Esophageal- and Gastroesophageal Junctional Cancer
Aspects on Staging, Treatment and Results

GUSTAV LINDER
Abstract

Esophageal- and gastroesophageal junctional (GEJ) cancer is the sixth cause of cancer-related death worldwide. Some improvements in care are attributed to nationwide disease-specific registries, preoperative staging and increased understanding of mechanisms affecting patient selection. Surgery, however, is a cornerstone for treatment where minimally invasive surgery and increased understanding of perioperative physiology may be beneficial. The aims of this thesis were to validate the Swedish national registry for esophageal and gastric cancer (NREV) and to explore mechanisms in patient selection, perioperative physiology, treatment-related outcomes and staging.

A validation study with re-abstracted data on 400 patients determined NREV comparable to other similar registries and to have a completeness of 95.5%. Overall accuracy was 91.1% throughout the registry and timeliness to reporting was adequate.

In a cohort of 4112 patients from NREV, high education level was associated with an increased probability of being allocated to curative treatment, as was the presence of a multidisciplinary treatment conference. High education level was associated with improved survival.

By measuring intramucosal pH (pH$_i$) in 32 patients, to describe perfusion in the gastric conduit during esophagectomy, a reduction in perfusion was seen at all surgical steps altering vascular supply to the conduit but foremost after gastric tube construction by linear stapling. Patients with low pH$_i$, on the first postoperative day were more prone to anastomotic insufficiency.

In 116 patients undergoing esophagectomy (65 open and 51 minimally invasive), a retrospective cohort study regarding surgical oncological results and postoperative complications was conducted. Lymph node yield was increased, peroperative blood loss and in-hospital stay were reduced with minimally invasive esophagectomy. Postoperative complications were unaffected by surgical approach.

In a prospective study of nineteen patients, whole-body integrated PET/MRI was compared to PET/CT in preoperative staging. PET/MRI was safe and feasible. Accuracy and correlations between modalities were good regarding tumor characteristics and N- and M-staging. In T-staging there were discrepancies indicating differences between modalities.

The thesis presents data on the quality of NREV for future research and elaborates on patient selection, staging, perioperative physiology and treatment-related outcomes for patients with esophageal- and GEJ cancer.

Keywords: Esophageal cancer, Education level, Tonometry, Lymphadenectomy, PET/MRI

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"A little look saves a lot of talking."
- Ivor Lewis (1895–1982)
To Johanna, Hilda, Tuva and Majken

-You are the formidable chaos that brings order to my life
List of Papers

This thesis is based on the following papers, which are referred to in the text by their Roman numerals.


IV Linder, G., Jestin, C., Sundbom, M., Hedberg, J. Increased lymph node yield with minimally invasive compared to open esophagectomy, *Manuscript*.

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### Abbreviations

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<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>AC</td>
<td>Adenocarcinoma</td>
</tr>
<tr>
<td>ARDS</td>
<td>Acute respiratory distress syndrome</td>
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<tr>
<td>ASA</td>
<td>American society of anesthesiologists</td>
</tr>
<tr>
<td>ASCO</td>
<td>American society of clinical oncology</td>
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<tr>
<td>CI</td>
<td>Confidence interval</td>
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<tr>
<td>COPD</td>
<td>Chronic obstructive pulmonary disease</td>
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<tr>
<td>CT</td>
<td>Computed tomography</td>
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<tr>
<td>DAG</td>
<td>Directed acyclic graph</td>
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<tr>
<td>DCE</td>
<td>Dynamic contrast enhancement</td>
</tr>
<tr>
<td>dCRT</td>
<td>Definitive chemoradiotherapy</td>
</tr>
<tr>
<td>ΔpCO₂</td>
<td>Difference between arterial and intramucosal pCO₂</td>
</tr>
<tr>
<td>DWI</td>
<td>Diffusion weighted imaging</td>
</tr>
<tr>
<td>ECG</td>
<td>Electrocardiogram</td>
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<tr>
<td>ERP</td>
<td>Enhanced recovery program</td>
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<tr>
<td>EUS</td>
<td>Endoscopic ultrasonography</td>
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<tr>
<td>FDG</td>
<td>Fluorodeoxyglucose</td>
</tr>
<tr>
<td>GEJ</td>
<td>Gastroesophageal junction</td>
</tr>
<tr>
<td>GERD</td>
<td>Gastroesophageal reflux disease</td>
</tr>
<tr>
<td>Gy</td>
<td>Unit of ionizing radiation dose, Gray</td>
</tr>
<tr>
<td>HR</td>
<td>Hazard ratio</td>
</tr>
<tr>
<td>ICD</td>
<td>International statistical classification of diseases and related health problems</td>
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<tr>
<td>ICU</td>
<td>Intensive care unit</td>
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<tr>
<td>IQR</td>
<td>Inter quartile range</td>
</tr>
<tr>
<td>KKÅ97</td>
<td>Swedish classification of surgical procedures</td>
</tr>
<tr>
<td>kV</td>
<td>Unit of electromotive force, kilovolt</td>
</tr>
<tr>
<td>LGA</td>
<td>Left gastric artery</td>
</tr>
<tr>
<td>mAs</td>
<td>Unit of electric current, milliampereseconds</td>
</tr>
<tr>
<td>mBq</td>
<td>Unit of radioactive decay, millibequerel</td>
</tr>
<tr>
<td>MDC</td>
<td>Multidisciplinary treatment conference</td>
</tr>
<tr>
<td>MICE</td>
<td>Multiple imputation by chained equations</td>
</tr>
<tr>
<td>MIE</td>
<td>Minimally invasive esophagectomy</td>
</tr>
<tr>
<td>MRI</td>
<td>Magnetic resonance imaging</td>
</tr>
<tr>
<td>nCRT</td>
<td>Neoadjuvant chemoradiotherapy</td>
</tr>
<tr>
<td>nCT</td>
<td>Neoadjuvant chemotherapy</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
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<tr>
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<tr>
<td>NREV</td>
<td>National registry for esophageal and gastric cancer</td>
</tr>
<tr>
<td>OPCS-4</td>
<td>Office of population censuses and surveys classification of interventions and procedures, version 4</td>
</tr>
<tr>
<td>OR</td>
<td>Odds ratio</td>
</tr>
<tr>
<td>PACS</td>
<td>Picture archiving and communication system</td>
</tr>
<tr>
<td>pCO₂</td>
<td>Partial pressure of carbon dioxide</td>
</tr>
<tr>
<td>PET</td>
<td>Positron emission tomography</td>
</tr>
<tr>
<td>pHₐ</td>
<td>Arterial pH</td>
</tr>
<tr>
<td>pHᵢ</td>
<td>Intramucosal pH</td>
</tr>
<tr>
<td>R₀</td>
<td>Radical resection</td>
</tr>
<tr>
<td>R₁</td>
<td>Non-radical resection</td>
</tr>
<tr>
<td>SCC</td>
<td>Squamous cell carcinoma</td>
</tr>
<tr>
<td>SD</td>
<td>Standard deviation</td>
</tr>
<tr>
<td>SECC</td>
<td>Svenska esofagus och cardiocancer registret</td>
</tr>
<tr>
<td>SEMS</td>
<td>Self-expandable metallic stent</td>
</tr>
<tr>
<td>SGV</td>
<td>Short gastric vessels</td>
</tr>
<tr>
<td>SKL</td>
<td>Swedish association of local authorities and regions</td>
</tr>
<tr>
<td>SUV</td>
<td>Standardized uptake value</td>
</tr>
<tr>
<td>SWEGIR</td>
<td>Swedish general internet registry</td>
</tr>
<tr>
<td>T₁</td>
<td>Weighted sequence in MRI</td>
</tr>
<tr>
<td>T₂</td>
<td>Weighted sequence in MRI</td>
</tr>
<tr>
<td>TNM</td>
<td>Classification of malignant tumors</td>
</tr>
<tr>
<td>VATS</td>
<td>Video-assisted thoracoscopic surgery</td>
</tr>
<tr>
<td>VOI</td>
<td>Volume of interest</td>
</tr>
</tbody>
</table>
Introduction

Cancer in the esophagus and gastroesophageal junction are diseases with high mortality and increasing incidence for adenocarcinoma\textsuperscript{1,2}. Improved treatment for esophageal- and gastroesophageal junctional (GEJ) cancer is achieved with a multimodal treatment approach\textsuperscript{3}. Curative treatment includes careful preoperative staging and planning with multidisciplinary treatment conferences for individualized treatment plans, including neoadjuvant treatment, followed by demanding resectional surgery, or definitive chemoradiotherapy.

To monitor the effect of new treatment strategies and to evaluate quality in care, disease-specific registries play an important role. Basic principles of research dictate that the results from any given study is only as good as the underlying data from which conclusions are drawn. A validated registry reduces noise and provides a steadfast base for epidemiologic research. One such epidemiologic area of interest involves the underlying mechanisms of treatment selection, such as the effect of the patient’s education level on intended treatment for esophageal- and GEJ cancer.

Regardless of who is treated for esophageal- or GEJ cancer, the postoperative course and long term outcome for this patient group are dependent on optimal treatment and vigilant postoperative care. Esophageal surgery for malignancy is very demanding and by nature associated with complications. Additional understanding of perioperative physiology could improve surgical outcomes and minimize adverse events, such as anastomotic insufficiency. With aim to reduce postoperative complications, reduce operative trauma and facilitate postoperative recovery, minimally invasive procedures are gaining ground in the field and can in many cases be an alternative to open surgery\textsuperscript{4}. Evaluating the surgical oncological results of any existing or new treatment for esophageal- or GEJ cancer is adamant to ensure optimal outcome. New diagnostic modalities should also be evaluated to the same extent. Whole-body and fully integrated \textsuperscript{18}F-FDG-PET/MRI is a recent and promising modality for staging and diagnostics in esophageal- and GEJ cancer with potential benefits in enhanced tissue resolution with reduced exposure to radiation for the patient.
Background

Epidemiology
Esophageal- and gastroesophageal junctional cancer is the sixth cause of cancer related death causing 400,200 deaths globally in 2012. The same year there were 455,800 new cases globally accounting for 3.2 % of all cancer diagnoses5. There are large (21-fold) variations in incidence worldwide and a skewed gender distribution with esophageal cancer being three to four times more common in males than females5. Two subtypes of esophageal cancer are dominant; adenocarcinoma (AC) and squamous cell carcinoma (SCC). In most of the western-world-countries the incidence of esophageal AC has increased since the 1970s while the incidence of SCC has declined6. Globally, SCC of the esophagus is still much more common and AC only comprises 12 % of esophageal cancer globally in 20127. In the highest risk area, the “esophageal cancer belt”, an area geographically stretching from eastern China to the Middle east and eastern Africa, the incidence rate of esophageal cancer has been reported at endemic sites as more than 100 per 100,000 annually8. Even with SCC incidence declining, the worldwide burden of esophagogastric cancer is on the rise with estimates of an increase from 1,500,000 new cases annually in 2005 to 2,110,000 in 20259. In the United States SCC was surpassed by AC as the most common histological type in the 1990s10,11 and followed by Sweden in 2002. If cancer of the gastroesophageal junction is included (ICD-10: C16.0) the transition to AC, in Sweden, is similar in time to that of the United States12.

Etiology
As in many types of cancer, the etiology of esophageal cancer is multifactorial and the risk increases with age. There is evidence placing smoking and an excessive intake of alcohol, especially combined, at the top of known risk factors for developing esophageal SCC13,14. Other less proven risk factors for SCC are consumption of salted meats15, achalasia, intake of hot beverages and lye corrosion16,17. Risk factors for developing esophageal and GEJ AC include gastroesophageal reflux disease (GERD), via Barrett’s esophagus, obesity, smoking, low intake of fruit and vegetables and possibly hiatal her-
nia. The presence of Helicobacter Pylori have been proposed to diminish the risk of developing esophageal AC, but not AC of the GEJ.

Diagnosis and symptoms

The cardinal symptom of esophageal- and GEJ cancer is dysphagia. Dysphagia typically only becomes apparent at a late stage when less than 1/3 of the esophageal lumen remains for passage of food. Gradual progression of lumen obstruction may also lead to adaptation of eating habits with a transition to soluble foods. Thus one of the main reasons why esophageal- and GEJ cancers have such a poor prognosis is the lack of early symptoms and often late diagnosis at an advanced stage. In geographical areas of high incidence (China, Japan) there could be cost-effectiveness in the application of endoscopic screening programs. Frequent endoscopy in these populations could also explain the fact that early cancers (high grade dysplasia, T1a, T1b, N0) are more common findings in these areas. In western-world-countries the incidence is too low and the cost and possible harm of endoscopic screening deemed too high for general endoscopic screening programs. In patients with Barrett’s esophagus, endoscopic surveillance with rigorous biopsy protocols such as the Seattle-protocol, for early diagnosis of AC is still somewhat controversial although guidelines have been developed to help guide the strategy for surveillance and treatment. Newer screening modalities, e.g. analyzing exhaled volatile organic compounds, are under evaluation at a research stage but not implemented in clinical practice.

Other symptoms of esophageal- and GEJ cancer include malodorous breath, vomiting, retrosternal pain, weight loss and cachexia.

Staging

If clinical suspicion of an esophageal- or GEJ cancer arises, a prompt endoscopy should be performed. A computed tomography (CT) of the abdomen and thorax is warranted in all cases and constitutes the backbone of staging to evaluate local and peripheral spread. Staging modalities also include endoscopic ultrasound (EUS) to evaluate tumor depth and tumor-adjacent regional lymphnodes, magnetic resonance imaging (MRI) or ultrasonography for enhanced tissue imaging of primarily hepatic lesions, and positron emission tomography (PET) to scan for lymph node- or metastatic disease. Newer modalities introduced in the staging workup are PET-CT and PET-MRI.
Positron emissions tomography

Positron emissions tomography captures information on metabolic processes in the body. In tumor cells, metabolic demands are high due to rapid cell-growth and replication. Utilizing radionucleotide tracers most commonly attached to glucose, such as $^{18}$F-fluorodeoxyglucose ($^{18}$F-FDG), tumors or metastases can be identified utilizing the PET technology. PET imaging was originally performed without other simultaneous imaging. Today PET-scans are increasingly read alongside CT or even MRI, aiding the question of the location of tumor mass by the magnification of its metabolic demands. The main goal and rationale for performing PET-CT in the diagnostic work-up of esophageal- or GEJ cancer patients is to rule out metastatic disease$^{29,30}$ prior to surgical resection or definitive chemoradiotherapy. Since 2015, the Swedish national guidelines recommend PET-CT imaging in all patients with esophageal- or GEJ cancer planned for curative treatment.

![Figure 1. Fusion-image of T2-weighted sequence and $^{18}$F-FDG-PET acquired with fully integrated 3.0 Tesla PET/MRI in a patient with a gastroesophageal junctional cancer with two regional lymph node metastases.](image-url)
Magnetic resonance tomography

MRI has been available for diagnostic imaging in clinical staging of malignant disease since the 1990s. Although staging for esophageal- and GEJ-cancer is routinely performed with CT, the advancements and increasing availability of MRI is making this modality more commonly used as an adjunct to CT in staging. MRI is an imaging modality with a potential for higher tissue resolution, compared to CT, at the price of being more time-consuming, cumbersome for the patient and expensive. In patients with suspected or indefinable metastases or cysts/lesions of the liver parenchyma, an MRI is often recommended based on its superior ability to detect or differentiate benign lesions from malign lesions. Recent developments in MRI include stronger magnetic fields (3.0 Tesla), application of specific sequencing or intravenous contrast agents along with dynamic investigations to further enhance tissue imaging. Due to the movement artifacts of the heart and lungs, breathing- and ECG-gated examinations with pulsed sequence imaging are advances important for MRI of the esophagus and posterior mediastinum. In esophageal cancer, imaging with T1- and T2-weighted sequences are commonly used, in similarity with investigations of other types of cancer. Two recently introduced types of MRI sequences have been investigated, diffusion weighted imaging (DWI) and dynamic contrast enhancement (DCE). Both sequences show some results in determining tumor response to neoadjuvant treatment. Intraluminal contrast-enhancement with per oral water during MRI has also been tested with promising results regarding tumor definitions.

Figure 2. SIGNA™ PET-MRI system, by courtesy of GE Healthcare
Treatment

Multimodal treatment with neoadjuvant chemoradiotherapy (nCRT), or chemotherapy (nCT), followed by surgical resection has been proven effective in reducing mortality and increasing overall survival in esophageal cancer as compared to surgical treatment alone\textsuperscript{39,40}.

Neoadjuvant therapy

In most European countries, standard treatment is nCRT according to the CROSS-regime (carboplatin and paclitaxel with concurrent external radiation to 41.4Gy\textsuperscript{3} followed by radical resection. Similar strategies for neoadjuvant chemoradiotherapy are used in the United States but in other countries e.g., Japan and the United Kingdom the standard treatment is often pre- or perioperative chemotherapy e.g., the OE02-regime (cisplatin, fluorouracil (CF)), MAGIC/modified MAGIC-regime (epirubicin, cisplatin/oxaliplatin and fluorouracil/capecitabine (ECF/ECX/EOX)) and resectional surgery\textsuperscript{41-45}. The recently published the OE05-trial\textsuperscript{44} with a tougher preoperative treatment, four cycles (epirubicin, cisplatin and capecitabine (ECX)), showed a greater proportion of complete tumor response but did not show a survival benefit compared to the two cycles of preoperative CF in the OE02 regime. This might be due to the increased toxicity of triple agent treatment leading to fewer patients completing the neoadjuvant treatment. Although there are studies that favor perioperative chemotherapy with CF compared to surgery alone\textsuperscript{45}, no thorough comparison of preoperative treatment with CF and perioperative treatment with ECF/ECX has been performed.

In GEJ cancer, perioperative therapy with the FLOT-regime (fluorouracil, leucovorin, oxaliplatin and docetaxel), has shown promising results compared to perioperative ECF/ECX in a recently published phase-II-trial (FLOT4-AIO-trial)\textsuperscript{46}. In addition the FLOT3-trial showed favorable survival for patients with limited metastatic disease with perioperative FLOT where 36/60 patients proceeded to surgery after restaging\textsuperscript{47}. Preliminary data, presented in abstract form by Al-Batran et al. at ASCO in 2017 from the phase-III-part of the FLOT-4 trial indicated improved median survival from 35 to 50 months, improved progression free survival as well as a greater proportion of patients progressing to the intended surgery in the FLOT group. The proposed preliminary drawbacks were increased neutropenia with an associated increased infection rate.

The introduction of new chemotherapy regimens, such as FLOT, may well impact treatment strategies in the near future for adenocarcinoma of the distal esophagus or gastroesophageal junction. There is no broad consensus to date on the best neoadjuvant treatment although a recent study suggests benefits in the addition of radiotherapy to chemotherapy in esophageal- and GEJ cancer\textsuperscript{48}, in a Scandinavian setting. Ongoing studies such as the
ESOPEC-trial\textsuperscript{49}, comparing FLOT and CROSS-regimes, and the Neo-AEGIS-trial\textsuperscript{50}, comparing MAGIC and CROSS-regimes, will hopefully shed further light on neoadjuvant treatment.

Surgery

The most common procedure for the resection of an esophageal- or GEJ cancer in Europe is the Ivor Lewis\textsuperscript{51,52} esophagectomy, a two-stage operation with two field lymphadenectomy. This procedure, initially described in 1945, involves a laparotomy with gastric mobilization and tubulation of the stomach to form a gastric conduit followed by a right-sided thoracotomy with resection of the affected portion of the esophagus. A gastroesophageal anastomosis is constructed, hand sewn or stapled, in the thoracic cavity after gastric conduit pull-up. In the original description of the procedure it was performed as two separate operations with the laparotomy, mobilization of the stomach and Witzel-jejunostomy in the first operation. Following a recovery period, the second operation, where resection of the tumor, gastric pull-up and gastroesophageal anastomosis to the gastric fundus was conducted. Possible benefits of this approach was that the recovery period might have worked as ischemic preconditioning for the partly devascularized gastric conduit, decreasing the risk of an anastomotic insufficiency on ischemic grounds as discussed further below.

Another standardized technique is the McKeown three-field operation\textsuperscript{53} beginning with a right-sided thoracotomy and mobilization of the esophagus followed by a laparotomy and construction of a gastric conduit. The anastomosis is constructed in the neck through a left sided cervical incision following resection of the esophagus. Lastly esophagectomy is also possible as described by Orringer, through a laparotomy utilizing a transhiatal technique for esophageal and mediastinal access and a cervical gastroesophageal anastomosis bypassing the need for a thoracotomy\textsuperscript{54}. 


Minimally invasive esophagectomy

Minimally invasive esophagectomy (MIE)\textsuperscript{55}, first introduced in 1991, is an adaptation of the above mentioned procedures to a laparoscopic and/or thoracoscopic approach. Minimally invasive esophagectomy can be performed either as a three-field esophagectomy with a video-assisted thoracoscopic approach (VATS) and the abdominal part as open surgery with most commonly a cervical anastomosis or the inverse with a laparoscopic abdominal part and a thoracotomy with an intrathoracic anastomosis. Both techniques are in the literature referred to as hybrid-MIE. Totally minimally invasive esophagectomy with both thoracoscopic and laparoscopic approach, has emerged as a safe and many times favored alternative to open surgery\textsuperscript{4}. The technical advances with improved optics and mounting experience in laparoscopic and thoracoscopic surgery have made MIE available to an increasing number of patients with cancer in the esophagus and gastroesophageal junction.

The oncological result or safety, when introducing a minimally invasive procedure or any new medical treatment, should not be compromised. A systematic review from 2012 by Dantoc et al. demonstrated satisfactory or even improved surgical oncological results, such as increased lymph node yield with MIE\textsuperscript{56}. However, these results were extrapolated from relatively old and disparate case-series. MIE has been performed since 2013 at the author’s institution, and in 2014-2015, 36 % of all esophagectomies in Sweden were performed as minimally invasive procedures, predominantly at two tertiary centers\textsuperscript{57}.
Complications to surgery

Esophagectomy has the highest postoperative mortality rate (3-10 %) of all gastrointestinal surgical procedures. The most common early postoperative complications are pulmonary complications including pneumonia, aspiration, pleural effusion, pneumothorax, tracheal- or bronchial injury, acute respiratory distress syndrome (ARDS) and pulmonary- edema or embolism. Minimally invasive procedures have been shown to reduce pulmonary complications following esophagectomy.

Anastomotic insufficiency

Anastomotic insufficiency is a feared complication to esophagectomy, often-times associated with long duration of complex postoperative care, deterioration of patient health, organ dysfunction and an associated increased risk of postoperative death. This complication is thought to occur in 10-20 % but ranges in the literature from low single digits to above forty percent. The anastomotic insufficiency in itself can cause severe mediastinitis with an inflammatory systemic response, respiratory insufficiency and sometimes ARDS. Early detection of an anastomotic insufficiency is crucial and the treatment should be swift and aggressive including early endoscopic evaluation of the anastomotic region upon suspicion. The treatment options for anastomotic insufficiency includes conservative treatment with prolonged fasting, self-expandable covered metallic stents (SEMS), endoscopic- or surgical drainage or even, in the most severe cases, resection of the gastric conduit or anastomotic region with esophageal diversion through an end-
esophagostomy. In Sweden, SEMS are predominantly used for treatment of anastomotic insufficiency with acceptable outcome. The incidence of anastomotic insufficiency after esophagectomy in Sweden (2012-2016) was 7-17%.

There is no single cause for all cases of anastomotic insufficiency. Instead it is mainly thought to be multifactorial. One major proposed cause of anastomotic insufficiency is ischemia. Ischemia can be caused from vertical tension in the gastric conduit but also from overzealous devascularization or surgical trauma, compression at the hiatus leading to venous congestion or even gastric distention in the early postoperative period caused by pyloric constriction. In the case of a cervical anastomosis, the gastric conduit needs to reach further. This can oftentimes be managed by performing a narrower, thus longer, gastric tube but might still lead to tension or impaired perfusion causing ischemia, to some extent explaining the increased insufficiency rate in this anastomotic type (15-35%). Other unrelated postoperative complications, such as sepsis, that results in severe hypotension or even perioperative hypotension caused with/without use of vasopressors, can increase the risk of anastomotic insufficiency on ischemic grounds by compromising splanchnic blood flow. Irradiation of the gastric fundus has also been proposed to increase insufficiency rates.

Additional postoperative complications affecting patients after esophagectomy include infections, cardiac arrhythmias, laryngeal nerve palsy, injury to the thoracic duct with subsequent chylothorax, and hemorrhage. Delayed gastric emptying can occur in some patients due to denervation of the pylorus causing pyloric constriction. Endoscopic balloon dilation of the pylorus is a technique to manage this condition. The predominant late postoperative complication is anastomotic stricture occurring in approximately 30% of patients, as well as hiatal- or incisional hernia. Gastroesophageal reflux occurs in almost all patients and constitutes a need for lifelong proton pump inhibitor intake. Postoperative weight loss and cachexia may also occur due to persistent dysphagia and loss of stomach reservoir function and will also become imminent in the case of cancer recurrence.

Devices for perioperative monitoring of conduit perfusion

There are few readily available possibilities to monitor the circulation of the gastric conduit or the healing of the anastomosis in routine care. Efforts have been made to investigate perfusion of the conduit peroperatively utilizing laser Doppler technology, Indocyanine Green Fluorescent dye visual angiography and additional devices such as the O2C™ (LEA Medizintechnik, Gießen, Germany), which combines laser-Doppler technology with a white light tissue spectrometer. A previously well-described method for monitoring the perfusion of the gastric mucosa is gastric tonometry. Gastric
tonometry was initially used to assess splanchnic perfusion by anesthesiologists in the critically ill patient. The technique involves placement of a small balloon, at the tip of a catheter, in the intraluminal area of interest. The balloon has a semipermeable membrane allowing passive diffusion of carbon dioxide (CO₂), which at equilibrium with intramucosal CO₂, is measured by an infrared CO₂ sensor for determination of intramucosal partial pressure of carbon dioxide (pCO₂). Schröder et al. utilized tonometry in 2001 to study changes in pCO₂ in the gastric mucosa during esophagectomy and found that the ligation of the left gastric artery lead to an increase in pCO₂. An increase in pCO₂ in the gastric mucosa leads to a decrease in intramucosal pH (pHi), which in modern devices can be measured by a similar method. A pH below 7.1 indicates anaerobic metabolism and potentially ischemia. If anaerobic metabolism and ischemia is evident in the anastomotic region there is subsequently an increased risk of anastomotic insufficiency. Intraoperative investigations, utilizing tonometrically derived pH, of the microcirculatory changes in the intended anastomotic region of the gastric conduit, have not previously been measured at narrow intervals during esophagectomy.

Figure 5. Tonometry catheter utilized in the perioperative measurements of intramucosal pH in Paper III.

The postoperative course
The postoperative course is difficult to foresee for patients undergoing esophagectomy due to a high risk of postoperative complications in an aged and comorbid patient population. In many areas of surgery, notably colorec-
tal surgery, enhanced recovery programs (ERP) have reduced in-hospital stay and reduced postoperative complications\textsuperscript{82}. In upper gastrointestinal surgery there are guidelines for enhanced recovery in elective pancreati-
coduodenectomy\textsuperscript{83} to the same extent as in colonic or rectal/pelvic surgery\textsuperscript{84,85}. Guidelines specific for enhanced recovery in elective esopha-
agectomy do not exist in structured form, bearing in mind that ERP-concepts successful in e.g., colorectal surgery such as immediate postoperative oral intake for a speedier recovery may not at all be applicable in esophageal cancer surgery. There are no large randomized controlled trials to determine the effect of enhanced recovery in esophageal cancer surgery, although systematic reviews and pooled analysis of implemented enhanced recovery programs suggests benefits regarding rate of anastomotic insufficiencies, pulmonary complications and length of stay\textsuperscript{86}. The variability in existing programs is of course a concern hampering the possibility of firm conclusions. Although no formal ERP has been adopted at the author’s tertiary center, the median length of stay was reduced from 19 days (2007-2011) to 14 days (2012-2016) in patients undergoing esophagectomy. This could reflect the introduction of minimally invasive surgery, but also the general strive for shorter length of stay. Other possible factors for reduced length of stay are improvements in postoperative care, the rub-off effect from enhanced recovery programs in other surgical fields implemented at the present hospital or the need for cost effectiveness in public healthcare.

Pathologic staging

After resectional surgery the surgical specimen undergoes pathological examination forming grounds for the pathologic TNM staging (pTNM). In routine care in Sweden the surgical specimen is delivered to the pathology lab immediately, without prior formalin fixation. Following initial macro-
scopic analysis, focusing on total number of resected nodes and distance to proximal and distal resectional margins, a detailed histopathological diagnosis from microscopic analysis and immunohistochemistry is performed along with microscopic examination of resection margins. A tumor infiltrated, or near infiltrated (<1mm), resection margin, R1, is associated with poor long-
term prognosis\textsuperscript{87}. The prognostic significance of a positive circumferential margin in the era of neoadjuvant treatment has recently been questioned\textsuperscript{88,89}. In spite of this recent debate, a microscopically assessed radical resection, R0, is characterized by >1mm from proximal, distal and circumferential resection margins to tumor cells. In the clinical setting >5cm from resectional margins to the tumor are strived for.
Adjuvant treatment

The role of postoperative treatment of esophageal cancer remains unclear. Randomized trials of patients treated in the pre-millennial era with adjuvant radiotherapy did not show a significant improvement in survival by addition of adjuvant treatment, potentially owing to the increased rate of complications caused by the radiotherapy itself. Similar results were seen in the same era for adjuvant chemotherapy. In recent years, however, adjuvant radiotherapy, to patients with clinical stage-I and -II disease with positive resection margins as well as lymph node positivity, has been associated with improved survival in non-randomized settings. Adjuvant chemotherapy alone was in the above study by Wong et al. a predictor for improved survival as was the case in two additional recent studies evaluating adjuvant chemotherapy following neoadjuvant chemoradiotherapy. However, conflicting results have been presented. In squamous cell carcinoma a large Japanese randomized trial (JGOG9907) was closed early at interim analysis due to an advantage of neoadjuvant chemotherapy compared to adjuvant chemotherapy. Randomized controlled trials in the era of neoadjuvant treatment are warranted to explore the usefulness of adjuvant treatment. The future results from the ESOPEC-trial as well as the Neo-AEGIS-trial, both studies investigating regimes that include adjuvantly administered chemotherapy, are intriguing in this aspect.

Definitive oncologic treatment

Some patients may not be operable due to the advanced and/or technically challenging growth and location of the tumor. Other patients refuse surgery or are medically unfit to tolerate a physically demanding esophagectomy. These patients can be offered definitive chemoradiotherapy (dCRT) or solely radiotherapy with a curative intent. In definitive oncological treatment, radiotherapy is most often followed by chemotherapy with a platinum based cytotoxic agent in combination with fluorouracil. Newer combinations of chemotherapy such as FOLFOX (oxaliplatin, leucovorin, fluorouracil) have been evaluated although not increasing progression free survival but perhaps providing a more convenient method of administration. Other regimens are also emerging with addition of docetaxel to cisplatin (DP) to radiotherapy recently evaluated in a phase II randomized controlled trial. The trial presented more hematological toxicities and no benefit in survival for patients receiving DP and radiotherapy compared to patients receiving cisplatin, fluorouracil and radiotherapy. However, the addition of docetaxel to CF is currently being evaluated in a phase III randomized controlled trial in patients with recurrent disease. Variations in total radiation dose and fractions have been made, although not proving better results following higher radiation dose therapy (64.8 Gy vs. 50.4 Gy). In squamous cell carcinoma randomized studies have implied equivalent 2-year survival with dCRT in
responders compared to nCRT followed by surgical resection or compared to surgery alone. These results are, however, challenged. Some patients respond very well to oncologic treatment and although not, by a number of reasons, amenable for surgical resection in the initial staging may well become surgically resectable after dCRT. The patients’ performance status could also greatly improve after definitive oncologic treatment. In this group of patients, with persistent controlled disease as well as in patients treated with dCRT that later develop a loco regional recurrence, salvage esophagectomy may have to be taken into consideration. Salvage esophagectomy can be performed with low morbidity and mortality if concentrated to experienced centers. The long-term survival for selected patients is in parity with nCRT plus surgery although patients with persistent disease undergoing salvage esophagectomy have lower survival rates compared to patients with recurrent disease undergoing salvage surgery. On limited occasions and in a few select patients treated primarily with nCRT and surgery who later develop loco regional recurrence, salvage treatment with dCRT aimed at total tumor eradication is feasible and may improve survival, although palliative treatment or best supportive care is the general recommendation for these patients.

**Palliative treatment**

The ultimate goal of palliative treatment in esophageal- and GEJ cancer is to maintain the oral route for nutrition, relieve dysphagia and maintain an acceptable quality of life. Palliative chemotherapy and/or targeted cytotoxic therapy can provide an overall survival benefit for the patient compared to best supportive care. The esophageal obstruction and dysphagia caused by the tumor can be palliated by endoscopic balloon dilation, self-expandable metallic stents (SEMS) and/or internal or external radiation. SEMS are fastest in symptom relief but have disadvantages such as the possibility of stent migration and need for re-intervention. Loco regional control with high dose brachytherapy may provide an advantage in overall survival and a combination of SEMS and brachytherapy reduces the need for re-intervention.

**Long term survival**

Survival in patients receiving no active treatment for esophageal cancer can only be described as abysmal. The 5-year survival for operable patients with resectable tumors declining surgery presenting at clinical stage I, II and III have been estimated to 10.0 %, 9.8 % and 4.6 % respectively. For patients with resectable tumors but unfit for surgery, the corresponding 5-year survival was 4.7 %, 1.9 % and 1.6 % in the same study. Five-year survival rates after surgery alone are somewhat improving, but are generally low compared
to most other gastrointestinal malignancies. The results from the OE02-trial (2009) concludes that the addition of preoperative chemotherapy to surgery alone improved the 5-year survival from 17 % to 23 %\(^{41}\) and in another landmark study, CROSS (2012), the addition of neoadjuvant chemoradiotherapy to surgery improved 5-year overall survival from 34 % to 47 %\(^{3}\). The long-term follow-up from this study, presented in 2015 with median follow-up of 84.1 months for surviving patients, confirmed the survival benefit with an overall 5-year survival of 47 % in the group receiving neoadjuvant treatment plus surgery versus an overall 5-year survival of 33.0 % in the surgery alone group\(^{116}\).

Figure 6. Overall survival by treatment group in patients with esophageal- or GEJ cancer. Reprinted by permission from Elsevier: *The Lancet Oncology*, Neoadjuvant chemoradiotherapy plus surgery versus surgery alone for oesophageal or junctional cancer (CROSS): long-term results of a randomized controlled trial, Shapiro et al, ©2015.
Socioeconomics and esophageal cancer

Equality of healthcare for each individual patient is a basic principle that governs many publicly funded health care systems, like in Sweden. It is stated in Swedish law that care should be given equally, regardless of socioeconomic status. Socioeconomic status is a broad concept that constitutes many factors of which education, in addition to income, marital status, place of residence and occupation, play an important role. Poor education has in a previous study by Brusselaers et al. been associated with decreased survival after surgery for esophageal cancer\textsuperscript{117}. In addition to this, patients with low socioeconomic status, reflected by marital status, education and income, have an increased risk of attaining the disease\textsuperscript{118}. Studies regarding the effect of the patient’s education level on the choice of treatment in esophageal cancer are lacking.

Swedish national quality registries

Sweden is a country with a tradition of maintaining high-quality national registries administered by the Swedish Board of Health and Welfare. They include the Swedish Patient Register\textsuperscript{119}, the National Prescribed Drugs Register\textsuperscript{120} and the Swedish Cancer Register\textsuperscript{121} which harbours patient data, sex and place of residence, site of the tumour, histological type and basis for the diagnosis. The completeness of these registries is very high\textsuperscript{121}.

Important information on clinical data and outcome variables are lacking in these government managed registries even though they are powerful instruments for population based research. Therefore, national quality registries have developed over the years alongside the public databases\textsuperscript{122-126}. There are some 60 national quality registries financed by governmental support through the Swedish Association of Local Authorities and Regions (Sveriges kommuner och landsting, SKL). These registries are more disease specific and detailed with information on incidence, clinical manifestations, diagnostics, outcome of medical- or surgical treatment and follow-up.

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

Before the launch of the National Registry for Esophageal and Gastric Cancer (NREV), two separate databases on esophageal and gastric cancer were operational in the country. One was a clinical registry for gastric cancer (SWEGIR) and one a research based registry for esophageal- and gastroesophageal junctional cancer (SECC)\textsuperscript{127}. These two registries were merged into NREV, which was started on January 1\textsuperscript{st} 2006.
In March 2018 there were 14277 patients reported to the NREV including 4456 surgical procedures. The registry consists of data acquired in surveys. There are three separate surveys; a diagnostic-survey, a surgical treatment-survey and a follow-up-survey. In addition, there is a recently introduced survey on oncologic treatment, however this survey was not in clinical use during the study period thus beyond the scope of the present thesis.

**Diagnostic survey**

In the first survey, clinical data is collected from the time of diagnosis and contains, among other variables; time of referral, histological tumor type, preoperative staging modalities, clinical TNM-stage and intended treatment.

**Surgical survey**

If the patient undergoes surgical resection of the tumor, a second survey with details regarding the surgery is completed. In patients undergoing palliative surgical procedures without tumor resection only the first few variables of the second survey are warranted.

**Follow-up survey**

The third survey is completed at the clinical follow-up in patients that underwent tumor resection surgery with information regarding postoperative complications and definitive staging from the pathological investigation.

**Evaluating the data quality of a registry**

Patients included in medical audits have a better prognosis than those outside registration. In order to assess data quality, validation studies provide much information and can be performed when the registries are mature. In addition to being a valuable data source for observational research, a well maintained registry with high validity also offers the possibility of performing register based randomized trials providing a valuable combination of the randomized trial design and the population coverage of a registry.

In the evaluation of data quality in a registry, different aspects have to be attended to. First the issue of comparability, taking into account the statistics generated by the registry for different patient groups and over time. This part of registry evaluation focuses on the classification and coding routines of the registry and the basic definitions. The evaluation of comparability of the registry is essential for meaningful interpretation and allows for comparisons with other similar registries.

Second, the completeness of the registry must be appreciated. Completeness is a measure of to what extent all incident cancers in an underlying population are actually included in the evaluated registry. The evaluation of
completeness can be performed by a quantitative approach in which an evaluation is made regarding the extent to which all eligible cases have been reported. Another method is a qualitative approach that investigates the degree of completeness relative to other registries, or over time\textsuperscript{113}. A combination of the two approaches is possible.

Thirdly, the accuracy of the data in a registry should be valued. The accuracy, or validity, is an evaluation of the entries in a dataset. Brey et al. define validity as “the proportion of cases in a dataset with a given characteristic (e.g. site and age) which truly have the attribute”\textsuperscript{132}. There are different methods to evaluate validity. One method recently applied in the evaluation of data quality in the Swedish national prostate cancer registry is re-abstraction\textsuperscript{126}, in which a sample of registry data is compared with data from source medical records for evaluation of agreement.

Fourth, and finally, the timeliness in reporting can be evaluated. There are no formal prerequisites for evaluation of timeliness, however a delay in reporting could possibly affect the accuracy of data in the registry by introducing recall biases for the reporting personnel. By utilizing reference dates, such as date of diagnosis, or time of surgery, to the time the case is reported to the registry an estimation of the delay in reporting can be made.
The aim of this thesis was to evaluate the validity of the National Registry for Esophageal and Gastric Cancer and explore mechanisms in patient selection, perioperative physiology, treatment-related outcomes and staging in patients with esophageal- and gastroesophageal junctional cancer. The specific aims were:

I to evaluate data in the Swedish National Registry for Esophageal and Gastric Cancer, NREV, regarding comparability, completeness, accuracy and timeliness.

II to investigate the relationship between the patient’s education level and respective treatment allocation after the diagnosis of esophageal- and gastroesophageal junctional cancer and its subsequent impact on survival.

III to investigate changes in the perfusion of the gastric conduit at eight key steps during and after esophagectomy. A secondary aim was to explore if there were differences in perfusion between patients with or without anastomotic insufficiency.

IV to evaluate the introduction of minimally invasive esophagectomy at a tertiary referral center with focus on surgical oncological results. A secondary aim was to assess the effect on postoperative complications.

V to perform a structured evaluation of whole-body fully integrated $^{18}$F-FDG-PET/MRI versus $^{18}$F-FDG-PET/CT in preoperative staging of patients with esophageal- or gastroesophageal junctional cancer.
Patients and Methods

Patients

Papers I and II utilized data from NREV. The selection base for Paper I were the 2484 patients with esophageal and gastric cancer registered on the diagnostic survey of NREV during 2009 and 2010. From the selection base a randomized sample for the re-abstraction was made constituting 400 patients stratified for geographical location in order to secure a representative sample. Fourteen strata (140 patients) were from university hospitals and the remaining 26 strata (260 patients) originated from county hospitals according to catchment population, figure 7. In assessment of completeness, the selection base was instead all patients, with esophageal- and gastric cancer reported to the Swedish Cancer Registry, between 2009 and 2013.

![Figure 7](image)

*Figure 7. Number of patients selected for re-abstraction per region, hospital and their respective geographical location. Dot size correlates to number of patients. Circled dots represent university hospitals.*
Paper II included all patients with esophageal- or GEJ cancer reported to NREV from the founding of the registry in 2006 through 2012. Inclusion was based on ICD10 diagnoses; C15. *, C16.0A, C16.0B and C16.0X, all other diagnoses were excluded. The cohort constituted 4112 patients, 74 % were male and the median age was 70.

Paper III included 32 patients with esophageal- or GEJ cancer, 28 men (88 %), and median age 65 years, undergoing esophagectomy during 2013 through 2015 at Uppsala University Hospital. Only patients intended for conduit formation and gastric pull-up were eligible for the study.

Paper IV included all 116 patients that underwent elective transthoracic esophagectomy at Uppsala University Hospital between 2007 and 2016 (88 % men, median age 66 years). The diagnoses used for inclusion were the same as in Paper II.

In Paper V, patients with potentially curable esophageal- or GEJ cancer (cT1-4aN1-3, M0) were scanned for inclusion. They were deemed candidates for the study if they were planned for curative resection at a MDC. Nineteen patients, 17 men (89 %), median age 65, met the inclusion criteria and comprised the cohort for the study. One patient only performed a rudimentary MRI without PET and two patients withdrew consent prior to examinations and were therefore excluded. 16 patients remained for the analysis.

Study designs

A national validation study evaluating the comparability, completeness, accuracy and timeliness of NREV was conducted in Paper I as theoretically outlined in the background section of this thesis.

Paper II was a nationwide population based retrospective cohort study. A database was constructed linking data from NREV to the National Patient Registry, the Cause of Death Registry, the Prescribed Drug Registry, the Swedish Cancer Registry and educational data from the Education Registry. Data was extracted in 2014.

Paper III was a single-center prospective exploratory study of perioperative physiology during esophagectomy by means of gastric tonometry. Intraoperative measurements of pHi in the gastric conduit were performed at narrow intervals during surgery.

In Paper IV a single center retrospective cohort study was conducted. Data collection was performed by thoroughly reviewing medical charts and hospi-
tal administrative systems. Resectional radicality and lymph node yield were assessed by scrutiny of the clinical postoperative pathology reports. Included patients were divided into two groups based on surgical approach. Transhiatal surgeries were excluded.

Paper V was performed as a comparative prospective study of blinded radiological readings of $^{18}$F-FDG-PET/CT with $^{18}$F-FDG-PET/MRI in preoperative staging. Only patients planned for a clinically indicated $^{18}$F-FDG-PET/CT were eligible for the study. Included patients underwent both a clinical $^{18}$F-FDG-PET/CT as well as a study specific $^{18}$F-FDG-PET/MRI.

**Methods for evaluating the data quality of NREV**

In Paper I, comparability was evaluated by a review of coding routines, classifications, diagnostic- and procedural coding systems. The completeness was assessed by comparing patients, with esophageal- and gastric cancer, reported to the Swedish Cancer Registry with patients reported to NREV during a five-year study period. The data for said comparison was extracted on April 1st, 2015.

To evaluate accuracy, a re-abstraction of data from source medical records was performed. Patient medical charts were reviewed by validators at the hospital responsible for the initial completion of the survey. When an audit was not possible, medical charts were sent after by post and subsequently reviewed instead. The validators recoded data from medical charts in the same way as an original registration on a paper form and later transferred the recoded data to a digital worksheet. The re-abstracted data regarding the 60 variables from the surveys were analyzed for missing values, exact agreement and correlation to the original data.

By measuring number of days from certain index-dates acquired in the re-abstractions to the time for the completion of the original surveys an estimation of timeliness could be described. The index-dates used to describe timeliness were; biopsy date, date of surgery and four weeks after discharge.

**Education level and treatment allocation**

To define the exposure, patient education level was divided in three classes based on the highest attained number of years of schooling at the time for data extraction. Low education level was defined as $\leq 9$ years, intermediate education level 10-12 years and high education level $>12$ years of schooling. The definition of outcome in Paper II was the intended choice of treatment (treatment allocation). In most cases treatment allocation is determined at a MDC or in some cases only by the treating physician. Treatment allocation
is a mandatory variable reported on the diagnostic survey of NREV, and was in Paper I shown to be a variable of high validity.

**Tonometric measurements**

In Paper III, the perfusion of the gastric conduit was quantified, during and after esophagectomy, by measuring intramucosal pH (pHi) with a Datex Ohmeda S5, Tonometry Module (M-TONO, Datex Ohmeda, Helsinki, Finland). A tonometry catheter was placed intraluminal in the fundic region of the stomach at the site of the intended gastroesophageal anastomosis. Tonometry data was collected in 10-minute equilibration-cycles at baseline and after four predefined surgical steps hypothesized to alter the perfusion of the gastric conduit. Additionally pHi was measured at the end of surgery and at two postoperative time-points. The position of the tonometry catheter was confirmed manually by palpation after each key step before measurement. Intraoperative tonometry data was blinded to the operating team during surgery. In patients undergoing open thoracotomy, after onset of one lung ventilation and after resuming double lung ventilation, additional tonometry data was collected. To calculate pHi and to detect systemic changes in the patient during surgery, the tonometric measurements were related to simultaneously obtained arterial blood samples for analysis of arterial pH, pCO₂ and pO₂. Tonometrically measured intramucosal pCO₂ (p_iCO₂) and ΔpCO₂ was also registered.

**Operative procedures**

All patients received standard preoperative antibiotic prophylaxis as well as tromboprophylaxis with low molecular weight heparin. Open procedures were either performed as a two-field transthoracic Ivor Lewis esophagectomy, a three-field McKeown’s esophagectomy or a transhiatal esophagectomy. All open transthoracic procedures were in the left lateral position with a right-sided thoracotomy. The laparotomies were performed by upper midline incision. The only two transtiatal surgeries in paper III were performed as described by Orringer⁵⁴. Minimally invasive procedures were either three-field hybrid-MIE with thoracoscopy and laparotomy with a cervical gastroesophageal anastomosis or totally minimally invasive with an intrathoracic gastroesophageal anastomosis. The anastomotic technique for intrathoracic anastomoses in open surgeries were a side to end esophagogastric anastomosis constructed with a circular stapler and in minimally invasive surgeries with a linear stapler and hand-sewn as previously described by Irino et. al¹³⁴. Cervical anastomoses were performed through a left-sided cervical incision and hand-sewn. All surgeries except the transhiatal surgeries were performed
with a standardized two-field lymphadenectomy including removal of abdominal nodes from the suprapancreatic border, lesser curvature, left gastric artery and celiac trunk as well as the hiatal region. The mediastinal lymphadenectomy included subcarinal and paraesophageal nodes as well as clearance along the left and right main stem bronchi.

**Neoadjuvant treatment**

During the study periods, between 2007 and 2016, the regimen for nCT was three cycles of epirubicin and oxaliplatin, in combination with capecitabine (EOX) for patients treated for esophageal- and GEJ cancer at Uppsala University Hospital. Between 2007 and 2013 the predominant nCRT regimen was three cycles of oxaliplatin in combination with fluorouracil and concurrent external radiation to 44-50Gy. In recent years, 2014 to present day, nCRT was administered according to the CROSS-regimen with three cycles of carboplatin and paclitaxel with concurrent external radiation to 41,4Gy.

**18F-FDG-PET/CT**

During the study periods, a standard clinical protocol for PET/CT was utilized. PET-CT (Discovery, GE Healthcare™) was performed with five PET bed positions and 120 seconds per bed position. In clinical staging with PET/CT, the CT-protocol (120 kV; 10 mAs) with 1mm slice thickness includes intravenous contrast enhancement to facilitate anatomical localization, guiding and for attenuation correction. In two patients of paper V the PET/CT was performed without the use of intravenous contrast. In those patients the most recent clinical diagnostic CT with intravenous contrast was added to the PET/CT reading to ensure proper evaluation of clinical T-stage. In the study protocol for Paper V, patients were administered an 18F-FDG injection prior to examinations which was utilized in both the PET/CT and the immediately afterwards following PET/MRI.
**18F-FDG-PET-MRI**

All PET/MRI examinations were performed according to a study specific protocol on a 3 Tesla PET/MRI (SIGNA, 3.0T, 60cm, GE Healthcare™) with combined time-of-flight PET. The PET image-acquisitions were in 6 bed positions, with 180 seconds per position. The method for attenuation correction was fully integrated and performed in a whole body, free breathing 3D T1-weighted DIXON sequence (sequence parameters: TE, 1.11 and 2.23 ms; TR, 4 ms; 5° flip angle).

Aside from the attenuation correction sequence, a number of additional MRI sequences comprised the extensive study protocol (ECG- and breathing gated images, T2-weighted images and DWI). A contrast enhanced T1-3D sequence was also performed with and without per oral water intraluminal contrast enhancement. A paramagnetic hyperosmolar intravenous contrast media, gadoterate meglumine (Dotarem®, Gothia Medical AB, Bilddal, Sweden), was used for contrast enhanced imaging.
Structured radiologic readings

Patients in Paper V were assigned a consecutive number from 1-19 linking them to the performed PET/CT and PET/MRI examinations. Images were transferred to a separate study specific picture archiving and communications system (PACS) utilized in the radiological readings. One dedicated radiologist performed all PET/CT readings with the clinical radiological report censored and two dedicated radiologists performed all PET-MRI readings, first individually, and then together. The radiological readings were performed with radiologists blinded to patient and clinical data. Both fac-
tions utilized the same study specific preformed protocol for structured reading.

A three-dimensional volume of interest model (VOI) of the tumor component with greatest $^{18}$F-FDG-uptake was the method to calculate maximum standardized uptake values ($SUV_{\text{max}}$). The 7th edition of TNM classification of malignant tumors (TNM7)\(^{135}\) was the foundation for assessment of all clinical tumor, nodal and metastatic staging. Non-regional lymph nodes were not included in nodal stage assessment although they were in the assessment of the total number of radiological suspected lymph nodes. A comparison of clinical TNM-stage to pathological TNM-stage was not performed in Paper V.

### Statistical methods

All papers applied descriptive statistics where deemed appropriate. Specifically in Paper I, completeness and timeliness were described by descriptive statistics. Descriptive statistics were also applied in presentation of tonometric and postoperative data in Paper III, in analysis of baseline and perioperative data in Paper IV, and in description of tumor characteristics and examination parameters in Paper V.

In Paper I, Accuracy was analysed by calculating proportion with exact agreement, Pearson’s correlation was used for numerical values and dates. Cohen’s $\kappa$-statistics were applied to correlate ordinal values.

In Paper II, univariate and multivariate logistic regression was applied to estimate the effect of education level on the probability of allocation to curative treatment. Survival was displayed according to the Kaplan-Meier method and Cox proportional hazard models were used to assess the effect of exposure when adjusting for multiple variables. Missing data was handled by using the Multiple Imputation by Chained Equations (MICE) algorithm\(^{136}\). Separate models were fitted to the dataset in each iteration and the results were pooled using Rubin’s rules\(^{137}\).

In Paper III, differences in $\text{pH}_i$, $\Delta\text{pCO}_2$, $\text{pH}_a$ as well as postoperative parameters were calculated using Students t-test for normally distributed data, otherwise Wilcoxon rank-sum or Wilcoxon signed ranks test.

In Paper IV, Wilcoxon rank-sum test or Students t-test for continuous variables and Pearson’s $\chi^2$-test for ordinal variables were used to present differences between groups. Surgical oncological outcomes as well as postoperative complications were analyzed with multivariate logistic regression.
In Paper V, correlation assessments between PET/CT and PET/MRI on continuous variables were performed with Spearman’s or Pearson’s correlation tests and pairwise comparisons of measured tumor characteristics were analyzed by paired Student’s t-test or Wilcoxon signed ranks test. Inter-rater-agreement of clinical TNM-staging was analyzed by weighted and unweighted Cohen’s κ as well as percentages of exact agreement in similarity with Paper I. Scatterplots with best-fit lines were used for graphical presentation of radiological estimated tumor characteristics.

In Paper I and V, inter-rater agreements were calculated with Cohen’s κ-statistics. Interpretation of κ-values was according to criteria well described by Landis et al. A κ-value < 0 was interpreted as no agreement. A κ-value of 0 – 0.2 was characterized as slight agreement, 0.21 – 0.4 as fair, 0.41 – 0.6 as moderate, 0.61 – 0.8 as substantial and 0.81 – 1.0 was interpreted as near perfect agreement.

Potential covariates and confounding factors were in papers II and IV identified by using causal directed acyclic graphs (DAGs), figure 9.

Figure 9. Directed acyclic graph of associations between the exposure type of surgery and the outcome increased lymph node yield. Red dot; confounding factor, Green dot; ancestor of exposure, Blue dot; ancestor of outcome, Grey dot; unmeasured variable. Green arrow; causal pathway, Red arrow; confounding pathway. BMI; body mass index, ASA; American society of anesthesiologists
A p-value of < 0.05 was considered statistically significant in all Papers. Statistical analysis were performed with the R statistical software package in Papers I, II and III and STATA© version 14.2 (StataCorp, College Station, TX, USA) in Papers I, IV and V.

Ethics

The Regional Ethical Review Boards in Stockholm or Uppsala approved all studies. Written informed consent was obtained from all participants in Paper III and V.
Results

Paper I

Comparability
Surgical procedures were coded with a national coding system, “Klassifikation av kirurgiska åtgärder 1997” (KKÅ97). This system was similar to systems in the other Nordic countries and could be translated into e.g., Office of Population Censuses and Surveys Classification of Interventions and Procedures version 4 (OPCS-4). The ICD-10 system and the Siewert classification were used for coding of tumor location. In staging, TNM-6 and TNM-7 were used. In the study period, ICD-10, the Siewert classification and the TNM-system were implemented globally in the surgical community. Complications were initially coded only by diagnosis according to ICD-10 but after 2012 according to the Clavien-Dindo classification of surgical complications.

Coding routines and registration forms were found consistent with international and national guidelines\textsuperscript{141,142}.

Completeness
There was clinical information on 10 729 patients including 3492 resections (resection rate 32.5 %) in NREV. In comparison to the Swedish Cancer Registry where 6354 esophageal- and gastric cancers were reported during the completeness study period, 6069 patients were also reported to NREV. This amounted to a completeness of 95.5 % at the time of data extraction.

Accuracy
There were complete medical records on the diagnostic survey for analysis in 361 out of the 400 randomly selected patients for re-abstraction. 39 patients were deemed not eligible or available for re-abstraction, 11 were misclassified tumors and in the remaining 28 there were double registrations or unobtainable medical records despite several reminders that led to exclusion. In 129 out of 361 resectional surgery was performed and in 122 out of 129 (94.6 %) the surgical survey was completed. In 113 out of 122 (92.6 %) a completed follow-up survey was registered. The exact agreement of validat-
ed entries was 91.1 % over the entire registry, 6.5 % were incorrect and 2.4 % were missing, table 1.

Table 1. Overall accuracy and missing data from 361 re-abstractions from medical charts compared with in 2009 and 2010

<table>
<thead>
<tr>
<th>Survey</th>
<th>Total No of entries available for validation</th>
<th>No (%) of Missing data</th>
<th>No (%) of Incorrect</th>
<th>No (%) of Exact agreement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnostic</td>
<td>7220</td>
<td>123 (1.7)</td>
<td>602 (8.3)</td>
<td>6495 (90.0)</td>
</tr>
<tr>
<td>Surgical</td>
<td>3346</td>
<td>117 (3.5)</td>
<td>104 (3.1)</td>
<td>3125 (93.4)</td>
</tr>
<tr>
<td>Follow-up</td>
<td>1469</td>
<td>47 (3.2)</td>
<td>76 (5.2)</td>
<td>1346 (91.6)</td>
</tr>
<tr>
<td>Total</td>
<td>12035</td>
<td>287 (2.4)</td>
<td>782 (6.5)</td>
<td>10966 (91.1)</td>
</tr>
</tbody>
</table>

Diagnostic survey completed in 361 patients, surgical survey completed in 122 patients and follow-up survey completed in 113 patients

Tumor stage

In clinical T-stage (cT), there was exact agreement in 296 of 361 patients (82.0 %), κ-coefficient 0.77. There was an abundance of Tx in original registrations where medical records in actuality contained enough information for a more accurate clinical T-staging. Pathologic T-stage was more accurate than cT with exact agreement in 104 of 113 (92.0 %), κ-coefficient 0.92. N- and M-stage were of corresponding accuracy although inter-rater agreement was reduced in pathologic M-stage, table 2.
Table 2. Exact agreement and correlation between original and re-abstracted NREV-data for clinical and pathological TNM-stage. Panel a and d shows T-stage, panel b and e shows N-stage and panel c and f shows M-stage.

<table>
<thead>
<tr>
<th></th>
<th>Clinical T-stage</th>
<th>Re-abstraction</th>
<th></th>
<th>Pathological T-stage</th>
<th>Re-abstraction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>T0</td>
<td>T1</td>
<td>T2</td>
<td>T3</td>
<td>T4</td>
</tr>
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<td>1</td>
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</tbody>
</table>

Exact agreement = 820 per cent, Cohen's kappa = 0.77

<table>
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<tr>
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<th></th>
<th>Pathological N-stage</th>
<th>Re-abstraction</th>
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</thead>
<tbody>
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<td>N4</td>
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<td>0</td>
<td>0</td>
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</table>

Exact agreement = 794 per cent, Cohen's kappa = 0.71

<table>
<thead>
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<th>Clinical M-stage</th>
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<th>Pathological M-stage</th>
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</thead>
<tbody>
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<tr>
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<td>0</td>
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<td>0</td>
<td></td>
</tr>
</tbody>
</table>

Exact agreement = 874 per cent, Cohen's kappa = 0.78

Surgical characteristics (from the surgical survey)
Overall accuracy was high (93.4 %) in the surgical survey. Missing values accumulated in variables such as preoperative weight and height, preoperative stent or PEG, reducing the level of accuracy.

Dates
Accuracy in dates e.g., date of- first visit or referral, diagnosis, therapy decision, surgery and discharge ranged from 84.5 % to 96.7 % with near perfect correlations (0.99 to 1.0).

Follow-up
Variables concerning discharge had an exact agreement of 93.8 % to 94.7 % and correlation of 0.92 to 1.0. Accuracy in surgical complications and general complications were slightly lower, 92.9 % and 91.2 %, with κ-coefficients of 0.87 and 0.84
Figure 10. Missing data, exact agreement (%) and correlation of validated variables in NREV. Blue depicts good correlation (0.6–0.8) and orange depicts excellent correlation (0.8–1.0).

*Correlation with Pearson’s correlation test, all other correlation is by Cohen’s $\kappa$.

**Timeliness**

From diagnosis to registration of the diagnostic survey, the median time was 3.9 months with 77.6% of patients being reported within one year after diagnosis/date of diagnostic biopsy. From surgery to registration of the surgical survey, the median time was 3.4 months (76.9% within one year). For the follow-up survey the time and percentage were 4.1 months and 74.8% respectively.
Paper II

Baseline data
Analysis was based on 4112 patients. The duration of education was low in 1686 patients, intermediate in 1522 patients and high in 638 patients, corresponding to 41.0 %, 37.0 % and 15.5 % of the study population respectively. Educational data was missing in 266 patients (6.5 %). Patients in the high education level group were slightly younger and more often geographically located in the capital region and presented with less comorbidity. In all other aspects the three study groups were balanced.

Education level and treatment allocation
Overall, 1587 patients (38.7 %) were allocated to curative treatment. Thirty-six percent of patients in the low education level group were planned for curative treatment whereas the intermediate- and high education level groups were planned for treatment in 42.6 % and 46.4 % respectively.

Univariate analysis
Both intermediate education level, (OR 1.35, 95 % CI 1.17–1.55), and high education level, (OR 1.58, 95 % CI 1.31–1.90) were associated with an increased probability of curative treatment allocation.

Multivariate analysis
In multivariate logistic regression high education level and curative treatment were associated (adjusted OR 1.48, 95 % CI 1.08 – 2.03). Residing in geographical region south and west were positive predictors of curative treatment as was a MDC with an elevated adjusted OR of 3.13 (95 % CI 2.40 – 4.08). Negative predictors were geographical region central, squamous histopathology, positive N- and M-stage- disease, higher ASA-class and age as well as diagnosis of COPD, figure 11.
Figure 11. Graphic presentation of Odds ratios (OR) with 95 % confidence intervals (CI) from a multivariate logistic regression model for the outcome planned curative treatment.

Stratified analysis
Stratified multivariate regression confirmed or strengthened associations between high education level and allocation to curative treatment in men, patients > 70 years old and for patients with adenocarcinoma with adjusted ORs 1.47, (95 % CI 1.02 – 2.12), 1.61 (95 % CI 1.06 – 2.44) and 1.73 (95 % CI 1.13 – 2.64) respectively. The MDC was a predictor for allocation to curative treatment in all subgroups, supplementary table 1, Paper II.
Survival analysis

Multivariate Cox regression of patients planned for curative treatment revealed improved survival in patients with high education level (HR 0.82, 95 % CI, 0.69 – 0.99), lower age and ASA-class, early cTNM-stage as well as in patients without COPD-diagnosis.

A MDC was a positive predictor of survival for both patients allocated to palliative treatment (HR 0.73, 95 % CI 0.66 – 0.82) and patients allocated to no treatment at all (HR 0.69, 95 % CI 0.56 – 0.85), supplementary table 3, Paper II.

Overall survival

The unadjusted 5-year survival for those with known educational status was 13.3 % for patients with low education level, 17.7 % for patients with intermediate and 19.7 % for patients with high education level.

Figure 12. Kaplan-Meier curve depicting overall survival by education level. Log rank test, p < 0.001
Paper III

Baseline data

Twenty-one patients underwent an open transthoracic procedure (66 %), nine patients a Video Assisted Thoracoscopic Surgery/hybrid-MIE (28 %) and two patients a transhiatal esophagectomy (6 %). A cervical anastomosis was performed in 13 patients and an intrathoracic anastomosis in all others. Twenty-nine patients received neoadjuvant treatment and three did not.

Feasibility

The tonometry catheter had to be replaced in six patients at some point during surgery due to catheter malfunction, which resulted in 11 missing pH\textsubscript{i} measurements (4 %). No medical adverse events were reported.

Tonometric measurements

Surgical ligation of the SGV resulted in a mean pH\textsubscript{i} decrease from 7.33 to 7.29. Further decreases in mean pH\textsubscript{i} was detected after ligation of the LGA (7.26) and after conduit construction (7.15). Ischemia, indicated by a pH\textsubscript{i} below 7.1, was evident in nine patients (28 %), after conduit construction. Mean pH\textsubscript{i} increased steadily from completion of the gastroesophageal anastomosis and in the following measurements, figure 13A. Peroperative blood loss did not correlate to pH\textsubscript{i} after conduit construction.

Figure 13. Perioperative intramucosal pH (pH\textsubscript{i}) (Panel A) and ΔpCO\textsuperscript{2} (Panel B) in 32 esophagectomies. Dots show means and bars show the standard deviations. SGV, short gastric vessels; LGA, left gastric artery.
The tonometrically measured changes in $\Delta pCO_2$ were inverse to changes in pH$_i$, figure 13B. Mean arterial pH, pH$_a$, did not deviate in any direction during surgery, but increased postoperatively in the ICU, 7.35 to 7.42.

Anastomotic insufficiencies

Patients with major insufficiencies (n=4) determined by a Clavien-Dindo $\geq$ 3b had lower mean pH$_i$ in the ICU on the first postoperative day, 7.12, compared to patients without anastomotic insufficiency, 7.27, p=0.04, figure 14A.

In the postoperative setting, systolic blood pressure was higher in patients with anastomotic insufficiency by comparison, 118±17 vs. 113±16, p=0.013.

**Figure 14.** Perioperative pH$_i$ in patients with major anastomotic insufficiency (n=4) compared to patients without anastomotic insufficiency (n=26) (Panel A), and during Video-Assisted Thoracoscopic Surgery (VATS/hybrid-MIE, n=9) compared to open surgery (n=23) (Panel B). Dots show means and bars show the standard deviations. SGV, short gastric vessels; LGA, left gastric artery. (* p-value=0.04, Wilcoxon ranks sum test)

Surgical technique

No significant differences were detected in subgroup analysis of surgical approach (figure 14B) or type of anastomosis (figure 15), although a trend towards higher pH$_i$ after construction of the conduit and the anastomosis was seen in the VATS/hybrid-MIE group.
Figure 15. Perioperative pH\textsubscript{i} in patients with a cervical anastomosis (n=13) compared to patients with an intrathoracic anastomosis (n=19). Dots show means and bars show the standard deviations. SGV, short gastric vessels; LGA, left gastric artery.

Paper IV
Baseline data
There were 51 minimally invasive procedures (21 VATS/hybrid-MIE and 30 totally minimally invasive) and 65 open (53 two-field and 12 three-field) procedures. Some features were more common in the MIE group; cervical anastomosis (41 \% vs. 18 \%), neoadjuvant chemoradiotherapy (nCRT) (80 \% vs. 58 \%), radiological suspected metastatic lymph nodes on preoperative workup (51 \% vs. 33 \%) and higher mean BMI (27.7 vs. 25.7).

Perioperative data
There was no difference in mean duration of surgery between groups (315 vs. 303 minutes). Peroperative blood loss was lower in MIE (384 vs. 607 ml, p=0.036) as was total length of stay (14 vs. 15 days, p=0.042).

Lymph node yield and radicality
The median number of resected nodes was higher in the MIE group, 18 (13-23), (IQR), compared to 12 (8-16) in the open surgery group, p<0.001.
Grouped analysis of lymph node yield and quartile analysis are presented in figure 16.

MIE was a positive predictor for a higher lymph node yield in multivariate ordered logistic regression (adjusted OR 3.15, 95% CI 1.11 – 8.98, p=0.032), whereas nCRT decreased lymph node yield (adjusted OR 0.28, 95% CI 0.08 – 0.97, p=0.045), figure 17.

The rate of radical resection (distal, proximal and circumferential) was similar in both groups 89% and 88%, table 3.

Figure 16. Boxplot (Panel A) depicting total number of resected lymph nodes and bar-graph of quartiles of resected nodes (Panel B) in 116 patients undergoing esophagectomy for esophageal- or GEJ cancer, by type of surgery.

Figure 17. Odds ratios (OR) with 95% confidence intervals (CI) and graphic presentation of predictors of lymph node yield from a multivariate ordered logistic regression model in 116 patients undergoing esophagectomy for esophageal- or GEJ cancer. MIE; minimally invasive esophagectomy, BMI; body mass index, nCRT; neoadjuvant chemo-radiotherapy, nCT; neoadjuvant chemotherapy
Postoperative complications

Anastomotic insufficiencies were evenly distributed between groups, as were medical and surgical postoperative complications in unadjusted comparison, table 3. Multivariate ordered logistic regression analysis of postoperative medical and surgical complications revealed no significant differences in regards to surgical approach however trending towards increased postoperative medical complications with MIE, supplementary table 1 of Paper IV.
Table 3. Perioperative data on patients with esophageal- or GEJ cancer, 2007-2016, grouped by type of surgery

<table>
<thead>
<tr>
<th>Type of surgery</th>
<th>Open surgery</th>
<th>Minimally invasive surgery</th>
<th>p-value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Operation time (min), mean (SD)</td>
<td>303 (±57)</td>
<td>315 (±63)</td>
<td>0.265 §</td>
</tr>
<tr>
<td>Peroperative blood loss (ml), mean (SD)</td>
<td>607 (±481)</td>
<td>384 (±651)</td>
<td>0.036 §</td>
</tr>
<tr>
<td>Medical postoperative complications, No (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>38 (58%)</td>
<td>23 (45%)</td>
<td>0.623</td>
</tr>
<tr>
<td>Yes</td>
<td>27 (42%)</td>
<td>28 (55%)</td>
<td></td>
</tr>
<tr>
<td>Surgical postoperative complications, No (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>43 (66%)</td>
<td>31 (61%)</td>
<td>0.852</td>
</tr>
<tr>
<td>Yes</td>
<td>22 (34%)</td>
<td>20 (39%)</td>
<td></td>
</tr>
<tr>
<td>Length of stay (days), median (IQR)</td>
<td>15 (14-21)</td>
<td>14 (10-23)</td>
<td>0.042 ‡</td>
</tr>
<tr>
<td>Time in intensive care (days), median (IQR)</td>
<td>1 (1-2)</td>
<td>1 (1-2)</td>
<td>0.952 ‡</td>
</tr>
<tr>
<td>Anastomotic leak, No (%)</td>
<td>58 (89%)</td>
<td>43 (84%)</td>
<td>0.433</td>
</tr>
<tr>
<td>Resected lymph nodes, median (IQR)</td>
<td>7 (11%)</td>
<td>8 (16%)</td>
<td></td>
</tr>
<tr>
<td>R0-resection, No (%)</td>
<td>12 (8-16)</td>
<td>18 (13-23)</td>
<td>&lt;0.001 ‡</td>
</tr>
<tr>
<td>Tumor stage (TNM7), No (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage 0</td>
<td>18 (28%)</td>
<td>11 (22%)</td>
<td>0.378</td>
</tr>
<tr>
<td>Stage I</td>
<td>10 (16%)</td>
<td>7 (14%)</td>
<td></td>
</tr>
<tr>
<td>Stage II</td>
<td>20 (32%)</td>
<td>16 (32%)</td>
<td></td>
</tr>
<tr>
<td>Stage III</td>
<td>15 (24%)</td>
<td>16 (32%)</td>
<td></td>
</tr>
</tbody>
</table>

† χ²-test
‡ Mann-Whitney U-test
§ Two-sided t test

R0: tumor free resection margins by pathologic anatomical diagnosis from surgical specimen
TNM7: assessment of stage according to 7th edition of TNM classification of malignant tumors
IQR; inter quartile range, SD; standard deviation
Paper V

Baseline data

Sixteen patients underwent both examinations and were available for statistical analysis. There were no adverse events. The mean durations of the imaging studies were 84±65 minutes and 117±22 minutes for PET/CT and PET/MRI respectively (mean±SD). PET/CT was performed 64±9 minutes after 18F-FDG-injection. The corresponding delay from injection to imaging was 109±22 minutes for PET/MRI. Clinical characteristics of included patients are summarized below.

Table 4. Clinical characteristics of 16 patients undergoing staging for esophageal- or GEJ cancer with PET/MRI and PET/CT.

<table>
<thead>
<tr>
<th>Gender (M/F)</th>
<th>15/1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (Median, years)</td>
<td>65</td>
</tr>
<tr>
<td>Tumor type (AC/SCC/UD)</td>
<td>13/2/1</td>
</tr>
<tr>
<td>Tumor location* (Upper/Middle/Lower)</td>
<td>0/4/12</td>
</tr>
</tbody>
</table>

AC; adenocarcinoma, SCC; squamous cell carcinoma, UD; Undifferentiated carcinoma
* Center of tumor in upper, middle or lower third of the esophagus.

Tumor characteristics

As presented in table 5, best correlations between PET/CT and PET/MRI in regards to tumor characteristics and measurements were in estimation of tumor length, width and estimated distance to the tracheal bifurcation. Unilateral (greatest) tumor wall thickness and distance to the gastric cardia produced lesser estimates of correlation between modalities, figure 18.
Table 5. Estimated measures of tumor characteristics with PET/MRI and PET/CT in preoperative staging of 16 patients with esophageal- and GEJ cancer.

<table>
<thead>
<tr>
<th></th>
<th>Tumor length (mm)</th>
<th>Tumor width (mm)</th>
<th>Tumor wall thickness (mm)</th>
<th>Distance from tracheal bifurcation (mm)</th>
<th>Distance from gastric cardia (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PET/MRI (mean±SD)</td>
<td>73±35</td>
<td>35±16</td>
<td>17±8</td>
<td>55±32</td>
<td>20±28</td>
</tr>
<tr>
<td>PET/CT (mean±SD)</td>
<td>69±33</td>
<td>34±17</td>
<td>20±6</td>
<td>49±34</td>
<td>16±20</td>
</tr>
<tr>
<td>Difference (mean±SE)</td>
<td>4±5</td>
<td>1±2</td>
<td>2±2</td>
<td>6±4</td>
<td>4±5</td>
</tr>
<tr>
<td>p-value†</td>
<td>0.359</td>
<td>0.603</td>
<td>0.221</td>
<td>0.122</td>
<td>0.437</td>
</tr>
<tr>
<td>Correlation‡</td>
<td>0.857</td>
<td>0.913</td>
<td>0.640</td>
<td>0.902</td>
<td>0.675</td>
</tr>
</tbody>
</table>

† Paired t-test, ‡ Pearson’s correlation coefficient

PET; positron emissions tomography, MRI; magnetic resonance tomography, CT; computed tomography, SD; standard deviation, SE; standard error

Figure 18. Scatterplots of correlation between PET/MRI and PET/CT with best fit lines and 95 % CI of best fit lines from 16 patients undergoing staging for esophageal- or GEJ cancer. PET; positron emissions tomography, MRI; magnetic resonance tomography, CT; computed tomography.
Positive lymph nodes

PET/MRI detected a higher number of suspected positive lymph nodes than PET/CT, 2 (0-5), vs. 1 (0-2), median (IQR), p=0.015. The number of detected positive lymph nodes correlated well between modalities, correlation coefficient 0.911.

SUV$\text{max}$

Estimates of SUV$\text{max}$ were higher in PET/MRI compared to PET/CT (16.5 (10.7-23.1) vs. 12.8 (7.1-17.4), median (IQR), p<0.001). However, correlation between modalities was excellent, 0.912.

cTNM-stage

Clinical T-stage assessment

In clinical T-stage assessment between PET/MRI and PET/CT agreement was only fair. Exact agreement was 56 % and the unweighted κ-coefficient was 0.222. The weighted κ-coefficient, heeding also the magnitude of discrepancies, was somewhat higher, 0.333. PET/CT readings estimated a higher clinical T-stage than PET/MRI in six patients and vice versa in one. This difference, observed in absolute numbers, was not statistically significant (p=0.053).

Clinical N- and M-stage assessment

The exact agreement in clinical assessment of N-stage and M-stage between PET/MRI and PET/CT exceeded those of T-stage assessments. Exact agreement between modalities was 88 % and 94 % in N-stage and M-stage respectively. The unweighted κ-coefficient was 0.817 and the weighted κ-coefficient was 0.849 for N-stage. Since M-stage only can assume the value 0 or 1, all errors are of equal magnitude rendering unweighted and weighted κ-coefficients equal in M-stage. κ-coefficient was 0.871. Table 6 summarizes exact agreement, κ-coefficients and cross-tabulates T-, N-, and M-stage assessments between PET/MRI and PET/CT.
Table 6. Cross-tabulations, exact agreement and κ-coefficients of clinical TNM-stage in 16 patients radiologically staged with PET/MRI and PET/CT for esophageal- or GEJ-cancer.

<table>
<thead>
<tr>
<th>Clinical T-stage</th>
<th>PET/MRI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>T1</td>
</tr>
<tr>
<td>PET/CT T1</td>
<td>0</td>
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<tr>
<td>PET/CT T2</td>
<td>0</td>
</tr>
<tr>
<td>PET/CT T3</td>
<td>0</td>
</tr>
<tr>
<td>PET/CT T4</td>
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</tr>
</tbody>
</table>

Exact agreement = 56 %, Cohen’s κ = 0.333

<table>
<thead>
<tr>
<th>Clinical N-stage</th>
<th>PET/MRI</th>
</tr>
</thead>
<tbody>
<tr>
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<td>N0</td>
</tr>
<tr>
<td>PET/CT N0</td>
<td>5</td>
</tr>
<tr>
<td>PET/CT N1</td>
<td>0</td>
</tr>
<tr>
<td>PET/CT N2</td>
<td>0</td>
</tr>
<tr>
<td>PET/CT N3</td>
<td>0</td>
</tr>
</tbody>
</table>

Exact agreement = 88 %, Cohen’s κ = 0.849

<table>
<thead>
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<th>Clinical M-stage</th>
<th>PET/MRI</th>
</tr>
</thead>
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<td></td>
<td>M0</td>
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<tr>
<td>PET/CT M0</td>
<td>9</td>
</tr>
<tr>
<td>PET/CT M1</td>
<td>0</td>
</tr>
</tbody>
</table>

Exact agreement = 94 %, Cohen’s κ = 0.871

PET; positron emissions tomography, MRI; magnetic resonance imaging, CT; computed tomography, T-, N-, M-stage; Tumor, nodal and metastatic-stage according to 7th edition of TNM classification of malignant tumors.
General Discussion

The data quality of NREV

All scientific research utilizing observational data is highly dependent on the quality of said data. In Paper I a thorough evaluation of the data quality in NREV was conducted by means of a review of registration and coding routines as well as a completeness evaluation and a re-abstraction of 361 randomly selected reported patients for comparison to source medical records for evaluation of accuracy and timeliness.

In assessing comparability, Paper I concludes that, NREV is comparable with other Swedish registries as well as with international data. This allows for interesting diagnostic comparisons and facilitates international collaboration. The relative rareness of esophageal- and GEJ cancers in the western world lends support to the usefulness of multicenter, multinational studies to achieve sufficient caseloads to overcome the difficulties of underpowered studies. In registry studies the same principles apply and by combining several comparable registries the number of study participants can be increased immensely.

Some aspects of clinical information, useful in multi-registry comparisons and research collaboration, are still not covered by NREV and further developments of the registry to incorporate comprehensive data on oncological treatments have recently been undertaken. This addition, as well as other additions to the register, should be made with care to avoid making the reporting process cumbersome and the register incomprehensible. NREV was updated in 2017, in part based on the presented validation study, to exclude some of the most cumbersome parts that provided little clinical information but instead weighed heavily on the reporting official. The digital platform of the registry was also updated to facilitate reporting.

The Swedish Cancer Registry, against which NREV completeness was tested, has a close to complete coverage of the Swedish population as Swedish law mandates reporting to the registry. The diagnostic survey of NREV works dually as a registration to both NREV and the Swedish Cancer Register. Thus, all patients reported to NREV will appear in the Swedish Cancer Register by default. To identify missing patients, the unique personal identification number is routinely utilized to search the Swedish Cancer Register at least every three months for patients with esophageal- or gastric cancer not reported to the NREV. Any patient found in the Swedish Cancer
Registry not reported to NREV results in a reminder for completion of the diagnostic survey, as well as any following surveys, being sent to the responsible clinician. This method has yielded a high level of completeness, 95.5 %, which is also high in a European context\textsuperscript{144,145}. There are occasional lagging registrations, mainly in the surgical and follow-up surveys, which are issues currently being addressed in the national board for the NREV registry.

Registry validation can be performed in several ways. Optional tools include validation by comparison to other registries\textsuperscript{146}, a method applied by Brusselaers et al. in a study from 2015\textsuperscript{147} where TNM stage in 397 patients from a registry based comparison cohort were compared with TNM-stage from the Swedish Cancer Registry. To validate in this way is much speedier than re-abstraction but with the apparent drawback that source medical records are not available thus rendering conclusions more uncertain. Brusselaers et al. solved this by adding pathology reports sent by post from the source to the comparison cohort much in a similar way to the re-abstraction method of Paper I. Other methods of validation are continuous monitoring by dedicated registry personnel\textsuperscript{123} or even evaluation by international expert validators\textsuperscript{148}. The chosen method to evaluate the accuracy of NREV was re-abstraction of data from source medical records as described by Bray et. al\textsuperscript{132}. This method has been a preferred choice in both validation of the National Prostate Cancer Registry of Sweden\textsuperscript{126} and recently also the Swedish Quality Registry of Gynecologic Cancer\textsuperscript{149}. Even though the re-abstraction process is very time- and effort consuming it presents a theoretical advantage in the fact that apparent errors discovered in the source data during re-abstraction can be corrected, after the study is complete. This notion, however, is controversial since it introduces the risk of “contaminating” data by making corrections only in selected patients e.g., patients with anastomotic insufficiencies, and not in all which can predispose a form of selection bias. However, some discovered clerical errors such as double registrations or misclassified tumors could surely safely be removed.

Some of the validated variables most relevant for epidemiological research have been presented in detail in Paper I. In most variables there were acceptable or even excellent correlation and agreement between original and re-abstracted data. In designing future studies based on NREV data, it is useful to know not only that a variable is of high or low quality, but also the magnitude of error in a certain variable. If the magnitude of error can be appreciated, adjustments for the uncertainty can be made in the statistical analysis making the results more reliable.

Exact agreement and inter-rater reliability in clinical TNM-staging was similar to that of the Swedish National Prostate Cancer register\textsuperscript{126}. Pathologic T- and N-staging agreement exceeded clinical T- and N-staging as expected owing to definitive pathology results from the surgical specimen demonstrating the underlying uncertainty and difficulties of accurate clinical
staging. In M-staging, however, the pathology report did not strengthen but rather weakened the κ-coefficient from clinical M- to pathologic M-stage. Similar results regarding pathologic M-stage was also seen in a previous Swedish validation study\textsuperscript{147}. This is arguably due to the fact that M-stage is not part of the pathology report of the resected specimen.

Data regarding smoking habits was unfortunately one of the weakest variables with an abundance of missing or unknown values. In almost a third of the original registrations, as well as the re-abstractions, smoking status could not be characterized. This places roughly 35 % of the patients correctly in the smoking status unknown category. Combining the missing data of 19.9 % with the smoking status unknown category results in uncertainty about smoking habits in about half of all registered patients. This issue has been presented to the board of the registry and in the latest update of the registry reporting on smoking habits has been moved to the surgical survey in an attempt to improve data quality regarding the selected patients that undergo surgical treatment.

The median time to completion of the surveys ranged from 3.4 to 4.1 months, well matching Nordic comparators, i.e. 7.8 months in the Icelandic cancer register\textsuperscript{150} and 8.6 months in its Norwegian counterpart\textsuperscript{146}. In a European study of 116 cancer registers by Zanetti et al., the median time to completion of register data was 18 months\textsuperscript{151}. Possible ways to improve timely reporting could be the implementation of structures for completion of the forms at the multidisciplinary treatment conference by appointed and trained medical officials rather than, as oftentimes is the case, the time-pressed presenting surgeon.

**Limitations to Paper I**

A limitation of Paper I is that even the re-abstracted data is not necessarily the absolute truth. In some variables the original data could in fact be more accurate than the data re-abstracted by the expert validators. The re-abstraction is made from source medical records and any information not transferred to, or erroneously imputed in, the medical charts are either lost and blinded to the validators or misinterpreted as false. One example could be lymph node clearance during surgery. Only the operating surgeon can know the extent of lymphadenectomy with any certainty and may not have accurately described the extent in the operation report. Most variables, however, are much more straightforward with less uncertainty. Some categorical variables with few available categories and most patients in one category, e.g., pathological M-stage, will result in more patients of random agreement thus any disagreement will greatly weaken the κ-coefficient even though exact agreement can be very high. The opposite was noted for numerical variables, such as dates. These variables had lower exact agreement but almost perfect correlation due to many tiny differences between the original and re-abstracted values and were probably without clinical importance. A
disadvantage of presenting exact agreement and correlation in the above situations is that some of the variables might appear of lower quality than is clinically relevant but the methodology provides an easily understandable picture of the registry even if it overestimates the number of relevant errors.

**The impact of education level on treatment allocation**

The completion of the validation study in Paper I was groundwork for Paper II. In Paper II, NREV was utilized as a base for the epidemiological study of how the patient’s education level affected treatment allocation. A strength of Paper II, in comparison to many other cohort studies, was that the cohort comprised more than 95% of all patients diagnosed with esophageal- or GEJ cancers in Sweden during the study period and not limiting inclusion only to patients that had undergone treatment.

Allocation of patients with esophageal or GEJ cancer to curative or palliative treatment is based on tumor and patient related factors, most importantly tumor stage, comorbidities and physical fitness. The two most important questions to answer in any patient under consideration for esophageal- and GEJ cancer surgery are: 1) Is the tumor resectable? 2) Is the patient operable? The performance status of the patient is often assessed with specific scales to quantify functional impairment, e.g., the Karnofsky performance status scale, the WHO scale or the Lansky scoring system. In NREV the WHO scale has replaced the Karnofsky scale in recent years due to increased simplicity in assessment of performance status with the WHO scale. Other important features in assessing performance status are clinical tests, e.g., spirometry and stress ECG. By combining scoring systems with clinical tests and patient medical history, an estimation of patient fitness can be made. In fit patients with localized disease all treatment options are available. Patients with lower performance status but with a localized disease might not withstand nCRT in combination with demanding surgery but may still be allocated to curative treatment by surgery alone or dCRT. Palliative treatment or best supportive care is offered to patients with severe comorbidity and/or unresectable disease. Treatment allocation is not only dependent on patient performance but also subject to softer values such as the expertise, preference and inclination of the treating physicians, and on the preferences of the patient.

Paper II suggests that the patient’s education level affects intended treatment of esophageal- and GEJ cancer. This finding raises questions on the equality of healthcare provided at hospitals throughout Sweden. In France, Launay et al. found shorter survival in patients residing in socioeconomically deprived areas and in the Netherlands, Bus et al. suggests that curative treatment is offered to a greater extent to esophageal cancer patients with high socioeconomic status. The healthcare systems in these countries are
not equal to that of Sweden but the comparisons could still be valid. Similar translational findings are seen for other malignancies, e.g., prostate cancer\textsuperscript{154} and breast cancer\textsuperscript{155}, but also for pancreatic cancer patients with high socioeconomic status that were more likely to be operated in university hospitals\textsuperscript{156}. Even though it can be assumed that education level covaries with socioeconomic status, it is meaningful to investigate the impact of solely education level on cancer treatment in order to find areas where directed measures could accomplish the most in preventing these inequalities. A recent study in prostate cancer by Tomic et al. showed a higher probability of cancer detection at health check-up, less probability of waiting more than three months for surgery, higher probability of surgical treatment and lesser probability of R1 resection for patients with high income. Education level played a similar role but to a lesser extent\textsuperscript{157}.

Underlying mechanisms of how education impacts on the selection of treatment and outcome are not fully known or easily interpreted. A patient that fails to detect signs and symptoms of malignant disease may well be diagnosed at a more advanced tumor stage. In Paper II this proposed delay in diagnosis was appreciated by adjusting for clinical TNM-stage.

Communication between patient and doctor plays a role\textsuperscript{158} in a sense that patients must understand the underlying disease and the impact of possible treatments. All patients undergoing demanding surgery or receiving CRT must be properly informed prior to treatment and in essence provide some informed consent to treatment and the consequences thereof. This requires delicate communication skills and places demands on both the patient and physician communicatory skills. Communication difficulties and lack of understanding of treatment in esophageal- and GEJ cancer were more commonly reported in lower socioeconomic status groups in an interview-study by Lineback et al.\textsuperscript{159} Emphasis must therefore lie on well-tailored information, adequately adjusted to the patient at hand. In appreciation of this the procurement of disease- and treatment specific pamphlets or informative brochures with nationwide implementation could be of value. This could aid in informing patients and also make communication more uniform at an understandable level. Peer advice and the multidisciplinary team involvement has also been identified as crucial for information and support, in narrative responses from newly treated esophageal cancer patients\textsuperscript{160}. Conveying information in a setting with more than one profession represented could therefore be of value and improve patient perception, as could possibly patient group networks.

Patients with high education level have increased compliance to screening programs for breast- and cervical cancer\textsuperscript{161} indicating that education level may be a factor in adherence to treatment- plans and programs. In esophageal- and GEJ cancer, failure to follow postoperative surveillance programs could affect quality of life. In Paper IV, the Kaplan-Meier estimate of unadjusted overall survival depicts improved survival proportional to education
level. General health awareness and lifestyle associated with education level could thus be additional explanatory mechanisms. The Cox proportional hazards models of Paper II speak in favor of such mechanisms where patients with high education level had lower hazard ratios compared to patients with low education level when they were both planned for curative treatment.

The advantages of a MDC are effortlessly advocated in the field of esophageal- and GEJ cancer, but there are few results published in support of its positive effects on improved clinical outcomes. Improved timeliness to surgery, adherence to guidelines and increased probability of a complete staging have been attributed to the introduction of a multidisciplinary conference in one study\cite{162}. Paper II suggest other benefits of the MDC in that patients were more often offered curative treatment if presented at a MDC. This may, in part, be due to, but not easily dismissed as only, selection bias where curable patients are more often presented at a MDC. Centralization of esophageal- and GEJ cancer, and the associated increased availability of a MDC, to higher volume centers may also have influenced the finding. The MDC was also associated with improved survival for patients allocated to palliative treatment or no treatment at all. This most likely reflects the benefits of having multiple disciplines available for these patients rather than true effective treatment changes because of a MDC. Taking that into consideration, the findings add to the support, and usefulness, of the MDC.

**Limitations to Paper II**

The risk of residual confounding is the main limitation of Paper IV. A DAG analysis was performed beforehand striving to identify all possible covariates and confounders and adjust accordingly. Even so, both alcohol consumption and tobacco use are more common in patients representing low socioeconomic status\cite{163} and may influence survival, however, not necessarily treatment allocation. As presented in Paper I, NREV data on tobacco use is suboptimal thus missing in 63.6 % of all patients in the cohort, which was deemed too high for meaningful imputation. Primary and secondary diagnoses of COPD and/or myocardial infarction were instead utilized as a proxy for smoking and coronary vascular disease in the multivariable models. This is a way to address the issue but a weakness when drawing conclusions since other lifestyle related risk factors than smoking are associated with COPD and myocardial infarction diagnoses. There was no collected data on use of alcohol, physical fitness/activity, or dietary habits in the cohort. These are factors that may be associated with both exposure and outcome.

Some patients may have acquired longer education than registered due to alternative forms of education. However, this would be deemed as nondifferential misclassification and therefore dilute the results, driving them towards the null.
Perioperative assessment of conduit perfusion by tonometry

In patients allocated to curative treatment, esophageal resection is the cornerstone of multimodal treatment. When surgically preparing the gastric conduit during esophagectomy it is inevitable to divide both the short gastric vessels and the left gastric artery, relying on the right gastric artery, right to left gastroepiploic arcade and intramural circulation for blood supply to the conduit. The gastro-esophageal anastomosis is performed at the farthest point from the right gastroepiploic artery, with blood supply from collaterals\textsuperscript{164,165}. The anatomy of the epiploic vascular arcade varies as described in detail by the Koskas-classification. Four main types of vascular arcade along the greater curvature can be identified, figure 19. Type I, being the most predominant, has an intact vascular arcade between the right and left epiploic arteries with even blood supply to the greater curvature. In type II there is no vascular arcade between left and right epiploic arteries outside the stomach but instead vascular collaterals between the two branches inside the gastric wall at the major curvature, whereas type III is similar to type II but also have a thin collateral bridge outside the stomach wall between arteries. Type IV has an intact arcade between right and left epiploic arteries, but it is situated further away from the major curvature of the stomach in the omental adipose tissue of the gastrocolic and gastro-splenic ligament\textsuperscript{166}. 
In a necro-study of 39 cadavers by Ndoye et al. these vascular variations are proposed to be of Type I in 64.1% of cases, type II and III in 15.4% of cases respectively and type IV in 5.1% of cases. The anatomic variances are important to bear in mind when constructing the gastric conduit. In the event of a type IV anatomy the upper part of the gastric tube can easily be devascularized by accidentally dividing the epiploic artery when transecting the gastrocolic/gastrosplenic ligament leading to impaired perfusion at the summit of the conduit. The division of the left gastric artery has previously been suggested to be a major cause of transient ischemia in the anastomotic region. However, Paper III demonstrates the greatest reduction in pH to occur after completing the gastric conduit by linear stapling, a finding endorsed by another recent study of gastric perfusion. In the region of approximately four centimeters from the greater curvature there is a fine capillary network where arterial supply from the lesser curvature meets arterial
supply from the greater curvature constituting a circular blood flow. The location of these capillary network anastomoses near the curvature could speak in favor of performing a wider conduit bearing in mind that delayed gastric emptying is associated with a too wide conduit \(^{169}\). The tonometry measurements suggest that disruption of circular blood flow, or possibly the transection of the right to left epiploic intramural vascular collaterals by linear stapling, seems more important than the division of the left gastric artery. There might also be an additive effect of disrupting circular blood flow and epiploic intramural collaterals, to division of the SGV and the LGA that tips the scale in favor of ischemia. This ischemia, transient or not, is oftentimes undetectable by visual inspection during surgery \(^{170}\).

The multitude of intraoperative measuring points (six) is the main strength of Paper III and differs it from previously conducted perioperative tonometric studies. Among studies on perioperative perfusion three were identified that had applied more than three measurements during surgery. One study in sixteen patients by Boyle \(^{168}\) et al. registered four intraoperative measurements and compared tonometry measurements to laser Doppler flowmetry. In this study the greatest reduction in perfusion was seen after devascularization and measurements after conduit formation was inconclusive. Another study of 33 patients by Jacobi \(^{171}\) et al. reported five intraoperative measurements and concluded most impaired perfusion at the time for gastric pull up. However, this study measured intramucosal oxygen tension and not pH \(_i\). Finally a study by Irino \(^{74}\) et al. confirmed the findings of Paper III with six intraoperative measurements in 29 patients but utilized transmural pulse oximetry instead.

The observed recovery in pH \(_i\) from completion of the gastric conduit to the end of surgery suggests that the body adapts through various mechanisms and increases blood supply to the fundal region \(^{172}\). Another proposed mechanism is that mechanical manipulation of the fundic region during dissection and conduit formation ceases upon completion of the gastroesophageal anastomosis allowing conduit blood flow to increase and stabilize.

Patients with low pH \(_i\) in the morning of the first postoperative day were more prone to have an anastomotic insufficiency and altogether the anastomotic insufficiency rate, minor and major, (19 %) was higher than anticipated. Between 2006 and 2013 the anastomotic insufficiency rate was 9 % in Sweden. During the latter part of that period the national insufficiency rate increased to 12-16 % \(^{173}\), possibly owing to the learning curve of minimally invasive esophagectomy or the increasing application of nCRT in these years. However, the risk of anastomotic insufficiency after radiotherapy treatment appears to be dose related \(^{174}\) and may be reduced by carefully planned radiation protocols and selective surgery \(^{175}\).

The conclusions from Paper III that perfusion in the gastric conduit can be accurately measured with tonometry implies some clinical uses. In the strive to improve surgical outcomes, more recent devices for intraoperative
quantification of blood flow are emerging. The results from intraoperative measurements of gastric tonometry could serve as a knowledge base and tonometry as a method to validate these new devices when implementing them in clinical practice.

The fact that disruption of circular blood flow and division of intramural anastomoses by stapling of the stomach leads to relatively more ischemia than division of adjacent blood vessels could be applicable in other areas of surgery to reduce the risk of ischemia-induced anastomotic leaks.

Limitations to Paper III
The main limitation of Paper III is the small number of included patients resulting in an increased risk of a type-II statistical error and lacking statistical power for subgroup analysis. Another source of error in the postoperative setting is that there was no confirmation that the tonometry catheter was still located in the fundal region of the gastric conduit during the postoperative measurements, although measuring in this way is according to best clinical practice in tonometry for intensive-care purposes. Additionally, owing to the fact that there were several different types of procedures performed, there was an uneven distribution of the times between the intraoperative measurements, e.g., in patients with a cervical anastomosis the duration between conduit completion and construction of the gastroesophageal anastomosis was much shorter than in patients with an intrathoracic anastomosis where the time consuming esophageal dissection had to be performed between the measurement after conduit completion and the measurement after construction of the gastroesophageal anastomosis.

The effect of introducing minimally invasive esophagectomy
The aim of Paper IV was an evaluation of the introduction of MIE with focus on a comparison of surgical oncological results following MIE or open esophageal resection for cancer of the esophagus or GEJ. Aside from causing less operative trauma, the principles of resection should remain the same with radical clearance of the tumor and any regional lymph nodes with metastatic spread in order to cure the patient.

Paper IV included the first 51 MIE surgeries performed at the author’s center. The first 21 cases were hybrid-MIE and after successful implementation of this less technically demanding technique, the following 30 were totally minimally invasive. Reports propose the learning curve of MIE to be around 30-35 operations\textsuperscript{176-178} to overcome the technical difficulties but in other studies as much as 119 surgeries to surpass the learning curve regarding anastomotic insufficiency\textsuperscript{179}. Anastomotic insufficiencies accumulated in the earlier MIE-cases of Paper IV but were not more frequent in total com-
pared to open surgeries. That the mean duration of surgery was unaffected by the transition to MIE compared to open surgery is somewhat surprising. An increased duration of surgery could be anticipated in introducing a new technique, however, the operating team of surgeons had advanced laparoscopic procedures in bariatric surgery as the most common day-to-day workload and were thus well equipped for the transition to MIE. A reduction in duration of surgery over time was also noted when reviewing the MIE surgeries of Paper IV, figure 20. Also in Paper IV the peroperative blood loss was reduced, compared to open surgery, a finding endorsed by one previous study. The implementation of MIE presented in Paper IV produces comparable results to Nilsson et al reporting on the successful implementation of MIE at another Swedish university hospital in 173 patients over five years.

Figure 20. Graphic presentation of the first 51 cases operated with minimally invasive esophagectomy for esophageal- or GEJ cancer during the years 2013-2016. MIE; minimally invasive esophagectomy.

The learning curve of MIE being included in the cohort could predispose risks of postoperative complications. However, similar proportions of postoperative surgical complications were seen for both groups and no firm association between MIE and surgical postoperative complications were found. In all hybrid-MIE the gastroesophageal anastomosis was constructed cervical. A higher rate of anastomotic insufficiency was therefore anticipated, due to a larger proportion of cervical anastomoses in the MIE group. This as-
Assumption was based in part on a meta-analysis by Biere et al. in 2011 that concluded an increased risk of anastomotic insufficiency in cervical anastomoses\textsuperscript{182}. In Paper IV no differences between groups were found regarding anastomotic insufficiencies, heeding that the study was not solely powered for the analysis.

In recent years, MIE has become a favored approach for resection of esophageal- and GEJ cancer, in many centers. MIE reduces postoperative morbidity\textsuperscript{4,60,183} and proposedly even postoperative mortality\textsuperscript{184}. The advantages of nCRT and nCT are also well established as is an en-bloc resection of the tumor\textsuperscript{185}. In patients treated with nCT a recent multicenter propensity score matched study by Markar et al. showed that higher lymph node yield was associated with improved disease free survival and lower recurrence-rate within this group\textsuperscript{186}. In the same study the lymph node yield was significantly higher in patients treated with nCT compared to nCRT, implying that modern use of nCRT decreases the total number of resected lymph nodes\textsuperscript{187}, a finding also evident in Paper IV. Safe to say, there is an ongoing debate regarding the usefulness of extended lymphadenectomy in the era of nCRT-treatment\textsuperscript{188,189}.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure21.png}
\caption{Total number of resected lymph nodes in 116 patients undergoing open or minimally invasive esophagectomy for esophageal or GEJ cancer between 2007 and 2016, by type of surgery. Lines are from linear regression.}
\end{figure}

The surgical oncological outcomes of Paper IV imply that MIE is not inferior to open surgery when applied in a setting such as the present tertiary re-
ferral center. The learning curve has been surpassed and MIE is presently the standard surgical approach. Without compromising radicality MIE produced increased lymph node yields. This finding, of Paper IV, was confirmed in a multivariate regression model. Whether the increased lymph node yield owes to improved field of vision during surgery due to improved optics or a reduction in peroperative bleeding is somewhat beside the point. More pertinent is the notion that the pathologists might have improved their technique or thoroughness during the latter part of the study period in parallel to the introduction of MIE. Higher lymph node count on the postoperative pathology report by increased vigilance in pathologic examination has previously been described\(^\text{190}\). In analyzing lymph node yield by surgical approach over time at the present hospital it is evident that lymph node yield increases in general but is by comparison higher in MIE, figure 21. In absence of complete and undisputable evidence of the true reason for the increased lymph node yield it can be concluded that the increased yield with some certainty will benefit patients by increasing accuracy in pathologic staging\(^\text{191,192}\) and might also be beneficial in regards to survival and loco regional disease control\(^\text{193-195}\).

**Limitations to Paper IV**

The main limitation of Paper IV is that the minimally invasive procedures are introduced as well as carried out in the three latter years of the study period and that the decision on surgical approach was by surgeon’s preference. An attempt was made to adjust for this fact by treating year of surgery as a confounder in the multivariable model. The results could still be biased in that some high-risk patients, with advanced- or otherwise technically demanding tumors, could be unevenly selected to open surgery because the surgeon feels more adept with this technique in difficult cases. Tumor stage was adjusted for but there still might be residual confounding.

Surgeon experience was identified as a confounder in the DAG analysis but is an unmeasured variable in the study. That the same team of surgeons performed all surgeries would in part compensate for this by making the operative procedures and experience uniform. A final limitation is that the surgical oncological results are based on routine pathology reports rather than a study-specific pathologic examination protocol. Additional accuracy in interpreting results on microscopic radicality could have been added by letting a dedicated pathologist retrospectively review all surgical specimen slides, however, this would have had little impact on determining lymph node yield since that assessment is determined at a macroscopic level thus requiring the whole surgical specimen and not just saved microscopic slides.
The role of $^{18}$F-FDG-PET/MRI in preoperative staging

The validation study of Paper I, the epidemiologic approaches of Paper II and IV and the investigations of perioperative physiology of Paper III are all focused on the current status of treatment of esophageal- and GEJ cancers. Paper V evaluated a possible future field of diagnostics, one that is not yet introduced in clinical practice, the PET/MRI. MRI does not have as clear a role in the staging of esophageal- and GEJ cancers as it does in rectal cancer$^{196-198}$ where preoperative staging is performed with MRI by default. Some challenges in MRI of the mediastinum and upper gastrointestinal tract, e.g., free breathing and heartbeats, are not present in imaging of the lower abdomen and pelvis. These challenges were accounted for in the imaging sequences of Paper IV.

By compromising some spatial resolution, MRI produces more detailed images with enhanced resolution of tissue characteristics and provides functional information with a potential of being equivalent to EUS$^{199}$ in discriminating tumor growth and nodal involvement. Since accurate imaging is essential for treatment plans, improved imaging could facilitate therapeutic decision-making. For example, the discrimination between an esophageal tumor growing adjacent to, or growing into, the aortic adventitia or trachea, would most certainly be a separator between the choice of denying or approving surgery with curative intent. MRI has previously been shown to discriminate in this manner with some certainty$^{31,200}$.

The most apparent divider of the two investigated modalities in Paper V was the estimation of clinical T-stage. The fact that only fair inter-rater agreement was seen between PET/MRI and PET/CT in this aspect is disheartening at first glance. However if both modalities produced equal results regarding all evaluated aspects, the additional cost, increased duration of examination and increased patient discomfort of PET/MRI could not be justified. Intriguingly, an explanatory mechanism for the differences in T-staging could be overstaging with PET/CT. In seven patients there were disagreement between modalities on tumor stage. Six of these were staged higher with PET/CT than PET/MRI. However, the absence of raw evidence, such as the pathological T-stage and given the relatively few patients included, Paper V is underpowered to draw any conclusions in this aspect. Further studies comparing PET/CT and PET/MRI in these aspects are of value and are currently in the start-up phase in Sweden as well as in other countries.

The ongoing SANO$^{201}$ and ESOSTRATE trials$^{202}$ both focus on evaluating a watchful waiting strategy in patients characterized as complete responders after nCRT. In utilizing a surgery-as-needed approach, true complete responders must be distinguished from patients that appear to be complete responders but actually have residual disease. In the SANO-trial, endoscopic bite- on bite biopsies in combination with PET/CT and EUS with FNA are applied to determine complete response. Previous studies utilizing
dynamic MRI with intravenous contrast (Diffusion weighting and dynamic contrast enhancement) have both shown some results in detecting response to nCRT\textsuperscript{36,37}. A fully integrated system including PET and the dynamic imaging of MRI may therefore be a powerful tool, not only in clinical staging of esophageal- or GEJ cancer, but also in re-staging to assess complete response after neoadjuvant therapy. There are also promising results, in introducing the field of radiomics to dynamic MRI, such as in the evaluation of complete response in rectal cancer\textsuperscript{203}.

PET-CT has become gold standard for ruling out metastatic disease in patients planned for curative treatment of esophageal- or GEJ cancer\textsuperscript{204}. Due to centralization of esophageal- and GEJ cancers to larger volume centers, PET/CT is available to most patients undergoing preoperative staging in Sweden and Swedish national guidelines on esophageal cancer recommend the use of PET/CT\textsuperscript{205}.

The PET/MRI at the author’s institution became operational in 2015 and is one of only two fully integrated PET/MRI settings in the country. The access to PET/MRI is therefore limited mainly to study specific examinations in clinical trials. However, as in most new technology, availability will increase and costs will be reduced in time. Clinical implications of the results of Paper IV along with the current literature on MRI and PET/MRI is that some patients may benefit more from PET/MRI than PET/CT as an adjunct to the mandated CT investigation in preoperative staging. Said benefit would apply to esophageal- and GEJ cancer patients with inconclusive hepatic abnormalities on CT or if there is a suspicion that the tumor involves vital structures such as the trachea or aorta.

**Limitations to Paper V**

The fact that there is no comparison of radiological readings to pathological analysis of the surgical specimens is the main limitation of Paper V. There was an initial intent to include the pathological TNM in the analysis. However, all patients received nCRT and the down staging effect of nCRT would have rendered this comparison uncertain. A meaningful comparison of clinical TNM-stage from both modalities to pathological TNM-stage would have required a second set of radiologic examinations to be undertaken after nCRT had been completed. The funding was insufficient in this aspect. Additionally, nearly one third of the patients were found to have metastatic disease thus excluding chances of pathologic anatomical diagnosis from surgical resection.

Another limitation is the uneven distribution of assessors in the radiologic readings. One radiologist read the PET/CT investigations and two radiologists read PET/MRI investigations independently and then together formed a consensus for the analysis. The absence of a consensus reading in PET/CT could predispose a risk of more uncertainty in the measurements and estimations from this modality.
Conclusions

Paper I
NREV has good coverage of Swedish patients with esophageal- and gastric cancer. It contains comparable data with high validity reported in a timely fashion with margins for improvements.

Paper II
High education level is associated with a greater probability of curative treatment for esophageal- and GEJ cancers as well as with improved survival. Patients planned for palliative treatment or no treatment at all fare better if their case is presented at a multidisciplinary conference.

Paper III
It is possible to investigate changes in perfusion of the gastric conduit using tonometry. The division of the major gastric arteries and foremost linear stapling of the gastric conduit results in reduced perfusion. Low pH on the first postoperative day is associated with an increased risk of anastomotic insufficiency.

Paper IV
MIE results in superior lymph node yield without compromising radical resection. MIE was associated with less peroperative blood loss and a shorter length of stay but not with increased rate of postoperative complications.

Paper V
$^{18}\text{F-FDG-PET/MRI}$ is safe and feasible in staging of esophageal- and GEJ cancer. There is substantial agreement with $^{18}\text{F-FDG-PET/CT}$ regarding tumor characteristics, detected positive lymph nodes, $\text{SUV}_{\text{max}}$ values and excellent agreement in assessment of N- and M-stage. There was only fair agreement in assessment of T-stage, which was more often deemed higher with $^{18}\text{F-FDG-PET/CT}$. 
The groundwork from Paper I provide a better understanding of the underlying characteristics of data in the NREV. Future research projects based on data from the NREV can now utilize the assessment of data quality as a whole or in individual variables from Paper I in interpreting results.

The findings in Paper II that the presence of a multidisciplinary treatment conference (MDC) benefits the patient in terms of increased chance of curative treatment as well as survival are intriguing for future research. A national work group is under assembly to address the conformity and quality control of the MDCs for esophageal- and GEJ cancer. The availability of the MDC should be increased to ensure all diagnosed patients have access to the benefits of a MDC.

Newer modalities for perioperative monitoring of gastric conduit perfusion and viability are constantly evaluated to find that easy and reliable way to aid the surgeon during surgery and in the postoperative period. Advancements in microdialysis and its application in a new monitoring device with continuous graphic monitoring (OnZurf™-probe) are currently being tested at the author’s hospital in a prospective trial. The introduction of minimally invasive surgery and robotic surgery will make laparoscopic techniques with indocyanine green fluorescence visual angiography increasingly available to surgeons for direct visual confirmation of the conduit perfusion intraoperatively.

An up-and-running clinical protocol is now in place for the utilization of PET/MRI in clinical staging. There are ongoing studies to investigate if a watchful waiting strategy can be applied for esophageal- and GEJ-cancers, with complete response after nCRT, where surgery is utilized as needed (e.g. the SANO-trial). This approach leans heavily on the correct identification of true complete responders and differentiation of the patients who are not. Also, the vigilant watchful-waiting must include reliable diagnostics to early identify signs of disease progression or recurrence. PET/MRI could very well be an ideal radiologic modality for both determining response to neoadjuvant treatment, identifying complete responders as well as providing a near radiation-free option for surveillance at narrow intervals. Such a prospective study of PET/MRI in determining response to nCRT is under way.
Can


Det övergripande syftet med denna avhandling var dels att undersöka kvalitén på data i det nationella registret för esofaguscancer som bas för framtida forskning, dels att undersöka specifika faktorer associerade med patientselektion, perioperativ fysiologi, minimalinvasiv esofagektomi och stadieindelning, allt för att förbättra omhändertagandet för patienter med esofaguscancer. I denna avhandling ingår fem delarbeten.

**Delarbete I** var en valideringsstudie av NREV där registret utvärderades med avseende på jämförbarhet, täckningsgrad, överensstämmelse (validitet) och inrapporteringshastighet. Validitet testades genom att jämföra registerdata mot 400 nyregistreringar från re-abstraherade data. Resultaten av delarbete I gav vid handen att NREV hade mycket god täckningsgrad, 95.5 %. Data i registret var jämförbara utifrån ett nationellt och ett internationellt perspektiv. Ingående variabler i registret var valida med en total exakt överensstämmelse mellan ursprungliga och re-abstraherade data på 91.1 %. Inrapporteringshastigheten var i median 3.9 månader för diagnostiska data.
Delarbete II var en epidemiologisk studie, av 4112 patienter, baserad på data ur NREV som validerats i delarbete I. Målsättningen med delarbete II var att undersöka associationer mellan patientens utbildningsnivå och val av behandlingsstrategi hos patienter diagnosticerade med esofaguscancer samt dess eventuella efterföljande effekt på överlevnad. Inkluderade patienter analyserades grupperade på utbildningsnivå (låg ≤9 år, medel 10-12 år, hög >12 år). Patienter med hög utbildningsnivå visade sig ha större sannolikhet att erbjudas kurativt syftande behandling jämfört med patienter med låg utbildningsnivå, OR 1.48 (95 % CI 1.08 – 2.03). Högutbildade patienter som planerades för kurativ behandling hade även en förbättrad överlevnad i justerade analyser HR 0.82, (95 % CI 0.69 – 0.99). Patienter där behandlingsstrategi beslutades vid en multidisciplinär behandlingskonferens hade större sannolikhet att erbjudas kurativt syftande behandling samt förbättrad överlevnad.


Delarbete IV utvärderade införandet av minimalinvasiv esofagektomi (MIE) med avseende på kirurgiska onkologiska resultat och postoperativa komplikationer. Studien var en retrospektiv kohortstudie av samtliga patienter som opererats med öppen transthorakal (n=65) eller minimalinvasiv esofagektomi (n=51) på Akademiska sjukhuset mellan 2007 och 2016. DAG-analys användes för att identifiera potentiella störfaktorer. Minimalinvasiv esofagektomi ledde till ökat antal resekerade lymfkörtlar men var likvärdig öppen kirurgi med avseende på andra kirurgiska onkologiska resultat. MIE var också associerat med kortare vårdtid och mindre peroperativ blödning. Postoperativa komplikationer var likartade i båda grupperna.

Delarbete V var en prospektiv studie med syftet att strukturerat jämföra PET/MR med PET/CT avseende preoperativ stadieindelning vid (77.6 % inrapporterade efter 1 år), 3.4 månader för operationsdata (76.9 %) och 4.1 månader för uppföljningsdata (74.8 %).

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