection margin and based on risk factors that are associated with increased risk of lymph node metastasis: increased tumour depth and size, low differentiation, presence of lymphovascular invasion and ulceration. Oesophagectomy is used for cT2 tumours. Locally advanced OAC (cT3-T4, any cN, cM0 or any cT, cN+, cM0) are typically treated with neoadjuvant chemo(radio)therapy or perioperative chemotherapy in combination with oesophagectomy. Locally advanced OSCC are treated with neoadjuvant chemo(radio)therapy and oesophagectomy, or definitive chemoradiotherapy (and salvage oesophagectomy if needed). A commonly recommended chemoradiotherapy regimen consists of the chemotherapy drugs carboplatin and paclitaxel for 5 cycles and concurrent radiotherapy of totally 41.4 Gy in 23 fractions over 5 weeks (CROSS-regimen). Alternatively, the neoadjuvant chemotherapy may consist of a combination of fluorouracil (5-FU) and oxaliplatin (and folinic acid; FOLFOX-regimen) or 5-FU and cisplatin. In the case of perioperative chemotherapy for adenocarcinoma, treatment is either by the FOLFOX-regimen, FLOT-regimen (docetaxel, oxaliplatin, leucovorin and 5-FU administered as 24-hour infusions weekly four weeks before and after surgery) or 5-FU combined with cisplatin. cT4b tumours are often viewed as inoperable, but might be candidates for surgery if downstaging is achieved by neoadjuvant therapy. M1 disease is generally considered non-curative and warrants palliative treatment, although on-going research is evaluating if more aggressive treatment may be beneficial also for selected patients with limited M1-disease.[25, 26]

Resectional surgery

Oesophagectomy aims to obtain radical removal of the primary tumour together with regional lymphadenectomy.[2] Radicality is defined as R0 (no cancer cells at the resection margin), R1 (cancer cells at the resection margin) or R2 (macroscopically visible tumour at the resection margin).[6] After resection, continuity of the gastrointestinal canal is recreated by the use of a conduit, most commonly the stomach (otherwise bowel), joined by an anastomosis (Figure 3).[27] Oesophagectomy combined with resection of the proximal stomach is the most common method, but sometimes surgical removal of the stomach (total gastrectomy) combined with distal oesophagectomy is used for distal tumours. Different surgical approaches exist for oesophagectomies, which can be defined according to access (e.g. open transhiatal, open transthoracic or minimally invasive), extent of lymphadenectomy (e.g. two-field or three-field) and location of anastomosis (e.g. intra-thoracic or cervical). Certain combinations of factors define the specific procedures, such as the commonly used Ivor Lewis approach which includes an abdominal and right-sided thoracic approach, two-field lymphadenectomy (abdominal + mediastinal) and reconstruction using a gastric conduit which is joined by an intrathoracic anastomosis. The choice of method is dependent on factors such as tumour size, tumour location and surgeon preference.[27]

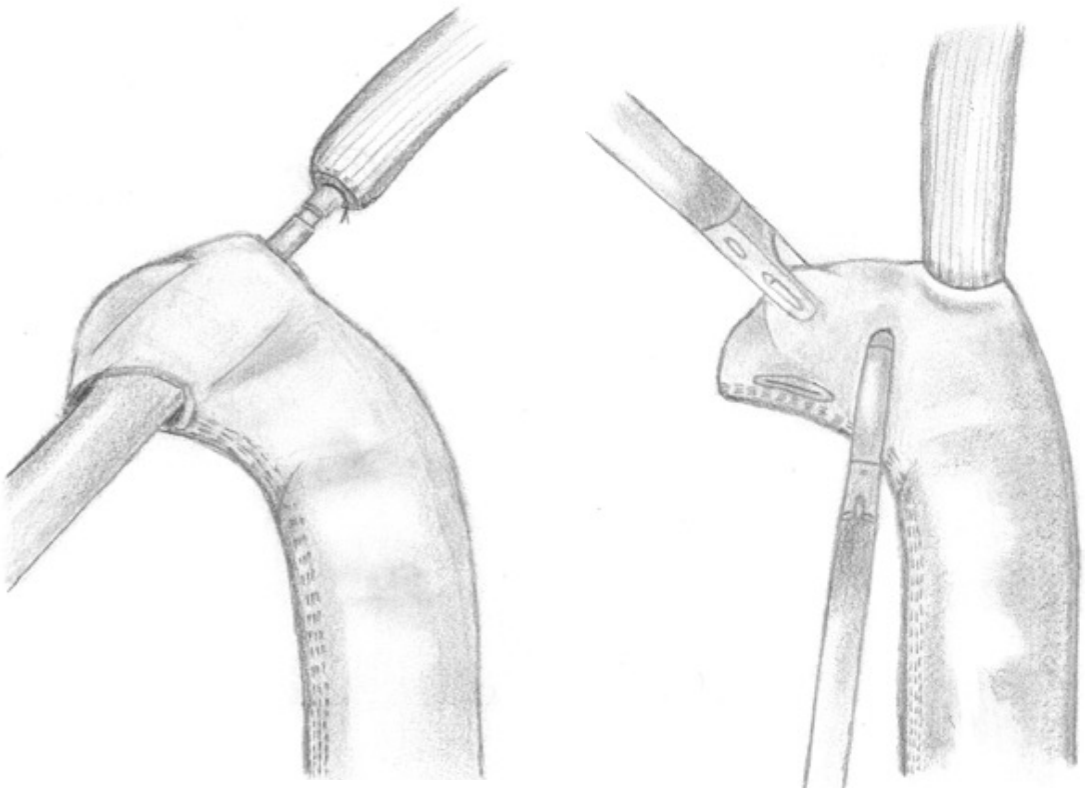

Figure 3. Creation of oesophagogastric anastomosis during surgery for oesophageal cancer. Illustration by the author.

Three factors of particular relevance to this thesis are surgeons' proficiency gain, minimally invasive surgery and lymphadenectomy, and these are discussed below.

Proficiency gain

Surgery for oesophageal cancer is complex and is associated with substantial surgical trauma and risk for complications and long-lasting morbidities. Surgery needs to be radical and at the same time cause as little morbidity to the patient as possible.[27] Previous studies have showed that a substantial number of oesophagectomies are needed for each surgeon to reach proficiency, i.e. to fully master the procedure in terms of complications or survival, in the range of 15-19 cases for optimized 30-day survival.[28, 29] One study included 5-year survival for which it showed that proficiency was reached at 59 cases.[28] These findings indicate that survival is decreased for patients who are operated on by surgeons with less experience of this specific procedure, and more importantly raises the question if the learning process can be improved so that surgeons reach proficiency after fewer operations. Another study assessed age of surgeons performing surgery for oesophageal cancer and long-term survival, and showed that survival was best if surgeons were aged 52-56 years, with decreased survival both before and after this "plateau".[30] A large cohort study and a systematic review and meta-analysis identified cumulative surgeon volume of oesophagectomies, rather than hospital volume, to be of importance in terms of improved long-term survival.[31, 32] In this thesis, we hypothesised that proficiency could be gained faster if the surgeons are of younger age and if they have a more intensive training period during a shorter time period.

Minimally invasive surgery

Minimally invasive oesophagectomy (MIO) is an umbrella term for procedures involving "keyhole" incisions in the abdomen and/or chest rather than traditional open incisions, such as laparoscopy instead of laparotomy and thoracoscopy instead of thoracotomy. MIO procedures can be divided into hybrid and total, with the difference that hybrid uses a combination of keyhole and open approaches (i.e. laparotomy and thoracoscopy) whereas total MIO only uses keyhole approaches throughout.[10] The rationale behind using MIO is that it may cause less surgical trauma, and by that perhaps prevent complications, improve postoperative recovery and prolong survival. Studies have indicated that compared to open oesophagectomy (OO), MIO is associated with fewer and less severe complications during and after surgery (especially pulmonary complications, e.g. pneumonia and respiratory insufficiency), shorter hospital stay, lower in-hospital mortality, and better quality of life up to one year after surgery.[33-37] The evidence is limited regarding the influence of surgical access in relation to long-term survival, mainly because few high-quality studies have been published. Among published studies are a small systematic review and meta-analysis and two small randomized controlled trials (RCTs), and these failed to show any difference in long-term survival after MIO and OO, possibly due to type II-error.[36-38] Therefore, further and larger studies on the topic are needed before any conclusions can be drawn regarding the influence of MIO versus OO in relation to long-term survival, which was the reason for conducting such research within the present thesis.

Lymphadenectomy

Oesophageal cancer easily spreads to mediastinal, abdominal and cervical lymph nodes.[39-41] The lymphatic drainage from the oesophagus is complex and vast, leading to a multidirectional and unpredictable spreading pattern of the cancer.[42] This complexity is exemplified by a phenomenon referred to as skip metastasising, mostly studied for OSCC, in which lymph node metastases are found beyond an area closer to the primary tumour with no lymph node metastases. A large proportion of patients with oesophageal cancer have skip metastasis, in some studies reported to be above 50%.[39, 43-45] This risk and the negative impact on survival by lymph node metastasis have fuelled the debate and prompted surgeons to perform extensive lymphadenectomy.[46] Lymphadenectomy has been studied more for OSCC than for OAC, for example in terms of whether two-field (abdominal + mediastinal) or three-field (abdominal + mediastinal + cervical) should be used. Regional recommendations may vary, but there seems to be no apparent advantage for three-field lymphadenectomy compared to two-field in terms of survival.[47, 48] Regarding the total number of lymph nodes to remove, the American clinical guidelines (AJCC) currently recommend removal of 10 lymph nodes for T1 tumours, 20 for T2 tumours and ≥30 for T3 and T4 tumours,[6] but these recommendations are heavily dependent on the results of a single study.[49] In conflict with the current guidelines, some studies published during the last couple of years have shown no effect of the degree of lymphadenectomy on long-term survival, and even indicated that extensive lymphadenectomy might decrease the survival in less advanced tumours.[50-52] The topic is further complicated by the increased use of neoadjuvant therapy which also downstages tumours in terms of pN-stage apart from pT-stage, wherefore lymphadenectomy might be more important for patients without neoadjuvant therapy.[52] In this thesis, we hypothesised that the various findings between studies is due to a trade-off between increased lymphadenectomy and improved survival up to a certain level, after which the survival plateaus or decreases with further lymphadenectomy due to the increased surgical morbidity.

RESEARCH AIMS

The overall aim of the thesis was to provide new knowledge that can help improve the survival in patients who are selected for curatively intended surgical treatment for oesophageal cancer. The specific aim of each included study was:

1) To clarify if surgeon age and annual surgeon operation volume affect the proficiency gain curves of surgeons who start conducting oesophagectomy for oesophageal cancer.
2) To assess if minimally invasive oesophagectomy or open oesophagectomy provides better long-term survival in oesophageal cancer based on relevant existing literature.
3) To compare minimally invasive oesophagectomy with open oesophagectomy in terms of long-term survival in a large cohort study.
4) To assess the role of various levels of lymphadenectomy during oesophagectomy in relation to long-term survival in oesophageal cancer.

MATERIALS AND METHODS

OVERVIEW

Table 1. Overview of materials and methods of included studies.

	Study I	Study II	Study III	Study IV
Design	Swedish population-based cohort study	Systematic review and meta-analysis	Swedish and Finnish population-based cohort study	Swedish and Finnish population-based cohort study
Data sources	Cancer Registry, Patient Registry, LISA[a], Registry of Licenced Health Personnel, Cause of Death Registry, medical records	Medline, Embase, Web of Science, Cochrane Library, hand-search in multiple sources	Cancer registries, patient registries, cause of death registries, medical records	Cancer registries, patient registries, cause of death registries, NREV[c], medical records
Study period	1987-2016	- 2018	2010-2019	2000-2019
Study size	1,384 patients	55 studies 14,592 patients	1,230 patients	2,306 patients
Main exposure	Surgeon age and annual surgeon volume	Minimally invasive vs open oesophagectomy	Minimally invasive vs open oesophagectomy	Level of lymphadenectomy
Main outcome	All-cause 1 to 5-year mortality	All-cause 5-year mortality	All-cause 5-year mortality	All-cause 5-year mortality
Covariates	Tumour stage, histological subtype, age, sex, neoadjuvant therapy, comorbidity and education	Age, physical status, tumour stage and neoadjuvant or adjuvant therapy	Age, sex, comorbidity, tumour stage, histological subtype, neoadjuvant therapy, country and hospital volume of oesophagectomy	Age, sex, comorbidity, tumour stage, histological subtype, neoadjuvant therapy, tumour sub-site, country, calendar year and hospital volume of oesophagectomy
Main statistical analysis	RA-CUSUM[b]	Random effects meta-analysis and meta-regression	Multivariable Cox regression	Multivariable Cox regression

[a]*The Longitudinal integration database for health insurance and labor market studies.*
[b]*Risk-adjusted cumulative sum analysis.*
[c]*Swedish National Register for Esophageal and Gastric Cancer.*

DATA SOURCES

Study I, II and IV in the thesis were based on information from national health data registries and medical records. Each data source was linked on the individual patient level by using the personal identity number assigned to each Swedish or Finnish permanent resident at birth or immigration.[53, 54]

The Swedish and Finnish Cancer Registries

The Swedish and Finnish cancer registries are nationally complete registries to which health care professionals are obliged to report all incident cases of cancer in the respective countries.[55-57] The registries contain data such as age, sex, tumour site and date of diagnosis.[55, 58] The Swedish Cancer Registry has above 98% completeness in the recording of the diagnosis of oesophageal cancer, and probably higher for those who undergo oesophagectomy.[59] The Finnish Cancer Registry has above 91% completeness for the diagnosis of oesophageal cancer.[58]

The Swedish and Finnish Patient Registries

The Swedish and Finnish Patient Registries contain information of all in-patient care and specialised out-patient care in Sweden and all in-patient care in Finland, respectively.[58, 60] All hospitals are by law obliged to report to these registries in the respective countries.[58, 61] Included are data such as age, sex, surgical procedures, date of surgery, hospital and diagnoses.[58, 62] The Swedish Patient Registry has a 99.6% positive predictive value for oesophagectomies for oesophageal cancer.[63] The Finnish Patient Registry has above 97% completeness for the diagnosis of oesophageal cancer.[58]

The Swedish Cause of Death Registry and Statistics Finland

The Swedish Cause of Death Registry contains information of all deaths of Swedish residents who die in Sweden or abroad, and since 2012 of non-residents who die in Sweden as well.[64] Statistics Finland contains data on all deaths of permanent residents in Finland.[65] The registries include date of death and main and contributing causes of death, provided by medical doctors who are obliged by law to report to the registries in the respective countries.[66, 67] Data are 100% complete for date of death and 99% complete for cause of death in both registries.[65, 67]

The Longitudinal integration database for health insurance and labor market studies (LISA)

LISA contains information on socio-economic variables of all Swedish residents aged 16 and above (since year 2010 from 15 years and above).[68] Data on the highest attained education are provided by Swedish schools and universities, and residents born abroad, aged 20-59, fill in self-reported questionnaires. Overall, the registry is above 97% complete.[69]

The Swedish Registry of Licenced Health Personnel

This registry contains data on all licensed health personnel in Sweden, such as date of obtained specialist competence of medical doctors. Data are 100% complete and are provided from

specialist certificate applications which are handled by the Swedish National Board of Health of Welfare.[70]

The Swedish National Register for Esophageal and Gastric Cancer (NREV)

NREV is a national quality registry for patients with oesophageal or gastric cancer. The registry was launched in 2006 and gathers information through surveys provided by medical doctors involved in the treatment of the patients. Included are variables such as clinical and pathological tumour stage, tumour histology, neoadjuvant therapy, tumour sub-site and number of resected and examined lymph nodes. The registry includes more than 95% of eligible patients. Across all variables the registry is at least 91% correct.[71]

Medical records

Medical records were retrieved from all hospitals in Sweden and Finland that conducted oesophagectomies during the study period. For each included patient the review of these records provided information about date of surgery and discharge, details about the oesophagectomy, including surgical approach and access, names of the surgeon(s) performing each operation, pathological stage of the tumour, number of regional lymph nodes, lymph node metastates and distant metastases, tumour histology, tumour sub-site, resection margins and use of neoadjuvant therapy.

STUDY DESIGN

Study I

Design

National Swedish population-based cohort-study.

Study cohort and exposures

Most patients who underwent curatively intended surgery for oesophageal cancer in Sweden between 1987 and 2010 were included. Patients with a diagnosis of oesophageal cancer were identified in the Swedish Cancer Registry. The Swedish Patient Registry was used to identify patients who had undergone oesophagectomy. Medical records provided detailed clinical information. LISA provided education level of the patients. The Swedish Registry of Licensed Health Personnel provided birth dates and year of obtained specialist competence of the surgeons. This information was used to dichotomize the surgeons by the median values of annual surgeon volume and age into the exposures "higher volume surgeons" and "lower volume surgeons" (≥4 and <4 cases per year) and "younger surgeons" and "older surgeons" (≥45 and <45 years). Annual surgeon volume was calculated by dividing the total number of oesophagectomies by years of active practice, defined as time from obtained specialist competence until retirement (defined at 65 years of age) or end of study, whichever occurred first. Surgeon age was defined as the age that each surgeon performed the first oesophagectomy in the cohort.

Outcomes

There were five outcomes: 1) all-cause 1 to 5-year mortality (main), 2) all-cause 30-day mortality, 3) reoperation rate (for any indication), 4) resection margins (R0 vs R1) and 5) number of resected and examined lymph nodes. Mortality rates (outcomes 1 and 2) were calculated from date of surgery until death, emigration or end of study (31 May 2016), whichever occurred first. Data on mortality were collected from the Swedish Cause of Death Registry. Data for outcomes 3-5 were retrieved from medical records.

Statistical analysis

Each oesophagectomy was arranged in chronological order for each surgeon, from first to last. Risk adjusted cumulative sum (RA-CUSUM) analysis was used to graphically plot the difference between observed and expected outcomes against patient number. The method has been described in detail elsewhere.[72] The expected outcome for each operation was calculated by using multivariable logistic regression, adjusted for seven potential confounders: pathological tumour stage (AJCC 7th edition: 0–I, II, III, or IV),[73] histological type (adenocarcinoma or squamous cell carcinoma), patient age (continuous), patient sex (male or female), neoadjuvant chemo(radio)therapy (yes or no), comorbidity (Charlson comorbidity score 0, 1, or ≥ 2, excluding oesophageal cancer)[74] and patient education (<10 years, 10–12 years, or >12 years of formal education). Change-point analysis was used to define the maximum deflection point in the RA-CUSUM graphs, at which the outcome changed from worse to better than expected. The outcomes before and after change points were compared by using two-sided X^2-test for binomial outcomes and two-sided Mann-Whitney U test for continuous outcomes, with an α-level of 0.05.

Study II

Design

Systematic review and meta-analysis.

Search strategy and selection criteria

All studies comparing curatively intended MIO (total or hybrid) with OO for oesophageal cancer published before 4th April 2018 were included. Medline, Embase, Web of Science and Cochrane Library were searched for the terms *oesophageal cancer*, *minimally invasive surgery* and *survival*. The search included synonym terms and different spellings. Additionally, a hand-search was conducted by forward-tracking papers published before 25th May 2018 from all studies selected from the search strategy, and by searching the reference lists of all included studies, the websites of the annual or biannual conferences of *The International Society for Diseases of the Esophagus*, *The Society of American Gastrointestinal and Endoscopic Surgeons* and *The European Association for Endoscopic Surgery* for abstracts published in 2007-2017, and the website of the Current Controlled Trials Register for unpublished clinical trials. Two unpublished studies were included by personal contacts (Mariette et al and Sihvo et al). Studies were included by 1) design: cohort study or randomized clinical trial, 2) topic: study patients undergoing oesophagectomy for oesophageal cancer, 3) exposure: comparing total or hybrid MIO with OO and 4) outcome: hazard ratios (HR) or Kaplan Meier curves of all-cause or disease-specific mortality with at least 3 years of follow-up. Exclusions were made for studies primarily including endoscopic procedures and for studies not published in English. One author

selected papers on titles and abstracts and two authors thereafter included studies based on full-text reviews. A third author decided on cases of disagreement.

Outcomes

There were four outcomes: 1) All-cause 5-year mortality, 2) all-cause 3-year mortality, 3) disease-specific 3-year mortality and 4) disease-specific 5-year mortality.

Statistical analysis

Adjusted HRs were preferred when available in order to decrease confounding. HRs were produced by manual extraction of data from Kaplan Meier curves, which was used together with the study size to calculate 95% confidence intervals (CI), for studies which only presented Kaplan Meier curves. For each outcome, random effects meta-analysis was used to produce pooled HRs with 95% CIs. Statistical heterogeneity was evaluated by I^2-test (low heterogeneity <25%, moderate 26-50%, moderate-high 51-75% and high >75%) and by X^2-test with an α-level of 0.05 (below indicating heterogeneity). Publication bias and small-study effects were evaluated by Egger's test of asymmetry in funnel plots, with an α-level of 0.1 (below indicating publication bias or small-study effect). Random-effects meta-regression was used to adjust for the following confounding factors (with categorisations in brackets): Patient age (median), physical status according to the American Society of Anesthesiologists (ASA) class (I, II, III or IV), pathological tumour stage (or clinical if pathological was not present [0-I, II-III or IV]) and neoadjuvant therapy (or otherwise adjuvant therapy [yes or no]). In a sensitivity analysis, studies using a historical cohort of OO as the comparison group were excluded in order to evaluate bias. The quality of all included studies was assessed by two authors using the Newcastle Ottawa scale for cohort studies,[75] or the Cochrane Collaborations Risk of Bias Tool (CCRBT) for randomized clinical trials.[76]

Study III

Design

Bi-national Swedish and Finnish population-based cohort study.

Study cohort and exposures

Patients who underwent curatively intended surgery for oesophageal cancer in Sweden between 2011 and 2015 and in Finland between 2010 and 2016 were included. The cancer registry of respective country was used to identify patients diagnosed with oesophageal cancer. The patient registries were used to identify the patients that had undergone an oesophagectomy. Clinical data were retrieved from medical records. The main exposure was MIO and the comparison group was OO. MIO was further divided into total MIO (laparoscopy, or laparoscopy and thoracoscopy) or hybrid MIO (laparoscopy and thoracotomy, or laparotomy and thoracoscopy).

Outcomes

There were five outcomes: 1) All-cause 5-year mortality (main), 2) all-cause 5-year mortality excluding deaths within 90 days after surgery, 3) all-cause 3-year mortality, 4) disease-specific 3-year mortality and 5) disease-specific 5-year mortality. Disease-specific mortality was defined as

oesophageal cancer being reported as the main or contributing cause of death. Follow-up was counted from date of surgery until death or end of study period, whichever occurred first. Follow-up data were collected from the Swedish Cause of Death Registry and Statistics Finland and were available until 31st December 2019 for all-cause mortality and 31st December 2018 for disease-specific mortality in both countries.

Statistical analysis

HRs with 95% CIs were calculated by Cox proportional hazard models, adjusted for eight possible confounders (with categorizations within brackets): age (continuous), sex (male or female), comorbidity (Charlson comorbidity score 0, 1 or ≥2 [excluding the oesophageal cancer]),[74] pathological tumour stage (pTNM/ypTNM AJCC 8th edition: 0, I, II, III or IV),[6] histological type (adenocarcinoma or squamous cell carcinoma), neoadjuvant chemo(radio)therapy (yes or no), country (Sweden or Finland), and annual hospital volume of oesophagectomy (continuous: 4-year moving average number of oesophagectomies at each hospital at the year of the operation and 3 years prior).[77] Additionally, radicality of resection (R0 or R1), number of lymph nodes (grouped in tertiles) and length of hospital stay (0-14, 15-30 and >30 days) were added to the main model to explore potential mechanisms. Complete case analysis was used because the frequencies of missing data were low.

Study IV

Design

Bi-national Swedish and Finnish population-based cohort study.

Study cohort and exposures

The cohort included patients who underwent curatively intended oesophagectomy for oesophageal cancer in Sweden between 2000 and 2015 and in Finland between 2000 and 2016. The cancer registries were used to identify patients with a diagnosis of oesophageal cancer, and the patient registries were used to identify the patients who had undergone oesophagectomy. Medical records provided clinical data, and data from NREV in Sweden were used to decrease missing data. The main exposure was the number of resected and examined lymph nodes, which was divided into 10 about equal size groups (deciles). Secondary exposures were: 1) number of lymph nodes analysed as a continuous variable, 2) number of metastatic lymph nodes in deciles (combining decile 1-5 into a common group due to many patients with no metastatic lymph nodes) and 3) ratio of metastatic to total number of lymph nodes (categorized as in exposure 3, however excluding patients with no resected lymph nodes).

Outcomes

The main outcome was all-cause 5-year mortality which was analysed for all exposures. Four secondary outcomes were analysed only in relation to the main exposure: 1) All-cause 5-year mortality excluding deaths within 90 days after surgery, 2) all-cause 3-year mortality, 3) disease-specific 3-year mortality and 4) disease-specific 5-year mortality. Disease-specific mortality was defined as oesophageal cancer being reported as main or contributing cause of death. Follow-up

data were provided by the Swedish Cause of Death Registry and Statistics Finland until 31st December 2019 for all-cause mortality and until 31st December 2018 for disease-specific mortality.

Statistical analysis

Multivariable Cox proportional hazards models provided HRs with 95% CIs. Time at risk was counted from date of surgery until death or end of follow-up, whichever occurred first. Complete case analysis was used due to low frequencies of missing. The main model included ten potential confounders (with categorizations within brackets): age (continuous), sex (male or female), comorbidity (Charlson comorbidity score 0, 1 or ≥2 [excluding the oesophageal cancer]), pathological T-stage (AJCC 8th edition: T0, Tis, T1, T2, T3, or T4), histological type (adenocarcinoma or squamous cell carcinoma), neoadjuvant therapy (chemotherapy, radiotherapy, chemoradiotherapy, or no neoadjuvant therapy), tumour location (proximal/middle or distal [including Siewert I and II]), country (Sweden or Finland), calendar year (continuous), and hospital volume (continuous with a 4-year moving average number of oesophagectomies at each hospital the year of the operation and 3 years earlier). Pathological N-stage (N0, N1, N2 or N3) was added in an explanatory model. For the main exposure and main outcome, two sensitivity analyses were conducted: 1) exclusion of patients with distant metastasis (pM1) and 2) adjustment of clinical T-stage instead of pathological T-stage for a subgroup of the cohort (79.1%) with these data present.

Stratified analyses were conducted for age (below and above median [65 years]), sex (male and female), comorbidity (Charlson comorbidity score 0, 1 and ≥2), pathological T-stage (T0, Tis/T1/T2 and T3/T4), histological type (adenocarcinoma and squamous cell carcinoma), neoadjuvant therapy (chemotherapy, radiotherapy/chemoradiotherapy and no neoadjuvant therapy), tumour subsite (proximal/middle and distal), country (Sweden and Finland), calendar year (below and above median [2011]), annual hospital volume (below and above median [13]) and pathological N-stage (N0 and N1-N3).

RESULTS

STUDY I

During the study period 1987-2010 there were 1,820 eligible patients, and 139 surgeons involved. We excluded 103 surgeons with too small case series to allow them to reach a plateau in the proficiency gain curves, leaving 36 surgeons for the study. These surgeons did oesophagectomy on 1,384 patients (76.0% of the entire cohort), who remained for final analysis. The main characteristics of the patients are presented in Table 2. "Lower volume surgeons" performed 1.13-3.75 operations per year and "higher volume surgeons" performed 4-12 operations per year. "Younger surgeons" were aged 34-44 years and "older surgeons" were aged 45-59 years.

Table 2. Characteristics of 1,384 patients included in study I.

	Surgeon volume		Surgeon age	
	Lower	Higher	Older	Younger
	Number (%)[a]			
Total	1,384 (100)		1,384 (100)	
	574 (41.5)	810 (58.5)	471 (34.0)	913 (66.0)
Age, years				
<60	168 (29.3)	236 (29.1)	137 (29.1)	267 (29.2)
60-70	237 (41.3)	336 (41.5)	191 (40.6)	382 (41.8)
>70	169 (29.4)	238 (29.4)	143 (30.4)	264 (28.9)
Sex				
Male	422 (73.5)	605 (74.7)	354 (75.2)	673 (73.7)
Female	152 (26.5)	205 (25.3)	117 (24.8)	240 (26.3)
Tumour histology				
Adenocarcinoma	305 (53.2)	454 (56.2)	294 (62.6)	465 (51.0)
Squamous cell carcinoma	268 (46.8)	354 (43.8)	176 (37.5)	446 (49.0)
Tumour stage				
0-I	161 (28.0)	175 (21.6)	121 (25.7)	215 (23.5)
II	204 (35.6)	303 (37.6)	180 (38.3)	327 (36.0)
III	171 (29.8)	266 (33.0)	142 (30.2)	295 (32.5)
IV	37 (6.4)	62 (7.7)	27 (5.7)	72 (7.9)

[a]*Frequencies for certain variables do not add up to 100% due to missing values.*

"Higher volume surgeons" had a change-point at 14 cases for 1 to 5-year mortality compared to "lower volume surgeons" who had a change-point at 31 cases (Figure 4), where mortality decreased from 67.2% to 57.1% ($p = 0.05$) compared to 67.8% to 64.9% ($p = 0.88$) (Table 3). Earlier change-point were identified for "higher volume surgeons" compared to "lower volume surgeons" also for the outcomes 30-day mortality and R1 resection margin (Table 3). Overall reoperation rates were lower and number of removed and examined lymph nodes were higher for "higher volume surgeons" compared to "lower volume surgeons", although no change-points could be identified.

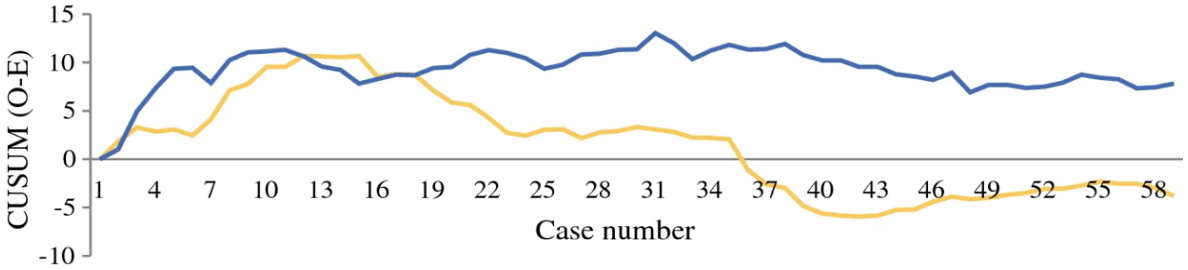

Figure 4. Proficiency gain curves in study I for higher-volume surgeons (yellow line) and lower volume surgeons (blue line) conducting oesophagectomies in terms of 1 to 5-year mortality.

Table 3. Outcomes in study I comparing higher and lower volume surgeons conducting oesophagectomies.

Outcome	Annual volume	Proficiency gain curve change-point (Number)	% with outcome (Number/Total Number)		
			Before change-point	After change-point	Change -point P-value
1 to 5-year mortality	Higher	14	67.2% (82/122)	57.1% (216/378)	0.05
	Lower	31	67.8% (187/276)	64.9% (50/77)	0.88
30-day mortality	Higher	16	4.5% (10/221)	2.5% (15/589)	0.05
	Lower	37	5.3% (26/490)	3.6% (3/84)	0.50
R1 resection margin	Higher	16	20.9% (49/235)	13.0% (62/476)	0.03
	Lower	22	21.5% (50/233)	16.0% (40/252)	0.08

"Younger surgeons" had a change-point at 13 cases for 1 to 5-year mortality, where mortality decreased from 63.4% to 56.9% (p = 0.19), and "older surgeons" had a change-point at 48 cases (Figure 5) with a reduction in mortality from 65.5% to 52.2% (p = 0.20) (Table 4). Earlier change-points were furthermore identified for "younger surgeons" for the outcomes 30-day mortality and R1 resection rate (Table 4). "Younger surgeons" had lower reoperation rates and higher number of removed and examined lymph nodes compared to "older surgeons", although a change-point was only identified for "older surgeons" regarding reoperation rate.

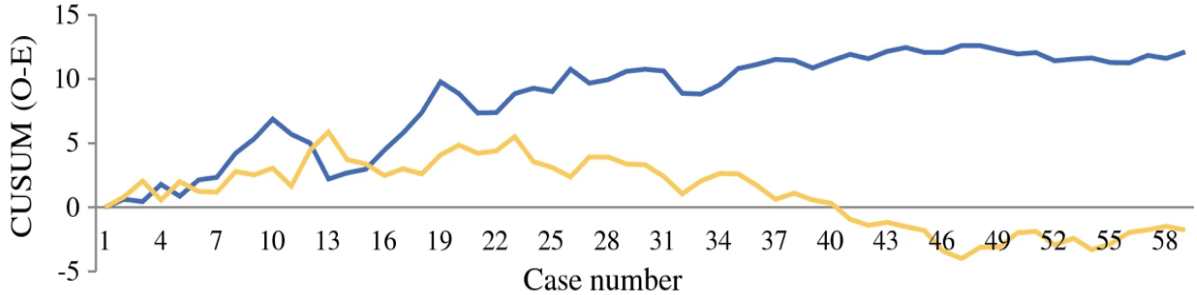

Figure 5. Proficiency gain curves in study I for younger surgeons (yellow line) and older surgeons (blue line) conducting oesophagectomies in relation to 1 to 5-year mortality.

Table 4. Outcomes in study I comparing younger and older surgeons conducting oesophagectomies.

Outcome	Age group	Proficiency gain curve change-point (Number)	% with outcome (Number/Total number)		
			Before change-point	After change-point	Change-point P-value
1 to 5-year mortality	Younger	13	63.4% (78/123)	56.9% (257/452)	0.19
	Older	48	65.5% (167/255)	52.2% (12/23)	0.20
30-day mortality	Younger	18	5.2% (15/288)	2.4% (15/625)	0.03
	Older	31	5.7% (21/366)	2.9% (3/105)	0.24
R1 resection margin	Younger	7	18.8% (21/112)	14.9% (103/693)	0.29
	Older (1)[a]	16	25.0% (49/196)	17.4% (34/195)	0.07
	Older (2)[a]	56	21.3% (81/380)	18.2% (2/11)	0.80

[a]*Two change-points were identified.*

STUDY II

In total, 1,509 unique studies were identified by the electronic search in Medline, Embase, Web of Science and Cochrane Library. An additional 10 studies were identified by alternative search strategies. In total, 55 studies met the inclusion criteria and were selected for meta-analysis. Of these, 53 were cohort studies and 2 were randomized controlled trials. The total number of patients was 14,592, including 7,358 (50.4%) who had undergone MIO and 7,234 (49.6%) who had undergone OO. Of all 55 studies, 34 had follow-up data regarding all-cause 5-year mortality (main outcome).

The meta-analysis for all-cause mortality showed a survival benefit of 18% in favour of MIO (HR 0.82, 95% CI 0.76-0.88). There was little statistical heterogeneity between the included studies (I^2 = 12%, 95% CI 0%-41%, X^2 = 0.26) and no sign of publication bias by visual inspection or statistical testing of the funnel plot (Egger test = 0.32). In the sensitivity analysis restricted to studies which did not use a historical comparison group of OO (n=27), the survival benefit remained for MIO (HR 0.83, 95% CI 0.76-0.90). Meta-regression did not reveal any confounding effect of age, ASA-class, tumour stage or chemo(radio)therapy.

MIO was also followed by decreased all-cause 3-year mortality (HR 0.85, 95% CI 0.80-0.92), disease-specific 3-year mortality (HR 0.84, 95% CI 0.77-0.92) and disease-specific 5-year mortality (HR 0.83, 95% CI 0.75-0.91).

STUDY III

A total of 1,264 patients who underwent oesophagectomy for oesophageal cancer were included in study III. Of these, 470 (37.2%) underwent MIO and 794 (62.8%) OO. Within the MIO group, 172 (36.6%) underwent hybrid MIO and 298 (63.4%) total MIO. Characteristics of the patients are described in Table 5.

Table 5. Characteristics of 1,264 included patients in study III.

	OO	hMIO/tMIO	hMIO	tMIO
	Number (%)[a]			
Total	794 (62.8)	470 (37.2)	172 (13.6)	298 (23.6)
Age				
<60	205 (25.8)	119 (25.3)	33 (19.2)	86 (28.9)
60-70	369 (46.5)	201 (42.8)	79 (45.9)	122 (40.9)
>70	220 (27.7)	150 (31.9)	60 (34.9)	90 (30.2)
Sex				
Male	640 (80.6)	375 (79.8)	141 (82.0)	234 (78.5)
Female	154 (19.4)	95 (20.2)	31 (18.0)	64 (21.5)
Pathological tumour stage				
0	11 (1.4)	8 (1.7)	6 (3.5)	2 (0.7)
I	274 (34.5)	193 (41.1)	68 (39.5)	125 (42.0)
II	114 (14.4)	82 (17.4)	26 (15.1)	56 (18.8)
III	243 (30.6)	130 (27.7)	48 (27.9)	82 (27.5)
IV	139 (17.5)	51 (10.9)	22 (12.8)	29 (9.7)
Tumour histology				
Adenocarcinoma	615 (77.4)	382 (81.3)	139 (80.8)	243 (81.5)
Squamous cell carcinoma	177 (22.3)	85 (18.1)	30 (17.4)	55 (18.5)

[a]*Frequencies for certain variables do not add up to 100% due to missing values.*

Most patients (n=1,230, 97.3%; 771 OO and 459 MIO) had complete data on all confounders and were included in the final analyses. MIO was associated with 18% lower risk of all-cause 5-year mortality compared to OO (HR 0.82, 95% CI 0.67-1.00 [P=0.048]) (Table 6). Adjustment for additional variables in the explanatory model slightly attenuated the results (HR 0.86, 95% CI 0.70-1.05). Hybrid MIO had 13% lower risk of all-cause 5-year mortality compared to OO (HR 0.87, 95% CI 0.68-1.11) and total MIO was associated with even lower risk of all-cause 5-year mortality of 23% (HR 0.77, 95% CI 0.60-0.98). The secondary outcomes all-cause 90-day to 5-year mortality, all-cause 3-year mortality, disease-specific 3-year mortality and disease-specific 5-year mortality showed similar results in favour of MIO, however not statistically significant (Table 6).

Table 6. HRs with 95% CIs for MIO compared to OO in study III.

	Open oesophagectomy	**Minimally invasive oesophagectomy**
	HR (95% CI)[a]	
All-cause 5-year mortality	1.00 (reference)	0.82 (0.67-1.00)
All-cause 90-day to 5-year mortality	1.00 (reference)	0.83 (0.67-1.02)
All-cause 3-year mortality	1.00 (reference)	0.86 (0.69-1.06)
Disease-specific 5-year mortality	1.00 (reference)	0.89 (0.72-1.10)
Disease-specific 3-year mortality	1.00 (reference)	0.91 (0.73-1.15)

[a]*Adjusted for age sex, comorbidity, tumour stage, histological subtype, neoadjuvant chemo(radio)therapy, country, and hospital volume of oesophagectomy.*

STUDY IV

During the study period, 2,605 patients were eligible for inclusion in study IV. Among these, 2,459 (94.4%) had information on number of removed and examined lymph nodes, and among these 2,306 (93.8%) had complete information on all variables which included them in the analyses. Characteristics of these patients are presented in Table 7.

Risk of all-cause 5-year mortality was statistically significantly decreased in decile 2 (4-8 lymph nodes), 7 (21-24 lymph nodes) and 8 (25-30 lymph nodes) (Table 8). The lowest point estimate was observed in decile 8 (HR 0.73, 95% CI 0.57-0.93). The risk of mortality in the 10th (highest) decile was close to that of decile 1 (HR 0.94, 95% CI 0.72-1.21). Further adjustment for pathological N-stage in the explanatory model decreased the risk of mortality in all deciles compared to the 1st, with the lowest point estimate still in decile 8 (HR 0.47, 95% CI 0.36-0.61).

Exclusion of patients with distant metastasis and additional adjustment for clinical T-stage instead of pathological T-stage did not alter the results. Analysis of number of resected and examined lymph nodes as a continuous variable was not associated with risk of mortality. Risk of all-cause 90-day to 5-year mortality was similar to that of all-cause 5-year mortality. Decile 8 showed decreased risk of all-cause 3-year mortality and disease-specific 5-year mortality, but not for disease-specific 3-year mortality. An association between degree of lymphadenectomy and survival was more apparent for patients with T3/T4 tumours and among those who had not received neoadjuvant therapy (Table 9).

Table 7. Characteristics of 2,605 patients included in study IV.

Lymphadenectomy, decile (range: number)	**1 (0-3)**	**2 (4-8)**	**3 (9-11)**	**4 (12-14)**	**5 (15-17)**	**6 (18-20)**	**7 (21-24)**	**8 (25-30)**	**9 (31-39)**	**10 (40-88)**
	Number (%)[a]									
Total	247 (100)	328 (100)	233 (100)	240 (100)	233 (100)	224 (100)	228 (100)	272 (100)	225 (100)	229 (100)
Age										
<60	70 (28.3)	92 (28.0)	77 (33.0)	61 (25.4)	71 (30.5)	61 (27.2)	52 (22.8)	75 (27.6)	55 (24.4)	68 (29.7)
60-70	94 (38.1)	139 (42.4)	100 (42.9)	116 (48.3)	98 (42.1)	90 (40.2)	97 (42.5)	130 (47.8)	100 (44.4)	97 (42.4)
>70	83 (33.6)	97 (29.6)	56 (24.0)	63 (26.3)	64 (27.5)	73 (32.6)	79 (34.6)	67 (24.6)	70 (31.1)	64 (27.9)
Sex										
Male	175 (70.9)	253 (77.1)	182 (78.1)	179 (74.6)	186 (79.8)	177 (79.0)	179 (78.5)	214 (78.7)	171 (76.0)	181 (79.0)
Female	72 (29.2)	75 (22.9)	51 (21.9)	61 (25.4)	47 (20.2)	47 (21.0)	49 (21.5)	58 (21.3)	54 (24.0)	48 (21.0)
Pathological T-stage										
T0	26 (10.5)	48 (14.6)	33 (14.2)	31 (12.9)	38 (16.3)	32 (14.3)	23 (10.1)	24 (8.8)	27 (12.0)	18 (7.9)
Tis	12 (4.9)	9 (2.7)	6 (2.6)	4 (1.7)	5 (2.2)	4 (1.8)	9 (4.0)	5 (1.8)	5 (2.2)	4 (1.75)
T1	68 (27.5)	72 (22.0)	35 (15.0)	53 (22.1)	45 (19.3)	39 (17.4)	43 (18.9)	40 (14.7)	41 (18.2)	19 (8.3)
T2	49 (19.8)	60 (18.3)	50 (21.5)	46 (19.2)	45 (19.3)	44 (19.6)	42 (18.4)	57 (21.0)	28 (12.4)	42 (18.3)
T3	67 (27.1)	117 (35.7)	94 (40.3)	90 (37.5)	84 (36.1)	92 (41.1)	99 (43.4)	120 (44.1)	106 (47.1)	121 (52.8)
T4	20 (8.1)	19 (5.8)	13 (5.6)	15 (6.3)	12 (5.2)	11 (4.9)	11 (4.8)	25 (9.2)	18 (8.0)	23 (10.0)
Tumour histology										
Adenocarcinoma	139 (56.3)	204 (62.2)	164 (70.4)	161 (67.1)	170 (73.0)	166 (74.1)	163 (71.5)	188 (69.1)	152 (67.6)	181 (79.0)
Squamous cell carcinoma	101 (40.9)	117 (35.7)	64 (27.5)	77 (32.1)	62 (26.6)	56 (25.0)	61 (26.8)	82 (30.2)	72 (32.0)	48 (21.0)

[a]*Frequencies for certain variables do not add up to 100% due to missing values.*

Table 8. HRs with 95% Cis for all-cause 5-year mortality comparing patients across 10 groups of approximately equal sizes (deciles) of number of resected and examined lymph nodes in study IV.

Lymphadenectomy, decile (range: number)	HR (95% CI)[a]
1 (0-3)	1.00 (reference)
2 (4-8)	0.77 (0.61-0.97)
3 (9-11)	0.94 (0.74-1.20)
4 (12-14)	0.86 (0.68-1.10)
5 (15-17)	0.81 (0.63-1.04)
6 (18-20)	0.89 (0.69-1.14)
7 (21-24)	0.76 (0.59-0.99)
8 (25-30)	0.73 (0.57-0.93)
9 (31-39)	0.82 (0.63-1.06)
10 (40-88)	0.94 (0.72-1.21)

[a] *Adjusted for age, sex, comorbidity, pathological T-stage, tumour histology, neoadjuvant chemo(radio)therapy, tumour location, country, calendar year, and annual hospital volume of oesophagectomy.*

Table 9. HRs with 95% CIs for all-cause 5-year mortality comparing patients across 10 groups of approximately equal sizes (deciles) according to the number of resected and examined lymph nodes, stratified by pathological T-stage and neoadjuvant therapy, in study IV.

Lymphadenectomy, decile (range: number)			
		Pathological T-stage	
	T0	Tis/T1/T2	T3/T4
		HR (95% CI)[a]	
1 (0-3)	1.00 (reference)	1.00 (reference)	1.00 (reference)
2 (4-8)	0.60 (0.25-1.40)	0.80 (0.54-1.19)	0.66 (0.49-0.91)
3 (9-11)	1.34 (0.58-3.09)	1.19 (0.79-1.78)	0.68 (0.49-0.95)
4 (12-14)	1.10 (0.47-2.59)	1.12 (0.74-1.67)	0.64 (0.46-0.90)
5 (15-17)	0.91 (0.40-2.10)	0.75 (0.48-1.18)	0.71 (0.51-1.00)
6 (18-20)	1.44 (0.63-3.32)	1.22 (0.80-1.85)	0.60 (0.43-0.85)
7 (21-24)	0.79 (0.29-2.19)	1.08 (0.70-1.68)	0.56 (0.40-0.78)
8 (25-30)	0.64 (0.23-1.79)	0.78 (0.50-1.22)	0.61 (0.44-0.84)
9 (31-39)	1.03 (0.40-2.66)	0.94 (0.58-1.52)	0.61 (0.44-0.85)
10 (40-88)	0.90 (0.30-2.69)	1.12 (0.68-1.84)	0.75 (0.54-1.04)
		Neoadjuvant therapy	
	Chemotherapy	Radio/chemoradiotherapy	No
		HR (95% CI)[a]	
1 (0-3)	1.00 (reference)	1.00 (reference)	1.00 (reference)
2 (4-8)	1.43 (0.58-3.51)	0.67 (0.44-1.00)	0.67 (0.49-0.90)
3 (9-11)	1.02 (0.42-2.49)	1.12 (0.75-1.69)	0.76 (0.54-1.06)
4 (12-14)	0.72 (0.28-1.82)	1.06 (0.70-1.60)	0.73 (0.52-1.01)
5 (15-17)	1.02 (0.43-2.42)	0.78 (0.50-1.23)	0.76 (0.53-1.07)
6 (18-20)	1.17 (0.49-2.77)	1.06 (0.69-1.61)	0.68 (0.47-0.98)
7 (21-24)	1.31 (0.56-3.03)	0.80 (0.49-1.30)	0.60 (0.41-0.86)
8 (25-30)	0.99 (0.43-2.29)	0.67 (0.43-1.06)	0.65 (0.46-0.92)
9 (31-39)	0.87 (0.36-2.07)	0.87 (0.51-1.49)	0.73 (0.52-1.03)
10 (40-88)	1.18 (0.51-2.75)	1.15 (0.67-1.96)	0.74 (0.52-1.05)

[a] *Adjusted for age, sex, comorbidity, pathological T-stage, tumour histology, neoadjuvant chemo(radio)therapy, tumour location, country, calendar year, and annual hospital volume of oesophagectomy (excluding variable stratified for).*

DISCUSSION

METHODOLOGICAL CONSIDERATIONS

Study design

Study I, III and IV were all population-based cohort studies. In a cohort study a group of individuals is followed over time from the assessment of an exposure to outcomes. The three cohort studies in the thesis share many methodological similarities in data sources and methods, including strengths and weaknesses. The large sample sizes, population-based designs with high participation rates and almost no loss to follow-up improves the statistical power, reduces biases and facilitates generalisability. Even though the registries used for the studies are of excellent quality, they lack certain specific information that was needed for this thesis. By collecting medical records, exposures could be studied in great detail and adjustment for confounders could be conducted. Systematic errors, or biases, affect the internal validity of a study. Systematic errors can broadly be divided into selection bias, misclassification bias and confounding. Moreover, random errors might also affect the internal validity of a study, but these errors are not explained by methodological flaws. Random errors can be decreased by larger study sizes, which is not the case for systematic errors. Finally, one needs to consider generalisability (external validity), which corresponds to how well the results of a study can be extrapolated to settings outside of the study population. These aspects are discussed below. Certain considerations regarding the systematic review and meta-analysis (study II) are discussed in the section below, but specific considerations are further discussed separately.

Internal validity

Selection bias

Selection bias can occur when patients included into a study have a different risk for the outcome than the source population, which might distort the exposure-outcome association either by over- or underestimation. Selection bias can occur at the exposure level, but also at the outcome level due to loss of follow-up. Study I, III and IV in the thesis are all population-based cohort studies which identified patients through highly complete national registries. This reduced the risk of selection bias at the exposure level. Selection bias in terms of loss to follow-up is also unlikely to have occurred due to the high completeness of the recording of mortality. Study II, which was a systematic review and meta-analysis, included many small single-centre studies and a few randomized controlled trials. These studies likely had substantially higher risk of selection bias at the exposure level, and also at the outcome level, and these risks are inevitably inherited by the systematic review and meta-analysis.

Information bias

Information bias occurs when a measurement does not correspond to the true value of the variable. When a participant is wrongfully defined according to a variable, there is misclassification bias, a type of information bias. Misclassification can occur for any measured variable, and as such can misclassify exposures, outcomes and covariates. When misclassification of the exposure is

dependent on the outcome, the bias is defined as differential, whereas if no such dependency exists it is defined as non-differential. Non-differential misclassification of a dichotomous exposure in general leads to a result closer to the null (dilution), whereas differential bias can either overestimate or underestimate the association. In study I, II and III the risk of misclassification of the exposure should be low, but is possibly higher for study IV (discussed further below). Some level of misclassification of data was likely to be present in the registries and medical records, and further misclassification cannot be ruled out due to the manual extraction process of data from the medical records. However, if misclassification did occur, it was probably non-differential which would most likely have affected the results towards the null, and not explain the presence of the associations detected. Some degree of misclassification of confounding factors could also have occurred.

Confounding

A confounder is defined as a variable that is associated with both the exposure and the outcome, but is not included in the causal pathway between the exposure and outcome. If unaccounted for in a study, the observed effect on the outcome might be an effect of a confounder, and not the exposure. Methods exist to avoid or account for confounding, including the study design, analyses with restriction, stratification and adjustment. Multivariable regression models were used in study I, III and IV, in which adjustments were made for the most important known confounding factors. The choice of factors to include in the models was made by a priori knowledge about prognostic factors. Still, unknown confounding or residual confounding might have affected the results to some degree. In study II, many of the included studies were observational in design, without adjustment for confounders. This was addressed by meta-regression which did not indicate bias by confounding for the defined variables, but because many studies lacked information on confounders, there was still a risk of bias by confounding affecting the results.

Random errors

Random errors occur due to variability of observations and relates to precision of estimates. If measurements are repeated random error decreases. A common way to assess precision is to present 95% confidence intervals or p-values. A 95% confidence interval is defined as the range of values that we would expect to observe from the output of a test in 95% of times, if the test was carried out an infinite number of times. P-values are measurements of the compatibility between the observed result and the null-hypothesis of a test. Commonly, a statistical significance level is set at $p = 0.05$, meaning that the null hypothesis is rejected if p is smaller than 5%. By using large study samples for all included studies, random errors were decreased, particularly the risk of type II-error (non-rejection of a false null-hypothesis). Multiple tests were carried out in study IV, which might have introduced type I-error (rejection of a correct null-hypothesis). However, by following a predefined study protocol with clear definitions of the main exposure and the main outcome, the risk of type I-errors was decreased.

External validity

External validity refers to how well the results of a study can be extrapolated to other populations than the one that was included in the study. Overall, the internal validity of the studies in the thesis may be regarded as high, especially in study I, III and IV. Moreover, study populations were drawn

from the entire population of Sweden (and Finland) in these studies. Therefore, the results of study I, III and IV are likely to have good external validity for countries with similar patterns of disease and treatment characteristics of oesophageal cancer as in Sweden (and Finland), such as other western countries. The external validity of study II is difficult to assess, but is most likely lower than for the other studies because of the less clearly defined population under study.

Systematic review and meta-analysis

Apart from the biases discussed above, there are certain biases specific for systematic reviews and meta-analyses.

Publication bias

Publication bias occurs in situations where the sum of published results show a skewed picture of an association, which could be due to a higher likelihood of publishing results which are statistically significant than those which are not. One way to assess publication bias is to construct a funnel plot, which plots the effect size for each study on the x-axis and the standard error on the y-axis. The method assumes that smaller studies without statistically significant results have a lower chance of getting published compared to larger studies without statistical significance as well as studies that show statistically significant results, independent of sample size. Upon asymmetry of the resulting funnel, publication bias has to be suspected. Apart from visual inspection, statistical testing of asymmetry in the funnel plot can be tested using Egger's test. Usually, a significance level is set at 0.1, where values below 0.1 indicate presence of publication bias. In study IV neither the funnel plots nor Egger's tests indicated publication bias for the 5-year mortality outcomes, but there was some indication of publication bias for the 3-year mortality outcomes.

Heterogeneity

In order to conduct a meta-analysis, studies need be similar enough in terms of study parameters such as population, intervention and outcome. Differences in design is referred to as clinical heterogeneity. There is also what is referred to as statistical heterogeneity, usually just referred to as heterogeneity, which is a measure of outcomes variance between studies. If the variance is larger than would be expected from chance, there is presence of heterogeneity, which indicate that some of the included studies suffer from bias. Heterogeneity can be assessed by X^2-test and I^2-test. The X^2-test tests the null-hypothesis that there is no statistical heterogeneity between the studies. A low p-value (statistical significance level usually set at 0.05) indicates presence of statistical heterogeneity. Heterogeneity can be dealt with by using random-effects meta-analysis rather than fixed-effects meta-analysis. The I^2-test is a test that allows for quantification of statistical heterogeneity, and the output is frequency of variance between studies that is due to statistical heterogeneity rather than chance, assessed according to predefined categories. The included studies in study II were assessed to have low statistical heterogeneity for all outcomes, except for all-cause 3-year mortality for which statistical heterogeneity was moderate.

GENERAL DISCUSSION

Study I

Study I showed that proficiency was gained faster for higher volume surgeons and for younger surgeons in relation to long-term survival, compared to lower volume surgeons and older surgeons, respectively. Similar results were observed for the secondary outcomes short-term mortality and resection margin status.

Strengths of the study include its population-based design, which limits the risk of selection bias. The risk for misclassification of exposures, covariates and outcomes was low due to the use of high-quality registry data, complemented by data from medical records. Confounding was controlled for by adjusting for the established and most important prognostic factors. Weaknesses of the study include that the difference in surgeon volume between lower and higher volume surgeons was small. It is possible that greater differences in proficiency might have been observed with bigger differences. Surgeons up to 44 years of age were included in the group of younger surgeons, which might not be viewed as young age in the context in other settings. However, the differences were still large enough to observe differences in proficiency. Surgeons included in the beginning of the study period might have had experience of oesophagectomies before the start of the study, which would lead to misclassification of the case numbers. However, because the study included many years, this could only have occurred for a small number of the surgeons and should therefore not affect the overall results of the study. Power was somewhat limited, which might have introduced type-II error.

Study I is, to the best of our knowledge, the first to assess proficiency gain of oesophagectomy for oesophageal cancer, regarding the specific surgeon factors examined. Previous studies have shown that survival among patients undergoing surgery for oesophageal cancer improves after proficiency has been reached for surgeons.[28] Moreover, studies have shown that higher volume surgeons perform better than lower volume surgeons in terms of long-term survival, and that there is an "ideal age" for surgeons at which performance is optimized.[30, 31] The result regarding surgeons reaching proficiency after fewer operations by higher annual surgery volumes follows a logical reasoning of facilitating faster learning by higher intensity during the learning process. The results regarding surgeon age are somewhat more controversial and could possibly be explained by loss of dexterity and decreased ability to learn new skills by increased age.

Study I points towards a need of organizing intense training for selected and relatively young surgeons before allowing them to start performing surgery for oesophageal cancer independently, for example by simulator training and structured fellowships. Such a strategy may improve survival for patients undergoing surgery for oesophageal cancer.

Study II

The results of study II indicate that long-term survival in oesophageal cancer is improved by MIO compared to OO.

Strengths of the study include the extensive search strategy in multiple databases, as well as manual search strategies, which decreases the risk of not including eligible studies. However, studies in other languages than English could have been missed. The risk of publication bias was deemed low. Statistical heterogeneity between included studies was low which means that variance in results is not likely to be due to systematic errors. Confounding was addressed by meta-regression, which did not show any major influence of important confounding factors. However, covariate data for the meta-regression was not possible to be extracted from all studies wherefore there is still a risk of confounding biasing the results. Confounding due to calendar year of surgery was addressed in a sensitivity analysis excluding studies using historical cohorts of open oesophagectomy as comparison, which did not change the results. A weakness of the study is the risk of selection bias because many of the included studies were of small study samples without population-based design. Apart from not being able to include covariate data from all studies, a combination of clinical and pathological tumour stage as well as a combination of neoadjuvant and adjuvant therapy was used in the analyses, which might have introduced misclassification.

In 2012, a systematic review and meta-analysis was published comparing survival after MIO and OO, but only 4 studies (and 750 patients in total) were included. Although the study failed to show any difference between MIO and OO, the pooled point-estimate for all-cause 5-year mortality was similar to that of study II in the thesis (HR 0.88, 95% CI 0.65-1.21).[38] Since then, two RCTs have been published, but neither were able to show a statistically significant difference between MIO and OO for long-term survival. However, both showed trends towards improved survival after MIO and since both studies were small they might suffer from type II-error.[36, 37] MIO has been shown to be associated with lower risk of severe postoperative complications, especially pulmonary complications when thoracotomy is avoided.[35, 78] Moreover, severe complications might affect long-term prognosis negatively.[79-81] Therefore, it is possible that improved survival after MIO is mediated through fewer or less severe complications. Possibly, patients receiving MIO are left more immunocompetent, making them more resistant to tumour recurrence, thus improving survival.

Study II provides evidence of the superiority of MIO to OO in terms of improved long-term survival in oesophageal cancer.

Study III

Study III showed that long-term survival was improved by MIO compared to OO. This improvement was especially apparent after total MIO, and less so for hybrid procedures.

Strengths of the study include the population-based design with inclusion of almost all eligible patients, thereby minimizing the risk of selection bias at exposure level. The complete follow-up reduced the risk of selection bias at the outcome level. The risk of confounding was limited by adjusting for the most well-established prognostic factors. The risk of misclassification bias was in general low, but was unavoidable for pathological tumour stage, which included a combination of pTNM and ypTNM for which prognosis differs between equivalent, in particular early, stages. The main weakness of the study is that the study period coincides with the introduction of MIO in

Sweden and Finland, which means that proficiency was likely greater for OO than MIO, but this should bias the results in favour of OO and not the opposite.

The results of study III are supported by the findings of study II, which showed a survival benefit in favour of MIO of the same magnitude. The two RCTs on the topic have shown similar trends, but have not been able to show statically significant results.[36, 37] The results of study III might be explained by fewer complications after MIO compared to OO, [35, 78] a factor that can reduce long-term survival.[79-81] However, adjustment for length of hospital stay as a proxy for complications only slightly attenuated the results, but a survival benefit still remained for MIO. A recent study showed that MIO was associated with more complications but better short-term survival than OO, which questions this mechanism.[82] Possibly, overall recovery is quicker after MIO, regardless of complications which might have a positive effect on long-term survival.

Study III provides evidence of the superiority of MIO over OO regarding long-term survival in oesophageal cancer.

Study IV

Study IV showed that long-term survival was most consistently improved by resecting 20-30 lymph nodes during surgery for oesophageal cancer. Improved survival was especially apparent for T3/T4 tumours and for patients who had not received neoadjuvant therapy, for which survival was most improved by resection of 21-24 lymph nodes.

Strengths of the study include its population-based design with high participation rate. The risk of selection bias due to loss to follow-up was virtually non-existent due to the highly complete follow-up. Non-differential misclassification was likely to be present for the exposure as the number of counted lymph nodes likely varies between pathologists and hospitals.[83] However, by interpreting the overall trend of the results, the influence of this bias was reduced. Misclassification was also likely to have occurred to some degree of the covariate pathological T-stage (similarly discussed in the general discussion of study III). The risk of bias by confounding was reduced by adjusting the results for the most important prognostic factors. Even though the overall size of the cohort was large, the categorisation into deciles of lymphadenectomy reduced the power, which might have introduced type II-errors, especially in the stratified analyses. Type I-error cannot be ruled out for some of the results, because multiple tests were conducted.

Previous studies have shown conflicting results regarding the prognostic benefit of various extent of lymphadenectomy.[50-52, 84-86] Discrepancies might be due to differences in study designs and in the definitions of the exposure, because some of the studies compared few and broad levels of lymphadenectomy. Current guidelines recommend a higher level of lymphadenectomy in order to optimize long-term survival for locally advanced tumours compared to study IV.[6] The results of study IV are likely to be due to a trade-off between improved survival by increased removal of tumour mass and decreased survival by increased surgical trauma. Lymphadenectomy seemed to be more advantageous for advanced tumour stages which is likely due to the positive association between increased T-stage and N-stage.[49, 87] Moreover, increased survival was observed for

increased lymphadenectomy in patients who did not receive neoadjuvant therapy, which is likely due to downstaging of N-stage by neoadjuvant therapy, downplaying the role of lymphadenectomy.[86, 88, 89]

Study IV indicates that survival in oesophageal cancer is not improved by removal of more than 30 lymph nodes. The optimal number seems to be in the range of 20-30 lymph nodes for patients with locally advanced tumour stages and for those without neoadjuvant therapy, and less for other patients.

CONCLUSIONS

1) Proficiency for oesopaphageal cancer surgery seems to be gained faster by increased operation volumes during a shorter time period and among younger surgeons.

2) Minimally invasive oesophagectomy may increase the long-term survival in oesophageal cancer compared to open oesophagectomy.

3) Extensive lymphadenectomy (above 30 lymph nodes) during oesophagectomy may not improve long-term survival in oesophageal cancer, but removal of 20-30 lymph nodes may be beneficial in patients with locally advanced tumours and those not receiving neoadjuvant therapy.

POINTS OF PERSPECTIVE

Advances in the treatment of oesophageal cancer during the last decades have contributed to an improved survival, but the overall survival is still poor. This thesis identified areas which, if implemented in a clinical setting, may increase survival rates further. Future studies are needed to verify the findings regarding annual surgeon volume and surgeon age for faster proficiency gain and if other categories of age and annual volume show even greater differences. This could have a major impact on surgical training regimes.

Study II and III showed similar results in the magnitude of the advantage of MIO compared to OO in terms of improved long-term survival, but the biological mechanism is unclear. Future studies should address this, e.g. by various sensitivity analyses and by analysing biochemical inflammation responses after MIO and OO.

In order to better understand the prognostic role of lymphadenectomy during surgery for oesophageal cancer, further research is needed in regard to anatomical sites of lymphadenectomy, apart from the number of resected lymph nodes alone.

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