From DEPARTMENT OF CLINICAL SCIENCE, INTERVENTION AND TECHNOLOGY (CLINTEC), DIVISION OF SURGERY
Karolinska Institutet, Stockholm, Sweden

NUTRITIONAL STATUS AND DYSPHAGIA IN PATIENTS WITH OESOPHAGEAL CANCER – THE IMPACT OF ONCOLOGICAL AND SURGICAL TREATMENT

Jessica Ericson

Stockholm 2021

Published by Karolinska Institutet.
Printed by Universitetsservice US-AB, 2021

ISBN 978-91-8016-044-5

Nutritional status and dysphagia in patients with oesophageal cancer – the impact of oncological and surgical treatment
THESIS FOR DOCTORAL DEGREE (Ph.D.)

By

Jessica Ericson

The thesis will be defended in public at Lecture hall B 64 in Karolinska University Hospital, Huddinge

Friday April 16th, 2021 at 09.00

Principal Supervisor:
Associate Professor Ioannis Rouvelas
Karolinska Institutet
Department of Clinical Science, Intervention and Technology
Division of Surgery

Co-supervisors:
Professor Magnus Nilsson
Karolinska Institutet
Department of Clinical Science, Intervention and Technology
Division of Surgery

Associate Professor Mats Lindblad
Karolinska Institutet
Department of Clinical Science, Intervention and Technology
Division of Surgery

Opponent:
Professor Tommy Cederholm
Uppsala University
Department of Public Health and Caring Sciences
Clinical Nutrition and Metabolism

Examination Board:
Associate Professor Robert Bränström
Karolinska Institutet
Department of Molecular Medicine and Surgery
Division of Endocrine Surgery

Associate Professor Folke Hammarqvist
Karolinska Institutet
Department of Clinical Science, Intervention and Technology
Division of Surgery

Associate Professor Lars Ellegård
University of Gothenburg
Department of Medicine
Division of Internal Medicine and Clinical Nutrition

To Kenneth, Simon, Ebba.

POPULAR SCIENCE SUMMARY OF THE THESIS

Oesophageal cancer is the seventh most common cancer globally and there are two major subtypes, adenocarcinoma, and squamous cell carcinoma. The major risk factors for adenocarcinoma are obesity and reflux of acid and for squamous cell carcinoma tobacco smoking and overconsumption of alcohol. The most common symptom of oesophageal cancer is difficulty swallowing (dysphagia) due to obstruction of the oesophagus caused by the tumour. Consequently, weight loss at time of diagnosis is very common. Pain while swallowing (odynohagia) is another common symptom affecting the food intake. Dysphagia to solid food might not occur until two-thirds of the oesophageal lumen is involved by the tumour. This late onset of symptoms results in an advanced stage of the disease at time of diagnosis.

Curative intent treatment of oesophageal cancer depends on tumour stage and most commonly combines oncological pretreatment (chemotherapy or chemotherapy combined with radiotherapy), so-called neoadjuvant treatment, followed by surgery where most part of the oesophagus is removed. Stomach is the most common organ used to replace oesophagus with and is often transformed to a tube. Malnutrition due to the difficulties to eat is a risk factor for compliance to neoadjuvant treatment and is associated with complications after surgery.

The surgical procedure, oesophagectomy, is an extensive operation due to the anatomical location of the oesophagus and it often involves surgery in the abdomen, the chest, and sometimes in the neck. During the last years several minimally invasive techniques have been developed and gained popularity aiming to minimize the surgical trauma. Several studies report weight loss up to 12% during the first six months after oesophagectomy. This is partly due to the altered anatomy including the removal of the lower oesophageal sphincter and the reduction of the volume of the stomach, which is pulled up into the chest, and partly due to faster bowel movements as a result of vagotomy. Furthermore, the aforementioned changes result in reflux, delayed gastric emptying, dumping syndrome, diarrhoea, appetite loss and eating difficulties.

The purpose of this thesis was to investigate how patients` dysphagia is affected by the neoadjuvant treatment and if patients who undergo minimally invasive oesophagectomy lose less weight compared to those who undergo open surgery. Moreover, how energy intake, total energy expenditure and body weight might change before and after neoadjuvant treatment as well as after oesophagectomy. Finally, we wanted to explore whether patients with prolonged time to surgery after completed neoadjuvant treatment have a better weight and dysphagia development compared to patients with standard time to surgery, and if patients malnourished at diagnosis suffer from less postoperative complications in case they have a prolonged time to surgery after neoadjuvant treatment.

In **study I** we assessed patients before, during and after neoadjuvant treatment regarding dysphagia. We found that there was a significant improvement in dysphagia already after the first week of chemotherapy and the patients were able to swallow more solid foods. Further improvement was noted after completion of neoadjuvant treatment before surgery. This study suggests awaiting the effect of chemotherapy, before decision-making whether a patient is in need of insertion of stent or feeding tube prior to surgery to secure nutrition intake.

In **study II** we compared the weight loss during first year after oesophagectomy between minimally invasive techniques and traditional open surgery. We could not find any significant difference in weight loss between the groups. However, patients operated with minimally invasive surgery seemed to lose less weight compared to patients operated with open surgery in case of severe postoperative complications, but the difference wore off 6 months after surgery.

In **study III** we looked at total energy expenditure in relation to energy intake and weight development before and after neoadjuvant treatment and at 3 and 6 months after oesophagectomy. We found a negative energy balance at baseline and at 3 months after surgery. Weight decreased at all time points compared to baseline with the greatest weight loss three months after surgery.

Study IV was part of a larger randomized controlled trial comparing patients with either standard (4-6 weeks) or prolonged (10-12 weeks) waiting time to oesophagectomy after completed neoadjuvant treatment. We wanted to evaluate if prolonged delay to surgery had a positive effect on patients´ weight and dysphagia development. Patients in the standard time to surgery group lost significantly more weight between completion of neoadjuvant treatment and surgery compared to the group with delayed time to surgery that increased their weight significantly during the prolonged time and did almost have the same weight as before the start of treatment. Dysphagia improved significantly in both groups between start of treatment and operation. Furthermore, we specifically compared patients malnourished before the start of treatment between the two groups with regards to complications after surgery and no difference could be demonstrated.

In summary, dysphagia improved significantly during neoadjuvant treatment suggesting that dietary modifications may be sufficient with no need of tube feeding or stenting before surgery. Nutritional interventions and follow up are important to maintain or improve energy intake and prevent weight loss already at the time of diagnosis, during the neoadjuvant treatment and during the first three months after surgery. Prolonged time to surgery after completed neoadjuvant treatment was beneficial for patients´ weight gain.

POPULÄRVETENSKAPLIG SAMMANFATTNING AV AVHANDLINGEN

Cancer i matstrupen (esofagus) är den sjunde vanligaste cancerformen i världen. Det finns två huvudtyper av matstrupscancer; adenocarcinom och skivepitelcancer. Huvudsakliga riskfaktorer för adenocarcinom är övervikt och långvarigt problem med magsaft som backar upp i matstrupen (refluxsjukdom) och för skivepitelcancer är det främst rökning och överkonsumtion av alkohol. Det vanligaste symtomet på matstrupscancer är svårighet att svälja (dysfagi) vilket beror på att tumören hindrar passagen genom matstrupen och patienterna har ofta förlorat mycket i vikt vid diagnos. Smärta vid sväljning (odynofagi) är ett annat vanligt symtom som påverkar matintaget. Det är först när två tredjedelar av matstrupslumen påverkas av tumören som man får svårighet att svälja fast föda vilket resulterar i att många söker läkare först i ett sent skede av sjukdomen.

Botande behandling av matstrupscancer beror på tumörstadium som oftast består av en kombination av onkologisk förbehandling (cytostatika eller cytostatika kombinerad med strålning), så kallad neoadjuvant behandling, och därefter opereras större delen av matstrupen bort. Matstrupen ersätts oftast med en del av magsäcken som görs om till en tub. Undernäring till följd av svårigheterna att äta ökar risken för att inte kunna fullfölja den onkologiska förbehandlingen samt är förknippat med komplikationer efter operation. Bortopererandet av matstrupen, esofagektomi, är en stor och omfattande operation där man opererar både i brösthålan, i bukhålan och ibland även vid halsen. På senare år har titthålskirurgi (minimalinvasiv kirurgi) utvecklats och blivit allt mer populär för att minska det kirurgiska traumat. Många studier rapporterar upp till 12 % viktförlust under de första sex månaderna efter operationen. Viktförlusten beror delvis på den förändrade anatomin där man inte längre har någon övre magmun, en mindre magsäck som är uppdragen i brösthålan och snabbare tarmrörelser p.g.a. att man delat vagusnerven. Detta resulterar i långsammare magsäckstömning, reflux, dumping, diarré, aptitlöshet och ätsvårigheter.

Syfte med denna avhandling var att undersöka hur patienternas dysfagi påverkas av den neoadjuvanta behandlingen, om viktförlusten efter esofagektomi minskar efter minimalinvasiv kirurgi jämfört med öppen kirurgi. Vidare om energiintag, total energiförbrukning och kroppsvikt före och efter neoadjuvant behandling samt efter esofagektomi förändras. Slutligen ville vi utforska om patienter som väntar längre tid på kirurgi efter avslutad neoadjuvant behandling har en bättre vikt- respektive dysfagiutveckling.

I **delstudie I** följde vi patienter före, under och efter neoadjuvant behandling avseende dysfagi. Vi kunde se att dysfagin minskade signifikant redan efter den första veckans cytostatikabehandling och patienterna kunde svälja mat i fastare konsistens. Sväljförmågan förbättrades sedan ytterligare under den neoadjuvanta behandlingen fram till esofagektomin. Denna studie visade att man kan avvakta effekt av cytostatikabehandlingen innan man fattar beslut om stenting (rör i matstrupen) eller inläggning av matningsslang in i magsäcken för att säkerställa näringsintaget i väntan på operation.

I **delstudie II** jämförde vi viktförlust under första året efter esofagektomi mellan olika operationstekniker: minimalinvasiv kirurgi och traditionell öppen kirurgi. Resultatet visade inte någon signifikant skillnad i viktförlust mellan de olika grupperna. Patienter som opererades med minimalinvasiv kirurgi minskade mindre i vikt jämfört med de som opererades med öppen kirurgi i de fall de fick allvarliga komplikationer efter operationen, skillnaden försvann dock vid 6 månader efter operation.

I **delstudie III** undersökte vi den totala energiförbrukningen i relation till energiintag samt viktutveckling innan och efter neoadjuvant behandling samt 3 och 6 månader efter esofagektomi. Kroppsvikten minskade signifikant vid varje mättillfälle jämfört med baslinjen medan den största viktnedgången sågs 3 månader efter operationen. Vi såg en negativ energibalans vid baslinjen och vid 3 månader efter operationen.

Delstudie IV var en del av en större randomiserad kontrollerad studie där man jämförde patienter med standard (4–6 veckor) eller fördröjd (10–12 veckor) väntetid till esofagektomi efter avslutad neoadjuvant behandling. Vi ville undersöka om den längre väntan till operation kunde ha en positiv effekt på vikt- och dysfagiutvecklingen. Patienter med standardväntan till operation förlorade signifikant mer i vikt mellan avslutad neoadjuvant behandling och operation jämfört med gruppen med förlängd väntan som ökade sin vikt signifikant under den längre väntetiden och hade nästan samma vikt som innan start av behandling. Dysfagin förbättrades signifikant för både grupperna mellan behandlingsstart och operation. Vi delade också upp patienterna i undernärda eller ej innan start av behandling för att se om det var någon skillnad avseende komplikationer efter operationen vilket inte kunde påvisas.

Sammanfattningsvis så minskade patienternas dysfagi märkbart under den neoadjuvanta behandlingen vilket pekar på ett värde i att invänta effekten av cytostatikabehandlingen och under tiden konsistensanpassa maten. Nutritionsinsatser och uppföljning är viktigt för att bibehålla eller förbättra energiintag och förebygga viktförlust redan vid diagnostillfället, under den neoadjuvanta behandlingen samt under de tre första månaderna efter operation. Den förlängda tiden efter avslutad neoadjuvant behandling var fördelaktig för patienternas förmåga att öka i vikt.

ABSTRACT

The most common symptom of oesophageal cancer is difficulty swallowing, dysphagia, due to the tumour obstructing the oesophageal lumen often resulting in weight loss. In patients diagnosed with oesophageal cancer malnutrition is reported in 60-85%.
Neoadjuvant treatment with subsequent oesophagectomy is the standard curative intent treatment in most countries. Neoadjuvant treatment, either neoadjuvant chemoradiotherapy (nCRT) or perioperative chemotherapy (pCT), might cause further symptoms affecting nutritional intake and thereby cause weight loss.
Oesophagectomy is an extensive procedure where the oesophagus is removed and most often replaced with a gastric tube conduit affecting patients´ nutritional intake due to the altered anatomy. During recent years different minimally invasive techniques has been introduced in order to minimize the surgical trauma.
Most of the patients receive a feeding jejunostomy during surgery securing nutritional intake during the time they, often, are restricted from eating orally and during the time they increase their oral intake.

In **Study I** we assessed dysphagia in patients undergoing neoadjuvant treatment before oesophagectomy. Patients received either neoadjuvant chemotherapy (nCT) or nCRT, both with induction chemotherapy for 1 week. The dysphagia improved significantly after first cycle of chemotherapy with further improvements after completed neoadjuvant treatment. There was no correlation between dysphagia relief and histological response.

In **Study II** we compared weight development after open Ivor Lewis oesophagectomy to minimally invasive Ivor Lewis oesophagectomy (MIIL) or minimally invasive McKeown oesophagectomy (MIMK). We found no significant difference between weight development after the greater surgical trauma associated with open surgery and the minimally invasive approaches. We saw a non-significant trend towards a lower risk of 10% or more weight loss at 3 months after surgery in case of severe postoperative complications after MIIL compared to open IL.

In **Study III** we assessed the energy intake and the total energy expenditure (TEE) before and after neoadjuvant treatment and at 3 and 6 months after oesophagectomy. We found a negative energy balance at baseline and at 3 months after surgery. Mean weight decreased significantly at all time points compared to baseline with the greatest weight loss at 3 months postoperatively.

In **Study IV** we compared weight and dysphagia development between standard and prolonged waiting time to oesophagectomy after completed nCRT. We also compared patients malnourished or not at baseline in each group for risk of postoperative complications. Patients gained weight during the prolonged time to surgery and almost returned to the same weight as at baseline. Dysphagia improved significantly in both groups, with a further but nonsignificant improvement during the prolonged time to surgery. Malnutrition at baseline did not affect postoperative complications between the groups.

In conclusion, patients´ dysphagia improved during neoadjuvant treatment suggesting nutritional interventions as first line treatment awaiting effect of chemotherapy. There was no difference in weight loss between open and minimally invasive oesophagectomy. Results from this thesis also suggests that early nutritional interventions and follow up regarding energy and protein intake is important to maintain or prevent weight loss during the neoadjuvant treatment and during the first three postoperative months. We did also see a beneficial effect on patients´ weight development after prolonged time to surgery after completed neoadjuvant treatment compared to standard time to surgery.

LIST OF SCIENTIFIC PAPERS

I. Sunde B, **Ericson J**, Kumagai K, Lundell L, Tsai J, Lindblad M, Rouvelas I, Friesland S, Wang N, Nilsson M.
Relief of dysphagia during neoadjuvant treatment for cancer of the esophagus or gastroesophageal junction.
Diseases of the Esophagus, 2016, 29 (5), 442-447. PMID: 25809837.

II. **Ericson J**, Lundell L, Klevebro F, Kamiya S, Nilsson M, Rouvelas I.
Long-term weight development after esophagectomy for cancer – comparison between open Ivor Lewis and minimally invasive surgical approaches.
Diseases of the Esophagus, 2019, 32 (4), 1-9. PMID: 30351390.

III. **Ericson J**, Lundell L, Lindblad M, Klevebro F, Nilsson M, Rouvelas I.
Assessment of energy intake and total energy expenditure in a series of patients who have undergone oesophagectomy following neoadjuvant treatment.
Clinical Nutrition ESPEN, 2020, 37, 121-128. PMID: 32359733.

IV. **Ericson J**, Klevebro F, Sunde B, Szabo E, Halldestam I, Smedh U, Wallner B, Johansson J, Johnsen G, Kjus Aahlin E, Johannessen H-O, Hjortland G-O, Bartella I, Schröder W, Bruns C, Rouvelas I, Nilsson M.
Weight development, dysphagia, and malnutrition in patients with esophageal cancer – randomized comparison between standard and prolonged time to surgery after neoadjuvant chemoradiotherapy.
Manuscript.

CONTENTS

LIST OF ABBREVIATIONS

AC	Adenocarcinoma
ASA	American Society of Anaesthesiologists
BMI	Body Mass Index
BW	Body weight
C-D	Clavien Dindo score
EI	Energy intake
EN	Enteral nutrition
ERAS	Enhanced recovery after surgery
ERP	Enhanced recovery programme
ESPEN	The European Society for Clinical Nutrition and Metabolism
GLIM	The Global Leadership Initiative on Malnutrition
GI	Gastrointestinal
IC	Indirect calorimetry
IL	Open Ivor Lewis oesophagectomy (in study II)
MDT	Multidisciplinary team
MIO	Minimally invasive oesophagectomy
MIIL	Minimally invasive Ivor Lewis oesophagectomy
MIMK	Minimally invasive McKeown oesophagectomy
nCRT	Neoadjuvant chemoradiotherapy
nCT	Neoadjuvant chemotherapy
ONS	Oral nutrition supplements
PAL	Physical activity level
pCT	Perioperative chemotherapy
PN	Parenteral nutrition
POD	Postoperative day
RCT	Randomised controlled trial
REE	Resting energy expenditure
SCC	Squamous cell carcinoma
SWA	SenseWear Armband
TEE	Total energy expenditure

1 INTRODUCTION

Oesophageal cancer is the seventh most common cancer in the world and the sixth most common cause of cancer-related death globally and the 5-year survival for all diagnosed with oesophageal cancer is less than 20%. Only 30-40% of the patients are resectable at diagnosis (1) mainly due to the elasticity of the oesophagus resulting in late onset of symptoms and an advanced stage at the time of diagnosis contributing to the poor prognosis (2, 3). Dysphagia is the most common symptom (2), present in 90% of the patients (4), contributing to reduced oral intake and 60-85% of the patients are malnourished already at the time of diagnosis (5).

For patients diagnosed with oesophageal cancer the common practice in most centres for curative intent treatment is neoadjuvant treatment followed by surgery, oesophagectomy, (6-9) with an improved overall 5-year survival of nearly 50% compared to 33% in surgery alone group (9). The oncological treatment might give symptoms worsening nutritional intake (10, 11) but on the other hand, improvement in dysphagia after chemotherapy have also been observed (12, 13).

There are many complicating factors related to oesophagectomy, making it one of the procedures with the highest impact on patients' quality of life in the field of elective gastrointestinal (GI) surgery. During the recent years minimal invasive oesophagectomy (MIO) has become the standard approach in many countries (14) as a strategy to improve short-and long-term outcomes after oesophagectomy by minimizing the surgical trauma (6, 15-17) and with less postoperative complications (18).

Several studies report weight loss up to 12% during the first six months after oesophagectomy (19-21) and more than half of the patients have lost more than 10% of their preoperative weight at 12 months after surgery (19) which is partly due to the permanently altered anatomy when reconstructing the GI contingency. These changes are associated with long-term functional disorders affecting the nutritional intake negatively (22, 23).

Nutrition is an essential part in oesophageal cancer management (24) and the aim of this thesis was to contribute with more knowledge about the patients´ nutritional status according to different preconditions and at different time points during the treatment trajectory to be able to improve nutritional interventions.

The effect of neoadjuvant treatment on dysphagia was noticed by oncologists (25) but this effect was not examined prospectively; in **study I** we assessed patients´ dysphagia and weight development before and after neoadjuvant treatment.
The improvement in short- and long-term outcomes after minimal invasive oesophagectomy compared to open surgery has been studied and hypothetically patients might lose less weight after MIO, which we compared in **study II.**
Information of energy and protein intake in relation to total energy expenditure (TEE) before and after neoadjuvant treatment as well as after oesophagectomy is scarce so **study III** was conducted to explore this.

Further, in **study IV** we did evaluate if delayed time to surgery compared to standard time to surgery might have a positive effect on patients´ ability to improve weight and dysphagia and if malnutrition at baseline would affect the risk of postoperative complications between the groups.

2 BACKGROUND

2.1 OESOPHAGEAL CANCER

2.1.1 Epidemiology

In the 21st century cancer is expected to be the leading cause of death and single most important obstacle to increasing life expectancy in all countries in the world (26). Contributing reasons are aging, growth of the population and changes in prevalence and distribution of main risk factors associated with socioeconomic development.

Oesophageal cancer is the seventh most common cancer in the world and the sixth most common cause of cancer-related death globally, making it responsible for 1 in 20 cancer deaths in 2018 (26). Oesophageal cancer has a male dominance of 70% and the incidence increases with age (2, 26). There are two major histological subtypes of oesophageal cancer, squamous cell carcinoma (SCC) and adenocarcinoma (AC), were SCC accounts for 90% of the cases worldwide when AC is the most increasing type.

SCC is most common in East Africa, South America and the so-called oesophageal cancer belt beginning in northern China and stretches through central Asia to northern Iran while AC is especially prevalent in North America, Europe and Australia (2). The 5-year survival for all patients diagnosed with oesophageal cancer is less than 20%.

2.1.2 Risk factors

The geographic and socioeconomic differences in oesophageal cancer are strikingly between the two major subtypes (26, 27). The risk for SCC increases with recurrent chemical or physical injury to the oesophageal mucosa (2). The major risk factors for SCC in high-income countries are tobacco smoking and overconsumption of alcohol while in other parts suspected risk factors include betel quid chewing and thermal injury due to drinking very hot beverages (2, 26). In other lower income countries (parts of Asia and south of Sahara in Africa) the risk factors are not yet elucidated. Other contributing risk factors for SCC are low intake of vegetables and fruits, and deficiencies in micronutrient, for example vitamin A and vitamin E (2).

The declining incidence of SCC in certain areas in Asia may be derived from better economic preconditions and dietary improvements while the reduction in high-income countries presumably are caused by decline in cigarette smoking (26).

For AC the major risk factors in high-income countries are obesity, with central or visceral obesity, and gastro-oesophageal reflux of acid and/or bile (2, 26). Obesity can increase reflux by an increased intra-abdominal pressure. Both obesity and gastro-oesophageal reflux are associated with Barrett oesophagus, a preneoplastic tissue where squamous oesophageal epithelium is replaced by columnar intestinal-type mucosa (2). Tobacco smoking is a risk factor even for AC and so are male sex, high intake of red meat, and low intake of fruit and vegetables.

2.1.3 Clinical presentation

In early stages oesophageal cancer is often asymptomatic (28). The most common symptom of oesophageal cancer is difficulty swallowing, dysphagia, due to tumour obstruction (2, 29, 30) or combined with unintentional weight loss (often ≥10% in the preceding 3-6 months) (28). Other symptoms are odynophagia (pain when swallowing), new onset of dyspepsia, heartburn, chest pain or anaemia (28).

The late onset of symptom is due to the elasticity of the oesophagus where dysphagia to solids might not occur until two-thirds of the oesophageal lumen is affected by the tumour resulting to an advanced stage at the time of diagnosis which contributes to the poor prognosis (2, 3). Late symptoms indicating advanced tumour disease are hoarseness and severe cough caused by involvement of the left laryngeal nerve and tumour fistula from the oesophagus to the respiratory tract, respectively (31).

2.1.4 Diagnosis and staging

When patients present with symptoms indicating oesophageal cancer an endoscopy is performed, the gold standard for detection and diagnosis of oesophageal cancer, and biopsies of suspicious lesions are taken (2, 28). The next step is staging of the tumour performed by positron emission tomography (PET) together with computed tomography (CT) were CT is more sensitive to evaluating local-regional lesions and PET distant metastases (28).

If no distant metastases are detected an endoscopic ultrasonography can be performed to determine tumour depth and nodal involvement. Clinical and pathological staging is important for best treatment option and should be performed according to the TNM (tumour-lymph node-metastasis) classification. The final and appropriate treatment recommendation for each patient individually is based on a multidisciplinary team (MDT) meeting (31, 32) where comorbidities, physical performance and age are also taken into account (32).

2.1.5 Dysphagia

Dysphagia is present in 90% of the patients at the time of diagnosis (4) and seem to be the primary contributor to malnutrition rather than the metabolic effect from the tumour (33).

Dysphagia caused by tumour is referred to as oesophageal or “low” dysphagia, which is different from oropharyngeal or “high” dysphagia often seen in neurological patients (34).

There are special instruments to measure patient´s ability to swallow, where Ogilvie and Watson are the most common for low dysphagia assessment and have recently been validated for use in assessing dysphagia in oesophageal malignancy (35).

Ogilvie score grades dysphagia in five levels, 0=no dysphagia, 1=normal diet avoiding certain foods such as raw apple and steak, 2=semi-solid diet, 3=fluids only, 4=complete dysphagia even for liquids (36). The Watson scale consist of a composite score of questions evaluating ability and frequency of problems to swallow nine different types of foods and liquids: never, sometimes or always and thereafter adding the scores in the range 0-45 where 0=no dysphagia and 45=total dysphagia (37, 38). Ogilvie score is the most adapted clinical used instrument, also named as Atkinson (39) and Mellow Pinkas (40), and is also used in our clinic, Department of Upper Abdominal Diseases, Karolinska University Hospital, to grade patients' dysphagia.

Since neoadjuvant treatment prolongs the time from diagnosis to surgery problems may arise regarding the management of dysphagia to secure nutrition during the oncological treatment period until surgery. Earlier, self-expanding metal stents were frequently inserted to relieve dysphagia but they often migrated during neoadjuvant therapy (41). In 2016, the European Society of Gastrointestinal Endoscopy (ESGE) guidelines came with recommendation against self-expanding metal stents due to adverse events such as stent migration and chest discomfort (42), as well as complications which may compromise the opportunity for curative surgery (43).

Apart from oesophageal stents there are other ways to secure nutritional intake. In a review published in 2018 no optimal nutritional approach could be concluded among oesophageal stenting, feeding jejunostomy, gastrostomy or nasogastric feeding (44). Percutaneous endoscopic gastrostomy (PEG) placement may be contraindicated for oesophageal cancer patients scheduled to undergo a gastric tube reconstruction during oesophagectomy, and a nasogastric feeding tube for enteral nutrition (EN) support is therefore the preferred alternative (42).
A fast start of neoadjuvant treatment combined with close nutritional support can provide relief of dysphagia without invasive treatment (45).

2.2 TREATMENT

Surgical resection alone, oesophagectomy, has been the primary treatment for locally advanced oesophageal and junctional cancer for decades, but the prognosis postoperatively remained unsatisfactory leading investigators to evaluate the combination of chemotherapy, with or without radiotherapy, followed by surgery (46). Earlier studies had provided evidence for survival benefit for neoadjuvant treatment compared to surgery alone (7, 8).
Patients with cervical SCC are recommended definitive chemoradiotherapy, which can be considered an alternative standard of care for SCC of the mid and lower oesophagus (2).

For patients with unresectable tumours several options for palliative treatment are available including chemotherapy, external radiotherapy, local radiotherapy (brachytherapy), oesophageal stents, surgical placement of gastrostomy or jejunostomy (2, 28). The same applies to more than 50% of the patients initially treated with curative intent and later develop recurrence disease.

In this thesis only patients treated with neoadjuvant treatment followed by oesophagectomy were included.

2.2.1 Oncological treatment

Over the years there have been numerous strategies aiming to improve the treatment results of oesophageal cancer patients by adding neoadjuvant chemotherapy (nCT), neoadjuvant chemoradiotherapy (nCRT) or perioperative chemotherapy (pCT) to the oesophagectomy (32).

Treatment practices vary around the world for locally advanced oesophageal cancer but there is a global consensus that surgery alone no longer should be the standard of care (32).

One of the first randomised controlled trials (RCT) comparing nCT to nCRT was the NeoRes I trial showing that nCRT results in a higher histological response rate without affecting survival (47).

An important study regarding neoadjuvant treatment in oesophageal cancer patients is the CROSS study comparing nCRT with subsequent oesophagectomy to surgery alone demonstrating 14% increase in overall 5-year survival for both AC and SCC (9).

For patients with tumours in the gastroesophageal junction pCT has shown improved survival compared to surgery alone (48, 49). Previous pCT regimens were associated with high toxicity so a modified regimen was developed, FLOT (5-Fluorouracil, Leucovorin, Oxaliplatin, Docetaxel) showing better tolerance, higher tumour response and, improved overall survival compared to its precursors (50-52).

In 2014 a study group suggested that prolonged time to surgery after nCRT increases histopathological response without affecting survival in patients with oesophageal or junctional cancer (53), which was in line with results reported in rectal cancer patients (54).

2.2.2 Surgery

2.2.2.1 History

The first successful transthoracic resection for oesophageal cancer was performed in 1913 by Franz John A. Torek who used an external rubber tube for reconstruction. In 1946 Ivor Lewis described a two-stage transthoracic oesophagectomy with gastric mobilisation (14). The Ivor Lewis procedure is suitable for tumours in the distal oesophagus, but it is difficult to access the upper and middle thirds of the oesophagus as well as performing an anastomosis high in the chest. Thus, an alternative procedure was introduced by McKeown in 1976, a three-incision approach, including a left cervical anastomosis.

For patients less fit for extensive surgery and in no condition to undergo thoracotomy, a transhiatal approach is preferable, first performed for oesophageal carcinoma by Turner in 1933 (14, 31).

The preferred technique for reconstruction after an oesophagectomy is gastric tubulisation and pull-up (54).

The first MIO was described in 1992 and over the last years various techniques have been implemented aiming to minimise the surgical trauma and the use of minimally invasive approach is increasing (14, 55). The first randomised controlled trial (RCT) comparing open surgery to MIO, published in 2012 showed significantly less pulmonary infections within 2 weeks postoperatively, less blood loss, shorter hospital stay and better quality of life for MIO, and comparable results regarding the radicality (6, 14). A disadvantage is the long learning curve for MIO (14, 55). Robot-assisted MIO is a further development of minimally invasive approach with shorter learning curve and was first described in 2005 (14).

2.2.2.2 Surgical approaches

For patients with very early stage tumours limited to the mucosa or submucosa a local endoscopic treatment, endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD), is the first choice (2, 28, 32).
For more advanced tumours the standard of care is nCRT or pCT followed by oesophagectomy (32). Surgery can be performed as Ivor Lewis, McKeown or transhiatal oesophagectomy, both as open, exclusively minimally invasive or as hybrid (some parts of the operation as open and some parts as minimally invasive) procedure. The transthoracic Ivor Lewis or McKeown procedures are more often performed compared to transhiatal approach allowing adequate thoracic lymph node dissection (56) and it is well established that the presence and greater number of lymph node metastases is associated with worse prognosis (57).

In the western world, with a higher frequency of AC located in the distal third of the oesophagus and the gastroesophageal junction, the Ivor Lewis technique with resection of the lowest part of the thoracic oesophagus and with anastomosis often performed in the middle mediastinum is the most used technique (32, 58, 59). The two-stage Ivor Lewis approach includes an abdominal part where the stomach is mobilised, and the surrounding lymph nodes are resected followed by access to the right thorax where the oesophagus and the regional lymph nodes are removed (59). The stomach is then pulled up into the chest and a gastric tube is formed using the greater curvature of the stomach. Finally, an intrathoracic oesophagogastric anastomosis is performed (59, 60).

For tumours in the upper and middle thirds, of the oesophagus the three-stage McKeown procedure is more suitable since the Ivor Lewis procedure may not guarantee adequate resection margin to the tumour (56). The McKeown procedure involves mobilisation of the whole thoracic oesophagus and its surroundings lymph nodes through the right chest followed by abdominal mobilisation of the stomach, gastric tube formation and finally left cervical incision with pull up of the conduit and formation of anastomosis in the neck (14, 32, 59).

A cervical anastomosis is technically less challenging compared to the intrathoracic one but associated with a higher incidence of anastomotic leak. On the other hand, an anastomotic leakage in the neck is often less severe and can be easier managed (56).

The least invasive transhiatal oesophagectomy is suitable for patients with lower oesophageal and junctional tumours and assessed not to be in condition to undergo a thoracotomy. It involves an abdominal part with mobilisation of the stomach as well as the lower and middle oesophagus through hiatus followed by a left cervical incision, mobilisation of the proximal oesophagus and finally pull up of the gastric conduit and anastomosis in the neck. (14, 59). This approach reduces the surgical trauma and may prevent postoperative complications such as pneumonia and mediastinitis (14) but on the other hand provides limited exposure of the tumour as well as less extensive lymphadenectomy (59).

2.2.2.3 ERAS/ERP

Enhanced recovery after surgery (ERAS) is a standardised program of clinical care to improve the perioperative course and was first introduced in colon cancer surgery (61). In oesophageal cancer surgery it was first introduced as a fast-tracking pathway after Ivor Lewis oesophagectomy (62). In oesophageal cancer surgery the enhanced recovery program (ERP) has been developed and modified over the years but the main concept is fluid restriction during surgery, avoidance of unnecessary placement of drains, immediate postoperative extubation, early mobilization, early removal of nasogastric tube, early start of jejunal tube feeding and active pain control (63-65).

2.2.2.4 Postoperative complications

Postoperative complications are classified after the Clavien Dindo score (C-D), grades I-V (66). The cut off for severe complications is ≥IIIb, where grade IIIb requiring intervention under general anesthesia, grade IV is a life-threatening complication requiring ICU-management (IVa; single organ dysfunction, IVb; multi organ dysfunction) and grade V is death.

Oesophagectomy is a complex operation with many potential complications (67) and is historically associated with considerably morbidity and mortality (68). During the last decade significant improvements regarding morbidity, mortality, and survival after oesophagectomy have been made. The improvements are due to centralisation (69), the minimally invasive approach (6) and oncological treatments (8), but still anastomotic leakage, airway fistulas, postoperative pulmonary complications, and chylothorax may occur (70).

One of the most feared postoperative complications after oesophagectomy is anastomotic leakage, occurring in up to 20% of the cases (71), with a reported 30-day mortality up to 35.7% (70, 72). As described above the intrathoracic anastomosis is associated with less anastomotic leakage and better functional results compared to the cervical anastomosis (56, 70).

The longer the gastric conduit tube is made (as in McKeown procedure) the higher the risk of ischemia at the gastric tip caused by higher tension and the naturally limited circulation to the proximal part of the stomach (70, 73) which may be the cause of more ischemia in cervical anastomosis leading to leakage (68).

Another possible cause of anastomotic leakage is nCRT, where radiation to the proximal part of the stomach (gastric fundus) increases the risk (74, 75). Other contributing factors are obesity, heart failure, diabetes, renal insufficiency and tobacco use (76). Anastomotic leak prevention should, among other things, focus on preoperative nutritional status and resuming early postoperative EN (70, 77).

The treatment of anastomotic leaks depends on the extent of circumferential involvement as well as the state of the patient. The management can be: (i) conservative, (ii) endoscopic interventional treatment, and (iii) surgical revision (70).
As a result of anastomotic leakage, a stricture postoperatively is likely to occur and is treated with endoscopic dilatation. Anastomotic strictures are seen in significantly higher proportion in patients after McKeown procedure compared to after Ivor Lewis procedure (56.2% versus 6.2%) (68).

The cervical anastomosis is also associated with increased risk for vocal cord palsy (68, 70, 73), which is probably caused by the cervical dissection close to the recurrent laryngeal nerve and may also result in aspiration and cough reflex disorders (73).

Fewer complaints of dysphagia, dumping syndrome, and regurgitation after an intrathoracic anastomosis compared to cervical anastomosis have also been reported (68).
Finally, it seems to be no difference in occurrence of chyle leakage between the two approaches (73).

2.3 NUTRITIONAL STATUS AND NUTRITIONAL SUPPORT

Malnutrition is reported to be prevalent in 60-85% of the oesophageal cancer patients at the time of diagnosis (5). Malnutrition is, according to The European Society for Clinical Nutrition and Metabolism (ESPEN), defined as a state resulting from lack of intake or uptake of nutrition leading to an altered body composition, decreased fat-free mass, and body cell mass which thereafter results in diminished physical and mental function as well as impaired clinical outcome from disease (78).

During the years, different criteria to diagnose malnutrition have been suggested with the most recent from Global Leadership Initiative on Malnutrition (GLIM) (79). The diagnosis is set in two steps, starting with screening for patients at risk for malnutrition using a validated screening tool and thereafter a combination of one phenotypic criterion together with one etiological is required for the diagnosis of malnutrition.
The phenotypic criterion is defined as weight loss >5% within past 6 months/>10% beyond 6 months, low body mass index (BMI) (<20 if <70 years, or <22 if ≥70 years), or reduced muscle mass. The etiological criterion is defined as reduced food intake or assimilation of ≤50% of energy requirements >1 week/any reduction for >2 weeks, or any chronic GI condition that adversely impacts food assimilation or absorption, or inflammation due to acute disease/injury or is chronic disease-related. The second step also includes severity grading of the malnutrition.

In previous studies, the definition of malnutrition is often referred to as weight loss of >5% over 1-3 months or >10% in the last 6 months or indefinite of time (33, 80, 81).

To support muscle mass and physical function there is a strong recommendation to increase the level of physical activity for all cancer patients (82). Regarding prehabilitation, it has been concluded that preoperative exercise therapy does contribute to decreased postoperative complication rates, shorter length of hospital stay and training of the inspiratory muscles decreased pulmonary complications in patients undergoing abdominal surgery (83).

2.3.1 Before treatment

Oesophageal cancer is one of the cancer types with the highest risk for weight loss and malnutrition (24) making early nutritional interventions crucial.
Nutritional assessment including measuring body weight, recent weight loss, nutrition history to determine food intake and severity of dysphagia are an important and easy first step in identification and treatment of malnutrition (10).

Dysphagia, as earlier mentioned, is often the primary symptom for patients suffering from oesophageal cancer (30) combined or not with odynophagia (2). Many patients have already adapted to their new situation by chewing more thoroughly and have modified the consistency of food texture, often unconsciously (10, 30).
Usually patients with dysphagia experience difficulties swallowing only some types of food where meat and soft bread initially are the most challenging textures (3). The patients might exclude foods and only chose very soft and easy-to-swallow foods making them at risk for deficiencies of both macro- and micronutrients as well as fluid intake.

Dysphagia may vary and change over time, so food modifications are needed regularity. Nutritional counselling by a dietitian helps the patients to modify the consistency of food optimising the nutrient intake and, if needed, receive prescription of oral nutrition supplements (ONS).
The recommendations for dietitian follow up is once every fortnight during the diagnostic phase (84) to be able to detect low energy and protein intake and continued weight loss. If the patient, despite of dietary modifications and ONS, continue to lose weight other options for nutrition support is nasogastric feeding tube or surgical jejunostomy for EN support or parenteral nutrition (PN) (3).
An intensive nutritional support by a dietitian may decrease severe postoperative complications in oesophageal cancer patients (84).

2.3.2 During oncological treatment

Malnutrition is a risk factor for bad compliance to chemoradiotherapy and improved outcome is achieved by early and frequent contact with a dietitian, every one or two weeks during nCRT (4, 29, 33, 84). Side effects associated to chemotherapy affecting nutritional status are esophagitis, stomatitis, nausea, vomiting and diarrhoea whereas reactions to radiotherapy, which is often given simultaneously to chemotherapy, are also oesophageal inflammation as well as odynophagia and oesophageal narrowing, making swallowing painful and difficult (10, 11).
Continued personalised nutritional advices and ONS may increase dietary intake and prevent

weight loss (5) and ONS can improve weight gain before surgery (33). Nutritional support by EN to patients receiving nCT or nCRT results in weight maintenance, reduced toxicity, and prevention of treatment interruption (85).

The loss of muscle mass might be difficult to detect in obese cancer patients but is associated with higher incidence of toxicity during treatment (86), making it important to be observant of earlier or ongoing weight loss in these patients.

2.3.3 Post oesophagectomy

As previously described, oesophagectomy is an extensive procedure with dissection within the chest cavity, the abdomen and sometimes also in the neck (3, 6). Weight loss of 5-12% during the first six months after oesophagectomy is reported in several studies (19, 20, 22). Patients operated with MIO have a faster recovery and mobilisation with better respiratory function compared to open surgery resulting in improved capacity to handle adverse events (6, 16, 87).

The oesophagectomy permanently alters the anatomy with resection of the lower oesophageal sphincter, partial resection of the stomach, which is formed to a gastric tube and pulled up into the chest. The vagotomy performed during oesophagectomy may result in dysmotility of the gastric remnant and pylorus dysfunction (88).

2.3.3.1 Surgery-related complications and nutrition

The most common complications related to surgery are pulmonary complications, anastomotic leak, chyle leak and laryngeal nerve injury (24).

The vocal cord paralysis due to laryngeal nerve injury may result in aspiration leading to pulmonary infection (89) while in some patients hoarseness is the only symptom of recurrent nerve damage (24). By delaying oral intake after oesophagectomy cervical anastomotic leak can be reduced (90) and prevention of aspiration by oral diet modifications and/or tube feeding are crucial for nutritional maintenance (24).

When anastomotic leakage is confirmed the patient is fasting and the nutrition should be administered via enteral route downstream the leakage or via PN if EN is not an option (91). Not only does the anastomotic leakage affect oral intake in the initially postoperative period but also henceforth due to higher incidence of anastomotic stricture (92). Prophylactic PPI (proton pump inhibitors) treatment commonly reduces the incident of dysphagia caused by benign anastomotic strictures (93).

During oesophagectomy, lymphadenectomy is performed and the incidence of chyle leakage after surgery is up to 18% and treatment is mainly a low-fat diet or nil-by-mouth with PN if not refractory leakage needing surgery (94). Chyle is generally milky in colour but during the initial postoperative phase when the fat intake is low it can be clear (67). The use of low-fat formula EN as a routine the first 7 days after oesophagectomy might prevent chyle leakage (95). The flow of chyle increases by the amount of fat intake and by physical activity, especially of torso or upper extremity exercises (96).

A “fat free” diet contained of <0.5 g fat/serving and medium chain triglycerides (MCT) can be used since they do not require transport via the lymphatic system. The EN with MCT allows continued intestinal feeding reducing the risk of bacterial translocation and deficiency of fat-soluble vitamins (24) compared to a “fat free” oral diet. The chyle leakage leads to significant loss of essential proteins and immunoglobulins, fat, vitamins, electrolytes and water (21) and the total energy composition of chyle is approximately 200 kcal/L (96).

2.3.3.2 Enteral and oral nutrition

During the first days after oesophagectomy, regardless approach, most centres advocate a nil-by-mouth regime supported by EN (97), delaying start of oral intake to decrease risk of anastomotic leakage, aspiration pneumonia and mediastinitis (90, 97, 98) while others state early oral feeding is safe (99-101).

The ERAS concept recommend early oral feeding after surgery but it remains unclear whether this can be applicable in the early postoperative phase after oesophagectomy (102). In the recently published guidelines for ERAS post oesophagectomy no recommendation regarding start of oral feeding was made but the importance of early EN was underlined (103). These recommendations are in line with “ESPEN guidelines: Clinical nutrition in surgery” stating there are no controlled data supporting immediate oral intake for patients after oesophagectomy (83).
Placement of a feeding jejunostomy during operation is recommended and effectively prevents severe weight loss during the postoperative period (98, 104). Routine discharge with supplementary feeding via a jejunostomy tube is recommended and many of the problems connected to consuming a full oral diet shortly after oesophagectomy will then be avoided (64) and patients´ nutritional requirements are met during the time they adjust to an increase of oral nutrition.

A review of nutritional effects after oesophagectomy, published in 2016, concluded that focus has been on EN in the immediate perioperative period with limited information on extended EN (after discharge from hospital) and how this may affect weight development (19). Studies focusing on extended home EN suggest that even though patients lose weight it might be to a lesser extent and may improve quality of life (105-107).
To encourage appetite the EN is preferably given during night (3, 105) but some patients report significant disruption to sleep with overnight feeding so a regimen with feeding in late afternoon and/or evening is then preferable (108, 109). The oral intake is not reduced when patients receive proper amount of tube feeding (23, 108, 110, 111) and the nutritional goal are met with a significantly higher total nutritional intake in patients receiving EN compared to patients with only per oral intake (108).

In a study from the Netherlands comparing early to late oral intake after oesophagectomy they found that patients in the early per oral group, without EN, lost more weight during the first months compared to patients awaiting oral intake and initially received EN, but this difference was eliminated in the following months (99).

Another study comparing early oral intake to conventional late oral feeding stated that early oral feeding post oesophagectomy is safe (100). The patients in early oral group began intake of liquid food at will at postoperative day (POD) 1 and proceeded to soft food. The conventional group received EN and nil-by-mouth the first 7 postoperative days. The patients' mean intake was 172 mL at POD 1 and 1803 mL at POD 7, but no calculation of kilocalories (kcal) was made, there was no clarification of type of liquids consumed and they did not report weight development. In the same study, it was also showed that gastric emptying for liquid food was significantly faster after oesophagectomy compared to before surgery.

The opinions regarding when to start the oral intake after oesophagectomy differs between centres but a transition regarding consistency from liquid diet to soft diet with addition of EN which decreases as oral intake increases seem to be the same.
Follow up by dietitian is suggested 2-3 times per week during hospital stay (84).

2.3.3.3 Surgical techniques and nutrition

The different surgical approaches also affect patients' nutrition in different ways. Patients undergoing McKeown oesophagectomy have worse functional results compared to patients operated with Ivor Lewis procedure (68). Patients operated with McKeown have more problems with dysphagia, dumping, higher incidence of recurrent laryngeal nerve palsy and more frequent problems with regurgitations as well as higher rate of benign anastomotic stricture requiring dilatation. However, the peristaltic activity is not dependent on the level of the anastomosis and the gastric conduit empties slowly after both Ivor Lewis and McKeown procedures (112).
After McKeown procedure more of the gastric fundus is retained leaving more ghrelin producing cells stimulating appetite (113).

2.3.3.4 Nutritional consequences

Factors negatively affecting nutritional intake post oesophagectomy seem to change and the initially early satiety due to the smaller gastric reservoir and the reduced motor function slowly recovers over time (88), as well as the gastric emptying of solid foods which is markedly prolonged in approximately 50% of the patients one week after oesophagectomy significantly increases over time (114).

Dumping syndrome is also due to the smaller gastric reservoir, divided in early and late forms, where early dumping is more common (88, 115). Early dumping, 10 to 30 minutes after food intake, results from an accelerated gastric emptying of hyperosmolar content from the gastric conduit to the small intestine (115). The body ambition to balance this hyperosmolarity leads to shift in fluids from the intravascular compartment to the small bowel causing distension and intravascular volume contraction.
Early dumping comes with a variety of symptoms including bloating, diarrhoea, nausea, tachycardia, and fatigue.
Late dumping, 1-3 hours after a meal, is caused by the rapid delivery of high concentration of

carbohydrates into the small intestine followed by rapid absorption of glucose into the blood. The high level of glucose in the blood results in excessive release of insulin causing hypoglycaemia, where some of the symptoms are shakiness and decreased consciousness. Dietary modifications relieve the symptoms in most of the patients but approximately 3-5% of the patients with severe symptoms are unaffected to dietary modifications (114). The symptom can be relieved with a reduction of fluids, especially sweetened, in favour for more solid foods as well as a decrease of carbohydrates and increase of protein and fat (115). Simple sugars should be avoided, and complex carbohydrates are preferred. With increasing time after surgery the dumping syndrome is improved (116).

The postprandial satiety gut hormone response is exaggerated after oesophagectomy, compared to preoperatively, which might affect early satiety, body weight and GI symptoms (117). Another hormone, ghrelin, secreted by the fundic glands in the stomach stimulating appetite has been found to be temporary reduced first 6 months after oesophagectomy (118). During the first year after surgery, before the body adapts to the new circumstances, the inhibited passage of foods with high viscosity, reflux and absence of hunger affect nutritional intake and weight loss (23). The energy and protein intake as well as micronutrients have been found to be below recommendations 12 months after oesophagectomy (119).

Long-term impaired nutritional status after oesophagectomy may be due to malabsorption and many patients have steatorrhea indicating exocrine pancreatic insufficiency (120, 121) requiring pancreatic enzyme replacement therapy (122). If a pyloromyotomy or pyloroplasty is part of the oesophagectomy this might increase the risk for dumping and diarrhoea (21, 88, 116).

Recommended follow up by a dietitian is every other week after discharge until patients are weight stable and then every 3 months until 12 months after surgery (83, 84, 119).

Long-term functional disorders after oesophagectomy affecting nutritional intake negatively is delayed gastric emptying, gastroesophageal reflux, aspiration, dumping syndrome, diarrhoea, appetite loss, eating difficulties and odynophagia (22, 23).

Persisting problems 5 years after oesophagectomy that impair food intake resulting in great weight loss (≥15%) are eating difficulties, appetite loss, nausea and vomiting, pain, diarrhoea and fatigue (123). Still 10 years after oesophagectomy some patients reported severe problems such as reflux, eating difficulties, diarrhoea and appetite loss (124) while other patients reported excellent nutritional status and no problems associated to eating even though GI side effects were common (125).

2.4 NUTRITIONAL ASSESSMENT

To be able to evaluate nutritional status and identify patients need of nutritional interventions it is important to measure actual body weight and receive information about nutrition history (10).

Weight status also include recent weight loss, usual body weight and duration of eventual

weight change.
The nutrition history is important to determine adequacy of food intake and how it has been affected by the tumour as well as the severity of dysphagia. Further, information of difficulties swallowing certain texture or type of food, odynophagia or appetite loss is needed for correct diet modifications and interventions.

2.4.1 Energy expenditure

The TEE in free-living people can be measured with double labelled water (DLW), preferred in research but not convenient in the clinical setting (126)**.** The gold standard measuring resting energy expenditure (REE) in hospitals and in cancer patients is indirect calorimetry (IC) (82). For more mobile patients a physical activity level (PAL) is added to the REE for right amount of energy requirement, the TEE.

An easy way to measure energy expenditure even outside hospital and for several days is by a mobile device, Sense Wear armband (SWA, BodyMedia, Pittsburgh, PA), which has been used in different settings to evaluate TEE and PAL. The use of SWA to measure energy expenditure has been validated in several studies in healthy subjects and have a 92% accuracy compared to DLW (127).
The SWA was validated in a pilot study and they found the armband to provide accurate and reliable estimation of REE and TEE also in cancer patients (128) and another study concluded that SWA offer a suitable alternative to IC after liver resection but has a magnitude of error at 8.74 kcal/kg per day (129).

Even though the SWA are still widely used as research tool (130) they are no longer available for purchase (131). After being acquired by another company in 2013, first the support and thereafter the production of SWA was discontinued (130, 131).

2.4.2 Energy and protein requirements

Energy requirements can easily be predicted by using rule of thumb assuming TEE to be 25-30 kcal/kg body weight (BW) per day depending on patient´s physical activity and performance status (82). The rule of thumb of 30 kcal/kg BW per day is suggested in a small study to be suitable for estimating TEE in patients with oesophageal cancer, and is closer to the values estimated via IC than the Harris-Benedict formula (132).

"ESPEN guidelines on nutrition in cancer" recommend 25-30 kcal/kg BW per day and 1-1.5 g protein/kg BW per day (82) and after surgery the ESPEN guidelines recommend 25-30 kcal/kg BW per day and 1.5 g protein/kg BW per day (83). These recommendations are for ideal body weight and needs to be adjusted for calculations regarding requirements for overweight and obese patients.

3 RESEARCH AIMS

The overall aim of the thesis was to increase the knowledge in how the disease and different treatment components affect nutritional status in patients with oesophageal cancer undergoing neoadjuvant treatment and subsequent oesophagectomy. The more specific aims addressed in the studies are the following:

- To assess the effect of neoadjuvant treatment in dysphagia in oesophageal- and gastrooesophageal junction cancer patients *(Study I)*.

- To compare weight development between traditional open oesophagectomy and minimally invasive techniques *(Study II)*.

- To describe energy intake and energy expenditure before and after neoadjuvant therapy and after oesophagectomy *(Study III)*.

- To examine the weight and dysphagia development before nCRT (baseline) and at the time points of oesophageal cancer surgery in patients randomised in standard or prolonged time of surgery as well as if malnutrition at baseline affects the risk of postoperative complications in the two groups *(Study IV)*.

4 MATERIALS AND METHODS

4.1 OVERVIEW OF THE STUDIES

Table 1. Overview of materials and methods for studies I-IV.

	Study I	**Study II**	**Study III**	**Study IV**
Design	Prospective cohort	Retrospective cohort	Prospective cohort	Randomised Controlled Trial
Data source	Medical records from Karolinska University Hospital, NREV, questionnaires (Ogilvie, Watson, VAS appetite)	INCA, medical records from Karolinska University Hospital	SWA, food diaries, medical records from Karolinska University Hospital	Dataset from multicentre RCT in Sweden, Norway, and Germany
Study period	2011-2013	2004-2016	2015-2017	2015-2019
Study time	Before oncological treatment, after first chemotherapy cycle and before surgery	Day before surgery, 3, 6 and 12 months after surgery	Before and after oncological treatment, 3 and 6 months after surgery	Before oncological treatment, 4-6 or 10-12 weeks after oncological treatment and after surgery
Outcome	Dysphagia, weight development, appetite, and histological response	Weight development, use of enteral nutrition	Weight development, total energy expenditure, energy and protein intake	Weight development, dysphagia, role of malnutrition in postoperative complications
Number of patients included	35	225	20	249
Statistical analysis	ANOVA	Chi-square, logistic regression models, unpaired *t*-test, generalized estimating equation	Paired *t*-test, Wilcoxon signed-rank	Wilcoxon signed-rank, Mann-Whitney U, paired *t*-test, Chi-square or Fisher´s exact

NREV; National register for esophageal and gastric cancer, INCA; National Cancer register, SWA; SenseWear Armband, RCT; Randomised Controlled trial.

4.2 STUDY I

4.2.1 Study design

This is a prospective single centre cohort study performed at Karolinska University Hospital between February 2011 and September 2013. Inclusion criteria were patients diagnosed with cancer in the oesophagus or gastroesophageal junction with local disease considered tolerating neoadjuvant treatment with subsequent oesophagectomy and with dysphagia grade ≥1, according to Ogilvie. The patients were included by the two main authors BS and JE at first visit at the out-patient clinic after decision at the weekly MDT meetings. Patients who received neoadjuvant treatment outside Karolinska University Hospital were excluded. Data regarding patients were retrieved from medical records and the national register for oesophageal and gastric cancer (NREV). The neoadjuvant treatment started within one week after baseline assessment and comprised of Cisplatin and 5-Fluorouracil day 1-5 during week 1, 4 and 7. In patients who also received radiotherapy the treatment was given in 20 fractions á 2 Gy started at the first day of chemotherapy cycle two.

4.2.2 Outcomes

The main outcomes were to compare dysphagia and appetite before neoadjuvant treatment, after first chemotherapy cycle and after completion of neoadjuvant treatment. We also assessed if relief in dysphagia was associated with histological response. We did also follow the weight development at the same time points.

We evaluated the patients´ dysphagia, either by visit at outpatient clinic or by telephone, and two different instruments were used: Ogilvie score and Watson score.

Ogilvie score grades dysphagia in five levels; 0=no dysphagia, 1=normal diet avoiding certain foods such as raw apple and steak, 2=semi-solid diet, 3=fluids only and, 4=complete dysphagia for even liquids (36) and is routinely used at our department to assess dysphagia.

Watson score, 0-45 (0=no dysphagia and 45=total dysphagia), with nine different types of liquids and solids where “never”, “sometimes” and “always” can be chosen for ability to swallow each type of food (37).

The appetite was evaluated using The Edmonton Symptom Assessment System (ESAS) VAS appetite score, a visual analogue scale were 0 corresponding to very good appetite, and 10 corresponding to no appetite (133).

Histological response was assessed in the resected specimen using Chirieac modification of the Mandard scoring system (134). Chirieac A is complete histological response with no remaining tumour, Chirieac B <10% of the tumour cells viable, Chirieac C 11-50% of the tumour cells viable and Chirieac D with >50% viable tumour cells.

4.2.3 Statistical analysis

To examine the effect of neoadjuvant treatment on dysphagia, appetite, and weight changes at the three time points a general linear model, repeated measures analysis of variance (ANOVA) was performed. Repeated measures ANOVA was also used to examine correlation between improvement in dysphagia score and histological response. IBM SPSS Statistics (Version 22.0. Armonk, NY, USA: IBM Corp.) was used for all analyses.

4.2.4 Ethics

All patients did sign a written informed consent form. The study protocol was approved by the local ethic committee (2005/1509-31/3 and 2013/708-31/3).

4.3 STUDY II

4.3.1 Study design

This is a retrospective observational single centre cohort study performed at Karolinska University Hospital. Patients included in this study was one group comprised of the first 41 consecutive patients that underwent minimally invasive oesophagectomy with a cervical anastomosis, McKeown procedure (MIMK), between June 2012 and December 2016. The second group included the first 84 consecutive patients operated with minimally invasive oesophagectomy with an intrathoracic anastomosis, Ivor Lewis procedure (MIIL), from July 2014 to December 2016. These two minimally invasive surgery groups were separately compared to 100 consecutive patients who underwent traditional open thoraco-abdominal Ivor Lewis oesophagectomy (IL) from March 2004 to May 2012.

Inclusion criteria were patients operated with oesophagectomy (IL, MIIL or MIMK) and only patients referred from Stockholm county due to incomplete follow up in patients from other regions. Patients operated with colon or jejunal interponate were excluded from the study. Patient related data: age at time for surgery, weight, length, neoadjuvant treatment and EN/PN was retrieved from medical records. Procedure related information, type and location of the tumour including TNM classifications, C-D scores, American Society of Anaesthesiologists (ASA) was retrieved from INCA (national cancer register). Patients were followed from the day before surgery and at 3, 6 and 12 months postoperatively.

4.3.2 Outcomes

The main outcome was weight development during first year after oesophagectomy comparing type of surgical approach i.e. MIO or open oesophagectomy. We also examined if and for how long the patients used EN as well as compared severe postoperative complications according to C-D score (66) between the surgical techniques.

4.3.3 Statistical analysis

Chi-Square test was used to analyse the differences between the groups and IL group was reference for separate comparison with each of the minimally invasive groups. For the evaluation of ≥10% weight loss at 3 and 6 months postoperatively in patients with or without postoperative complication C-D ≥IIIb as well as need of enteral nutrition at 3 and 6 months postoperatively, logistic regression models were applied to calculate univariable and multivariable adjusted odds ratios with 95% confidence intervals (CI). Included in the multivariable model were prespecified variables based on clinical, relevant, known factors affecting oesophagectomy and weight loss and the confounders used for adjustment were sex, ASA score, clinical tumour stage, neoadjuvant treatment, and operation technique. Unpaired sample *t*-test were used calculating mean weight and BMI with 95% CI before and after oesophagectomy as well as weight change in percent with the IL group as a reference. To calculate p-values for weight development at all four time points during the first year after surgery by operation technique as well as stratified by incidence of severe postoperative complications or not, a generalized estimating equation (GEE) was used. The analyses were performed in STATA® version 13 software (StataCorp, College Station, Texas, USA).

4.3.4 Ethics

The study protocol was approved by the local ethic committee (2013/222-31/4 and 20151292-31/1.

4.4 STUDY III

4.4.1 Study design

This is a prospective single centre study performed at Karolinska University Hospital from December 2015 to April 2017. The aim was to assess TEE using SWA Mini® as well as energy and protein intake in oesophageal cancer patients submitted to modern multimodality therapy. Patients scheduled for neoadjuvant treatment followed by oesophagectomy were eligible for the study. The patients were recruited at the outpatient clinic after decision at MDT. Twenty patients were finally included.

4.4.2 Outcomes

The main outcomes were TEE in relation to energy intake (EI) in patients before and after neoadjuvant treatment and at 3 and 6 months after oesophagectomy. Body weight was measured at all four occasions and we calculated protein intake.

Measurements were performed before start of neoadjuvant treatment (baseline), after completion of neoadjuvant treatment (4-6 weeks before scheduled oesophagectomy) and finally at three and six months postoperatively.

The patients´ TEE and PAL was measured using the mobile multi sensor device SWA Mini® (BodyMedia, Pittsburgh, PA). The SWA Mini collects physiological data from 4 sensors: accelerometer (3-axis), galvanic skin response, skin temperature and heat flux. The *3-axis accelerometer* measures motion and steps taken, the *galvanic skin response* measures how active the person is, the *skin temperature* measures the body surface temperature and the *heat flux* measures the rate at which heat dissipate from the body. Patients' characteristics: gender, age, weight, height, smoking status, and handedness, were entered into a specific software (SenseWear® Software version 8.1) before analysis. The SWA Mini is wearable on both arms (according to manufacturer) and was if possible, placed on the non-dominant upper arm, over the triceps muscle and secured by an adjustable strap. The patients were carefully instructed to wear the device for three consecutive days and only remove it while showering or bathing.

During the same three days the patients wore the SWA, they kept a food diary writing down everything they ate and drank including ONS and EN. All patients received thorough instructions how to register each type of food and drink consumed and to be as precise as possible by measuring each food with household utensils or, if possible, weigh the food. Patients' food intake was calculated in the Dietitian Net Pro software, version 17.11.12 (based on the database from the Swedish Food Agency).

The recommended energy requirement was 30 kcal/kg BW per day and at each time point according to the ESPEN guidelines in both cancer and surgery (82, 83) as well as our department´s guidelines. According to our local guidelines the corresponding values for overweight patients were calculated as following: BW at BMI 25+25% of the overweight x 30 kcal/kg BW per day. The recommended protein requirement was also according to the ESPEN guidelines and was before surgery 1.0-1.5 g protein/kg BW per day (82), where we sat the cut off to 1.0 g protein/kg BW per day, and after surgery 1.5 g protein/kg BW per day (83). The intake of energy and protein were considered adequate if the mean intake during the three days was 100% of estimated requirements.

4.4.3 Statistical analysis

Shapiro-Wilk test was used to verify the assumption of normal distribution of the examined variables, except for the variable TEE/kg BW after neoadjuvant treatment, which was skewed. The comparison of mean weight, BMI, energy intake, protein intake, TEE and PAL between different time points compared to baseline were conducted using paired sample *t*-test in all variables except TEE/kg BW after neoadjuvant treatment where Wilcoxon signed-rank test was performed. The comparison of median weight development, PAL, energy intake and TEE at different time points compared to baseline were estimated by Wilcoxon signed-rank test. The analyses were conducted in STATA, version 14.1 and 16.0 software (StataCorp, College Station, Texas, USA).

4.4.4 Ethics

The study protocol was approved by the local ethic committee (2015/435-31/2 and 2015/2005-32) and the patients signed a written informed consent.

4.5 STUDY IV

4.5.1 Study design

This is part of the RCT NeoRes II, comparing patients to either standard (4-6 weeks) or prolonged (10-12 weeks) waiting time to oesophagectomy after completed nCRT. Patients diagnosed with oesophageal or junctional type I or II cancers were enrolled in the study from May 2015 to April 2019.

4.5.2 Outcomes

Main outcomes were to evaluate weight and dysphagia development before nCRT (baseline) and at the time points of standard and prolonged delay of surgery, as well as if malnutrition according to the GLIM criteria at baseline affects the risk of postoperative complications comparing the two groups (79). Cut off for malnutrition was weight loss >5% within the past 6 months or low BMI (<20 if <70 years or <22 if ≥70 years) together with C-reactive protein (CRP) >5 mg/L or dysphagia grade 2 according to Ogilvie. We compared postoperative complications between the groups using the C-D score (66).

4.5.3 Statistical analysis

Shapiro-Wilk test was used to examine normal distribution of the variables. Wilcoxon signed-rank test was applied for comparison of weight and dysphagia between baseline and surgery within each group. For comparison of differences in weight between the groups from baseline to surgery Mann-Whitney U test was used. For analyses of changes in weight for patients malnourished or not at baseline, from baseline to time of standard or prolonged delay of surgery within each group, paired *t*-test was used for variables with normal distribution and for skewed data Wilcoxon signed-rank test was used. For comparison between standard or prolonged time to surgery regarding postoperative complications in patients malnourished or not at baseline Chi-Square test or Fisher´s exact test was used. Univariable logistic regression model was performed for analyses of postoperative complications in patients malnourished at baseline between the two groups. The statistical analyses were performed using STATA® version 16.0 software (StataCorp, College Station, Texas, USA).

4.5.4 Ethics

The NeoRes II trial was registered in Clinicaltrials.gov NCT02415101 and approved by the Research Ethics Committees in Sweden (Regionala etikprövningsnämnden i Stockholm, approval numbers: 2014/748-31, 2015/1271-32, 2016/626-32), in Norway (REK Sør-Øst 2014/1938), and the Institutional Review Board of the University of Cologne in Cologne, Germany (IRB approval number: 17-012). All participants signed written informed consent.

5 ETHICAL CONSIDERATIONS

All studies in this thesis were approved by the local ethic committee in Stockholm, as previously mentioned. Study IV was also approved by Research Ethics Committees in Sweden and ethical committees in Norway and Germany. Study IV was registered in Clinicaltrials.gov. All participants in study I, III and IV signed written informed consent.

The studies were performed in accordance with the Declaration of Helsinki.

As in most research the participants in the present studies did not benefit from them, but to my opinion the patients found it meaningful to contribute to new knowledge.

In study I-III the patients after consultation were asked to participate by a colleague or me and were carefully informed that participation was voluntary, and we emphasised their right to discontinue at any time without explanation.
To avoid extra visits to the hospital, we arranged to meet the patients at the same time with their doctor's appointment at the outpatient clinic or when appropriate some of the follow-ups were performed by telephone.

All data were encoded, and all analyses were performed on a group level with exception for the supplementary tables in study III where we showed individual energy and protein intake for each participant but without possibility for identification.

6 RESULTS

6.1 STUDY I

Of 43 eligible patients 35 were included and assessed before start of neoadjuvant treatment and after first cycle of chemotherapy. The first 15 patients included were patients participating in a RCT and randomized to nCT or nCRT.
Due to severe side effects three patients were not able to complete the treatment and of the remaining 32 patients 8 patients received chemotherapy and 24 chemoradiotherapy before oesophagectomy.

There was significant improvement in mean dysphagia scores after first cycle of chemotherapy seen in both Ogilvie score and Watson score, 1.89 to 1.07 ($p<0.001$) and 27.0 to 16.5, respectively ($p<0.001$), Table 2. The dysphagia at baseline allowed a majority of the patients to only consume fluids and remaining patients were able to swallow semi-solid food. The improvement in dysphagia after the first cycle of chemotherapy corresponded to the ability to eat more solid foods as vegetables, potatoes, fish, bread, and pasta and as many as 40% could swallow meat.

Further statistically significant ($p<0.001$) improvement in dysphagia was seen after completion of treatment in both groups and in both Ogilvie score and Watson score, 0.63 and 9.41, respectively. After completion of treatment 60% were able to swallow meat.

There were 13 patients (37%) requiring support of enteral or parenteral nutrition mostly during a limited period of time.

The same improvement was seen regarding appetite score, which significantly improved for all patients from 3.83 at baseline to 2.60 after first cycle of chemotherapy ($p=0.03$).

All patients’ mean weight remained stable during the entire treatment period, 77.3 kg to 76.8 kg ($p=0.94$), Table 2.

There was no association between the presence of histological response or degree of response and relief of dysphagia (Watson $p=0.446$ and Ogilvie $p=0.181$), Figure 1.

Table 2. Development of dysphagia, weight, and appetite during neoadjuvant treatment.

Mean	**Baseline**	**After chemotherapy cycle 1**	**p-value***	**After completed neoadjuvant therapy**	**p-value****	**p-value*****
All patients						
Included patients	35	35		32		
Weight	77.3	77.4	1.00	76.8	0.84	0.94
Appetite score	3.83	2.60	**0.03**	2.91	1.00	0.11
Dysphagia score						
Ogilvie	1.89	1.06	**<0.001**	0.63	0.08	**<0.001**
Watson	27.03	16.46	**<0.001**	9.41	0.06	**<0.001**
Chemoradiotherapy						
Included patients	25	25				
Weight	77.4	77.5	1.00	76.6	0.45	0.71
Appetite score	4.33	2.70	**0.03**	3.52	0.59	**0.03**
Dysphagia score						
Ogilvie	2.00	1.00	**0.01**	0.65	0.27	**<0.001**
Watson	29.27	16.45	**0.01**	8.75	0.01	**<0.001**
Chemotherapy						
Included patients	10	10		8		
Weight	77.2	76.9	1.00	77.3	1.00	1.00
Appetite	3.00	2.60	1.00	1.50	0.48	0.07
Dysphagia score						
Ogilvie	1.70	1.10	0.14	0.62	0.38	**0.03**
Watson	22.55	14.55	0.19	9.87	0.87	0.11

*p-value for difference between baseline and cycle one. **p-value for difference after cycle one and after completed neoadjuvant therapy. ***p-value for whole treatment period from baseline to after completed neoadjuvant therapy. Repeated measurement analysis of variance was used for significance testing.
Bold signifies p<0.05.

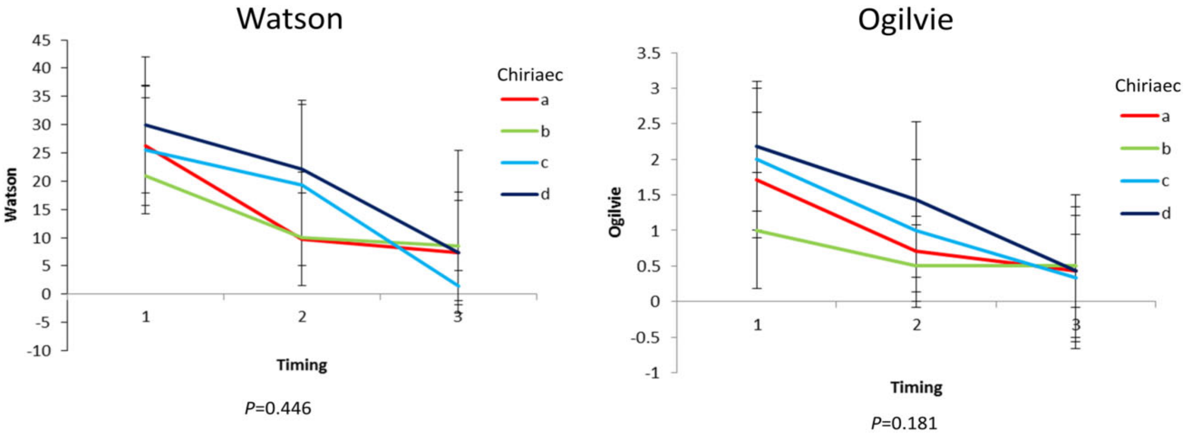


Figure 1. Correlation between dysphagia development (Watson, Ogilvie) before (1), during (2) and after (3) neoadjuvant therapy and histological tumour response according to Chirieac. A-7, B-4, C-3, D-16.

6.2 STUDY II

Two hundred and twenty-five patients were included in the study. There were more patients in the two minimally invasive surgery groups that had undergone neoadjuvant treatment compared to IL group (MIIL: 76.2%, MIMK: 70.7% and IL: 57.0%).

Almost all patients operated with minimally invasive approach received a feeding jejunostomy during surgery while the corresponding number was 75% in the IL group.

No significant differences regarding severe postoperative complications (C-D IIIb-V) were seen between the groups.

The weight loss was similar, with a trend towards less weight loss after MIO, for the three groups included and the mean weight loss during the first year was 13.1% (±4.1), 11.2% (±6.1) and 9.6% (±7.5) in IL, MIIL and MIMK group, respectively (p=0.85 and p=0.95, respectively), Table 3. On the other hand, significantly less weight loss was recorded after MIIL compared to IL when calculated with GEE at the four measuring points, Figure 2. There was no difference in weight loss of at least 10% of the preoperative weight at 3 and 6 months after surgery for MIIL and MIMK patients compared to IL group, Table 4. Patients operated with MIIL had a lower, but not significant, risk of losing ≥10% of their preoperative weight 3 months after surgery in circumstances of severe postoperative complications (C-D ≥ IIIb) compared to IL group, but this difference was not seen at six months postoperatively, Table 4.

The median period of time using EN varied considerably within the groups with 23.5 days (range 0-2033 days) in IL group, 54.5 days (range 0-338 days, p<0.001) in MIIL group and 57.0 days (range 0-538 days, p=0.022) in MIMK group. More patients in MIMK group needed EN for a longer period of time compared to IL (OR 1.90, 95% CI 0.60-6.07, 6 months after surgery) while patients in IL group received PN more frequently one month after surgery.

Table 3. Weight and BMI[d] before and after oesophagectomy stratified by surgical technique, per cent weight loss at each time point compared to baseline and weight loss at 3 months after surgery in patients with Clavien-Dindo score ≥IIIb.

Mean (SD)	**IL[a]**	**MIIL[b]**	**Difference (95% CI)**	**MIMK[c]**	**Difference (95% CI)**
Preoperative, n	99	84		41	
Body weight, kg	79.7 (16.5)	80.5 (15.3)	-0.8 (-5.5-3.9)	73.8 (14.9)	5.8 (-0.1-11.7)
BMI[d], kg/m^2	25.5 (4.3)	26.1 (4.2)	-0.6 (-1.8-0.7)	24.3 (3.9)	1.2 (-0.3-2.7)
3 months after surgery, n	91	81		39	
Body weight, kg	73.5 (15.3)	74.1 (13.6)	-0.6 (-4.9-3.8)	67.8 (13.2)	5.7 (0.1-11.2)
BMI[d], kg/m^2	23.5 (4.0)	24.0 (3.7)	-0.5 (-1.7-0.6)	22.3 (3.4)	1.2 (-0.3-2.6)
Change in weight, %	-8.5 ± 2.2	-7.4 ± 1.9	-1.2 (-2.6-0.3)	-8.0 ± 3.1	-0.5 (-2.5-1.4)
6 months after surgery, n	82	73		33	
Body weight, kg	71.3 (13.6)	72.5 (13.8)	-1.7 (-5.5-3.2)	65.6 (12.9)	5.7 (0.2-11.2)
BMI[d], kg/m^2	22. 7 (3.4)	23.4 (3.7)	-0.7 (-1.8-0.4)	21.5 (3.2)	1.2 (-0.2-2.5)
Change in weight, %	-10.8 ± 3.0	-9.4 ± 2.9	-1.3 (-3.4-0.8)	-10.0 ± 4.4	-0.8 (-3.5-2.0)
12 months after surgery, n	77	39		23	
Body weight, kg	69.0 (12.6)	70.5 (13.3)	-1.5 (-6.5-3.5)	66.3 (10.7)	2.6 (-3.1-8.4)
BMI[d], kg/m^2	22.2 (3.2)	22.7 (3.7)	-0.6 (-1.9-0.8)	22.1 (2.5)	0.1 (-1.3-1.6)
Change in weight, %	-13.1 ± 4.1	-11.2 ± 6.1	-1.9 (-5.5-1.7)	-9.6 ± 7.5	-3.5 (-7.7-0.8)
Mean weight loss at 3 months after surgery for C-D ≥ IIIb, n	29	19		16	
Body weight, kg	-8.4 (4.3)	-5.2 (3.7)	-3.1 (-5.6- -0.7)	-6.4 (4.7)	-2.0 (-4.8-0.8)
Change in weight, %	10.1 ± 3.5	6.6 ± 4.1	-3.5 (-6.2- -0.9)	8.5 ± 6.1	-1.6 (-4.7-1.5)

[a] Open Ivor Lewis, [b] Minimal Invasive Ivor Lewis, [c] Minimal Invasive McKeown, [d] Body Mass Index.

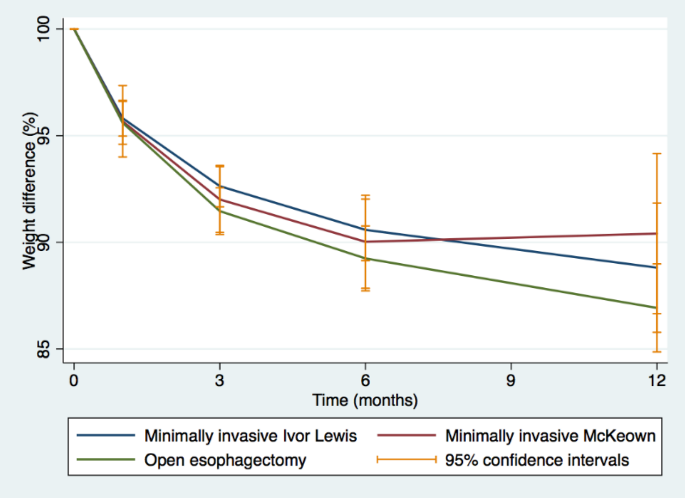


Figure 2. Weight development during first year after oesophagectomy, p-value IL versus MIIL: 0.045 and p-value IL versus MIMK: 0.176.

Table 4. Univariable and multivariable regression models of weight loss at 3 and 6 months postoperatively and use of enteral nutrition at 3 and 6 months postoperatively stratified by surgical technique.

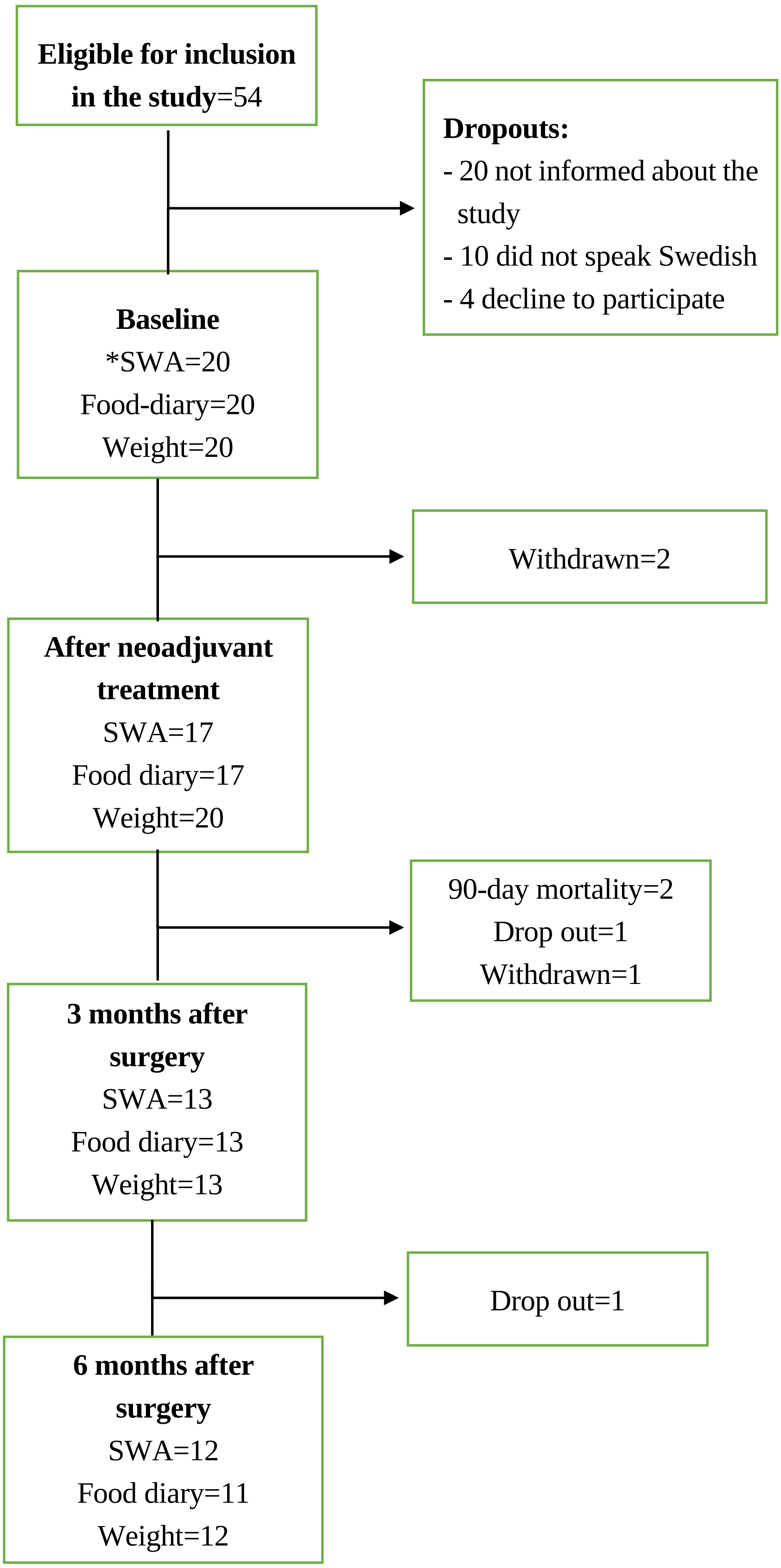
	IL[a]	MIIL[b]	MIMK[c]
≥10% weight loss		Odds ratio (95% CI)	
Univariable model ≥10% weight loss 3 months postop	1.0	0.80 (0.44-1.45)	0.67 (0.31-1.44)
Multivariable model ≥10 % weight loss 3 months postop*	1.0	0.99 (0.52-1.87)	0.80 (0.36-1.77)
Univariable model ≥10 % weight loss 6 months postop	1.0	0.92 (0.52-1.65)	0.72 (0.35-1.50)
Multivariable model ≥10 % weight loss 6 months postop*	1.0	1. 03 (0.56-1.91)	0.79 (0.37-1.68)
Patients with Clavien Dindo score ≥IIIb		Odds ratio (95% CI)	
Univariable model ≥10 % weight loss 3 months postop	1.0	0.23 (0.06-0.97)	0.41 (0.11-1.58)
Multivariable model ≥10 % weight loss 3 months postop*	1.0	0.22 (0.04-1.10)	0.33 (0.07-1.50)
Univariable model ≥10 % weight loss 6 months postop	1.0	0.86 (0.24-3-06)	1.07 (0.27-4.22)
Multivariable model ≥10 % weight loss 6 months postop*	1.0	1.31 (0.29-5.85)	1.17 (0.24-5.64)
Use of enteral nutrition		Odds ratio (95% CI)	
Univariable model enteral nutrition 3 months postop	1.0	0.99 (0.48-2.01)	1.81 (0.80-4.11)
Multivariable model enteral nutrition 3 months postop*	1.0	0.97 (0.46-2.06)	1.74 (0.74-4.11)
Univariable model enteral nutrition 6 months postop	1.0	0.98 (0.36-2.70)	2.05 (0.67-6.25)
Multivariable model enteral nutrition 6 months postop*	1.0	0.81 (0.28-2.37)	1.90 (0.60-6.07)

[a] Open Ivor Lewis, [b] Minimal Invasive Ivor Lewis, [c] Minimal Invasive McKeown.
*Adjusted for sex, ASA score, clinical tumour stage, neoadjuvant treatment, and operation technique.

6.3 STUDY III

From November 2015 to April 2017, we enrolled 20 patients submitted for neoadjuvant treatment and subsequent oesophagectomy to the study of whom 12 fulfilled the study protocol, Figure 3.

Figure 3. Flow chart demonstrating the recruitment of patients.



* SWA, SenseWear Armband

The patients wore the SWA on an average of 98.6%, 97.6%, 99.1% and 97.8% of the scheduled time points, respectively. However, six patients wore the SWA for just 2 days on one occasion each, and one of these patients carried the SWA for only 1 day at another occasion.

Nineteen patients received nCRT while one patient received nCT. All patients who underwent oesophagectomy had a minimally invasive approach of whom 17 patients (85%) had an intrathoracic anastomosis (Ivor Lewis) and two patients (10%) had a cervical anastomosis (McKeown). One patient was not resected due to metastatic disease discovered during surgery and received an oesophageal stent followed by palliative treatment. Two operations were converted to open surgery for technical reasons. One patient underwent adjuvant chemotherapy due to initial uncertainty about tumour location and type. Seven patients had severe postoperative complications classified as C-D ≥ IIIb.

Mean body weight decreased significantly during the preoperative period (p=0.005 and p=0.007, from 6 months before baseline to baseline and after neoadjuvant treatment, respectively) (Figure 4). The greatest weight loss, mean 5.6 kg, was seen at 3 months postoperative (p≤0.001), Table 5.

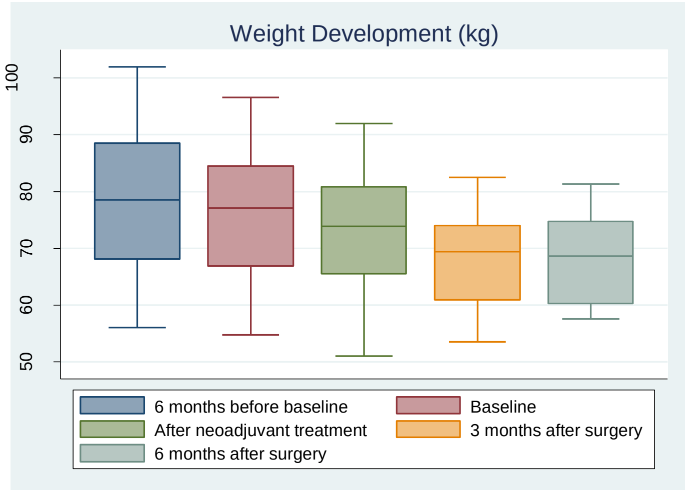


Figure 4. Median body weight expressed in kg at 6 months before baseline (p=0.005), at baseline, after completion of neoadjuvant treatment (p=0.010) and at 3 (p=0.002) and 6 (p=0.006) months after oesophagectomy, respectively. p-values are in comparison to baseline and estimated by Wilcoxon signed-rank test.

Patients mean PAL at baseline was 1.4 corresponding to “seated work with no option of moving around, and with some leisure activity” (135). This figure remained the same after neoadjuvant treatment and declined, compared to baseline, after surgery to 1.3 (same corresponding activity as 1.4) at both 3 and 6 months postoperatively, Table 5.

The mean EI was 2033 kcal (1730-2336 kcal) per day at baseline, this increased to 2236 kcal (2012-2461 kcal) after neoadjuvant treatment (p=0.012). The mean EI decreased at 3 months after surgery to 1759 kcal (1559-2059 kcal), p=0.155, and increased again at 6 months postoperatively. Table 5, Figure 5.

The mean TEE at baseline was 2259 kcal (2077-2440 kcal) per day and did almost stay the same after completion of neoadjuvant treatment, 2124 kcal (1943-2305 kcal), where after a significant decrease at 3 months after oesophagectomy was seen, 1929 kcal (1754-2105 kcal), p=0.004. The TEE was still at a significant lower level at 6 months after surgery compared to baseline, Table 5, Figure 6.

The mean protein intake followed the same curve as the EI with increased intake after neoadjuvant treatment compared to baseline (p=0.037), decreased at 3 months after surgery (p=0.177) and thereafter increased at 6 months after oesophagectomy (p=113), Table 5.

Only 30.0% (6/20) of the patients reached the recommended requirements of EI/kg BW per day (adjusted for overweight) at baseline, according to ESPEN guidelines on nutrition in cancer (82) and the guidelines of our department, which increased to 52.9% after neoadjuvant treatment. At 3 months after surgery this figure was 30.8% and at 6 months 54.5%, according to ESPEN guideline: Clinical nutrition in surgery (83).
Almost the same curve was seen in protein intake/kg BW per day (adjusted for overweight), with 65.0% of the patients at baseline and 88.2% after neoadjuvant treatment meeting the lower level of requirements. After oesophagectomy only one patient (7.7%) reached the protein requirement at 3 months after surgery and 18.2% (2/11) at 6 months.
Worth noticing is that mean EI and mean protein intake increased and decreased at the same time points but at 6 months after surgery EI was at similar levels as baseline while protein intake was at a non-significant lower level, Table 5.

Table 5. Mean weight, BMI, energy intake, protein intake, Total Energy Expenditure (TEE) and Physical Activity Level (PAL) in oesophageal cancer patients at the different time points during the courses of treatment.

	6 months before baseline[†] (n=20)	**p-value**	**Baseline** (n=20)	**p-value**	**After neoadjuvant treatment** (BW, BMI n=20) (SWA, EI n=17)	**p-value**	**3 months postoperative** (n=13)	**p-value**	**6 months postoperative** (n=12)	**p-value**
Weight (kg)	79.0 (72.8-85.1)	**0.005**	76.0 (70.1-82.0)		73.2 (67.9-78.5)	**0.007**	67.6 (62.1-73.1)	**<0.001**	68.2 (63.2-73.2)	**0.002**
BMI[a] (kg/m^2)	25.7 (24.3-27.1)	**0.008**	24.7 (23.4-26.1)		23.9 (22.6-25.1)	**0.010**	22.2 (20.9-23.6)	**<0.001**	22.3 (21.2-23.4)	**0.002**
Energy intake (kcal)			2033 (1730–2336)		2236 (2012-2461)	**0.012**	1759 (1459-2059)	0.155	2106 (1536-2675)	0.884
Energy intake/kg BW[b] (kcal)*			27.5 (23.8-31.1)		32.3 (28.4-36.1)	**0.008**	26.4 (21.6-31.2)	0.650	30.8 (22.6-39.1)	0.548
Protein intake (g)			83 (74-91)		88 (80-97)	**0.037**	70 (60-80)	0.177	73 (55-92)	0.113
Protein intake/kg BW[b] (g)*			1.1 (1.0-1.3)		1.3 (1.1-1.4)	**0.047**	1.1 (0.9-1.2)	0.549	1.1 (0.8-1.4)	0.370
TEE[c] (kcal)			2259 (2077-2440)		2124 (1943-2305)	0.468	1929 (1754-2105)	**0.004**	1996 (1819-2173)	**0.028**
TEE[c]**/kg BW** (kcal)			29.9 (28.1-31.8)		29.7 (27.2-32.2)	0.653	28.6 (26.6-30.7)	0.394	29.5 (26.7-32.2)	1.000
PAL[d]			1.4 (1.3-1.5)		1.4 (1.3-1.5)	0.889	1.3 (1.2-1.4)	0.065	1.3 (1.2-1.4)	0.121
Mean energy intake compared to mean energy expenditure, kcal (CI[e]**)**										
Energy Intake vs. TEE[c] (kcal)			-226 (-456 – 4)	0.178	112 (-123 – 348)	0.652	-171 (-431 – 89)	0.054	90 (-343 – 523)	0.327

All values are expressed as mean with 95% CI[e]. p-values are in comparison to baseline. Bold signifies $p<0.05$.

*Adjusted for overweight, †Reported by patients. [a]Body Mass Index, [b]Body Weight, [c]Total Energy Expenditure, [d]Physical Activity Level, [e]Confidence Interval.

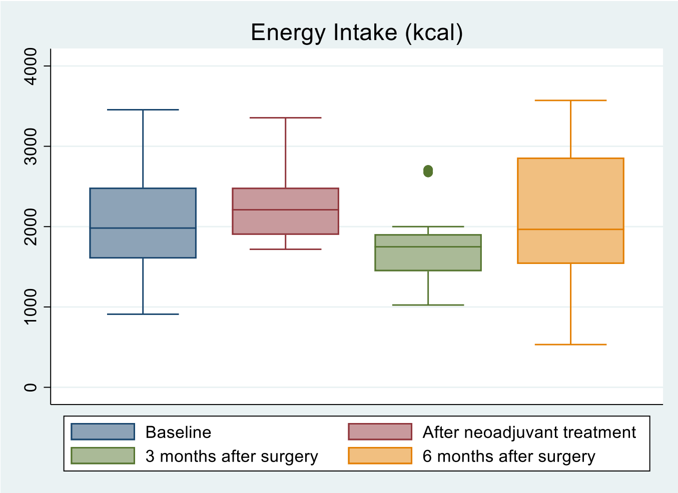


Figure 5. Median energy intake expressed in kcal at baseline, after completion of neoadjuvant treatment (p=0.009) and at 3 (p=0.101) and 6 (p=1.000) months after oesophagectomy, respectively. P-values are in comparison to baseline and estimated by Wilcoxon signed-rank test.

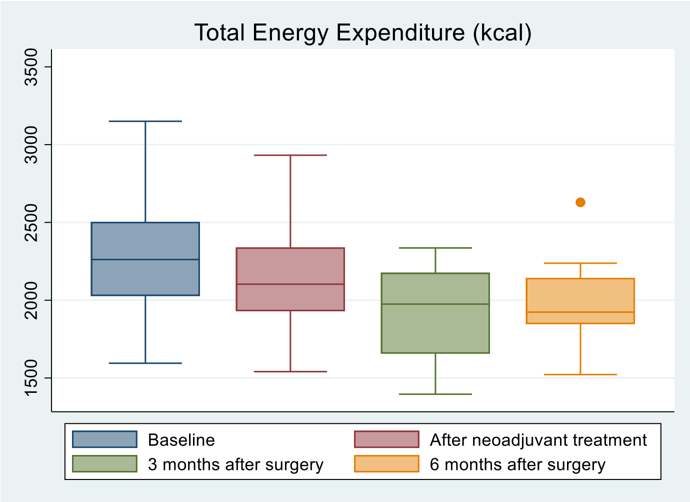


Figure 6. Median total energy expenditure (TEE) expressed in kcal at baseline, after completion of neoadjuvant therapy (p=0.246) and at 3 (p=0.005) and 6 (p=0.031) months after oesophagectomy, respectively. P-values are in comparison to baseline and estimated by Wilcoxon signed-rank test.

6.4 STUDY IV

There were 249 patients included in the trial where 125 were randomized to standard treatment and 124 to prolonged delay to surgery. Mean weight loss before diagnosis was similar between the groups with 6.0% (0-28.1%) in standard arm and 5.2% (0-29.9%) in the prolonged delay arm. From baseline to surgery the mean weight loss in the standard arm was 2.66 kg and in the prolonged delay arm 0.65 kg (p<0.001). The patients in the prolonged waiting time to surgery group increased their weight significantly, 1.91 kg (p<00.1), during the extended time to surgery and had returned to approximately the same weight as baseline (p=0.131), Figure 7. The same weight development was seen within the malnourished and non-malnourished subgroups. The mean dysphagia score improved significantly from baseline to surgery in both trial arms (p-values<0.001) where a further, but not significant (p=0.223), improvement during the prolonged waiting time to surgery was noted, Figure 8.

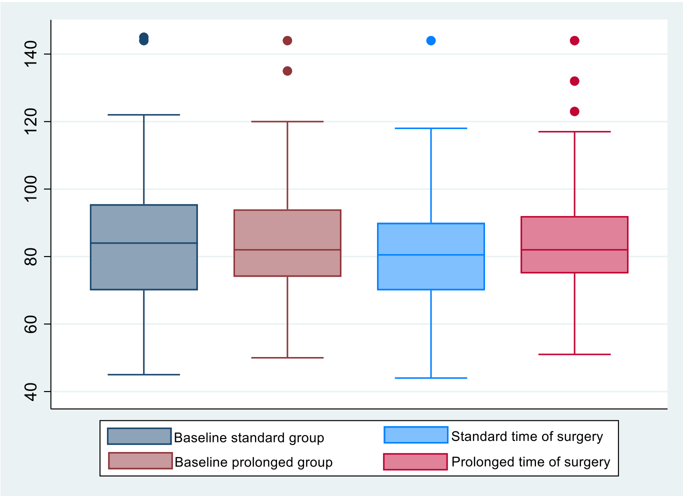


Figure 7. Median weight development in kg baseline to time for surgery. Standard time to surgery group, p-value <0.001. Prolonged time to surgery group, p-value=0.131.

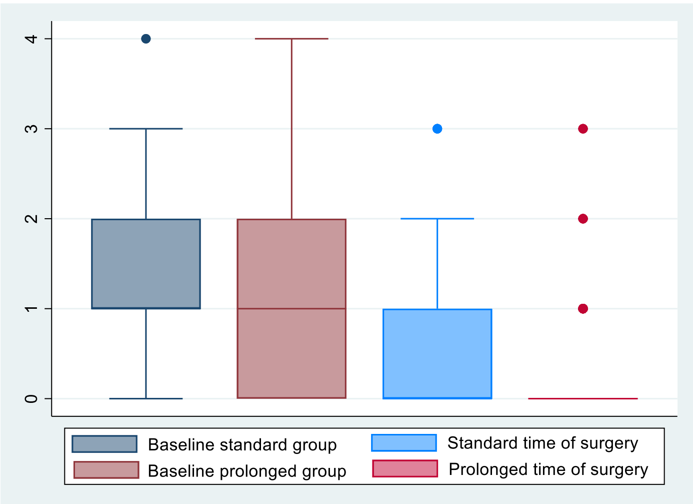


Figure 8. Median dysphagia development according to Ogilvie score baseline to surgery. Standard time to surgery group, p-value <0.001. Prolonged time to surgery group, p-value <0.001.

There were no significant differences between the two groups regarding postoperative complications when divided in malnourished or not malnourished patients at baseline according to GLIM criteria (p=0.340 for C-D II-V and p=0.760 for C-D IIIb-V), see Table 6. Focusing only on patients malnourished at baseline in each group, we did not see any differences regarding overall nor severe postoperative complications (odds ratio 0.90, 95% CI: 0.29-2.77 and odds ratio 1.13, 95% CI: 0.32-4.00), Table 7.

Table 6. Complications after surgery in patients malnourished or not malnourished at baseline according to GLIM criteria, comparison between standard time to surgery and prolonged time to surgery.

N (%)	**Standard time to surgery 4-6 weeks**		**Prolonged time to surgery 10-12 weeks**		**p-value**
	Malnourished	Not malnourished	Malnourished	Not malnourished	
All patients	28 (100.0)	88 (100.0)	22 (100.0)	83 (100.0)	0.572
Clavien Dindo II-V	16 (57.1)	58 (65.9)	12 (54.5)	65 (78.3)	0.340
Clavien Dindo IIIb-V	7 (25.0)	30 (34.1)	6 (27.3)	31 (37.3)	0.760
Anastomotic leak	4 (14.3)	17 (19.3)	4 (18.2)	18 (21.7)	1.000
Pneumonia	8 (28.6)	26 (29.5)	7 (31.8)	20 (24.1)	0.829

Table 7. Univariable logistic regression model for postoperative complications in patients with malnutrition according to GLIM at baseline.

Odds Ratio (95% confidence interval)	**Clavien Dindo II-V**	**p-value**	**Clavien Dindo IIIb-V**	**p-value**
Standard time to surgery	1.0		1.0	
Prolonged time to surgery	0.90 (0.29-2.77)	0.854	1.13 (0.32-4.00)	0.856

7 DISCUSSION

7.1 RESULTS DISCUSSION

7.1.1 Study I

In this prospective cohort pilot study, we found that neoadjuvant treatment with platin-5FU-based chemotherapy, with or without the addition of radiation, significantly reduced dysphagia in patients with oesophageal and gastroesophageal junction cancer. This effect was statistically significant already after the first cycle of chemotherapy. Appetite did also improve significantly during the neoadjuvant treatment. There was no association between relief of dysphagia and histological response.

In a previous study improvement in dysphagia was seen after two cycles of chemotherapy, with no association between improvements of dysphagia and histological response (12) and in another study improved or stable dysphagia after completed nCT was reported, but not after nCRT (136). In a more recent study, dysphagia improved after first cycle of chemotherapy with maintenance of weight (45), as seen in our study.

Esophagitis due to radiotherapy develops in up to 28% of patients aggravating swallowing difficulties (8). However, in our study no patients receiving radiation did report swallowing discomfort or worsen appetite and there was no difference between patients receiving nCRT or nCT.

In the present study 37% needed EN or PN, for different reasons and mainly for a limited period, highlighting individualised and close nutritional support, also supported in another study (45).

The proportion of patients with histological response, 23% with partial and 23% with complete response, was in line with other studies (8, 137, 138). Surprisingly, there was no difference in improvement of dysphagia between patients with clear histological response and patients with no or very little histological response. The improved dysphagia seems to be explained by reduced tumour volume and not to histological response.

The result from this study has increased the knowledge in managing dysphagia from time of diagnosis, during neoadjuvant treatment and until surgery. Previous studies have suggested that neoadjuvant treatment may have a significant negative impact on the nutritional status of patients with oesophageal cancer compared to those undergoing surgery alone (5, 139, 140) but this was not supported by our findings.

The main limitation of this study is the small number of patients as well as that the data were collected at only one centre thus increasing the risk of selection bias. This study may introduce type II error however, the findings were so clear that this is unlikely to completely explain our finding. The strength of the study is the prospective collection of data reducing the risk of information bias.

7.1.2 Study II

The implementation of minimally invasive techniques aims to minimize the surgical trauma, and different benefits as mentioned before have been shown (6, 14), but data regarding the impact of MIO on weight development are scarce.
In this retrospective study comparing weight development from baseline up to one year post surgery after different surgical techniques there was no significant difference between the traditional open Ivor Lewis oesophagectomy (IL) compared to MIIL or MIMK. However, there was a trend towards less weight loss after MIO, with 11.2% and 9.6% weight loss at 12 months for MIIL and MIMK respectively, compared to 13.1% for IL. In patients suffering from severe complications (C-D score ≥ IIIb) after MIIL, there was a non-significant trend towards a lower risk of ≥10% weight loss 3 months postoperatively compared to IL.

We noticed the most distinct weight loss during the first three month after surgery regardless approach. Most studies have a follow-up regarding weight at six months postoperatively and several studies report 5-12% weight loss during that time (19-22).
Interestingly, in our cohort, we found that patients who had undergone MIMK slightly increased their weight 6 to 12 months after surgery while patients after IL and MIIL continued to lose weight but to a less extent. During surgery patients operated with McKeown procedure retain more of the gastric fundus, where majority of the cells producing ghrelin are present, compared to the Ivor Lewis approach (113), which might be decisive for the patients appetite.

There were more patients in the MIO groups receiving feeding jejunostomy (98.8% and 97.6% in the MIIL and MIMK, respectively) compared to IL (75.0%) owing to change in treatment tradition over the years. To address the possible bias of this discrepancy on weight loss, we performed a separate analysis only including patients with a jejunostomy, but the results remained the same.

Patients receiving supportive EN at home after oesophagectomy still lose weight but to a lesser extent and may have an improved quality of life (105-107). The positive effect of extended support of EN was shown in patients malnourished before MIO receiving EN (500-1000 kcal/day) for 3 months after discharge which reduced the risk of malnutrition and improved their quality of life (106).

Patients after MIMK were supported by EN for a longer time compared to the other two groups, median 57.0 days (0-538 days, p=0.022 compared to IL), which may be explained by the higher incident of anastomotic leakage in these patients resulting in strictures and dysphagia. The McKeown procedure is also associated with increased vocal cord paralysis, which might lead to risk for aspiration due to difficulties swallowing. These two complications may require diet modifications and longer need of EN explaining the longer need of EN for patients after MIMK. van Workum et al. reported better function after intrathoracic anastomosis compared to cervical anastomosis with less dysphagia, anastomotic strictures and recurrent laryngeal nerve palsy (68).

This study is a retrospective single centre study with all the associated limitations. The inherent risk of confounding due to differences in baseline characteristics between the three groups was addressed by adjustment using multivariable regression models. Another limitation is the fact that the different surgical techniques of oesophagectomy are unevenly distributed over the years during the study period which contributes with an inherent risk of residual confounding by possible and successive improvements in perioperative care as well as increasing caseload due to centralisation over the recent years.

7.1.3 Study III

In this prospective cohort study following patients before neoadjuvant treatment to six months after oesophagectomy we found weight to steadily decrease during preoperative phase and the first 3 months after surgery due to negative energy balance. This confirms previously described negative energy balance in these patients (5, 33).

Early routine counselling and proper nutritional support have a positive impact on patient's nutritional status and reduce the risk of invasive management of malnutrition (10, 33).
A group of patients receiving intensive nutritional support delivered by a dietitian increased their weight from their first visit to outpatient clinic until oesophagectomy compared to a control group (84). All patients in the intervention group received nutritional counselling by a specialised dietitian at first visit and control group did only receive preoperative dietary counselling when initiated by a doctor. Patients in the intervention group were contacted every 1-2 weeks during the treatment trajectory by either the surgical dietitian or the oncology dietitian.

In our study, according to international guidelines, all patients were offered counselling by a specialist dietitian throughout the pre and postoperative phases, which might contribute to the improvement of energy intake during the neoadjuvant treatment period. The improved energy intake is most certain combined with the positive effect of chemotherapy on patients´ dysphagia (141). The TEE was unchanged before and after neoadjuvant treatment but with a persistent weight loss emphasizing the need of nutritional support during this phase.

Our data showed fewer patients reaching the requirements in EI at baseline and at 3 months after surgery compared to after neoadjuvant treatment and at 6 months post oesophagectomy. Regarding the protein intake more patients met the requirements before compared to after oesophagectomy. However, the requirements were set to a lower level (i.e. 1.0 g protein/kg BW per day) before surgery while after surgery the requirement was 1.5 g protein/kg BW per day which can partly explain our findings.
There are few studies reporting nutritional intake before and after oesophagectomy. Ludwig et al. reported 78% (25/32) of the patients approximately 3 years after oesophagectomy to reach recommended EI based on ideal body weight (21), which probably is translated to 100% of estimated requirements.

In a previous study, they reported 77% (54/70) to reach the energy requirements and 91% (64/70) reached the requirements for protein six months after oesophagectomy (119). Another

study with patients after both oesophagectomy and total gastrectomy reported sufficiently energy and protein intake at three months after surgery in 61% (23/38) and 55% (21/38) of the patients, respectively, and at six months postoperatively the corresponding numbers were 94% (32/35) and 77% (27/35), respectively (108). In these studies, they used a mean intake >90% of estimated requirements as adequate, according to risk of error in self-reporting.
In a study by Ryan et al. a median intake >75% of estimated energy and protein requirements was considered as adequate (104).

In our study we used 100% of requirement as adequate but in retrospect it might have been more accurate to use both 75% and 90% as margins given the possible underreporting, insecurity in reporting, and the limitations of correct evaluation of the food diaries.

Food intake can be measured by a 24 h recall where patients start with the last meal and recall 24 h back or measured by food record where the patients write down everything they eat and drink for usually 3 consecutive days, preferably 2 weekdays and 1 day during the weekend (142). In food record the food is weighed or estimated by using household utensils, where the weighing method often is regarded the golden standard. The 3 day food record seem to be more accurate regarding actually energy intake compared to a longer period of 5 or 7 days (143).
In the present study there was no requirement whether the patients should report weekdays or days during the weekend. On the other hand, it was important to start reporting the next day after receiving the SWA and food diary in order to decrease potential information bias.

The reliability in reported nutritional intake in food diary is often limited by misreporting (144). Based on previous studies it has to be taken into account that an underestimation of EI is reported to be 10-20% regardless gender while overestimation is a rare problem (144). The same confounders are most probably apparent in our study.
TEE decreased significantly at three months after oesophagectomy and a decrease was recorded for EI, despite supplementation of EN, which might be explained by increased response of postprandial satiety gut hormones; glucagon-like peptide 1 (GLP-1) and peptide YY (PYY), present in patients after oesophagectomy (117, 145).

The results of this study highlight the need of close follow up to secure compliance of extended EN and increased food intake. As already mentioned, some recent studies focusing on extended home EN indicated that patients continued to lose weight but to a lesser extent leading to improved quality of life (105-107).

Different mechanisms cause weight loss after oesophagectomy and regular follow up with evaluation of symptoms affecting dietary intake is important for prompt food modifications, adjustment of EN and interventions to avoid weight loss. Common causes of weight loss after oesophagectomy are delayed gastric conduit emptying, dysphagia and dumping syndrome (23, 146) where dietary modifications can relieve some of the symptoms. Further factors impairing food intake are eating difficulties, early satiety, inhibited passage due to high viscosity, reflux and absence of hunger (22, 23).

The impaired function in the gastric conduit affects food intake thus making it difficult to reach required amount of energy and protein intake. Ludwig et al. found dysphagia to certain foods, mostly bread and steak, in 52% (25 of 48) of the patients 6 months after oesophagectomy and after 1 year 38% (18 of 48) of the patients reported periodic dysphagia to certain foods if they forgot to chew thoroughly (21).

The main limitation of this study was the difficulties recruiting a larger number of patients, partly due to limited presence of a dedicated dietitian at the outpatient clinic when needed and partly due to limited SWA devices. Unfortunately, this affected the inclusion of otherwise eligible patients.

7.1.4 Study IV

In this study patients in the group with prolonged time to surgery after completed neoadjuvant treatment had a significantly better weight development compared to the group with standard time to surgery. There was no difference regarding the effect of malnutrition at baseline on the incidence of postoperative complications between standard and prolonged waiting time to oesophagectomy.

Nutritional intake is often affected due to tumour location in this group of patients and oncological treatment may further affect their nutritional status negatively. The symptoms affecting nutritional intake arising from nCRT usually take a few weeks to wear off. The interval time between nCRT and surgery offers patients the opportunity to improve their nutritional status before oesophagectomy (147) and with prolonged time to surgery patients have extended time to recover. As seen in the present study, patients waiting longer for surgery gained weight during the prolonged time. The result is in line with another study where weight improved 12 weeks after completion of nCRT (148).

The improvement of dysphagia during nCRT has been demonstrated in previous studies (141, 149) and is in line with the present study where dysphagia further improved, non-significantly, during the prolonged time to surgery.

Malnutrition is a risk factor for postoperative complications, especially after upper GI surgery (83). To improve clinical outcomes throughout the treatment of patients with oesophageal cancer, identification and treatment of weight loss and malnutrition are important (10). Preoperative malnutrition according to GLIM criteria was investigated among patients undergoing GI surgery and they found malnutrition to be common and associated with increased risk of severe complications after surgery (150). Conversely, another study did not find any correlation between preoperative weight loss of 10% or more and postoperative complications (151).

Regular follow up of body weight and screening for nutritional problems during the treatment phases are valuable though it changes over time (152) requiring close observations and support of a dietitian with different strategies according to severity of malnutrition (33). Malnutrition being a risk factor for bad compliance to nCRT is well known and prompt nutritional intervention including diet modifications and ONS is important to preserve or restore nutritional status (10) and intensive nutritional support by a dietitian is correlated with preoperative weight maintenance and a decrease in severe complications after oesophagectomy (84).

The main strength in this study is the randomised multicentre design with complete follow up. A limitation is that patients with considerable weight loss and problems with dysphagia hypothetically might not want to participate in the study in case they are randomised to prolonged time to surgery. Another limitation is that the originally trial was designed based on another primary outcome namely, to compare complete pathological response between the arms.

7.2 METHODOLOGICAL DISCUSSION

Studies can be either experimental or observational and in this thesis they all are observational, even though study IV is a sub study with data from an experimental trial.

The two main types of observational studies are cohort and case-control studies. All studies in this thesis are cohort studies, with all patients having oesophageal cancer and are followed during neoadjuvant treatment (I), after oesophagectomy (II) or before and after the neoadjuvant treatment as well as after oesophagectomy (III and IV).

7.2.1 Validity

In research it is vital to obtain accuracy in estimation of the results and the two components of accuracy is validity and precision. Errors in estimation that may affect the results can be random or systematic, the latter are commonly referred to as bias.
Bias is the opposite to validity and, estimates with little systemic errors can be described as valid. Random error is the opposite to precision and, estimates with little random errors can be described as precise. The more people included in a study the less errors in case of random error. If systematic error the error remains irrespective of inclusion of more people.
Biases can be classified into three broad categories namely selection bias, information bias and confounding (153). The errors may result in an under or overestimation of the results and affect the internal validity.

7.2.1.1 Selection bias

Selection bias can arise when individuals are differently likely to be included in a study.
In study I, initially only patients included in an ongoing RCT were asked to participate, but eventually during the course of the study period all patients fulfilling the criteria were eligible for inclusion. In study II, with a retrospective design, all patients living within the region were included in the analysis. Consequently, the risk for selection bias in these two studies is reduced.
In study III, patients who were more affected by the disease might have been less keen to participate. Moreover, the study was affected by limited availability of a dedicated dietitian in periods with heavy workload as well as limited number of devices available for use. All these

above-mentioned factors have limited our inclusion possibilities, adding an obvious risk for selection bias, which may impact our results. Furthermore, of 20 patients included only 12 patients managed to complete the study.
In study IV, as part of an RCT, the risk of selection bias was reduced since all eligible patients were asked to participate in the trial.

7.2.1.2 Information bias

Information bias can arise when the information collected about or from study participants is incorrect; information bias is also called misclassification. This can occur for example when typing height in a box instead of weight or miss to put a full stop when typing figures. Recall bias is a common information bias and people have different ability remembering.
In studies I-III data were collected from medical records where information can have been incorrectly registered. Additionally, in study II and III data were retrieved from a register with the aforementioned risks.

In study III and IV patients` weight at six months before diagnosis was self-reported with an obvious risk of information bias. However, this bias is probably evenly distributed in the groups in study IV due to the randomised design. Moreover, self-reported body weight has previously been showed to have a good validity (22).

In study III, the weight was measured at the outpatient clinic at two occasions before surgery while the measurements after surgery were mostly performed at home. Patients were instructed to measure their weight in light in-door clothes, but this obviously could not be controlled. Even at the outpatients' clinic patients were weighed at different times during the day at the different time points depending on their doctor appointment.
Thus, the validity in weight development can be therefore hampered in all the studies.

In study III we used SWA to measure TEE and even if the SWA underestimates the TEE (126, 154) it is possible to see differences over time in patients to detect increased or decreased requirement during treatment.
SWA has mainly been validated on healthy people and not in patients with cancer, but "ESPEN guidelines on nutrition in cancer patients" concluded that while the REE might be higher in patients with cancer, TEE appears to be similar to healthy controls though the former are less physically active (82).

The registration of food and drinks consumed in the food diary is difficult to control and some of the patients weighed their food while others measured the food using household utensils or reported amount. A low rate of the patients reached the energy and protein recommendations, which raises the question if it was because of underreporting or if the actual intake was low. In a review it was found 11.9-44% being under reporters in studies using estimated food records and 14.3-38.5% being under reporters in studies using weighed food records (144). On average the underestimation of EI was 10.4-20.2%.
It can be hypothesised that the same patients misreported in the same way at all the occasions making the differences between the time points fairly reliable.

7.2.1.3 Confounding

To be a confounder the variable need to be associated with both the exposure and the outcome. Confounding can be dealt with using one of two methods in the data analysis, stratification or regression models (153). When controlling for confounding as in regression models associations that were made may disappear leaving a true result.
Residual confounding in an analysis is the remaining error after adjustments have been made. In study II we used the known confounders gender, ASA score, clinical tumour stage, neoadjuvant treatment, and operation technique in our regression analyses in order to reduce the risk of confounding. In study IV, the risk of confounding is reduced due to the randomised design.

7.2.1.4 Random errors

Random errors can either be type I or type II error. Type I error is when a null hypothesis is rejected, even though it is accurate and should not be rejected. Type II occurs when one accepts a null hypothesis that is actually false. These errors often occur due to small sample sizes.
In study I, due to small sample size, a type II error was considered regarding no or little histological response but significant relief of dysphagia.

7.2.1.5 Generalisability

Generalisability or external validity is the validity of applying the conclusions of a scientific study outside the context of that study.
Studies I-III were performed at a single centre and the sample sizes are small making it difficult to generalise. However, in study I the result of decreased dysphagia after first cycle of nCT as well as after completion of nCT or nCRT was significant even in this small population indicating possible external validity. The modest trend towards less weight loss after MIO compared to open Ivor Lewis in study II indicates that minimising the surgical trauma seems to be beneficial for patients with oesophageal cancer but a larger scale trial must address this question. This is of extra importance since MIO is gaining popularity worldwide.

Postoperative weight loss after oesophagectomy is well known and study III confirms previous studies (19-21). This together with decrease in energy and protein intake after surgery highlight the importance of nutritional support and close follow up in the first three months post oesophagectomy which can be generalised and implemented in other hospitals.

Finally, in study IV a beneficial weight development was noted for the patients in the prolonged time to surgery group compared to the standard group, which may be of significance in tolerating such a demanding procedure. If the oncological outcomes are not jeopardised by the longer waiting time the medical team together with the patient could have a more flexible timeline to schedule the forthcoming surgery based on individual's recovery after nCRT.

8 CONCLUSIONS

The overall conclusions in this thesis are:

- Patients experienced significantly relief of dysphagia already after the first cycle of nCT which further improved after completion of both nCT and nCRT.
- Relief of dysphagia did not correlate to histological tumour response after neoadjuvant treatment.
- The greater trauma associated with traditional open oesophagectomy did not result in more weight loss compared to minimally invasive surgical techniques.
- There was a non significant trend towards a lower risk of losing ≥10% at 3 months after MIIL compared to open Ivor Lewis in patients that did suffer from severe postoperative compications (C-D ≥IIIb).
- The initiation of nutritional interventions to achieve and maintain energy balance must be at time of diagnosis and the most vulnerable time for negative energy balance is at baseline and at three months after oesophagectomy.
- To achieve or maintan nutritional status regular follow up thorughout the neoadjuvant treatment and during the first three month after oesophagectomy is important.
- Prolonged time to surgery compared to standard time to surgery was beneficial for patients weight and patients in prolonged time to surgery group had almost the same weight at time for oesophagectomy as at baseline.
- Dysphagia improved significantly in both prolonged time to surgery and standard time to surgery and improved further, but not significantly, during the longer time to surgery.
- There was no difference in postoperative complications between patients malnourished at baseline and the timing of surgery.

9 POINTS OF PERSPECTIVE

9.1 CLINICAL IMPLICATIONS

To maintain and/or improve nutritional status, early interventions are needed for patients with oesophageal cancer. In this group of patients where dysphagia and weight loss are common symptoms, early and regular follow up by a specialised dietitian, as previous suggested, can effectively capture symptoms affecting energy intake and weight development. With the results from study II and study III, and support from the literature, we have introduced visit to a dietitian already at first visit to the outpatient clinic at our department for early nutrition interventions. Further, we introduced standardised and regular follow up by a dietitian every two weeks during the investigation phase and during the initial period post oesophagectomy until patients are weight stable without support of enteral nutrition and without nutritional issues requiring special attention.

9.2 FUTURE RESEARCH

- It would be of clinical value to perform a larger scale study with more participants using food diaries at the same time-points as in study III, with close follow up to be able to detect possible misreporting of food intake.

- As the two major subtypes of oesophageal cancer, SCC and AC, are considered two different types of cancers there would be of interest to separate the patients for follow up regarding dysphagia and weight development throughout the treatment trajectory.

- MIO is gaining popularity worldwide. Robot oesophagectomy is the latest development within the field of oesophageal cancer surgery. It would be interesting to do a direct comparison between patients who undergo MIIL oesophagectomy compared to those with robot assisted one with regards to weight development and need of use of EN.

- There are data supporting that extended home EN may be beneficial for patients who undergo oesophagectomy. I would like to investigate whether prolonged home EN 3 months post oesophagectomy has a positive impact on patients weight development and health related quality of life.

- Chyle leakage is a known postoperative complication after oesophagectomy. I would like to study if patients after extended lymph node dissection, with potential higher risk of leakage, would benefit from EN containing MCT fat compared to standard EN from start in terms of fewer postoperative complications and faster recovery.

- Furthermore, in case of verified chyle leakage I would like to compare immediate total PN to EN containing MCT-fat for a faster reduction in chyle leak.

10 ACKNOWLEDGEMENTS

This thesis has been done with contribution, advices, support, and encouragement from several people.
Particularly, I would like to warmly thank:

All patients participating in the studies.

Ioannis Rouvelas, my main supervisor, for your never-ending encouragement, patience, and support. For prompt answers and always being available. For believing in me and being able to make me feel confident when I am struggling, for being the best main supervisor I could ever have!

Magnus Nilsson, my co-supervisor, for your support and making my PhD journey possible. For prompt response, insight thoughts and for improvements of the manuscripts.

Mats Lindblad, my co-supervisor, for your support, valuable comments and for improving the manuscripts.

Gerd Faxén-Irving, my mentor, for support and encouragement.

Fredrik Klevebro, for your support, encouragement and help with the statistics and your ability to make it more understanding.

Jon Tsai, for a short period my main supervisor, for your support.

Lars Lundell, for your passion in research and for improving the manuscripts.

Koshi Kumagai, for help with the statistics in paper I.

Hélène Jansson, for your valuable support, help and always being so nice and quick in answering my e-mails.
Nina Gustafsson, for your patience and help. **Agneta Wittlock**, for your prompt answers and guidance.

Jörgen Larsson, my first manager as a dietitian at *Gastrocentrum*, for introducing me to research and for letting me be a part of the Nordic Nutrition Academy. **Greger Lindberg**, for your belief in dietitians.

Berit Sunde, my dear friend, colleague, and fellow PhD student. It has been joyful to do this journey with you; all the laughter, walks and congresses.

Catarina Lindqvist, my dear friend, fellow research dietitian and colleague, for all support, wise advices, long fruitful discussions, laughter and as a travel partner to congresses.

Ylva Orrevall, for your support and advices.

Andrianos Tsekrekos, Gabriella von Döbeln, Klara Nilsson, **Magnus Konradsson** and all colleagues in the research group for oesophageal and gastric cancer.

Ulla Nuutinen, Helena Sundlöf and Ramona Karlsson, for tremendous cooperation at the outpatient clinic, all talks, and laughs. **Ingela Nyberg**, the first contact nurse I worked with, thank you for always involving me at an early stage at the outpatient clinic and contributing to my, since long time now, obvious position at the clinic. **Jan-Erik Holm**, for talks and laughs.

Ella Veidemann, my manager, for good cooperation and for finding solutions for me to be away from clinic and continuing my journey as a PhD student. **Christina Lejon**, former *samordnade chefsdietist*, for your encouragement and inspiration with long term goals.

Elisabet Lundström and Lotta Klinge-Härberg, my present and former managers, for your support.

All my **former and present dietitian colleagues** at Karolinska University Hospital, for support and laughter.

All the staff throughout the years at the wards at ÖAK, lately oesophageal and gastric (esovent) ward.

Anna Richardsson, my best friend, for always listening, encourage me, believing in me and reminding me why I am doing this. **Annika Wallin**, my best friend, for believing in me and all long walks and talks.

All my friends, for all support and all good times taking my mind of the hard work being a PhD student.

Jennie Bäckman, my beloved sister, for always believing in me, all our nights at IKEA, "long" walks with all laughter.

Mina älskade föräldrar, **Jan-Erik och Cerstin**, för all kärlek, allt stöd, att ni alltid finns där för mig och tror på mig.

Kenneth, my beloved husband, for your support, patience, and love. For always having a small bottle of chilled champagne in case there is something to celebrate.
Simon and Ebba, my beloved children, thank you for all understanding and encouraging words and putting everything into perspective.
This would not been possible without you. You mean the world to me.

11 REFERENCES

1. Schneider BJ, Urba SG. Preoperative chemoradiation for the treatment of locoregional esophageal cancer: the standard of care? Seminars in radiation oncology. 2007;17(1):45-52.

2. Smyth EC, Lagergren J, Fitzgerald RC, Lordick F, Shah MA, Lagergren P, et al. Oesophageal cancer. Nature reviews Disease primers. 2017;3:17048.

3. Kight CE. Nutrition considerations in esophagectomy patients. Nutrition in clinical practice : official publication of the American Society for Parenteral and Enteral Nutrition. 2008;23(5):521-8.

4. Bozzetti F. Nutritional support in patients with oesophageal cancer. Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer. 2010;18 Suppl 2:S41-50.

5. Mariette C, De Botton ML, Piessen G. Surgery in esophageal and gastric cancer patients: what is the role for nutrition support in your daily practice? Annals of surgical oncology. 2012;19(7):2128-34.

6. Biere SS, van Berge Henegouwen MI, Maas KW, Bonavina L, Rosman C, Garcia JR, et al. Minimally invasive versus open oesophagectomy for patients with oesophageal cancer: a multicentre, open-label, randomised controlled trial. Lancet (London, England). 2012;379(9829):1887-92.

7. Sjoquist KM, Burmeister BH, Smithers BM, Zalcberg JR, Simes RJ, Barbour A, et al. Survival after neoadjuvant chemotherapy or chemoradiotherapy for resectable oesophageal carcinoma: an updated meta-analysis. The Lancet Oncology. 2011;12(7):681-92.

8. van Hagen P, Hulshof MC, van Lanschot JJ, Steyerberg EW, van Berge Henegouwen MI, Wijnhoven BP, et al. Preoperative chemoradiotherapy for esophageal or junctional cancer. The New England journal of medicine. 2012;366(22):2074-84.

9. Shapiro J, van Lanschot JJB, Hulshof M, van Hagen P, van Berge Henegouwen MI, Wijnhoven BPL, et al. Neoadjuvant chemoradiotherapy plus surgery versus surgery alone for oesophageal or junctional cancer (CROSS): long-term results of a randomised controlled trial. The Lancet Oncology. 2015;16(9):1090-8.

10. Riccardi D, Allen K. Nutritional Management of Patients With Esophageal and Esophagogastric Junction Cancer. Cancer control : journal of the Moffitt Cancer Center. 1999;6(1):64-72.

11. Jordan T, Mastnak DM, Palamar N, Kozjek NR. Nutritional Therapy for Patients with Esophageal Cancer. Nutrition and cancer. 2018;70(1):23-9.

12. Ribi K, Koeberle D, Schuller JC, Honegger H, Roth A, Hess V, et al. Is a change in patient-reported dysphagia after induction chemotherapy in locally advanced esophageal cancer a predictive factor for pathological response to neoadjuvant chemoradiation? Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer. 2009;17(8):1109-16.

13. Knox JJ, Wong R, Visbal AL, Horgan AM, Guindi M, Hornby J, et al. Phase 2 trial of preoperative irinotecan plus cisplatin and conformal radiotherapy, followed by surgery for esophageal cancer. Cancer. 2010;116(17):4023-32.

14. Gisbertz SS, Hagens ERC, Ruurda JP, Schneider PM, Tan LJ, Domrachev SA, et al. The evolution of surgical approach for esophageal cancer. Annals of the New York Academy of Sciences. 2018.

15. Luketich JD, Pennathur A, Awais O, Levy RM, Keeley S, Shende M, et al. Outcomes after minimally invasive esophagectomy: review of over 1000 patients. Annals of surgery. 2012;256(1):95-103.

16. Nagpal K, Ahmed K, Vats A, Yakoub D, James D, Ashrafian H, et al. Is minimally invasive surgery beneficial in the management of esophageal cancer? A meta-analysis. Surgical endoscopy. 2010;24(7):1621-9.

17. Levy RM, Trivedi D, Luketich JD. Minimally invasive esophagectomy. The Surgical clinics of North America. 2012;92(5):1265-85.

18. Yibulayin W, Abulizi S, Lv H, Sun W. Minimally invasive oesophagectomy versus open esophagectomy for resectable esophageal cancer: a meta-analysis. World J Surg Oncol. 2016;14(1):304.

19. Baker M, Halliday V, Williams RN, Bowrey DJ. A systematic review of the nutritional consequences of esophagectomy. Clinical nutrition (Edinburgh, Scotland). 2016;35(5):987-94.

20. Couper G. Jejunostomy after oesophagectomy: a review of evidence and current practice. The Proceedings of the Nutrition Society. 2011;70(3):316-20.

21. Ludwig DJ, Thirlby RC, Low DE. A prospective evaluation of dietary status and symptoms after near-total esophagectomy without gastric emptying procedure. American journal of surgery. 2001;181(5):454-8.

22. Martin L, Lagergren J, Lindblad M, Rouvelas I, Lagergren P. Malnutrition after oesophageal cancer surgery in Sweden. The British journal of surgery. 2007;94(12):1496-500.

23. Haverkort EB, Binnekade JM, Busch OR, van Berge Henegouwen MI, de Haan RJ, Gouma DJ. Presence and persistence of nutrition-related symptoms during the first year following esophagectomy with gastric tube reconstruction in clinically disease-free patients. World journal of surgery. 2010;34(12):2844-52.

24. Steenhagen E, van Vulpen JK, van Hillegersberg R, May AM, Siersema PD. Nutrition in peri-operative esophageal cancer management. Expert review of gastroenterology & hepatology. 2017;11(7):663-72.

25. Touchefeu Y, Archambeaud I, Landi B, Lievre A, Lepere C, Rougier P, et al. Chemotherapy versus self-expanding metal stent as primary treatment of severe dysphagia from unresectable oesophageal or gastro-oesophageal junction cancer. Digestive and liver disease : official journal of the Italian Society of Gastroenterology and the Italian Association for the Study of the Liver. 2014;46(3):283-6.

26. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA: a cancer journal for clinicians. 2018;68(6):394-424.

27. Xie SH, Lagergren J. Social group disparities in the incidence and prognosis of oesophageal cancer. United European gastroenterology journal. 2018;6(3):343-8.

28. Short MW, Burgers KG, Fry VT. Esophageal Cancer. American family physician. 2017;95(1):22-8.

29. Odelli C, Burgess D, Bateman L, Hughes A, Ackland S, Gillies J, et al. Nutrition Support Improves Patient Outcomes, Treatment Tolerance and Admission Characteristics in Oesophageal Cancer. Clinical Oncology. 2005;17(8):639-45.

30. Javle M, Ailawadhi S, Yang GY, Nwogu CE, Schiff MD, Nava HR. Palliation of malignant dysphagia in esophageal cancer: a literature-based review. The journal of supportive oncology. 2006;4(8):365-73, 79.

31. Lagergren J, Lagergren P. Oesophageal cancer. BMJ (Clinical research ed). 2010;341:c6280.

32. Borggreve AS, Kingma BF, Domrachev SA, Koshkin MA, Ruurda JP, van Hillegersberg R, et al. Surgical treatment of esophageal cancer in the era of multimodality management. Annals of the New York Academy of Sciences. 2018;1434(1):192-209.

33. Bower MR, Martin RC, 2nd. Nutritional management during neoadjuvant therapy for esophageal cancer. Journal of surgical oncology. 2009;100(1):82-7.

34. Malagelada JR, Bazzoli F, Boeckxstaens G, De Looze D, Fried M, Kahrilas P, et al. World gastroenterology organisation global guidelines: dysphagia--global guidelines and cascades update September 2014. Journal of clinical gastroenterology. 2015;49(5):370-8.

35. Persson J, Engstrom C, Bergquist H, Johnsson E, Smedh U. Validation of instruments for the assessment of dysphagia due to malignancy of the esophagus. Diseases of the esophagus : official journal of the International Society for Diseases of the Esophagus / ISDE. 2018.

36. Ogilvie AL, Dronfield MW, Ferguson R, Atkinson M. Palliative intubation of oesophagogastric neoplasms at fibreoptic endoscopy. Gut. 1982;23(12):1060-7.

37. Watson DI, Pike GK, Baigrie RJ, Mathew G, Devitt PG, Britten-Jones R, et al. Prospective double-blind randomized trial of laparoscopic Nissen fundoplication with division and without division of short gastric vessels. Annals of surgery. 1997;226(5):642-52.

38. Dakkak M, Bennett JR. A new dysphagia score with objective validation. Journal of clinical gastroenterology. 1992;14(2):99-100.

39. Atkinson M, Ferguson R. Fibreoptic endoscopic palliative intubation of inoperable oesophagogastric neoplasms. British medical journal. 1977;1(6056):266-7.

40. Mellow MH, Pinkas H. Endoscopic laser therapy for malignancies affecting the esophagus and gastroesophageal junction. Analysis of technical and functional efficacy. Archives of internal medicine. 1985;145(8):1443-6.

41. Mao-de-Ferro S, Serrano M, Ferreira S, Rosa I, Lage P, Alexandre DP, et al. Stents in patients with esophageal cancer before chemoradiotherapy: high risk of complications and no impact on the nutritional status. European journal of clinical nutrition. 2016;70(3):409-10.

42. Spaander MC, Baron TH, Siersema PD, Fuccio L, Schumacher B, Escorsell A, et al. Esophageal stenting for benign and malignant disease: European Society of Gastrointestinal Endoscopy (ESGE) Clinical Guideline. Endoscopy. 2016;48(10):939-48.

43. Jones CM, Griffiths EA. Should oesophageal stents be used before neo-adjuvant therapy to treat dysphagia in patients awaiting oesophagectomy? Best evidence topic (BET). International journal of surgery. 2014;12(11):1172-80.

44. Huddy JR, Huddy FMS, Markar SR, Tucker O. Nutritional optimization during neoadjuvant therapy prior to surgical resection of esophageal cancer-a narrative review. Diseases of the Esophagus. 2018;31(1).

45. Cools-Lartigue J, Jones D, Spicer J, Zourikian T, Rousseau M, Eckert E, et al. Management of Dysphagia in Esophageal Adenocarcinoma Patients Undergoing Neoadjuvant Chemotherapy: Can Invasive Tube Feeding be Avoided? Annals of surgical oncology. 2015;22(6):1858-65.

46. Mariette C. What is the optimal neoadjuvant treatment for locally advanced oesophageal adenocarcinoma? Ann Oncol. 2017;28(3):447-50.

47. Klevebro F, Alexandersson von Dobeln G, Wang N, Johnsen G, Jacobsen AB, Friesland S, et al. A randomized clinical trial of neoadjuvant chemotherapy versus neoadjuvant chemoradiotherapy for cancer of the oesophagus or gastro-oesophageal junction. Ann Oncol. 2016;27(4):660-7.

48. Cunningham D, Allum WH, Stenning SP, Thompson JN, Van de Velde CJ, Nicolson M, et al. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. The New England journal of medicine. 2006;355(1):11-20.

49. Ychou M, Boige V, Pignon JP, Conroy T, Bouché O, Lebreton G, et al. Perioperative chemotherapy compared with surgery alone for resectable gastroesophageal adenocarcinoma: an FNCLCC and FFCD multicenter phase III trial. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2011;29(13):1715-21.

50. Homann N, Pauligk C, Luley K, Werner Kraus T, Bruch HP, Atmaca A, et al. Pathological complete remission in patients with oesophagogastric cancer receiving preoperative 5-fluorouracil, oxaliplatin and docetaxel. International journal of cancer. 2012;130(7):1706-13.

51. Schulz C, Kullmann F, Kunzmann V, Fuchs M, Geissler M, Vehling-Kaiser U, et al. NeoFLOT: Multicenter phase II study of perioperative chemotherapy in resectable adenocarcinoma of the gastroesophageal junction or gastric adenocarcinoma-Very good response predominantly in patients with intestinal type tumors. International journal of cancer. 2015;137(3):678-85.

52. Al-Batran SE, Homann N, Pauligk C, Goetze TO, Meiler J, Kasper S, et al. Perioperative chemotherapy with fluorouracil plus leucovorin, oxaliplatin, and docetaxel versus fluorouracil or capecitabine plus cisplatin and epirubicin for locally advanced, resectable gastric or gastro-oesophageal junction adenocarcinoma (FLOT4): a randomised, phase 2/3 trial. Lancet (London, England). 2019;393(10184):1948-57.

53. Shapiro J, van Hagen P, Lingsma HF, Wijnhoven BP, Biermann K, ten Kate FJ, et al. Prolonged time to surgery after neoadjuvant chemoradiotherapy increases histopathological response without affecting survival in patients with esophageal or junctional cancer. Annals of surgery. 2014;260(5):807-13; discussion 13-4.

54. Irino T, Tsekrekos A, Coppola A, Scandavini CM, Shetye A, Lundell L, et al. Long-term functional outcomes after replacement of the esophagus with gastric, colonic, or jejunal conduits: a systematic literature review. Diseases of the esophagus : official journal of the International Society for Diseases of the Esophagus / ISDE. 2017;30(12):1-11.

55. Nilsson M, Kamiya S, Lindblad M, Rouvelas I. Implementation of minimally invasive esophagectomy in a tertiary referral center for esophageal cancer. Journal of thoracic disease. 2017;9(Suppl 8):S817-s25.

56. van Workum F, Berkelmans GH, Klarenbeek BR, Nieuwenhuijzen GAP, Luyer MDP, Rosman C. McKeown or Ivor Lewis totally minimally invasive esophagectomy for cancer of the esophagus and gastroesophageal junction: systematic review and meta-analysis. Journal of thoracic disease. 2017;9(Suppl 8):S826-s33.

57. Mariette C, Piessen G, Briez N, Triboulet JP. The number of metastatic lymph nodes and the ratio between metastatic and examined lymph nodes are independent prognostic factors in esophageal cancer regardless of neoadjuvant chemoradiation or lymphadenectomy extent. Annals of surgery. 2008;247(2):365-71.

58. Ye T, Sun Y, Zhang Y, Zhang Y, Chen H. Three-field or two-field resection for thoracic esophageal cancer: a meta-analysis. Ann Thorac Surg. 2013;96(6):1933-41.

59. Rubenstein JH, Shaheen NJ. Epidemiology, Diagnosis, and Management of Esophageal Adenocarcinoma. Gastroenterology. 2015;149(2):302-17.e1.

60. Palazzo F, Evans NR, 3rd, Rosato EL. Minimally invasive esophagectomy with extracorporeal gastric conduit creation--how I do it. Journal of gastrointestinal surgery : official journal of the Society for Surgery of the Alimentary Tract. 2013;17(9):1683-8.

61. Fearon KC, Ljungqvist O, Von Meyenfeldt M, Revhaug A, Dejong CH, Lassen K, et al. Enhanced recovery after surgery: a consensus review of clinical care for patients undergoing colonic resection. Clinical nutrition (Edinburgh, Scotland). 2005;24(3):466-77.

62. Cerfolio RJ, Bryant AS, Bass CS, Alexander JR, Bartolucci AA. Fast tracking after Ivor Lewis esophagogastrectomy. Chest. 2004;126(4):1187-94.

63. Low DE, Kunz S, Schembre D, Otero H, Malpass T, Hsi A, et al. Esophagectomy--it's not just about mortality anymore: standardized perioperative clinical pathways improve outcomes in patients with esophageal cancer. Journal of gastrointestinal surgery : official journal of the Society for Surgery of the Alimentary Tract. 2007;11(11):1395-402; discussion 402.

64. Preston SR, Markar SR, Baker CR, Soon Y, Singh S, Low DE. Impact of a multidisciplinary standardized clinical pathway on perioperative outcomes in patients with oesophageal cancer. The British journal of surgery. 2013;100(1):105-12.

65. Low DE, Allum W, De Manzoni G, Ferri L, Immanuel A, Kuppusamy M, et al. Guidelines for Perioperative Care in Esophagectomy: Enhanced Recovery After Surgery (ERAS(®)) Society Recommendations. World journal of surgery. 2019;43(2):299-330.

66. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Annals of surgery. 2004;240(2):205-13.

67. Yeung JC. Management of Complications After Esophagectomy. Thoracic surgery clinics. 2020;30(3):359-66.

68. van Workum F, van der Maas J, van den Wildenberg FJ, Polat F, Kouwenhoven EA, van Det MJ, et al. Improved Functional Results After Minimally Invasive Esophagectomy: Intrathoracic Versus Cervical Anastomosis. Ann Thorac Surg. 2017;103(1):267-73.

69. Wouters MW, Karim-Kos HE, le Cessie S, Wijnhoven BP, Stassen LP, Steup WH, et al. Centralization of esophageal cancer surgery: does it improve clinical outcome? Annals of surgical oncology. 2009;16(7):1789-98.

70. Grimminger PP, Goense L, Gockel I, Bergeat D, Bertheuil N, Chandramohan SM, et al. Diagnosis, assessment, and management of surgical complications following esophagectomy. Annals of the New York Academy of Sciences. 2018;1434(1):254-73.

71. Seesing MFJ, Gisbertz SS, Goense L, van Hillegersberg R, Kroon HM, Lagarde SM, et al. A Propensity Score Matched Analysis of Open Versus Minimally Invasive Transthoracic Esophagectomy in the Netherlands. Annals of surgery. 2017;266(5):839-46.

72. Junemann-Ramirez M, Awan MY, Khan ZM, Rahamim JS. Anastomotic leakage post-esophagogastrectomy for esophageal carcinoma: retrospective analysis of predictive factors, management and influence on longterm survival in a high volume centre. European journal of cardio-thoracic surgery : official journal of the European Association for Cardio-thoracic Surgery. 2005;27(1):3-7.

73. Deng J, Su Q, Ren Z, Wen J, Xue Z, Zhang L, et al. Comparison of short-term outcomes between minimally invasive McKeown and Ivor Lewis esophagectomy for esophageal or junctional cancer: a systematic review and meta-analysis. OncoTargets and therapy. 2018;11:6057-69.

74. Goense L, van Rossum PSN, Ruurda JP, van Vulpen M, Mook S, Meijer GJ, et al. Radiation to the Gastric Fundus Increases the Risk of Anastomotic Leakage After Esophagectomy. Ann Thorac Surg. 2016;102(6):1798-804.

75. Klevebro F, Friesland S, Hedman M, Tsai JA, Lindblad M, Rouvelas I, et al. Neoadjuvant chemoradiotherapy may increase the risk of severe anastomotic complications after esophagectomy with cervical anastomosis. Langenbecks Arch Surg. 2016;401(3):323-31.

76. Kassis ES, Kosinski AS, Ross P, Jr., Koppes KE, Donahue JM, Daniel VC. Predictors of anastomotic leak after esophagectomy: an analysis of the society of thoracic surgeons general thoracic database. Ann Thorac Surg. 2013;96(6):1919-26.

77. Chen KN. Managing complications I: leaks, strictures, emptying, reflux, chylothorax. Journal of thoracic disease. 2014;6 Suppl 3:S355-63.

78. Cederholm T, Barazzoni R, Austin P, Ballmer P, Biolo G, Bischoff SC, et al. ESPEN guidelines on definitions and terminology of clinical nutrition. Clinical nutrition (Edinburgh, Scotland). 2017;36(1):49-64.

79. Cederholm T, Jensen GL, Correia M, Gonzalez MC, Fukushima R, Higashiguchi T, et al. GLIM criteria for the diagnosis of malnutrition - A consensus report from the global clinical nutrition community. Clinical nutrition (Edinburgh, Scotland). 2019;38(1):1-9.

80. Cederholm T, Bosaeus I, Barazzoni R, Bauer J, Van Gossum A, Klek S, et al. Diagnostic criteria for malnutrition - An ESPEN Consensus Statement. Clinical nutrition (Edinburgh, Scotland). 2015;34(3):335-40.

81. Weimann A, Braga M, Harsanyi L, Laviano A, Ljungqvist O, Soeters P, et al. ESPEN Guidelines on Enteral Nutrition: Surgery including organ transplantation. Clinical nutrition (Edinburgh, Scotland). 2006;25(2):224-44.

82. Arends J, Bachmann P, Baracos V, Barthelemy N, Bertz H, Bozzetti F, et al. ESPEN guidelines on nutrition in cancer patients. Clinical nutrition (Edinburgh, Scotland). 2017;36(1):11-48.

83. Weimann A, Braga M, Carli F, Higashiguchi T, Hubner M, Klek S, et al. ESPEN guideline: Clinical nutrition in surgery. Clinical nutrition (Edinburgh, Scotland). 2017;36(3):623-50.

84. Ligthart-Melis GC, Weijs PJ, te Boveldt ND, Buskermolen S, Earthman CP, Verheul HM, et al. Dietician-delivered intensive nutritional support is associated with a decrease in severe postoperative complications after surgery in patients with esophageal cancer. Diseases of the esophagus : official journal of the International Society for Diseases of the Esophagus / ISDE. 2013;26(6):587-93.

85. Chen MJ, Wu IC, Chen YJ, Wang TE, Chang YF, Yang CL, et al. Nutrition therapy in esophageal cancer-Consensus statement of the Gastroenterological Society of Taiwan. Diseases of the esophagus : official journal of the International Society for Diseases of the Esophagus / ISDE. 2018;31(8).

86. Anandavadivelan P, Lagergren P. Cachexia in patients with oesophageal cancer. Nature reviews Clinical oncology. 2016;13(3):185-98.

87. Takeuchi H, Kawakubo H, Kitagawa Y. Current status of minimally invasive esophagectomy for patients with esophageal cancer. General thoracic and cardiovascular surgery. 2013;61(9):513-21.

88. Donington JS. Functional conduit disorders after esophagectomy. Thoracic surgery clinics. 2006;16(1):53-62.

89. Lerut TE, van Lanschot JJ. Chronic symptoms after subtotal or partial oesophagectomy: diagnosis and treatment. Best practice & research Clinical gastroenterology. 2004;18(5):901-15.

90. Bolton JS, Conway WC, Abbas AE. Planned delay of oral intake after esophagectomy reduces the cervical anastomotic leak rate and hospital length of stay. Journal of gastrointestinal surgery : official journal of the Society for Surgery of the Alimentary Tract. 2014;18(2):304-9.

91. Messager M, Warlaumont M, Renaud F, Marin H, Branche J, Piessen G, et al. Recent improvements in the management of esophageal anastomotic leak after surgery for cancer. European journal of surgical oncology : the journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology. 2016.

92. van der Schaaf M, Lagergren J, Lagergren P. Persisting symptoms after intrathoracic anastomotic leak following oesophagectomy for cancer. The British journal of surgery. 2012;99(1):95-9.

93. Johansson J, Oberg S, Wenner J, Zilling T, Johnsson F, von Holstein CS, et al. Impact of proton pump inhibitors on benign anastomotic stricture formations after esophagectomy and gastric tube reconstruction: results from a randomized clinical trial. Annals of surgery. 2009;250(5):667-73.

94. Weijs TJ, Ruurda JP, Broekhuizen ME, Bracco Gartner TCL, van Hillegersberg R. Outcome of a Step-Up Treatment Strategy for Chyle Leakage After Esophagectomy. Ann Thorac Surg. 2017;104(2):477-84.

95. Moro K, Koyama Y, Kosugi SI, Ishikawa T, Ichikawa H, Hanyu T, et al. Low fat-containing elemental formula is effective for postoperative recovery and potentially useful for preventing chyle leak during postoperative early enteral nutrition after esophagectomy. Clinical nutrition (Edinburgh, Scotland). 2016.

96. CR P. Nutritional Management of Chyle Leaks: An Update. Practical Gastroenterology. 2011;94:12-32.

97. Lassen K, Revhaug A. Early oral nutrition after major upper gastrointestinal surgery: why not? Current opinion in clinical nutrition and metabolic care. 2006;9(5):613-7.

98. Sica GS, Sujendran V, Wheeler J, Soin B, Maynard N. Needle catheter jejunostomy at esophagectomy for cancer. Journal of surgical oncology. 2005;91(4):276-9.

99. Berkelmans GHK, Fransen L, Weijs TJ, Lubbers M, Nieuwenhuijzen GAP, Ruurda JP, et al. The long-term effects of early oral feeding following minimal invasive esophagectomy. Diseases of the esophagus : official journal of the International Society for Diseases of the Esophagus / ISDE. 2018;31(1):1-8.

100. Sun HB, Liu XB, Zhang RX, Wang ZF, Qin JJ, Yan M, et al. Early oral feeding following thoracolaparoscopic oesophagectomy for oesophageal cancer. European journal of cardio-thoracic surgery : official journal of the European Association for Cardio-thoracic Surgery. 2015;47(2):227-33.

101. Pan H, Hu X, Yu Z, Zhang R, Zhang W, Ge J. Use of a fast-track surgery protocol on patients undergoing minimally invasive oesophagectomy: preliminary results. Interactive cardiovascular and thoracic surgery. 2014;19(3):441-7.

102. Kingma BF, Steenhagen E, Ruurda JP, van Hillegersberg R. Nutritional aspects of enhanced recovery after esophagectomy with gastric conduit reconstruction. Journal of surgical oncology. 2017;116(5):623-9.

103. Low DE, Allum W, De Manzoni G, Ferri L, Immanuel A, Kuppusamy M, et al. Guidelines for Perioperative Care in Esophagectomy: Enhanced Recovery After Surgery (ERAS((R))) Society Recommendations. World journal of surgery. 2018.

104. Ryan AM, Rowley SP, Healy LA, Flood PM, Ravi N, Reynolds JV. Post-oesophagectomy early enteral nutrition via a needle catheter jejunostomy: 8-year experience at a specialist unit. Clinical Nutrition. 2006;25(3):386-93.

105. Donohoe CL, Healy LA, Fanning M, Doyle SL, Hugh AM, Moore J, et al. Impact of supplemental home enteral feeding postesophagectomy on nutrition, body composition, quality of life, and patient satisfaction. Diseases of the esophagus : official journal of the International Society for Diseases of the Esophagus / ISDE. 2017;30(9):1-9.

106. Wu Z, Wu M, Wang Q, Zhan T, Wang L, Pan S, et al. Home enteral nutrition after minimally invasive esophagectomy can improve quality of life and reduce the risk of malnutrition. Asia Pacific journal of clinical nutrition. 2018;27(1):129-36.

107. Zeng J, Hu J, Chen Q, Feng J. Home enteral nutrition's effects on nutritional status and quality of life after esophagectomy. Asia Pacific journal of clinical nutrition. 2017;26(5):804-10.

108. Baker ML, Halliday V, Robinson P, Smith K, Bowrey DJ. Nutrient intake and contribution of home enteral nutrition to meeting nutritional requirements after oesophagectomy and total gastrectomy. European journal of clinical nutrition. 2017;71(9):1121-8.

109. Halliday V, Baker M, Thomas AL, Bowrey D. Patient and Family Caregivers' Experiences of Living With a Jejunostomy Feeding Tube After Surgery for Esophagogastric Cancer. JPEN Journal of parenteral and enteral nutrition. 2015.

110. Stratton RJ, Stubbs RJ, Elia M. Short-term continuous enteral tube feeding schedules did not suppress appetite and food intake in healthy men in a placebo-controlled trial. The Journal of nutrition. 2003;133(8):2570-6.

111. Froghi F, Sanders G, Berrisford R, Wheatley T, Peyser P, Rahamim J, et al. A randomised trial of post-discharge enteral feeding following surgical resection of an upper gastrointestinal malignancy. Clinical nutrition (Edinburgh, Scotland). 2016.

112. Johansson J, Sloth M, Bajc M, Walther B. Radioisotope evaluation of the esophageal remnant and the gastric conduit after gastric pull-up esophagectomy. Surgery. 1999;125(3):297-303.

113. Takiguchi S, Adachi S, Yamamoto K, Morii E, Miyata H, Nakajima K, et al. Mapping analysis of ghrelin producing cells in the human stomach associated with chronic gastritis and early cancers. Digestive diseases and sciences. 2012;57(5):1238-46.

114. Lee HS, Kim MS, Lee JM, Kim SK, Kang KW, Zo JI. Intrathoracic gastric emptying of solid food after esophagectomy for esophageal cancer. Ann Thorac Surg. 2005;80(2):443-7.

115. Ukleja A. Dumping syndrome: pathophysiology and treatment. Nutrition in clinical practice : official publication of the American Society for Parenteral and Enteral Nutrition. 2005;20(5):517-25.

116. Boshier PR, Huddy JR, Zaninotto G, Hanna GB. Dumping syndrome after esophagectomy: a systematic review of the literature. Diseases of the esophagus : official journal of the International Society for Diseases of the Esophagus / ISDE. 2017;30(1):1-9.

117. Elliott JA, Docherty NG, Eckhardt HG, Doyle SL, Guinan EM, Ravi N, et al. Weight Loss, Satiety, and the Postprandial Gut Hormone Response After Esophagectomy: A Prospective Study. Annals of surgery. 2017;266(1):82-90.

118. Koizumi M, Hosoya Y, Dezaki K, Yada T, Hosoda H, Kangawa K, et al. Postoperative weight loss does not resolve after esophagectomy despite normal serum ghrelin levels. Ann Thorac Surg. 2011;91(4):1032-7.

119. Haverkort EB, Binnekade JM, de Haan RJ, Busch OR, van Berge Henegouwen MI, Gouma DJ. Suboptimal intake of nutrients after esophagectomy with gastric tube reconstruction. Journal of the Academy of Nutrition and Dietetics. 2012;112(7):1080-7.

120. Heneghan HM, Zaborowski A, Fanning M, McHugh A, Doyle S, Moore J, et al. Prospective Study of Malabsorption and Malnutrition After Esophageal and Gastric Cancer Surgery. Annals of surgery. 2015;262(5):803-7; discussion 7-8.

121. Huddy JR, Macharg FM, Lawn AM, Preston SR. Exocrine pancreatic insufficiency following esophagectomy. Diseases of the esophagus : official journal of the International Society for Diseases of the Esophagus / ISDE. 2013;26(6):594-7.

122. Kiefer T, Krahl D, Osthoff K, Thuss-Patience P, Bunse J, Adam U, et al. Importance of Pancreatic Enzyme Replacement Therapy after Surgery of Cancer of the Esophagus or the Esophagogastric Junction. Nutrition and cancer. 2018;70(1):69-72.

123. Martin L, Lagergren P. Risk factors for weight loss among patients surviving 5 years after esophageal cancer surgery. Annals of surgical oncology. 2015;22(2):610-6.

124. Schandl A, Lagergren J, Johar A, Lagergren P. Health-related quality of life 10 years after oesophageal cancer surgery. European journal of cancer (Oxford, England : 1990). 2016;69:43-50.

125. Greene CL, DeMeester SR, Worrell SG, Oh DS, Hagen JA, DeMeester TR. Alimentary satisfaction, gastrointestinal symptoms, and quality of life 10 or more years after esophagectomy with gastric pull-up. The Journal of thoracic and cardiovascular surgery. 2014;147(3):909-14.

126. Johannsen DL, Calabro MA, Stewart J, Franke W, Rood JC, Welk GJ. Accuracy of armband monitors for measuring daily energy expenditure in healthy adults. Medicine and science in sports and exercise. 2010;42(11):2134-40.

127. Frappier J, Toupin I, Levy JJ, Aubertin-Leheudre M, Karelis AD. Energy expenditure during sexual activity in young healthy couples. PloS one. 2013;8(10):e79342.

128. Cereda E, Turrini M, Ciapanna D, Marbello L, Pietrobelli A, Corradi E. Assessing energy expenditure in cancer patients: a pilot validation of a new wearable device. JPEN Journal of parenteral and enteral nutrition. 2007;31(6):502-7.

129. Hughes MJ, Harrison EM, Wigmore SJ. Energy Expenditure After Liver Resection: Validation of a Mobile Device for Estimating Resting Energy Expenditure and an Investigation of Energy Expenditure Change After Liver Resection. JPEN Journal of parenteral and enteral nutrition. 2015.

130. Welk G, Kim Y, Shook RP, Ellingson L, Lobelo RL. Validation of a Noninvasive, Disposable Activity Monitor for Clinical Applications. Journal of physical activity & health. 2017;14(7):546-51.

131. McClung HL, Ptomey LT, Shook RP, Aggarwal A, Gorczyca AM, Sazonov ES, et al. Dietary Intake and Physical Activity Assessment: Current Tools, Techniques, and Technologies for Use in Adult Populations. American journal of preventive medicine. 2018;55(4):e93-e104.

132. Ceolin Alves AL, Zuconi CP, Correia MI. Energy Expenditure in Patients With Esophageal, Gastric, and Colorectal Cancer. JPEN Journal of parenteral and enteral nutrition. 2016;40(4):499-506.

133. Bruera E, Kuehn N, Miller MJ, Selmser P, Macmillan K. The Edmonton Symptom Assessment System (ESAS): a simple method for the assessment of palliative care patients. Journal of palliative care. 1991;7(2):6-9.

134. Chirieac LR, Swisher SG, Ajani JA, Komaki RR, Correa AM, Morris JS, et al. Posttherapy pathologic stage predicts survival in patients with esophageal carcinoma receiving preoperative chemoradiation. Cancer. 2005;103(7):1347-55.

135. Nordic Nutrition Recommendations 2012 : integrating nutrition and physical activity. Copenhagen: Nordic Council of Minsters; 2014.

136. Blazeby JM, Sanford E, Falk SJ, Alderson D, Donovan JL. Health-related quality of life during neoadjuvant treatment and surgery for localized esophageal carcinoma. Cancer. 2005;103(9):1791-9.

137. Bachmann R, Bachmann J, Hungbauer A, Schmehl J, Sitzmann G, Konigsrainer A, et al. Impact of response evaluation for resectable esophageal adenocarcinoma - a retrospective cohort study. International journal of surgery. 2014;12(10):1025-30.

138. Stahl M, Walz MK, Stuschke M, Lehmann N, Meyer HJ, Riera-Knorrenschild J, et al. Phase III comparison of preoperative chemotherapy compared with chemoradiotherapy in patients with locally advanced adenocarcinoma of the esophagogastric

junction. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2009;27(6):851-6.

139. Nagaraja V, Cox MR, Eslick GD. Safety and efficacy of esophageal stents preceding or during neoadjuvant chemotherapy for esophageal cancer: a systematic review and meta-analysis. Journal of gastrointestinal oncology. 2014;5(2):119-26.

140. Pellen MG, Sabri S, Razack A, Gilani SQ, Jain PK. Safety and efficacy of self-expanding removable metal esophageal stents during neoadjuvant chemotherapy for resectable esophageal cancer. Diseases of the esophagus : official journal of the International Society for Diseases of the Esophagus / ISDE. 2012;25(1):48-53.

141. Sunde B, Ericson J, Kumagai K, Lundell L, Tsai JA, Lindblad M, et al. Relief of dysphagia during neoadjuvant treatment for cancer of the esophagus or gastroesophageal junction. Diseases of the esophagus : official journal of the International Society for Diseases of the Esophagus / ISDE. 2016;29(5):442-7.

142. Biro G, Hulshof KF, Ovesen L, Amorim Cruz JA. Selection of methodology to assess food intake. European journal of clinical nutrition. 2002;56 Suppl 2:S25-32.

143. Gibson RS. Principles of nutritional assessment. 2. ed. ed. New York: New York : Oxford University Press; 2005.

144. Poslusna K, Ruprich J, de Vries JH, Jakubikova M, van't Veer P. Misreporting of energy and micronutrient intake estimated by food records and 24 hour recalls, control and adjustment methods in practice. The British journal of nutrition. 2009;101 Suppl 2:S73-85.

145. Elliott JA, Jackson S, King S, McHugh R, Docherty NG, Reynolds JV, et al. Gut Hormone Suppression Increases Food Intake After Esophagectomy With Gastric Conduit Reconstruction. Annals of surgery. 2015;262(5):824-29; discussion 9-30.

146. Poghosyan T, Gaujoux S, Chirica M, Munoz-Bongrand N, Sarfati E, Cattan P. Functional disorders and quality of life after esophagectomy and gastric tube reconstruction for cancer. Journal of visceral surgery. 2011;148(5):e327-35.

147. Steenhagen E. Preoperative nutritional optimization of esophageal cancer patients. Journal of thoracic disease. 2019;11(Suppl 5):S645-s53.

148. Noordman BJ, Verdam MGE, Onstenk B, Heisterkamp J, Jansen W, Martijnse IS, et al. Quality of Life During and After Completion of Neoadjuvant Chemoradiotherapy for Esophageal and Junctional Cancer. Annals of surgical oncology. 2019;26(13):4765-72.

149. Sunde B, Johnsen G, Jacobsen AB, Glenjen NI, Friesland S, Lindblad M, et al. Effects of neoadjuvant chemoradiotherapy vs chemotherapy alone on the relief of dysphagia in esophageal cancer patients: secondary endpoint analysis in a randomized trial. Diseases of the esophagus : official journal of the International Society for Diseases of the Esophagus / ISDE. 2019;32(2).

150. Skeie E, Tangvik RJ, Nymo LS, Harthug S, Lassen K, Viste A. Weight loss and BMI criteria in GLIM's definition of malnutrition is associated with postoperative complications following abdominal resections - Results from a National Quality Registry. Clinical nutrition (Edinburgh, Scotland). 2020;39(5):1593-9.

151. van der Schaaf MK, Tilanus HW, van Lanschot JJ, Johar AM, Lagergren P, Lagergren J, et al. The influence of preoperative weight loss on the postoperative course after esophageal cancer resection. The Journal of thoracic and cardiovascular surgery. 2014;147(1):490-5.

152. Allum W, Lordick F, Alsina M, Andritsch E, Ba-Ssalamah A, Beishon M, et al. ECCO essential requirements for quality cancer care: Oesophageal and gastric cancer. Critical reviews in oncology/hematology. 2018;122:179-93.

153. Rothman KJ. Epidemiology: An Introduction: OUP USA; 2012.

154. St-Onge M, Mignault D, Allison DB, Rabasa-Lhoret R. Evaluation of a portable device to measure daily energy expenditure in free-living adults. The American journal of clinical nutrition. 2007;85(3):742-9.

Tre instrument för att undersöka vilken typ av mat Du kan äta samt Din aptit

Watson score

Nedan följer ett antal påståenden angående Din sväljningsförmåga. Var god kryssa i det svarsalternativ som bäst stämmer överens för Dig.

På grund av mina problem med att svälja har jag svårt att:

	Aldrig	Ibland	Alltid
dricka vatten	☐	☐	☐
dricka mjölk	☐	☐	☐
äta yoghurt eller fil	☐	☐	☐
äta kräm, sylt eller gelé	☐	☐	☐
äta omelett eller mosad potatis	☐	☐	☐
äta kokta grönsaker, potatis eller fisk	☐	☐	☐
äta mjukt, vitt bröd eller pasta	☐	☐	☐
äta färsk frukt, t ex äpple	☐	☐	☐
äta kött, t ex fläskkotlett	☐	☐	☐

Dysfagi gradering enligt Ogilvie

Välj det exempel som bäst stämmer överens med det Du kan äta.

Jag har:

- ☐ 0= förmåga att äta all sorts föda;
- ☐ 1= förmåga att äta viss fast föda;
- ☐ 2= förmåga att äta enbart viss mosad föda;
- ☐ 3= förmåga att inta enbart flytande föda;
- ☐ 4= oförmåga att inta vare sig fast eller flytande föda

ESAS (Edmonton Symptom Assessment Scale)

Ring in den siffra som bäst beskriver hur du har mått senaste dygnet.

God aptit ______________________________ Ingen aptit

0 1 2 3 4 5 6 7 8 9 10

Inklusion/Uppföljning 15–20 dagar efter induktionskur/Innan kirurgi

Efternamn:

Datum:

Studienummer: