Upper Gastrointestinal Research
Department of Molecular Medicine and Surgery
Karolinska Institutet, Stockholm, Sweden

# HEALTH-RELATED QUALITY OF LIFE AFTER OESOPHAGEAL CANCER SURGERY FOR PREDICTION OF MORBIDITY AND MORTALITY

Therese Djärv


Karolinska Institutet

Stockholm 2010

Published by Karolinska Institutet.


ISBN 978-91-7457-004-5

Printed by
REPROPRINT AB
Stockholm 2010
www.reproprint.se
Gårdsvägen 4, 169 70 Solna

TILL
MAMMA OCH PAPPA

*”what constitutes happiness is a matter of dispute...*
*some say one thing and some another,*
*indeed, very often, the same man says different things at different times:*
*when he falls sick he thinks health is happiness, when he is poor, wealth”*

*Aristotle 384-322 BC*

# ABSTRACT

This thesis investigates the health-related quality of life (HRQL) among surgically treated oesophageal cancer patients.

The established curative treatment for oesophageal cancer is extensive surgery with a high risk of morbidity and a limited chance of long term survival. Only every third patient is suitable for surgery. Subjective outcomes such as HRQL are therefore of particular importance among this group of patients.
In three of the four studies (I, II, IV) included in this thesis, a nationwide Swedish cohort of oesophageal cancer patients, operated in 2001-2005, was used, while in study III a British cohort of operated patients was used. In all studies, HRQL was assessed with an international validated core questionnaire on the symptoms and functions of cancer (EORTC QLQ-C30). Studies I, II and IV also included an oesophageal cancer specific module (EORTC QLQ-OES18). In Studies I and III a difference in transformed mean scores of at least 10 points on a scale of 0-100 was used as a cut-off for clinical relevance. In Studies II and IV raw scores were categorised into good or poor HRQL.
In Study I, the long term HRQL after oesophageal cancer surgery was investigated. HRQL was shown to be similar both six months and three years postoperatively, which suggests that the long-standing HRQL level is already established at six months. The HRQL was poorer than that of the general population.
Study II assessed if patient and tumour characteristics affect HRQL six months postoperatively. Sex, age and BMI showed no associations while co-morbidity and tumour characteristics such as histology and tumour stage affected HRQL. The findings may be useful for clinical decision making.
Study III explored if both baseline HRQL and changes in HRQL from baseline to six months' follow-up was associated with survival. Dyspnoea at baseline was associated with an increased risk of mortality. Not recovering physical function and worsening of pain and fatigue were linked with a higher risk of mortality. Therefore, changes in HRQL might be prognostic and of importance when planning follow-up and supportive care.
Study IV analysed whether postoperative HRQL was associated with survival. Poor HRQL measures were associated with increased risk of mortality. This knowledge could be used for prognostic discussions and intensity of the clinical follow-up.
In conclusion, this thesis shows that measures of HRQL could aid decision-making prior to treatment and in planning the follow-up of oesophageal cancer patients.

Keywords: Oesophageal cancer, Surgery, Health-related quality of life, HRQL, Survival

# LIST OF PUBLICATIONS

This thesis is based on the following papers, which will be referred to by their Roman numerals (I-IV):

I Djärv T, Lagergren J, Blazeby JM, Lagergren P
**Long-term health-related quality of life following surgery for oesophageal cancer.**
*British Journal of Surgery 2008; 95(9):1121-6.*

II Djärv T, Blazeby JM, Lagergren P
**Predictors of postoperative quality of life after esophagectomy for cancer.**
*Journal of Clinical Oncology 2009;27(12):1963-8*

III Djärv T, Metcalfe C, Avery K, Lagergren P, Blazeby JM
**Prognostic value of changes in health-related quality of life scores during curative treatment for esophago-gastric cancer**.
*Journal of Clinical Oncology 2010; 28 (10): 1666-70*

IV Djärv T, Lagergren P.
**Postoperative quality of life associated with survival in oesophageal cancer patients.**
*Submitted manuscript*

# CONTENTS

# LIST OF ABBREVIATIONS AND MEDICAL TERMS

| Abbreviation/ Medical Term | Explanation |
|---|---|
| AC | Adenocarcinoma |
| Anorexia (cancer) | Loss of desire to eat, prompted by the growing tumour[1]. |
| ANS | Autonomic nerve system. A part of the peripheral nerve system working without consciousness and regulating most organs. Divided in the parasympathetic part which controls salivation, lacrimation, urination, digestion and defecation while the sympathetic part controls actions requiring quick responses such as "fight or flight reaction" |
| Anterior | The front surface of the body, placed in front. |
| BMI | Body Mass Index. Weight(kg) /(length(m) *length(m)) |
| Bronchoscopy | Visualizing of airways via an instrument inserted from the mouth or nose. |
| Cachexia (cancer) | Multi factorial syndrome with disturbed immune system, loss of muscle mass and fat causing fatigue and possible loss of weight[2,3]. |
| Caudal | Near the tail/hind parts of the body, or inferior. |
| Cervical | Near the neck. |
| CT | Computed tomography, medical 3D imaging via radiology. |
| En bloc, en bloq | Removing everything from the vertebral column to the pericard in one piece to minimize tumour during oesophageal cancer surgery. |
| Eradicating | Taking out all lymph nodes in the areas |
| Gastrocopy | Visualising of the oesophagus, stomach and duodenum via an instrument inserted via the mouth. |
| Gastroplasty | Plastic surgery to the stomach. |

| | |
|---|---|
| Hepatomegaly | Enlarged liver. |
| HRQL | Health-related quality of life. |
| Laparascopy | Operation in the abdomen through a small incision with aid from a camera. |
| Laparatomy | Operation in the abdomen. |
| LES | Lower Esophageal sphincter. |
| Lymphadenopathy | Disease of the lymph nodes or swollen/enlarged nodes. |
| Mediastinum | The middle section of the chest cavity with all organs except for the lungs. |
| N/A | Not available. |
| Parasympatic nerve | See ANS. |
| PET | Positron emission tomography, a nuclear medical 3D imaging. A biological active molecule is added to the patient and detected by gamma rays. |
| RCT | Randomized Controlled Trial. |
| Referred pain | Pain perceived at a site remote from the origin of an injury, such as pain in the left arm during a heart attack. |
| SCC | Squamous cell carcinoma |
| SECC-registry | Swedish Esophageal and Cardia Cancer registry, a nationwide cohort collected between 2001 and 2005. |
| Sympathetic nerve | See ANS. |
| Thoracoscopy | Visualisation of lungs and chest cavity via a camera inserted through the chest wall. |
| TNM | Classification of malignant tumours, se page 19.<br>Tumour (lymph) Nodes Metastasis. |
| Upper gastrointestinal database | A hospital-based cohort started in 2000 in Bristol, U.K. |
| Virchovs node | The signal node, an enlarged hard node just above the left clavicle suspected of containing metastases from abdominal malignancy. |

# INTRODUCTION

*The Context and Theoretical Framework*

This book is a scientific thesis in medicine. The book includes the background to the four studies undertaken, an account of the four studies and a concluding discussion of methodological issues. The theoretical framework mainly conforms with earlier relevant scientific articles published in international medical journals. All of these articles have strengths and weaknesses, but since the aim has been to produce a comprehensive text, those characteristics have not been given space.

*Oesophageal Cancer*

The word oesophagus derives from the Greek *oisein* (to carry) and *phagos* (to eat) and is the Latin name for the foodline. Oesophageal cancer is aggressive and the cure is through extensive surgery with typically long recovery time. Oesophageal cancer is a physically and emotionally devastating disease affecting the general wellbeing and quality of life and fundamental aspects of life e.g. eating, drinking and socializing[4-6].

*Health-Related Quality of Life*

Health-related quality of life (HRQL) is a concept assessing symptoms and functions related to a disease or its treatment from the patient's perspective. It is hypothesized that HRQL's multidimensional subjective approach provides early indications of how the patient as a host responds to for example a cancer and how well he is recovering after treatment[7].

*Rationale for the Thesis*

Little is known about long term HRQL following oesophageal cancer surgery. It is for example uncertain whether the postoperative symptoms or problems are transient or persistent even if the patients' survival is similar to that of the general population[8]. It is unknown to what extent clinical features such as patient or tumour characteristics influence the HRQL and little is known whether a change in patient-reported deterioration or postoperative differences between patients are actually associated with survival. In a disease with such poor prognosis all warning signs can be of great importance.

Finally, this thesis focuses on patients with curative-intending treatment who, we need to bear in mind, constitute the minority of oesophageal cancer patients.

## THE OESOPHAGUS

### Gross Anatomy

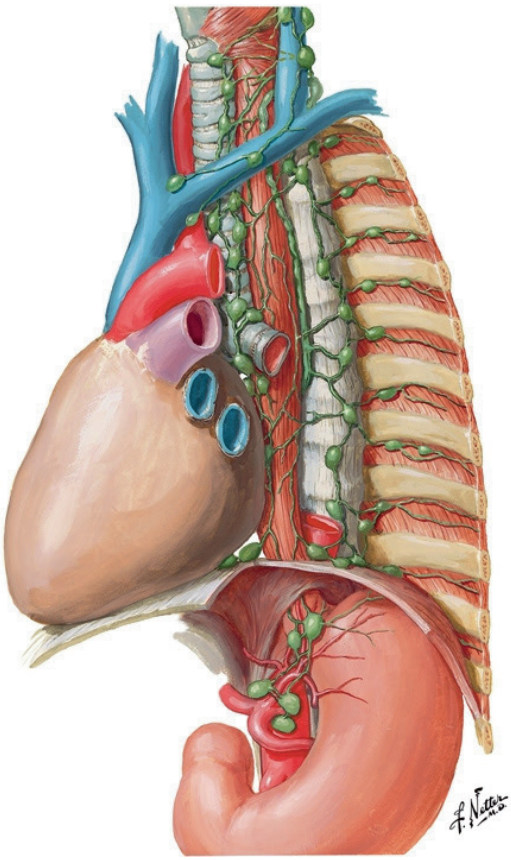

Figure 1. The oesophagus and its anatomic relations.
*Netter Illustration from www.netterimages.com, © Elsevier Inc. All rights reserved.*

The oesophagus is an 18 to 26 cm long muscular tube running from the pharynx to the stomach[9]. It commences around 18 cm from the incisor teeth at the level of the inferior part of cricoid cartilage, just beneath the laryngeal prominence known as the Adam´s apple. Descending between the trachea and spine it passes behind the tracheal bifurcation and the aortic arch. Further down it passes anterior of the aorta and close to the left atrium of the heart, to enter the diaphragmatic hiatus before ending at the oesophagogastric junction. It is well protected in the thoracic cage. The location could delay the detection of a tumour until it has already spread, and necessitate complicated operations since it is close to vital organs.

**Histology**

In the cross-section, the oesophagus consists of four layers. Outermost *the fibrous adventitia*, followed by *the muscular layer* - with an external longitudinal layer, and an internal circular layer. The upper part of the inner layer comprises voluntarily controlled striated muscle fibres, while the lower third consists of involuntarily controlled smooth muscle fibres. At the caudal end there is a thickening and interconnection of muscle fibres, forming the lower oesophageal sphincter (LES). Within the muscular layer is *the loose connective tissue layer* – the submucosa and innermost *the muscosa* with thin smooth muscles and squamous epithelium. The oesophagus lacks serosa which allows tumours to spread easier and challenges repair of luminal disruptions[9].

**Innervations**

The autonomic nerve system's sympathetic fibres mediate discomfort and pain, regulate vessel construction and peristaltic activity. The parasympathetic nervus vagus mediates mechanical, chemo and thermo stimuli, regulates glandular secretion and motor innervations for distal smooth muscles and the LES. The vagal nerves give rise to the recurrent laryngeal nerve on both sides. Both these nerves linger around the oesophagus and might be injured during surgery, especially on the left side, where it hooks around the aortic arch. Such injury might result in hoarseness, difficulties in swallowing and aspiration with respiratory problems[9].

**Lymphatic Drainage**

Lymph is drained in a network of channels in the oesophageal submucosa. Lymph from the proximal third is drained via deep cervical nodes to the thoracic duct, while lymph from the middle third drains into superior and inferior mediastinal nodes, and the lower third drains via gastric and celiac nodes to the cisterna chyli[9]. The cisterna chyli is connected to the thoracic duct, which allows metastases to spread in all directions. The flow is unpredictable, meaning that no particular lymph node is typically affected first, as in the case of breast cancer and the sentinel node[10,11].

**Physiology**

While processed food is voluntary moved backwards, it triggers the closure of the airway and enters the oesophagus under involuntary control. While peristaltic waves propel the food downwards the normally collapsed oesophagus distends up to a couple of centimetres[9]. This yielding capacity allows the tumour to grow almost unnoticed. After the food has entered the stomach, the LES, in conjunction with a sphincter in the upper oesophagus and the diaphragm, prevents the backflow of food and gastric acid (reflux)[9].

# OESOPHAGEAL CANCER

## Histological Types

Oesophageal cancer has several different origins although two types serve for up to 90% of all cases, i.e. squamous cell carcinomas (SCC) and adenocarcinomas (AC)[12]. More rare types include other carcinomas, melanomas, carcinoids, and lymphomas[13]. SCC are often found in the middle, or perhaps more commonly in lower part, while three quarters of the AC originate in the lower part of the oesophagus[12-14]. Only a minority of the patients have tumours in the upper oesophagus[12-14].

## Occurrence

Oesophageal cancer is the sixth most common cancer-related cause of death worldwide[15]. SCC is particularly common in southern and eastern Africa, Japan and in a geographic belt from northern Iran to north central China, where the highest incidence in the world (27 cases per 100,000 males) can be found[15]. There is a stable or decreasing number of SCC in most populations[16,17]. In contrast, AC is striking Western nations such as North America and Western Europe with an increasing incidence[9,16-18]. The sex ratio differs from 7:1 in eastern Europe to close to unity in high risk areas [15]. The sex variation for SCC can be explained by different exposure to the main risk factors, although no explanation for the sex pattern in AC has yet been found[17,19-21]. The highest rate of AC, reported among white males, is for reasons yet unknown, in the United Kingdom (U.K.)[18]. Both histological types have an unexplained marked variation between different ethnic groups within the same geographic region[9]. In Sweden there are approximately 400 new cases of oesophageal cancer reported annually, which corresponds to approximately 1% of all tumours annually reported to The National Board of Health and Welfare[22].

## Risk Factors

Established risk factors for AC are; reflux, Barretts esophagus (an abnormal change in cells of the lower oesophagus, due to chronic reflux) and high body mass index (BMI)[13,19,23,24], while the main risk factors for SCC are tobacco smoking and alcohol intake, especially in combination[13,25]. Furthermore, SCC has also been associated with low intake of fruit and vegetables[24] and low socioeconomic status[13,25]. Several risk factors have been debated e.g. environmental carcinogens, malnutrition in central Asia, China and southern Africa, hot tea in Iran as well as hot mate in south America, heredity among families with tylosis and genetic predisposition in Japan and among US Japanese[13,15]. Infection with Helicobacter pylori has been found to be protective, probably due to reduced acidity from gastric atrophy and the production of ammonia[26].

## Symptoms

Early symptoms are rare although symptoms arise from local obstruction, local invasion and metastasis. The first symptom in the large majority of the patients is difficulties in swallowing solid or fluid foods (dysphagia), which is experienced due to oesophageal obstruction[12,13,27,28]. At that time, patients have often gradually changed their dietary habits and more than half of the patients have experienced weight loss likely due to dysphagia, anorexia or cancer-cachexia[12,29]. The obstruction can further result in reflux or vomiting[12]. Symptoms from the local invasion might be pain (from the oesophagus or referred to the back and the right upper abdominal corner)[28] or hoarseness and coughing due to laryngeal nerve overgrowth[12]. In addition to these oesophageal cancer-specific symptoms, general cancer symptoms such as fatigue could be present.

## Diagnosis

Physical examination might reveal a patient who has lost weight, but usually shows no other signs[13]. In the presence of metastatic disease, lymphadenopaty might be found, especially in the left supraclavicular fossa (Virchovs node) or hepatomegaly[13]. When a tumour is suspected, a patient usually performs both a gastroscopy with biopsies and a computed tomography (CT) with intravenous contrast medium of the chest, abdomen and pelvis for evaluation of the extent of the tumour, involved lymph nodes and distant metastasis[12,13]. Furthermore, an endoscopic ultrasound (EUS) with simultaneous fine needle aspiration could be performed for local and regional tumour staging[13]. Suspicion of local invasions in the airways prompts a broncoscopy[30]. Finally, a positron emission tomography (PET) has high sensitivity for detecting distant metastases, which can be confirmed or excluded with a precise location via a CT[30]. In some cases a thoracoscopic or a laparoscopic staging can be performed, but since they are invasive they are more rarely used.

## Classification/Staging the Tumour

Staging is of great importance to the determination of treatment strategy, and it is usually set via a the tumour-node-metastasis (TNM) classification system[31]. The TNM stage is basic data for grouping to tumour stage 0-IV as shown in Table 1 and 2.

Table 1. Staging with TNM for oesophageal cancer according the 5th version of TNM Classification of malignant tumours.

| **Primary tumours depth of wall invasion (T)** | |
|---|---|
| TX | Primary tumour cannot be assessed |
| T0 | No evidence of tumour |
| Tis | Carcinoma in situ |
| T1 | Tumour invades submucosa |
| T2 | Tumour invades muscularis propria |
| T3 | Tumour invades adventitia |
| T4 | Tumour invades nearby structures |
| **Occurrence of regional lymph nodes (N)** | |
| NX | Regional nodes cannot be assessed |
| N0 | No regional node metastases |
| N1 | Regional node metastases |
| **Occurrence of distant metastases (M)** | |
| MX | Distant metastases cannot be assessed |
| M0 | No distant metastases |
| M1 | Distant metastases<br>M1a- in celiac lymph nodes (lower tumours) or cervical nodes (upper tumours)<br>M1b- other distant metastases |

Sobin L.H., Wittekind Ch, TNM Classification of Malignat Tumours. 5th ed. New Jersey: Reprinted with the kind permission of John Wiley & Sons Inc.

Table 2.
**Grouping from TNM to stage 0-IV**

| | |
|---|---|
| Stage 0 | TisN0M0 |
| Stage I | T1N0M0 |
| Stage IIA | T2N0M0, T3N0M0 |
| Stage IIB | T1N1M0, T2N1M0 |
| Stage III | T3N1M0, T4 any N or M0 |
| Stage IV | Any T, any N, M0 |
| Stage IVA | Any T, any N, M1a |
| Stage IVB | Any T, any N, M1b |

## Prognosis

Patients are often diagnosed at an advanced stage, and more than 50% of the patients have metastatic disease or an unresectable tumour when diagnosed[12,13]. Curatively-intended treatment is only offered to those with local advanced disease without metastatic spread. The overall 5-year survival rate is as low as 10% in Europe[15], while the unselected postoperative 5-year survival is about 31%[32]. Survival is closely connected to the tumour stage, where stage 0 has a 95% 5-year survival after curative surgery, stage I: 50-80%, stage II: 10-40% and stage III: 10-15%[13]. Patients with stage IV under palliative therapy have a median survival outlook of less than one year[13]. The majority of the patients undergoing surgery have stage III at the time of diagnosis[12,13]. Recurrences are likely to come within the first postoperative year[11], so patients who survive for three years have the same prognosis as the general population[8].

## Curative Treatment

There are three main curative treatment options; radiotherapy, chemotherapy and surgery, which can be combined[13]. Several randomized controlled trials (RCTs) have evaluated survival, tumour response and complications as primary endpoints but often lacked in statistical power to detect any differences in outcome between treatment groups[33]. However, a continuous re-evaluation of management strategies is important[12]. So far, surgery is the standard single treatment, and the established curative treatment for fit patients is radical surgery[13,34,35]. Swedish patients are only offered surgery as a curative treatment.

### *Therapy without Surgery*

Radiotherapy alone, given to non-fit patients, has shown conflicting results compared to surgery alone[36-38]. Combined radiotherapy and chemotherapy has shown a similar survival rate to neoadjuvant chemoradiotherapy followed by surgery[39,40], but prolonged median survival compared to radiotherapy alone[41,42]. In the U.K., combined chemo and radiotherapy is offered as a curative to patients not fit for surgery with a locally advanced cancer (AC or SCC: T2N1M0, T3N0/1M0 and SCC: T3/4N0/1M0).

### *Neoadjuvant Treatment*

Neoadjuvant treatment means any oncological treatment, such as radiotherapy or chemotherapy, prior to surgery. The use of neoadjuvant therapy differs between countries, for example patients in the U.K. with locally advanced cancers (AC/SCC in stages T2N1M0, T3N0/1M0) are offered neoadjuvant therapy, while it is less common in Sweden. A recent meta-analysis of twelve studies including 2097 patients concluded that preoperative chemotherapy might be beneficial for survival compared to surgery alone, but further studies are needed, since a risk of increased toxicity and preoperative mortality was found[34]. Neoadjuvant radiotherapy did not improve the survival rate, compared to surgery alone, in a meta-analysis of data from 1147 patients[43]. Combined neoadjuvant chemotherapy and radiotherapy could be beneficial in several ways; chemotherapy reaches micro-metastases outside the radiation field and enhances radiosensitivity, while radiation suppresses locoregional recurrences. Out of eight RCTs investigating benefits with combined neoadjuvant radiotherapy and chemotherapy, two had sufficient power and neither reported any benefit[13,44].

## Preoperative Care

The extensive surgery demands a fit patient who is preferably examined by a multidisciplinary team of surgeons, oncologists, radiologist, anaesthetics, nurses, physiotherapist and dieticians. Further, tests for cardiac- and pulmonary function are performed.

**The Operation**

According to Swedish data only one quarter of the patients with oesophageal cancer are operated; the majority of the patients are probably excluded, since they are not fit for surgery and/or have an unresectable tumour[32]. The operation offers a chance of cure, but involves a high morbidity and mortality risk. There are two main possible approaches; transthoracic or transhiatal. The transthoracic approach is commonly used in Sweden.

The transthoracic approach usually combines a laparatomy (upper abdominal incision) for dissection of the stomach and lower oesophagus, including extensive dissection of nodal tissue along the celiac trunk with branches[45] with a right sided posterolateral thoracotomy at the fifth intercostal space for further dissection of the upper oesophagus (Ivor Lewis).
The right side is used for middle or proximally located tumours, while some surgeons prefer to approach lower tumours from the left[45]. During the thoracic part, one lung will be deflated for easier dissection of the mediastinum. The method facilitates a good overview and easier en bloc techniques.

The transhiatal approach aims to minimize surgical damage by way of blunt dissection of the oesophagus up to the lower pulmonary veins from an upper abdominal incision, thereafter a neck incision is made to strip the upper oesophagus. Although not yet proven, it has been claimed that fewer respiratory complications, lower risk of mediastinitis, and a shorter operation time are among the advantages[9].

In both techniques the stomach, or sometimes the jejunum or colon, serves as [46]a substitute for the resected oesophagus. The anastomosis is placed in the upper thorax with transthoracic surgery, and in the neck with the transhiatal approach[45]. Four randomized controlled trials[47-49] and two meta-analyses[50,51] have been published, results showed that both techniques have a similar rate of complications and long term outcome[35]. Likewise both approaches are cancelled if metastases are found (sometimes called “open and close surgery”) and both include surrounding tissue in the surgical specimen[45]. During surgery, lymph nodes in two-fields, around the abdomen and lower half of the chest are removed. Some countries, such as Japan, also perform an extensive cervical lymphadenectomy (three-field) although long term HRQL is affected, and any benefits of such extensive node dissection are uncertain[11,52,53]. Studies on minimal invasive oesophagectomy, (exclusively scope resections), have suggested less risk of anastomotic leaks and faster postoperative recovery. Randomized controlled trials are, however, lacking[54].

**Postoperatively**
The patient usually initially stays in the intensive care unit and is then cared for at a surgical ward. Oesophagectomy is one of the most extensive elective surgical procedures. Rates of deaths during surgery or close after are 4-10% and about 26-47% of the patients suffer from major morbidity within the first 30 days[12,13,55]. Complications in the SECC-registry were in declining order[55]: respiratory insufficiency, cardiac complications, serious infection, technical, (postoperative bleeding, reoperation, damage to the recurrent laryngeal nerve or thoracic duct), leakage of anastomosis or necrosis in substitute, early anastomotic stricture with severe dysphagia needing intervention and others. Postoperative care is continuous for about three years, usually with check-ups after 3, 6, 9, 12, 18, 24 and 36 months.

**Postoperative Adjuvant Therapy**
Postoperative radiotherapy has been debated. Regarding survival, cases of shorter survival due to irradiation-related deaths such as bleeding gastric ulcers[56], similar survival but fewer recurrences[57], as well as longer survival for patients with over three positive lymph nodes[58] have been reported. Results for radiotherapy compared to chemotherapy were similar[59].

**Recurrences**
Recurrences develop quickly; six months after surgery about 8% of the patients have already developed a recurrence and approximately every third patient, irrespective of histological type, suffered a recurrence within one year[11,12]. The survival time after a recurrence is usually only a few months[11]. Recurrences are likely to appear locally in the mediastinum and upper abdomen or distantly through haematogenous spreading to the liver, skeleton or other places[11,60]. Cervical recurrences are rare[11,60].

**Palliative Treatment**
Since at least 50% of the patients are not suitable for curative treatment[13] at the time of diagnosis, palliative treatment is of great importance. Examples of goals for such treatment could be to relieve dysphagia or to preserve HRQL[27,61-63].
Since recurrences after curative treatment are common and second-line treatments are sparse, palliative care plays an important role even in patients' undertaken curative-intended treatment.

# QUALITY OF LIFE

## The Concept of Quality of Life

No generally agreed-upon definition of ´quality of life´ exists, and many of us seem by intuition to see quality of life as an abstract evaluation of central values of life or as "the essence of existence" without needing any definition[64]. The term quality of life can be found in several different disciplines, for example it has referred to "the good life", meaning her life is not bad for herself among philosophers since Antiquity, while in psychology it refers to the mental state, in sociology to welfare and in economics to the gross domestic product[64,65]. Furthermore, how the term has been defined and measured has also changed over time; after the Great Depression in 1930 western cultures evaluated if people were well fed, educated and worked fewer hours, while in the 1960s individual happiness was more important[65]. In 1948 the World Health Organisation introduced a wider concept of health by defining it as "*a state of complete physical, mental and social well-being, and not merely the absence of disease*". Afterwards, medical researchers have diverted their interest to patient-reported outcomes[65], meaning any report coming directly from the patient about a health condition and its treatment without the intervention of an observer[66]. The present thesis does not evaluate patient-reported outcomes in this broad perspective, but it relates to symptoms and functions that might be affected by disease or medical treatment, which corresponds to "health-related quality of life", HRQL. This term highlights that the person is a patient and the focus is burden of disease. Most definitions of HRQL agree that "*HRQL is a multidimensional construct which encompasses patients´ perceptions of both negative and positive aspects of at least four dimensions; physical, emotional, social functions as well as disease and treatment related symptoms*"[67]. Although the palette of definitions is exhaustive enough to suit even the most discerning researcher, many skirt around a definition by letting the meaning of HRQL instruments intuitively be understood without stating a definition[67].

## The Concrete Nature of HRQL

When reducing the term HRQL to a concrete level, it often assess symptoms and functions in a subjective way that can only be understood from the patient's point of view. The word symptom derives from the Greek *σύμπτωμα*, meaning misfortune or accident, while the Latin word *sympthoma* refers to indication or sign[68,69]. Previously and still today, symptoms differ from signs. Signs are more objective and observable such as body temperature, while symptoms are the patients' subjective evidence of disease and their expression of it, such as having pain[70]. Professional care providers often view symptoms as disease (progress) indicators or side effects from treatment, and symptoms are therefore used as an empirical guide to diagnosis[70-72]. They might find interest in symptom occurrence (frequency, duration, intensity) and its distress (degree of discomfort)[70]. Patients, on the other hand, might talk about symptoms as reminders of a lethal cancer[72] and sensations or symptoms with consequences for their daily life[70]. The daily life consequences might be difficult to capture merely by symptoms, therefore HRQL often also assesses functions as a measure of the more complex compound of

symptoms affecting the ability to lead a normal, everyday life. Even if the functions and symptoms objectively appear to be similar within or between patients, the burden can still be experienced differently. It is assumed that this is due to a perceptual process with individual selection dependent on both body and mind[70,71,73,74]. In a cancer patient, this might be exemplified by metastases producing a constant level of factors affecting pain receptors, but the number of symptoms reported by the patients depends on personality, genetic disposition, learned response etc. The individual influences on HRQL have been described both as the widely-used conceptual model by Wilson and Cleary in 1995 and as response shift by Sprangers in 1996[75,76].

**HRQL as a Conceptual Model**

In 1995, Wilson and Cleary constructed a model that integrates biological and psychological aspects of health and their relationship with HRQL outcomes[75]. The aim was to unite biomedical paradigms, focusing on etiological agents for therapeutic grouping of patients and the social science paradigms with an all-encompassing focus, particularly on the contribution of social structures to illness[75,77]. The model has been considered valuable since it both emphasises that quality of life is just one component of possible outcomes, and it stresses that health is not physical status without patient input[77,78].

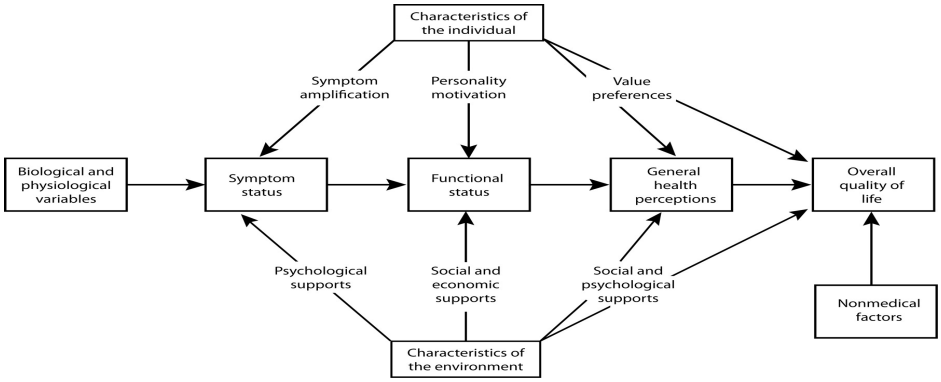


Figure 2. Conceptual model by Wilson and Cleary of factors influencing patient outcomes such as HRQL. Adapted with permission from "Linking clinical variables with health-related quality of life. A conceptual model of patient outcomes." 273(1):59-65. Copyright© 1995 American Medical Association. All rights reserved.

Simplified, the model describes five levels of subjective outcomes. Starting at the left on a cell level with biological and psychological variables and moving right to an individual level with symptom status (e.g. cognitive and physical symptoms), moving on further to the right, where the individual is integrated as a member of a society by demanding a functional status (e.g. physical, social, and psychological functioning). The general health perception is a subjective evaluation, integrating all the precedent outcomes and generating overall quality of life as an interpretation of how satisfied a person is with her life at large.

**HRQL and Individual Influences**

Along with the exploration of conceptual models, other individual influences on HRQL are sought for. Differences in HRQL between people have been explained by differences in lifestyle[79] and genetic variations, e.g. regarding pain and fatigue[80]. An interesting ongoing project is the international GENEQOL Consortium[81], which intends to investigate the genetic disposition of patient-reported quality-of-life outcomes. Five important quality-of-life outcomes have been identified as initial targets; negative psychological affect, positive psychological affect, self-rated physical health, pain and fatigue. The goal is to identify biological pathways, genes and genetic variants in order to detect patients' susceptibility to poor quality of life and consequently target interventions. This is more than likely only the threshold of a new era in HRQL research.

**Response Shift- Changes over Time**


When measuring HRQL longitudinally in patients, who are faced with a major event such as cancer surgery, it might be difficult to know what to compare the data with. Patients might for example calibrate their own scale based on previous health conditions or personal priorities. This change in interpretation of the meaning has been described as response shift. Response shift was first described in educational research[76,82,83] as changes in the meaning of a target due to recalibration of internal standards, reprioritizing of values and reconceptualisation of its construct. 'Recalibrations' can be exemplified by a patient's experience of the severest possible pain before surgery, whereas after surgery that pain was reconsidered to be only mild compared to the severity of the postoperative pain. 'Reprioritization' means that a cancer patient with poor prognosis might not find interest in maintaining good physical function compared to maintaining emotional or social functions. 'Reconceptualisation' means that patients might change beliefs in life such as being religious close to the end of their lifetimes. The phenomenon 'response shift' was described as a model in 1999 by Sprangers et al[83].

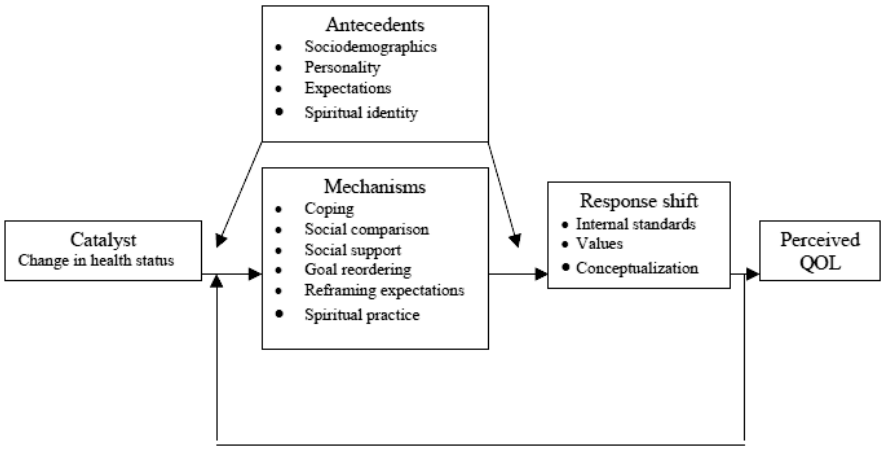


Figure 3. Theoretical model of response shift developed by Sprangers and Schwartz 1999. Reprinted with permission from Social Science and Medicine, 48, 1507-1515, Copyright© 1999, Elsevier Science.

This model suggests that whether or not a change in health status (catalyst) is reported in HRQL (perceived QOL) is based on patient characteristics (antecedents), such as education (sociodemographics) and personality. In conjunction with coping strategies and social support (mechanisms), they are input for a self-evaluation (response shift) of the changed status before it is reported. Response shift is hypothesised to occur more often in patients, who improve or deteriorate since they, in contrast with stable patients, are expected to re-evaluate their situation. A meta-analysis of the effect size indicated that it seems to be relatively small but may result in underestimation of true change in quality of life[84]. The largest effect has been found for global quality of life, physical function, fatigue and pain[84,85]

A combination of the facts presented above emphasises why HRQL could never be measured objectively; its intrinsic value lies in its subjectivity.

**The Rationale for HRQL in Clinical Research**

In medical care, treatment is offered with three main aims 1) to increase longevity, 2) to prevent future morbidity and 3) to make the patients feel better[78]. In the last decade outcomes related to aim three, such as impact of treatment on HRQL, have become standard practice in high quality clinical cancer trials[65,67]. HRQL has been found valuable in palliative care, when cure is no longer possible, as the balance power when two treatments achieve main results of equal value[67,86,87]. One example is that survival was similar but HRQL was better preserved if radiotherapy was given continuously rather than intermittently in advanced breast cancer patients[88]. HRQL assessments have also revealed the need for treating radiotherapy-induced fatigue with physiotherapy[89]. Moreover, a review found associations between HRQL and survival, suggesting that HRQL is a prognostic marker[90]. Finally, patients expect to receive a realistic individual prognosis[91] and feel a need to discuss HRQL with their physician[92].

**Instruments for measuring HRQL**

HRQL can be assessed through existing or study-specific interviews or questionnaires. The questionnaires might be terminal-based or printed and preferably filled in by the patient himself but if necessary by proxy. The existing instruments can be grouped as[67]

- Generic – measure broad aspects of health independent of illness; examples are Medical outcomes Study-36 item short form (SF36) and Schedule for individual evaluation of quality of life (SEIQoL).
- Disease-specific – focus on disease specific issues; examples are European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 and Functional Assessment of Cancer Therapy (FACT-G).
- Aspect-specific – focus on certain aspects independent of other conditions; examples are Hospital Anxiety and Depression Scale (HADS) McGill Pain Questionnarie (MPQ) and Multidimensional Fatigue Inventory (MFI).

**Considerations before Choosing Instrument**

An instrument needs to be selected, depending on the purpose of the trial[93], e.g. if HRQL is a primary or secondary endpoint and which aspects (generic, disease, single symptom or treatment) are to be evaluated. It is important to bear in mind the study respondent's level of education, age range, language and cultural variations, in conjunction with the burden of assessments. Practical issues such as timing and frequency of assessments in relation to resources available, as well as procedures for missing answers, need to be considered[86]. Psychometric properties are of great importance and have four independent, important basic fundaments, which interrelate[67].

- *Validity* – Does the instrument measure what is wanted in a sensible manner? If it measures what is wanted, it might be evaluated by experts as comparisons with other known instruments and as correlations within or between other scales in the instrument. In a subjective instrument, as when measuring HRQL, validity can include the instrument correlating with other more observable events and behaving as anticipated[67].
- *Reliability* –Is the result random or reproducible, meaning would one patient produce the same answer to the same question every time if her condition remains unchanged?
- *Sensitivity* –Are differences *between* patients or groups that are believed to exist detected, e.g. differences between patients with a different health status?
- *Responsiveness* –Are changes over time *within* a group or individual detected if they improve or deteriorate?

## DEFINITION OF HRQL AND RATIONALE FOR CHOSEN INSTRUMENTS

In this thesis, HRQL has not been clearly defined *a priori*, instead it has been assessed through two commonly used disease-specific questionnaires, EORTC QLQC30 and EORTC QLQ-OES18.

Some arguments substantiate this choice of instrument; since HRQL was a main endpoint it should have solid documentation and assess both general cancer issues and oesophageal cancer-specific issues. Since the majority of the patients were most likely to be middle-aged it was important to have a validated translation of the questionnaire in Swedish, while still being of international use. Other benefits were the inexpensive and easy administration.

## THE EUROPEAN ORGANISATION FOR RESEARCH AND TREATMENT OF CANCER (EORTC) AND ITS QUESTIONNAIRES

EORTC is an international grant-supported organisation initiated in Belgium in 1962 by oncologists from the EU countries and Switzerland. Their aim is to develop, conduct, coordinate and stimulate translational and clinical research in Europe[94]. Their quality-of-life group developed an integrated measurement system for clinical trials in 1986. A modular approach was adopted to ensure generalisability while still enabling questions relevant to particular groups of patients. The result was a core questionnaire assessing HRQL issues relevant to most cancer patients (QLQ-C30) and several cancer-specific modules including oesophageal cancer (QLQ-OES18).

The questionnaires assess HRQL multidimensionally and are designed for self-administration in cross-culture settings[94]. They include both single items answering one single aspect, such as constipation–*Have you been constipated?* and multi-item scales consisting of several questions for complex symptoms such as fatigue – *Did you need to rest?,- Have you felt weak? -Were you tired?* All questions refer to the past week.

The questionnaires have been translated into several languages, including Swedish, and involve translations by two independent native speakers[95].

**The General Cancer Core Questionnaire - QLQ-C30**

QLQ-C30 was developed in 1987 and since then five versions with slight differences (mainly adding hobbies to role function and changed response alternatives for physical function) have been evolved. It has been translated into 81 languages and used in over 3000 studies[94,95]. For comparison purposes, reference values, stratified for age and sex from the general Swedish population, exist; see page 32[96].

*Information*

The latest version (3.0) contains 30 questions (*q*) giving nine scales and six single items (see appendix):

- Global quality of life scale (*q29-30*).
- Functional scales: physical (*q1-5*), role (*q6-7*), emotional (*q21-24*), cognitive (*q20, 25*), and social (*q26-27*).
- Symptom scales: fatigue (*q10,12,18*), nausea & vomiting (*q14-15*) and pain (*q9, 19*).
- Single items: dyspnoea (*q8*), insomnia (*q11*), appetite loss (*q13*), constipation (*q16*), diarrhoea (*q17*) and perceived financial impact by disease (*q28*).

The responder is asked to answer the question based on the past week. Each question has four possible response alternatives: 1) "Not at all" 2) "A little" 3) "Quite a bit" 4) "Very much". Global quality of life has a seven-grade scale rising from 1) "Very poor" to 7) "Excellent".

*Psychometric Properties*

Several tests of psychometric properties have been performed with satisfying results[97-102]. The initial version (1.0) was tested on 305 lung cancer patients from 13 countries and the alternations in the latest version (3.0) were tested in 2000 among 622 head and neck cancer patients from 12 countries[101]. Validity was tested as correlations between scales. The results showed that global quality of life correlated with most scales. Likewise fatigue correlated with most scales after treatment. And as expected, physical function correlated with role function both before and after treatment. Likewise pain correlated to social function after treatment. But, to conclude, the questionnaire was stated as a valid measure of HRQL among cancer patients. Regarding clinical validity, disturbed emotional function was found among patients with metastatic disease and, as expected, associations were found with performance status, weight loss and treatment toxicity. Reliability for scales was assessed with Cronbachs alpha. The results showed a skewed distribution towards maximum function for cognitive and social functions. Furthermore, uncommon symptoms in lung cancer patients (diarrhoea and constipation) were rare. The reliability was stated as good (>0.7) for pre-treatment global quality of life, emotional function, fatigue and pain and for all post-treatment items expect for role function. The reliability was improved for the changed physical function in version 3.0[101].

Responsiveness was addressed such as changes over time, which was found for patients with changed performance status.

**The Oesophageal Specific Questionnaire QLQ-OES18**

QLQ-OES18 assesses issues specific for oesophageal cancer. The first version, QLQ-OES24, was published in 1996 and developed based on interviews with patients, health care providers and literature[103].

*Information*

The questionnaire includes 18 questions (*q*) forming four scales and six items (see appendix) with response alternatives as for QLQ-C30:

- Symptom scales: dysphagia (*q31-33*), eating difficulties (*q36-39*), reflux (*q44-45*), oesophageal pain (*q46-48*),
- Single items: trouble swallowing saliva (*q34),* choking (*q35*), dry mouth (*q40*), taste problems (*q41*), coughing (*q42*), speech difficulties (*q43*).

*Psychometric Properties*

During the validation, published in 2003, on 591 oesophageal cancer patients from six countries, questions about burping and hair loss were withdrawn and the questionnaire was revised to QLQ-OES18[104].

Validity was tested as correlations to the QLQ-C30 scales. Results showed that correlations were generally low (Pearson's r <0.4) except for oesophageal pain, which, as expected, correlated to the QLQ-C30 pain score and eating difficulties correlating to social function and fatigue.

Clinical validity was tested presuming the questionnaire could detect differences between groups of curative and palliative patients. Results showed that patients with curative-intended treatment scored significantly better at baseline than palliative patients. Patients who had undergone an oesophagectomy reported poorer postoperative social function and more nausea but less dysphagia than other patients.

Reliability was assessed with Cronbachs alpha, and stated as good (above 0.7) in 60% of the scales. The highest value was found for eating difficulties and dysphagia scales while reflux and pain showed weaker results.

**Interpreting the Results from EORTC Questionnaires**

To evaluate results from EORTC questionnaires in a context, results could be reported in several ways (e.g. as raw scores and transformed scores see, page 43): comparing results to other published data or using cut-offs based on "clinical significance"[105]. In HRQL, research terms such as "clinical relevance" or "clinical significance" have gained ground as initial cut-offs, followed up by a statistical cut-off before results are approved[67]. Both cut-offs complement each other, statistical significance determines if our results can be explained by chance fluctuations alone but statistical significance can easily be found in a large sample without having any clinical meaning for the patients[67]. Although clinical significance is subjective[67], the *minimal clinically important difference* has been defined as the smallest difference patients notice as beneficial, and a change that would cause clinicians to consider a change in the management of the patient[67]. Two general approaches to interpreting the minimal clinically important difference are described in EORTC's scoring manual[105]: the *anchor-based* approach below, meaning comparison of HRQL scores with clinical changes or results, and the *distribution-based* approach, meaning comparisons based on statistical distribution of result. The anchor-based method is recommended if possible[106,107].

*Anchor-based Method*

Two milestone studies have evaluated the clinically relevant cut-off value on QLQ-C30. The study most referred to was performed by Osoba et al in 1998[108]. In that study, breast and lung cancer patients filled in the QLQ-C30 once prior to and twice following chemotherapy, along with a subjective significance questionnaire asking the patient "*Since last time I filled out a questionnaire, my global quality of life/physical/emotional/ social function is*…; response options ranged from 1) "Very much worse" to 7) "Very much better". Conclusions were that on a 0-100 scale, a 5-10 point shift corresponded to a slight change, a 10-20 point shift to a moderate change, and a shift of more than 20 points corresponded to considerable change. Earlier, King[109] had performed a retrospective study, in which she compared clinical changes in performance status, weight loss, toxicity and severity of disease to HRQL scores from 14 studies; she found that on a 0-100 scale, a change in 5 points was interpretable as a relativelysmall change whereas 15 points corresponded to a relatively large change[109]. She concluded that a difference of 10 points in mean score may in clinical settings represent significant symptom control. Furthermore, the level of 10% has also been found by other researchers[93,110,111] and gained acceptance as clinically relevant[67].

*Distribution-based Method*

The distribution-based method might be useful when patient-data or reference data are lacking although they are based on the actual distribution of results. Either the between-patients variability (standard deviation of patients baseline), or the within-patients variability (standard deviation of change over time)[93,105] can be used. In the study by Osobas et al[108], the results were in line with the results from the anchor-based method.

**Presenting the Results from EORTC Questionnaires**

A common post-treatment comparison level is baseline HRQL, measured before a course of treatment is to be decided on or induced. Ideally, baseline would be before the disease has developed but this is not feasible in clinics. As a surrogate, baseline HRQL can be expected to be similar to that of the corresponding general population. Scores from the general population in Sweden published in 2000 are presented in Table 3 to give an indication of expected "normal" values in QLQ-C30. No such data exists for QLQ-OES18.

Table 3. Reference values for males and female in the age group 60-69 years assessed among the Swedish general population[96]. The scale range is from 0 to 100. A high score on functioning scales and global quality of life corresponds to a good function, while a high score on symptoms corresponds to many symptoms.

| | **Male reference 60-69 years** | **Female reference 60-69 years** |
|---|---|---|
| | Mean score N=278 | Mean score N=271 |
| Global Quality of life | 77 | 78 |
| **Functioning scales** | | |
| Physical function | 88 | 87 |
| Role Function | 87 | 87 |
| Emotional function | 86 | 84 |
| Cognitive function | 87 | 90 |
| Social function | 91 | 92 |
| **General symptom scales** | | |
| Fatigue | 20 | 20 |
| Nausea & Vomiting | 2 | 3 |
| Pain | 18 | 21 |
| **General symptom items** | | |
| Dyspnoea | 19 | 16 |
| Insomnia | 17 | 23 |
| Appetite loss | 2 | 4 |
| Constipation | 4 | 9 |
| Diarrhoea | 5 | 4 |
| Financial difficulties | 5 | 7 |

# BIOLOGICAL MECHANISMS FOR CANCER SYMPTOMS

## General Cancer Symptoms

Biological mechanisms for common symptoms are poorly understood and interact in a complex way. To illustrate, two common symptoms - fatigue and pain - will be discussed. Fatigue has been associated with levels of proinflammatory cytokines (IL1, IL6, TNFa) probably due to tissue damage and cell death[80,112]. Likewise, treating anaemia has been suggested to be of major importance for quality of life outcomes including fatigue[113-115]. Nutritional factors such as alternation in abilities to process nutrients, increased energy requirements and decreased energy intake and closely related cancer anorexia and cachexia are possible reasons for fatigue[1-3,29,116]. Furthermore, stress, anxiety and depression are the most common comorbidities of fatigue[117]. Finally, cancer patients might acquire an altered circadian rhythm resulting in changed social function, increased fatigue and pain, as well as shorter survival[118]. Pain is commonly present among 55-95% of terminal cancer patients[119], possibly due to metastases resulting in local ischemia, nerve pressure and inflammation. Interestingly, the severity of pain has been studied, and certain gene expressions seem to be associated with greater needs of pain killers[80]. Furthermore, pain it self might cause nausea via connections to the autonomic nerve system. Lately, the term *clustering*, meaning coexistence of more than three symptoms such as pain, fatigue and poor appetite, has evolved as a concept[120]. It has been suggested that symptom clusters might have an adverse effect on patient-reported outcomes and a synergetic effect on predictors of morbidity[120].

## Oesophageal Specific Symptoms

Common symptoms for operated oesophageal cancer patients are typically related to eating, and about 4-68% of the patients suffer a certain mixture of symptoms called early dumping[121,122]. Early dumping is due to the lack of vagal reflexes (after vagotomy) which accommodate, relax and empty the stomach, resulting in a raised pressure gradient from the stomach to the intestine. In conjunction with the removed portioning mechanism of the antrum and pylorus, this results in premature gastric emptying[122,123]. Early dumping includes symptoms such as nausea, vomiting, cramping stomach pain, flushing, heartbeat, vertigo and diarrhoea about 30-60 min after intake of food. In contrast, patients might also suffer from constipation due to opiates, postoperative weaknesses of bowel muscles and intra-abdominal adherences. Furthermore, operated patients have a smaller gastric volume, resulting in increased gastric wall tension after eating a normal meal, which results in fatigue, feeling full, nausea and premature satiety. Problems with eating and dysphagia postoperatively might be due to an anastomotic stricture, and reflux is due to the excision of the lower oesophageal sphincter and distorting anatomy.

## HRQL IN CURABLE OESOPHAGEAL CANCER PATIENTS

### Patient and Tumour Characteristics

Baseline scores for patients with planned curative treatment are in general typically good for functional scales, although patients are likely to report problems with fatigue, pain, insomnia, appetite loss, dysphagia, eating difficulties, reflux, oesophageal pain, dry mouth, taste problems and coughing[6,124]. Regarding patient characteristics, long term scores have been similar for sexes, but dumping might occur more often among women and younger patients[125] , younger patients might also have poorer emotional function[125,126].

To the best of my knowledge, no studies have primarily investigated differences between BMI-groups or influence of comorbidities on HRQL among cancer patients.

Regarding tumour characteristics, patients with a more advanced tumour stage have poorer global quality of life and social function, more fatigue and appetite loss[127] compared to less advanced stages. One difference has been found between histological types, namely more pain among patients with SCC than those with AC[128]. Furthermore, in one study patients with SCC were more likely to be selected for chemoradiation than neoadjuvant therapy and surgery. The chemoradiation group generally had worse baseline functions and more dysphagia but deteriorated less during treatment[124].

### Treatment Related Factors, Recovery and Recurrences

Curative treatments have at least a short negative influence on HRQL[6,124,126,128-135].

Clinically relevant differences at baseline between patients selected for curative surgery versus palliative patients have been shown regarding global quality of life, physical function, role function, social function, fatigue, pain, dysphagia, trouble swallowing saliva and dry mouth[104].

Regarding the surgical approach, patients undergoing transhiatal surgery recover their physical function earlier than those with a transthoracic approach[129]. Patients with a cervical anastomosis report better physical and social function and less reflux than those with a thoracic anastomosis[125,136]. Patients with a junctional AC report better global quality of life, role and social function and less fatigue if they are treated with total gastrectomy rather than transthoracic oesophagectomy[133].

Surgical factors, such as surgeon or hospital volume, do not seem to influence HRQL negatively[137,138].

Postoperative complications such as reoperation, anastomosis leakage, infections or respiratory insufficiency affect physical and role function, while infections and cardiac complications negatively affect the global quality of life[138]. Interestingly, fatigue and dyspnoea at baseline have been found predictive for in-hospital mortality and major complications, although no differences regarding either history of respiratory disease or in the test for pulmonary function could be found between groups[134].

The recovery period for HRQL outcomes seems to be somewhere between six to twelve months from baseline[6,124,130-132,139,140]. HRQL scores on a 100-point scale are worst at six weeks postoperatively with a reduction of at least 30 points in mean score for physical function, role function, social function and at least a 15 point increase in mean score for fatigue, nausea and vomiting, dyspnoea, diarrhoea, dry mouth, taste problems and coughing[124,132].
Patients who suffer from tumour recurrence report poorer HRQL and never recover to baseline[130,141], although it is unclear how early recurrences can affect HRQL and early recurrences have so far only been shown to affect constipation[134].

**Overall Survival and Long term HRQL**

In all, eight studies have evaluated associations between baseline HRQL and survival[127,134,135,142-146]. Baseline physical function was predictive in five studies, fatigue in two studies, while the following outcomes were predictive in one study each: global quality of life, role function, social function, reflux and appetite loss[90].
One study found that an improvement in emotional function from baseline to post-treatment was associated with better survival[143].
Likewise, postoperative scores for social function, dysphagia and pain have been found prognostic for survival[135,147] .
Longer term follow-ups, i.e. two to five years, have shown that patients might almost regain their HRQL, but certain aspects are more prone to remain negatively affected, such as global quality of life, physical function and role function, as well as symptoms from fatigue, reflux and diarrhoea, from which they might not fully recover[6,124,126,129,130,148]. However, emotional function has actually been shown to improve, while dysphagia decreases, especially in survivors[6,128,143].

# THE AIMS OF THE STUDIES

The **overall aim** of this thesis was to identify influences HRQL, and to clarify whether HRQL can predict morbidity and survival among patients operated on for oesophageal cancer.

To be able to accomplish the overall aim, the following **specific aims** were formulated:

I) To clarify which deteriorated postoperative HRQL outcomes are to be considered transient with time after surgery, and which are long-standing.

II) To establish the influence of specific patient characteristics (age, sex, BMI and comorbidity) and tumour characteristics (location, histological type and stage) on postoperative HRQL.

III) To elucidate the prognostic value (chance of long term survival) of changes in HRQL-scores before and after surgery.

IV) To ascertain the prognostic value (chance of long term survival) of HRQL-scores assessed six months after surgery.

**The aims were stated in order to:**

- Find clinical warning signs for poor prognosis.
- Increase knowledge for improvement of clinical follow-ups.
- Facilitate basic data for informed consent treatment.

# MATERIAL AND METHODS

## DESIGN AND DATA COLLECTION

This thesis uses clinical data from two research databases. Studies I, II and IV are based on the nationwide Swedish Esophageal and Cardia Cancer registry (SECC-registry), while Study III derives from the British single centre Upper gastrointestinal database. An overview of the designs, data collection and methods used are presented in Table 4.

Table 4. Overview of material and methods in the four studies.

| | **Study I** | **Study II** | **Study III** | **Study IV** |
|---|---|---|---|---|
| **Design** | Prospective cohort | | | |
| **Source population** | Sweden's population | | Avon, Somerset and Wiltshire area | Sweden's population |
| **Cohort** | SECC-registry | | Upper gastrointestinal database | SECC-registry |
| **Exposure** | Curative surgery for oesophageal cancer | Patient and tumour characteristics | Changes in HRQL-scores from before to after treatment | Postoperative HRQL-scores |
| **Outcome** | Long term HRQL | Risk of poor HRQL | Risk of mortality | |
| **HRQL measurements** | QLQ-C30, QLQ-OES18 | | QLQ-C30 | QLQ-C30, QLQ-OES18 |
| **Scoring of HRQL** | Transformed 0-100 scale | Dichotomised | Transformed 0-100 scale | Dichotomised |
| **Adjustments in final model** | - | Sex, age, BMI, comorbidity, tumour stage, histology, type of operation, complications | Sex, age, performance status, cancer site, tumour stage, histology, type of treatment, baseline HRQL | Sex, age, comorbidity, tumour stage, histology, type of operation, complications |
| **Statistical methods** | Mann-Whitney U- test<br>Students t-test | Logistic regression models | Chi-square test<br>Cox proportional hazards models,<br>Assumption of proportional hazards models | Cox proportional hazards models,<br>Kaplan – Meier graph |

# COHORT

## The Swedish Esophageal and Cardia Cancer Registry

*Background*

Studies I, II and IV were based on a nationwide clinical data collection from patients who underwent surgical resection for oesophageal or cardia cancer in Sweden during the period April 2001 to December 2005. This research database was entitled Swedish Esophageal and Cardia Cancer Register (SECC-registry) and was based on a Swedish network of hospital departments involved in the diagnosis and treatment of oesophageal and cardia cancer patients. Virtually all (175 out of 179; 97%) of the eligible hospital departments in general surgery, thoracic surgery, oto-rhino-laryngology, oncology and pathology have participated. Around 90% of all surgically treated oesophageal cancer patients in Sweden have been prospectively included and followed up[149]. A total of 616 patients was included in the register until the stop date for inclusion of new patients in December 2005. The organisation behind the data collection was originally created as a population based case-control study concerning risk factors for oesophageal and cardia cancer[149], whereas it was later (in 2001) directed towards clinical research.

*Data Collection*

The registry was coordinated and administrated by a central project manager (Eja Fridsta), who was the key person in the data collection. All data were collected by starting off with a histopathology report on a confirmed oesophageal or cardia cancer from the pathology department and thereafter contacting physicians for informed consent from the patient and retrieval of individual data. Non-participating clinics and missing informed consents, mainly due to physicians not asking patients, explained the missing data on 10% of the patients. Based on a detailed study protocol, the collected data was thoroughly reviewed via manual scrutiny of medical reports by a handful of clinicians and researchers in our group. Variables such as tumour characteristics (site, stage and histological type), preoperative physical examinations, comorbidities, neoadjuvant treatment, surgical treatment, complications, length of hospital stay, and place of discharge were collected. The database contains HRQL measurements, assessed postoperatively six months, three years and five years after surgery.

*Validity and Reliability*

Certain aspects within the registry suggest good validity and reliability. The high national coverage, and the detailed manual data collection performed prospectively by researchers, not personally involved in the treatment of the patients, are among the methodological advantages. Another important advantage was that the collection of HRQL data was obtained anonymously, i.e. the patients sent their answers to an unknown central registry, and not to their physician or hospital department.

**The Upper Gastro-Intestinal database in Bristol, U.K.**

*Background*

Study III is based on the database described below. The United Bristol Healthcare Trust in southwest Britain started a prospective cohort named the Upper gastrointestinal database in November 2000.

Patients were recruited from a total population of 1.66 million[150] and included in the Avon, Somerset and Wiltshire Cancer network.

The aim of the database was to collect a prospective research database for upper gastrointestinal cancers such as oesophageal, cardia, gastric, liver and pancreas. Totally, 216 oesophageal cancer patients were included in the database when I started my work on it.

*Data Collection*

After referral to the participating hospitals the patients were asked for informed consent. Patients were asked for socio demographics and HRQL data either in hospital or in conjunction with a home visit, while the clinical data such as tumour characteristics (site, stage and histological type), preoperative physical examinations, comorbidities, neoadjuvant treatment, surgical treatment, complications, length of hospital stay, and place of discharge were gathered by means of a manual review of records.

A first HRQL assessment was performed in hospital within 30 days prior to surgery or up to 9 days after initiating non-surgical treatment. This first HRQL assessment was labelled baseline HRQL.

Follow-up data were collected six weeks, then 3, 6, 9, 12, 18, 24 and 36 months after the operation.

*Validity and Reliability*

Data on participating patients was almost complete and missing data was rare, which increases the internal validity. Furthermore, the prospective data collection was based on a predefined protocol, which increased validity and reliability.

## HRQL MEASUREMENT

In all four studies, HRQL measurement has been carried out using the two questionnaires (QLQ-C30 and QLQ-OES18) developed by the EORTC and described in the background (pages 29-30) and attached in the appendix. There has been a hypothesis-driven and literature-based[6,127,131,134,135,144,146,147,151] selection of outcomes to minimize multiple testing as presented in Table 5.

Table 5. List of selected outcomes from the EORTC QLQ-C30 and QLQ-OES18 per study.

| STUDY | I | II | III | IV |
|---|---|---|---|---|
| Global | | | | |
| Quality of life | ● | ● | ● | ● |
| **Functioning scales** | | | | |
| Physical | ● | ● | ● | ● |
| Role | ● | ● | ● | |
| Emotional | ● | ● | ● | |
| Social | ● | ● | ● | ● |
| Cognitive | ● | | ● | |
| **General cancer symptoms** | | | | |
| Fatigue | ● | ● | ● | ● |
| Nausea | ● | | ● | |
| Pain | ● | ● | ● | ● |
| Dyspnoea | ● | ● | ● | ● |
| Insomnia | ● | | ● | |
| Appetite loss | ● | ● | ● | ● |
| Constipation | ● | | ● | |
| Diarrhoea | ● | ● | ● | |
| Financial impact | ● | | ● | |

| STUDY | I | II | III | IV |
|---|---|---|---|---|
| **Oesophageal cancer symptoms** | | | | |
| Eating difficulties | ● | ● | | |
| Reflux | ● | ● | | |
| Oesophageal pain | ● | | | ● |
| Dysphagia | ● | ● | | ● |
| Coughing | ● | ● | | |
| Dry mouth | ● | | | |
| Taste problems | ● | | | |
| Choking | ● | | | |
| Speech difficulties | ● | | | |
| Trouble swallowing saliva | ● | | | |

### Time Frame and Performance of HRQL Assessments

Patients in the SECC-registry have answered the questionnaire in Swedish. It was sent per mail to their home address after informed consent and up to three reminding letters were sent out, if appropriate. The time window both for the assessment after six months in Studies I, II and IV, as well as for the three years' assessment used in Study I was +/- three months. In the Upper gastrointestinal database, patients filled in the questionnaire while hospitalised or at home, and if needed, one reminding telephone call was made. If data were still missing, patients were telephoned for additional responses. The baseline and six months' follow-up were used in Study III. The time window for the baseline was within 29 days before initiation of therapy, and for chemoradiated patients up to 9 days after the start of treatment. The time window for the six months' assessment was 180 days (-56/+48 days).

**Scoring, Interpretation and Presentation**

EORTC's QLQ-C30 scoring manual[105] declares that results can be reported in several ways e.g. as raw scores (response alternatives 1,2,3,4) or transformed scores. Transformation of the raw answers occurs according to the formula below[105,152]:

*Range* is the difference between maximum (4) and minimum (1) possible response alternative. All questions, thus have range 3, except for global qols range of 6.

1) The raw answers are transformed to a raw score (RS) by:
$RS = (answer_1 + answer_2 + \ldots + answer_n)/n$
n= number of question within a scale

2) Linearly transformation from RS to score(S) between 0-100.
For functional scales: $S = (1 - ((RS-1)/range) * 100$
Global quality of life and symptom scales/items: $S = ((RS -1)/range) * 100$

*Studies I and III*
All responses were transformed to a score between 0-100 according to the scoring manual. A high score on functional scales and global quality of life represented a high level of function and better quality of life, whereas a high score on symptoms indicated more symptoms. A difference of at least 10 points between different time points or between patients was considered to be of clinical relevance in accordance with previous literature[108,109]. In Study I, mean scores were compared to age-and-sex matched strata of the Swedish general population.

*Studies II and IV*
In Studies II and IV responses were dichotomised. The cut-off was based on clinical relevance, meaning a response of at least 3 "Quite a bit" would make a clinician react. Patients who responded with at least one 3 "Quite a bit" or 4 "Very much" to any item within a functional scale were categorised as having "Poor function"; otherwise, patients were categorised as having "Good function". Likewise, answers on the symptom scales and items were dichotomised into "Symptomatic" if the patient produced at least one response of 3 "Quite a bit" or 4 "Very much" otherwise patients were dichotomised into "No or minor symptoms" (except for the dysphagia scale with an opposite response direction). A response of 4 or less (i.e., worse than the mean score of the total group) to either of the two questions on the global quality of life scale, was considered to represent a "Poor global quality of life"; otherwise, the patient was considered to have a "Good global quality of life".

**Missing Data**
Missing items were treated according to the scoring manual[105] and were not imputed or estimated; instead if a patient for example did not respond to dyspnoea, he was excluded from analyses of dyspnoea but included in all other analyses of functions and symptoms. Regarding multi-item outcomes, patients were included if they had answered at least half of the questions and the answers were then divided by the number of answered questions.

## STATISTICAL METHODS

**Study I**

Mean scores of the individual transformed scores were calculated and presented with 95% confidence intervals. A difference of at least 10 points between time points was examined with a statistical significance test. Though the results were not normally distributed, the non-parametric Mann-Whitney U test was used and the level of statistical significance used was 5% ($\alpha$=0.05). Results of QLQ-C30 were compared to age-and-sex stratified values in the general population, and if a difference of at least 10 points was found, statistical significance was examined with a Students t-test.

**Study II**

A selection of outcomes was made based on previous literature[6,129,131,146] so as to minimize the risk of results due to chance (Table 5). Reponses were dichotomised as described on page 47. Associations between preoperative patient and tumour characteristics and postoperative HRQL were examined using logistic regression models and presented in the form of odds ratios (ORs) with 95% confidence intervals (CIs). Adjustment was made in a basic model, including sex, age and tumour stage and moreover in a multivariable model, including BMI, comorbidity, complications, and type of operation.

**Study III**

Two hypotheses were advanced. Firstly, in changes of at least 10 points in the baseline score, associations between patients and survival were assessed. Secondly, a change of 10 points or more when subtracting the individual baseline score from the follow-up score was examined for association with survival. Cox proportional hazard models[153] were used, and results were presented as Hazard ratio with 95% confidence intervals. Both hypotheses were adjusted for sex, age, performance status, cancer site, tumour stage and histology. The second hypothesis was also adjusted for treatment and baseline score of examined item (or scale). Due to the number of statistical tests, our criterion for statistical significance was $p<0.01$. The assumption of proportional hazards was evaluated and a test of unbiased estimation and accurate confidence interval coverage probabilities was carried out[154].

**Study IV**

A selection of outcomes, based on previous literature[127,134,135,144,146,147], so as to minimize the risk of results due to chance, was made (Table 5). Responses were dichotomised as described above (page 47). Associations between HRQL and survival were evaluated using Cox proportional hazard models and presented as Hazard ratios with 95% confidence intervals. Adjustments were made for sex, age, tumour stage, comorbidity, histology, operation type and postoperative complications within 30 days of surgery. A survival graph was drawn using the Kaplan-Meier method.

# RESULTS

## STUDY PARTICIPANTS

Table 6. Participation rate of patients in Studies I-IV.

| | I | II | III | IV |
|---|---|---|---|---|
| | Number of patients (%) | | | |
| In original cohort | 358 (100) | 586 (100) | 216 (100) | 614 (100) |
| **Alive after:** | | | | |
| - six months | 280 (78) | 463 (79) | 169 (78) | 490 (80) |
| - three years | 117 (33) | --- | ---- | --- |
| **Answered HRQL of alive:** | | | | |
| - at baseline | -- | -- | 188 (87) | -- |
| - after six months | 93 (79)* | 355 (77) | 132 (78) | 401 (82) |
| - after three years | 87 (74)* | -- | -- | -- |

* Only patients alive at three years (117) were eligible for the study, number and percentage is based on those.

Table 7. Selected characteristics of the participants of Studies I-IV

| | I | II | III | IV |
|---|---|---|---|---|
| | Number of patients (%) | | | |
| **Male sex** | 62 (71) | 287 (81) | 91 (69) | 326 (81) |
| **Mean age** | 66 | 66 | 64 | 66 |
| **Comorbidities** | | | | |
| Yes, at least one | 57 (66) | 244 (69) | N/A | 274 (68) |
| **Tumour location** | | | | |
| Upper or middle | 12 (14) | 57 (16) | N/A | 64 (16) |
| Lower | 39 (45) | 139 (39) | N/A | 158 (39) |
| Cardia (Siewert II-III) | 36 (41) | 158 (44) | N/A | 179 (45) |
| Stomach | -- | --- | 38 (29) | -- |
| **Tumour stage** | | | | |
| 0-I | 34 (39) | 75 (21) | 15 (11) | 84 (21) |
| II | 36 (45) | 115 (32) | 22 (17) | 120 (30) |
| III | 13 (15) | 146 (41) | 82 (62) | 162 (40) |
| IV | 3 (3) | 19 (5) | 13 (10) | 33 (8) |
| Unknown | 1 (1) | -- | -- | 2 (1) |
| **Histology** | | | | |
| Adenocarcinoma | 68 (78) | 269 (76) | 104 (79) | 303 (76) |
| Squamous cell carcinoma | 19 (22) | 87 (25) | 28 (21) | 98 (24) |
| **Treatment** | | | | |
| Surgery | 80 (92) | 313 (88) | 61 (46) | 356 (89) |
| Neoadjuvant and surgery | 4 (5) | 22 (6) | 46 (35) | 24 (6) |
| Radical chemoradiotherapy | -- | -- | 25 (19) | -- |
| Adjuvant therapy | 3 (3) | 20 (6) | N/A | 21 (5) |
| **Complications** | | | | |
| Yes, at least one | 36 (41) | 153 (43) | N/A | 183 (46) |

## STUDY I – LONG TERM HRQL

Of the 358 patients who underwent potentially curative surgery, the 117 patients (33%) who were alive after three years were eligible for this study. Of these 117 patients, 93 (79%) returned the six months' questionnaire and 87 (74%) their three years' questionnaire. Out of the 117 patients, 78 (67%) patients had returned both the six months' questionnaire and the three years' questionnaire. The missing questionnaires were mainly due to administrative errors (15% of the six months' and 17% of the three years' questionnaires).

### Comparisons over Time

In general, there were no clinically relevant differences (≥10 in mean scores) in the total group of patients between the assessments after six months and after three years. There were differences corresponding to a mild clinical change (5-10 points) regarding less fatigue, appetite loss, diarrhoea and financial difficulties, and increased dysphagia, reflux and dryness of the mouth after three years, compared to six months. Separate analyses to discover the direction of changes among the majority of the patients revealed that most patients remained on the same level of HRQL (individual mean score change within 10 points), and the proportions of patients who improved or deteriorated were similar. The greatest proportion of patients improved in fatigue (47%), oesophageal pain (45%) and reflux (42%). The aspect on which most patients deteriorated was dysphagia (32%).

### Comparisons with the General Population

When mean HRQL scores from the QLQ-C30 questionnaire were compared to an age and sex-matched random sample of the Swedish general population, the patients showed clinically relevant and statistically significant poorer HRQL. Aspects of role and social functions, fatigue, nausea and vomiting, loss of appetite and diarrhoea were particularly affected. Furthermore, female patients also reported a poorer global quality of life, physical and emotional function scores, compared to the matched female general population.

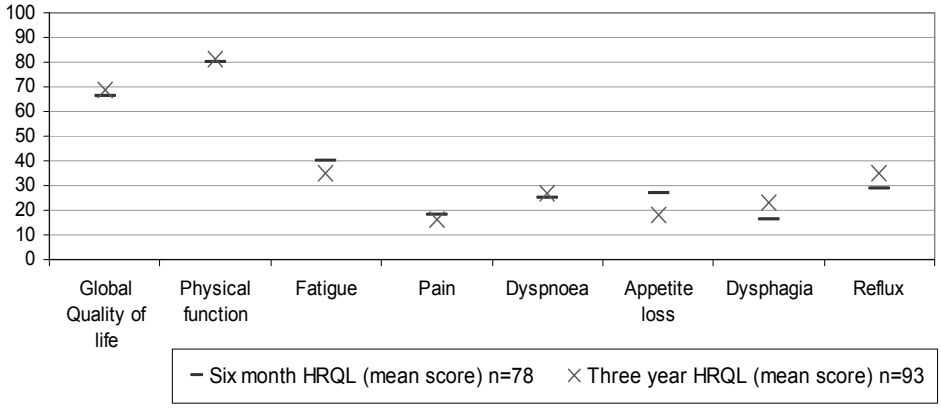


Figure 4. Mean score six months and three years postoperative.

## STUDY II – INFLUENCES ON HRQL

Of 586 patients treated with intended curative oesophagectomy, 463 (79%) patients were alive six months postoperatively and thus eligible for the study. Of these, the 355 (77%), who completed the questionnaire, remained for final analysis. Missing questionnaires were mainly due to administrative errors, such as delayed registration of the patients (14%).

### Patient Characteristics

Regarding associations between patient characteristics and HRQL, no associations were seen for sex. Middle-aged patients had a decreased risk of poor emotional function (OR 0.53 95% CI 0.30-0.93) compared to the younger age group. A lower risk of having poor social function was found among patients with high BMI (OR 0.77 95% CI 0.62-0.96). Patients with comorbidities had a statistically significant, almost doubled increase in risk of poor physical function (OR 1.87, 95% CI 1.13-3.08), role function (OR 1.94, 95% CI 1.16-3.25), fatigue (OR 2.17, 95% CI 1.31-3.60), and diarrhoea (OR 1.87, 95% CI 1.04-3.34) compared to those without comorbidities.

### Tumour Characteristics

Patients with AC had a statistically significant decreased risk of poor global quality of life (OR 0.43, 95% CI 0.24-0.75), physical function (OR 0.36, 95% CI 0.20-0.64), role function (OR 0.45, 95% CI 0.25-0.80), fatigue (OR 0.49, 95% CI 0.28-0.88), pain (OR 0.41, 95% CI 0.22-0.74), dyspnoea (OR 0.42, 95% CI 0.23-0.78) and coughing (OR 0.46, 95% CI 0.25-0.86) compared to patients with SCC. Furthermore, an advanced tumour stage (III-IV) indicated a statistically significant increased risk of poor role function (OR 2.30, 95% CI 1.23-4.30), loss of appetite (OR 2.40, 95% CI 1.23-4.66) and eating difficulties (for stage II OR 2.26, 95% CI 1.19-4.29 and for stage III-IV OR 1.80, 95% CI 1.00-3.23) compared to patients with tumour stage 0-I. Regarding the location of the tumour, a middle or upper location was statistically significantly associated with an increased risk of poor global quality of life (OR 2.61, 95% CI 1.28-5.32), physical function (OR 2.09, 95% CI 1.05-4.16) as well as a higher risk of dyspnoea (OR 2.76, 95% CI 1.35-5.61) and coughing (OR 3.88, 95% CI 1.80-8.34) compared to patients with tumours of the gastric cardia.

## STUDY III – CHANGES IN HRQL AND SURVIVAL

Of 216 selected patients, 169 completed curative treatment and were alive at the six months' follow-up. Of these, 132 (78%) had two complete HRQL assessments. Missing questionnaires were mainly due to administrational failure at baseline (13%), while at the follow-up this was mainly due to the fact that the patient had died or did not complete the planned treatment (22%).

**Differences in Baseline Scores between Patients**

Patients reporting at least 10 points higher score on the baseline dyspnoea had an 18% increase in the likelihood of death (HR 1.18 95% C.I. 1.05-1.33, p-value 0.006). No associations were found for global quality of life, physical function, role function, emotional function, social function, cognitive function, fatigue, nausea, pain, dyspnoea, insomnia, loss of appetite, constipation, diarrhoea or financial impact.

**Changes in the Individual Score between Baseline and Follow-up**

Regarding the change within a patient between baseline and postoperative HRQL a better recovery of physical function was associated with a lower risk of death six months after treatment (HR 0.85, 95% C.I. 0.76-0.96, p-value 0.007). Likewise, a higher risk of death was found for patients with a 10 point increase in problems with pain (HR 1.20, 95% C.I. 1.09-1.33, p-value < 0.001) and fatigue (HR 1.16, 95% C.I. 1.04-1.30, p-value 0.009). There was no evidence of non-proportional hazards in any of the models presented.

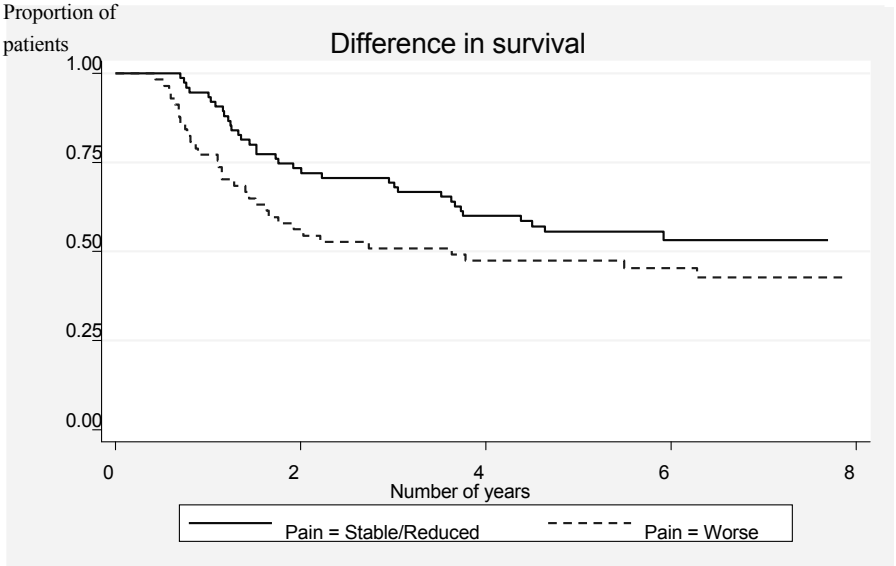


Figure 5. Survival graph for patients illustrating differences between patients with stable or reduced pain versus those with at least a 10 point deterioration.

## STUDY IV – POSTOPERATIVE HRQL AND SURVIVAL

Of the 614 patients who underwent potentially curative surgery for oesophageal or cardia cancer, 124 died before six months' follow-up and of those, who were alive, 89 (18%) had missing data mainly due to administrative errors such as delayed registration six months postoperatively. The remaining 401 (82%) patients responded to the six months' HRQL assessment. Patients were followed up for at least five years.

Nearly every third patient was categorised as having poor global quality of life. Cox proportional showed a 55% increased risk of death for these patients, compared to those having good global quality of life (HR 1.55, 95% CI 1.19-2.02, p <0.01). Almost half of the patients (48%) were categorised as having a poor physical function and these had a 56% increased risk of death (HR 1.56, 95% CI 1.23-1.99, p <0.01) compared to patients having good physical function. Regarding social function, one third of the patients was classified as poor, and these patients had a 52% increased risk of mortality (HR 1.52, 95% CI 1.19-1.94, p <0.01). About half of the patients reported that they were symptomatic from fatigue and they had a 65% increased risk of mortality (HR 1.65, 95% CI 1.30-2.11, p <0.01). Approximately one third of the patients was categorised as being symptomatic from pain and dyspnoea with Cox proportional hazard ratios showing an increased mortality of 45% and 54% respectively (HR 1.45, 95% CI 1.22-1.87, p <0.01 and HR 1.54, 95% CI 1.19-2.01, p <0.01 respectively). One of the highest hazards of death was found among the third of patients classified as symptomatic from loss of appetite which showed an increased mortality of 69% (HR 1.69, 95% CI 1.32-2.14, p <0.01). Only 9% of the patients were categorised as having symptomatic dysphagia and they had a 69% increased risk of death (HR 1.69, 95%C.I. 1.13-2.51, p 0.01). Symptomatic oesophageal pain was seen in 37% of the patients resulting in an increased mortality of 29% compared to those stating that they had no or minor symptoms (HR 1.29, 95% C.I. 1.02-1.65, p 0.04).

Table 8. Summary table of the results from Studies I-IV.

| Outcome | Findings |
|---|---|
| Global quality of life scale | Might be affected by tumour location and histology.<br>Postoperative value predictive for survival. |
| **Functioning scales** | |
| Physical function | Might be affected by comorbidities, tumour location and histology. A lack of recovery and a poor postoperative score associated with risk of shorter survival. |
| Role function | Might be affected by comorbidities, tumour stage and histology. |
| Emotional function | Might be better among middle-aged. |
| Cognitive function | No findings. |
| Social function | Might be better among the overweight.<br>Postoperative poor function associated with risk of shorter survival. |
| **General symptom scales** | |
| Fatigue | Might improve in the long term.<br>Might be affected by comorbidities and tumour histology.<br>Deterioration from baseline and a poor postoperative score is associated with risk of shorter survival. |
| Nausea & vomiting | No findings. |
| Pain | Deterioration from baseline as well as symptoms postoperatively associated with risk of shorter survival.<br>Might be affected by comorbidities and tumour histology. |
| **General symptom items** | |
| Dyspnoea | A poor baseline score and symptoms postoperatively associated with risk of shorter survival.<br>Might be affected by comorbidities, tumour location and histology. |
| Insomnia | No findings. |
| Appetite loss | Might improve in the long term.<br>Might be affected by tumour stage.<br>Postoperative symptoms associated with risk of shorter survival. |
| Constipation | No findings. |
| Diarrhoea | Might improve in the long term.<br>Might be affected by comorbidities. |
| Financial difficulties | Might improve in the long term. |
| **Oesophageal-specific symptom scales** | |
| Dysphagia | Might deteriorate in the long term.<br>Postoperative symptoms associated with risk of shorter survival. |
| Eating difficulties | Might be affected by tumour stage. |
| Reflux | Might deteriorate in the long term. |
| Oesophageal pain | Postoperative symptoms associated with risk of shorter survival. |
| **Oesophageal-specific items** | |
| Trouble swallowing saliva | No findings. |
| Choking | No findings. |
| Dry mouth | Might improve in the long term. |
| Taste problems | No findings. |
| Coughing | Might be affected by comorbidities, tumour location and histology. |
| Speech difficulties | No findings. |

# DISCUSSION

**Cohort Studies**

There are two main types of epidemiological studies; observational and experimental. Observational studies can be analytic or descriptive and designed as case-control studies, cohort studies, ecological studies or cross sectional studies. Experimental studies in clinical settings are often performed as randomized controlled trials, which have been proclaimed as "the gold standard" for scientific results[155]. The main aim of randomisation is to reduce errors but in clinical research it might be unethical or unfeasible to randomise patients, and other strategies must be used instead to combat errors. Meta-analyses have shown that overall results from several experimental and observational studies are usually almost identical[155,156] and the design is therefore more of an issue for internal validity[155-157]. All four studies within this thesis are observational since it would have been impractical or impossible to randomise patients based on the studied exposures. The study design used in all four studies was cohort studies. A cohort study could be defined as a study in which a group of people with defined exposure is followed, so as to determine the incidence of an outcome, e.g. mortality or HRQL. The cohort might be compared to a group without the exposure, to determine the influence of the exposure[158]. The main advantage with cohort studies is that the researchers are able to collect data on the exposure before the outcome has occurred. Disadvantages include difficulties in tracing patients (lost to follow-up) and thereby missing data. Furthermore, observational studies could be either prospective, if the study was initiated before the outcome has occurred, or retrospective, if the outcome has already occurred when the study is initiated. All four studies within the thesis are considered prospective cohort studies since the outcome's mortality and HRQL were unknown at the point in time of the inclusion of new patients.

**Validity**

The result of an epidemiological study is an estimate, which might be influenced by random or systematic errors. An estimate free of systematic errors is said to be perfectly valid[158]. The *validity* of a study is often divided into internal and external validity. Internal validity defines how well the study effects have been measured, or the lack of bias[158]. External validity defines how well the study results could be applied on people outside the studied population, i.e. generalisability[158]. Good internal validity is a prerequisite for external validity. Systematic errors are often named bias, and refer to any systematic error that results in incorrect estimate of the associations between exposure and risk of disease[158,159]. Bias may result in the over or underestimating of results, thereby reducing the internal validity[159]. Bias could be reduced by the study design, not the sample size. There are over 70 types of bias, classified within three main groups; selection bias, information bias and confounding[159].

**Selection Bias**

Selection bias means that differences exist in the exposures between participants and non-participants, resulting in the study population not representing the target population. Whether these differences exist or not is usually unknown, and selection bias is therefore suspected rather than observed[158].

Surgical research often has selection bias by assorting patients depending on, for example, age before an oesophagectomy is performed by a specialised doctor at a specialised hospital. The literature on oesophageal cancer is often based on single-centres with different possible routines in the referral and acceptance of patients, resulting in selection bias and difficulties in comparisons between studies.

A major reason for selection bias is loss of follow-up or missing data[158]. In Studies I, II and IV data from the population-based and nationwide SECC-registry were used. To be able to label a study population-based, the coverage of cases in a defined geographic region has to be as complete as possible. The coverage in the SECC-registry was 90% of the operated patients in Sweden, which is good. Non-participation was due to the diminished participation of five centres. Even if Studies I, II and IV used the same database of a total of 616 patients, the sample size analysed in each study differs. In Study I the three year follow-up had not passed for all patients. In Study II we excluded patients who had a curative surgery but non-radical pathological specimen, since they were concluded to have a palliative surgery and recurrences would confound the results. In Study IV we excluded two patients with palliative operations, but kept all other patients in the SECC-registry since we wanted to analyse association between HRQL and survival.

Regarding the missing six months' HRQL in Studies I, II and IV the risk of selection bias should be negligible, since it was mainly due to slow initial administration, not the patient's own choice.

In Study III, a single centre cohort was used, selection bias could exist between patients treated at the included hospitals who were thereby given possibilities of participating in the study versus patients treated at other hospitals and thereby excluded from possibilities of participating in the registry. Among patients included in the study, the participation rate baseline HRQL assessment was high (87%), reducing the risk of selection bias.

**Information Bias**

Information bias, also called misclassification, means errors in the measuring of the outcome or exposure. It can be differential if it differs between subjects with or without exposure or outcome, or non-differential if missing data is unrelated to the exposure and outcome. Differential misclassification may cause unpredictable distortion of the risk estimate, while non-differential misclassification should rather dilute any effect[158].

*Data Collection*

In Studies I, II and IV the SECC-registry was used. The registry should have a low risk of information bias due to the fact that only a handful of clinicians and researchers, working outside the participating hospitals, extracted data, as opposed to all participating clinicians at their hospitals making their own interpretation as to what and how to report data.

Furthermore, the exposure and outcome were noted, based a strict and predefined protocol without prior knowledge of future studies´ exact combinations of exposure, such as curative surgery or the outcomes HRQL or mortality. Therefore any misclassification should be non-differential, which is possible even if the protocol's definition was followed stringently. For example, even if the complication myocardial infarction was clearly defined, it is possible that the documentation in the medical records differs between doctors and centres. Also, the outcome myocardial infarction was assessed binarily (yes or no), but in the clinic a myocardial infarction could range from a new Q-wave on the ECG to a severe clinical condition. Likewise, in Study II our grouping of comorbidities might have been too rough.

In Study III a core staff followed a predefined study protocol before any treatment or outcome was known. Since the data is collected from a single centre, the risk of differences in documentation between patients should be small, and the risk of misclassification could thereby be even smaller than in the SECC-registry. Regarding HRQL outcomes in all four studies, the self-completing of questionnaires without insight from a care provider at the local hospital might have reduced the risk of information bias (e.g. observer expectation bias). On the other hand, there might be some element of *selective reporting*[100] present, meaning that patients want to contribute correctly by reporting symptoms they think researchers might find interesting. In Study III, baseline (before start of treatment) assessment was used. However, the baseline assessment might have been affected by the awareness of the cancer diagnosis, symptoms from it, or upcoming major surgery, which might cause non-differential misclassification. Unfortunately, the time point for baseline differed between patients in different treatment strategies. Furthermore, a handful of patients filled in their baseline after the start of chemotherapy but before the likelihood of developing side effects, and their baseline might have caused a differential misclassification.

*HRQL Instruments*

To reduce information bias, validated questionnaires were used to assess HRQL in all four studies. However, further improvement can be achieved. Since all tests assume a lack of errors, the cut-off of Cronbach's alpha= 0.7 is acceptable, but a value of 0.8-0.9 would have been a more desirable level for good reliability[67]. During the validation of QLQ-OES18 as many as 42% of the scales had a lower alpha than the predefined cut-off (0.7); it was stated as a weakness but the questionnaire was not further revised[104]. The number of patients in the validation was also a bit too low to allow watertight stratified validation[104].

Within the questionnaires there is a risk of information bias. A patient can easily fill in wrong answer by mistake, thereby causing a random error, especially when the scale is reversed after the initial questions on QLQ-OES18. Such misclassification should be non-differential, and it was not highlighted as a problem during testing[104].

**Confounding**

Confounding is derived from the Latin word *confundere* meaning to mix together and serves for the "confusion of effects". A confounder is an external factor interfering with both the exposure and outcome, but not acting in the causal pathway.

There are no statistical models to discriminate between a confounder and a variable intermediary in the causal pathway. Instead, control of confounders can include restricting the study design and the use of statistical analyses allowing adjustments based on previous literature and clinical knowledge[159].

In Studies II, III and IV adjustments were discussed with experienced oesophageal cancer surgeons, and statistical methods were discussed with statisticians. In Studies II and IV we unfortunately lacked some potentially important confounders, such as baseline HRQL, performance status, tobacco smoking, alcohol intake and weight loss. Even if the histological type SCC is closely connected to alcohol intake and tobacco smoking, and adjustments can thereby be indirectly made for these variables, it would have been even more valuable if the direct data had been available for adjustments. However, self-reported alcohol intake and smoking habits are difficult to assess reliably and blood sample tests only reveal recent use[160,161]. Study III provided both baseline HRQL and performance status, but lacked data about comorbidities and complications.

**Precision and Random Errors**

Precision concerns how close to bull's eye the dart arrow has landed. It is influenced by random errors (chance) and can be tested with the size of confidence intervals and p-values. A common confidence interval is 95%, meaning that in 95 of 100 similar studies the mean score of the studies will be within the confidence interval. P-values measure whether the *null hypothesis* (that no relation between exposure and outcome exists) is true or not. The p-value also answers the probability of observing an association at least as strong as the actual observation. In medical research, the p-value is often used as a dichotomy (yes or no) for decision making, meaning that the predefined level of p (often 0.05) determines whether a study has a significant result or not. This approach could be criticised, since there are many other aspects of a study that need to be taken into account. Nevertheless, there is a need to define a level of p in advance.

*Type I Errors*

Type I errors occur when the null hypothesis is rejected despite being true ("false positive"). Therefore, unexpected findings when many tests are performed simultaneously could be due to the type I error multiple testing or a true result. Type I errors could be reduced by larger sample size and fewer tests. In order to reduce risk of multiple testing, in Studies II and IV we performed a selection of outcomes that we deemed to be of highest relevance rather than testing all HRQL outcomes. Still, in Study II a drawback of exploring several HRQL outcomes simultaneously might have emerged. In Study III we *a priori* decided not to adjust for multiple testing, but instead used a difference of at least 10 points between assessments before analysing p-values.

*Type II Errors*

Type II errors occur when the null hypothesis is not rejected despite being false ("false negative") or plainly speaking "an absence of effect is not proof of lack of effect". Type II errors are reduced by an increased sample size. The lack of effects in Study I could have been due to a small sample size, but the power calculations were satisfying, so other explanations might be more likely.

In Study III gastric cancer patients were included to increase the statistical power. Since gastric cancer patients are similar regarding risk factors, symptoms, treatment and HRQL outcomes, we found it reasonable to increase power by including them.

# HRQL MEASUREMENTS

## Choice of Instrument

Philosophers have forwarded criticism that quality of life in medical research often assesses outcomes in order to measure effectiveness of treatment[64]. It has been highlighted as a problem to lump together disparate issues such as physical symptoms (pain, fatigue) and emotional states (how happy or depressed), with social and occupational functioning in one single category, thus measuring instrumental onsets (what´s good for us as means for other purposes, e.g. working for money) and final values (what's finally good for us in life, e.g. happiness) at one time[64]. The QLQ-C30 mainly focuses on physical functioning and clinical symptoms, while cognitive and emotional aspects are covered in less detail [162]. To achieve a better understanding of changes in HRQL, a disease-specific instrument could be supplemented with a generic, an aspect or a study-specific questionnaire measuring the meaning of illness, fears and hopes[86] [163-167]. So, even if the questionnaires used are perfect, we could have missed aspects of importance to patients, thereby affecting the internal validity.

## Scoring of the Questionnaires

*Transformation of Scores*

The EORTC questionnaires generate categorical ordinal data from ordered response alternatives with descriptive labels such as "Not at all" and "Very much". In Studies I and III the scoring was made according to the scoring manual[105], meaning linear transformation to a score between 0-100. By doing this, single items retain their origin form as categorical data, meaning that there is an order between values, although distances between them are meaningless and unknown. The transformed individual score for single items can only be 0 points, 33 points, 67 points or 100 points. These ordinal values are by nature only comparable to a limited extent, meaning e.g. that if patient A has 67 points and patient B has 67 points they have the same HRQL, but if patient C has 33 points we know it is lower but it is impossible to know the difference, since simple subtraction (67-33 =34) can not be done in a non-linear relation. Therefore, and due to the fact that single items can only take a limited amount of outcomes, the subtraction of the individual scores in order to find a 10 point change or not in Study III can be questioned; instead we could just have looked for deterioration or improvement as a binary outcome on single items. Regarding multi-item scales, the patient's result could end up in up in several different categories, and it might then be more relevant to use a predefined cut-off even in individuals. But the problems with multi-item scales are that it is assumed that equal weight shall be given to all questions within a scale, every score is worth the same and the distance between every response alternative is equal. Both subjective weighting of items within a function and a more sophisticated scaling such as the VAS-scale, a simple line from 0 "no pain" to 10 "worst possible pain" would be interesting[105]. To circumvent the issue of categorical data, response alternatives have numbers (1,2,3,4) and the text "Very much" could be seen as merely informative.

*Dichotomizing of Raw Scores*

The scoring method of dichotomizing, used in Studies II and IV, was chosen to be able to perform logistic regression and adjust for confounders. The cut-off based on raw answers was chosen so as to be independent of distribution of answers and to be clinically understandable. The same cut-off was used for all questions and therefore one single answer of "Quite a bit" or "Very much" qualified the patient to poor HRQL. This approach dilutes rather than concentrates our results. However, the worst scenario is for physical function, which has five questions, if a patient answers "Not at all" to four of them and "Quite a bit" to one, it produces the fairly good score 87, but with our dichotomising the patients was assessed as "Poor function". However, retrospectively, this does not seem to be a big issue since only around 1% of the patients, classified as having "Poor physical function", scored as high as 87. To avoid fishing, we did not explore alternative cut-offs, even if others were possible, e.g. the mean score of the total group. This cut-off would be based on the actual study sample, but could be hampered by a skewed distribution, a small study sample and outliers. Furthermore, the mean score could be misleading in single items. To exemplify, in Study IV our mean scores for the single-item diarrhoea was 32 points. The distribution among the four possible individual outcomes was 0 points: 38%, 33 points: 36%, 67 points: 18% and 100 points: 8%. If the same categories as in Studies II and IV are used, ("No or minor symptoms" and "Symptomatic") all of 62% would be "Symptomatic" even if 74% report problems with diarrhoea bothering them as "Not at all" or "A little". A third possible cut-off is the median score. It is not dependent on sample size or sensitive for outliers but automatically classifies half of the patients as poor and half as good, irrespective of how they have answered, and finally, the patients with the median score play a crucial role irrespective of which category they are included in.

**Clinical Interpretation**

*Mean Scores, Clinical Significance*

The consideration of the clinical relevance and usefulness of a study is of great importance, albeit a complex matter. First of all, even if HRQL assessments are common in clinical trials it is still possible, or rather likely, that clinicians do not have a sensitive understanding of, for example, a mean score of 70 points (out of 100) for physical function among cancer patients. To improve this, reporting of additional raw scores might be helpful[105]. Secondly, as discussed above, mean scores are complex to interpret and compare. Thirdly, nothing is known as to whether an improvement of 10 points in the mean score for a group of patients is of equal importance over the entire scale, such as changing from 20 points to 30 points versus from 80 points to 90 points. Fourthly, even if the 10 point cut-off for clinical relevance is widely used, only two studies have examined this cut-off and none in oesophageal cancer patients. Furthermore, improvement seems to be noticed earlier than deterioration[110], therefore it has been suggested that different cut-offs could be used for improvement (5 points) and deterioration (10 points). Also using a cut-off of 10 points in the mean score change ignores the distribution of results. In Study I we only found a weak mean score deterioration (5 points)

regarding reflux, even though the greatest portion (42%) reported increased reflux of at least 10 points. The explanation for the "lack" of associations might be that the patients, who had improved, generally had greater changes or existence outliers. The supplementary table, stating the proportion of patients with improvement /stable /deteriorated HRQL, might help the reader to understand changes better. The table also reinforces the conclusion that the majority of patients are likely to have a stable postoperative HRQL regarding most outcomes. An additive clinical method for judging numbers presented by the computer is to look at results on correlating scales. In Study III, the findings of association between survival on the correlating physical function and fatigue should minimize risk of random findings. Another clinically recognised method is to decide treatment effect by numbers needed to treat (NNT). It can be calculated when a trial has a binary outcome, such as the portion of patients having good or poor quality of life[67]. It is uncommon in HRQL research, probably because clinical trials evaluating treatment rarely have HRQL measured binarily as a primary outcome. Still, if for example, two interventions for dysphagia are compared and evaluated with HRQL, instead of presenting mean scores and concluding that a clinically relevant difference between groups exists, one could calculate the number of patients needed to treat for one patient to gain a 10-point benefit.

*Response Shift*

Response shift is most likely to be present when measurements are made before and after major treatment[83]. As patients start to recover from major cancer surgery, such as oesophagectomy, it is possible that they cope with the disease and report better HRQL than expected[168]. In Study III, where measurements were made before and after treatment, the presence of response shift might have diluted our results. However, detecting response shift is difficult, and it was described by Fayers and Hays as a dolphin swimming in the ocean and every now and then emerging to breathe; everyone (every researcher) knows it is there and can witness when it emerges from the water, but when and where it is going to surface exceeds our current understanding[169]. Study I also included repeated measurements, and our findings of a constantly low HRQL might even be a deteriorated HRQL.

*Timing*

The time point of six months to assess HRQL in all four studies was carefully chosen, based on previous literature and an attempt to slip between confounding of recovery and influence by tumour recurrence[6,11,60,124,130-132,140,141]. A benefit from choosing a later time point is that the disease-free patients are more likely to have recovered to a large extent and patients with recurrences are more likely to have developed measurable changes in HRQL. But since it is clinical research, choosing an earlier time point might lead to earlier awareness and thereby be of greatest importance.

# FINDINGS AND EXPLANATIONS

## STUDY I – LONG TERM HRQL

The long term (three years) HRQL seems to be comparable to levels measured six months postoperatively, and generally worse than the general population. Certain aspects seem to be more commonly improved, such as fatigue and pain, while reflux and dysphagia seem to increase in the majority of patients. The sums of the weaknesses discussed above are the use of 10 points as cut-off both for improvement and deterioration and a possible small sample. Previous literature supports some of the findings in the study[6,124,126,129,132]. Fatigue has been seen to improve in the long term, which is in line with our findings, but still the level of fatigue is higher than that in the general population. In contrast, dysphagia has also decreased in previous studies[6,128], although our patients reported an increase. Some biological mechanisms are likely to explain the findings. The improvement in fatigue and pain might reflect that patients have not recovered fully six months after surgery. Dysphagia is likely to be due to a local recurrence or a postoperative stricture, but since all patients were alive three years postoperatively, and recurrences are known to come quickly, a possible explanation is strictures. The deteriorated reflux is a common effect of the operation.

## STUDY II – INFLUENCES ON HRQL

The main finding was associations between tumour characteristics and poor HRQL, but rarely with patient characteristics, including age, sex and BMI, except for comorbidities, which negatively affected HRQL. Methodological issues were discussed above, and one issue is that our dichotomizing might not be optimal. Likewise our grouping of for example comorbidities might have been too rough. There are no previous studies with a main aim to evaluate differences between patients´ characteristics and tumour characteristics among oesophageal cancer patients. Some explanations are likely for the findings. The lack of differences between sexes and age groups might suggest that HRQL in cancer patients mainly depends on their disease. Furthermore, ongoing projects, such as the GENEQOL might reveal interesting information[81]. The findings of associations between comorbidities and poorer HRQL should not surprise any clinician, since all diseases have symptoms, and patients with additional diseases should be more likely to suffer from poorer health. The associations between a more advanced tumour stage and poorer HRQL might reflect a more extensive operation, complications and poorer prognosis. Information about alcohol intake and smoking habits might explain both the differences between histological types and different locations, since a higher tumour is more likely to be a SCC than an AC.

## STUDY III – CHANGES IN HRQL AND SURVIVAL

The main finding of the study was an increased risk of mortality among patients with more problems with dyspnoea at baseline and among patients who did not recover physical function six months after surgery. There was also an increased mortality risk in patients reporting lack of recovery from fatigue or pain after six months.

The major weaknesses are that the cohort is based on a single centre with a possible source of selection bias, a relatively small sample, gastric patients were also included, and the time point for baseline.

A previous study has found baseline dyspnoea as prognostic for major morbidity after oesophagectomy[134]. Since only few studies have investigated changes in HRQL and none in oesophageal cancer patients, the results were compared to other cancer patients. Interestingly, pain has been found associated with survival in both prostate cancer patients and head and neck cancer patients, as well fatigue has been found associated with survival in patients with prostate cancer[146,170]. Findings of an association with survival for changes between baseline and follow-up suggest that HRQL aspects mirror the natural course of disease with quick lethal recurrences. The associations between baseline dyspnoea could both be a random finding and a true finding, reflecting an influence of factors that might affect prognosis such as comorbidities or the general health condition.

## STUDY IV – POSTOPERATIVE HRQL AND SURVIVAL

The main findings of Study IV were the associations found between poor HRQL six months after surgery and the risk of mortality. The risk ranged from a 29% increase for patients with oesophageal pain to 69% for patients with loss of appetite and dysphagia.

The weaknesses discussed above are mainly the dichotomizing of HRQL based on raw answers and the time point of six months.

There is only one previous similar study[147] which investigated three month postoperative HRQL in relation to survival. Our findings are in line with that study, in that the previous study found social function and pain to be prognostic. The findings in this study of more HRQL items being prognostic, compared to what was found in their study, could be explained by the fact that patients after three months are still recovering from surgery to a larger extent than they are after six months.

A biological mechanism explaining the findings is a higher level of tumour recurrences in the group with poorer HRQL.

# CONCLUSIONS

Some conclusions can be drawn from the four studies included in the thesis, namely:

- Patients who undergo curative surgery for oesophageal cancer are unlikely to recover in most aspects of HRQL within three years.

- A more advanced oesophageal tumour stage negatively affects postoperative role function, loss of appetite and eating difficulties.

- A lower location of the oesophageal tumour might come with better postoperative global quality of life and physical function, as well as less dyspnoea and coughing.

- Patients with oesophageal adenocarcinoma might have better postoperative global quality of life, physical function, role function as well as less fatigue, pain, dyspnoea and coughing, compared to patients with oesophageal squamous cell carcinoma.

- Comorbidity among oesophageal cancer patients negatively affects postoperative physical function, role function, fatigue and diarrhoea.

- Age, sex and BMI do not affect postoperative HRQL in oesophageal cancer patients.

- Baseline dyspnoea could be prognostic for survival in groups of oesophageal cancer patients undergoing curatively-intended treatment.

- Oesophageal cancer patients without lack of recovery of physical function or persistent problems with fatigue and pain after curatively-intended treatment could be running an increased risk of mortality.

- Oesophageal cancer patients with a poor postoperative global quality of life, physical function, social function, or patients being symptomatic from fatigue, dyspnoea, loss of appetite, dysphagia or oesophageal pain run a higher risk of mortality.

# IMPLEMENTATIONS

A researcher needs to process and interpret results so as to provide clinically useful information, otherwise there is a risk of research becoming merely an academic exercise[171]. Our main aim, to clarify association between postoperative HRQL and survival, has been achieved and our main findings were in line with our hypothesis. If this has been the invitation to break down our aims and speculated benefits of the results to a clinically useful level, then the patients themselves have been the motivators. Oesophageal cancer patients´ and their relatives' experience of a patient's step from being healthy to being close to death are very rapid[5,172]. It also seems to happen without warning although the delay in diagnosing is partly due to unawareness of severity in symptoms[4]. There is therefore a huge need of information about the expected outcome of the operation and recovery time[173]. The results of the four studies are interpreted below in relation to our three aims regarding how HRQL could be implemented in the clinical prognostic jigsaw.

**Clinical Warning Signs and Prognosis.**
When meeting a patient, a doctor can, with support from Studies III and IV, use poor or deteriorated HRQL measures as a reason to bring up a discussion of a possible poor prognosis. Certain aspects such as generally poor HRQL, failure to recover physical function, increased pain or fatigue, deserve attention. Our findings are not likely to improve the individual prognosis but possibly the accuracy of it.

**Further Knowledge for Improvement of Follow-ups**
The most common initial oesophageal cancer symptom is dysphagia. The findings of recurrent dysphagia in a major part of the long term survivors in Study I, in conjunction with the lack of relevance in changes of it in Study III, support the claim that dysphagia is more likely to be due to stricture than to recurrence. Still, dysphagia could be a sign of a recurrence, a few patients in Study IV had severe dysphagia, and the hazards ratio of mortality in that group of patients was among the highest. Therefore, dysphagia needs to be followed up. Symptoms such as fatigue, and difficulties in handling daily activities due to physical limits should prompt clinical attention according to Studies III and IV. Study II improves the knowledge of the effect of
comorbidities on HRQL, which points to the need for physicians to work multidisciplinarily, with the aim of optimizing for example the lung or heart function. Likewise, if comorbidities are not present in a patient with poor HRQL, Study IV indicates that doctors should actively seek for recurrence or other explanations, instead of accepting the presence of severe fatigue in older patients.

**To Facilitate Basic Data for Informed Consent Treatment**

Even if the aim of surgical operations for oesophageal cancer is to cure, information on side effects and their duration is important. Study I verifies that side effects remain for a long period of time, while Studies III and IV suggest that deterioration in certain HRQL aspects should raise the issue of limitation in treatment. Study II reminds us of relativity in age, a healthy 80- year-old might tolerate surgery better than an otherwise poorly 60-year-old.


Cartoon reproduced with kind permission of *growing old disgracefully*.

# FUTURE RESEARCH

There are several possible issues for future research in the area of this thesis. Some methodological issues have been sparsely explored and deserve attention, such as how to present HRQL, especially in other ways than as mean scores. Alternatives for dichotomizing the responses need to be further explored, as well as alternative methods for scoring; presentation including weighting of questions and alternative response alternatives would be interesting.

It would also be interesting to study which outcomes should be analysed at what time point, so as to avoid multiple tests and random findings. Likewise, it would be interesting to find out how differences in generic instruments such as SEIQoL, or comorbidities such as depression, could explain variations in individual baseline HRQL, as well as the longer term outcome.

Closely related to methodological issues, it is important to study how HRQL could be implemented in daily clinical care. Today, clinicians usually appreciate the importance of HRQL outcomes, but not how to use them[171]. Research addressing clinical implementations should have priority.

Another interesting and sensitive topic is to search for biological explanations for subjective symptoms such as tumour recurrence. This type of studies would possibly address the problems with lack of clinical use, since results might easily be understood by clinicians. Other interesting biological mechanisms are the individual comorbidities, or rather their self-rated severity of the disease. In patients with SCC in the larynx, pre-treatment levels of haemoglobin have been found to be prognostic[174] and likewise, potential influence of levels of haemoglobin and inflammatory markers, including tumour factors and CRP, would be interesting to evaluate among oesophageal cancer patients[127].

The often claimed reason for association between HRQL and mortality is tumour recurrences, but this remains to be proven.

# POPULÄRVETENSKAPLIG SAMMANFATTNING

## BAKGRUND

Cancer i matstrupen, esofagus, utgör i Sverige endast 1% av alla cancerfall, vilket motsvarar ca 400 nya fall per år. Cancern är vanligare globalt sett och av någon okänd andledning ökar den i Europa och Sverige. Eftersom matstrupen ligger djupt skyddad innanför bröstkorgen och är eftergivlig i sin natur kan cancern utvecklas ganska ostört utan upptäckt.

Sväljningssvårigheter och viktnedgång är de vanligaste symptomen. När en patient väl får sin diagnos har tumören ofta vuxit sig stor lokalt och även spridit sig som fjärrmetastaser (dottertumörer).

Den etablerade behandlingen med botande syfte är kirurgi. Operationen är omfattande och påfrestande för patienten och den efterföljs ofta av allvarliga komplikationer, varför patienten som opereras bör vara i god fysisk form. Tyvärr är det bara cirka en fjärdedel av patienterna som både är i fysisk form och har en tumör som är i ett så pass tidigt stadium att den kan opereras bort. För övriga patienter är prognosen mycket dålig med en förväntad överlevnad på ett år. Trots lyckad operation är det bara cirka 30% som överlever fem år (svenska data). Ett år efter operation har ungefär en tredjedel fått återfall, och deras förväntade överlevnad är då endast några månader.

Hälsorelaterad livskvalitet saknar en tydlig gemensam definition men de flesta är överens om att det är multidimensionellt och omfattar fysiska, emotionella och sociala aspekter av hälsa utifrån patientens perspektiv. Livskvalitet mäts ofta genom att en patient besvarar en enkät med frågor om symptom och funktioner. Hos cancerpatienter finns flera biologiska förklaringar för påverkan på livskvaliteten. Dels påverkar cancern patientens upplevda trötthet och smärta och dels påverkar kirurgisk behandling patientens svälj- och magtarmfunktion, med till exempel halsbränna och diarre som följd.

Tidigare studier har visat att patienter som opereras för matstrupscancer behöver minst sex till tolv månader på sig för återhämtning avseende livskvaliteten, men väldigt lite är känt om den långsiktiga livskvaliteten. Likaså är det okänt huruvida livskvaliteten efter operation, eller förändringar i livskvalitetsmått under perioden före till efter operation, är kopplade till överlevnad.

## METODER

Avhandlingen omfattar fyra delarbeten. **Delarbete I, II och IV** är baserade på ett svenskt kirurgiskt forskningsregister för matstrupscancer (SECC-registret), omfattande totalt 616 patienter. Detta motsvarar ca 90% av alla patienter som opererades i Sverige under perioden 2001 till 2005.

**Delarbete III** är baserat på en databas byggd på patienter från ett centra i Bristol, England, där hitills 260 matstrupscancerpatienter har inkluderats. I samtliga arbeten har livskvalitet mätts med enkäter utvecklade av ett europeiskt nätverk för forskning och cancerbehandling, European Organisation for Research and Treatment of Cancer (EORTC). EORTCs har en enkät för generella cancersymptom (QLQ-C30) samt en specifik enkät för matstrupscancersymptom (QLQ-OES18). Ett exempel på en av de fem frågorna som ingår i begreppet ”fysisk funktion” är –”Har du haft problem med att ta en kort promenad under den senaste veckan?” Svarsalternativen är: ”Inte alls”, ”Lite”, ”En hel del” samt ”Mycket”. När patienten svarat på samtliga frågor i enkäten omvandlas svaren enligt en manual till ett värde mellan 0 och 100, där ett högt värde för funktioner innebär att patienten har bra funktion medan ett högt värde för symptom betyder att patienten har mycket problem med symptom.

I **delarbete I** jämfördes livskvaliteten sex månader efter operation med livskvaliteten tre år efter operation. Medelvärdet för hela gruppen räknandes vid bägge tillfällena. Om minst en 10 poängs skillnad (skala 0-100) mellan tidpunkterna hittades, tolkades det som kliniskt intressant.
I **delarbete II** undersöktes eventuella samband mellan livskvalitet och olika patientrelaterade faktorer såsom kön, ålder, andra sjukdomar och övervikt samt cancerrelaterade faktorer såsom tumörstadium, tumörens läge i matstrupen och tumörens vävnadstyp. För att kunna justera för störfaktorer, samt räkna ut en skillnad i risk för bra eller dålig livskvalitet med relativa risker, grupperades patienternas svar i ”bra” eller ”dålig” funktion respektive om betydande symptom förelåg eller inte.
I **delarbete III** utvärderades en eventuell koppling mellan överlevnad och skillnader i livskvaliet före och efter behandling med botande syfte. En skillnad på 10 poäng (skala 0-100) mellan värdet före och efter behandlingen klassades som kliniskt intressant. Samband mellan kliniskt intressanta skillnader och överlevnad testades i särskilda statistiska analyser.
I **delarbete IV** utvärderades det om skillnader i livskvalitet efter operation var kopplat till överlevnad. Relativa risker räknades och samma gruppering som i delarbete II användes.

## RESULTAT

### Delarbete I

Inga kliniskt relevanta skillnader i hälsorelaterad livskvalitet kunde påvisas mellan sex månader och tre år efter operation. Det fanns dock en tendens till minskad trötthet, aptitförlust och diarré samt försämrad sväljförmåga i den senare utvärderingen. Jämfört med Sveriges befolkning hade patienterna sämre social funktion och mer trötthet, illamående och diarré. Tabeller över andelen patienter som hade förbättrats, varit stabila respektive försämrats mellan mätpunkterna visade att majoriteten av patienterna varit stabila i sin livskvalitet.

**Delarbete II**
Patientrelaterade faktorer såsom kön, ålder och övervikt inverkade inte nämnvärt på livskvaliteten medan samtidig förekomst av andra sjukdomar påverkade den negativt. Bland de cancerrelaterade faktorerna visade sig vävnadstypen och tumörstadiet vara kopplat till livskvaliten efter operation.

**Delarbete III**
Patienternas självupplevda andningsbesvär före den i botande syfte genomgågna behandlingen visade sig vara kopplat till överlevnaden. Även skillnader mellan livskvalitet före och efter operation var kopplat till överlevnad. Patienter som inte återfick sin fysiska funktion eller som rapporterade en ökad trötthet eller smärta hade sämre chans till överlevnad.

**Delarbete IV**
Patienternas livskvalitet sex månder efter operation visade sig vara kopplad till chansen för överlevnad. Om patienten hade klassats ha dålig fysisk funktion befanns en 56% ökad risk för död jämfört med personer som hade god fysisk funktion.

## DISKUSSION

**Delarbete I**
Medelvärdet för hela grupper kan vara missvisade på grund av att få patienter med mycket avvikande värden får stort inflytande. Likaså kan hälften ha förbättras och andra hälften förämrats lika mycket, med resultatet att medelvärdet förblir oförändrat. Även gränsen 10 poäng kan ha varit suboptimal då tidigare metodologiska studier har visat att förbättringar kan märkas tidigare än försämringar.

**Delarbete II och IV**
I analyserna användes en metod för att klassa patientens livskvalitet som ”bra” eller ”dålig”, vilket kan ha medfört viss felklassifikation. Troligast har sådan felklassifikation spätt effekter snarare än att den kan förklara positiva samband. Tidpunkten sex månader efter operation bedömdes som optimal i glappet mellan påverkan från ofullständig återhämtning av sin livskvalitet och påverkan från återfall i cancern.

**Delarbete III**
Vid upprepade mätningar kan värdena påverkas av att en patient ändrat uppfattning om svårighetsgraden av exempelvis smärta, d.v.s. den smärta som patienten nu klassar som svår är ingenting mot vad den var innan operation. Detta medför att patienten inte klassar sin smärta lika högt på skalan, d.v.s. denne svarar ”Lite” istället för ”En hel del”. Om detta har skett kan vi inte svara på, men om det gjort det har det sannolikt spätt ut resultatet. Vidare kan det ha funnits bättre alternativ till den gräns vi använt som kliniskt relevant (10 poäng).

## SLUTSATSER OCH TILLÄMPNINGSOMRÅDEN

Förändringar i livskvalitet, eller livskvalitet uppmätt efter operation bland patienter med matstrupscancer verkar vara kopplat till överlevnad. En tänkbar förklaring är att patienter som har sämre livskvalitet kan ha drabbats av återfall i cancern eller har andra sjukdomar som påverkar möjligheten till återhämtning. Denna information skulle man kunna använda i det kliniska mötet mellan doktor och patient. Redan innan operation kan man ge patienten en realistisk bild av återhämtningstiden och den framtida livskvaliteten, och om en patient vid uppföljning efter operation uppvisar dåliga värden avseende livskvalitetsmått skulle man kunna se det som en öppning för att diskutera eventuella behandlingsbegränsningar, samt en eventuellt dålig prognos, med patient och anhöriga. Vid en sådan situation måste man dock ta hänsyn till att andra sjukdomar förefaller påverka livskvaliteten och doktorer måste sannolikt samverka över specialiteterna för att optimera behandlingen av patientens andra sjukdomar i syfte att öka livskvaliteten under den kvarvarande tiden i livet.

Vidare verkar inte kön, ålder och övervikt påverka livskvaliteten efter operation, vilket innebär att man som doktor inte bör nöja sig med exempelvis ålder som förklaring till en dålig livskvalitet. Istället bör man leta efter andra sjukdomar eller cancerfaktorer som förklaring.

Livskvalitet har av denna avhandling att döma en viktig roll att fylla i det kliniska pusslet avseende att få ihop rätt behandling och en realistisk prognos.

Nyckelord: Livskvalitet, HRQL, esofaguscancer, prognostisk faktor, överlevnad

# ACKNOWLEDGEMENTS

Denna avhandling har vuxit fram tack vare många personers insatser, jag vill uppmärksamma några personer som betytt mycket för mig längs vägen:

Först och främst, denna avhandling hade inte funnits om inte **patienter, kliniker och forskare** hade hjälpt till att skapa SECC-registret och the Upper gastrointestinal database. Otroligt tack för er värdefulla insats!

**Pernilla Lagergren**, min huvudhandledare. En bättre handledare och guide till forskningens fascinerande värld hade inte varit möjlig! Genom stort och smått har du glatt, entusiastiskt och tålmodigt lotsat mig. Din inbjudande attityd som får en att tro att forskningen behöver en och din fingertoppskänsla för forskning är imponerande! Tack svar på såväl stora som små frågor, hembakta muffins och samtal om livets vardagligheter!

**Jesper Lagergren**, min bihandledare tillika brilliant ledare av forskargruppen UGIR. Din nyfikna rastlöshet i väntan på resultat är fascinerande och motiverande. Likaså din vilja att läsa manus och ge feedback, ta dig an nya idéer och driva gruppens kunskapsläge framåt. Ditt mål är att UGIR skall leva utan dig, visst det går säkert, men aldrig med samma fart och iver.

**Jane M Blazeby**, co supervisor. Your knowledge is as impressive as your willingness to share it. Thanks for expecting a lot, always reminding me to "read up" on something as well as for being a critical mind when reading manuscripts, and of course for outstanding hospitality while I was in Bristol.

**Chris Metcalfe and Kerry Avery**, co authors. Thanks for generous sharing of your knowledge and all the help with practical issues in Bristol.

**Eja Fridsta**, den kloka organisatören bakom SECC. Du har en fantastisk förmåga att ta upp ett oväntat intressant ämne vid kopiatorn, vilket väcker tankar och skapar trivsel. Likaså är din talang att hitta ett nytt angreppssätt när man kört fast beundransvärd.

**Margrete Gellervik**, forskningssekreterare och adminstratör. Tack för all adminstrativ hjälp från början till slut, men främst för att du är intresserad av människorna bakom forskningsresultaten och för alla dina sociala insatser för UGIR.

**Ulrika Eriksson**, forskningssekreterare. Främst för ditt glada skratt som sprids i korridoren som ett skönt avbrott, men likaså för din talang att informera gruppen och kommunicera resultat utåt.

The late, **Maud Marsden**, for excellent lingvistic corrections of all manuscript.

**Kathy Gow Sjölund,** för språkgranskning av avhandlingen. Du tackade tveklöst ja med kort varsel och stor iver, jag är otroligt tacksam!

Tidigare och nuvarande medlemmar i ESOGAR/UGIR: **John Blomberg, Evangelos Chandanos, Konstantinos Charonis, Hanna Dahlstrand, Maryam Derogar, Emma Eklund, Catarina Jansson, Yulan Lin, Mats Lindblad, Anna Lindam, Yunxia Lu, Rickard Ljung, Hedvig Löfdahl, Helena Nordenstedt, Lena Martin, Jenny Oddsberg, Magdalena Plecka Östlund, Dan Razavi, Ioannis Rouvelas, Maartje van der Schaaf, Richard Shore, Tomas Sjöberg Bexelius, Krister Sjödahl, Martin Rutegård.** Från den dag då Tomas förmedlade kontakten med gruppen har ni alla funnits där för allt från dagligt kaffeprat via spontana kunskapsutbyten till stora inspirerande seminarium. Jag är stolt över att tillhöra en grupp som denna, det är ett sant privilegium!

**Sari Ponzer**, extern mentor. Vi har inte haft mycket kontakt, men när det gäller dig, räcker minnet av hur du leder möten, driver frågor och hinner med allt som inspiration!

Akutkliniken, som styrs av det kompletterande radarparet **Olle Lindström** och **Per Lindmarker** genom modernt lyhört strategiskt ledarskap. Mina närmaste chefer och schemaläggare som varit generösa i planeringar och uppmuntrat forskning **Latifa Rulu, Anna Eriksson, Martin Holzmann, Per Skoglund** och **Ann-Sofie Jansson Rehnberg**. Min handledare **Per Svensson** för aktiv handledning och ständig support. **Margita Berg** för att du blir varm när du talar om statistik och för att du anordnade en predisputation, Likaså, alla mina kollegor som gör var dag (natt) till ett rent nöje, specialistläkare: **Kerstin Adamsson, Muntasir Al Haya, Gunilla Caneman, Karin Ekenbäck, Lars- Göran Ekman, Anna Ekvall, Magdalena Elinder, Jessica Fryckstedt, Jan Hansén, Oskar Hägglund, Anna Jansson, Hans Johnsson, Sabir Kerimov, Ursula Kloszewska, Ulf Ludvigs, Mahmood Mahmood, Anette von Rosen, Peter Sand, Per Skoglund, Annika Smårs, Lars Westerberg, Jan Östergren**, ST-läkare; **Johannes Arpegård, Tamara Barlow, Einar Eriksson, Umut Heilborn, Elisabeth Johannesson, Charlotte Kaviani, Cecilia Lundström, Mikael Nilsson, Eva Piscator, Linda Rydén Lujan, Jesper Scholander, Helena Sundberg, Ulrika Wallgren**, underläkare**; Lisa Arnetz, Peter Eisenlauer, Cecilia Enander, Ingrid Fugmann, Daniel Karlsson, Jacqueline Khorami, Björn Kolsrud, Semra Köylüoglu, Magnus Lundbäck, Anna Nagander, Maryam Nirvani, Manar Radif, Linn Ryberg, Ida Wahlström, Michael Wilczek, Katja Wyss, Joel Ohm, Jonas Lundmark, Mikael Birge, Robert Saxelin, Natalia Stern, Sofia Ygberg**. Likaså **ALLA övriga medarbetare på akutkliniken** som varmt tagit emot mig från första dagen. Jag har många gånger fascinerats av de snabba växlingarna mellan allvarliga och oseriösa diskussioner och är oerhört tacksam för alla kloka råd jag fått genom åren!

”KTH-gänget” med hangarounds; **Anna och Joel, Björn och Sofie, Lina och Gustaf, Tomas och Sandra, Hanna och Jonas, Henke och Karro, Jenny och Niklas, Anna och Jesper, Maria och Daniel** samt KTH-juniorerna **Filip, Olivia, Hugo, Oliver, och Emilia**. Er finns mycket att tacka för, från allehanda upplevelser med Smirnoff på pumpflaska och ”Booty dance” via Närs-fyren, Gagnef, Sandön, Lybeck och Paris till hummerskivor. Tack för att ni alltid ställelr upp på allt från ständigt husbygge till impellerleverans, men främst för ni är just vänner som ger glädje och perspektiv.

**Calle och Carro** med föräldrar och trillingar. Med er kan man aldrig veta vad man skall lära sig näst, aborrrensning eller frakt av får medelst eka. För att ert inspirerande dårskap sällan vet gränser men alltid hittar sin tilltalande lösning!

**Anna och Thomas med Agnes**. För alla otaliga gånger har vi spontant dykt upp hos er, blivit serverade en utmärkt middag med dessert, underhållits av trolleri och fått ro att läsa tidningar.

**Emma**, vår eminenta hustomte! För allehanda insatser och för ditt ständiga leende!

**Erik och Marianne, Tomas och Inga, Jan och Monica**, det spelar ingen roll om det var länge sen sist, era famnar är alltid lika varma !

**Mamma Hjördis och pappa Bert,** för erat eviga intresse för vad jag än gör och för outstanding ”internetservice” . För att ni accepterat ”kan själv” och låtit mig vingla fram min egen väg utan att låta mig cykla i diket!

**Sofia**, älskade syster yster, ingen är så klok som du samtidigt som du ständigt förvånar mig med både din envishet och din humor. Och maken **Christoffer**, för din matlagning och dina ständiga infall, må det bli fler skidresor med hepp-hepp-hepp!

Mormor **Gerda** för bästa tänkbara sommarlov som barn och för att du tillsammans med **Henrik**, visar hur man lever livet med livskvalitet när man är över 85år. Jag vill bli som du! Och morfar **Knut**, idag hade du varit stoltast!

Förvärvade kära släktingar; **Lars och Cristine med Viktor, Josefin och John samt Lena med Emma och Johanna**, naturligtvis för förstaklassig ALL-inclusive service när än man dyker upp. Men också för allt kul, de ständigt nya projekten och för att man alltid kan lita på att folkbildningen i någon mån fortgår, även om det resulterar i baggsanering. Dessutom extra tack för ”kusintid” med Jackie som möjliggjort skrivandet.

**Margareta och Nils-Åke, Jens och Marie med Hanna och Marcus, Katarina och Jesper med Amanda och Henrik**, för alla trevliga sammankomster under åren, för ert intresse för mitt arbete men främst för att ni ihärdigt hållt kontakten när vi varit urusla på det.

**Inger och Sven**, i varmt minne! Det var ni som en gång fick mig att förstå tjusningen med forskning och initierade den. Jag saknar ert eviga tålamod och era underfundiga ärligheter.

**Fredrik**, min älskade! För att du respekterar grundande beslut och dissekerar ogrundande, för dina konsekvensanalyser och för din uppfinningsrikedom men också för dina rena stolligheter som skapar kaos och medför att man aldrig kan ana hur en dag skall sluta. Tack för att du rubbar mina cirklar! Purr!

Sist och minst, **Jaqueline**, älskade dotter! Än vet du inte mycket om livets bestyr men jag vet att dina spontana avbrott för att påminna om hur nödvändigt (och gott) det kan vara äta vinbär just nu påminner mig om något av det viktigaste i livet, att njuta just nu!

Slutligen har jag varit generöst finanserad och erbjudits fin utbildning av Karolinska Institutet samt haft möjlighet att genomföra inspirerande forskningsresor tack vare Radiumhemmets forskningsfonder. Tack!

# REFERENCES


1. Laviano A, Meguid MM, Rossi-Fanelli F: Cancer anorexia: clinical implications, pathogenesis, and therapeutic strategies. *Lancet Oncol* 2003 (4): 686-94
2. Fearon KC, Voss AC, Hustead DS: Definition of cancer cachexia: effect of weight loss, reduced food intake, and systemic inflammation on functional status and prognosis. *Am J Clin Nutr* 2006 (83): 1345-50,
3. Stewart GD, Skipworth RJ, Fearon KC: Cancer cachexia and fatigue. *Clin Med* 2006 (6): 140-3
4. Watt E, Whyte F: The experience of dysphagia and its effect on the quality of life of patients with oesophageal cancer. *Eur J Cancer Care* 2003 (12): 183-93
5. Kirby JD: Quality of life after oesophagectomy: the patients' perspective. *Dis Esophagus* 1999 (12): 168-71
6. Lagergren P, Avery KN, Hughes R, et al: Health-related quality of life among patients cured by surgery for esophageal cancer. *Cancer* 2007 (110): 686-93
7. Salo JC: Surgery for esophageal cancer: quality of life matters. *Ann Surg Oncol* 2009 (17): 12-3
8. Sundelof M, Ye W, Dickman PW, et al: Improved survival in both histologic types of oesophageal cancer in Sweden. *Int J Cancer* 2002 (99): 751-4
9. Jobe BA, Thomas CR, Hunter JG. (2009) Esophageal Cancer: principles and practice. New York: Demos Medical Publishing
10. Nishihira T, Sayama J, Ueda H, et al: Lymph flow and lymph node metastasis in esophageal cancer. *Surg Today* 1995 (25): 307-17
11. Dresner SM, Griffin SM: Pattern of recurrence following radical oesophagectomy with two-field lymphadenectomy. *Br J Surg* 2000 (87): 1426-33
12. Daly JM, Fry WA, Little AG, et al: Esophageal cancer: results of an American College of Surgeons Patient Care Evaluation Study. *J Am Coll Surg* 2000 (190): 562-72
13. Enzinger PC, Mayer RJ: Esophageal cancer. *N Engl J Med* 2003 (349): 2241-52
14. Siewert JR, Stein HJ, Feith M, et al: Histologic tumor type is an independent prognostic parameter in esophageal cancer: lessons from more than 1,000 consecutive resections at a single center in the Western world. *Ann Surg* 2001 (234): 360-9
15. Parkin DM, Bray F, Ferlay J, et al: Global cancer statistics, 2002. *CA Cancer J Clin* 2005 (55):74-108

16. Vizcaino AP, Moreno V, Lambert R, et al: Time trends incidence of both major histologic types of esophageal carcinomas in selected countries, 1973-1995. *Int J Cancer* 2002 (99): 860-8
17. Trivers KF, Sabatino SA, Stewart SL: Trends in esophageal cancer incidence by histology, United States, 1998-2003. *Int J Cancer* 2008 (123): 1422-8
18. Bollschweiler E, Wolfgarten E, Gutschow C, et al: Demographic variations in the rising incidence of esophageal adenocarcinoma in white males. *Cancer* 2001 (92): 549-55
19. Lindblad M, Rodriguez LA, Lagergren J: Body mass, tobacco and alcohol and risk of esophageal, gastric cardia, and gastric non-cardia adenocarcinoma among men and women in a nested case-control study. *Cancer Causes Control* 2005 (16): 285-94
20. Cook MB, Dawsey SM, Freedman ND, et al: Sex disparities in cancer incidence by period and age. *Cancer Epidemiol Biomarkers Prev* 2009 (18): 1174-82
21. Rutegard M, Nordenstedt H, Lu Y, et al: Sex-specific exposure prevalence of established risk factors for oesophageal adenocarcinoma. *Br J Cancer* 2010 (103): 735-40
22. The National Board of Health and Welfare (Socialstyrelsen). Cancer Incidence in Sweden 2008. Access date, 4 April, 2010: http://www.socialstyrelsen.se/uppfoljning/statistik/statistikdatabaser
23. Lagergren J, Bergstrom R, Nyren O: Association between body mass and adenocarcinoma of the esophagus and gastric cardia. *Ann Intern Med* 1999 (130): 883-90
24. Brown LM, Swanson CA, Gridley G, et al: Adenocarcinoma of the esophagus: role of obesity and diet. *J Natl Cancer Inst* 1995 (87): 104-9
25. Brown LM, Hoover R, Silverman D, et al: Excess incidence of squamous cell esophageal cancer among US Black men: role of social class and other risk factors. *Am J Epidemiol* 2001 (153):114-22
26. Ye W, Held M, Lagergren J, et al: Helicobacter pylori infection and gastric atrophy: risk of adenocarcinoma and squamous-cell carcinoma of the esophagus and adenocarcinoma of the gastric cardia. *J Natl Cancer Inst* 2004 (96): 388-96
27. Javle M, Ailawadhi S, Yang GY, et al: Palliation of malignant dysphagia in esophageal cancer: a literature-based review. *J Support Onco*l 2006 (4): 365-73, 379
28. Bird-Lieberman EL, Fitzgerald RC: Early diagnosis of oesophageal cancer. *Br J Cancer* 2009 (101): 1-6
29. Laviano A, Meguid MM, Inui A, et al: Therapy insight: Cancer anorexia-cachexia syndrome--when all you can eat is yourself. *Nat Clin Pract Oncol* 2005 (2): 158-65
30. van Vliet EP, Heijenbrok-Kal MH, Hunink MG, et al: Staging investigations for oesophageal cancer: a meta-analysis. *Br J Cancer* (98): 547-57

31. AJCC, American Cancer Society. AJCC Cancer Staging Manual. 5th edition. Philadelphia, Lippincott- Raven, 1997
32. Rouvelas I, Zeng W, Lindblad M, et al: Survival after surgery for oesophageal cancer: a population-based study. *Lancet Oncol* 2005 (6): 864-70
33. Barnett SA, Rizk NP: Randomized clinical trials in esophageal carcinoma. *Surg Oncol Clin N Am* 2010 (19): 59-80
34. Malthaner RA, Collin S, Fenlon D: Preoperative chemotherapy for resectable thoracic esophageal cancer. *Cochrane Database Syst Rev 3*: 2006 CD001556
35. Wu PC, Posner MC: The role of surgery in the management of oesophageal cancer. *Lancet Oncol* 2003 (4): 481-8
36. Earlam R: An MRC prospective randomised trial of radiotherapy versus surgery for operable squamous cell carcinoma of the oesophagus. *Ann R Coll Surg Engl* 1991 (73): 8-12
37. Badwe RA, Sharma V, Bhansali MS, et al: The quality of swallowing for patients with operable esophageal carcinoma: a randomized trial comparing surgery with radiotherapy. *Cancer* 1999 (85): 763-8
38. Earlam R, Cunha-Melo JR: Oesophageal squamous cell carcinoma: I. A critical review of surgery. *Br J Surg* 1980 (67): 381-90
39. Stahl M, Stuschke M, Lehmann N, et al: Chemoradiation with and without surgery in patients with locally advanced squamous cell carcinoma of the esophagus. *J Clin Oncol* 2005 (23): 2310-7
40. Bedenne L, Michel P, Bouche O, et al: Chemoradiation followed by surgery compared with chemoradiation alone in squamous cancer of the esophagus: FFCD 9102. *J Clin Oncol* 2007 (25): 1160-8
41. Cooper JS, Guo MD, Herskovic A, et al: Chemoradiotherapy of locally advanced esophageal cancer: long-term follow-up of a prospective randomized trial (RTOG 85-01). Radiation Therapy Oncology Group. *Jama* 1999 (281): 1623-7
42. al-Sarraf M, Martz K, Herskovic A, et al: Progress report of combined chemoradiotherapy versus radiotherapy alone in patients with esophageal cancer: an intergroup study. *J Clin Oncol* 1997 (15): 277-84
43. Arnott SJ, Duncan W, Gignoux M, et al: Preoperative radiotherapy for esophageal carcinoma. *Cochrane Database Syst Rev*: 2005 CD001799
44. Bosset JF, Gignoux M, Triboulet JP, et al: Chemoradiotherapy followed by surgery compared with surgery alone in squamous-cell cancer of the esophagus. *N Engl J Med* 1997 (337): 161-7
45. Lerut T, Coosemans W, Decker G, et al: Surgical techniques. *J Surg Oncol* 2005 (92): 218-29
46. Goldminc M, Maddern G, Le Prise E, et al: Oesophagectomy by a transhiatal approach or thoracotomy: a prospective randomized trial. *Br J Surg* 1993 (80): 367-70

47. Hulscher JB, van Sandick JW, de Boer AG, et al: Extended transthoracic resection compared with limited transhiatal resection for adenocarcinoma of the esophagus. *N Engl J Med* 2002 (347): 1662-9
48. Chu KM, Law SY, Fok M, et al: A prospective randomized comparison of transhiatal and transthoracic resection for lower-third esophageal carcinoma. *Am J Surg* 1997 (174): 320-4
49. Jacobi CA, Zieren HU, Muller JM, et al: Surgical therapy of esophageal carcinoma: the influence of surgical approach and esophageal resection on cardiopulmonary function. *Eur J Cardiothorac Surg* 1997 (11): 32-7
50. Hulscher JB, Tijssen JG, Obertop H, et al: Transthoracic versus transhiatal resection for carcinoma of the esophagus: a meta-analysis. *Ann Thorac Surg* 2001 (72): 306-13
51. Rindani R, Martin CJ, Cox MR: Transhiatal versus Ivor-Lewis oesophagectomy: is there a difference? *Aust N Z J Surg* 1999 (69): 187-94
52. Nishihira T, Hirayama K, Mori S: A prospective randomized trial of extended cervical and superior mediastinal lymphadenectomy for carcinoma of the thoracic esophagus. *Am J Surg* 1998 (175): 47-51
53. Baba M, Aikou T, Natsugoe S, et al: Quality of life following esophagectomy with three-field lymphadenectomy for carcinoma, focusing on its relationship to vocal cord palsy. *Dis Esophagus* 1998 (11): 28-34
54. Gemmill EH, McCulloch P: Systematic review of minimally invasive resection for gastro-oesophageal cancer. *Br J Surg* 2007 (94): 1461-7
55. Viklund P, Lindblad M, Lu M, et al: Risk factors for complications after esophageal cancer resection: a prospective population-based study in Sweden. *Ann Surg* 2006 (243): 204-11
56. Fok M, Sham JS, Choy D, et al: Postoperative radiotherapy for carcinoma of the esophagus: a prospective, randomized controlled study. *Surgery* 1993 (113): 138-47
57. Teniere P, Hay JM, Fingerhut A, et al: Postoperative radiation therapy does not increase survival after curative resection for squamous cell carcinoma of the middle and lower esophagus as shown by a multicenter controlled trial. French University Association for Surgical Research. *Surg Gynecol Obstet* 1991 (173): 123-30
58. Xiao ZF, Yang ZY, Miao YJ, et al: Influence of number of metastatic lymph nodes on survival of curative resected thoracic esophageal cancer patients and value of radiotherapy: report of 549 cases. *Int J Radiat Oncol Biol Phys* 2005 (62): 82-90
59. A comparison of chemotherapy and radiotherapy as adjuvant treatment to surgery for esophageal carcinoma. Japanese Esophageal Oncology Group. *Chest* 1993 (104): 203-7
60. Law SY, Fok M, Wong J: Pattern of recurrence after oesophageal resection for cancer: clinical implications. *Br J Surg* 1996 (83): 107-11

61. Soreide JA, Gronbech JE, Mjaland O: Effects and outcomes after palliative surgical treatment of malignant dysphagia. *Scand J Gastroenterol* 2006 (41): 376-81
62. Blazeby JM, Vickery CW: Quality of life in patients with cancers of the upper gastrointestinal tract. *Expert Rev Anticancer Ther* 2001 (1): 269-76
63. Sreedharan A, Harris K, Crellin A, et al: Interventions for dysphagia in oesophageal cancer. *Cochrane Database Syst Rev:* 2009 CD005048
64. Brulde B. (2003) Teorier om livskvalitet (Theories on quality of life). Lund, Studentlitteratur
65. Cella DF, Tulsky DS: Quality of life in cancer: definition, purpose, and method of measurement. *Cancer Invest* 1993 (11): 327-36
66. Osoba D: Translating the science of patient-reported outcomes assessment into clinical practice. *J Natl Cancer Inst* 2007 (Monogr): 5-11
67. Fayers Peter MD. (2007) Quality of life: Assessment, Analysis and Interpretation of Patient-reported Outcomes Great Britain, JOHN WILEY & SONS LTD
68. Cavallin C: Projekt Runeberg, Swensk-Latinsk Ordbok. Access 5 May 2010: http://runeberg.org/swelatin/2/0344.html
69. Rhodes VA, Watson PM: Symptom distress--the concept: past and present. *Semin Oncol Nurs* 1987 (3): 242-7
70. Rhodes VA, McDaniel RW, Matthews CA: Hospice patients' and nurses' perceptions of self-care deficits based on symptom experience. *Cancer Nurs* 1998 (21): 312-9
71. Leventhal HJ, F.E. (1983) Laboratory and field experimentation development of a theory of self regulation; In Behavior science and nursing theory. Mosby, St Louis
72. Armstrong TS: Symptoms experience: a concept analysis. *Oncol Nurs Forum* 2003 (30): 601-6
73. Brenner P, Wrubel, J. (1989) The Primacy of Caring: Stress and Coping in Health and Illness. Menlo Park, California, Addison-Wesley Publishing Co
74. van Wijk CM, Kolk AM: Sex differences in physical symptoms: the contribution of symptom perception theory. *Soc Sci Med* 1997 (45): 231-46
75. Wilson IB, Cleary PD: Linking clinical variables with health-related quality of life. A conceptual model of patient outcomes. *Jama* 1995 (273): 59-65
76. Sprangers MA: Response-shift bias: a challenge to the assessment of patients' quality of life in cancer clinical trials. *Cancer Treat Rev* 22 *Suppl* 1996 (A): 55-62
77. Sousa KH, Kwok OM: Putting Wilson and Cleary to the test: analysis of a HRQOL conceptual model using structural equation modeling. *Qual Life Res* 2006 (15): 725-37

78. Guyatt GH, Ferrans CE, Halyard MY, et al: Exploration of the value of health-related quality-of-life information from clinical research and into clinical practice. *Mayo Clin Proc* 2007 (82): 1229-39
79. Gotay CC, Kawamoto CT, Bottomley A, et al: The prognostic significance of patient-reported outcomes in cancer clinical trials. *J Clin Oncol* 2008 (26): 1355-63
80. Reyes-Gibby CC, Wu X, Spitz M, et al: Molecular epidemiology, cancer-related symptoms, and cytokines pathway. *Lancet Oncol* 2008 (9): 777-85
81. Sprangers MA, Sloan JA, Veenhoven R, et al: The establishment of the GENEQOL consortium to investigate the genetic disposition of patient-reported quality-of-life outcomes. *Twin Res Hum Genet* 2009 (12): 301-11
82. Schwartz CE, Sprangers MA: Methodological approaches for assessing response shift in longitudinal health-related quality-of-life research. *Soc Sci Med* 1999 (48): 1531-48
83. Sprangers MA, Schwartz CE: Integrating response shift into health-related quality of life research: a theoretical model. *Soc Sci Med* 1999 (48): 1507-15
84. Schwartz CE, Bode R, Repucci N, et al: The clinical significance of adaptation to changing health: a meta-analysis of response shift. *Qual Life Res* 2006 (15): 1533-50
85. Schwartz CE, Sendor M: Helping others helps oneself: response shift effects in peer support. *Soc Sci Med* 1999 (48): 1563-75
86. Avery K, Blazeby JM: Quality of life assessment in surgical oncology trials. *World J Surg* 2006 (30): 1163-72
87. Gotay CC, Moore TD: Assessing quality of life in head and neck cancer. *Qual Life Res* 1992 (1): 5-17
88. Coates A, Gebski V, Bishop JF, et al: Improving the quality of life during chemotherapy for advanced breast cancer. A comparison of intermittent and continuous treatment strategies. *N Engl J Med* 1987 (317): 1490-5
89. Smets EM, Visser MR, Willems-Groot AF, et al: Fatigue and radiotherapy: (B) experience in patients 9 months following treatment. *Br J Cancer* 71998 (8): 907-12
90. Montazeri A: Quality of life data as prognostic indicators of survival in cancer patients: an overview of the literature from 1982 to 2008. *Health Qual Life Outcomes* 2009 (7): 102-23
91. Hagerty RG, Butow PN, Ellis PM, et al: Communicating with realism and hope: incurable cancer patients' views on the disclosure of prognosis. *J Clin Oncol* 2005 (23): 1278-88
92. Detmar SB, Aaronson NK, Wever LD, et al: How are you feeling? Who wants to know? Patients' and oncologists' preferences for discussing health-related quality-of-life issues. *J Clin Oncol* 2000 (18): 3295-301
93. Movsas B: Quality of life in oncology trials: a clinical guide. *Semin Radiat Oncol* 2003 (13): 235-47

94. EORTC. Aims and Mission, History. Access date: 7 July 2010. http://www.eortc.org/about/Directory2009-2010/01%20Background.html
95. Dewolf L, Koller M, Velikova G, Johnson C, Scott N, Bottomley A. (2009) EORTC Quality of life Group Translation Procedure. Brussel
96. Michelson H, Bolund C, Nilsson B, et al: Health-related quality of life measured by the EORTC QLQ-C30--reference values from a large sample of Swedish population. *Acta Onc*ol 2000 (39): 477-84
97. Aaronson NK, Ahmedzai S, Bergman B, et al: The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst* 1993 (85): 365-76
98. Ringdal K, Ringdal GI, Kaasa S, et al: Assessing the consistency of psychometric properties of the HRQoL scales within the EORTC QLQ-C30 across populations by means of the Mokken Scaling Model. *Qual Life Res* 1999 (8): 25-43
99. Hjermstad MJ, Fossa SD, Bjordal K, et al: Test/retest study of the European Organization for Research and Treatment of Cancer Core Quality-of-Life Questionnaire. *J Clin Oncol* 1995 (13): 1249-54
100. Groenvold M, Klee MC, Sprangers MA, et al: Validation of the EORTC QLQ-C30 quality of life questionnaire through combined qualitative and quantitative assessment of patient-observer agreement. *J Clin Epidemiol* 1997 (50): 441-50
101. Bjordal K, de Graeff A, Fayers PM, et al: A 12 country field study of the EORTC QLQ-C30 (version 3.0) and the head and neck cancer specific module (EORTC QLQ-H&N35) in head and neck patients. EORTC Quality of Life Group. *Eur J Cancer* 2000 (36): 1796-807
102. Bredart A, Bottomley A, Blazeby JM, et al: An international prospective study of the EORTC cancer in-patient satisfaction with care measure (EORTC IN-PATSAT32). *Eur J Cancer* 2005 (41): 2120-31
103. Blazeby JM, Alderson D, Winstone K, et al: Development of an EORTC questionnaire module to be used in quality of life assessment for patients with oesophageal cancer. The EORTC Quality of Life Study Group. *Eur J Cancer* 1996 (32A): 1912-7
104. Blazeby JM, Conroy T, Hammerlid E, et al: Clinical and psychometric validation of an EORTC questionnaire module, the EORTC QLQ-OES18, to assess quality of life in patients with oesophageal cancer. *Eur J Cancer* 2003 (39): 1384-94
105. Fayers PM, Aaronson NK, Bjordal K, et al. 2001. The EORTC QLQ-C30 Scoring Manual 3rd Edition. Brussel, European Organisation for Research and Treatment of Cancer.
106. Guyatt GH, Osoba D, Wu AW, et al: Methods to explain the clinical significance of health status measures. *Mayo Clin Proc* 2002 (77): 371-83

107. Revicki D, Hays RD, Cella D, et al: Recommended methods for determining responsiveness and minimally important differences for patient-reported outcomes. *J Clin Epidemiol* 2008 (61): 102-9
108. Osoba D, Rodrigues G, Myles J, et al: Interpreting the significance of changes in health-related quality-of-life scores. *J Clin Oncol* 1998 (16): 139-44
109. King MT: The interpretation of scores from the EORTC quality of life questionnaire QLQ-C30. *Qual Life Res* 1996 (5): 555-67
110. Ringash J, O'Sullivan B, Bezjak A, et al: Interpreting clinically significant changes in patient-reported outcomes. *Cancer* 2007 (110): 196-202
111. Redelmeier DA, Guyatt GH, Goldstein RS: Assessing the minimal important difference in symptoms: a comparison of two techniques. *J Clin Epidemiol* 1996 (49): 1215-9
112. Miaskowski C, Dodd M, Lee K, et al: Preliminary Evidence of an Association Between a Functional Interleukin-6 Polymorphism and Fatigue and Sleep Disturbance in Oncology Patients and Their Family Caregivers. *J Pain Symptom Manage*. In press 2010
113. Glaspy J: The impact of epoetin alfa on quality of life during cancer chemotherapy: a fresh look at an old problem. *Semin Hematol* 1997 (34): 20-6
114. Glaspy J, Bukowski R, Steinberg D, et al: Impact of therapy with epoetin alfa on clinical outcomes in patients with nonmyeloid malignancies during cancer chemotherapy in community oncology practice. Procrit Study Group. *J Clin Oncol* 1997 (15): 1218-34
115. Demetri GD, Kris M, Wade J, et al: Quality-of-life benefit in chemotherapy patients treated with epoetin alfa is independent of disease response or tumor type: results from a prospective community oncology study. Procrit Study Group. *J Clin Oncol* 1998 (16): 3412-25
116. MacDonald N, Alexander HR, Bruera E: Cachexia-anorexia-asthenia. *J Pain Symptom Manage* 1995 (10): 151-5
117. Reich SG: The tired patient: psychological versus organic causes. *Hosp Med*. 1986 (7): 142-54
118. Sephton S, Spiegel D: Circadian disruption in cancer: a neuroendocrine-immune pathway from stress to disease? *Brain Behav Immun* 2003 (17): 321-8
119. Hutton N, McGee A, Dunbar C: A guide to cancer pain management. *Br J Community Nurs* 2008 (13): 464-470
120. Dodd MJ, Miaskowski C, Lee KA: Occurrence of symptom clusters. *J Natl Cancer Inst* 2004 (Monogr): 76-8
121. Parekh K, Iannettoni MD: Complications of esophageal resection and reconstruction. *Semin Thorac Cardiovasc Surg* 2007 (19): 79-88
122. Burrows WM: Gastrointestinal function and related problems following esophagectomy. *Semin Thorac Cardiovasc Surg* 2004 (16): 142-51

123. Silbernagl S, Lang F. 2000. Color Atlas of Pathofysiology. Thieme Medical Publishers. New York.
124. Avery KN, Metcalfe C, Barham CP, et al: Quality of life during potentially curative treatment for locally advanced oesophageal cancer. *Br J Surg* 2007 (94): 1369-76
125. McLarty AJ, Deschamps C, Trastek VF, et al: Esophageal resection for cancer of the esophagus: long-term function and quality of life. *Ann Thorac Surg* 1997 (63): 1568-72
126. Viklund P, Wengstrom Y, Rouvelas I, et al: Quality of life and persisting symptoms after oesophageal cancer surgery. *Eur J Cancer* 2006 (42): 1407-14
127. McKernan M, McMillan DC, Anderson JR, et al: The relationship between quality of life (EORTC QLQ-C30) and survival in patients with gastro-oesophageal cancer. *Br J Cancer* 2008 (98): 888-93
128. Gockel I, Gonner U, Domeyer M, et al: Long-term survivors of esophageal cancer: Disease-specific quality of life, general health and complications. *J Surg Oncol*, 2009
129. de Boer AG, van Lanschot JJ, van Sandick JW, et al: Quality of life after transhiatal compared with extended transthoracic resection for adenocarcinoma of the esophagus. *J Clin Oncol* 2004 (22): 4202-8
130. Blazeby JM, Farndon JR, Donovan J, et al: A prospective longitudinal study examining the quality of life of patients with esophageal carcinoma. *Cancer* 2000 (88): 1781-7
131. Reynolds JV, McLaughlin R, Moore J, et al: Prospective evaluation of quality of life in patients with localized oesophageal cancer treated by multimodality therapy or surgery alone. *Br J Surg* 2006 (93): 1084-90
132. Blazeby JM, Sanford E, Falk SJ, et al: Health-related quality of life during neoadjuvant treatment and surgery for localized esophageal carcinoma. *Cancer* 2005 (103): 1791-9
133. Barbour AP, Lagergren P, Hughes R, et al: Health-related quality of life among patients with adenocarcinoma of the gastro-oesophageal junction treated by gastrectomy or oesophagectomy. *Br J Surg* 2008 (95): 80-4
134. Healy LA, Ryan AM, Moore J, et al: Health-related quality of life assessment at presentation may predict complications and early relapse in patients with localized cancer of the esophagus. *Dis Esophagus* 2008 (21): 522-8
135. Fang FM, Tsai WL, Chiu HC, et al: Quality of life as a survival predictor for esophageal squamous cell carcinoma treated with radiotherapy. *Int J Radiat Oncol Biol Phys* 2004 (58): 1394-404
136. Schmidt CE, Bestmann B, Kuchler T, et al: Quality of life associated with surgery for esophageal cancer: differences between collar and intrathoracic anastomoses. *World J Surg* 2004 (28): 355-60
137. Rutegard M, Lagergren P: No Influence of Surgical Volume on Patients' Health-Related Quality of Life After Esophageal Cancer Resection. *Ann Surg Oncol*, 2008 (9): 2380-87

138. Viklund P, Lindblad M, Lagergren J: Influence of surgery-related factors on quality of life after esophageal or cardia cancer resection. *World J Surg* 2005 (29): 841-8
139. Parameswaran R, McNair A, Avery KN, et al: The Role of Health-Related Quality of Life Outcomes in Clinical Decision Making in Surgery for Esophageal Cancer: A Systematic Review. *Ann Surg Oncol*, 2008 (9): 2372-9
140. Brooks JA, Kesler KA, Johnson CS, et al: Prospective analysis of quality of life after surgical resection for esophageal cancer: preliminary results. *J Surg Oncol* 2002 (81): 185-94
141. Zieren HU, Jacobi CA, Zieren J, et al: Quality of life following resection of oesophageal carcinoma. *Br J Surg* 1996 (83): 1772-5
142. Blazeby JM, Brookes ST, Alderson D: Prognostic value of quality of life scores in patients with oesophageal cancer. *Br J Surg* 2000 (87): 362-73
143. Blazeby JM, Brookes ST, Alderson D: The prognostic value of quality of life scores during treatment for oesophageal cancer. *Gut* 2001 (49): 227-30
144. Chau I, Norman AR, Cunningham D, et al: Multivariate prognostic factor analysis in locally advanced and metastatic esophago-gastric cancer--pooled analysis from three multicenter, randomized, controlled trials using individual patient data. *J Clin Onco*l 2004 (22): 2395-403
145. Park SH, Cho MS, Kim YS, et al: Self-reported health-related quality of life predicts survival for patients with advanced gastric cancer treated with first-line chemotherapy. *Qual Life Res* 2008 (17): 207-14
146. Bergquist H, Johnsson A, Hammerlid E, et al: Factors predicting survival in patients with advanced oesophageal cancer: a prospective multicentre evaluation. *Aliment Pharmacol Ther* 2008 (27): 385-95
147. van Heijl M, Sprangers MA, de Boer AG, et al: Preoperative and Early Postoperative Quality of Life Predict Survival in Potentially Curable Patients with Esophageal Cancer. *Ann Surg Oncol*, 2009 (1): 23-30
148. De Boer AG, Genovesi PI, Sprangers MA, et al: Quality of life in long-term survivors after curative transhiatal oesophagectomy for oesophageal carcinoma. *Br J Surg* 2000 (87): 1716-21
149. Lagergren J, Bergstrom R, Lindgren A, et al: Symptomatic gastroesophageal reflux as a risk factor for esophageal adenocarcinoma. *N Engl J Med* 1999 (340): 825-31
150. National Cancer Research Network. Avon, Somerset & Wiltshire. Access date: 10 July 2010. http://ncrndev.org.uk/index.php?option=com_content&task=view&id=76&Itemid=124
151. Efficace F, Bottomley A, Smit EF, et al: Is a patient's self-reported health-related quality of life a prognostic factor for survival in non-small-cell lung cancer patients? A multivariate analysis of prognostic factors of EORTC study 08975. *Ann Onco*l 2006 (17): 1698-704

152. EORTC Quality of Life Group EQ. Access date: 7 Aug 2010 http://groups.eortc.be/qol/
153. Kirkwood BR SJ: Essential Medical Statistics. (2003) 2nd Ed. Oxford, Blackwell Science
154. Vittinghoff E, McCulloch CE: Relaxing the rule of ten events per variable in logistic and Cox regression. *Am J Epidemiol* 2007 (165): 710-8
155. Concato J, Shah N, Horwitz RI: Randomized, controlled trials, observational studies, and the hierarchy of research designs. *N Engl J Med* 2000 (342): 1887-92
156. Benson K, Hartz AJ: A comparison of observational studies and randomized, controlled trials. *N Engl J Med* 2000 (342): 1878-86
157. La Caze A: Evidence-based medicine must be. *J Med Philos* 2009 (34): 509-27
158. Rothman K, Greenland S, Lash T. (2008) Modern epidemiology. 3rd edition. Philadelphia, Lippincott Williams & Wilkins
159. Delgado-Rodriguez M, Llorca J: Bias. *J Epidemiol Community Health* 2004 (58): 635-41
160. Chick J, Kemppainen E: Estimating alcohol consumption. *Pancreatology* 2007 (7): 157-61
161. Dhalla S, Kopec JA: The CAGE questionnaire for alcohol misuse: a review of reliability and validity studies. *Clin Invest Med* 2007 (30): 33-41
162. Kemmler G, Holzner B, Kopp M, et al: Comparison of two quality-of-life instruments for cancer patients: the functional assessment of cancer therapy-general and the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-C30. *J Clin Oncol* 1999 (17): 2932-40
163. Moorey S, Greer S, Watson M, et al: The factor structure and factor stability of the hospital anxiety and depression scale in patients with cancer. *Br J Psychiatry* 1991 (158): 255-9
164. Cohen SR, Mount BM, Tomas JJ, et al: Existential well-being is an important determinant of quality of life. Evidence from the McGill Quality of Life Questionnaire. *Cancer* 1996 (77): 576-86
165. Koller M, Kussman J, Lorenz W, et al: Symptom reporting in cancer patients: the role of negative affect and experienced social stigma. *Cancer* 1996 (77): 983-95
166. Fitzsimmons D, George S, Payne S, et al: Differences in perception of quality of life issues between health professionals and patients with pancreatic cancer. *Psychooncology* 1999 (8): 135-43
167. Bottomley A: Where are we now? Evaluating two decades of group interventions with adult cancer patients. *J Psychiatr Ment Health Nurs* 1997 (4): 251-65
168. Lazarus RS: Coping theory and research: past, present, and future. *Psychosom Med* 1993 (55): 234-47

169. Fayers P, Hays R. (2005) Assessing quality of life in clinical trials. New York, Oxford University Press Inc
170. Mehanna HM, Morton RP: Does quality of life predict long-term survival in patients with head and neck cancer? *Arch Otolaryngol Head Neck Surg* 2006 (132): 27-31
171. Sloan JA, Cella D, Frost MH, et al: Quality of life III: translating the science of quality-of-life assessment into clinical practice-an example-driven approach for practicing clinicians and clinical researchers. *Clin Ther 25 Suppl* 2003 (D): D1-5
172. Andreassen S, Randers I, Naslund E, et al: Patients' experiences of living with oesophageal cancer. *J Clin Nurs* 2006 (15): 685-95
173. Andreassen S, Randers I, Naslund E, et al: Information needs following a diagnosis of oesophageal cancer; self-perceived information needs of patients and family members compared with the perceptions of healthcare professionals: a pilot study. *Eur J Cancer Care (Engl)* 2007 (16): 277-85
174. Fein DA, Lee WR, Hanlon AL, et al: Pretreatment hemoglobin level influences local control and survival of T1-T2 squamous cell carcinomas of the glottic larynx. *J Clin Oncol* 1995 (13): 2077-83

# APPENDIX

# EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: _____

Your birthdate (Day, Month, Year): _____

Today's date (Day, Month, Year): 31 _____

| | | Not at All | A Little | Quite a Bit | Very Much |
|---|---|---|---|---|---|
| 1. | Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase? | 1 | 2 | 3 | 4 |
| 2. | Do you have any trouble taking a long walk? | 1 | 2 | 3 | 4 |
| 3. | Do you have any trouble taking a short walk outside of the house? | 1 | 2 | 3 | 4 |
| 4. | Do you need to stay in bed or a chair during the day? | 1 | 2 | 3 | 4 |
| 5. | Do you need help with eating, dressing, washing yourself or using the toilet? | 1 | 2 | 3 | 4 |

## During the past week:

| | | Not at All | A Little | Quite a Bit | Very Much |
|---|---|---|---|---|---|
| 6. | Were you limited in doing either your work or other daily activities? | 1 | 2 | 3 | 4 |
| 7. | Were you limited in pursuing your hobbies or other leisure time activities? | 1 | 2 | 3 | 4 |
| 8. | Were you short of breath? | 1 | 2 | 3 | 4 |
| 9. | Have you had pain? | 1 | 2 | 3 | 4 |
| 10. | Did you need to rest? | 1 | 2 | 3 | 4 |
| 11. | Have you had trouble sleeping? | 1 | 2 | 3 | 4 |
| 12. | Have you felt weak? | 1 | 2 | 3 | 4 |
| 13. | Have you lacked appetite? | 1 | 2 | 3 | 4 |
| 14. | Have you felt nauseated? | 1 | 2 | 3 | 4 |
| 15. | Have you vomited? | 1 | 2 | 3 | 4 |
| 16. | Have you been constipated? | 1 | 2 | 3 | 4 |

Please go on to the next page

| **During the past week:** | **Not at All** | **A Little** | **Quite a Bit** | **Very Much** |
|---|---|---|---|---|
| 17. Have you had diarrhea? | 1 | 2 | 3 | 4 |
| 18. Were you tired? | 1 | 2 | 3 | 4 |
| 19. Did pain interfere with your daily activities? | 1 | 2 | 3 | 4 |
| 20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television? | 1 | 2 | 3 | 4 |
| 21. Did you feel tense? | 1 | 2 | 3 | 4 |
| 22. Did you worry? | 1 | 2 | 3 | 4 |
| 23. Did you feel irritable? | 1 | 2 | 3 | 4 |
| 24. Did you feel depressed? | 1 | 2 | 3 | 4 |
| 25. Have you had difficulty remembering things? | 1 | 2 | 3 | 4 |
| 26. Has your physical condition or medical treatment interfered with your family life? | 1 | 2 | 3 | 4 |
| 27. Has your physical condition or medical treatment interfered with your social activities? | 1 | 2 | 3 | 4 |
| 28. Has your physical condition or medical treatment caused you financial difficulties? | 1 | 2 | 3 | 4 |

## For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|
| Very poor | | | | | | Excellent |

30. How would you rate your overall quality of life during the past week?

| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|
| Very poor | | | | | | Excellent |

# EORTC QLQ – OES18

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

| **During the past week:** | | **Not at all** | **A little** | **Quite a bit** | **Very much** |
|---|---|---|---|---|---|
| 31. | Could you eat solid food? | 1 | 2 | 3 | 4 |
| 32. | Could you eat liquidised or soft food? | 1 | 2 | 3 | 4 |
| 33. | Could you drink liquids? | 1 | 2 | 3 | 4 |
| 34. | Have you had trouble with swallowing your saliva? | 1 | 2 | 3 | 4 |
| 35. | Have you choked when swallowing? | 1 | 2 | 3 | 4 |
| 36. | Have you had trouble enjoying your meals? | 1 | 2 | 3 | 4 |
| 37. | Have you felt full up too quickly? | 1 | 2 | 3 | 4 |
| 38. | Have you had trouble with eating? | 1 | 2 | 3 | 4 |
| 39. | Have you had trouble with eating in front of other people? | 1 | 2 | 3 | 4 |
| 40. | Have you had a dry mouth? | 1 | 2 | 3 | 4 |
| 41. | Have you had problems with your sense of taste? | 1 | 2 | 3 | 4 |
| 42 | Have you had trouble with coughing? | 1 | 2 | 3 | 4 |
| 43. | Have you had trouble with talking? | 1 | 2 | 3 | 4 |
| 44. | Have you had acid indigestion or heartburn? | 1 | 2 | 3 | 4 |
| 45. | Have you had trouble with acid or bile coming into your mouth? | 1 | 2 | 3 | 4 |
| 46. | Have you had pain when you eat? | 1 | 2 | 3 | 4 |
| 47. | Have you had pain in your chest? | 1 | 2 | 3 | 4 |
| 48. | Have you had pain in your stomach? | 1 | 2 | 3 | 4 |