

# Aspects of mechanical dysphagia

Assessment, treatment and consequences

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To Majken and Gunnar with love



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## Assessment, treatment and consequences

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### ABSTRACT

**Background:** Dysphagia is a symptom that negatively impacts patients' quality of life. In the present thesis, aspects of dysphagia were explored in patients with primary achalasia and in patients diagnosed with cancers of the oesophagus or of the gastro-oesophageal junction.

**Aims:** To validate commonly used dysphagia scores for malignant strictures of the oesophagus; to evaluate surgical and conservative treatments against primary achalasia, as well as evaluate stent treatments for dysphagia in advanced oesophageal cancer; and to describe and evaluate body composition, sarcopenia, and physical performance before and during follow-up after resection surgery in patients with oesophageal cancer.

### Methods and results:

Paper I – A randomized controlled trial was performed in which laparoscopic myotomy was compared to endoscopic dilatation for achalasia-associated dysphagia, using treatment failure as the primary variable. At the five-year follow-up, there was a significant difference in favour of the surgical approach with fewer treatment failures. Both dysphagia and QoL were better in the operated group at three years, although these differences diminished at five years. Treatment costs in the operated group were significantly higher.

Paper II – A validation of scales for assessment of dysphagia due to malignancy was made in patients with cancer of the oesophagus. Self-reported dysphagia from the Watson score, Goldschmid score and the Ogilvie score was compared to a food diary and to the already validated QoL questionnaire, QLQ-OG25. All scores had good reliability, and the Ogilvie score and QLQ-OG25 had the strongest correlation.

Paper III – A randomized controlled trial was conducted to explore the potential difference in stent migration between a conventional semi-covered stent, and a fully covered stent of a newer design, in palliative treatment of dysphagia due to malignancy. The primary variable was the frequency of migration > 20 mm. There were no significant differences in any of the studied variables of dysphagia, QoL or re-intervention frequency, indicating that a fully-covered stent of a newer design is similar to a conventional semi-covered stent with regard to migration.

Paper IV – Body composition and sarcopenia were investigated in a prospectively collected patient cohort with cancer of the oesophagus who were planned for surgery with curative intent. Prior to surgery, a majority of the patients displayed deteriorated physical performance; almost two of five were judged to be severely malnourished in spite of a normal BMI, and one of five had sarcopenia. Muscle mass continued to deteriorate for at least three months post-operatively. High physical performance, female sex and a high global QoL score positively predicted overall survival.

**Conclusions:** The Ogilvie score and the dysphagia module in QLQ-OG25 can be selected for assessment of dysphagia due to malignancy. In primary achalasia, laparoscopic myotomy gives a better long-term result and can thus be recommended as a primary treatment method. A fully-covered stent of a newer design is comparable to a conventional semi-covered stent with regard to migration. Patients with potentially curable oesophageal cancer have a high pre-operative prevalence of malnutrition and sarcopenia in spite of normal average BMI. Surgery has a long-lasting catabolic impact. This highlights the importance of optimal pre- and post-operative nutritional support in oesophageal cancer.

**Keywords:** Dysphagia, Watson, Ogilvie, Goldschmid, QoL, Sarcopenia, Laparoscopic myotomy, Achalasia, Oesophageal cancer.

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# POPULÄRVETENSKAPLIG SAMMANFATTNING

**Titel:** Aspekter på mekanisk dysfagi – utredning, behandling och konsekvenser

**Bakgrund:** Sväljningssvårigheter, så kallad dysfagi, är ett symtom som har en betydande effekt på patienters livskvalitet. Dysfagi påverkar välbefinnande, näringsstatus och möjligheten till social samvaro. Cirka 300 000 personer i Sverige har någon form av dysfagi. Symtomet kan orsakas av såväl godartade (benigna) som elakartade (maligna) sjukdomar.

Hos patienter med matstrupscancer eller cancer i övre magmunnen är dysfagi det symtom som påverkar livskvaliteten mest negativt. Cancer i matstrupen är den åttonde vanligaste cancerformen i världen. Det finns två typer av cancer i matstrupen och körtelcancertypen är en av de cancerformer som har snabbast ökande nyinsjuknande i västvärlden. I Sverige är sjukdomen mer ovanlig, varje år drabbas cirka 600 personer i Sverige. Sjukdomen diagnostiseras ofta sent och har då en dålig prognos varför behandlingen ofta bara blir lindrande och stödjande (palliativ). Vid palliativ behandling kan behandlingen omfatta strålning, cellgiftsbehandling eller stentbehandling. Det senare innebär att ett självexpanderande metallnätsrör läggs in i matstrupstumören så att nedsväljning av mat och dryck underlättas.

Akalasi är en godartad sjukdom i matstrupen som ger dysfagi på grund av att nervceller i matstrupen går förlorade vilket leder till muskelkramp i nedre magmunnen. Vid akalasi syftar behandling till att vidga nedre magmunnen, vilket till exempel kan bestå i att töja ut (dilatera) nedre magmunnen eller att kirurgiskt klyva muskelfibrerna. Det är inte klart vilken behandlingsmetod som är bäst vid akalasi.

Oavsett orsaken till dysfagin är det mycket viktigt att kunna mäta sväljningsförmågan med metoder som är vetenskapligt utvärderade, och att erbjuda patienter behandling som är effektiv, rimligt säker och som vilar på evidensbas. Här behöver hälsoekonomiska och livskvalitetsmässiga aspekter också vägas in.

## **Avhandlingsprojektet har haft följande syften:**

1. Att översätta och testa frågeformulär för dysfagi för att fastställa om dessa på ett pålitligt sätt kan mäta och gradera sväljningssvårigheter även vid cancersjukdom.
2. Att utvärdera behandlingsstrategier vid tillstånd som har dysfagi som huvudsymtom såsom akalasi och vid palliativt inriktad behandling av matstrups- och magmuns-cancer, avseende lindring av dysfagi, resultat, livskvalitet och hälsoekonomi.
3. Att undersöka och beskriva hur patienter, som ska genomgå en operation för matstrups- och magmuns-cancer som syftar till bot, ser ut precis före operationen avseende dysfagi, kroppssammansättning och livskvalitet, och hur detta utvecklas under tre månader efter operationen.

**Delarbete I:** Långtidseffekter av två behandlingar mot dysfagi på grund av akalasi undersöks. Patienter med akalasi som har lottats till behandling med ballongvidgning eller titthålsoperation, följs upp. I detta arbete undersöks även hur livskvalitet och hälsoekonomi påverkas av respektive behandling.

**Delarbete II:** Validering av tre befintliga mätinstrument för dysfagi till malign sjukdom och till svenska språket. Dessutom undersöker vi vilket instrument som stämmer bäst med patientens faktiska matintag och med en tidigare validerad livskvalitetsskala.

**Delarbete III:** Jämför risk för stentglidning mellan en heltäckt stent av nyare utformning och en konventionell halvtäckt stent vid palliativ behandling av dysfagi sekundärt till matstrups- och magmuns-cancer.

**Delarbete IV:** Är ett beskrivande arbete där patienter inför kirurgi för matstrups- och magmuns-cancer undersökts avseende sväljförmåga, livskvalitet, styrka, uthållighet och kroppssammansättning och hur det påverkar komplikationer och resultat. Dessutom undersöker vi om någon av dessa variabler kan förutse komplikationer och risk för död.

**Resultat och konklusioner:** Behandling med kirurgisk titthåls-muskelklyvning av övre magmunnen har kliniska fördelar jämfört med upprepad ballongvidgning av nydiagnostiserad akalasi på lång sikt, upp

till fem år. Metoden kan därför övervägas som förstahandsval, trots att den kirurgiska strategin har högre initiala medicinska kostnader.

Risken för att stentet glider ur position inte är ökad vid användande av en modern heltäckt stentdesign jämfört med en konventionell halvtäckt stent. Det fanns en tendens till att en heltäckt stent kan vara fördelaktig när det gäller lindring av dysfagi hos patienter med längre överlevnad, men detta behöver studeras ytterligare.

Trots normalt BMI var undernäring vanligt hos patienter som var planerade för matstrupskirurgi. Varken undernäring eller nedsatt muskelmassa och styrka var oberoende riskfaktorer för komplikationer eller död. Matstrupskirurgi har uttalade kroppsnedbrytande effekter som yttrar sig i förlorad muskelmassa och som fortsätter lång tid efter operationen. Detta tydliggör behovet av optimal näringsbehandling före operationen men även under lång tid därefter.

# THESIS AT A GLANCE

Paper	Question	Method	Result	Conclusion
<b>I</b>	Is there a difference in the rate of treatment failures in a comparison of treatment of achalasia with laparoscopic myotomi vs pneumatic dilatation?	Prospective randomized study comparing two different methods to treat achalasia. Median follow-up 81.5 months.	The surgical strategy had a significantly lower rate of treatment failure. Both methods had significant improvement effects on dysphagia.	Long-term follow-up shows that laparoscopic myotomy is superior to pneumatic dilatation but has higher initial medical costs.
<b>II</b>	Validation and translation of three dysphagia scores.	Back-translation method was used. Results obtained with the translated scores were compared to a food diary, to an already validated scale and to each other.	All scores showed good reliability for assessing malignant dysphagia. The Ogilvie score and the QLQ-OG25 score had the highest correlation to the food diary.	All the investigated scales proved to have a good to excellent reliability and reproducibility. The correlations between scores were strong, and the scales may thus be used for assessment of dysphagia due to oesophageal malignancy.
<b>III</b>	Does stent design have an impact on the risk of stent migration in palliative treatment of malignant strictures in the oesophagus?	Prospective randomized study comparing different stent designs in palliative treatment of oesophageal cancer.	Contrary to the hypothesis, the fully covered stents did not migrate more than the semi-covered stent.	Fully covered stents do not migrate more than semi-covered stents and may provide better dysphagia relief in patients with a longer survival prognosis.
<b>IV</b>	What is the status on body composition, dysphagia, muscle-strength, working capacity and, QoL in patients with oesophageal cancer prior to surgery? How do these variables develop under the post-operative period?	Descriptive study on prospectively collected cohort data on patients with dysphagia and oesophageal cancer.	In spite of normal BMI, 37% had severe malnourishment, 86% had a lowered physical performance, but only 20% were sarcopenic. All body composition variables except fat mass were declined up to three months after surgery.	Oesophageal cancer is associated with a high degree of undernutrition and sarcopenia. Resection surgery caused long-lasting catabolic effects, highlighting the importance of optimal pre-, peri- and post-operative nutrition.

# LIST OF PAPERS

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

**I. Treatment of achalasia with laparoscopic myotomy or pneumatic dilatation: Long-term results of a prospective, randomized study**

**Jan Persson • Erik Johnsson • Srdjan Kostic • Lars Lundell • Ulrika Smedh**  
*World Journal of Surgery 2015; 39:713–720*

**II. Validation of instruments for the assessment of dysphagia due to malignancy of the oesophagus**

**Jan Persson • Cecilia Engström • Henrik Bergquist • Erik Johnsson • Ulrika Smedh**  
*Submitted manuscript*

**III. Fully covered stents are similar to semi-covered stents with regard to migration in palliative treatment of malignant strictures of the esophagus and gastric cardia: Results of a randomized controlled trial**

**Jan Persson • Ulrika Smedh • Åse Johnsson • Bo Ohlin • Magnus Sundbom • Magnus Nilsson • Lars Lundell • Berit Sunde • Erik Johnsson**  
*Surgical Endoscopy 2017; 24 February (Epub ahead of print).*

**IV. Body composition and sarcopenia before and after surgery with curative intention in a cohort of patients with oesophageal cancer or cancer of the gastro-oesophageal junction**

**Jan Persson • Monika Fagevik Olsén • Britt-Marie Iresjö • Ulrika Smedh**  
*Submitted manuscript*

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# ABBREVIATIONS

LOS	lower oesophageal sphincter
LM	laparoscopic myotomy
PD	pneumatic dilatation
OC	oesophageal cancer
GOJ	gastro-oesophageal junction
CGOJ	cancer in the gastro-oesophageal junction
SEMS	self-expandable metallic stent
scSEMS	semi-covered self-expandable metallic stent
fcSEMS	fully-covered self-expandable metallic stent
QoL	quality of life
EORTC	European organization for research and treatment of cancer
QLQ-OES18	quality of life questionnaires oesophagus 18 questions
QLQ-OG25	quality of life questionnaires oesophago-gastric 25 questions
PGWB	personal general well-being score
GSRS	gastrointestinal symptom rating scale
GOE	gastro-oesophageal endoscopy
BMI	body mass index (kg/m <sup>2</sup> )
FFM	fat free mass (kg)
FM	fat mass (kg)

LTM	lean tissue mass (kg)
ICU	intensive care unit
HR	hazard ratio
CI	confidence interval
SGA	Subjective global assessment (to evaluate nutritional status)
HRM	high resolution manometry
CRT	chemo-radio therapy
nCRT	neo-adjuvant chemo-radio therapy
DEXA	dual-energy x-ray absorptiometry
ICC	intraclass correlation coefficient
ITT	intention to treat
PP	per protocol



# INTRODUCTION

Dysphagia, or “difficulty swallowing”, is derived from the Greek word *dys*, meaning bad or disordered, and the root *phag*, meaning eat. In the literature, there are several early historical references to dysphagia; one of the early descriptions of dysphagia symptoms was given by Avicenna (circa 980-1037) in his encyclopaedia of medicine, called Canon. In spite of this symptom being known for a long time, there are still many aspects of dysphagia that remain to be clarified.

There are two main types of dysphagia; first is oropharyngeal dysphagia, which arises from abnormalities of muscles, nerves or structures of the oral cavity, pharynx, and upper oesophageal sphincter. The second type is oesophageal dysphagia, which is within the scope of this thesis.

Oesophageal dysphagia is a common symptom in benign diseases such as achalasia, eosinophilic oesophagitis, and benign peptic strictures and, of course, in strictures of the oesophagus due to malignancy. The prevalence of dysphagia, regardless of cause, is reported to be around 4 % in the adult population [1] and increases with age. This means that there are around 300 000 persons in Sweden who experience swallowing difficulties to a greater or lesser extent. Diseases affecting oesophageal motility are generally associated with dysphagia for both liquid and solid food, whereas obstructive disorders, such as cancer strictures, generally present with inability to swallow solid food.

In patients with cancer in the oesophagus, dysphagia is the one symptom that patients report has the strongest negative impact on Quality of Life (QoL) [2]. A likely reason for this is that dysphagia not only complicates food intake but has secondary negative effects on the sense of well-being, nutritional state, and social interactions.

## **Aetiology**

### **Some benign causes of oesophageal dysphagia**

The one benign disorder investigated in this work is achalasia. There are other benign conditions that also feature dysphagia, but, since those were not investigated here, they will only be mentioned briefly below.

Achalasia is a rare disorder for which dysphagia is the cardinal symptom [3]. The incidence is 1 out of 100 000 persons per year in Sweden. It is a progressive neuro-motor disorder where inhibitory ganglionic cells of the myenteric plexus of the oesophagus are irreversibly lost. This results in an impaired ability to relax the lower oesophageal sphincter (LOS), causing functional obstruction and widening of the oesophagus proximally. This results in a variety of symptoms including dysphagia, regurgitation, pulmonary problems, chest pain, and impaired QoL. At a late stage of the disease, so-called mega-oesophagus may occur. Manometry examination of the oesophagus is needed to confirm the achalasia diagnosis. A variety of different treatments have been tried, but in later years the two most common are repeated pneumatic dilatations by endoscopy, and laparoscopic surgical myotomy with the addition of a fundoplication. While the cause of achalasia is not known, auto-immune disease, or a reaction to a viral infection, have been suggested as possible etiological factors.

Eosinophilic oesophagitis (EO), first described as a disease in 1993 [4], has in recent years gained greater interest. It is an allergic inflammatory disorder that causes dysphagia. The prevalence is described to be around 1 % [5].

Peptic strictures secondary to gastro-oesophageal reflux are the most commonly seen benign cause of dysphagia among upper gastro-intestinal surgeons, even though the prevalence of EO is higher.

Chagas disease can in late stages present with a clinical picture similar to that of achalasia [6]. This is a tropical parasitic disease that affects autonomic nervous transmission in the GI tract, and frequently results in cardiac manifestations, but also in changes in oesophageal motility and an increase in LOS pressure [6]. It is a rare disease that is endemic on the American continent from southern USA to Argentina. The treatment for the dysphagia, which develops at a very late stage of this disease, is the same as for achalasia.

### **Malignant causes of oesophageal dysphagia**

A long history of swallowing difficulties, typically for many years, is very rarely due to malignancy but rather to a benign underlying condition. In contrast, progressive dysphagia that has recently (two to three weeks) presented must be considered as potentially being due to cancer. Tumours of the oesophagus or the gastro-oesophageal junction (GOJ) may be benign or malignant and consist of a primary tumour or a metastasis from another primary organ. The majority of tumours that concern the oesophagus and result in dysphagia are primary malignancies. The oesophageal cancer (OC) diagnosis is typically established at a late stage with a subsequent poor prognosis and the overall five-year survival in Sweden is only 10-15% [7]. This is because the tumour usually does not give rise to any particular symptoms until approximately 2/3 of the oesophageal circumference is engaged or the lumen of the stricture is < 14 mm. Due to an advanced tumour stage at diagnosis, and/or to other serious concomitant medical disorders, or simply because of too poor a general condition, palliative treatment is the only option that can be offered to a majority of patients (> 70 % in

Sweden) [7] presenting with OC or cancer of the oesophageal junction (CGOJ).

Oesophageal cancer has two subtypes, adenocarcinoma (AC) and squamous epithelium cancer (SeC). OC is the eighth most common cancer type in the world. Globally, 90 % of these cancers originate from squamous epithelium. However, in the Western world [7], oesophageal AC is more common than SeC and, although rather rare, it is one of the cancers that show the fastest increase in incidence [8, 9]. One explanation is probably that over-weight and reflux disease are two important risk factors. As a result, AC is more common than SeC in the oesophagus in Sweden today.

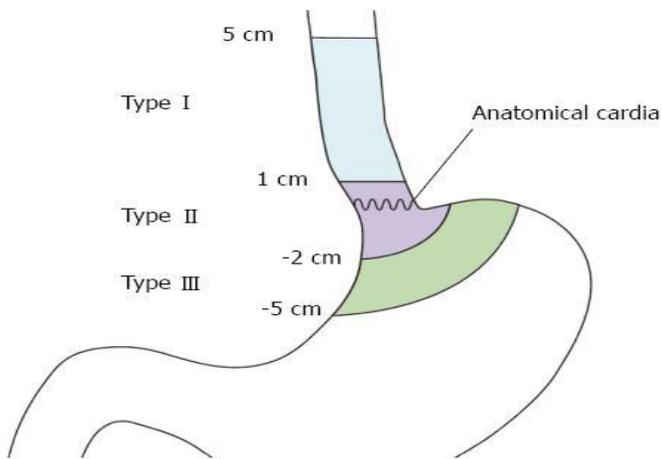
CGOJ has the same risk factors as AC of the oesophagus and often develops from metaplastic mucosal transformation, so called Barret's oesophagus [10, 11] (Figure 1).



*Figure 1.* An endoscopic view of Barret's oesophagus

CGOJ is divided into three subtypes according to Siewert [12]. Cancers involving the GOJ are defined according to the Siewert classification [12], which is based on the position of the epicentre of the tumour in relation to the GOJ. In Siewert type 1 the epicentre of the tumour is located above (>1 cm) the junction, in Siewert type 2 the epicentre of the tumour is < 1cm from the junction, and in type 3 the tumour's epicentre is between 2 and 5 cm below the junction. See Figure 2 below.

*Figure 2.* The Siewert classification of cancers in the gastro oesophageal junction



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In this dissertation, patients with OC or CGOJ (Siewert type 1 or 2) were included according to this definition. In contrast, since the treatment of Siewert type 3 was according to the gastric cancer guidelines, Siewert type 3 cancers were not part of this thesis. In all these cancer types, treatment with a curative intent involves major surgery, often in combination with neoadjuvant treatment that for the most part includes radio- and chemotherapy. This is further outlined below.

## **Assessment of dysphagia**

First and foremost, taking a detailed patient history is crucial and a physical examination must be made. In order to objectively evaluate the dysphagia symptomatology and severity, a scale or self-scoring system may be used [14-17]. There are several such scales, most of which have been developed for dysphagia of benign or mixed aetiology.

There is as yet no validated scale or instrument for evaluating dysphagia due to malignant disease that can be effectively used in clinical praxis, however, other than the EORTC scoring systems (see below). One aim in this dissertation was therefore to validate three well-known scales for dysphagia assessment in patients with malignant strictures of the oesophagus.

After physical examination, patients with dysphagia should be examined with gastro-oesophageal endoscopy (GOE). This should be done promptly within a few days, especially if the history of dysphagia is short and if the patient has experienced weight loss, which is suggestive of a malignant aetiology. With GOE, it is possible to inspect the mucosa and confirm or rule out visible tumours or signs of metaplasia, and it has the advantage that biopsies can be taken. Tumours which otherwise could easily be missed on various x-ray examinations can thereby be detected and diagnosed at an earlier stage. If no obvious macroscopic tumour-suspected findings can be visualised, there may still be a rationale for biopsies to be taken to confirm benign explanations for dysphagia, such as EO. If GOE shows a dilated oesophagus or if the patient has a history that gives reason to suspect achalasia, the next investigation should be manometry. This test is used to evaluate patients in which dysphagia or reflux disease is suspected. Manometry measures the pressure in the upper and lower oesophageal sphincters, determines the effectiveness and coordination of propulsive movements, and detects abnormal contractions. Yet another way to investigate the function and appearance of the oesophagus once a malignant cause has been excluded

with GOE is a Barium swallow x-ray [18]. This is a series of plain thoracic x-rays taken while the patient swallows a Barium bolus.

When a tumour is detected or suspected at GOE, a tumour staging is done with computer tomography (CT) of the abdomen and chest. The aim is to determine whether the cancer is localized, or if there is evidence of tumour spread or local invasion of adjacent organs, as well as to discover any suspected lymph node involvement. According to the Swedish national treatment guidelines [7], a Positron emitting tomography (PET scan) [19] should be added to exclude the risk for occult spread of the cancer disease such that patients can be spared futile surgery.

If the tumour stage is such that a curative surgical approach is judged possible, a further evaluation of the patient's physical performance and lung capacity is made.

## **Treatment of Dysphagia**

### **Treatment of achalasia**

A variety of different treatments have been tried for achalasia, including major open surgical interventions via the trans-thoracic and/or the abdominal route, dilatation with rigid instruments such as Savary-Gilliard dilators [20], and pharmacological treatments including Botox injections in the LOS [21, 22]. In later years, the two most common treatments used have been repeated pneumatic dilatations by endoscopy or laparoscopic surgical myotomy with the addition of a fundoplication [23-27]. Although there are some studies that compare treatment options, there are only a few studies that concern long-term results of minimally invasive treatment options for achalasia [24-28]. In particular, data regarding cumulative costs for treatments (health

economy), quality of life effects and treatment patency over the long-term are limited.

## **Treatment of malignant disease**

### *Curative intention*

The curative treatment for OC and GOJ is surgical resection. During the most recent decade, survival has improved after curative treatment, due to improved surgical techniques, involving lymphadenectomy and improved staging, as well as the addition of neoadjuvant chemo-radiotherapy (nCRT) [29-31]. There are national and regional Swedish guidelines for care of OC, and treatment decisions and recommendations regarding the patients in this dissertation were made accordingly, unless otherwise specified. In brief, after diagnosis and staging, a functional assessment is made. If the patient is judged able to withstand curative treatment with acceptable risks and the tumour stage is not too advanced, allowing for a radical resection (normally < cT4a and M0), there are three different paths forward: 1) Neoadjuvant chemo-radiotherapy (nCRT) followed by surgery; 2) Surgery alone; and 3) Chemo-radiotherapy alone. The best chance for long-term survival is given by combined nCRT and radical surgical resection. Treatment recommendations are decided in a multi-disciplinary treatment conference. Early cancers (T1a) can be treated endoscopically with endoscopic mucosal resection (EMR) or endoscopic mucosal dissection (ESD) [32, 33], sometimes with the addition of adjuvant treatments. Since T1a tumours are subclinical and the patients do not suffer from dysphagia for mechanical reasons, these tumours were not included in this dissertation.

### *Surgery for cancer*

The majority of the OC in Sweden is situated in the lower 2/3 of the oesophagus. The surgical procedure that is the most common approach today for these tumours was described in 1946 by Ivor Lewis [34, 35] and is still used in a slightly modified form. It is a massive operation which until recently only was performed via an open combined approach. As an alternative to the Ivor Lewis procedure, depending on the level of the tumour within the oesophagus, other surgical procedures, including the McKeown's procedure [36] involving a neck anastomosis, may be selected.

Regardless of the chosen surgical approach, the surgical goal is always to achieve a radical resection with appropriate tumour margins, together with a safe reconstruction and well-functioning substitute, resulting in long-term survival with acceptable or good quality of life for the patient.

Today, there is a trend towards hybrid or completely minimally invasive surgery by the aid of laparoscopic, and in some centres also thoracoscopic, technology. This may be achieved with 2D or 3D techniques or robotic surgery. The cancer patients in this dissertation who were treated with surgical resection all underwent open standard surgical procedures. Further details regarding the surgical procedures for cancer are provided in Methods and in Paper IV.

### *Chemotherapy and radiotherapy*

When the treatment aim is to cure, and provided the patient is judged suitable for a combination treatment, chemotherapy (usually Cisplatin + 5-FU) is administered as a neo-adjuvant before surgery. It is usually combined with external radiation (40 Gy). There is today no evidence that supports post-operative adjuvant treatment as a standard option, mainly because patients become weakened by the major surgery and may thus not be able to withstand additional adjuvant therapy. However, adjuvance may be considered in individual cases as a salvage strategy

in the case of incomplete or R1 resection. Moreover, chemoradiotherapy can in select cases be offered as the sole treatment to patients with a technically curable disease but who are judged unfit to undergo surgery. Then, a radiation dose of up to 64 Gy can be given locally.

### *Palliative treatment*

The aim of palliative treatment is to maintain or improve quality of life for the patient by alleviating negative symptoms and, if possible, to prolong life. Because a majority of the patients with OC or CGOJ are only eligible for palliative treatment due to poor performance level and/or advanced tumour stage, it is highly important to alleviate the symptoms with an efficient method or a combination of methods that do not burden the patients more than necessary.

There are several methods to palliate these patients, including providing best supportive care in the terminally ill, as well as offering radio- and/or chemotherapy to patients with better general condition and a longer life expectancy. As mentioned above, since dysphagia is a symptom that is very common and has a strong negative impact on quality of life [2], providing dysphagia relief and facilitating swallowing is a core goal of the palliative therapy. This can involve radiotherapy or stent treatment. Radiotherapy can be administered as either external radiation or internal radiation, so called brachytherapy [37, 38]. Both methods have good results on the dysphagia but are resource demanding since repeated treatments are necessary and the effect has a slow onset. Repeated treatments and hospital visits may also be burdening for the patients. In contrast, stent therapy is easily accessible and has a rapid-onset effect on the dysphagia. Stent insertion with self-expandable metallic stents (SEMS) has for the last two decades evolved as the most used treatment to relieve dysphagia in these patients [37, 39-41].

Even though endoluminal brachytherapy has shown advantages regarding dysphagia relief and QoL in patients with a somewhat longer survival [37], oesophageal stent insertion still remains the main option

in many institutions, and this is due to its simplicity and the often short life expectancy in this patient category.

## **A historical background of stents**

The first commercially available stent was introduced in 1959. It consisted of a silicon rubber tube which was inserted in the oesophagus through a laparotomy and an open gastrostomy, and carried extremely high complication and mortality rates [42]. Not until the mid-1970s were the first endoscopically placed oesophageal plastic stents available. The first commercially available SEMS in the 1990s were uncovered and were associated with re-intervention rates of up to 30-50 %, most commonly due to stent obstruction secondary to tumour or inflammatory tissue in-growth [43, 44].

A variety of different SEMS designs equipped with a plastic lining covering the exterior surface of the stent were subsequently developed to prevent this complication [45]. Unfortunately, whereas the smooth lining of the first generation of covered stents helped to prevent tumour in-growth, those SEMS did not attach well to the oesophageal wall. A common and acknowledged disadvantage of fully-covered SEMS (fcSEMS) is therefore a high risk (20–39 %) for stent dysfunction due to dislocation [38, 46-49]. This leads to insufficient relief or recurrence of dysphagia. Semi-covered stents (scSEMS), i.e. covered in the mid portion and with bare mesh endings, were developed to lessen the risk for stent dislocation. Although scSEMS are associated with less migration-related events, they can still migrate and, in addition, re-obstruction in the uncovered endings still occurs [38, 46, 50]. This has led to the development of a newer generation of fcSEMS that have been modified design-wise to at least theoretically prevent stent migration. Whether these changes in design are indeed effective in reducing risk for stent migration as compared to conventional scSEMS has not previously been investigated in a randomized setting.

## **Consequences of dysphagia**

Dysphagia will in most cases reduce nutritional intake. A prolonged reduction in nutritional intake, even if small, will of course have physiological consequences over time. Thus, patients with dysphagia will often display weight loss, low BMI and loss of muscle volume and strength (Sarcopenia) [51], similar to what is seen in starvation [52]. Dysphagia has a profound negative effect on QoL [2]. In order to elucidate effects of various treatments, regardless of the aetiology of the dysphagia, QoL measures are therefore important to consider along with other quality indicators. More, longer term follow-up studies of QoL measures, in particular with regard to patients with achalasia, are as yet sparse.

Weight loss is common in cancer patients in general, and patients who are undernourished are considered to have a shortened life expectancy [53, 54]. In addition, undernourishment can increase surgical risk, particularly in patients who undergo major procedures [55-60]. It is not clear whether such results from patients undergoing other major procedures can be extrapolated to involve patients with oesophageal cancer as well. In several aspects, OC offers a particularly challenging situation from a nutritional standpoint. First, patients have often had dysphagia and experienced weight loss before treatment; second, the treatment itself may be regarded as a massive physiological challenge; and, third, the end result of the operation will normally entail a reduced ability to eat for an extended period of time.

Absolute body weight or body mass index (BMI) are measures that are used clinically for objective assessment of nutritional status in surgical patients. However, severe undernourishment and sarcopenia can be present in patients with normal body weight or even in obesity. There are a few studies describing body composition measures in patients with

OC or CGOJ before surgery [61, 62] and one study in which body composition is investigated during the first 9 days after [63]. However, less is known about body composition before surgery and the prevalence of sarcopenia, and of the prospective development of body composition and nutritional status for a longer period after open oesophageal resection surgery for cancer.

## **The concept of validity**

The concept of validity may be viewed as complex. Some of the validity parameters that were investigated as part of the present dissertation (Paper II) are: internal and external validity, construct validity, criterion validity and statistical conclusion validity [64]. A brief summary follows below.

Internal validity refers to the risk that external events can influence the outcome. External validity addresses the question of whether the results are comparable with other measurements of the same variable, and whether these measures can be thought to be generalizable, and, furthermore, whether the study subjects are representative for the variable studied. Criterion validity describes whether a test is comparable against a gold standard and is closely connected to external validity. Statistical conclusion validity addresses whether a protocol can answer the chosen endpoints without type I or type II errors.

Other important factors with scores and questionnaires are, first, the reliability (or consistency), which measures whether the result of a scale is reproducible. Reliability comprises of internal consistency and stability (test-retest reliability). In this context, sensitivity refers to a scale's ability to detect differences between groups or differences over time.

Except for the dysphagia module in the EORTC questionnaires, there are, to my knowledge, no dysphagia scales that are validated in the

Swedish language and apply to malignant dysphagia. The reproducibility and validity of these scales in detecting dysphagia due to malignancy are not yet known.

## AIMS

The overall aim of this thesis was to explore different aspects of dysphagia in patients with oesophageal disease with regard to the assessment, treatment and consequences of dysphagia.

The specific aims were:

- To validate dysphagia questionnaires in order to reliably measure and grade swallowing difficulties in patients with malignant disease, after first having translated them to Swedish.
- To evaluate both curative and palliative treatment strategies in conditions, both benign and malignant, for which dysphagia is a main symptom.
- To explore QoL in patients with achalasia, and in oesophageal malignancy, conditions that each cause oesophageal dysphagia, before and after specific treatments.
- To compare health-economic outcomes in different treatment strategies for achalasia.
- To describe body composition, nutritional status, sarcopenia, and physical performance in patients with dysphagia due to cancer of the oesophagus or the gastro-oesophageal junction, who are planned for surgery with a curative intention. Further, to explore the development of the above-mentioned variables during the first three months after surgery.



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# PATIENTS AND METHODS

## Design

This thesis is designed to address different aspects of dysphagia in patients with mechanical oesophageal dysphagia in both benign and malignant disease. I also wanted to investigate different treatments, as well as their impact on patients' QoL in both a general sense and a disease-specific way. A further purpose was to describe body composition in patients with dysphagia secondary to oesophageal cancer and how it develops post-operatively. The thesis is comprised of four studies. An overview is presented in Table 1.

In Paper I, the aim was to investigate the long-term outcome after two minimally invasive treatments for achalasia. The study size was determined by power analysis based on an estimate of a 30 % difference in dysphagia score, an alfa value of 5 % and a power of 80 %, which gave a sample size of 70 patients in each arm. The inclusion of patients was stopped after 53 evaluable patients for practical reasons. A CONSORT flow chart of this study is shown in Figure 3. The included patients had not received any treatments, surgical or otherwise, for achalasia prior to the start of the study. The subjects were randomized to two arms: repeated pneumatic endoscopic dilatation (n= 28) or a laparoscopic operation with a Heller myotomy and a fundoplication (n= 25). The short-term (one year) outcome of this material has already been presented [23, 65]. Patients were followed up at > 5 years (median 81.5 months) after treatment. The main variable was treatment failure, which was defined as follows:

1. Incomplete symptom control or symptom relapse that required more than three additional treatments other than those given initially (surgery or one to two dilatations at an interval of about ten days).
2. Relapse which required treatment occurring within three months after the initial treatment series.

3. A serious complication or side effects after treatment that required a switch-over to the alternative strategy.
4. The patient required or requested alternative treatment or another treatment due to dissatisfaction with the allocated therapy.
5. The responsible physician recommended that the patient should undergo another treatment after consulting with the trial committee.

In addition, treatment success was determined. As secondary variables, the frequency and degree of dysphagia were determined, as were QoL and health economy.

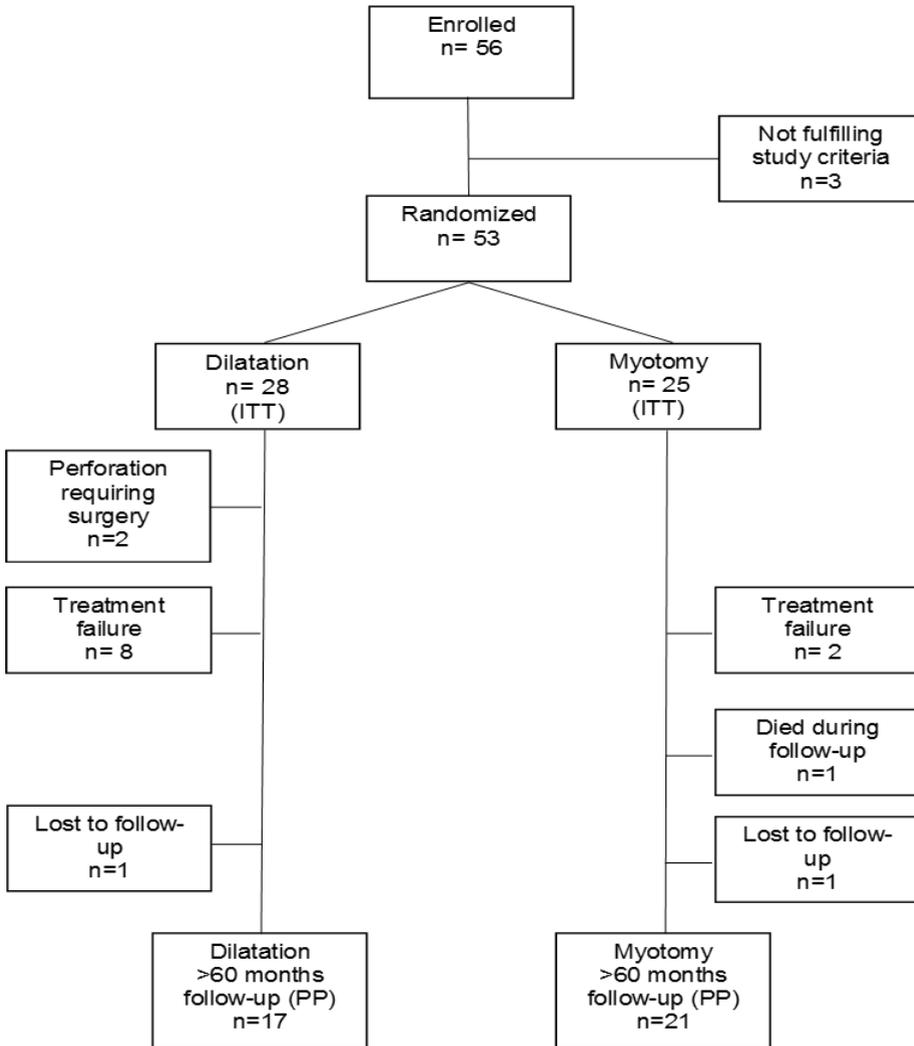


Figure 3. Flow chart over Paper I (Reprinted from Paper I, with permission)

**Table 1.** Overview of the designs, demographics, endpoints, and sources of data of the different papers included in this dissertation

	Paper I	Paper II	Paper III	Paper IV
Design	Prospective randomized controlled study with 2 study arms.	Validation study comparing scores with each other and with the food diary.	Prospective randomized controlled study with 2 study arms.	Descriptive study with the same intervention in all patients.
Sample	n= 53	n= 64	n= 95	n= 76
Median age year (min-max)	44.0 (17 – 78)	66.7 (41 – 87)	71.7 (48 – 91)	67.0 (33 – 85)
Sex n= female	30 (56.5 %)	25 (40.6 %)	24 (25.3 %)	10 (13.0 %)
Endpoints	Treatment failures, treatment success, dysphagia, QoL and health economy.	Validation and translation of dysphagia scores.	Stent migration, effects on dysphagia, QoL and re-intervention frequency.	Description of body composition and its progress, dysphagia, physical performance, QoL and complications.
Sources of data	Clinical record forms, dysphagia scores, QoL questionnaires, telephone surveys and medical charts.	Dysphagia scores, QoL questionnaires, medical charts and food diaries.	Clinical record forms, chest x-ray, dysphagia scores, QoL questionnaires and medical charts.	Bioimpedance spectroscopy, dysphagia scores, cardiac stress test, QoL questionnaires and medical charts.

The specific aim in Paper II was to validate three well known dysphagia scores for malignant disease with the help of 35 patients with oesophageal cancer and 29 healthy controls. Prior to this, each scale was translated to Swedish using the back-translation method [66].

The study sample size was empirically decided after consultation with a statistician. A power analysis for the Watson score, global QoL and dysphagia measured with QLQ-OG25, using the differences detected in this study, reveals a power between 81 % and 99 %.

The scales were: the Watson scale, the Ogilvie scale and the Goldschmid scale. The validated EORTC scales QLQ-C30 and QLQ-OG25 were used for external control comparisons. In addition, another external control condition was used; the patients were asked to keep a food diary for four consecutive days, such that the type of food possible to swallow could be assessed versus the respective dysphagia scale. On day 10, the patients were interviewed and again asked to fill in the scales, to control for individual variability. To allow for additional external validity testing, a group of 29 healthy volunteers with no history of dysphagia were asked to participate. The healthy volunteers in the control group were asked to fill in the questionnaires once. A timeline of the study is shown in Figure 4 below.

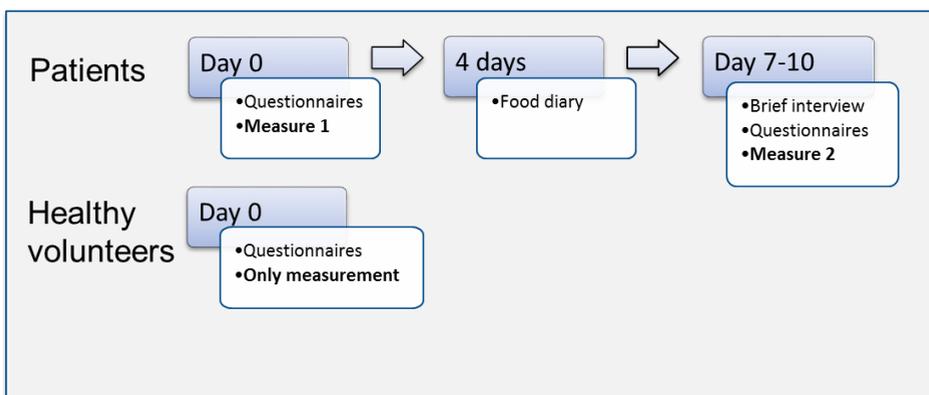


Figure 4. Timeline of the data collection in paper II

In paper III, the aim was to test whether stent design affects the risk for stent migration in a prospectively randomized setting. Patients with dysphagia due to OC or CGOJ, and who were eligible for best supportive care, were asked to participate. The study size was determined by power analysis, using an estimation that there would be a 25 % difference in migration rate between groups. The patients included were randomized to receive either a newer design of a fully-covered stent (n= 48) or to a conventional, semi-covered stent in standard use (n= 47). The hypothesis was that the newer fully-covered design would migrate to a higher degree than the semi-covered stent. The primary variable was stent migration > 20 mm, which was objectively measured using chest x-ray. As secondary variables, we studied effects on dysphagia, QoL and re-intervention frequency. For study flow see Figure 5, and for further details regarding the methodology, please see Paper III.

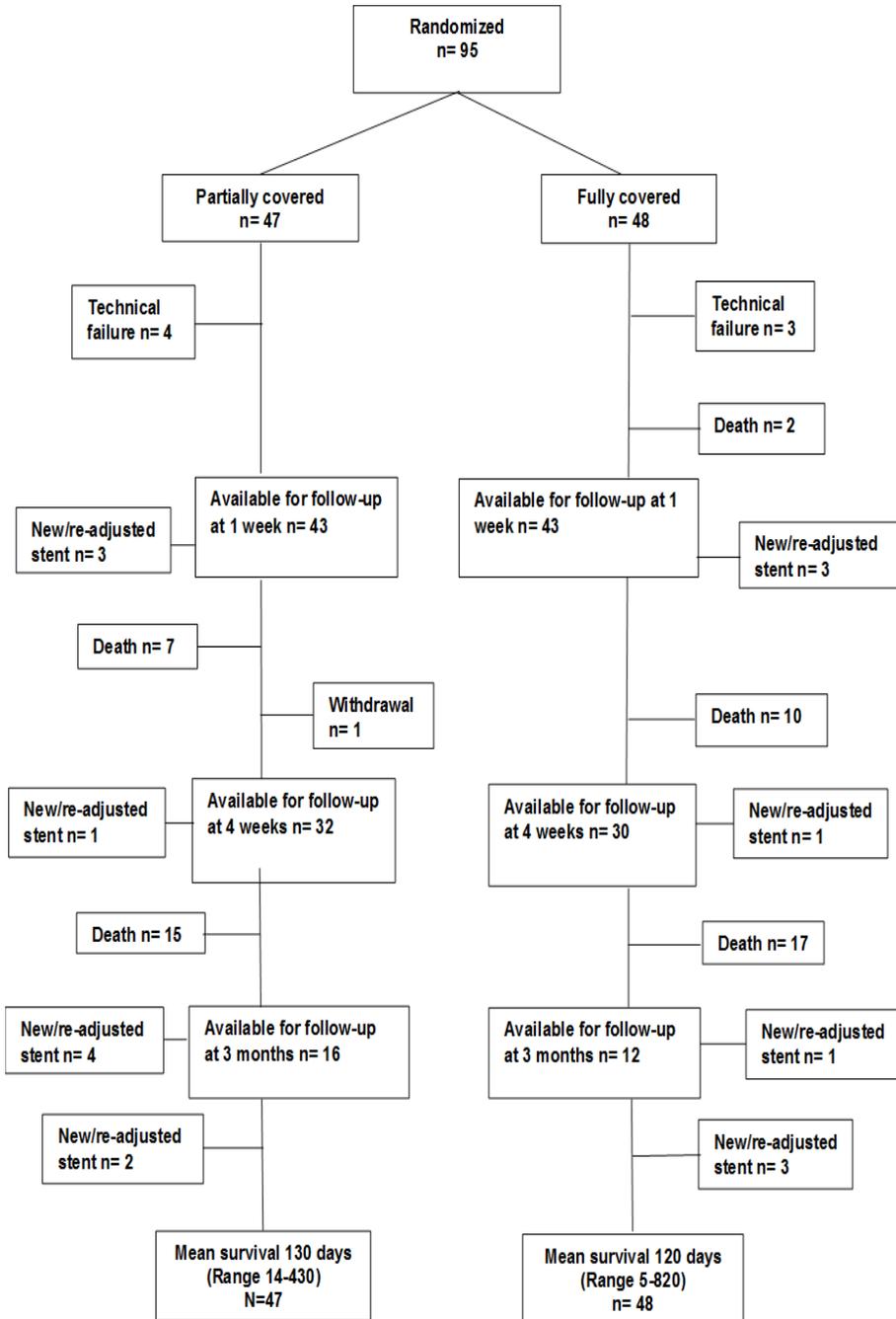
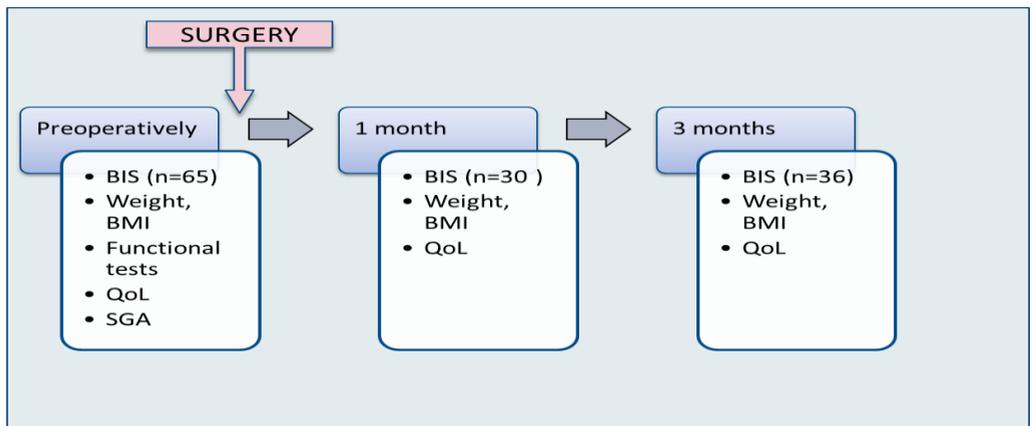


Figure 5. Flow chart over Paper III (Reprinted from Paper III, with permission)

Paper IV was an observational study designed to describe biometric measures including body composition, sarcopenia, physical performance, dysphagia and quality of life (QoL) pre-operatively, in a prospectively collected cohort (n= 76) with OC or GOJ. A second aim was to investigate possible changes in body composition and QoL variables in a follow-up after surgery. The third aim was to assess whether there could be a possible relation between any of these pre-operative variables and morbidity, length of stay, QoL or mortality. A timeline of the study is shown in Figure 6 below.



*Figure 6.* A schematic overview of the timeline of the data acquisition in Paper IV (For further details, see Paper IV)

For this purpose, a cohort of patients diagnosed with OC or CGOJ who were offered surgery with a curative intent, with or without nCRT, were asked to participate. The patients were prospectively collected over a five-year period and all received the same surgical treatment. Consequently, no power analysis was made. Prior to surgery, body weight, length, body mass index, functional tests (cardiac stress test and grip strength), SGA and quality of life measures were collected. At

follow-ups one and three months after surgery, BIS and weight were again measured, and data regarding quality of life were collected. Details regarding the methodology and a flow chart of the inclusion protocol are given in Paper IV.

## **Interventions**

### *Paper I – Comparing laparoscopic myotomy to endoscopic dilatation for achalasia-associated dysphagia*

In patients allocated to endoscopic pneumatic dilatation, a dilatation balloon of 30–40 mm was placed endoscopically with the aid of a guide wire at the level of the gastro-oesophageal junction under fluoroscopic guidance. Balloon insufflation was made to 10 psi for 60 s. At the initial index treatment, women were dilated to 30 mm and men to 35 mm. If symptom relief from the first dilatation was insufficient, another dilatation was performed within ten days using 35 mm balloons for women and 40 mm balloons for men.

Patients allocated to surgical myotomy had a laparoscopic operation. The lower oesophageal sphincter myotomy involved division of the entire muscle layer down to the mucosa at least 5 cm above the GOJ and 2–3 cm into the ventral aspect of the stomach to include the sling fibres of the cardia. To prevent the risk of gastro-oesophageal reflux, a partial fundoplication according to Toupet [67] was added. This fundoplication method was chosen because our centre has vast experience of this method and there are long-term follow-up data that show superior results with this method for preventing reflux as compared to an anterior wrap [68].

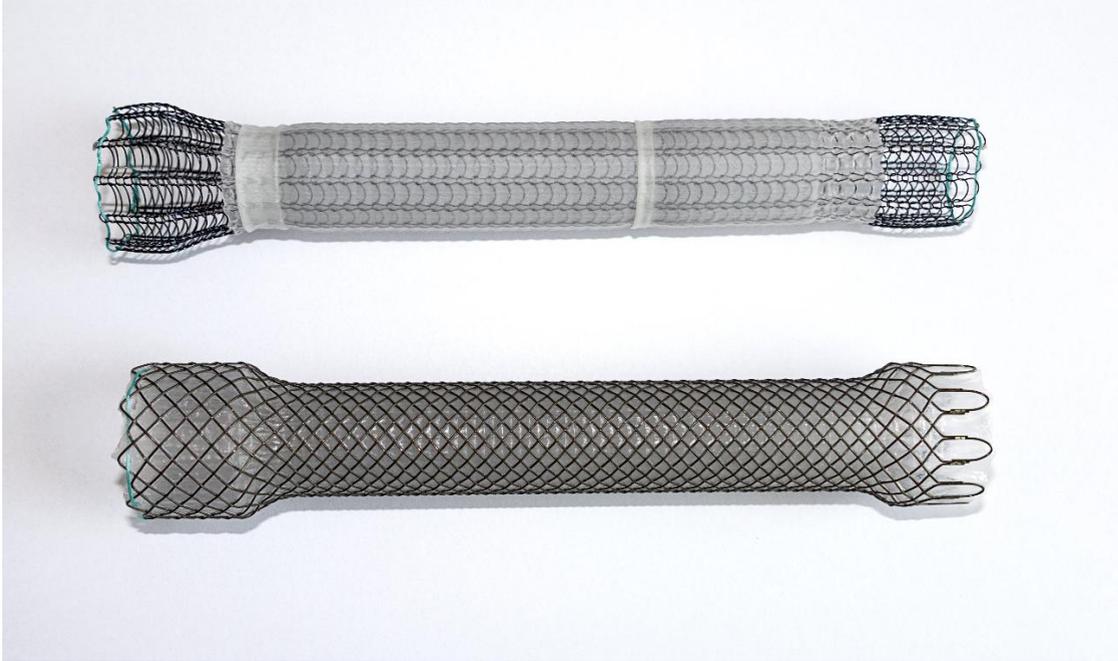
### *Paper II – Validation of scales for assessment of dysphagia due to malignancy*

Three well-known dysphagia scores were translated to Swedish by a native English-speaking translator and then back to English by a

different translator. The differences between the second translation and the original scale were assessed and found to have only minor dissimilarities that were judged to have no importance. The scales were: the Watson scale, the Ogilvie scale and the Goldschmid scale. EORTC scales QLQ-C30 and QLQ-OG25 were used for control comparisons. Thirty-five native Swedish-speaking patients diagnosed with dysphagia due to cancer of the oesophagus or gastro-oesophageal junction were asked to fill in Swedish versions of the scales. The patients also kept a food diary for four consecutive days, such that the type of food possible to swallow could be assessed versus the respective dysphagia scale. On day 10, the patients were interviewed and again asked to fill in the scales, to control for individual variability. In addition, a control group consisting of 29 native Swedish-speaking healthy volunteers was also asked to fill in the Swedish questionnaires once. Correlation analyses were made between the different scales and against the EORTC scale QLQ-OG25, and swallowing ability, as assessed with food diaries.

*Paper III – Stent designs and migration in treatment of dysphagia due to malignancy*

Patients with cancer in the oesophagus or in the gastro-oesophageal junction who had been offered palliative treatment were asked to participate. Patients were randomized to receive either an scSEMS or an fcSEMS. The patients were sedated during the intervention. The upper margin of the tumour was marked with a metallic clip and, under fluoroscopic guidance, a guide-wire was then passed down through the tumour. When the endoscope had been removed, the allocated stent was inserted over the wire and positioned in relation to the clips. The different stents used in the study are depicted in Figure 7.



*Figure 7. Stent designs used in Paper III: A conventional, semi-covered Ultra-flex stent (top) and a newer design, fully covered Wall-flex stent (below)*

#### *Paper IV – Body composition and sarcopenia in patients with OC and CGOJ*

After pre-operative assessment and a routine work-up including measurement of body composition parameters, the patients underwent elective oesophageal resection surgery. The Ivor Lewis procedure, which was typically used in the present investigation, was performed as follows, in brief: First, an upper midline incision was done and the stomach was mobilised. The minor curvature and the gastro-oesophageal junction were resected so that a gastric conduit could be constructed with a linear stapling device. After this, the laparotomy was closed and the patient was turned to a left side position. A right sided, anterior-posterior thoracotomy was performed between the fifth and sixth ribs to allow for access to the posterior mediastinum. The oesophagus, including the gastro-oesophageal junction with

surrounding soft tissue including the azygos vein and thoracic duct, as well as the minor curve and fundus of the stomach, was resected *en bloc*. A standard, two-field lymphadenectomy was routinely performed in conjunction with the oesophagus resection. Finally, an end-to-side anastomosis was constructed between the remaining oesophageal end and the gastric conduit. The anastomosis was either hand sewn or stapled using a circular stapling device.

## **Assessment tools used in the thesis**

### *Assessment of dysphagia*

Several dysphagia assessment instruments are described in the literature. In this thesis, the Watson dysphagia score, the Ogilvie score and the Goldschmid score were used and investigated. These scores were selected since they have been frequently used in a variety of other studies to assess dysphagia of benign and malignant aetiologies. In addition, the EORTC QLQ-OG25 and QLQ-OES18 were used, which are validated for malignant disease and contain a module for dysphagia measures.

The Watson dysphagia score [14, 17] was initially designed for assessing symptoms in reflux disease before and after surgical treatment. The score consists of questions regarding the ability to swallow food items of nine different viscosities and solidities, and the frequency of problems swallowing these specific food types: never, sometimes or always. The scores are added and provide a range of 0-45 where 45 reflects the worst possible dysphagia. The Watson score was used in Papers I-IV.

The Ogilvie score [16], which was developed for malignant dysphagia but never validated for this purpose, is a 5-graded scale 0-4 where 4 is total inability to swallow, was used in Papers II and III.

The Goldschmid score [15], which was originally developed for patients with dysphagia of mainly benign aetiology is graded from 0-5 where 0 is inability to swallow and 5 is normal function, was used in Paper II. In addition, the dysphagia modules in the EORTC symptom-specific QOL scales QLQ-OES18 [69] was used in Paper IV, and the QLQ-OG25 [70] was used in Papers II and III.

### *Assessment of stent migration*

Stent migration was determined by direct measurement. This was accomplished by using conventional frontal and lateral chest X-rays. The stent position was measured on the lateral projection in relation to the thoracic vertebrae and the aortic arch by a senior thoracic radiologist. Since the stents are slightly different in appearance and easily recognisable (Figure 7), blinding was not possible.

### *Assessment of QoL*

In patients with a benign disease (Paper I), QoL was assessed with the Personal General Well-Being (PGWB) score [71-74] and the Gastrointestinal Symptom Rating Scale (GSRS) [75]. The PGWB is a generic instrument giving a total score, as well as six different domains (anxiety, depressive mood, positive wellbeing, self-control, general health, and vitality). The GSRS is a disease-specific instrument measuring six different scales (reflux, pain, indigestion, constipation, diarrhoea, and dysphagia).

In patients with OC or CGOJ, QoL was evaluated using both generic instruments and a symptom-specific instrument from the European Organization for Research and Treatment of Cancer (EORTC). The QLQ-C30 [76] measures global QoL in patients with cancer and is composed of multi-item functional scales, symptom scales, and single-item measures. In addition, the QLQ-OES18 [69] (Paper IV) and the QLQ-OG25 [70] (Papers II and III) were used. These are symptom-

specific instruments specifically developed for cancer and should be used together with the QLQ-C30.

#### *Assessment of body composition and sarcopenia*

Body composition was measured using bio-impedance spectroscopy analysis (BIS) [77] in patients with OC and CGOJ, planned for resection surgery with a curative intention (Paper IV). BIS is a validated method and is found to correlate to measurements with dual-energy x-ray absorptiometry (DEXA), magnetic resonance tomography and computer tomography [78-80].

Sarcopenia was assessed in relation to working capacity, muscle strength and lowered muscle mass, and two of the three variables had to be fulfilled to set the diagnosis of sarcopenia [51].

Muscle mass was determined by fat free mass (FFM) measured with BIS, and the fat free mass index (FFMI) is calculated by FFM divided by square length in meters. The reference values for low muscle mass measured with FFMI were taken from the ESPEN consensus guidelines regarding diagnostic criteria for malnutrition [81].

#### *Assessment of complications*

In Paper IV, complications were measured using the Clavien-Dindo method [82] which retrospectively, by reviewing medical charts, rank a complication based on the therapy used to treat it.

#### *Assessment of oesophageal motor function and mucosal structure*

Oesophageal manometry was used in Paper I to identify patients with characteristic alterations on oesophageal manometry consistent with achalasia, i.e. high pressure of the LOS together with insufficient relaxation of the sphincter when swallowing. At the time of the design of the study reported in Paper I, the more exact and information dense method “High resolution manometry” was not yet in standard use, which

is why there is no information regarding any different subtypes of achalasia in this material (see Discussion, paragraph 3).

GOE was used to exclude or verify malignant causes of dysphagia (Papers I - IV) and just after randomisation in Paper III, which was the only planned endoscopy in that study protocol.

#### *Assessment of nutritional status*

As part of the study protocol, nutritional status was assessed by a dietician using the Subjective Global Assessment (SGA) [83] (Paper IV). SGA is a validated questionnaire used by a professional that evaluates nutritional status and nutritional risk.

### **Treatment of benign disease**

Achalasia was treated with either laparoscopic myotomy of the LOS in combination with a fundoplication according to Toupet [67] or with repeated endoscopically pneumatic dilatations (Paper I). The methods are described above in “Interventions”.

### **Treatment of malignant disease**

Patients who were offered best supportive care after MDT conference, and who were offered stent treatment as part of the palliative treatment strategy, were asked to participate in the study of Paper III, where they were randomized to receive either an scSEMS or an fcSEMS. In paper IV, patients who were offered nCRT and/or resection surgery were asked to participate in the study. The surgery is described under “Interventions” above.

## Statistical evaluations

Statistical evaluations were made with IBM SPSS Statistics version 22 software in all the Papers. In Papers II and IV, SAS system version 9 was used as well. All significance tests in all four papers were two-sided and conducted at the 5 % significance level ( $p < 0.05$ ). A summary of the statistical methods used in each Paper is shown in Table 2. The specific analyses are also indicated in legends to figures and tables.

Table 2. Overview of statistical methods used in Papers I – IV

Statistical Methods	Paper			
	I	II	III	IV
<b>Descriptive statistics</b> Mean, SD, Median, Minimum and Maximum for continuous variables	x	x	x	x
Number and % for categorical variables	x	x	x	x
<b>Statistical analyses</b> For comparison between two groups:				
• Mann-Whitney U-test for continuous variables	x	x	x	x
• Student's T-test for continuous QoL variables	x			x
• Fisher's exact test for dichotomous variables		x	x	x
• Chi-Square test for dichotomous variables	x		x	x
• Mantel-Haenszel chi-square test for ordered categorical data		x		
Changes over time within group				
• Sign test for ordered categorical variables		x		
• Wilcoxon signed rank test for continuous variables		x		x
Survival statistics				
• Kaplan-Meier plots	x		x	x
• Cox proportional hazard analysis				x
• Standardized mortality ratio				x
• Log-rank test	x		x	
<b>Validation statistics</b> Reliability: (Test-retest)				
• Percent agreement and Cohen's Weighted Kappa for ordered categorical variables		x		
• Bland-Altman plot, distribution of difference between test and retest, intra individual standard deviation, and intra-class correlation coefficient (Shrout-Fleiss) for continuous variables		x		
Correlation analysis				
• Spearman rank correlation coefficient		x		x

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*Paper I – Comparing laparoscopic myotomy to endoscopic dilatation for achalasia-associated dysphagia*

For the primary end-point, failure, and other dichotomous variables, comparisons between the two groups were made with the Chi-square test. For comparison between the two groups, the two-sample t-test was used for the continuous QoL variables and the Mann-Whitney U-test for other continuous variables. Survival analyses were applied to the variable time to treatment failure with Kaplan-Meier plots and log-rank test.

*Paper II – Validation of scales for assessment of dysphagia due to malignancy*

The Mann-Whitney U-test was used for comparing continuous variables between two groups. Reliability was evaluated with test-retest, where the ordinal categorical variables (Ogilvie and Goldschmid) were analysed with percent agreement and Cohen's weighted Kappa value. For test-retest analysis of the continuous variables (Watson, Dysphagia module QLQ-OG25 and Global QoL), Bland-Altman plots, distribution of differences between test and retest, intra-individual standard deviations, and intra-class correlation coefficients (ICC) were used. Systematic differences between measure 1 and measure 2 were compared using the Sign test for ordinal categorical variables and the Wilcoxon Signed Rank test for continuous variables. Known group validation between patients and healthy controls was done with Fisher's exact test for dichotomous variables and the Mantel-Haenszel Chi-square test for ordered categorical variables. For known group validation of continuous variables, the Mann-Whitney U-test, and effect sizes, were used. For external validation, the correlations between the different scores were first theoretically estimated and then observed with the Spearman rank correlation coefficient ( $r_s$ ).

*Paper III – Stent designs and migration in treatment of dysphagia due to malignancy*

For the primary end-point, migration, and other dichotomous variables, comparisons between two groups were made with the Chi-square test. In addition, Fisher's exact test was used where group sizes were small (Table 6), this is also the case for the "Dilatation during stent procedure" (Paper III). The Mann-Whitney U-test was used to compare continuous variables between the two groups. Patient survival in the different stent groups was compared using log-rank tests.

*Paper IV – Body composition and sarcopenia in patients with OC and CGOJ*

For comparison between two groups, the two-sample t-test was used for normally distributed continuous data, the Mann-Whitney U-test for other continuous data, the Mantel-Haenszel chi-square test for ordered categorical variables and Fisher's exact test for dichotomous variables. For evaluation of changes over time, the Wilcoxon signed rank test was used for continuous variables. Correlation analyses were made using the Spearman rank of correlation ( $r_s$ ). Values of  $r_s > 0.4$  were regarded as a moderate, and  $r_s > 0.8$  as a strong, correlation. Survival analyses were made with Cox proportional hazard analysis with Hazard ratio (HR) with a 95% confidence interval and Kaplan-Meier plots. Standardized mortality ratio (SMR) with a 95% confidence interval was calculated for total population and selected subgroups.

## **Ethical considerations**

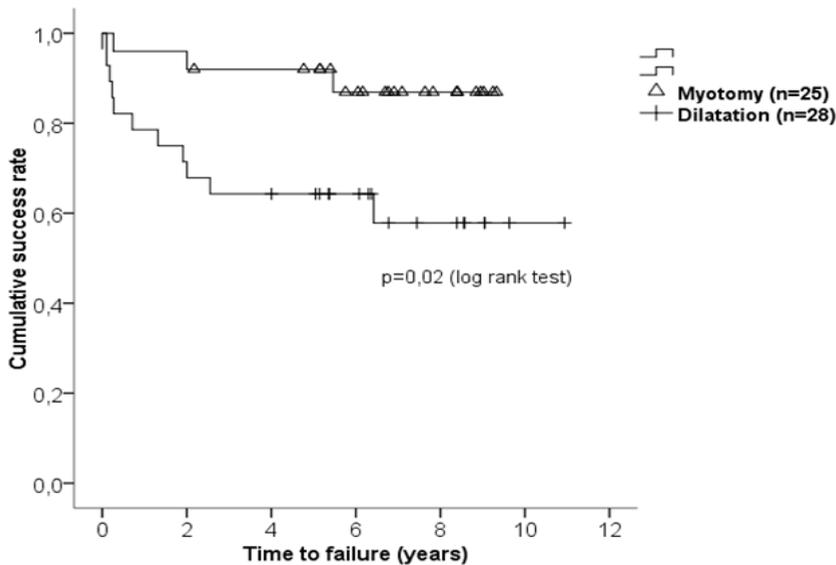
During the whole course of this thesis, a continuous discussion was held concerning ethical aspects. All four studies were performed according to the Declaration of Helsinki and its later amendments, and to the Ethical Review Act. The study protocols were approved by the Ethical Review Board Authorities in Stockholm (Paper III) and in Gothenburg (Papers I, II and IV). Written informed consent was obtained from each participant before inclusion in each of the respective trial. All trials are also registered in the [www.ClinicalTrials.gov](http://www.ClinicalTrials.gov).



## RESULTS AND COMMENTS

### *Paper I – Comparing laparoscopic myotomy to endoscopic dilatation for achalasia-associated dysphagia*

The long-term efficacy and patency of laparoscopic myotomy and fundoplication were compared to endoscopic dilatation of the LES for the treatment of achalasia, over the long term. The primary variable was the accumulated numbers of treatment failures. At five years, 36 % in the PD group and 8 % in the LM group, including two patients who were lost to follow-up (one in each arm), were judged as treatment failures ( $p=0.016$ ) (Table 3). The Kaplan–Meier analysis showed a significantly shorter time to treatment failure for the PD strategy ( $p=0.02$ ) (Figure 8).



*Figure 8.* Kaplan-Meier plot of treatment failures in patients treated with laparoscopic myotomy vs. repeated endoscopic dilatations in Paper I. There was a significant difference between the groups, showing an advantage for the surgical treatment option. (Reprinted from Paper I, with permission)

Both treatments significantly improved dysphagia but there was no difference between groups. When comparing size of improvement, we noted a better effect in the Watson score for the LM group at three years ( $p= 0.05$ ), but this significance was no longer present at five years. The global QoL measured with PGWB was higher in the LM group at three years ( $p= 0.024$ ) but this difference also decreased over time (Table 4).

The direct medical costs were lower for the PD strategy at 60 months and for the entire study period. The total medical cost for each patient during the first 60 months was \$13,215 after LM as compared to \$5,247 for PD ( $p< 0.001$ ). This was mainly caused by the difference in the initial treatment costs (Paper I).

*Comments:*

Measuring the cumulative incidence of treatment failure as the primary variable is a new way to assess outcome after achalasia treatment which I think is more objective and reflects the clinical management over time compared to the traditional way of evaluating symptoms. The LM strategy was more expensive, but costs must be viewed against the effectiveness of the treatments. These patients have a large symptom burden and it is clear that LM gives a better result in the short run and has fewer early adverse events which, altogether, can motivate the higher cost.

*Table 3.* Failures at three and five years after treatment (adapted from Paper I). Failures were significantly fewer in patients treated surgically, at all time points. Data were analysed with the Chi-square test.  $P < 0.05$  (\*) was considered significant. (Reprinted from Paper I, with permission)

	Dilatation (n=28)	Myotomy (n=25)	p-value
Failures at three years, no (%)	9 (32%)	1 (4%)	0.008 (*)
Changing strategy during follow-up, no (%)	7 (25%)	2 (8%)	0.10 (NS)
Failures at five years, no (%)	10 (36%)	2 (8%)	0.016 (*)
Failures during total follow-up, no (%)	11 (39%)	3 (12%)	0.025 (*)
Changing strategy during follow-up, no (%)	8 (28%)	2 (8%)	0.056 (NS)

Table 4. Watson score and QoL (PGWB) at three and five years. (Reprinted from Paper I, with permission)

<b>Per protocol analysis</b>	<b>Dilatation (n=17)</b>	<b>Myotomy (n=21)</b>	<b>p-value</b>
<b>Watson score</b>			
Median (min-max)			
Watson score three years	15 (0-42)	8 (0-34)	0.11 (NS)
Difference Watson score Pre-op - three years	13 (-20-34)	20 (0.5-42)	0.05 (*)
Watson score five years	16,5 (0-43)	10,5 (0-42)	0.47 (NS)
Difference Watson score Pre-op - five years	16.5 (-9-33)	18 (-3-36.5)	0.32 (NS)
<b>PGWB</b>			
Mean (SD)			
PGWB total three years	98 ( $\pm$ 20)	114 ( $\pm$ 10)	0.024 (*)
PGWB anxiety	23 ( $\pm$ 5.9)	27 ( $\pm$ 2.6)	0.021 (*)
PGWB depr mode	15 ( $\pm$ 2.5)	17 ( $\pm$ 1.3)	0.058 (NS)
PGWB pos wellb	16 ( $\pm$ 3.6)	18 ( $\pm$ 2.8)	0.057 (NS)
PGWB self contr	15 ( $\pm$ 2.3)	17 ( $\pm$ 1.0)	0.014 (*)
PGWB gen health	14 ( $\pm$ 3.4)	16 ( $\pm$ 2.7)	0.057 (NS)
PGWB vitality	16 ( $\pm$ 4.7)	18 ( $\pm$ 2.9)	0.098 (NS)
GSRS three years			NS (in any dimension)
PGWB five years			NS (in any dimension)
GSRS five years			NS (in any dimension)

The Mann-Whitney U-test was used for data evaluation of dysphagia whereas Student's t-test was used for comparisons of QoL measures.  $P < 0.05$  (\*) was considered significant. NS= not significant.

Watson dysphagia score has a range from 0 (no dysphagia) to 45 (severe dysphagia). PGWB has a range from 0 to 132. In Sweden, the norm value in healthy people is 102.9 [71].

*Paper II – Validation of scales for assessment of dysphagia due to malignancy*

In Paper II, we attempted to validate the three scales for assessing dysphagia for malignant strictures. Validation statistics were adopted for this purpose. The three scales studied were translated to Swedish with the help of two different translators. The back-translation method was used. The reliability of the dysphagia scales of Watson score, Ogilvie score and Goldschmid score were analysed. Thus, we found that reliability and stability in the categorical variables (Ogilvie and Goldschmid) showed a value of Weighted Kappa, indicative of a moderate strength of agreement, and, for the Watson score and the Dysphagia module of QLQ-OG25, the Intra-class Correlation Coefficients were good to excellent, respectively. Correlation between all scales was good to excellent with high values of correlation coefficients ( $r_s$ ) with the strongest correlations between the Ogilvie score and the dysphagia module in QLQ-OG25. These latter two scores also had the strongest correlation to the food diary (Table 5).

*Comments:* A possible confounding factor with regard to the Goldschmid scale, which was noted when the results were already evaluated, is that the scales had been presented to the participants in the same consecutive order; the Goldschmid score appeared right after the Ogilvie score. These two scales are quite similar, but the scoring appears in reverse order, which may explain that the healthy control group indicated severe dysphagia when measured with Goldschmid. This leads to there being no significant difference in dysphagia between the patients and the control group when measured with this particular score.

Table 5. Outcome of the correlation analyses comparing the relationships between the investigated scales and between the scales and the food diary.

	Reliability (test – retest)	Correlation to other scores	Criterion validity (compared to food diary)
Ogilvie score	Moderate strength of agreement <sup>1</sup>	Excellent <sup>3</sup>	High <sup>3</sup>
Goldschmid score	Moderate strength of agreement <sup>1</sup>	Good <sup>3</sup>	Intermediate <sup>3</sup>
Watson score	Good strength of relationship <sup>2</sup>	Good <sup>3</sup>	Intermediate <sup>3</sup>
Dysphagia (QLQ-OG25)	Excellent strength of relationship <sup>2</sup>	Excellent <sup>3</sup>	High <sup>3</sup>

Test-retest for ordinal categorical variables was made with Weighted Kappa<sup>1</sup>. For continuous variables the Intra-class correlation coefficient<sup>2</sup> was analysed. Correlations were examined with Spearman's rank correlation test<sup>3</sup>. Precise numerical values statistical outcomes are shown in Paper II.

### *Paper III – Stent designs and migration in treatment of dysphagia due to malignancy*

In Paper III, an fcSEMS and an scSEMS, for palliative treatment of dysphagia due to malignancy, were compared with regard to migration distance and frequency as the primary variables. There were no significant differences either in stent migration distance or in the migration frequency between the stent in standard use (scSEMS) and the newer fully-covered stent (fcSEMS), 20.0 % vs 37.2 %, respectively; ns, (Table 6).

Dysphagia was measured with three different instrument scales, and there was a significant reduction in both groups but no significant difference between groups (Table 7).

There were 15 (scSEMS) vs. eight (fcSEMS) re-interventions after stent placement in total over the studied three months. Again, a tendency toward a lesser need for re-interventions was seen in the fcSEMS group ( $p = 0.083$ ) (Table 6).

Neither QoL nor survival showed significant differences between groups. In addition, overall QoL was similar to previous reports on this patient category, supporting that the groups were representative.

*Comments:* The hypothesis in this study was that the semi-covered stent in standard use has a lower migration risk compared to the newer fully-covered design. The results show that the null-hypothesis could not be rejected, however, since the fcSEMS was at least similar with regard to migration to the conventional scSEMS. This suggests that modern designs of fcSEMS, similar to the fcSEMS used in this study, do not have a higher migration rate than scSEMS. A weakness with this study is that it was not designed to show equality or non-inferiority prior to its start. In addition, there was a numerical difference in migration rate in a magnitude that would be clinically relevant in favour of the fcSEMS group, which suggests that fcSEMS might be beneficial or at least comparable to scSEMS with regard to stent migration. Should, in retrospect, a hypothetical power calculation for a two sided, non-inferiority setting been done, and the actual migration rates and sample size from this study be used, a non-inferiority limit of 10% and a 5% significance level would yield a power of about 90% [84]. This together supports that the fcSEMS and the scSEMS used in this study have at least similar outcomes regarding stent migration.

Table 6. Stent migration > 20 mm, migration distance in millimetres and numbers of endoscopic re-interventions. (Reprinted from Paper III.)

	scSEMS	fcSEMS	p-value
<b>Stent migration &gt; 20 mm number of cases</b>			
At one week	4	4	0.971 <sup>1</sup> 0.740 <sup>3</sup>
At one month	3	1	0.293 <sup>1</sup> 0.615 <sup>3</sup>
At three months	4	1	0.154 <sup>1</sup> 0.358 <sup>3</sup>
Total numbers at three months	11 (25.6 %)	6 (13.3 %)	0.145 <sup>1</sup>
Total number during survival	16 (37.2 %)	9 (20.0 %)	0.068 <sup>1</sup>
<b>Migration distance in millimetres</b>			
One week median (min-max)	2.0 (-20 – 70)	0 (-30 – 144)	0.243 <sup>2</sup>
One month median (min-max)	5.5 (-39 – 50)	2.5 (-16 – 91)	0.415 <sup>2</sup>
Three months median (min-max)	10.5 (-11 – 42)	0 (-7 – 33)	0.270 <sup>2</sup>
Proximal migration at one week (n = yes)	8 (24.2%)	13 (36.1%)	0.231 <sup>1</sup>
<b>Numbers of endoscopic re-interventions</b>			
One week	6 (13.9 %)	5 (11.6 %)	0.744 <sup>1</sup>
One month	5 (15.6 %)	2 (6.7 %)	0.288 <sup>1</sup>
Three months	4 (25.0 %)	1 (8.3 %)	0.322 <sup>1</sup>
Total interventions at three months	15 (34.9 %)	8 (18.6 %)	0.083 <sup>1</sup>

Migration in the proximal direction is denoted as negative values. The accumulated numbers at three months and during the subjects' life span are also shown. Pearson Chi-Square test<sup>1</sup>, the two-tailed Mann-Whitney U-test<sup>2</sup> or the Fischer's exact test<sup>3</sup> were used for data evaluation.

P < 0.05 was considered significant.

*Table 7.* Dysphagia measured with three different scales. Results are presented as median, range and n= numbers of patients per group. Reprinted from Paper III, with permission.

<b>Watson score</b>	scSEMS	fcSEMS	p-value
Pre-stent dysphagia	34.0 (0.0 – 45.0) n= 45	36.7 (5.5 – 45.0) n= 44	0.138
One week	30.0 (0.0 – 44.0) n= 33	29.5 (0.0 – 45.0) n= 30	0.731
One month	22.5 (4.5 – 40.0) n= 27	21.7 (0.0 – 45.0) n= 20	0.897
Three months	19.0 (0.0 – 44.5) n= 12	4.0 (0.0 – 40.5) n= 9	0.125
<b>Ogilvie</b>			
Pre-stent dysphagia	2.0 (2.0 – 4.0) n= 45	3.0 (2.0 – 4.0) n= 45	0.565
One week	1.5 (0.0 – 3.0) n= 33	2.0 (0.0 – 4.0) n= 32	0.190
One month	1.0 (1.0 – 3.0) n= 27	1.0 (0.0 – 3.0) n= 22	0.483
Three months	1.0 (0.0 – 4.0) n= 12	0.0 (0.0 – 3.0) n= 9	0.081
<b>QLQ OG-25 Dysphagia module</b>			
Pre-stent dysphagia	66.7 (11.1-100.0) n= 43	77.8 (11.1-100.0) n= 43	0.479
One week	33.3 (0.0 – 100.0) n= 33	44.4 (0.0 – 100.0) n= 30	0.766
One month	33.3 (0.0 – 77.8) n= 27	44.4 (0.0 – 77.8) n= 21	0.842
Three months	22.2 (0.0 – 100.0) n= 12	0.0 (0.0 – 44.4) n= 8	0.067

The two-tailed Mann-Whitney U-test was used for data evaluation.  $P < 0.05$  was considered significant.

*Paper IV – Body composition and sarcopenia in patients with OC and CGOJ*

First, the body composition measures, prevalence of sarcopenia and biometrical measures were described just before surgery. We found that the present patient cohort, when compared to normal values derived from a European control material [85, 86], displayed normal BMI and FFM prior to surgery regardless of sex ( $p > 0.05$ , ns). There was no significant difference in fat mass in men compared to women, which would otherwise be expected, ( $p > 0.05$ , ns), probably reflecting that overweight is common in this patient group and is considered a risk factor for oesophageal cancer. In spite of a normal display of BMI and body weight on average, one out of five were sarcopenic and one out of three of the patients in the cohort were severely malnourished (SGA C) prior to surgery (for details see Paper IV).

In the studied cohort, a majority (more than four out of five) of the patients displayed a lower than normal working capacity on a cardiac stress test [87] before surgery, and almost one out of five had a lower grip strength compared to age-matched healthy volunteers. Although global QoL was lower on average in the cancer patients than in the healthy reference population, significance was not reached. In contrast, all functional QoL scores were significantly lowered (see Paper IV). Dysphagia measured with the dysphagia module in QLQ-OES18 showed that the patients had significantly more problems with swallowing prior to surgery vs. the reference population.

During the post-operative period, all body composition measures were also significantly lower at one and three months after surgery, except for fat mass (Paper IV). Global QoL seemed lower one month after surgery but had increased after three months to a value slightly higher than the reference population. However, the data did not reach significance. Detailed results of functional QoL scores are shown in Table 4 in Paper IV. Dysphagia scores were improved at one and three months but no significance was reached. An overview is presented in Table 8.

Table 8. Schematic summary of some variables and subsequent post-operative changes compared to pre-operatively, in Paper IV.

Variable	preoperatively	1 month postop	3 months postop
Body mass index	$\pm 0$	↓	↓
Fat free mass	$\pm 0$	↓	↓
Fat mass	$\pm 0$	(↓)	$\pm 0$
Dysphagia	↑	(↓)	(↓)
Physical function	$\pm 0$	↓	$\pm 0$

There was a tendency to less severe complications for women, which was strengthened by the finding that women stayed at the ICU for a significantly shorter period. However, univariate logistic regression analysis could not identify any single biometric or pre-operative QoL variable that correlated with severe complications (Clavien-Dindo > IIIa).

Spearman correlation analysis showed that the only baseline variable that correlated with hospital stay and/or days at the ICU was BMI, which had a moderate positive correlation with ICU days. A high SGA (SGA C) indicative of undernutrition during the pre-operative period showed a significantly shorter hospital stay and fewer days of care at the ICU. Sarcopenia and low physical performance according to the pre-operative cardiac stress test did not affect length of hospital stay or days at the ICU compared to patients who were not sarcopenic or who had normal performance.

Surprisingly, we found no significant difference in the mortality of the resected patients compared to the Swedish standard mortality ratio when

we analysed the resected female cohort separately, indicative of a better long term survival than the male patients. When analysing risk of death, we found three parameters to be significant: female gender was associated with a lower Hazard ratio (HR), as were high values in global QoL. A low physical performance level had a very high HR (for details see Paper IV).

Comments: In this descriptive study, the inclusion criteria were all consecutive patients judged suitable for the surgery at a single center. The patient cohort was comparable to other published materials with regard to demographics and baseline values [88-92]. Together, these findings may thereby be regarded as representative for this patient category.

# GENERAL DISCUSSION

## Assessment of dysphagia

Assessment of dysphagia is one important part of this dissertation, which is highlighted with regard to benign (Paper I) as well as malignant (Papers II, III and IV) aetiology. As already outlined in the Introduction, there are different ways to assess dysphagia, and here, my focus was on using scores which are well-known in the surgical literature. In Papers I and III, the focus was to use these scales to elucidate the impact of treatments given against dysphagia. In Paper IV the prevalence of dysphagia prior to surgery and the development of dysphagia up to three months after surgery is described. In Paper II, the goal was instead to evaluate the assessment scores per se, by applying validation statistics in order to determine the reliability of each respective scale for use in patients with dysphagia due to malignancy.

There may of course be some limitations with solely using scores to evaluate dysphagia; patients may, for example, over- as well as underestimate the severity of their symptoms. A strength of the studies performed here was that longitudinal comparisons were made (Papers I, III and IV), which may help provide a truer picture of the patients' symptom experience over time. In addition, intra-individual comparisons were applied in the validation of scores for dysphagia assessment (Paper II). For practical reasons, the methods of assessment used in Papers II, III and IV will be discussed further below with regard to treatment outcomes.

In patients with achalasia, assessment of dysphagia is necessary to determine the severity of the condition in order to diagnose, to make treatment decisions, and for follow-up of the condition. In Paper I, in which two treatments of dysphagia due to achalasia were compared, dysphagia and QoL scores were used in order to determine possible changes in dysphagia before and after treatment. The dysphagia scores which were chosen, including the Watson score, are validated for benign

disease, but not to the Swedish language, or for dysphagia due to malignant disease [14-16]. Moreover, the patients were assessed using conventional manometry after GOE investigation in order to set the achalasia diagnosis. It could be argued that a more modern technology should have been used, such as High resolution manometry (HRM). This method was not in standard clinical use when the present thesis was initiated, however. After HRM was introduced, our knowledge of achalasia has increased and resulted in sub-classification of the disease [93, 94]. There are now three known subtypes of achalasia: Classic achalasia (type I), achalasia with pan pressurization (type II) and vigorous achalasia (type III). This sub-classification may be helpful when choosing treatments since it may predict treatment response, and is included in the Chicago classification of oesophageal motility disorders [95]. Two studies in which HRM was used for group stratification indicated that, in type II achalasia, a better treatment response can be anticipated, whereas, in type III achalasia, treatments are less effective [26, 96]. Rohof et al. [26] showed in a material from the European achalasia trial that, independent of treatment arm, the success rate was significantly higher in patients with type II, compared with both type I and type III, achalasia. In type II achalasia, success rate was significantly higher for PD vs LM. In type III achalasia, there was a large significant difference in success in favour of LM, whereas, in type I achalasia, no such difference was seen. At the time when this dissertation was initiated, HRM technology was, however, not yet available, nor was the Chicago classification [95]. Our investigation did not distinguish between any subclasses of achalasia, but since the treatment arms were randomized, the results may be regarded as being representative for a mixed clinical material.

A second focus of this dissertation was to study aspects of dysphagia due to malignancy. In Paper II, the goal was to validate the Watson score, the Ogilvie score and the Goldschmid score for evaluation of dysphagia of malignant aetiology, by applying validation statistics as the approach. For this purpose, a structured translation of the scores to

Swedish was performed, by adopting the back-translation methodology [66]. This revealed only minor differences between the versions after re-translation to English, and those were judged not to be significant. The translated versions (Appendix I in Paper II) were therefore considered valid regarding the Swedish language. The scores were compared to the EORTC dysphagia module QLQ-OG25, which is validated for malignancy, and to a self-reported food diary as an “external” control [97]. The subsequent statistical tests revealed that all the investigated scores had high reliability and reproducibility (Table 5), although the Ogilvie scale had the strongest correlation to the food diary and to the QLQ-OG25 dysphagia module.

From a clinical standpoint, the validation of the scales is of value for several reasons. First, having access to validated scores, which are simple to understand and to use, can contribute to determining the presence and degree of dysphagia more objectively, and may help facilitate comparisons between individuals. Validated, easily applied dysphagia scores may perhaps aid in making treatment decisions, such as determining the need for stent placement or additional nutritional support. Second, having access to a validated score may be useful for evaluating changes in dysphagia over time, for example, to grade effectiveness of various treatments with regard to swallowing ability in a clinical, as well as in a scientific, situation. Thirdly, the results on dysphagia derived in Paper III, in which the Watson and Ogilvie scores were used, may be regarded as valid.

Patients with dysphagia due to advanced malignancy of the oesophagus or GOJ describe dysphagia as a strongly negative symptom that reduces QoL [2]. In Paper III, dysphagia was evaluated in palliative patients with advanced malignant disease using the Watson score, Ogilvie score and the dysphagia module in EORTC QLQ-OG25. Thusly, similar to what was done in Paper I, dysphagia was assessed before and up to three months after treatment had been given. As could be expected, the assessment scales showed that patients experienced a high degree of dysphagia before treatment, and they overall experienced rapidly

improved dysphagia after SEMS placement. In addition, the Ogilvie score and the QLQ-OG25 dysphagia module seemed to better detect the greater dysphagia relief in the fcSEMS group, even if significance was not reached (Tables 4 and 7). This may further imply that these scales could be preferable for dysphagia assessment in oesophageal malignancy given the results reported in Paper II, in which the Ogilvie score and the EORTC scales proved slightly more sensitive.

## **Treatment of dysphagia**

From the literature, and from the results obtained in this thesis, it is evident that patients benefit from achalasia treatments aimed at relieving dysphagia. However, it is of course important to select treatments that are safe, effective, that show patency over time, and from which patients experience improvement. Here, efficacy of treatments intended to relieve dysphagia were investigated in patients with achalasia (Paper I) and in patients with oesophageal cancer (Paper III), over the longer term.

### *Benign oesophageal dysphagia due to achalasia*

With regard to achalasia, many treatments have been tried in the past to alleviate the symptoms of dysphagia in achalasia patients [20-22, 98]. At the start of this study, PD and myotomy were the most common therapies. With open myotomy surgery, a two-step strategy had been developed, which entailed first trying repeated dilations and then if necessary advancing to the more invasive surgical approach. The rationale for this was not built on any actual scientific evidence, but it was judged as a way to avoid a major surgical procedure unless absolutely necessary. With the introduction of laparoscopic surgery, this approach came into question, and, in order to create an evidence base for decisions on which therapy to use, this study was designed.

We found that the cumulative incidence of treatment failures was significantly larger in the PD group, predominantly during the first three years after the initiation of therapy but also after 80 months (Table 3). The symptom relief measured as improvement of the Watson score and the QoL was significantly higher at three years in favour of the LM, but these differences diminished over time. This diminution is probably a reflection of the natural progressive course of the achalasia disease, where symptoms gradually worsen. Treatments can, however, provide symptom relief for several years (Paper I). In the literature, a cumulative increase in failures over the longer term is evident irrespective of which treatment is used [27, 28, 99].

In contrast to the improvements demonstrated in Paper I and the study by Kostic et al. [23], the European Achalasia Trial (EAT) reported no difference between PD versus LM either early or after two years [24]. The EAT study had a different approach, where the primary variable was patient perceived therapeutic success rather than failure. In contrast to our protocol, repeated dilatations were allowed and included in the EAT study. Moreover, the success rate was measured using the Eckardt score [100], which is a patient-rated score that measures dysphagia, chest pain, regurgitation and weight loss. We suggest that treatment failure based on the need for re-interventions may be a more robust and objective way to measure outcome, particularly when comparisons are made against a surgical approach, for which repeated treatments are not necessary. In a recent meta-analysis by Cheng et al. [99] containing 498 patients, where our study together with four other studies are included, LM compared with PD was considered to have a better short-term (one year) efficacy, but the long-term (five years) remission rate showed no difference between groups. Furthermore, LM showed fewer immediate post-therapeutic adverse events. Taken together, this would suggest that the LM treatment may not only be more effective with regard to improving swallowing function, but also a safer treatment to receive.

Since this study was launched, there has been some development regarding new treatment modalities for achalasia. Per-oral endoscopic

myotomy (POEM) was first described by Pasricha et al. in 2007 [101], and the first series was presented by Inoue et al. 2010 [102]. This is an endoscopic procedure in which the LES is dissected and divided submucosally. POEM may be described as a form of natural orifice transluminal endoscopic surgery (NOTES) [103]. There are as yet no long-term follow-up studies available on this technology for achalasia. Although the data appear promising, it is important to keep in mind that achalasia is a progressive neurological disease. As was noted in our study on treatment of achalasia, as well as in the above cited meta-analysis [99], the early results were very promising with regard to QoL and dysphagia scores [23], but, as seen in the five-year follow up (Paper I), patients in general reported a worsening of symptoms. Therefore, in order to compare outcomes of different treatment options for achalasia, not only the degree and stage of the disease, but the *timing* of the treatment, must be taken into consideration.

Along with the effectiveness of a treatment and patients' QoL, it is also of course important to evaluate the treatment costs. In Paper I in this dissertation, the direct medical costs of the different studied treatments were therefore investigated. As might be expected, costs were lower for the PD strategy at 60 months and for the entire study period as well (Table 4 in Paper I). This was mainly caused by the difference in the initial treatment costs, i.e. the surgical intervention. Put into context, however, the absolute costs must be seen against the effectiveness of the treatments. Based on the present data (Paper I) and the cited meta-analysis [99], it is clear that LM gives a better result and has fewer early adverse events. Results reported in Paper I further indicate that LM seemed to have a better patency for patients with primary achalasia with no previous treatment, and the surgical treatment option was associated with fewer doctors' visits. Given the subtypes of achalasia that have been recently described, it is possible that a pre-operative assessment using the HRM [93] could help to further improve patient treatment selection, and thus lead to improved results. Taken together, LM may be

regarded as the primary treatment method of choice for patients with newly diagnosed, untreated achalasia.

### *Treatment of dysphagia due to malignancy*

In addition to exploring treatments for dysphagia of a benign aetiology, treatments aimed at providing palliation of dysphagia due to malignant strictures of the oesophagus and GOJ, were investigated. In Paper III, two stent designs were compared, and the migration rate and frequency were used as the primary variable.

In the development of SEMS for use in dysphagia due to malignancy, several different improvements of the design of the SEMS have been adopted, including the application of a plastic lining covering the SEMS, to prevent tumour in-growth and subsequent reoccurrence of the dysphagia. Since the plastic lining cover is known to greatly increase the risk of stent dislocation [38, 46-49], we hypothesised that, in spite of other design changes, the fcSEMS would have a higher risk for migration compared to a conventional scSEMS. Here, the two stent types studied were similarly effective in providing dysphagia relief (Table 7). Moreover, there was no significant difference in migration rates between the two investigated SEMS types (Table 6). Nevertheless, there was a clear tendency to a lower migration rate during total, life-time follow-up, and the total numbers of re-interventions at three months were in favour of the fcSEMS (Table 6).

In the literature, most studies that have focused on comparing stent patency have used patient symptomatology and numbers of GOE investigations to evaluate treatment response [24, 104]. However, as is well known, patients with OC or CGOJ often have negative unspecific symptoms in the chest and stomach due to the disease, and may as well experience symptoms from the stent as such, particularly during the first days after stent placement. There is therefore a risk that patients not only may be subjected to unnecessary GOE investigations, but also that

movements of the stent may remain undetected until the stent is completely dislocated. In this dissertation, a different approach was therefore used in which the stent positioning was determined by chest x-ray. Since there may be artefacts in using this technology, for example, due to respiratory movements of the chest [105, 106], and since the respective stents were placed with a 2 cm overlap of the tumour at each end, we regarded a 20 mm or more difference in positioning to be necessary to qualify as stent migration. During follow-up, a few patients who reported an increase in negative symptoms and who did undergo GOE had stents in place and, thus, their symptoms were unrelated to any stent migration, and no explanation could be found (Paper III). Another interesting result was that nearly 25% of the stents that did migrate, did so in the oral direction (Table 6). Therefore, using chest x-ray direct measurement methodology may be recommended before symptom-aided GOE as a variable for this type of study.

A main finding in this study was of course that the fcSEMS had at least the same patency with regard to risk of migration as the conventional scSEMS (Table 6). This was surprising, in particular since the fcSEMS had a slightly lower radial force [107] as compared to the scSEMS, and, in addition, the latter has uncovered flare endings. Together, this could be assumed to provide better patency for the scSEMS. However, there was no significant difference in migration, indicating that the design improvements made to the fcSEMS, including placing the plastic lining inside the SEMS, a different shape of the flare endings and a multi-wired mesh instead of a knitted mesh of nitinol, effectively reduces the risk of migration. This is of direct clinical relevance, since a fully covered stent offers less risk of tumour in-growth in the stent endings, and it could thus be of better value over time. Such a tendency to an advantage was also noted with regard to dysphagia relief in patients whose survival extended >3 months, but this was not fully significant (Table 7). This result motivates further investigations in patients with a longer life expectancy, perhaps using brachytherapy for comparison [37, 38].

## Consequences of dysphagia

Dysphagia has severe consequences for the individual, regardless of its aetiology. In this dissertation, I focused on several parameters that reflect the impact that dysphagia has on a patient, including QoL (Papers I, III and IV), and physiological manifestations in a patient group for which dysphagia is a main symptom (Paper IV). In the latter paper, we thus determined QoL, body composition, sarcopenia, physiological performance, nutritional status and strength in patients with OC or CGOJ planned for resection surgery.

### *Dysphagia and Quality of Life*

During the past decades, there has been greater awareness of the importance of not solely using physical variables to evaluate treatment effects, but also to measure patients' subjective experiences of the treatment given. In this dissertation, QoL scores were used to assess patients' perceived situation and symptoms before an intervention (Papers I, III and IV) and thereafter, in order to assess the effectiveness of a treatment (Papers I, III and IV). It is clear that, regardless of aetiology, patients with dysphagia experience a lower global QoL compared to the general population (Table 1 in Paper I; Table 4 in Paper III and Table 2 in Paper IV), a finding which is consistent with previous observations [89, 91, 92, 108-112].

In patients with benign dysphagia (Paper I), the PGWB and GSRS scores were used for measuring global QoL, and symptom specific QoL, at follow-ups made at three and five years. Although both treatments improved QoL, patients that received LM had a significantly higher global QoL at three years as compared with the PD patients. In addition, the LM group had a global QoL that was well over the reference value for a healthy reference material [71]. At five years, however, this difference had diminished. Furthermore, we also found that achalasia patients described low QoL prior to any treatment (Table 4). As

mentioned previously, this observation emphasizes the importance of measuring QoL repeatedly and over the longer term in achalasia patients. The available treatments target symptoms rather than the cause of the underlying disease, which later in the disease can reduce the benefit of an intervention. One can only speculate on the natural course of the disease if left untreated, and to my knowledge there are no studies that describe such changes in QoL, or in dysphagia. As mentioned in the Introduction, achalasia is a rare disease that can be treated but most likely not yet be cured, and which will cause significant suffering. Although both treatments proved to have low risks in this study, an oesophageal perforation can be deleterious and, at worst, fatal [113]. In addition, it was evident in Paper I that perforation significantly increased treatment costs. It is therefore apparent that there can be great advantages in concentrating treatment and research to multi-disciplinary teams with expertise in oesophageal physiology, surgery and endoscopy, for this rather rare disease.

Another aim of the dissertation was to investigate malignant dysphagia and its impact on QoL. For this purpose, QoL questionnaires from EORTC, which are well validated in many languages including Swedish, and are constructed to measure QoL in cancer patients, were used (Papers II-IV). QLQ-C30 is a questionnaire that measures global QoL, QLQ-OES18 measures symptom-specific QoL in oesophageal cancer, and QLQ-OG25 measures symptom-specific QoL in both gastric and oesophageal cancer. In Paper II, the QoL forms were used as an external reference for the dysphagia scores. In this mixed material, with palliative and potentially curable patients, the global QoL values were similar to those of patients having potentially curable disease in Paper IV, and a (50%) higher global QoL compared to the strictly palliative patients in Paper III. This is consistent with the notion that QoL becomes worse with a more advanced disease. It also emphasizes the importance of offering well-functioning, evidence-based palliative treatments directed at improving quality of life, such as SEMS treatment.

One interesting but not surprising observation was that QoL is very subjective and is influenced by the patient's situation and expectations, as was observed in Paper IV where there was no significant difference in global QoL between the patients and the normal reference material pre-operatively. Another interesting observation in Paper IV was that mean global QoL was numerically higher three months after treatment with major surgery compared to the reference population. There could be several possible explanations for this. One is that patients may perceive a sense of being "cured" and having a feeling that everything is going in the right direction, which can later change to a more sober attitude, which could be described as a "honeymoon effect". A similar pattern has been reported in patients undergoing obesity surgery [114].

An overall summary of the QoL results in the present dissertation is that treatment of mechanical dysphagia, regardless of cause, has a beneficial impact on patients' global QoL. Providing dysphagia treatment will of course have other physiological effects as well, since nutritional intake is then facilitated.

### *Dysphagia and physiological functions*

Mechanical dysphagia is a common symptom in OC and CGOJ. The dysphagia will usually restrict nutritional intake, and secondary effects on the organism will eventually become evident. Patients with OC or CGOJ are especially vulnerable since most experience a worsening of dysphagia symptoms as the cancer disease progresses; subsequently the risk of developing malnutrition and weight loss will increase. Severe malnutrition is known to have a negative impact on risk for complications and mortality in cancer disease in general [53]. Patients with potentially curable OC or CGOJ are offered massive surgical treatment, which will impact the physiology and ability to eat as well. In addition to investigating QoL measures, I chose to describe some relevant physiological measures in this patient group in which

mechanical dysphagia is common. Thus, a prospective cohort of patients with OC and CGOJ was investigated before and after oesophageal resection surgery aimed at cure. Paper IV describes biometric measures including body composition, sarcopenia, physical performance, nutritional status, and dysphagia. As could be expected, a significant share of the patients in this cohort were found to be undernourished prior to surgery; 37 % had SGA C, indicative of severe malnourishment. This was likely due to mechanical dysphagia, since this was a common symptom. The pre-operative median dysphagia score was 17.5, as compared to 0.8 in a healthy reference population (Paper IV), consistent with this suggestion. In addition, nearly 20% displayed sarcopenia according to consensus definitions [51]. One interesting finding was therefore that average body weights and BMI were in the normal range (Paper IV). It is well documented [115] that BMI is a less than perfect way to detect malnutrition, and our data clearly show that this also applies for this particular patient category.

One parameter that was investigated in the cohort pre-operatively was sarcopenia. The prevalence and value of sarcopenia in OC has gained some recent interest; over the past few years a couple of studies have been published in which measures of body composition have been reported in patients with OC, before and after nCRT. Except for one retrospective investigation in which muscle function was also taken into consideration [61], the studies that concern sarcopenia so far in OC or CGOJ in fact only refer to reductions of muscle volume. Thus, determinations of a construct muscle volume index (SMI) derived from CT scans, which is a routine investigation tool in pre-operative staging in OC, have been denoted as “sarcopenia” [62, 116, 117]. However, the concept of sarcopenia depends not only on muscle volume, but on *muscle function* as well, and international consensus definitions exist [51].

In this dissertation, such consensus definitions of sarcopenia were therefore adopted [51] (Paper IV); BIS was used for determining body

compositions measures and FFMI, and sarcopenia was subsequently calculated with regard to muscle strength and/or performance level. In our cohort, a sarcopenia prevalence of 20 % was found in patients planned for surgery. This may be viewed as quite consistent with the slightly higher (37 %) prevalence of severe undernourishment, as reflected by SGA C (Paper IV), but contrasts with a recent study by Paireder et al. [62] in which a very high prevalence of sarcopenia (61.5 %) was reported. Since Paireder did not take muscle function into consideration and only used a muscle volume proxy, it is of course difficult to directly compare those data to ours (Paper IV). In our cohort, BIS was used to determine lean body mass and FFMI, and, whereas BIS has high reproducibility and is validated against DEXA [79], it may slightly overestimate lean body mass compared to gold standard DEXA. It can thus not be ruled out completely that the prevalence of sarcopenia in our cohort could be slightly higher than 20%. Another possibility is that our patients may perhaps be very well maintained nutritionally. Our surgical department has a long standing clinical standard protocol and research program for the early identification and follow-up of cancer patients at nutritional risk, such that additional nutritional support, when needed, can be provided.

Another goal of this investigation was to explore the possible impact of oesophageal surgery by investigating body composition parameters during follow-up at one and three months post-operatively. The impact of oesophageal cancer surgery on body composition measures has been described during the immediate (< 9 days) post-operative period [63]. However, the development of body composition alterations during longer term follow-up has, to our knowledge, not been described before in this patient category. We found that the effect of the surgery was more prolonged than expected: all body composition measures reflecting muscle mass were continuously lowered up to three months after the procedure (Paper IV). Since absolute fat mass remained unchanged, the endpoint result was a higher relative fat mass compared to pre-operative measures. Taken together, this shows that oesophageal resection surgery

clearly has profound additional catabolic effects that are long lasting, in a group of patients that already show a high prevalence of under-nourishment and sarcopenia to begin with. There are of course a number of factors that each or together can contribute to such a long lasting catabolic challenge, including a massive surgical trauma, peri-surgical inflammatory onset, a possibly prolonged catabolic effect of the disease and/or nCRT, the conduit reconstruction which results in a smaller reservoir capacity for food, the truncal vagotomy, and a secondary loss of hunger signalling [53, 118-123].

Before surgery, patients displayed a lowered physical function as reflected by significantly reduced exercise capacity as well as grip strength (Paper IV), and at three months, reported no significant difference with regard to fatigue compared to pre-operative values (Paper IV). Therefore, together with the sustained reduction in fat free mass seen at 1 and 3 months post-operatively, it is reasonable to suggest that sarcopenia prevalence likely increases further up to three months after oesophageal resection surgery. In contrast to two other reports where low muscle volume was used as a proxy for sarcopenia [62, 117], preoperative sarcopenia was not found to be a risk factor for morbidity in the present cohort, nor in a study by Grotenhuis et al. [116]. It is quite well established, however, that sarcopenia is closely associated with lowered physical performance [51, 124] and is an overall risk factor for death in cancer disease [125]. Since loss of muscle mass is particularly difficult to compensate for, these results are consistent with the view that patients with OC should be closely monitored with regard to nutritional status and body composition pre- as well as post-operatively. Thusly, appropriate measures can be initiated early such that malnutrition and sarcopenia prevalence may be reduced, and at best, prevented.

A third aim of Paper IV was to explore whether there could be a relation between any pre-operative biometric measures, sarcopenia, and/or nutritional status measured with SGA, with regard to length of stay,

QoL, morbidity, or mortality. We found no single variable that correlated with more serious complications according to Clavien-Dindo, and low physical performance was the only pre-operative factor that was correlated to increased risk for mortality. Dysphagia and malnutrition can of course lead to reduced physical capacity and to a lowered ability to cope with severe complications. There is some evidence that a pre-operative working capacity of 80 W or less, as assessed with a cardiac stress test, negatively influences the patient's chances to survive oesophageal resection surgery [126]. Although none of the patients in Paper IV performed less than 80 W prior to surgery, we still found an increased overall mortality risk based on reduced individual performance levels adjusted for age and sex [87].

The long term impact of oesophageal resection surgery was described in a patient cohort in which dysphagia was present. Prevalence of sarcopenia and undernutrition was high, and presumably increased together with sustained loss of lean mass during follow-up, in spite of close monitoring and support. It is clear that a lowered physical performance, a measure closely associated with catabolism and undernutrition, increased the risk for over-all mortality. The present findings highlight the importance of provision of nutritional support to patients at risk, before surgery, during the early postoperative period, and the months following. It also emphasizes that body weight or BMI alone may be insufficient in detecting catabolic effects pre-operatively in this patient group. The present data may thus be of value for the surgical team in optimising the patient for surgery, and during follow-up.



## CONCLUSIONS

- The correlation between all dysphagia questionnaires is good to excellent with the strongest correlations between the Ogilvie score and the dysphagia module in QLQ-OG25. These latter two scores also have the strongest external validity.
- Laparoscopic myotomy gives a better result and has fewer early adverse events than pneumatic dilation and may thus be regarded as the primary treatment method of choice for patients with newly diagnosed, untreated achalasia.
- A fully covered SEMS of a newer design is comparable to a conventional semi-covered SEMS with regard to migration, and may thus be recommended for use for palliation of patients with cancers of the oesophagus and gastro-oesophageal junction.
- QoL is reduced in patients suffering from dysphagia regardless of the underlying cause. Provision of treatment for dysphagia improves QoL. For patients with achalasia, symptoms may recur after several years, perhaps due to the progressive nature of the disease.
- Health-economic costs are higher for a laparoscopic myotomy surgery compared to pneumatic dilatation for achalasia. However, since patients experience a better overall improvement up to five years after treatment, this higher cost can be judged as acceptable.
- Patients with potentially curable cancer of the oesophagus or gastro-oesophageal junction have a high prevalence of malnutrition and sarcopenia in spite of normal average BMI. Surgery has a long lasting catabolic impact, as reflected by continued loss of muscle mass for at least three months post-

operatively. A low physical performance level is associated with an increased overall mortality risk.

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## FUTURE PERSPECTIVES

This dissertation has covered the area of methodology and technical development regarding dysphagia, and it is important to continue and implement our results clinically and with regard to the new techniques that are evolving in oesophageal surgery. As pointed out in the *Introduction*, dysphagia is a clinical symptom that has been known for a long time and for which there is still a need for additional research. Diseases such as achalasia and cancers of the oesophagus are relatively rare conditions, and research could thus be facilitated and clinical surgical care improved if the patients were treated at units specialised in oesophageal surgery. Access to evidence-based methods and treatments will help in furthering the understanding of the conditions that cause mechanical dysphagia. Here, assessment scales were validated in Swedish for dysphagia caused by malignancy. A future clinical goal could be to implement, for example, the Ogilvie scale in clinical practise and for quality follow-up purposes as an aid in monitoring dysphagia.

For the surgeon, some of the results derived in this dissertation may be used as an evidence base for treatment decisions in patient care. Further investigations directed at exploring POEM as a treatment against achalasia, and continuing research regarding fully covered SEMS in cancer palliation, may help to improve future treatment strategies for patients suffering from dysphagia. Last but not least, evaluation of nutritional status, body composition, and physical function assessment may be beneficial in the work-up of patients prior to surgery and thereafter, to improve care and possible survival. Follow-up investigations over longer periods and in a larger, multicentre cohort would then be essential to better identify patients at risk for complications and death due to undernourishment. In the present era of introducing minimally invasive oesophageal resection surgery, investigations of the role of surgical trauma in the catabolic challenge after surgery and its consequences are important goals.



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# **APPENDIX**

Paper I - IV