Anastomotic defect after Ivor Lewis esophagectomy – early prediction and economic consequences

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DOCTORAL DISSERTATION

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| **Title and subtitle** Anastomotic defect after Ivor Lewis esophagectomy – early prediction and economic consequences | | | |
| **Abstract**  Esophageal surgery has developed from daring and experimental procedures to routine surgical procedures during the latest one hundred years. Some decades ago, outcome after surgery was affected by postoperative mortality measured by two-digit numbers. Complications after esophageal resection are still common and very demanding, but early detection and early (minimally invasive) treatment can reduce the effect of a complication. The most demanding postoperative complication is anastomotic leakage, which still occurs in over 10% of patients.  This thesis is focused on methods for early prediction of anastomotic defects and description of the economic consequences of complications after esophageal resection. In paper I, II and V the method of surface microdialysis is developed and studied, aiming for use in a clinical setting. Paper III is a health-economy description of the cost of esophagectomy and postoperative complications. In paper IV, early postoperative endoscopy using a new standardized assessment model of the surgical reconstruction is studied.  Results and conclusions  Paper I: Surface microdialysis can be used on small bowel to differentiate between ischemic segments and segments with normal blood flow.  Paper II: Surface microdialysis can be used on the gastric tube and ischemia at the proximal part of the gastric tube can be identified with surface measurements.  Paper III: The mean total healthcare cost in Region Skåne for an esophagectomy without postoperative complications is approximately 335 000 SEK. The mean total healthcare cost for an esophagectomy with a major complication is approximately 808 400 SEK. The complication with the highest total health care cost (approximately 1 022 000 SEK) is anastomotic leakage.  Paper IV: The new endoscopy score developed and studied in this paper can help predict development of anastomotic defects. This facilitates optimal postoperative management and early treatment of anastomotic leakage.  Paper V: Surface microdialysis measurements from the gastric tube reconstruction can predict anastomotic defect. Artificial neural network technique determined the specific time point (postoperative day 1 at 24 hours after surgery was completed) and the specific substance (glucose) with the strongest association to anastomotic defect. | | | |
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**J Surg Res. 2016 Jul;204(1):39-46. doi: 10.1016/j.jss.2016.04.001. Epub 2016 Apr 9.**

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**Paper II**

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**J Surg Res. 2020 Jan;245:537-543. doi: 10.1016/j.jss.2019.07.060. Epub 2019 Aug 27.**

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**Hospital costs and health-related quality of life from complications after esophagectomy.**

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**Eur J Surg Oncol. 2021 May;47(5):1042-1047. doi: 10.1016/j.ejso.2020.09.032. Epub 2020 Sep 29.**

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**Paper IV**

**Early endoscopic assessment after esophagectomy can predict anastomotic complications: a novel scoring system.**

**Åkesson O, Heyman I, Johansson J, Rissler P, Falkenback D.**

**Surg Endosc. 2021 Apr 9. doi: 10.1007/s00464-021-08472-4. Online ahead of print.**

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**Paper V (Manuscript)**

**Postoperative surface microdialysis in prediction of anastomotic defect after esophagectomy. Oscar Åkesson, MD, Pernilla Abrahamsson, PhD, Göran Johansson, MS, Michael Haney, PhD, MD, Dan Falkenback, PhD, MD, Michael Hermansson, PhD, MD, Martin Jeremiasen, PhD, MD, and Jan Johansson PhD, MD.**

# Introduction

All surgical procedures are associated with the risk of complications occurring during the surgical procedure itself or during the recovery process. In general, extensive surgical procedures are associated with larger risk of complications than less extensive procedures.

It is fair to say that surgeons today are well aware of risks of complications and there has been considerable research and efforts trying to limit the rates and severity of complications. Patients and health care professionals unite in this important mission to reduce the impact of complications after surgery.

Esophageal resection is an extensive and demanding procedure for patients, surgeons and anaesthesiologists. During the early development of modern day esophageal resection surgery, complication rates were tremendous with operative mortality measured by two-digit numbers. General improvement during the last fifty years have reduced postoperative mortality after esophagectomy to approximately 2% and reduced the occurrence and severity of complications in general. The focus nowadays is not just reducing mortality but also reducing less dramatic complications to improve patient outcome and quality of life after surgery. Many factors are important in this improvement; preoperative prognostication, patient preparation, improved surgical technique, better surgical instruments, more advanced anaesthesiology and intensive care, more active postoperative mobilization and rehabilitation.

In spite of this, serious complications still occur. The quest to reduce complications and improve the surgical result led to this thesis. The work is focused on methods for early detection of anastomotic defects which could lead to better treatment strategies, and to describe the medical and economic consequences of complications for patients and society.

# Background

"Men occasionally stumble over the truth, but most of them pick themselves up and hurry off as if nothing ever happened." Winston Churchill

## Resection and reconstruction

Esophageal resection with simultaneous reconstruction of gastrointestinal continuity has been performed for about one hundred years. The first successful esophageal resection was performed in 1877 by Vincenz Czerny, Heidelberg.[1, 2] Czerny performed a resection of the cervical part of the esophagus without restoring continuity. The distal end of the resected esophagus was sutured to the skin and the patient was fed through a tube passed into the stoma. The procedure was later used by Theodore Billroth (Czerny´s teacher) and others and up until 1885 nine resections were reported of which four patients survived for more than three months.[2]

At the turn of the century the technical possibilities in anaesthesiology were developing through research including animal experiments. Ferdinand Sauerbruch developed a technique for high pressure ventilation during sedation. This made thoracotomy possible as an access route to the intrathoracic esophagus as described by Sauerbruch in 1905. Esophageal resection via thoracotomy was attempted in three patients. Resection could not be performed and the patients died from mediastinitis.[3]

In 1908 Voelker, Heidelberg, performed resections of the distal esophagus with simultaneous esophagogastric anastomosis. An abdominal incision and transhiatal approach was used. One of the three patients operated on survived.[2]

At the same time many attempts were made using stomach or intestines as reconstruction to bypass the intrathoracic esophagus. Carl Beck, New York, showed in animal experiments in 1905 that the stomach could be divided to create a tube along the greater curvature which could reach up into the thoracic cavity.[2] The procedure was used successfully in 1913 by Willy Meyer, New York, to bypass an esophageal carcinoma.[2]

In 1907 Caesar Roux, Lausanne, interposed a subcutaneous jejunal segment from the cervical esophagus to the stomach leaving the benign esophageal stricture in situ. [2, 3] In 1911 Georg Kelling, Dresden, performed a subcutaneous interposition of the transverse colon from the cervical esophagus to the stomach. The operation did not succeed but it was the first reported attempt at this reconstruction. [2-4]

In 1912, Wilhelm Roepke, Barmen, tried to bypass an esophageal carcinoma by making a conduit of the stomach which could be stretched to the level of the neck. Unfortunately the anastomosis to the cervical esophagus was not successful.[3] Martin Kirschner, Königsberg, presented in 1920 a procedure with cervical anastomosis of a gastric conduit, leaving esophagus in situ. It was performed on four patient who all died postoperatively.[2-4]

Esophageal resection was encumbered with great challenges during early development. First, the surgical aspect of thoracic dissection of which surgeons of that time had limited experience, secondly the anaesthesiological aspect of sedation, anaesthesia and ventilation during a thoracic procedure and thirdly advanced reconstructions the gastrointestinal tract with abdominal organs transferred to the thoracic or cervical level of the esophagus. Furthermore, these developing steps were taken in the pre-antibiotic era.

Wolfgang Denk, Wien, in 1913 developed a method in experiments on animals and cadavers in which the esophagus could be pulled out from the thorax without thoracotomy. The esophagus was divided via a cervical incision and pulled out through the hiatus via an abdominal incision. Continuity would later be restored by an extrathoracic skin tube.[3] Denk never succeeded with this procedure in patients but attempts were made by others in the following decades. Up until 1941, 32 procedures were reported of which three patients survived.[2] Grey Turner, Newcastle upon Tyne, had some success with this method with the first successful pull through operation in 1933. The benefit of the procedure was the avoidance of thoracotomy but the operative mortality of the method in Grey Turnes hands was 40 %.[2] Not many other surgeons took up this procedure since the transthoracic procedure was developing at this time.

The first successful esophageal resection with simultaneous reconstruction, often referred to, was performed by Franz Torek, New York, in 1913.[2-4] A patient with esophageal cancer underwent esophageal resection via left thoracotomy and was reconstructed with an external rubber tube from the cervical esophagus to the stomach. Ether was used as an anaesthetic agent during the operation which was conducted without artificial ventilation. Torek could never repeat this successful procedure but attempts were made by others during the following decades. In 1941 Ochsner and DeBakey summarized the Torek procedure. They reported 58 cases of which 17 patients had survived, an operative mortality of 71 %.[2]

In 1929, the Japanese surgeon Tohru Ohsawa, Kyoto, performed the first successful esophageal resection with an intrathoracic esophagogastric anastomosis.[1] Thoracotomy was done without positive pressure ventilation.[2] In 1933 Ohsawa reported nineteen resections of which eight patients survived.[2, 4] During the following decades anaesthesiology and ventilation during intrathoracic surgery improved as well as the surgical procedures to resect and reconstruct the upper gastrointestinal tract but successful esophageal resections with primary anastomosis were rare.

In 1946 the Welch surgeon Ivor Lewis presented a procedure for esophageal resection with an intrathoracic esophagogastric anastomosis which is still one of the main standard procedures in esophageal surgery today.[2, 5]

Modern esophageal surgery developed quickly after the second world war. Developments in anaesthesiology, surgical technique, antibiotics and postoperative management paved way for better results after esophageal resection with primary anastomosis. In 1954 operative mortality was 33% (Garlock) and 18% (Sweet) respectively in two reports.[2]

## Esophagectomy and reconstructions

Today the main procedures for esophageal resection are the Ivor Lewis esophagectomy, the McKeown esophagectomy and the transhiatal approach.[6] These three procedures have specific advantages and disadvantages and the range of complications are likewise specific for each procedure. Moreover, rates of postoperative complications for the same procedure differs greatly between operating centres.

The main indication for esophagectomy is cancer of the esophagus or the esophagogastric junction but some benign disease is also treated with esophagectomy for example end-stage achalasia, advanced esophageal stricture and Chagas disease. The following discussion of esophageal surgery and complications is based on surgery for malignant disease.

### Ivor Lewis esophagectomy (IL)

This procedure is a two-field operation (abdomen and chest) with en bloc resection of intrathoracic esophagus and mediastinal lymph nodes and cardia and lesser curvature of the stomach including gastric lymph nodes. A gastric tube is made along the greater curvature of the stomach and an intrathoracic esophagogastric anastomosis is made. Advantages are good oncological result with a high lymph node yield, relatively low anastomotic leakage (AL) rate and low rate of recurrent laryngeal nerve injury (RLNI). Disadvantages are required single lung ventilation which potentially increases the risk of postoperative pulmonary complications and difficulties in management of an intrathoracic AL should it arise.[7] It is not appropriate for cervical lesions and proximal intrathoracic lesions where the proximal resection level cannot be reached via the thoracotomy.

### McKeown esophagectomy (MK)

The McKeown esophagectomy is a three-field operation (neck, chest, abdomen) with en bloc resection of esophagus and cardia with lymph nodes similar to IL. The gastric tube is pulled up via the cervical incision and anastomosed to cervical esophagus. Advantages are good oncological result with high lymph node yield and easily managed AL should it occur. The procedure can be used for proximal lesions. With minimal invasive (thoracoscopic) approach, single lung ventilation can sometimes be avoided in the prone position thereby minimizing pulmonary complications. Disadvantages are higher AL rate and higher RLNI compared to IL.[7]

### Transhiatal esophagectomy (TH)

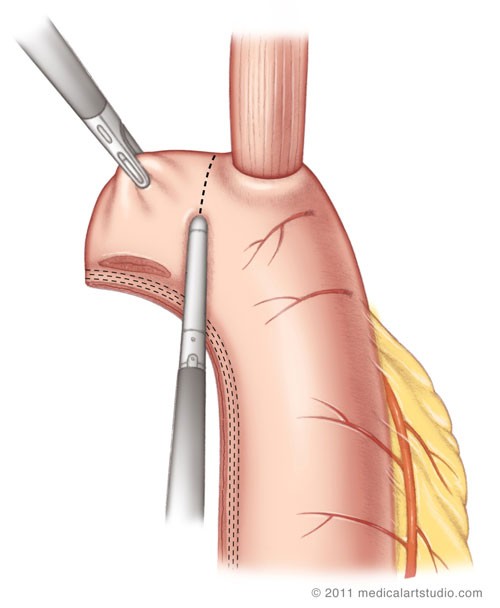
Transhiatal esophagectomy is performed via abdominal and cervical access without thoracotomy. Abdominal preparation of the gastric tube is similar to IL and MK procedures. Esophageal dissection from the abdomen as proximal as possible under direct vision is followed by blunt manual dissection of the proximal intrathoracic esophagus. The specimen is taken out via a cervical incision and the esophagogastric anastomosis is created at the cervical level. Advantages are no thoracotomy reducing pulmonary morbidity and easily managed AL at the cervical level. Disadvantages are increased rate of RLNI and dysphagia compared to IL, higher rate of AL compared to IL and difficulties in lymph node resection in the mediastinum.[7]

## The gastric tube

In all of the procedures described above the gastric tube made from the stomach is used as a conduit where the gastroesophageal anastomosis is constructed in the fundic part of the gastric tube. Other reconstructions are possible, the most common alternative being interposition of colon from proximal esophagus to the stomach after esophageal resection. In the following only gastric tube reconstruction will be discussed.

After preparation of the gastric tube the area of the anastomosis is solely supplied by one single artery, right gastroepiploic artery, RGA. This implies a reduction in the normal blood flow and makes the anastomotic area vulnerable to any further decrease in local tissue perfusion.[8-11]

The clinical experience is that when necrosis occurs in the anastomotic area it never affects the esophagus but only the gastric side of the anastomosis. This observation supports the idea that decreased blood flow to the top of the gastric tube plays a major role in anastomotic defects and leakage.[12-14]



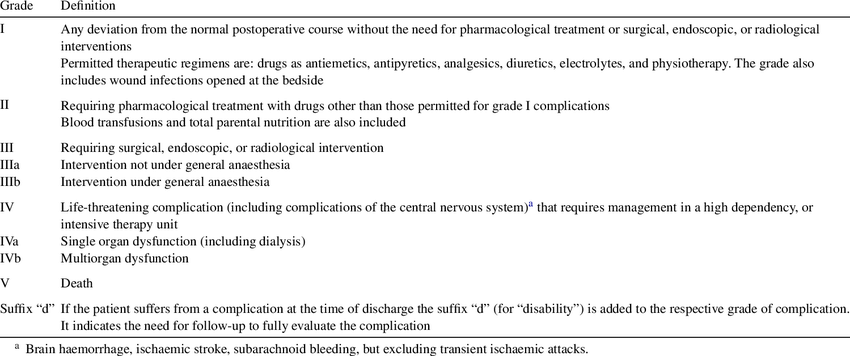
**Figure 1.** The stapled esophago-gastic anastomosis. With permission from medicalartstudio

## Complications after esophagectomy

Common and severe complications after esophagectomy include pulmonary infection (PI), atrial fibrillation (AF), anastomotic leakage (AL), chyle leakage (CL) and recurrent laryngeal nerve injury (RLNI).[15-17]

Different classifications are used to describe and grade complications. The Clavien-Dindo classification is a common score to grade the severity of postoperative complications. It is based on the diagnosed complication and the management thereof.[18] Complications after esophagectomy are often graded as III or IV as surgical, endoscopic or radiological intervention is often needed. See Table 1 below.

**Table 1**. Clavien-Dindo classification (Modified from Dindo et al 2004)



Recently the Esophagectomy Complications Consensus Group (ECCG) has defined various complications related to esophagectomy.[19, 20] The severity of complications is graded and determined on the management needed to resolve the problem. ECCG has produced international data and raised awareness of specific complications associated with esophagectomy. This data can be seen as an overview of complications of modern esophageal surgery.

Analysis of ECCG data from more than 6000 esophagectomies from 39 operating centres between 2015 and 2018 showed a 30-day and 90-day mortality of 2.0% and 4.5% respectively. Other severe complications were as follows; pneumonia 13.9%, atrial dysrhythmia 14.7%, anastomotic leakage 12.5%, chyle leakage 4.6%, recurrent laryngeal nerve injury 4.4%. Severity of complications after esophagectomy were high as graded by Clavien Dindo. Approximately 60% of the patients had some complication. 31.5% of the patients had minor complications graded as I or II according to Clavien-Dindo. 15.2% of the patients had complications graded as IIIa and 17.3% had severe complications graded as >IIIb.[16]

Everyone can understand that a postoperative complication causes suffering or in the best case, inconvenience for the patient. For several reasons we found that it would be important to describe the economic consequences of complications after esophagectomy. In a publicly funded health care system, distributing economic resources can be difficult, and health economy is a necessary tool to clarify cost and effectiveness of different priorities. A better understanding of economic consequences of complications can aid in prioritizing primary, secondary and tertiary prevention.

## Anastomotic leakage

The esophagogastric anastomosis is still the weak link after esophageal resection with AL rates well over 10 %. Intrathoracic AL is a devastating complication which can cause pleural effusion, mediastinitis and multiple organ failure needing endoscopic or surgical intervention and escalation in level of care to intensive care units. AL leads to higher rates of in-hospital death and of 90-day mortality, 18.1% in a nationwide study from Sweden.[21, 22] It also leads to worse long-term survival and higher risk of recurrent disease.[15, 23] Furthermore AL is associated with longer in-hospital treatment and increased healthcare cost.[23, 24] Early detection and treatment can improve outcome.[25, 26] It is considered that early (postoperative day 1-3) anastomotic leakage is caused by technical failure in making the anastomosis. Later anastomotic defect seems to be associated with poor healing.

Ischemia, inadequate local tissue perfusion in the gastric tube at the site of the anastomosis, is an important factor in poor anastomotic healing resulting in postoperative necrosis and/or leakage.[8, 13, 14, 27]

ECCG has defined, subdivided and graded anastomotic defects, bringing clarity to this important topic and making research and clinical diagnosis and treatment more uniform.[19] See Table 2 below.

According to this definition anastomotic defects are divided into “anastomotic leakage” and “conduit necrosis”. The severity of the defect is determined by the clinical intervention needed to treat the complication. It is important to recognize that patients with an endoscopically defined conduit necrosis type I or anastomotic leakage type I may have a completely normal postoperative recovery without any clinical signs of anastomotic defect.

**Table 2.** Definitions of complications related to esophagectomy according to ECCG. With permission from Wolter Kluwer Health Inc.



## Prediction of anastomotic defects

Preoperative prediction of postoperative complications and specifically anastomotic defect is difficult. No specific test can predict the postoperative outcome. Old age is associated with AL as well general comorbidity, especially obesity and obstructive pulmonary disease.[28]

Postoperatively, prediction and early detection of complications would be valuable in limiting the consequences of postoperative complications. Some studies suggest a combination of biomarkers to predict complications.[29, 30] The most commonly used biomarkers are C-reactive protein and leukocyte count. Both are reliable in excluding anastomotic leakage with a high negative predictive value.[31] In recent years early postoperative endoscopy has shown promising results in predicting AL.[12, 25, 26, 32]

## Prevention of post-operative complications after esophagectomy

Subspecialisation and centralization of advanced surgical procedures as well as minimal invasive techniques such as laparoscopy and thoracoscopy have been important factors in reducing mortality and morbidity.[33-36]

Programs for enhanced recovery, ERAS, have been successful in reducing complications[37] but no patient-specific preventive interventions in the postoperative care have been described.

Kitegawa et. al. in a recent editorial pointed out the need to prevent post-esophagectomy pneumonia as an important step in reducing mortality and morbidity.[38]

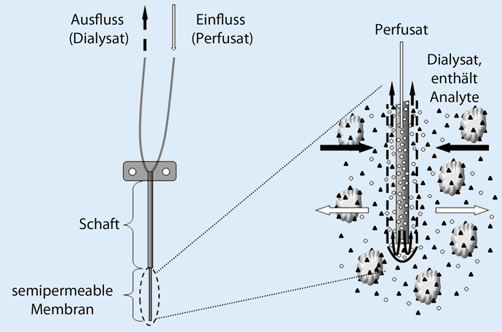
## Treatment of anastomotic defects

There is no international consensus on the treatment of AL.[39] Minor anastomotic defects may not need intervention.[40] Defects which affect the patients recovery or physiology needs surgical or endoscopic treatment and are defined as leakage type II or III or as conduit necrosis type II or III. First line therapy in many situations is endoscopic treatment, either placing an endoluminal stent to cover the defect or the recently developed endoscopic assisted vacuum therapy (EVAC) to drain the anastomotic area and prevent leakage.[39, 41-43] If this fails or the defect is extensive surgical resection will be necessary with increased morbidity and mortality.[21, 22]

Early detection of anastomotic defect seems important since intervention can be initiated before the patient deteriorates.[12, 25, 26, 41]

## Microdialysis

Microdialysis (MD) is a method for measuring local tissue concentrations of substances. The microdialysis system consist of a pump, a sampling probe and an analysing unit. The sampling probe is composed of two thin tubes connected via a semi-permeable membrane. Dialysis fluid (perfusate) is pumped at constant flow rate, typically 1-5 microliters/minute, into the chamber of the semi-permeable membrane via the in-flow tube whereafter the dialysate is collected in vials connected to the out-flow tube. Exchange of substances by passive diffusion will occur over the semi-permeable membrane and concentrations of these substances can be measured in the dialysate. The analyser consists of highly sensitive chemical detectors which require only a few microliters of fluid.[44, 45]



**Figure 2.** The principle of microdialysis sampling. With permission from Springer Nature.

MD measures the local tissue concentration of extracellular substances.[46] It can be used to study local tissue concentration of drugs and biochemical substances in contrast to conventional blood sampling which measures systemic concentrations of substances. A prerequisite is that the semi-permeable membrane obviously must come into contact with the target tissue, commonly by puncture of the target organ. MD is used in many settings to study pharmacological and metabolic processes in animals and humans. In clinical routine care it has mainly been used as a technique to monitor brain metabolism after neuro-trauma[44] (as part of the “Lund concept” for treating head injury[47]).

In MD studies on tissue metabolism, the following substances are commonly measured: lactate, glucose, pyruvate and glycerol. These four substances reflect the metabolic process and is often used to distinguish aerobic from anaerobic metabolism indicating ischemia. In general, in anaerobic conditions there is increase in lactate and decrease in pyruvate reflecting lack of oxygen in the metabolic process, reduction in glucose indicating decreased supply (perfusion) and increased consumption and elevation in glycerol indicating disintegration of the cellular membrane.[45]

In clinical research MD has been used to study local metabolism of the heart during cardiac surgery [48], postoperative local metabolism in reconstructive surgery after transplantation of free flaps [49], local liver metabolism after liver transplantation [50-53] and metabolism of the abdominal cavity after various abdominal procedures.[54]

## Microdialysis in gastrointestinal surgery

The use of MD in abdominal surgery has been focused on bowel ischemia and anastomotic leakage. Most authors use intraperitoneal MD probes to study intraperitoneal change in biochemistry. It has been shown that results from MD probes depend on their location in the abdominal cavity and that probes in direct vicinity of an anastomosis are more likely to identify metabolic change associated with an anastomotic leakage.[55]

Several studies show that measurements from conventional intraperitoneal MD probes can predict anastomotic leakage after colon resection.[56-60] The main result from these studies is that postoperative elevation in intraperitoneal lactate is associated with anastomotic leakage after colon resection. In some studies, change in levels of inflammatory cytokines (IL-6, IL-10, TNF-alpha) and lactate-pyruvate ratio have preceded anastomotic leakage after rectal resection.[58, 61]

One study on MD after various abdominal procedures identified elevated lactate-pyruvate ratio and lower glycerol concentration in patients who developed postoperative complications.[62]

Intraperitoneal MD measurements have been performed after emergency surgery in some studies.[63, 64] In these studies, elevated lactate-pyruvate ratio were associated with severe postoperative complications. Results of MD measurements of concentrations of glycerol and glucose are diverging and contradictory in these papers. One study on acute gastrointestinal perforations showed diverging results from intraperitoneal MD probes between upper (perforated ulcer) and lower (colon-rectum) gastrointestinal perforations. [65]

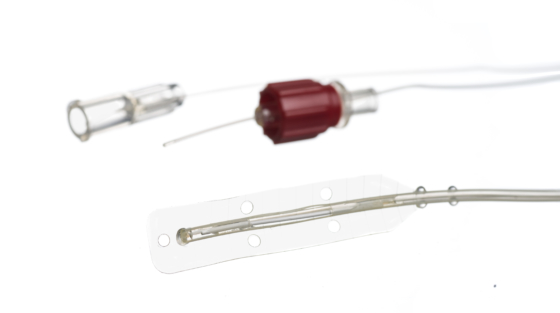
These studies are generally non-randomized, include a low number of participants, have different outcome and mixed study populations.[54] It is difficult to make clear conclusions on specific concentrations of specific metabolic substances in association with postoperative complications. However, intraperitoneal metabolic change can be measured by MD probes before complications are diagnosed by any other modality.

## Microdialysis in esophageal surgery

MD has been used to detect ischemia of free jejunal flaps after proximal esophageal resection in one study. Low MD glucose concentration was associated with ischemia of the jejunal flap as verified by reoperation. In cases of ischemia the calculated lactate-glucose ratio was higher than in non-ischemic flaps.[66] Conventional MD probes placed intrathoracically have been used in an attempt to detect complications after Ivor Lewis esophagectomy. No specific metabolic substance was predictive of anastomotic leakage but a logistic regression model of MD data demonstrated predictability for anastomotic leakage before clinical signs were observed.[67] In 2021 a study on local metabolism of the peri-anastomotic region of the gastric tube reconstruction was published, demonstrating feasibility of the method of surface microdialysis in clinical practice.[68]

## Surface microdialysis

In 2011 Abrahamsson et. al. published results from an animal study on MD measurements (lactate, glucose, pyruvate, glycerol) from the surface of the heart. The surface measurements were in concordance with an intraparenchymal MD probe during normal aerobic conditions and ischemia.[69] Similar results were later published from measurements on the liver.[70] These findings gave rise to development of a modified MD probe for use on organ surfaces.[71] Indeed, the development of the surface MD (S-MD) probe widened the possible future use of MD measurements on the gastrointestinal tract, avoiding organ puncture and possible risks of complications associated with puncture.



**Figure 3.** Microdialysis probe for surface sampling. With permission from Senzime AB.

# Aims of the thesis

“Out of intense complexities, intense simplicities emerge.” Winston Churchill

The overall aim of the thesis was to try to improve diagnostic methods and prediction with regards to anastomotic defects after esophagectomy with gastric tube reconstruction and to describe the economic consequences of complications after esophagectomy.

## Specific aims

Paper I To explore technical feasibility of S-MD on bowel and investigate the methods´ possibility to detect ischemia in a bowel segment.

Paper II To investigate diagnostic accuracy of S-MD in partial and complete ischemia on a gastric tube reconstruction. To investigate if increasing systemic blood pressure could affect local metabolism of the gastric tube.

Paper III To describe the health care costs of post-esophagectomy complications and to describe the effect of post-esophagectomy complications on patient quality of life.

Paper IV To investigate if early postoperative endoscopy and a new endoscopic score could predict future anastomotic defects in the gastric tube reconstruction. To investigate if biopsies from the gastric tube could be predictive of future anastomotic defects.

Paper V To explore technical feasibility of S-MD in humans. To investigate diagnostic possibilities of S-MD in prediction of future anastomotic defects of the gastric tube reconstruction.

# Material and methods

"Success is the ability to go from one failure to another with no loss of enthusiasm." Winston Churchill

## Paper I and II

Both studies were approved by the animal ethics committee Umeå University, Umeå, Sweden. Dnr A33-14.

These experiments were performed in the animal laboratory facility at Umeå University. Swedish landrace pigs were used. A standardized anaesthesia protocol was followed during the experiments. Anaesthesia was induced by intravenous sodium pentobarbital, 10 mg/kg. Continuous infusions of fentanyl 20 microg/kg/h, midazolam 0.3 mg/kg/h and sodium pentobarbital 5 mg/kg/h were used to maintain anaesthesia. The animals were tracheotomized and normo-ventilated. By cutdown technique, a central venous line was introduced via the external jugular vein and catheters for endovascular pressure measurements were inserted in the common carotid artery and the superior caval vein. Hemodynamic data was recorded continuously and blood samples were taken hourly.

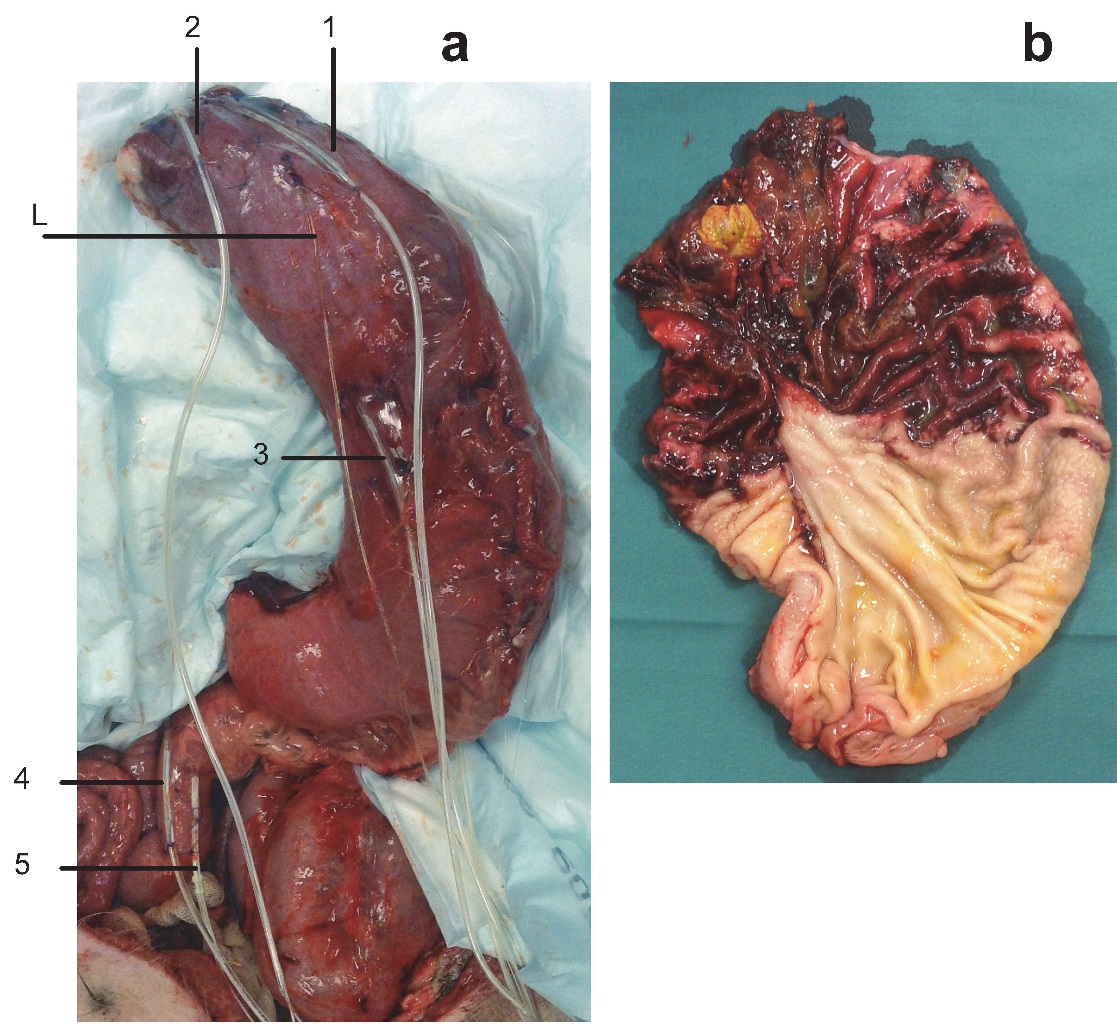
In paper I, S-MD probes were placed on a segment of the small bowel and ischemia was induced by complete division of the mesentery to the bowel segment.

In paper II, S-MD probes were attached to the proximal and middle section of the stomach. Transection of distal esophagus, resection of the minor part of the stomach and division of blood vessels to the stomach was performed leaving only the right gastroepiploic artery (RGA). Ischemia at the top of the gastric tube was induced by division of RGA at the middle section of the gastric tube and verified by an intramural oxygen partial pressure probe at the top of the gastric tube.

In both experiments control S-MD probes and conventional MD probes were placed on normal, non-ischemic bowel and the peritoneal cavity respectively. Concentrations of metabolic substances were measured every 20 minutes for 4 hours.

In paper II intervention with intravenous fluids was performed as an attempt to improve local ischemia.

At the end of the experiments, large biopsies were cut out from the bowel and stomach at the S-MD probe sites and control sites.



**Figure 4.** Gastric tube with microdialysis probes attached in (**a**). The gastric tube opened along the greater curvature in (**b**). A distinct difference between ischemic and normal mucosa is seen. Photo by O. Åkesson.

## Paper III

The study was approved by the regional ethics committee at Lund University, Lund, Sweden. Dnr 2014/400 and amendment 177/17

Data from the Swedish national register for esophageal and gastric cancer (NREV) and the regional register for health care consumption in Region Skåne (RSVD) was extracted and crossmatched for patients undergoing esophagectomy for esophageal or junctional cancer in Region Skåne between 2010 and 2015. Cost analysis was based on health care consumption, both in-patient and out-patient visits, and identified by diagnosis codes (ICD-codes). Follow-up was 1 year after surgery. Patients undergoing surgery during 2015 were excluded since the follow-up was too short at the time when the data was extracted, leaving 132 participants.

Costs for each visit (in- and out-patient) and the cost of procedures during these visits were calculated. Visits associated with ICD-codes unrelated to esophageal cancer were excluded. Only ICD-codes (diagnoses) not occurring prior to surgery were considered complications. Cost of re-operation was attached to the hospitalization episode when the re-operation was performed, which in eight cases were during the same hospitalization episode as the index operation.

Based on the Clavien-Dindo classification complications were defined as minor (grade I-II) or major (grade III and IV).

Health related quality of life (HRQoL) was evaluated by sending out a QLQ-C30 form to all survivors one year after diagnosis of esophageal cancer.

## Paper IV

The study was approved by the regional ethics committee at Lund University, Lund, Sweden. Dnr 2014/400.

60 patients planned for Ivor Lewis esophagectomy were included at a single institution. Based on our clinical experience an endoscopy scoring system was developed. Three locations of the gastric tube reconstruction were assessed and scored 0-2 with regards to signs of ischemia and necrosis. On post-operative day (POD) 7 or 8 patients underwent transoral endoscopy of the gastric tube reconstruction. The endoscopy of the reconstruction was recorded and biopsies were taken from the top of the gastric tube. The endoscopy videos were assessed retrospectively by three experienced endoscopists and surgeons, blinded to patient name and identification number, and scored in consensus using the combined endoscopy score.

Biopsies were assessed and graded with regards to signs of ischemia (0-2) by one experienced pathologist.

Outcome was anastomotic defect according to ECCG definitions at discharge or at 30-day follow-up visit.

Multiple logistic regression was performed of patient and tumor characteristics, including combined endoscopy score and histopathology score, possibly associated with poor healing of the anastomosis.

## Paper V

The study was approved by the regional ethics committee at Lund University, Lund, Sweden. Dnr 2014/400.

The same cohort of patients as in paper IV was investigated. During the esophagectomy, after the anastomosis was constructed, S-MD probes were attached onto the outer surface of the gastric conduit and the esophageal remnant, one probe on each side of the anastomosis approximately one centimetre from the circular staple line. The S-MD probes were tunneled out through the thoracic wall before closing the thoracotomy. The probes were connected to microdialysis pumps and the microdialysis process started immediately at the end of the surgical procedure. The flow rate was 0,5 microliters/min. Dialysate samples were collected at 2-hour intervals during the postoperative ICU-phase and at 4-hour intervals during the rehabilitation phase on the standard surgical ward. Samples were frozen (-20 C) for later analysis.

On POD 7 the S-MD probes were removed by pulling them off from the reconstruction and out through the thoracic wall.

Outcome was anastomotic defect according to ECCG definitions at discharge or at 30-day follow-up visit. Participants were grouped based on the outcome occurring or not. Microdialysis data from the two groups was compared using artificial neural network (ANN) techniques in trying to identify predictive value of MD measurements related to the outcome anastomotic defect.

## Statistics

In paper I and II we have compared concentrations of metabolic substances between microdialysis probes in different positions i.e., ischemic vs non-ischemic tissue. Data from the probes were tested for characteristics of distribution and did not differ from the normal distribution. We analyzed the difference between probes in different locations at each time point (interprobe comparison) and difference for each probe over time compared to starting time (intraprobe comparison). Mean values + 95% confidence intervals are presented.

In paper I and II comparison of microdialysis data was done by t-tests. In paper II, correction for multiple comparison was done by Bonferroni correction but did not affect the significant differences.

Histopathology scores (of ischemia) from each microdialysis probe site were compared. In paper I mean histopathology score for each probe position was compared to control (non-ischemic) by Wilcoxons signed-rank test (non-parametric data, paired comparison). In paper II mean histopathology scores from the probe positions were compared in pairs, A vs B and A vs C, by a paired t-test (normal distribution).

Hemodynamic parameters and blood samples from each hour during the experiments showed normal distribution and were compared to baseline by a paired t-test.

In paper III analysis of patient characteristics related to major postoperative complications was done by a Mann-Whitney test (Wilcoxons rank sum test) (difference between groups). Healthcare cost calculations were based on diagnosis codes and procedure codes for every visit (in- and out-patient) related to the esophagectomy. The cost for reoperation could not be separated from the initial surgery when the reoperation was done during the same hospitalization episode and therefore the cost of initial surgery was higher in this group. The total healthcare cost was compared between the three groups no-, minor- and major complications presented as mean values with 95% confidence intervals.

Multivariate linear regression was used to show association between complications and increased total health care costs.

In paper IV we have compared two outcomes, anastomotic defect and no anastomotic defect. The distribution of endoscopy scores was compared between the groups by Wilcoxons rank sum test (Mann-Whitney test) (two independent groups).

The histology score was dichotomized in two groups, normal (0) and ischemia and necrosis (1 and 2) and the distribution of the scores was set up in a contingency table. Comparison between outcomes was done by Fisher´s exact test.

Association between possible predictive factors and the two outcomes was analysed by multiple logistic regression.

In paper V microdialysis values during a four-day period are analysed to find association with development of anastomotic defect. It was not known if a specific time point or a specific substance would be associated with anastomotic defect. As an exploratory approach artificial neural network (ANN) technique was used. The ANN is a system of data nodes, connected to and influencing each other forming patterns of associations between input, variables, and outcome. An ANN model can be trained to recognize an outcome when variables are associated to each other in a certain pattern.

In the first step a prediction model was established using all microdialysis variables during the first four postoperative days. Modelling continued until the ANN model with highest AUC value was found (AUC=1.0). In the second step the variables and time point identified in the first step were analysed to find the prediction value for anastomotic defect of the specific substances.

The result from the second step in the ANN analysis was validated by logistic regression with backward elimination.

# Results

“Success is not final, failure is not fatal, it is the courage to continue that counts.” Winston Churchill

## Paper I

S-MD probes were possible to attach to the surface of small bowel and yielded dialysate which could be analysed for metabolic substances. The histopathological score of ischemia was significantly different in biopsies from the ischemic segment compared to control, verifying severe ischemia in the segment. At one hour after inducing ischemia significant difference from baseline was observed in concentrations of lactate (elevated) and glucose (decreased) in S-MD measurements from the ischemic segment. S-MD concentrations of pyruvate were significantly decreased and glycerol concentrations were significantly higher compared to baseline only in the middle of the ischemic segment from 2 hours on after inducing ischemia.

## Paper II

An esophageal transection and stomach resection similar to a gastric tube reconstruction could be performed uneventfully in a pig model. S-MD probes could be attached to the outside surface of the gastric tube and yielded dialysate which could be analysed for metabolic substances. Ischemia at the top of the gastric tube was verified by intraparenchymal measurements of oxygen partial pressure and by histopathological examination of biopsies from S-MD probe sites. S-MD lactate concentrations from the top of the gastric tube were significantly higher than baseline and control probes from 1 hour on after inducing ischemia. Lactate concentrations decreased at the top of the gastric tube after intervention with intravenous fluid. S-MD glucose concentrations decreased in all probe positions from 1 hour on after inducing ischemia. The relative decrease was largest in measurements from the top of the gastric tube.

## Paper III

132 patients undergoing esophagectomy for esophageal or junctional cancer were analysed. 75% of the participants experienced some postoperative complication, 30 % of which were graded as severe (Clavien-Dindo grade III or IV). Most common complications were cardiac complications 24%, pneumonia 23%, laryngeal nerve paresis 14%, anastomotic leakage 6 % and wound infection 6%. Different general complications such as nausea, breathing problems, stomach pain, vomiting and diarrhea defined as “other complications” occurred in 40% of patients.

Preoperative patient characteristics was not associated with severity of complications.

Mean total healthcare costs for esophagectomy were 335 016 SEK for patients with no complication, 438 320 SEK and 808 401 SEK for patients with minor and major complications respectively.

The highest cost of complications and total healthcare costs for specific complications were as follows:

Anastomotic leakage 598 770 SEK and 1 021 272 SEK respectively

Laryngeal nerve paresis 264 965 SEK and 772 890 SEK respectively

Postoperative pneumonia 252 574 SEK and 685 986 SEK respectively

The reported quality of life in general (QALY-weight) was not significantly different between the groups of complications.

## Paper IV

57 of the 60 patients included were available for analysis. 11 (19%) of these patients developed anastomotic defects. None of the defects were diagnosed before endoscopy on POD 7/8. 7 of 8 patients who received a combined endoscopy score of > 4 developed anastomotic defects. 3 patients of 45 who received a combined endoscopy score of < 2 developed anastomotic defects. The distribution of endoscopy scores between the two groups anastomotic defect vs. no anastomotic defect was significantly different.

Histopathology assessment of biopsies from the top of the gastric tube had low predictive value for anastomotic defect. Biopsies with a histopathology score of 0 or 1 indicated low probability for development of anastomotic defect (negative predictive value 0.85)

Multiple logistic regression identified the combined endoscopy score as the only predictive factor for anastomotic defect.

## Paper V

59 of the 60 included patients were available for analysis. S-MD of the gastric tube reconstruction after Ivor Lewis esophagectomy was feasible in a clinical setting. Attachment and removal of the MD probes was uncomplicated. 11 patients were diagnosed with anastomotic defects according to ECCG definitions and 11 patients had no postoperative complication. The remaining 37 patients had complications not related to the anastomosis.

Technical failure of the microdialysis procedure was high. At 24 hours after the surgical procedure was completed, 14 % of the MD-probes did not produce dialysate and hence 48 of the 59 patients were included in the analysis at this time point. Technical failure increased over time and for this reason data from the first four postoperative days were analysed.

ANN modelling of MD data identified MD measurements from the first postoperative day as having the highest predictive value for anastomotic defect. The final ANN model had up to 100% correct predictions (85-100% depending on how data was randomized to training or testing).

MD data from the first operative day was also analysed by a logistic regression study. This confirmed predictive value for MD measurements in relation to anastomotic defect, but were less accurate than the ANN model with 55,6% correct predictions of anastomotic defect and 97,4% correct predictions for absence of anastomotic defect.

The difference between the esophageal and conduit probe (E vs. C), was analysed. A tendency to larger delta values in the AD group was shown but the difference was not statistically significant.

# Discussion

"Everyone has his day, and some days last longer than others." Winston Churchill

## Surface microdialysis

### Paper I

This study indicates that S-MD measurements can be used to detect ischemia in bowel. It is the first paper to use S-MD on bowel. Metabolic change was rapid and could be detected at the first measurements at 20 minutes after inducing ischemia. Elevation in concentrations of lactate and decrease in glucose concentrations in the ischemic segment were the most pronounced findings. The probe site at the middle of the ischemic segment was significantly separated from other probe sites for lactate and glucose concentrations. Pyruvate and glycerol concentration change was overall less pronounced. The largest difference from baseline was seen in the middle of the ischemic segment and not in probe sites on bowel closer to normal circulation.

Glucose is used by the cell to produce energy, as some might remember. Glucose is transported into the cell and converted to pyruvate through glycolysis. In aerobic conditions pyruvate is used through the citric acid cycle and the electron transport chain to produce energy, carbon dioxide and water. In anaerobic conditions pyruvate is instead used to produce energy and lactate.

In the ischemic segment the mesentery was completely divided along the bowel to prevent any blood flow to and from the segment creating a totally anaerobic environment. Hence no metabolic substances could be delivered to or escape from the segment.

A totally hampered blood flow to the bowel segment prevents further glucose delivery. As glucose is consumed through glycolysis producing pyruvate, local glucose is depleted indicated by the decrease and plateau of glucose concentration from 60 minutes on.

Early elevation and plateau of lactate concentration from 60 minutes on in the experiment indicates rapid metabolic depletion of its substrate pyruvate as seen in the decreased levels of pyruvate with a similar plateau phenomenon from 2 hours on. According to these observations the metabolic transition from aerobic to anaerobic metabolism is complete within one hour after inducing ischemia.

Blood samples from central venous blood showed no change in hemoglobin, white blood cell count or lactate during the experiment. This indicates that an ischemic bowel segment is not discovered by systemic blood tests the first 4 hours of ischemia. Since the mesentery was divided there was no venous blood flow from the ischemic segment to central venous blood. This can be an explanation for white blood cell count and lactate remaining at constant levels. The experimental time (four hours) can also be too short for detectable change in concentrations in central venous blood.

Microdialysis measurements are very specific for the environment in close vicinity of the semipermeable membrane.[72, 73] The results of these S-MD measurements should be interpreted considering that the concentrations of metabolic substances are measured from the ischemic organ rather than the peritoneal cavity. All earlier studies on abdominal microdialysis use conventional microdialysis probes which measures the peritoneal fluid and hence are not organ specific.

### Paper II

This study shows that S-MD measurements from a gastric tube model can detect and to some degree grade ischemia of the stomach. The S-MD probes can be attached and pulled off from the surface of the gastric tube with minimal injury to the tissue. It indicates that this method to measure concentrations of metabolic substances could be used in a clinical setting.

Metabolic change was rapid, glucose concentrations reaching a plateau level at 60 minutes after inducing ischemia, as described in paper I. The difference in concentration of lactate and glucose was statistically significant compared to baseline during the experiment but the difference between probe sites was not significant at most time points. There was a tendency for larger change from baseline at the top of the gastric tube compared to the middle section of the gastric tube for both substances. This could be explained by the partially preserved blood flow to the middle section of the gastric tube at the level of division of the right gastroepiploic artery. The intervention with intravenous fluid was not successful in raising mean arterial pressure or central venous pressure. It is not possible to conclude if the decrease in lactate measured by the S-MD probe at the top of the gastric tube was caused by the intravenous fluid intervention. However, it is possible that increased intravenous fluid volume could affect local tissue perfusion.

In this experiment metabolic change seemed to occur also in the control probe sites. Lactate change was measured in the small bowel control probe (no intended manipulation of blood flow) but not in the conventional probe in the peritoneal cavity. A tendency to decrease in glucose concentration was measured by all probes, even from the peritoneal cavity. It is possible that the extensive manipulation of the stomach in this experiment, including dividing all but one vessel to the stomach, can change the splanchnic hemodynamic as indicated by these measurements.[74] This question has not been addressed in this thesis.

### Weaknesses paper I and II

Small number of experimental animals rendered large confidence intervals for the mean values of concentration of metabolic substances. This made definite conclusions difficult especially for difference in concentrations between probe sites.

The microdialysis membrane of the S-MD probe is manufactured with a plastic cover leaving only the side intended to be placed on the tissue surface open for dialysis. We speculate that this eliminates contamination of the dialysate from surrounding fluids and specifically measures the metabolism of the target organ. This has not been investigated in these studies. It is also possible that the microdialysis membrane loses contact with the organ surface after attachment. In these experiments we could observe that the probes were still in place at the end of the experiment but a space between the organ surface and the dialysis membrane could have occurred. In spite of this, it seems reasonable that the S-MD probes are more tissue specific than conventional MD-probes where the microdialysis membrane is exposed circumferentially.

The technical failure rate was relatively high with malfunction of 1-2 probes in each experiment. Microdialysis is highly sensitive to technical failure due to small caliber in- and outflow tubes, delicate dialysis membranes and low perfusion rate. This affects the possible use of the method in a clinical setting.

In paper II the intervention with intravenous fluids interfered with interpretation of the results. Results could have been clearer without this intervention. The question if local tissue perfusion and ischemia can be changed by hemodynamic intervention remains to be answered.

### Paper V

This was initiated as the first attempt to use S-MD in humans. The method was feasible and safe in a clinical setting. Technical failure rate was high and this must be improved if S-MD shall be used in further studies.

Our hypothesis was that insufficient blood-flow to the proximal part of the gastric tube impairs anastomotic healing and would be detectable with S-MD before an anastomotic defect is clinically detectable. It is not known if one severe incident of poor local perfusion could lead to an anastomotic defect, or if less dramatic disturbances of the blood-flow over several days has more impact on the anastomotic healing. This study cannot clarify this question but it shows that local metabolism during the first 24 hour affects development of an anastomotic defect. This is important for several reasons. First, S-MD can give an early “warning sign” of anastomoses at risk and could be helpful in postoperative management. Secondly, it is possible that optimizing patient physiology during the first days after esophagectomy could lead to less anastomotic defects. Thirdly, early warning could be important in early detection and early treatment of anastomotic defects which can limit the clinical consequences of the complication.

The results must be interpreted considering the small number of participants in each group but the method seems promising in discriminating between a normal postoperative recovery and development of anastomotic defects.

The difference between the esophageal and the conduit probe was not statistically significant. We expected larger differences since necrosis of the anastomotic area affects the gastric conduit and other studies have indicated reduced blood flow to the anastomotic area of the gastric tube.[9, 27] Several possible reasons for this can be discussed. First, blood flow to the anastomotic area of the gastric tube is probably highly variable in different locations on the circumference of the anastomosis as some reports indicate.[8, 10] If the microdialysis membrane is not in the local ischemic area it will not indicate anaerobic metabolism and the focal necrosis will be undetected by the microdialysis probe. Secondly, the metabolism of the esophageal remnant has not been a matter of concern since it rarely, if ever, exhibits any ischemic signs on postoperative endoscopy. It is possible that the esophageal remnant is less vulnerable to anaerobic metabolism and that equal anaerobic conditions on each side of the anastomosis produces different tissue damage, necrosis, in the esophagus and the gastric tube. Thirdly, it is possible that the small number of patients in each group is the reason why an actual metabolic difference cannot be shown.

MD lactate and glucose concentrations exhibited the largest difference between esophageal and conduit probes in the anastomotic defect group. Pyruvate concentrations were not separated between the probes. This is similar to results in paper I and other reports on surface microdialysis.[70, 71] Reports on conventional microdialysis in abdominal surgery have shown diverging results with higher glucose concentration associated with postoperative complication. [61, 65] One possible explanation for this is that surface microdialysis specifically measures concentrations of substances in the target tissue whereas peritoneal microdialysis measures substances in the peritoneal fluid, more likely not specific of the organ of interest.

### Weaknesses paper V

Small number of participants which limits generalisability.

High rate of technical failure limiting the usefulness of the method in clinical practice.

It is not possible to control if the microdialysis membrane is in continuous contact with the target organ. It could be dislocated after placement rendering erroneous results.

Results are presented for the first four postoperative days only. It would be interesting to analyse how local metabolism develops over time but results from this study are limited by an increasing rate of technical failure over time making analysis of data difficult.

## Endoscopic prediction of anastomotic leakage.

### Paper IV

Recent reports have shown promising results for early postoperative endoscopy in assessment of the anastomosis and prediction of anastomotic complications post-esophagectomy.[12, 25, 26] Based on our clinical experience in managing anastomotic complications we invented a scoring system for assessment of the anastomosis and investigated if this scoring system would have any predictive value. We also investigated if biopsies from the gastric tube could be predictive of anastomotic complications. The main idea behind our understanding and prevention of anastomotic defects is that ischemia of the anastomotic area causes necrosis and poor healing. There has not been any standard method to investigate local tissue perfusion over time in a clinical setting. Local blood flow of the gastric tube has been studied in the perioperative time period by different methods of which indocyanine fluorescence seems to be most widely used.[8-11, 14, 27] Surface microdialysis may be one possible surveillance method.

Endoscopic evaluation and scoring depends on the endoscopists experience and how an endoscopy finding is interpreted and judged. The combined endoscopy score defines three distinct locations of the gastric tube reconstruction and a simple three-grade score to make assessment uniform. In our study the endoscopy scoring was predictive of future anastomotic defects.

Biopsies from the gastric tube in vicinity of the anastomosis could not be used in predicting AL. Sensitivity was low. Biopsies with a histopathology score of 0 or 1, showed a negative predictive value for AL of 0.85. Based on this study biopsies from the gastric tube can be taken even in close vicinity of the anastomosis without immediate complication (perforation) but it is not useful in predicting anastomotic defects.

### Weaknesses

The operating surgeons were the same individuals performing the endoscopy and the scoring, with a possible risk of bias. However the endoscopy videos were blinded to patient identification in an attempt to reduce this factor.

Endoscopic assessment and scoring sometimes leaves room for interpretation. In our experience with this score the main difficulty is judging whether a defect should be graded as 1 (signs of ischemia) or 2 (necrosis). Normal appearance (0) and obvious necrosis (2) are distinct findings but the decision between 1 and 2 is sometimes difficult. We scored the videos in consensus trying to minimize this problem.

The endoscopy score and the clinical outcome are different, but interfering, entities. There is a risk that the endoscopy assessment will influence the assessment and management of the postoperative rehabilitation even if there are no other signs or symptoms of a clinical problem.

## Economic consequences of anastomotic leakage

### Paper III

This is the first study on health economic consequences of complications after esophagectomy in Sweden. The study shows increasing health care cost with increasing severity of complications. From a health-economy perspective reducing major complications would reduce the total health care costs for esophagectomy. This concurs with the strict medical perspective that reducing severe complications off course means improving mortality rates and postoperative comorbidity. Based on this, preventive measures should be directed towards the most severe and the most common complications. The highest cost of complication was associated with anastomotic leakage, laryngeal nerve palsy and pneumonia. This stresses some important points in the surgical treatment of esophageal cancer:

For anastomotic leakage there are no specific preoperative predictive factors which can help in tailoring treatment. Reducing AL seems difficult since measures taken so far have not been successful enough with AL rates remaining high. Surgical technique in the construction of the anastomosis is of paramount importance. Recently, reports show increased rates of AL after minimal invasive esophagectomy.[41, 75] It seems that early detection and (minimally invasive) treatment is important in reducing the consequences of AL.[25, 26]

For laryngeal nerve palsy, meticulous surgical technique in identification and avoidance of the nerve is probably the most important measure to improve complication rates. Minimally invasive thoracic dissection with thoracoscopic or robotic surgery seems to be of importance.[76]

For pneumonia minimally invasive surgery and intensive postoperative mobilization through different enhanced recovery programs is important in avoiding this complication. [16, 75]

### Weaknesses

Cost of reoperation could not be separated from cost of initial surgery rendering a higher cost of initial surgery for the group with major complications.

The health care consumption in the RSVD register and costs connected to it is based on ICD-codes (diagnoses) from the patients´ record. Correct and detailed ICD-codes is sometimes missing making the extracted data inaccurate. (Pneumonia for example could be a minor problem with complete patient recovery after one weeks treatment with antibiotics or it could indicate pulmonary aspiration and ICU-treatment for several weeks.)

The small number of participants in this study makes general conclusions difficult, however the results are in line with a similar study.[24]

The study focus is the direct health care costs not taking into consideration the secondary effect on society, for example costs for sick leave and loss of production for informal caregivers.

# Conclusion

"Every day you may make progress. Every step may be fruitful. Yet there will stretch out before you an ever-lengthening, ever-ascending, ever-improving path. You know you will never get to the end of the journey. But this, so far from discouraging, only adds to the joy and glory of the climb." Winston Churchill

I conclude that S-MD can be used on the gastrointestinal tract to detect ischemia. It can be used in a clinical setting after esophagectomy as surveillance of an intrathoracic anastomosis and microdialysis measurements from the first postoperative day can indicate future anastomotic defects.

Early postoperative endoscopy and the combined endoscopy score can predict development of anastomotic defects.

Postoperative complications add suffering and increased health care consumption which increases costs after surgical treatment. Reducing postoperative complications is important in improving patient outcome after surgery and reducing health care cost for society.

# Future perspectives

“If you’re going through hell, keep going.” Winston Churchill

## Preoperative prediction

Oncological and surgical treatment of esophageal cancer continues to improve but the treatment is associated with risks of complications, long-time morbidity and risk of recurrent disease. The benefit of treatment must be weighed against these factors. It would be of great value if preoperative factors could be used in determining the best treatment for the individual patient. The complexity in assessing interfering factors´ impact on outcome has made this difficult so far. The use of artificial intelligence to support decision making is a developing field in medicine. Artificial intelligence and artificial neural networks seem like possible methods to improve selection of treatment and thereby improving outcome after treatment for each patient. Studies on large numbers of patients require advanced technology and high-quality registers but seem possible with multi-centre and multi-professional collaboration.

## Preoperative preparation - prehab

The process of patient preparation before surgery attracts increasing interest in perioperative research. Optimizing patient nutrition, physical ability and timing of surgery in relation to patient status and oncological treatment seems important in improving outcome after surgery. Making the best out of a complex situation with problems related to the disease itself and the neoadjuvant oncology treatment requires multi-professional dedicated teams in caring for these patients. Research in this field would probably also benefit from multi-professional research teams.

## Postoperative surveillance and intervention

Postoperative surveillance aims at detection of possible postoperative problems. If an emerging problem can be detected early, intervention can sometimes be initiated to prevent the problem from developing into a complication. Highly sensitive and specific surveillance methods are needed. Surface microdialysis can be used in postoperative surveillance of an anastomosis but more research on larger populations must be done before S-MD can become a clinical tool. Problems with high rate of technical failure must be addressed.

If a postoperative complication cannot be prevented, early detection is important since early treatment can limit the consequences of complications. In esophageal surgery minimally invasive and endoscopic treatment is becoming the standard first line option in many cases of anastomotic complications. AL rates still remain high but the consequences of AL can be reduced by early minimally invasive treatment. This possibility stresses the importance of early detection.

More research on early detection and treatment of (emerging) complications is imperative to improve patient outcome.

# Populärvetenskaplig sammanfattning

"This is the lesson: never give in, never give in, never, never, never, never -- in nothing, great or small, large or petty -- never give in except to convictions of honour and good sense. Never yield to force; never yield to the apparently overwhelming might of the enemy." Winston Churchill

En esofagektomi -en operation som innebär att hela eller delar av matstrupen opereras bort- är ett omfattande kirurgiskt ingrepp som innebär lång återhämtningstid för patienten samt risk för att komplikationer uppkommer efter ingreppet. Operationen utförs oftast för att behandla matstrupscancer. Esofagektomi med samtidig rekonstruktion av mag-tarmkanalen utvecklades under mitten av 1900-talet och omgärdades i början av hög risk för komplikationer och död i samband med ingreppet. Utveckling inom flera områden, anestesi och intensivvård, kirurgisk teknik och medicinteknik, postoperativ vård, diagnostik och interventioner har tydligt förbättrat patienters möjligheter att överleva operationen och återhämtningen med bibehållen livskvalitet. Även om risk för död i samband med ingreppet nu för tiden är låg (2-4%) så kvarstår betydande risker för allvarliga komplikationer i återhämtningsfasen. Upp till 60% av patienter som genomgått esofagektomi drabbas av någon sorts komplikation varav cirka hälften anses allvarliga med behov av ytterligare ingrepp eller åtgärder. I internationella sammanställningar är några av de vanligaste komplikationerna: lunginflammation 15%, hjärtrytmrubbningar 15%, anastomosläckage 12%, lymfläckage 5%, stämbandsförlamning pga nervskada 5%.

Den vanligaste operationsmetoden för matstrupsresektion är Ivor Lewis esofagektomi där magsäcken görs om för att kunna ersätta den del av matstrupen som tas bort. Den omgjorda magsäcken, ventrikeltuben, kopplas ihop, anastomoseras, med kvarvarande matstrupe i höger bröstkorgshalva. Denna rekonstruktion innebär att många blodkärl till ventrikeltuben måste delas och de kvarvarande blodkärl som försörjer ventrikeltuben kommer från bukhålan. Det i sin tur innebär en risk för dålig blodförsörjning till anastomosen mellan matstrupe och ventrikeltub.

Att i förväg prognosticera vilken patient som kommer att drabbas av postoperativa komplikationer är svårt. Allmänt kan sägas att hög ålder och andra samtidiga sjukdomar som påverkar organens funktion ökar risken för komplikationer. Att i förväg kunna beräkna den enskilde individens risk för komplikationer efter esofagektomi hade varit mycket värdefullt och hade varit en hjälp för optimering och individualisering av behandling av matstrupscancer. Dock utelämnar en sådan bedömning en betydande del i förloppet, nämligen själva det kirurgiska ingreppet och de postoperativa vårdinsatserna och det är möjligt att det är denna faktor som i själva verket är mest avgörande.

Med bakgrund i ovanstående inriktas det kliniska arbetet med att minska riskerna med matstrupskirurgi mot själva ingreppets utförande och den postoperativa återhämtningen. I vårdförloppet efter matsupskirurgi övervakas patienten noga för att eventuella komplikationer skall upptäckas tidigt så att behandlingsåtgärder kan insättas så snart som möjligt. Tidig behandling av komplikationer har ofta god prognos medan ett förlopp där komplikationen inte upptäcks eller rätt behandling inte insätts i tid kan leda till allvarliga konsekvenser för patienten.

Arbetena i denna avhandling syftar till att bättre kunna upptäcka risk för komplikationer för den enskilde patienten samt beskriva de ekonomiska konsekvenserna som esofagektomi och komplikationer därtill innebär för samhället.

I delarbete 1, 2 och 5 har vi utvärderat och utvecklat en ny teknik, yt-mikrodialys, för att kunna mäta ämnesomsättningen lokalt i operationsområdet efter operationen. Teorin bakom detta är att otillräckligt blodflöde till anastomosområdet ger förändrad (anaerob) ämnesomsättning och detta förutspår dålig läkning med risk för utveckling av anastomosläckage. Tidig indikation på förändrad ämnesomsättning skulle kunna leda till tidig behandling där konsekvenserna för patienten mildras.

I delarbete 1, som är en djurstudie på gris, har vi visat att yt-mikrodialys som metod fungerar för att mäta ämnesomsättning lokalt i tunntarm. Tidigare studier har visat metodens användbarhet på solida organ (lever, hjärta, bukspottskörtel) men delarbete 1 är första gången som denna teknik används på magtarmkanalen. Vi har visat att vi med hjälp av yt-mikrodialys kan uppmäta skillnader i ämnesomsättningen i tarm med normal blodförsörjning jämfört med tarm med upphävd blodförsörjning.

I delarbete 2, också en djurstudie på gris, har vi försökt efterlikna de kirurgiska förutsättningarna vid esofagektomi med ventrikeltubsrekonstruktion. Vi har skapat en kirurgisk modell för nedsatt blodförsörjning i en del av ventrikeltuben. Vi har visat att yt-mikrodialys går att applicera på ventrikeltub och att skillnader i ämnesomsättning lokalt i vävnaden i ventrikeltuben går att uppmäta i områden med god jämfört med dålig blodförsörjning.

I delarbete 5 har vi använt yt-mikrodialysmetoden för att mäta ämnesomsättningen lokalt i anastomosområdet efter esofagektomi under de sju första dagarna efter operationen. Vi har visat att metoden är användbar och säker i en klinisk situation. Vi har visat att mätvärden från ventrikeltuben första dagen efter operationen kan förutspå anastomosdefekt. Analysen av mätdata är gjord med hjälp av artificiellt neuralt nätverk som har fördelen att förutsättningslöst kunna komma fram till vilka värden och vilken tidpunkt i förloppet som har störst värde för prediktion. Studien påvisar också att en relativt hög andel av yt-mikrodialyskatetrarna slutade att fungera under studiens gång vilket ledde till uteblivna mätningar.

I delarbete 3 har vi redogjort för kostnader i region Skåne för matstupskirurgi och komplikationer. Samhällets totala sjukvårdskostnader för en matstrupsoperation utan komplikationer uppgår till cirka 335 000 kr. Om en allvarlig komplikation tillstöter ökar kostnaderna till cirka 808 000 kr. De komplikationer som innebär högst kostnad är anastomosläckage (cirka 1 021 000 kr), stämbandsförlamning pga nervskada (cirka 773 000 kr) och postoperativ lunginflammation (cirka 686 000 kr). (Ovanstående summor anges som medianvärde.) Slutsaterna av detta är att arbete med att förebygga och minska komplikationer efter matstrupskirurgi är viktigt inte bara för den enskilde patientens hälsa utan även för samhällsekonomin.

I delarbete 4 har vi undersökt den kirurgiska rekonstruktionen och anastomosen med endoskopi (kameraundersökning) dag 7 efter operationen. Vi har utvecklat och använt en ny skala baserad på det endoskopiska utseendet, för att bedöma risk för utveckling av anastomosdefekt. I detta arbete visas att vi med hjälp av endoskopiundersökning och bedömning av utseendet i rekonstruktionen dag 7 efter operationen, kan förutsäga utveckling av anastomosdefekt. Detta arbete ger möjligheter till prediktion och tidig behandling av anastomosdefekt vilket kan mildra konsekvenserna av komplikationen.

Sammanfattningsvis kan sägas att delarbetena i denna avhandling visar att det finns ett stort värde för patienter och samhället i att försöka förebygga postoperativa komplikationer. Vi har visat att det med hjälp av yt-mikrodialys och postoperativ endoskopisk undersökning går att prediktera utveckling av anastomosdefekt. Detta ger bättre möjlighet till tidig upptäckt och tidig behandling av anastomosdefekt vilket kan lindra konsekvenserna av denna komplikation.

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"Writing a book is an adventure. To begin with it is a toy then an amusement. Then it becomes a mistress, and then it becomes a master, and then it becomes a tyrant and, in the last stage, just as you are about to be reconciled to your servitude, you kill the monster and fling him to the public." Winston Churchill

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