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Health Related Quality of Life and Swallowing Problems in Oesophageal Cancer

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Health-Related Quality of Life and Swallowing Problems in Oesophageal Cancer
THESIS FOR DOCTORAL DEGREE (Ph.D.)

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This thesis is dedicated to all those whose narratives are a part of my research: patients, professionals and to my beloved family

ABSTRACT

Poor overall survival, swallowing problems and severe side-effects from multi-modality treatment characterize the situation of patients with oesophageal and gastro oesophageal junction carcinoma (GOJ). With the poor prognosis and abundance of symptoms in this disease it is particularly important to consider health-related quality of life (HRQoL) as an important outcome in clinical decision-making. Several trials have addressed outcomes regarding oncological therapies and surgery, though patient-reported outcomes (PRO) are to a large extent lacking in trials on oesophageal cancer patients.
This thesis addresses and aims to shed light on PRO and HRQoL with a special reference to swallowing problems (dysphagia) during and after neoadjuvant treatment and after surgery in oesophageal and GOJ carcinoma. Also, an aim is to report HRQoL collected one year after diagnosis in a Swedish population-based register.

The current main curative intent treatment regime used for oesophageal cancer is multimodal, including neoadjuvant oncological treatment and surgery. Due to a scarcity of research it is still unknown whether the addition of radiotherapy to neoadjuvant chemotherapy affects HRQoL and swallowing problems. In Sweden and Norway, a multi-centre randomised controlled trial compared neoadjuvant chemotherapy (nCT) and neoadjuvant chemoradiotherapy (nCRT) prior to surgery, acronymed NeoRes, and PRO using HRQoL instruments was and endpoint in the trial. At diagnosis, the vast majority of the patients were in the palliative stage. Thus, adding knowledge of HRQoL outcomes in these settings is also very important.

Paper I describes HRQoL outcomes collected in a nationwide Swedish population-based register twelve months after diagnosis. The outcomes were compared with a Swedish reference population and suggests that at one year after diagnosis of oesophageal cancer, subjects suffer with regard to most of the HRQoL aspects measured compared to the reference population, and particularly in the case of a palliative treatment intent. In addition, high levels of anxiety were reported in all subgroups and problems with swallowing were increased among those who received a palliative diagnosis and in those who were treated with definitive chemoradiotherapy. This study is important in order to increase knowledge of HRQoL outcomes in an unselected, a nation-wide population-based cohort.

Paper II, addresses patients treated with neoadjuvant therapy, at the Karolinska University Hospital. These patients were assessed regarding dysphagia prior to any treatment, after the first cycle of chemotherapy and after completion of neoadjuvant therapy, prior to surgery. Patients reported dysphagia relief as already after the first cycle of chemotherapy, and after completed neoadjuvant therapy. This study is important for clinical decision-making at diagnosis of oesophageal cancer, suggesting that stents or gastrostomies may not be needed during neoadjuvant treatment, before surgery.

Paper III addresses patient-reported dysphagia in the NeoRes trial. The data were collected before any treatment and after the conclusion of neoadjuvant therapy. In addition, we investigated whether dysphagia was correlated to histological response. This study confirmed the results of paper II, with an improved ability to eat solid food in both groups, although radiotherapy may also add side-effects that contribute to swallowing-problems. However, no correlation was detected between dysphagia response and histological response.
Paper IV investigated the HRQoL outcome in the NeoRes trial, measured prior to treatment, after ended neoadjuvant treatment and one, three and five years after surgery. In

comparisons between groups, differences were reported by patients regarding odynophagia after the termination of neoadjuvant therapy and coughing at three-year follow-up, both these symptoms was worse in patients treated with nCRT, compared to those receiving nCT. In addition, changes within groups in comparison with baseline were analysed. One finding is that regarding oesophageal-specific symptoms patients reported improvement to some extent. Conversely, functions and known treatment-related side-effects worsened after neoadjuvant therapy in both groups. In conclusion, patients reported significantly more severe symptoms and decreased functions after the termination of neoadjuvant treatment, and at three- and five-years follow-up, when radiotherapy was added.

Keywords: Oesophageal cancer, HRQoL, PRO, dysphagia, swallowing problems

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LIST OF SCIENTIFIC PAPERS

I. Sunde B, Lindblad M, Malmström M, Hedberg J, Lagergren P, Nilsson M. **Health-related quality of life one year after the diagnosis of oesophageal and junctional cancer: A population-based study from the Swedish National Registry for Esophageal and Gastric Cancer**. *Manuscript*

II. Sunde B , Ericson J, Kumagai K, Lundell L, Tsai J, Lindblad M, Rouvelas I, Friesland S, Wang N, Nilsson M. **Relief of dysphagia during neoadjuvant treatment for cancer of the esophagus or gastroesophageal junction**. Dis Esophagus, 2016 Jul, 29(5): 442-7.PMID:25809837.

III. Sunde B , Johnsen G, Jacobsen A-B, Glenjen NI, Friesland S, Lindblad M, Rouvelas I, Wang N, Lundell L, Lagergren P, Nilsson M. **Effects of neoadjuvant chemoradiotherapy vs chemotherapy alone on the relief of dysphagia in esophageal cancer patients: secondary endpoint analysis in a randomized trial.** Dis Esophagus, 2019 Feb 1; 32(2): 1-9. PMID:30084992.

IV. Sunde B , Klevebro F, Johar A, Johnsen G, Jacobsen A-B, Glenjen NI, Friesland S, Lindblad M, Ajengui A, Lundell L, Lagergren P, Nilsson M. **Health-related quality of life after neoadjuvant chemotherapy vs. chemoradiotherapy in curative treatment for oesophageal cancer: Results from the randomised NeoRes trial**. *Submitted manuscript*

CONTENTS

LIST OF ABBREVIATIONS

dCRT	Definitive chemoradiotherapy
Dysphagia	Swallowing problems
EORTC	European Organisation for Research and Treatment of Cancer
GOJ	Gastro-oesophageal junction
HRQoL	Health-Related Quality of Life
MDT	Multi-disciplinary Treatment conferences
nCT	Neoadjuvant chemotherapy
nCRT	Neoadjuvant chemoradiotherapy
NeoRes	**Neo**adjuvant Treatment and **Res**ection
NREV	National Registry for Esophageal and Gastric Cancer
PRO	Patient Reported Outcome
PROM	Patient Reported Outcome Measurement
RCT	Randomised controlled trial
QoL	Quality of Life

1 INTRODUCTION

1.1 ANATOMY OF THE OESOPHAGUS

The oesophagus, also called the food pipe, is a part of the digestive system and it is a hollow, muscular tube, approximately 18-26 cm long in adults with an internal dimension of around 2 cm. The upper third is composed of striated muscles, while the lower two-thirds is composed of smooth muscle. The muscles are controlled by the cranial nerves and the oesophageal myenteric nerve plexus. Food passes through contraction producing coordinated peristaltic waves, with an inner and outer layer of muscles. The primary peristaltic wave is 30 mm Hg or more, and starts with the pharynx and forces the food bolus through the oesophagus in 6 to 10 seconds. The waves controlled by the *medulla oblongata* continue until the bolus is cleared. Two sphincters, upper and lower, permits the food to flow in the right direction and the lower sphincter and but mainly prevents reflux. The anatomical oesophagus is close to both the lungs and the heart.

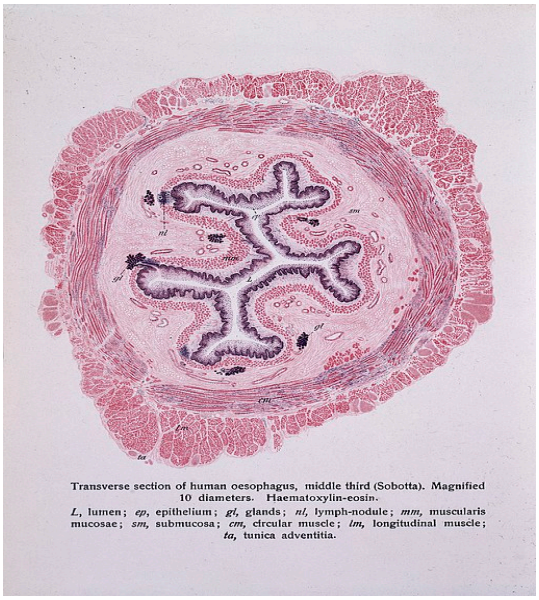

Figure 1. Transverse resection of human oesophagus, the middle third (Sobotta)

1.2 EPIDEMIOLOGY OF OESOPHAGEAL CANCER

Oesophageal cancer is an uncommon cancer ranked as ninth in incidence but as the sixth leading cause of cancer deaths globally, with approximately 572, 000 new cases diagnosed annually and an overall mortality (509, 000 deaths), signifying that oesophageal cancer was responsible for 1 in 20 deaths in 2018.[1]

Cancer is the leading cause and single most important barrier to increasing life expectancy globally in the 21st century. It is also the highest ranked health hazard among the noncommunicable diseases. Causes of cancer death vary substantially across countries and within each country, caused by the degree of economic growth and accompanying social and life style factors. It is also important to acknowledge that in many low- and middle-

income countries, there is a lack of high-quality cancer registry data. [1] Around 80% of the oesophageal cancer cases occur in less developed regions [2] and at diagnoses with ages above 65 years. Also 70% of all cases occur in men. [1-3]

There are two common types of oesophageal cancer that together account for > 98% of oesophageal cancer cases; adenocarcinoma and squamous cell carcinoma (SCC).[1,4,5] The most common type worldwide is SCC but this has changed in developing countries, in which adenocarcinoma is more common and has a rapidly rising incidence. [6]

Adenocarcinoma is currently the dominant histological type of oesophageal malignancy in North-American countries and several European countries [7] and is estimated to continue to rise in the upcoming decades. [8] In, Europe the highest rate of oesophageal cancer is in Western European countries, including the UK, Netherlands, Ireland and Belgium.[9] In Sweden, approximately 450-500 new cases of oesophageal cancer were diagnosed in 2016 and it is therefore considered a rare cancer disease, in similarity with the other Nordic countries.[10, 11] Oesophageal cancer and adenocarcinoma have been reported with a male to female ratio in incidence of 2.4:1 to 9:1.[2,7]

1.2.1 Causes of cancer

Causes of cancer are associated with socioeconomic development, and cancer transition is most striking in emerging economies, with a changing profile of common cancer types. Also, the Western lifestyle is described as a cause of cancer profiles.[12,13] Lastly, increasing age and population growth reflects the risks of developing cancer.[1]

1.2.2 Aetiology, risk factors and prevention of oesophageal cancer

The rising prevalence of reflux and obesity worldwide are discussed as being the main contributors to the incidence of oesophageal and GOJ cancer.[7,8] Smoking, tobacco and low intake of fruit and vegetables have been estimated to account for nearly 80% of carcinoma of the oesophagus while it has been suggested that sex hormones play a protective role.[5,9] The geographic and social group disparities of oesophageal cancer are striking with different etiologies.[1,14] Heavy drinking and smoking and their synergetic effects are major risk factors for SCC in Western settings. [9] Dietary, oesophageal injury and inherited susceptibilities may also contribute.[5] However, in low-income countries including parts of Asia and Sub-Saharan Africa with 90% of SCC world-wide the aetiology is currently unknown and the Indian Subcontinent, SCC is suspected to be caused by betel quid chewing. Also, in Southern American countries such as Uruguay, Brazil and Argentina, drinking very hot beverages especially tea is suspected to be a risk factor. Risk factors in Eastern and Southern Africa have yet to be elucidated.

The decline in SCC incidence in the USA, Australia, France and in the UK, is believed to be the result of decline in cigarette smoking, while a decline in SCC in high-risk areas in Asia is the result of economic gains and dietary improvements.[1] With the decline in SCC in high risk countries, the incidence of adenocarcinoma is rapidly rising, partially because of increased obesity and waist circumference, increasing prevalence of GERD, and supposedly decreasing levels of chronic infection with H. Pylori.[1,7,9] Other causes that have been discussed as explaining gender disparities include alcohol use in squamous cell carcinoma and more severe reflux among men with oesophageal adenocarcinoma together with a protective role of high estrogenic exposure and breastfeeding among women.[5] The

progression to adenocarcinoma is also believed to be secondary to the development of Barrett's oesophagus into dysplasia and adenocarcinoma.[8,9]
The prevention of cancer in the oesophagus and GOJ appear to be related to education about risk factors such as smoking, diet and obesity. A secondary form of prevention could be to treat pre-cancerous conditions, such as Barrett's oesophagus. In addition, aspirin is considered to be a form of chemoprevention, with several trials ongoing.[9]

1.3 PROGNOSIS

Prognosis of oesophageal carcinoma is worse than for most other cancers, with an approximately 10–22 % five-years overall survival rate.[2,7] At diagnosis, mostly of the patients are diagnosed at an advanced stage and therefore only offered palliative treatment.

However, the main curative treatment offered is surgical resection and with evidence from the last decades it should preferably be employed in combination with neoadjuvant treatment.[15,16] In patients treated with surgery, the 5-year survival rate has increased to 40%-45%[15,17,18] The CROSS trial, with randomisation between neoadjuvant chemoradiotherapy (nCRT) and surgery alone, reported a promising overall 5-year survival of 40% in all patients treated with nCRT and surgery, while patients diagnosed with SCC had over 60% overall and progression free survival when treated with nCRT and surgery, while 5-year survival after surgery alone was only 27%.[15,19]

1.4 CLINICAL PRESENTATION AND STAGING

At diagnosis dysphagia is the predominant symptom in more than 70%–90% of subjects and in most patients followed by weight loss.[20-22] Dysphagia is considered a late alarm symptom because of the elasticity of the esophageal wall, and only 25% of the patients are considered curative when having localised symptoms at the time of presentation.[23,24] Dysphagia occurs when the tumour obstructs to 2/3 of the circumference of the lumen. Initially, solid food is difficult to swallow and progresses to include fluids. Difficulty in ingesting solids is considered to suggest a mechanical obstruction.[24] Other early symptoms may include discomfort or occasional pain when swallowing, while absence of energy and strength, gastrointestinal bleeding, vomiting, indigestion, heart burn and chest pain are considered late symptoms.[9] Late symptoms indicating advanced disease are also hoarseness and a severe cough.[25]

Endoscopy is a crucial first-line investigation and an upper gastrointestinal endoscopy of the oesophagus and stomach enable direct visualization. It also enable a histological sample of tumour tissue to conclude the diagnosis.

At multidisciplinary team conferences (MDT), the optimal treatment is discussed, a CT scan or preferably a PET-CT scan is performed and enable the detection of lymph nodes and distant metastases. In addition re-evaluation of the oncological treatment effect is of paramount importance, and usually discussed again at a second MDT. Clinical and pathological staging is currently determined by the TNM, 8th edition. The staging system classifies lesions based on the depth of the tumour invasion (T stage), the status of the loco-regional lymph node (N stage) and the presence or absence of distant metastases (M stage)[26]

Before a decision is made about therapy, patients require a physical examination and control of comorbidities. If necessary, an exercise stress test on a bicycle to further measure

physical performance level, and spirometry is used to evaluate pulmonary function. At diagnosis, many patients are old with comorbidities and also are found to be too unfit to be treated curatively. In addition, the tumour may be diagnosed with overgrowth on other organs or major vessels or with distant metastasis, and palliative treatment and best supportive care are then the options available.

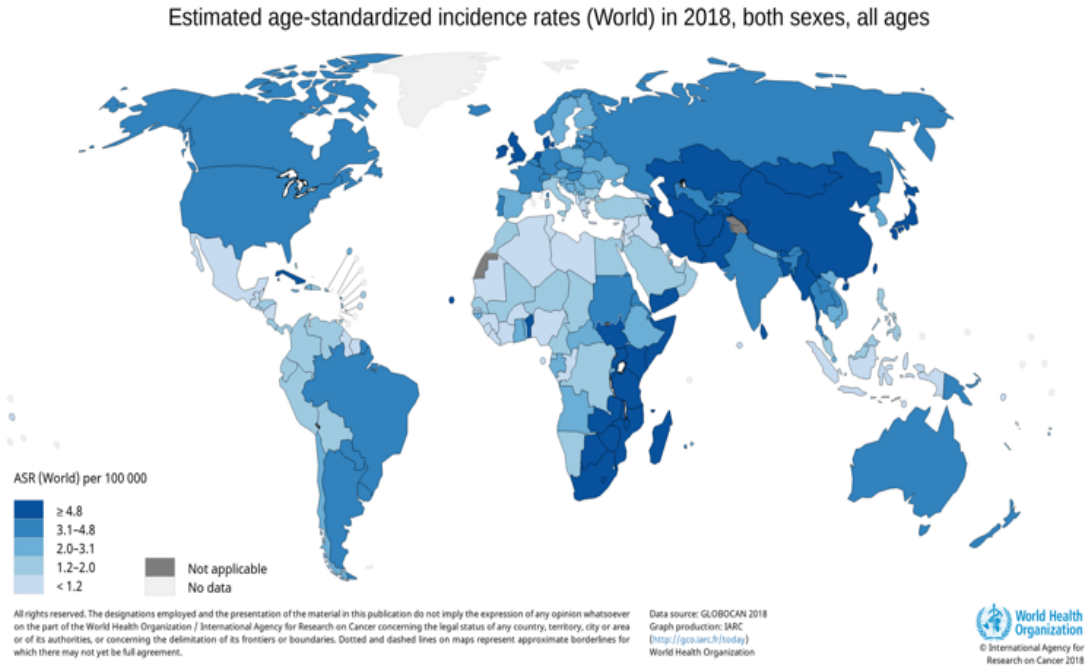

Figure 2. Age standardised incidence rates of oesophageal cancer both sexes and types 2018 statistics. Figure shows incidence areas worldwide. (Downloaded from WHO Globcan in 2019)

1.5 TREATMENT

1.5.1 Curative Treatment

Currently, the predominant curative treatment option in locally advanced tumour stages without distant metastasis, is neoadjuvant treatment followed by radical surgery. This strategy has been reported in several trials to improve survival compared to surgery alone.[15-17,27-29] When comparing between neoadjuvant chemotherapy (nCT) and neoadjuvant chemoradiotherapy (nCRT), the few available trials results have not hitherto been able to demonstrate any survival advantage of one regime over the other.[18,30-32] In this context it may be relevant to consider that treatment with dCRT has in some controlled trials documented to harbor the potential to offer long term survival. Hereby, it has to be recognised that the selection criteria in corresponding trials are critical and often includes patients not suitable for surgery.[33,34] The therapeutic armentarium in various stages of oesophageal cancer has changed significantly over the past decade with for instance the introduction and widespread implementation of minimal invasive surgical techniques and the pivotal role of endoscopic endoluminal resection for cure of early neoplastic lesions.[35-38]

By the use of modern oncological treatment, centralization of the surgical treatments, less surgical trauma inflicted on the patients and also with the improved perioperative care, within fast track programmes for enhanced postoperative recovery, the entire perioperative courses in patients with oesophageal cancer have dramatically changed. One of the consequences of the therapeutic refinements has been an improved quality of life for these patients. To continue with such progress, more research is required that focuses on patients experiences and extensive evaluations when introducing new methods and programmes.[39,40]

In order to attain a complete and comprehensive picture of the current status some uncertainties need to be discussed. Both surgery and oncological treatment of oesophageal cancer is encompassed with survival benefits, but treatment is also followed by surgery-related complications,[41] and toxicity from the treatment of oesophageal cancer is under reported, particularly long-term toxicity.[42,43] Moreover, the structure and content of prehabilitation programs as well as rehabilitation programs have to be better defined and elucidated. Thus, the decision of the optimal treatment for each individual patient with oesophageal cancer is complex.[22] Many important aspects of the complexity of the management of oesophageal cancer patients' are reflected by a recent paper from the UK, applying a Delphi process, including patients, stakeholders and health professionals. The objective was to reach a consensus of the most important outcomes variables in trials on oesophageal cancer surgery. This Delphi survey was motivated by the fact that literature data currently available were inconsistent, lacked standard methodology and were devoid of core outcome. A list of 10 priorities were constructed. Top of the list was to achieve optimal short and long-term survival (1–3), with minimal treatment related side-effects (4–6), without serious nutritional problems-sequelae (7), allowing patients to eat and drink normally (8), avoid problems with acid indigestion (9) and, last but not least to attain a normal overall quality of life (10).[44]

1.5.2 Surgery

Oesophagectomy dates back to the late 19th century and early 20:th centuries. In 1913, a 68-year-old woman who presented with progressive dysphagia and weight loss resulting from carcinoma underwent transthoracic resection which she survived for 12 years after surgery with a new oesophagus made from rubber.[45] Different surgical techniques and reconstructions have thereafter been introduced and widely adopted, but the most commonly used surgical technique is a two stages thoraco-abdominal approach (Ivor Lewis), used if the tumour is located in the lower-third of the oesophagus. The three-stage technique (McKeown) is used, primarily in cases with the tumour is located in the upper third of the oesophagus. A radical and complete lymph node dissection is generally recommended and traditionally incorporates a two or three field lymphadenectomy.[22,46] The most common technique for reconstruction is using a gastric tube, to substitute the oesophagus, made out of the greater curvature of the stomach with vascular supply from the right gastroepiploic vessels. The ensuing oesophago-gastrostomy is done either in the chest or in the neck.

Oesophagectomy is considered to be among the most demanding surgical procedures within the field of advanced gastrointestinal surgery. One important mechanism behind this is the ectensive surgical dissection required within at least two major body compartments (i.e. abdomen and chest). The complexity of oesophageal cancer surgery is illustrated by the high risk of postoperative complications. Postoperative complications within 30 days of surgery occur in the range of 40% to 60 % of the patients with a mortality rate of 2%–3%,

and in addition a recurrence rate from 32% to 54% the first postoperative year.[47-50] Mortality is also reported dependent of surgical volume.[49]

A relatively new surgical concept is endoscopic therapy, which includes mucosal (EMR) or submucosal resection (ESD). This is the preferred surgical approach in early intramucosal carcinoma of the oesophagus (T1a) or in neoplastic lesions. These premalignant lesions are in the Western world most frequently diagnosed in the Barrett´s oesophagus, submitted to endoscopic surveillance, often connected with or preceded by high-grade dysplasia. Accordingly, many of these Barrett's cases are offered radiofrequency ablative therapy (RFA) in order to eradicate the remained columnar lined oesophagus. Previously, treatment has traditionally been oesophagectomy if diagnosed with at least high grade dysplasia.[36] The tumour stage T1b is intriguing and challenging, when the absolute depth of submucosal invasion is critically important to assess, depending on the considerable risk of lymph node involvement, if the mid and deeper portions of the submucosa is involved.[36]

The options of curative surgery are improving and a preferred surgical technique today is minimally invasive oesophagectomy or open-minimal invasive hybrid techniques, with open chest following the minimal invasive completion of the abdominal part of the procedure. With the introduction of minimal invasive techniques, controlled trials have demonstrated reduced postoperative complications, especially pulmonary complications, as well as a lower risk of major intraoperative complications, and shortened length of stay. [51,52] Importantly, improved global quality of life, physical function and decreased pain as long as one year are reported after minimally invasive surgery compared to open surgery.[53] Robot-assisted oesophagectomy has been introduced in some centers and this technique has shown promising feasibility and safety but connected with higher costs. [54,55]

Despite the positive effects of the introduction of minimal invasive oesophagectomy, pulmonary complications are uniformly recognised as the most frequent postoperative complications and is seen in as many as 70% of the patients.[49,56] In addition, atrial fibrillation is common up to 20%–25% of patients both during and after the procedure to which can be added other serious cardiovascular complications.[41,49] However, the most severe and life-threatening surgical complications are conduit-ischemia and anastomosis leakage.[49,56] In this context it has to be recognised that early detection and active treatment of these complications have significantly improved by the centralization process and by the introduction of effective therapies.[57,58] Other significant and clinically relevant complications to be aware of during perioperative care are recurrent laryngeal nerve injury and chylothorax. Although less comprehensive studied, late and chronic symptoms and complaints after oesophagectomy have yet to be elucidated. These include functional conduit disorders such as dumping syndrome, delayed gastric emptying, dysphagia, oesophageal reflux and the herniation of viscera into the chest through the widened diaphragmatic hiatus.[49] It needs to be emphasized that complications in the perioperative phase not only expose the patients to a significant immediate risk but cause patients severely deterioration in several HRQoL domains also in the long-term perspective.[59-63]

Prevention from serious complications is always the best strategy and the selection of surgical technology has already been referred to. However, the selection of patients and referring the patient to high volume center are of vital importance to minimize the related risks.[9] Information is accumulating to show the importance of a number of factors during the prehabilitation phase of the preoperative preparation of the patients. [9]
Whether the addition of neoadjuvant chemo- or chemoradiotherapy increases the adverse effects of surgery remains controversial [15,17,41] but a recent metaanalysis suggested that nCRT was associated with more complications post-operatively. [64] Moreover, in the

NeoRes trial, where a direct comparison was made between nCT and nCRT no significant differences were reported between the groups regarding the number of surgical or nonsurgical complications, although complications were significantly more severe among patients allocated to nCRT.[41]

A pivotal role in the perioperative management of oesophagectomy patients has the Enhanced recovery programmes (ERP/ERAS) taken. The launch of these programmes seemed to have decreased morbidity, hospital stay and reducing health costs. Protocols optimise the care before, during and after surgery. It has further been suggested that increased fluid restriction with enchanced recovery programs may decrease the incidence of anastomotic leakage. In addition, nutritional protocols may further reduce the severity of anastomotic leakage. Lastly, preoperative information, early mobilisation, pain management and fluid control are reported to reduce pulmonary complications.[57]

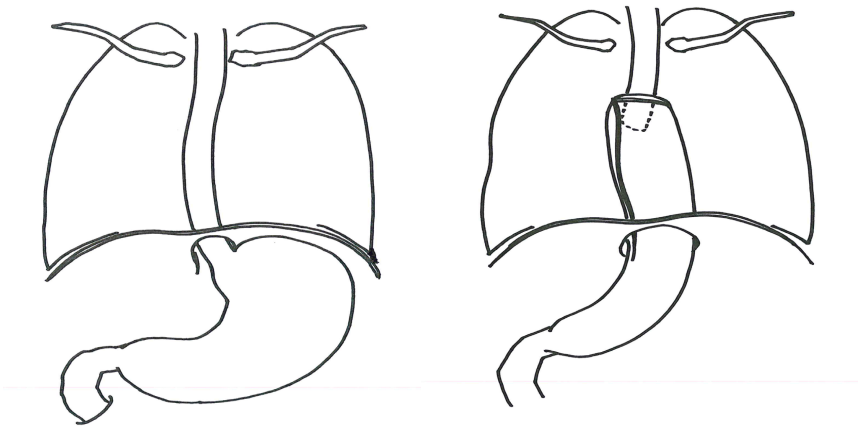

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Figure 3. *Oesophagus before resection* *Oesophagus after surgery with gastric tube reconstruction*

1.5.3 Oncological treatment

The main treatment in curative settings with advanced tumour stages is neoadjuvant treatment combined with surgery, and this has been reported in several trials to improve survival compared to surgery only.[15-17,27-29] In comparisons between neoadjuvant treatment with nCT and nCRT, the results from the few trials to elucidate these modalities have not yet shown any significantly improved survival rates within either modality.[18,30-32] In addition, definitive chemoradiotherapy has also been documented to have good survival effects. Here, the selection criteria often include that patients are not suited for surgery.[33,34] Especially patients with SCC have been shown to have good survival after dCRT.

It has been clearly shown that a single agent will be enough to optimise cure of oesophageal cancer. Thus, a combination of two or three agents is preferred. Historically, cisplatin and 5-Fluorouracil are the most common chemotherapy regimens, were developed in the 1970s, and show benefits in several other tumours.[4] In the 1980s, radiotherapy was used as the sole form of therapy in oesophageal cancer when patients were judged not to tolerate surgery. However, response rates were low and when chemotherapy was added, the response rates and survival rate increased. Neoadjuvant treatment with cisplatin is still

considered the gold standard chemotherapy for oesophageal cancer, with the effect of downstaging the tumour, eliminating micro metastasis, thereby facilitating radical resection.[65] Cisplatin and combined with 5-Fluorouracil is beneficial for improving five year survival compared to surgery alone.[29]

The benefit of adding radiotherapy is to debulk the local tumour and decrease the number of lymph node metastasis, thereby increasing the chance of an operation with tumour free resection margins. To date, three trials, including the NeoRes trial, have compared nCT and nCRT, resulting in a better complete histological response by adding radiotherapy, although no survival benefits have been reported.[18,30,32,66] Stahl et al reported a trend of improved survival with nCRT.[30] However, in published meta-analyses, survival benefits have been shown in treatment with both nCT and nCRT.[67,68] Newer treatments, such as the CROSS regime, combining carboplatin and the taxane paclitaxel with radiotherapy, have reported both benefits in survival, fewer complications and also HRQoL benefits.[15,69-71]

Radiotherapy treatment is evolving with high conformal treatments including intensity-modulated radiotherapy and volumetric modulated arc treatment. This enables oncologists to deliver high doses of radiation to the tumor with more precision, sparing the surrounding organs and tissues.[65] It is currently possible to avoid surgery if a complete response, assessed by endoscopic and PET investigations, is achieved and this is being adopted at some centres that use nCRT, with the concept of "surgery as needed".[16]

Despite promising results in curative settings, more than 70% of patients are at an advanced stage at which curative treatment is not possible and palliative treatments with chemotherapy, radiotherapies and stenting are widely used to palliate symptoms at diagnosis, together with the best supportive care.[40,72-78] In selecting a palliative treatment regime, no benefits regarding survival has been conclusively reported, although it has been suggested that the addition of oncological treatment with radiotherapy, chemotherapy or in combination, improve survival compared to no oncological treatment.[74,76,78-81] In addition, palliative care is a treatment that aims to relive instead of cure the symptoms caused by cancer, rather than curing, thereby improving quality of life of patients and their relatives.[40,82] Palliative care helps patients live a more comfortable life with relief from physical, psychosocial, spiritual and emotional problems. This is reported to be achieved in over 90% of advanced cancer patients supported through specialised palliative care units.[40] However, it is suggested to be a benefit if early integration of palliative care into the standard oncological care can be achieved, therefore an increased support within specialised oesophageal cancer care centres, is proposed to further improve HRQoL in palliative diagnosis.[40,83]

Treatment with chemotherapy and/or radiotherapy is related to substantial toxic adverse effects, and it is therefore of paramount importance to systematically monitor and evaluate symptoms during the disease trajectory.[9,84-87] In order to evaluate treatment-related side-effects in trials in particular, since 1983, the National Cancer Institute Common Toxicity Criteria (CTC) system has evolved.[88] The most recent version is CTCAE v5.0 (Common Terminology Criteria for Adverse Events). This instrument measures adverse events from 1 to 5 (mild, moderate, severe, life-threatening and death). A report on side-effects from current trials are mainly based on the clinicians' impressions of the patients' symptoms, and not on patient's own first-hand reports of their experiences with given drugs. In comparisons between, clinicians' documentation and patients' self-experienced symptoms, it is reported that clinicians systematically downgrade the severity of patients' symptoms. [89]

Platins are the oldest regime used and some side-effects are more documented than other chemotherapeutic agents.[43] Burmeister et al compared nCRT (with platins and 5-Fluorouracil) with surgery alone. They reported a toxic effect of nCRT, and the most common acute side-effects were oesophagitis, nausea and vomiting, infection, diarrhoea, mucositis, pneumonitis, neutropenia and increased creatinine levels.[16] Another trial by Burmeister et al compared nCT with nCRT and they reported grade 3 toxicites. Neutropenia, oesophagitis, infection, renal impairment, thromboembolism and nausea and vomiting were reported in both groups comparing Cisplantin and 5-Fluorouracil and 35 Gray in radiotherapy arm, no difference in grade 4 toxicity was reported in comparisons between groups.[66]

In the NeoRes trial, comparing nCT and nCRT (with cisplatin and 5-Fluoruracil), no difference was reported regarding Serious Adverse Events (SAE) grade 3 and over, between groups. However, the most reported SAE were nutritional deficiency and this was reported in both groups, but more cardiovascular events when treated with nCRT. Other serious adverse events were; infection, renal failure, nausea and vomiting reported in both groups. Three patients died during treatment, one in nCT and two in the nCRT group. [32]

Newer treatments, such as CROSS treatment (oxaliplatin, taxanes and 41.4 Gray radiotherapy), this trial compared surgery alone with nCRT. In patients, treated with nCRT any grade of event is reported in the nCRT group; and anorexia, constipation, fatigue, nausea, vomiting, neurotoxic effects, leukopenia and thrombocytopenia were the most common side-effects. One patient died after conclusion of nCRT.[15]

When adding radiotherapy, there is a risk of side-effects from the organs involved in the targeted dose. The oesophagus, lungs and heart are risk organs with dose-related effects and acute oesophagitis, dysphagia, strictures, fistulas and chronic ulcers are not uncommon side-effects from the oesophagus. Cardiac effects and damage with radiotherapy, is also increasing with dose and increases the risk factors for cardiovascular disease.[90] The known long-term effects of radiotherapy are coronary heart disease because of the vascular damage and the pulmonary effects of radiotherapy are pneumonitis that manifests months after the conclusion of treatment and creates a risk of lung fibrosis.[39]

1.5.4 Histological response and survival

It has been reported in two meta-analysis, a strong survival benefit with both nCRT and nCT with surgery compared to surgery alone. Also, a larger treatment effect with increased complete responses, is reported with nCRT compared to nCT. However, not any survival benefit has thus far been reported in favor of either nCRT or nCT.[31,65] The post-therapy pathologic stage is the most widely used and best predictor of outcome after neoadjuvant treatment and surgery. One of the measurements used is the Chirieac tumour regression scale. Using four categories the scale examines the extent of residual carcinoma in the specimen, called the tumour regression grade (TRG). TRG 1 means no residual carcinoma, TRG 2 means 1–10% residual carcinoma, TRG 3 means 11–50% residual carcinoma and TRG 4 means more than 50% residual carcinoma.[91]

Like in earlier trials, the main result of the NeoRes trial was the benefit of complete histological response among patients treated with nCRT (28%) versus (9%) nCT.[32] Despite a better histological response, the overall survival rate does not improve by adding radiotherapy.[18,92] In the NeoRes trial, the overall survival rate was reported as 40% in both treatment groups.[18]

2 HRQoL AND DYSPHAGIA

2.1 QUALITY OF LIFE

Quality of life (QoL) is a multidimensional concept with an individual's subjective perception of their "position in life" and broadly evaluates both positive and negative aspects of life. In this setting, health and global quality of life is an important domain in the overall quality of life. This is subjective and with different meanings from the patients perspective.[93] The meaning of health was broadened after World War II in 1948, and the WHO included quality of life as "a state of complete physical, mental and social well-being, and not merely the absence of disease ". [94,95] However, the earliest reference to quality of life is found in the Nichomachan Ethics, by Aristoteles (384–322 BC), in which happiness or well-being in particular, is considered important.

2.2 HRQoL

The concept of HRQoL includes a broader meaning and includes the aspects of QoL being affected by disease or treatment of disease.[93] Thus, HRQoL is recognised as a subjective measurement with a multidimensional covering of dimensions such as physical, psychological, occupational and social functioning.[93,96] A broadly used definition of HRQoL is "a multidimensional construct that represents the patient's evaluation of the impact of a health condition and its treatment on relevant aspects of life" and in the measurement of health, the definition has different meanings within the areas to which it is applied. [93,97,98] It is therefore important that the meaning of HRQoL is understood without a clearly stated definition.[93]

The history of HRQoL research derives from randomised controlled trials, using relatively objective measurements to measure clinical outcomes such as cure, biological response to treatment and survival. Subsequently, both clinicians and patients have advocated that subjective measurements should also be considered, not only measuring quality of life, but also symptoms and treatment related side-effects.[93]

The first modern instrument developed in clinical settings, was defined as a broad assessment of patients beyond physiological and clinical examinations being the Karnofsky Performance Status scale, and the scale was developed in 1947.[99] Though considered to only capture one dimension of QoL, with a range from 0 to 100, where 0 is considered "death" and 100 "normal" and the assessments are performed by health-care staff. The next generation of instruments was developed in the late 1970s and early 1980s, with the quantification of a general assessment of health. The instrument focused on physical functioning and psychological symptoms, impact of illness and reported distress and satisfaction with life experienced. Examples of instruments include the Sickness Impact Profile (SIP) and the Nottingham Health Profile (NHP). Also, in 1976, Priestman and Baum, developed the linear-analogue self-assessment (LASA) method, also called the visual analogue scale (VAS), with a 10 cm line, describing the extremes of a condition. One example of LASA is the Edmonton Assessment Scale (ESAS)[100,101] developed for use in palliative settings. It is a nine-item patient-rated symptom visual analogue scale.

QoL has been discussed in the medical literature since the 1960s[102], and became more important to health care as medical treatment extended length of life. The measurement of quality of life is important, because of a desire to measure outcomes beyond morbidity and biological functioning.[39,40,97]

An instrument currently used worldwide is the Medical Outcome Study 36-item Short Form Health Survey (SF-36) developed by Ware et al. in 1993. This instrument was intended to fill a gap between wide-ranging questionnaires and other relatively common single-item measures. It is designed, to provide assessment involving generic health concepts that are not specific to age, disease or treatment group. These *generic* instruments tended to cover a wide range of conditions and were able to compare patients against each other and against the population. Consequently, these instruments lacked ability to focus on issues of patients with a particular disease, and therefore lack the sensitivity to detect differences arising as a consequence of treatments especially compared within clinical trials. Today, this has led to *disease specific instruments*. Within cancer, there are three cancer-specific instruments: FACT-G (widely used in the US), the Rotterdam Symptom Checklist (RSCL) [103,104] and the European Organisation of Research and Treatment for Cancer (EORTC) QLQ-C30, with a broad variation between the instruments.[105] In addition, disease specific modules can be added. For example, oesophageal cancer-specific instruments [106-108] or condition specific instruments have been developed as those for chemotherapy-induced peripheral neuropathy, cancer cachexia and patient satisfaction.

2.3 PATIENT REPORTED OUTCOMES

Patient-reported outcomes (PRO) is considered an umbrella term for QoL and HRQoL research, including a broader definition considered to be "a measurement based on any report of the status of patient´s health condition that comes directly from the patient (i.e., study subject) about the status without interpretation of the patient´s response by a clinician or anyone else. A PRO can be measured by self-report or by an interview when the interviewer only records the patients´ response" including both measures in absolute terms (severity of symptom, sign or state of a disease) or as a change of a previous assessment.[93] This definition of PRO term is introduced by the Food and Drug Administration (FDA) in the USA and also by the European Medicines Agency (EMA). The most widely used trial outcomes are survival, treatment-related survival and surrogate's variables as treatment responses.[109] These outcomes and adding HRQoL create a stable base from which to draw conclusions from trials.[39] The measurement of PRO is also adopted as patient reported outcome measurement (PROM), it is also suggested that PRO could mean person-reported outcome.

2.4 CONCEPT OF HRQOL

In order to understand HRQoL, and the concept behind it and its determinants, a conceptual model by Wilson and Cleary is widely used. This model integrates the biological and psychological aspects of health and the way they affect HRQoL.[110] The model has been revised by Ferrans and colleagues,[111] and the model added the relationship between the individual characteristics and biological function, and thereby linking traditional clinical variables with HRQoL, by integrating the biological and psychological aspects of health outcomes.[93,111,112] The model describes five different levels of patient outcomes. The first level is the biological function. This includes cellular and whole organ functions. Symptoms are the next level, and includes emotional, cognitive and physical symptoms. Thirdly, the functional status in the model focuses on the optimisation of patients´ remaining functions, and includes physical, social, physiological and cognitive functions. The perception of general health is a subjective evaluation, and integrates the former components in the model, a synthesis of all different aspects of health. The last component of the model is overall quality of life a subjective evaluation, integrating the former four

levels and generating overall quality of life. It includes the happiness and satisfaction a subject is with the whole life. It is considered to be a complex model, but with highlights of important components.[111]

2.5 PSYCHOMETRIC PROPERTIES

Depending on the purpose of the research, an instrument must be carefully selected, depending on what is to be measured (trial outcomes, disease, symptoms, single outcome, generic). It is important to consider; the timing of measurements, the frequencies of measurements, available resources and procedures for missing questionnaires or items.[113,114] Furthermore, in choosing of instruments, their validity, reliability, sensitivity and responsiveness is important.[93] Validity considers whether the instrument measures what it is supposed to measures and reliability considers whether the results are random or reproducible. In addition, sensitivity measures whether the instruments are able to detect differences between patients or groups and responsiveness measures whether changes over time may be detected if they improve or deteriorate.[93]

EORTC QLQ-C30[105,115] was firstly released in 1993, for use in clinical trials because of a lack of common measurement of PRO. During the development, findings were that generally among groups of patients with more extensive or severe cancer disease they tended to have the lowest score on global, physical and role functions, and also scored highest on symptom scores on pain and fatigue scales. Also, when experiencing toxicity, lower scores were detected in global health/QoL, physical and role function together with symptoms such as nausea, pain and fatigue. It has also been suggested that female and younger persons score worse.[116] Several tests of psychometric properties have been performed to satisfy the use of QLQ-C30, both within several cancer diagnoses, stages of diseases and were cross-culturally tested in several countries globally.[93,105,115,117-120]

The instrument contains 30 questions with a four-graded Likert scale. It incorporates five functional scales (physical, role, cognitive, emotional, social) and three symptoms scales (fatigue, pain, nausea/vomiting), as well as a global health and quality of life scale, together with a number of single items that assess common symptoms reported by cancer patients (dyspnoea, loss of appetite, insomnia, constipation, diarrhoea) and the perceived financial impact. This is a self-administered instrument useful for making group comparisons.[115]

To complete the general cancer instrument EORTC QLQ-C30, disease-specific modules have been developed. The first oesophageal instrument QLQ-OES24 was tested by Blazeby and co-authors in[106] and was subsequently validated and updated to QLQ-OES18.[107] Additionally, an instrument for use in both oesophageal- and gastric cancer, QLQ-OG25, has been developed.[108] The modules are designed to collect information about disease- and treatment–specific symptoms and side-effects. There are differences between the modules, but all instruments cover common scales (dysphagia, eating, reflux, pain) and single items covering problems such as swallowing saliva, choked, dry mouth, taste, coughing, talking. Also, QLQ-OES24 and QLQ-OG25 covers symptoms of anxiety and odynophagia.[106,108]

The questionnaire items have four categories on a Likert scale: 1 not at all, 2 a little, 3 quite a lot and 4 very much. The global scales have a seven-step scale from “very poor” to “excellent”. A numeric score is usually computed according to the EORTC manual, and linear transection leads to a score from 0–100. A higher score on function means better function while a higher score on a symptom scale indicates more symptoms.[115]

Receiving a cancer diagnosis is a life-changing event and the treatment also has major physical, psychological and social effects and may therefore change the perceptions of quality of life and health. Thus, a response shift is defined as a "change in the meaning of a person's evaluation of a construct as a result of a change in a person's internal standards of measurement, a change in a person`s values, or redefinition of the construct". The response shift masks or exaggerates a treatment effect for patient-reported outcomes such as HRQoL. Response shift refers to changes in internal standards (recalibration), changes of values (reprioritizing) and changes in meaning of quality of life (reconceptualization).[67,93] Another way of assessing outcomes in which a response shift is considered is the then-test, which assesses both before and after at the same timepoints. Though, use of this test is considered to have a risk of recall bias.[67]

2.6 HRQoL OUTCOMES IN OESOPHAGEAL CANCER

In population-based studies it is suggested to use the general population as a comparator instead of using HRQoL outcomes from the diagnosis. This because patients are already affected by the disease at diagnosis.[121] However, randomised controlled trials that compare treatments outcome in order to collect baseline data are very important for enabling the analysis of treatment effect over time and differences between groups at baseline.

2.6.1 HRQoL outcomes with comparison of treatments in RCT's

Regarding oesophageal cancer there is a lack of trials and observational studies reporting HRQoL. A meta-analysis in oesophageal cancer, published in 2011, comparing oncological and surgical outcomes in trials, including 12 trials (1,854 patients) with randomised comparison of nCRT versus surgery, nine randomised comparisons of nCT versus surgery alone (1,981 patients) and two trials comparing nCRT with nCT (194 patients), concluded that a strong survival benefit of neoadjuvant treatments compared to surgery alone.[31] None of these papers have been able to present PRO.

Recently, the CROSS trial comparing nCRT with surgery alone, concluded that the overall survival rate was significantly higher in the nCRT group and with an acceptable treatment-related toxicity and postoperative complication rate [15,70]. The short-term HRQoL was recently published, and the authors concluded that no significant difference was found between groups at three, six, nine and twelve months after surgery with predefined outcomes (physical functioning, eating problems, global health/QoL, fatigue and emotional problems). However, in the nCRT group one week after termination of neoadjuvant therapy, all aspects of HRQoL were worse, but between six to nine months after surgery, outcomes returned to baseline levels, with the exception of fatigue and physical function.[69] Long-term HRQoL was published in 2018, reporting data with a median follow-up time of 105 months and reported no clinically relevant difference in HRQoL between treatment groups.[71]

HRQoL outcomes comparing definitive chemoradiotherapies have though been reported. A French trial, PRODIGE 5/ACCORD 17, comparing FLOLFOX with a regime of fluorouracil/cisplatin with 50 Gray radiotherapy, they revealed no HRQoL differences between the treatment groups. The patients included were considered unable or unwilling to undergo surgery, but were curable. Data were collected, at baseline, six months, one and three years, and both groups experienced lower physical and social functioning, as well as a further increase in fatigue and dyspnoea during treatment. However, patients treated with 5-Fluorouracil and cisplantin experienced a moderate improvement in dysphagia over time.

The authors concluded that it takes approximately six months until recovery to baseline HRQoL.[122]

The SCOPE-1 trial also compared definitive chemoradiotherapy by adding cetuximab to one group. This trial closed earlier because of futility. HRQoL outcomes have been published, and they reported high functional outcomes at baseline, while symptoms such as fatigue, insomnia and eating related symptoms (appetite loss, dysphagia, dry mouth) were revealed at baseline. During treatment, functional aspects decreased and symptoms also increased, but at six months after conclusion of treatment, recovery occurred. However, persisting problems with severe fatigue and insomnia were reported in 15% of the patients. At follow up at one year and 104 weeks, the scores were similar or better than before treatment.[123]

The landscape of HRQoL outcomes in trials have suffered from missing data, because collection of HRQoL can be administratively demanding. Thus, within several cancer diagnoses, many trials have been unable to present data with PRO. In trials on diseases with severe outcomes in particular there is a lack of publications on HRQoL outcomes.[113,124] In areas with successful HRQoL assessments this has facilitated the shift to greater patient-centredness in cancer care because a systematic assessment of symptoms is an important component of patient-centred care.[40] Inadequately reporting of HRQoL may lead to a loss of important information or may even mislead clinical decision-making. [125]

2.6.2 HRQoL and neoadjuvant treatment

In the CROSS trial, HRQoL was reduced in all aspects one week after termination of neoadjuvant treatment.[69] A prospective study by Blazeby et al. compared nCT, nCRT and surgery alone. They reported that during neoadjuvant treatment patients reported a reduction in several general aspects of HRQoL; worsening of physical, role and social function, problems with treatment related toxicity as fatigue, nausea and vomiting, dyspnoea, anorexia, diarrhoea and taste where increased, although oesophageal specific symptoms improved or remained unchanged during nCT, although dysphagia, eating problems, and reflux further deteriorated during radiotherapy, but were stable or improved before surgery[126] Similar results were obtained in a series of patients followed by Reynolds et al, who were treated with nCRT. Dysphagia was significantly improved but physical function and fatigue deteriorated significantly before surgery[127] Another study found that nCRT had a considerable temporary effect on most aspects of HRQoL.[128]

2.6.3 HRQoL after surgery

In a nationwide Swedish population-based register with collection of data between 2001 and 2005, HRQoL assessments have been collected and up-to-date, outcomes have been reported at six months and up to ten years after surgery. At six months after surgery, HRQoL was found to be severely impacted by surgery with a severe negative effect in functions, especially role and social functions and symptoms of fatigue, appetite loss, diarrhoea, dyspnoea and oesophageal symptoms with eating problems, coughing, reflux and oesophageal pain were commonly reported at six months and, at three-year follow-up after surgery, no improvement was detected.[47,129] In addition, complications during and after surgery have a detrimental effect on HRQoL at six months, five years and ten years after surgery.[59-63] However, at five-year follow up, HRQoL appears to recover to the same level as the background population, although in 14% of the patients who reported deterioration,

HRQoL was worse when compared with six months after surgery.[130] Major complications such as respiratory failure, pneumonia, anastomotic leakage and sepsis are found to be an independent predictor of several parameters of poor HRQoL. Dyspnoea, fatigue and eating difficulties in particular were prominent at all timepoints measured (six months, three and five years).[61] Survivors with a presence of comorbidity at baseline, or increased co-morbidity after surgery, reported poorer global health/QoL and worsening symptoms.[131] At ten-year follow up, HRQoL did not improve between 5 and 10 years. Instead, a decline in 23 out of 25 HRQoL aspects was reported and compared to an age and gender adjusted reference population. Ten-years survivors reported worse scores in all HRQoL aspects, with a significant deterioration in global health/QoL, role functioning, social functioning and most symptoms, the severest of which were reflux, eating problems, diarrhoea and appetite loss.[121,132] Moreover, emotional problems are substantial after oesophageal cancer surgery[133] and nutritional factors, such as eating difficulties and malnutrition, reduce HRQoL.[134,135] Neoadjuvant therapy and the female gender in particular seems to be associated with an increased risk of malnutrition following surgery of oesophageal carcinoma.[136]

In a meta-analyses, with 15 studies included, aimed at reporting HRQoL one year after surgery for oesophageal cancer, the findings indicated that patients will experience long-term deterioration after surgery, particularly a deterioration in social function and an increase of symptoms of fatigue, pain and coughing. The paper concluded that there was a need for better-quality evidence for several of the HRQoL outcomes measured, especially a need to provide prospective nationwide cohort studies.[137]

HRQoL measurement in oncology is considered to be on a fertile ground. Patients with cancer experience several symptoms and a reduction in functional ability. Many of these symptoms and functions are not achievable through laboratory tests or imaging procedures. Thus, it is necessary to rely on the patients' self-report of symptoms.[138]

2.6.4 HRQoL and palliative treatment

Palliative treatment in oesophageal cancer is offered to prolong survival, to offer symptom relief, and to thereby consequently improving HRQoL[124,139-141] Palliative treatments have not been reported with survival benefits between any treatment. Palliation of dysphagia is in focus in papers that report outcomes of treatments, and often, in retrospective, studies reporting treatment effects or side-effects.[73,80,142] However, in comparisons between treatment with brachytherapy and stents, it is considered that HRQoL is better in the long-term with brachytherapy while treatment with stents report better HRQoL in the short term[143] One review comparing PRO between palliative radiotherapy and chemotherapy, reports a lack of HRQoL outcomes in palliative settings and highlights the importance of reporting PRO in this setting. With a lack of survival benefits, PRO is therefore an important endpoint. In addition, more intensive treatment was seen to provide better HRQoL, even though toxicity increased. Patients appear to tolerate side-effects to a greater extent when they are hopeful about the treatment effect, and in information about side-effects may improve their coping ability. Only a few of the studies in the review reported clinically significant differences (4 out of 32), and the authors concluded that it is important to evaluate treatment effects on reported symptoms and quality of life.[82]

2.7 DYSPHAGIA

2.7.1 Dysphagia at diagnosis

Dysphagia, or "swallowing problems", is derived from the Greek word dys, meaning bad or disordered, and the root phag, meaning eat. Historically, there are several references of dysphagia symptoms, and one early description was given by Avicenna (980-1037 AD) in his encyclopedia of medicine, named Canon. Although, many aspects of dysphagia remains to be explained.

Dysphagia may be defined as either difficulty in initializing swallowing, usually described as oropharyngeal, or high dysphagia, or as a sensation that foods and/or liquids are obstructed in their passage through the mouth to the stomach (food sticks in the throat or chest), usually called oesophageal, or low, dysphagia. [23,144] An incidence of 33% of patients seeking acute health care have dysphagia, and in long-term-care facilities, 30-40% of patients have swallowing disturbances, mainly from neurological reasons.[145,146] In addition, dysphagia is estimated to affect up to 50% of people over the age of 60 years of age.[147] Consequently, it is important to distinguish between true oesophageal dysphagia from oropharyngeal dysphagia or other causes.[148] It is also important to distinguish between odynophagia (pain when swallowing), and dysphagia. This may be difficult in oesophageal cancer though odynophagia is reported to be more transient than dysphagia and only persists during the 15–30 seconds that the bolus takes to traverse the oesophagus.[149]

As previously mentioned, at diagnosis of oesophageal cancer dysphagia is the predominant symptom in more than 70%–90% of subjects and is followed by weight loss.[20-22] Dysphagia is considered a late alarm symptom because of the elasticity of the oesophageal wall and only 25% of patients are curative by having localised symptoms at the time of presentation.[23,24] Lastly, dysphagia occurs when the tumour obstructs 2/3 of the circumference of the lumen. Initially, solid food is difficult to swallow and the dysphagia usually progresses to include fluids. Additionally, difficulty in ingestion solids is considered to be the result of a mechanical obstruction, such as a tumour.[24]

Dysphagia in cancer is considered a key alarm symptom.[145,150] In the UK, with a high incidence of adenocarcinoma, there have been awareness campaigns have been conducted to raise public awareness of dysphagia and persistent heartburn, with the recommendation to visit a general practitioner if such symptoms are experienced.[151]

2.7.2 Palliation of dysphagia– a bridge to surgery

The main challenge in most patients with oesophageal cancer is the palliation of dysphagia. Experience and in-depth interviews with patients indicate that dysphagia is a troublesome symptom affecting all aspects of a patient`s daily life,[152] and which negatively impacts quality of life.[153]

Historically, dilatation has been used together with stenting to relieve swallowing problems. In 1885, the first intubation of malignant strictures was developed to palliate dysphagia but at that early time, stenting had a high incidence of rupture, fistulas and migration.[154] From the 1960s onwards, clinicians started to systematically investigate oesophageal stents for dysphagia, and in recent decades, self-expanding metal stents (SEMS) have taken a strong position,[155] especially in palliative settings, as well as during neoadjuvant treatment.[155,156] A

stent is supported by immediate relief of dysphagia and maintenance of nutrition. A stent placement is usually followed by immediate relief of dysphagia. Within a couple of days after stent placement, the ability to eat improves.[78,156,157] A number of papers, have investigated the role of stents as a bridge to surgery and reported safe early results with insertion of stents.[155,157,158] On the other hand, surgeons are reluctant to consider preoperative stents, because of their concern about perforation, difficulties in surgical dissection, and future tumour resectability. Furthermore, a French retrospective survey, investigated 2,944 patients, and reported that stents also have a negative outcome impact on oncological outcomes and are a predictor of poor prognosis.[159] Side-effects to be considered is that the employment carries a risk of perforation and may therefore jeopardize the planned neoadjuvant treatment[159]. There, is also a risk of the tumour cells spreading.[160] Peri-tumour inflammation causing fibrosis may further jeopardize the planned surgery.[159,161] During neoadjuvant treatment with tumour-debulking effects, approximately 32% of the stents have been reported to dislocate and chest discomfort has been reported with and incidence of 51%.[158,162] However, newer stents with a complete silicone lining, enabling the stents to be removed and allowing restaging before surgery show more promise with respect to the above mentioned problems. Also, biodegradable stents that dissolve in a few months are being discussed as alternatives to SEMS. It has also been reported that stents containing radioactive iodine have reported better relief of dysphagia and survival, although these are currently only being tested in palliative settings. [76] In recent years, papers have reported that among patients receiving stents, an approximately 30%-41% of the patients reports recurrent dysphagia.[142,162] The European Society of Gastrointestinal Endoscopy (ESGE) their recently made a recommendation to avoid application of SEMS as a bridge to surgery.[162]

Percutaneous Endoscopic Gastrostomy (PEG) is another procedure employed to ensure nutrition and prevent further weight loss during neoadjuvant treatment.[163] However, this is also considered more controversial, with a risk of damaging the future blood supply to the future gastric conduit, and thus contributing to anastomosis complications. In addition, a risk of tumor cell seeding with abdominal wall metastasis has also been reported.[164] However, it has also been reported that PEG employment does not endanger the surgical resection, but concerns with high adverse effect rates up to 36% and major rates of 22% at placements.[163,165] In addition, the use of feeding jejunostomy is considered to enhance nutrition during neoadjuvant treatment, but it requires a transabdominal procedure under general anesthesia. Such a procedures also carries a risk of infection, displacement, obstruction or other surgical complications, with delay in starting neoadjuvant treatment[166] After surgery, a feeding jejunostomy is often used, through the postoperative phase and until patients have recovered and are able to cover their nutritional needs orally, with the support of a dietician.

Nasogastric or nasojejunal feeding tubes are also proposed as a possible procedure but are also considered to sometimes being difficult for the patient to tolerate and have therefore been suggested as a short-term option, though a considerable risk of pneumonia has been reported with the tubes.[167] Parenteral nutrition to support patients during treatment is used, though in the short term, taken into account evidence that suggests side-effects as thrombophlebitis, and sepsis infection, as well not being cost-effective.[167] Lastly, endoscopic dilatation is used to improve swallowing. However, if the problems are caused by a tumour, this is not recommended because of a risk of tumour perforation.[168] After surgery and in other benign settings, dilatation is a treatment option here.

All, treatments used to palliate dysphagia are considered with their pros and cons. Thus, each patient must be carefully selected and requirements for nutritional support must be individualised during neoadjuvant treatment. The consequences of dysphagia, and consequently weight loss are important to consider in oesophageal cancer patients because a substantial weight-loss is important, due to a higher risk of surgical mortality and morbidity.[167,169]

Recently, a paper from the American Thoracic Society, reported in a retrospective series, comparing patients with or without gastrostomies. During the disease trajectory, patients needed expert nutritional support and it was recognised that patients with previous PEG placement seldom used their PEGs. The recommendation from these authors was to only place PEGs in a selective group of patients and instead increase nutritional support during treatment.[163] However, it has also recently been reported in oncological settings that patients experience relief of dysphagia during neoadjuvant treatment, challenging the need for invasive procedures.[170,171]

In HRQoL research a dysphagia scale is included in the oesophageal cancer-specific module and a few papers have reported that dysphagia during neoadjuvant treatment as well after termination of neoadjuvant therapy, dysphagia both improved and deteriorated.[126,127,172] Firstly, during treatment with induction nCT, dysphagia is reported to be relieved, [126,172] Secondly, during nCRT, dysphagia was reported to worsen[126] and thirdly, dysphagia was relieved or stabilised after termination of nCRT treatment.[126,127] However, it is suggested that in the vast majority of studies in which dysphagia is not the primary endpoint, may underestimate the improvement of dysphagia.[20] This is due to the inclusion of patients without dysphagia at baseline in the analyses, and is furthermore not considered if stents or other procedures to relieve dysphagia were used. This may also produce a source of bias in dysphagia assessment after surgery, in which interventions used to alleviate dysphagia, such as dilatations and stent placements, are rarely reported.[123]

2.7.3 Dysphagia measurement considerations

2.7.3.1 Ogilvie score[173]

The most commonly used scale in clinical practice is the Ogilvie score, also called the Atkinson score [173] and the Mellow Pinkas score [174]. In addition, this simple scoring system is widely used within studies and national registers and the score is also used in clinical practice. Dysphagia is graded on five levels (0=no problem to swallow or eat, 1=normal diet avoiding certain foods, 2= semi-solid diet, 3= fluids only, and 4= complete dysphagia, even with liquids). A newly published Swedish validation of the Ogilvie score suggests that the score is good to excellently reliable, with high internal consistency and stability (test-retest reliability) with good external consistency compared to the dysphagia scale in EORTC QLQ-OG25. The authors suggested using the Ogilvie score in especially clinical practice, in particular because of its simplicity.[175]

2.7.3.2 Watson dysphagia scale [176,177]

The Watson score was established to evaluate dysphagia in benign conditions. The Watson dysphagia score [177] combines information about difficulty in swallowing with a visual analogue scale independently applied to nine different types of liquids and solids, with a compound score from 0 to 45 (0= no dysphagia and 45=total dysphagia). The scale is easy to use and very applicable to use when interviewing patients and also very informative in evaluating difficulties in eating different types of food. The validation of the Watson scale was performed together with the Ogilvie score. The results show a good reliability and

reproducibility, suggesting that the Watson sale is particularly valid in clinical studies. In malignancy disease, patients often report intermittent or progressive swallowing problems and the instrument measures the frequency of difficulties.[175]

2.7.3.3 EORTC QLQ-OES24[106]

This instrument is the first version of an oesophageal cancer treatment module. It was developed in four phases: Phase I scrutinising literature within area and semi-structured interviews with patients and specialists, followed by a detailed interview with specialists, producing a list of QoL issues. Phase II constructing a provisional module with a list of items. Phase III pre-testing the provisional module on patients from European countries.

In a test of scale reliability and an evaluation of the validity of QLQ-OES24, a new version *QLQ-OES18*[107] was launched and tested prior to treatment and with a follow-up questionnaire in order to test the sensitivity to changes (Phase IV). Tests were performed on patients with oesophageal cancer with both curative options and palliative treatment modalities. The dysphagia scale was not changed in this new version, since the former version of the dysphagia scale showed an item correlation exceeding 0.40 and was reliable with a Cronbach's alpha over 0.71. The QLQ-OES18 has shown moderate to good reliability and discriminant validity, and is regarded as a clinically and psychometrically valid instrument for assessing dysphagia and other items included in the instrument.

In both QLQ-OES24 and QLQ-OES18, the dysphagia scale comprises three questions about whether patients have experienced the following symptoms or problems during the past week. Could you eat solid foods? Could you eat liquidized or soft foods and, lastly Could you drink liquids? It contains a four graded response alternative, 1 not at all, 2 a little, 3 quite a bit and 4 very much.

EORTC QLQ-OG25[108] This instrument has been validated to improve the assessment of HRQoL in both oesophageal and gastric cancer. The scale comprises three questions about dysphagia symptoms patients during the past week. Have you had problems eating solid foods? Have you had problems eating liquidized or soft foods, and lastly, Have you had problems drinking liquids?

The aim of the new instrument was to combine the existing oesophageal module with the gastric cancer module QLQ-STO22, and include a proposed new three-item dysphagia scale, among other scales. The items were already included in both scales but with different wording. During the completion, a semi-structured interview investigated patients' opinions and preferences for the items and scale. Patients were asked about which dysphagia scales they would keep in the new questionnaire and why they selected this option. In addition, observer records were also kept. The preferred dysphagia scale was the one used in QLQ-STO22, because being ease of understanding. Also, observers noted that patients completed this scale correctly. Multi-trait scaling analyses, reliability and validity tests indicates that the new instrument is reliable and valid.[108]

2.7.4 Consequences of oesophageal dysphagia and treatment

There are major nutritional consequences to be considered for patients as weight-loss followed by malnutrition and sarcopenia are common. Malnutrition is reported in over 60 % of diagnosed oesophageal cancer patients and thereby one of the highest frequencies within oncologic conditions.[167,169] Malnutrition in oesophageal cancer often combines low

intake due eating disability with cachexia, which is often combined with anorexia.[178] In addition, malnutrition may be caused by increased catabolism, because of infections or surgical intervention.[135,178,179] Dysphagia causes a seriously risk of cough by aspiration and pneumonia.[7,23,167] Patients at diagnosis with both dysphagia and a greater weight loss greater than 15%, and often also a low plasma albumin concentration, tend to be malnourished and often have disseminated disease at diagnosis.[169] During treatment trajectory it is necessary to continuously screen, assess and follow-up dysphagia, weight loss and other symptoms that cause negative quality of life.[9,167,171]

Dysphagia is the main symptom at diagnosis and if the patients experiences that swallowing problems recur after initial treatment, anxiety is common, mainly because of fear of recurrence. [133] However, benign causes such as strictures that require dilatations are also not uncommon. "Normal" gastrointestinal function is reported in lower than 20% of patients following oesophagectomy. Functional conduit disorders cause poor digestive function, and this includes dumping syndrome, delayed gastric emptying, dysphagia and reflux.[23] Dysphagia is also reported in up to 65% of patients after oesophagectomy [23,180]

In one study palliative patients' experience of dysphagia was investigated through interviews and subsequently patients completed a HRQoL questionnaire. The authors reported that five themes emerged, namely, recognizing dysphagia, the physical experience, the emotions evoked, the impact on social life and dysphagia and treatment. The patients included were only able to eat semi-solid food.[152] Patients reported that at diagnosis they never considered cancer as a cause of their dysphagia, and there was therefore a delay in receiving a diagnosis. In addition, the long time taken to finish a meal and the pain and choking symptoms were a cause for concern. They also experienced problems relating to mucus and phlegm. Weight loss and the emotional feelings evoked by dysphagia involved feelings of fear, insecurity and anxiety about eating. The impact on their social life was affected and they expressed severe concerns. Also, they were reluctant to eat in front of others, including close family members, because of embarrassment caused by the dysphagia. The main findings were that dysphagia is distressing and impacts the patients physical, emotional and social well-being.[152]

Several papers, included in four previous theses from Sweden have highlighted the need for support for patients and their relatives when they are diagnosed with oesophageal cancer, including support by subspecialized nurses working in multidisciplinary teams. [85,86,133,153,181-186] Andreassen et al, have focused on patients and family members need of information,[181-183] dysphagia, fatigue and uncertainty influenced patients everyday life, and information seeking was one strategy to manage illness.[182] Viklund et al. investigated the complex care pathway and reported that patients experienced a need of supportive care given by a specialist nurse and especially the need of nutritional support was dominated.[184] In addition, a well-organised and nurse led care pathway were found to be well-working and an appreciated model.[85] Malmstrom et al, have illuminated patients experiences of supportive care after oesophageal cancer surgery. The findings were that patients needed comprehensive supportive care after surgery and especially a need to develop a plan for the future including honest and realistic patient information of how to cope their new life-situation.[86] In addition, a proactive nurse-led telephone follow-up has a significant positive impact on the patient's ability to cope with a life with remaining side-effects from treatment.[185,186] Also, the European recommendation for the future care for oesophageal cancer patients urges the need of specialised multidisciplinary teams in order to improve HRQoL and survivorship.[9]

2.7.5 Histological response versus dysphagia relief

Because of dysphagia response during neoadjuvant therapy, many studies have addressed the question of whether clinical response of dysphagia is correlated to histological tumour response. Hitherto, the published studies that investigated this research question within different time-frames after or during neoadjuvant therapy, have not been able to detect any correlation between dysphagia response and histological tumour response. [172,187]

a *b*

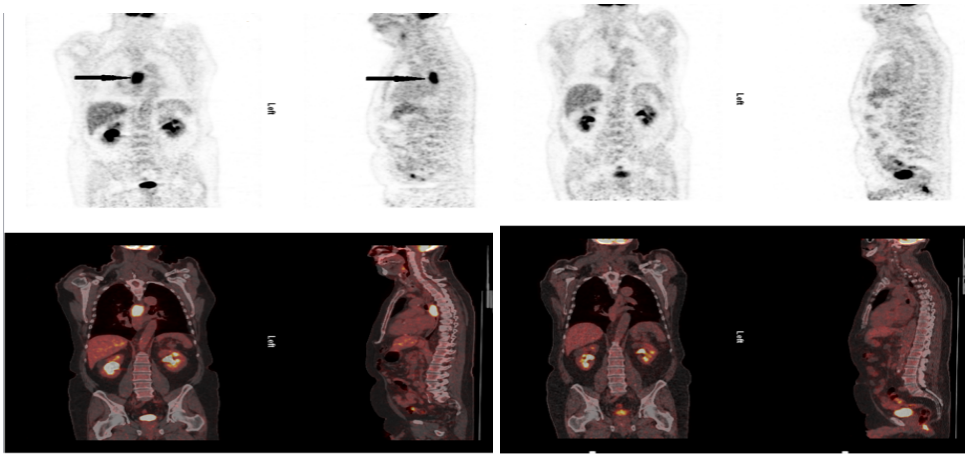


Fig. 4 FDG-PET/CT of a 72 years old male patient with T3N0M0 squamos cell carcinoma of middle oesophagus at diagnosis, before neoadjuvant chemo-radiotherapy. Black arrows is site of tumour FDG uptake.
Figure. 4b FDG-PET/CT images in unfused and fused states of the same patient as in figure , at follow-up examination four weeks following completion of neoadjuvant chemoradiotherapy. No remaining pathological uptake discovered in the tumour.

Courtesy dr Stefan Gabrielsson

3 AIMS

The overarching aims of this thesis is to increase the knowledge about HRQoL and swallowing problems in subjects diagnosed with oesophageal cancer.

The aim of paper I is to describe and analyse HRQoL one year after the diagnosis of oesophageal and GOJ carcinoma in an unselected nation-wide population-based cohort comprising both palliative and curative intent patients

The main aim of paper II is to prospectively assess changes in dysphagia during and after neoadjuvant therapy in a cohort of consecutive patients with oesophageal or GOJ carcinoma.

The main aim of paper III is to compare the effects on dysphagia of nCT and nCRT, and further to study the association between dysphagia response and histological tumour response to neoadjuvant therapy.

The main aim of paper IV is to study short- and long-term HRQoL among patients randomised in the NeoRes trial, comparing patients allocated to either nCT or nCRT.

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

	Paper I	Paper II	Paper III	Paper IV
Design	Population based cohort	Prospective cohort	Randomised controlled trial	Randomised controlled trial
Data source	NREV, Sweden	Karolinska University Hospital	Multicentre, Sweden and Norway	Multicentre, Sweden and Norway
Data Collection	2009–2016	2011–2013	2006–2013	2006–2018
Study time	One year after diagnosis	Before any treatment, after first chemotherapy cycle and before surgery	Before allocated treatment and after neoadjuvant treatment but before surgery	Before allocated treatment, after ended neoadjuvant treatment but before surgery, 1, 3 and 5 years after surgery
Outcome	HRQoL	Dysphagia, appetite, weight and histological response	Dysphagia, weight and histological response	HRQoL
Patients included	1156	35	156	165
Male gender %	82%	91%	82%	82%
Age median (range)	68 (29–93)	-	63 (39–75)	63 (37–75)
Adenocarcinoma %	69%	83%	73%	73%
Statistical analysis	Mean, MD, adjusted linear regression	ANOVA	Mann Whitney U test, linear regression, Wilcoxon rank sum, Chi-square	Mean, MD, linear mixed effects models with time interaction and linear regression

4 SUBJECTS AND METHODS

4.1 THE NEORES TRIAL

Papers II, III and IV are reports from the NeoRes (**Neo**adjuvant therapy for **Res**ectable Esophageal Cancer) trial. The trial was conducted within the Scandinavian Esophageal and Gastric Cancer Group (SEGCG), enrolling the first patient, in the third quarter of 2006 and the last patient in the first quarter of 2013. A final five-year follow-up ended in June 2018. The trial is registered at ClinicalTrials.gov: NCT01362127 and the trial was not funded by any commercially support.

4.1.1 Study cohort

In the NeoRes trial, centres in Sweden and Norway included patients and the sponsor of the trial was Karolinska University Hospital. In Sweden, four specialised surgical/oncological centres included patients (Stockholm, Umeå, Örebro and Göteborg), while in Sweden oncological treatment was also given at Mälarsjukhuset in Eskilstuna and Karlstad County Hospital. In Norway, three specialised centres included patients: St. Olavs Hospital in Trondheim, University Hospital in Oslo and Haukeland University Hospital in Bergen.

4.1.2 Eligibility criteria

Patients with histologically confirmed adenocarcinoma or squamous cell carcinoma of the oesophagus or GOJ (gastric cardia type I and II) were eligible for resection and oncological treatment was offered at inclusion. The disease stage at inclusion (T1N1 or T2-3N0-1 and M0-M1a) were defined according to the American Joint Committee on Cancer tumor-nodes-metastasis staging system 6th edition. Patients with cervical cancers were required to be resectable without laryngectomy. Patients with aged at 75 years or less with a performance status of 0–1 according to the WHO scale, and with resectable primary tumour, were assessed at the pre-randomisation evaluation. Blood samples were collected and values within normal limits of hematological and renal function were also required. The patients were not allowed to have any condtion that would render chemoradiotherapy unsuitable, as well as a life expectancy of at least three months. Written informed consent was given and signed by the patients.

4.1.3 Pre-treatment evaluation

Patients were diagnosed with an upper gastrointestinal endoscopy and Computed Tomography (CT) of the upper abdomen and chest. After a protocol amendment, the use of Fluorodeoxyglucose-Positron Emission Tomography (FDG-PET/CT) and endoscopic ultrasonography were recommended. Before treatment, evaluation of respiratory and cardiac functions tests were to be performed as well as an audiometry test, before oncological treatment.

4.1.4 Study design and statistical analysis

The trial is a prospective open phase II multicentre randomised clinical trial. The study population comprised patients diagnosed with adenocarcinoma or squamous cell carcinoma of the oesophagus or GOJ. The primary endpoint was histological complete primary tumour response (ypCR) after resection. Sample size calculation was performed to meet criteria of the primary endpoint, and resulted in 172 patients in order to meet criteria of 80 % power was calculated. To ensure meeting the primary outcome, 180 patients were to be included. The main analysis was performed on intention to treat basis.

All study data were collected and stored at Karolinska University Hospital and at each participating centre in accordance to applicable laws and reserach ethics. A web-based database was accessible to the investigators.

4.1.5 Randomisation

All patients were randomised at the Regional Cancer Centre in Stockholm, usually via fax and/or a telephone. Patients were stratified by histology, and a computer programme with block permutation was used at the randomisation. The allocation sequence was concealed from all investigators.

4.1.6 Ethics

The trial was performed in accordance with the Helsinki Declaration (as amended by Tokyo, Venice and Hong-Kong), and with the laws and regulations within the countries, that affords the greater protection of the individuals. The trial was registered in EUDRACT and accepted by the Swedish Medical Agency with ethical approval in both Sweden and Norway. The Swedish Research Ethics Committee in Stockholm, registration number 2006/738-32 and 2008-403-32, and in Norway: Central Norway Regional Health Authority with registration number 4.2008.416. The trial is registered in the Clinical Trials Database (https://clinicaltrials.gov; registration number NCT01362127).

4.1.7 Chemotherapy

Neoadjuvant treatment was started within two weeks of randomisation and three cycles, given at one, four and seven weeks of treatment with cisplatin (100 mg/m^2 day one) and 5-Fluorouracil (750 mg/m^2 at days one to five). Amendments were accepted during the trial. If patients were detected to have a hearing impairment, tinnitus or deterioration of renal functions Cisplatin was replaced by Carboplatin and Oxaliplatin in patients with adenocarcinoma and AUC 5 in patients with squamous cell carcinoma.

4.1.8 Chemoradiotherapy

Patients allocated to chemoradiotherapy received 40 Gray radiotherapy together with the same chemotherapy regimen as those allocated to chemotherapy alone. Radiotherapy started together with chemotherapy cycle number two, with 2 Gray daily, five days per week, over four weeks, using a photon beam linear accelerator. A three-dimensional dose planning system was used. To minimise doses to other organs, doses to the lungs exceeding 20 Gray were kept as low as possible and did not exceed one third of the lung. Volume to the hearts was kept at a minimum when the doses exceeded 30 Gray. Doses to both the kidneys were to be kept to a low volume and not exceed 12 Gray and to one kidney not to exceed 20 Gray. Maximum dose to the spinal cord was 40 Gray.
Patients were positioned and immobilised in a supine position with their heads on a standard headrest and preferably the arms above the head, in order to permit a multiple field technique. Patients with lower lung function were given a special attention to avoid radiation-induced pneumonitis and subsequent radiation fibrosis.

4.1.9 Surgery

The surgery was scheduled four to six weeks after completion of the allocated neoadjuvant treatments. In order to minimise morbidity and mortality, only centres with documented experience of cancer surgery of the oesophagus or GOJ and the stated procedure in protocol were allowed to participate. The operations were planned with a thoraco-abdominal resection with an intrathoracic anastomosis (Ivor Lewis procedure) for cancers in the distal third and cardia whereas a three-stage resection (Mc-Keown procedure) was carried out for

patients with tumours in the middle and upper part of the organ. If the individual surgeon considered it appropriate, other procedures were permitted. Other procedures included transhiatal esophagectomy, only employing laparotomy and a cervical incision for distal oesophageal and junctional cancers. Total gastrectomies were permitted for junctional tumours classified as Siewert II.

4.1.10 Assessments during treatment

Before any treatment, the patients' symptom were reviewed and assessed accordingly with blood samples, nutritional assessments and the use of the US National Cancer Institute`s Common Terminology Criteria for Adverse Events (NCI CTCAE v. 3.0), which was scale modified to this protocol. During neoadjuvant treatment, patients were assessed at least every third week and weekly during radiotherapy. Serious adverse forms (SAE) were reported to Stockholm Regional Cancer Centre and to the principal investigator in accordance with good clinical practice (GCP).

4.1.11 Follow-up

Follow-up visits after surgery were planned every third months during the first two years, and then every sixth months until five years after the end of treatment.

4.1.12 Health-related quality of life

Measurement of patient reported outcomes the EORTC their general HRQoL questionnaires QLQ-C30 and disease-specific modules were used. Assessments were performed before neoadjuvant treatment after completion of neoadjuvant therapy and at annual intervals during the follow-up after surgery, up to five years.

4.2 PAPER I

4.2.1 Study design

A cohort study population was registered from 1 January 2009 to 31 December 2016. The data used comprised prospectively collected exposure and outcome retrieved from the Swedish National Register for Esophageal- and Gastric Cancer (NREV). All patients alive one year after diagnosis and registered in the NREV completed patient-reported outcomes using the European Organisation of Research and Treatment their cancer general questionnaire QLQ-C30 and the oesophageal disease specific module QLQ-OG25 to describe health-related quality of life outcomes in patients diagnosed with both curative and palliative treatment of care. Known confounders (age, gender, histology) were adjusted for in the HRQoL analysis.

4.2.2 The Swedish National Register for Esophageal and Gastric Cancer (NREV)

The nationwide register was started in 2006, and up to today 95% of patients diagnosed with oesophageal cancer are registered. A validation study performed on the register, reported that 94% of the data registered are accurate.[188] Data is centrally monitored at the six Regional Cancer Centres in Sweden and all patients at diagnosis are required to be registered in the database. Responsibility for collecting PROMs was managed by the regional cancer centres from 2006 to May 2015. From May 2015 they are collected nationwide from the Regional Cancer Centre in Umeå.

4.2.3 Exposure

At diagnosis, the patients are registered in the register as either palliative or curative, and the intended treatment is also registered. This is usually decided at multi-disciplinary team conferences (MDT). In addition, patients were divided according to disease severity.

Patients with curatively intended treatment and who completed questionnaires are sub-classed according to T-stages (T0–T1 versus T2–T4) at diagnosis and treatment is determined with either surgery or definitive chemoradiotherapy in the curative cohort. In addition, the palliative cohort is classified according to metastasis (M1 disease), advanced tumour stage T4 (included both T4a and T4b) and other reasons, mainly comprising the low possibility of tolerating demanding palliative therapy. All included patients are categorised according to the above criteria's and included if alive one year after diagnosis.

4.2.4 Definitions of outcomes

The primary outcome of the study was HRQoL one year after cancer diagnosis comparing between palliative and curatively intended treatment and sub-groups. In addition, a comparison cohort of 4,910 Swedish age- and gender adjusted general population for collected in 2008 was used.

Data were sent by mail to all patients registered and alive one year after diagnosis. All reported items from the EORTC HRQoL both QLQ-C30 and QLQ-OG25 questionnaires were included in the analysis. The core questionnaire QLQ-C30 contains nine multi-item scales measuring global health/quality of life and functions (physical, role, emotional, cognitive and social) and multi-item symptom scales (fatigue, nausea and vomiting, and pain), and six single items measuring general cancer symptoms (dyspnoea, insomnia, loss of appetite, constipation, diarrhoea and financial problems).[115] The disease specific oesophageal module instrument (QLQ-OG25) contains one function scale measuring body image, six multi-item symptom scales (dysphagia, eating, reflux, odynophagia, pain, discomfort and anxiety) and nine single-item scales (eating with others, dry mouth, trouble with taste, trouble swallowing saliva, choked when swallowing, trouble with coughing, weight loss and hair loss).[108] However, the item hair loss was only answered if experienced. All items have a 4-point Likert scale from (1) "not at all", (2) "a little", (3) "quite a bit", and (4) "very much", with the exception of the global health/quality of life scale with a seven-point scale ranging from (1) "very poor" to (7) "excellent".

4.2.5 Statistical Analysis

HRQoL outcomes were described with mean and 95% confidence intervals. Adjusted mean differences were reported and statistically significance was tested only if relevant clinical significance was obtained with pre-defined mean differences. To aid the interpretation of differences, within the general cancer module EORTC QLQ-C30 we adapted clinical significance according to Cocks et al.[189] This was interpreted in all items with the exception of emotional function. We considered the emotional function and the oesophageal module QLQ-OG25 clinically worthwhile here in accordance with Osoba et al. [190] and King.[116] The statistical significance test was only performed if clinical significance was obtained. The analysis was performed using linear regression with adjustment for age as continuous data, gender as binary categorical data, histology as multilevel categorical data and also T stage in the curative cohort from T2–T4 as well as for definitive chemoradiotherapy.

4.2.6 Ethics

Ethical permission was granted by the Regional Research Ethics Committee in Sweden and with amendments (Dnr: 2013/596-31/3 and 2016/1486-32).

4.3 PAPER II

4.3.1 Study design

A cohort study performed at Karolinska University Hospital, included patients diagnosed with oesophageal cancer and GOJ after discussion at multidisciplinary team conferences

(MDT). Patients were screened for inclusion and included from February 2011 and to September 2013. Inclusion criteria comprised patients with resectable carcinoma of the oesophagus or GOJ considered to tolerate both neoadjuvant treatment and surgery. Patients with neoadjuvant treatment outside Karolinska University Hospital were excluded. Treatment given was mainly cisplatin and 5-Fluorouracil during weeks 1, 4 and 7 in the neoadjuvant setting, while in patients who also received radiotherapy the treatment started at cycle two, week 4.

4.3.2 Outcomes

Main outcome was to prospectively assess dysphagia and appetite before neoadjuvant therapy, after first cycle and after completion of neoadjuvant therapy. Secondarily, we assessed whether dysphagia response was associated with the presence of histological response.

The assessment of dysphagia was performed by the main author (BS) and (JE), called the secondary other in the paper. The assessment was performed during clinical visits or by telephone at baseline, after the first cycle of chemotherapy and after completion of neoadjuvant therapy before surgery.

To assess dysphagia, two instruments were used: *Ogilvie score,* which is a five-graded score and divides dysphagia into five levels where 0 equals no dysphagia, 1 is defined as eating normal diet but avoiding certain foods such as raw apples and meat, 2 is defined as intake of semisolid diet, 3 is defined as tolerating intake of fluids only, while 4 is defined as complete dysphagia, even for fluids. This instrument is used at our department to evaluate dysphagia.[173]

The *Watson scale* is mainly designed to evaluate benign diseases of the oesophagus, but is also used within studies of oesophageal carcinoma. The Watson scale uses a visual analogue scale that describes nine different types of solids and liquids using three response alternatives for each, to produce a composite score. With 0 corresponding to no dysphagia and 45 as total dysphagia.[176,177]

The *ESAS-VAS appetite* (Edmonton Symptom Assessment Scale) score that is mainly used in palliative settings was used to assess appetite. It contains a ten-graded visual analogue scale where 0 is absent symptom, meaning a good appetite and 10 worse possible, meaning no appetite.[100]

Histological primary tumour response, the tumour regression grade was assessed by Chirieac [91] a modification of the Mandard scoring system. Complete histological response is defined as no remaining tumour (A), B < 10% of the tumour cells viable, C 11-50% of the tumour cells viable, and D, defined as non-responders, with > 50% of the tumour cells are viable and remaining in the specimen.

4.3.3 Statistical analysis

Analysis of outcomes were measured at three time-points and a general linear model repeated measure (ANOVA) was performed to examine the treatment effect on dysphagia, appetite and weight changes. To examine correlation between the improvement in dysphagia and histological response of neoadjuvant therapy, also repeated measure ANOVA was used.

4.3.4 Ethics
All patients signed a written informed consent form. The study protocol was approved by the local ethics committee (Dnr: 2006/738-32, 2008/403-32, 2013/ 708-31/1)

4.4 PAPER III

4.4.1 Study design
Patient-reported dysphagia using PRO in a randomised controlled trial with the acronym NeoRes. The EORTC oesophageal cancer-specific modules were used to describe dysphagia before and after neoadjuvant treatment. In addition, we explored whether there was any relationship between dysphagia relief and histological tumour regression in the NeoRes trial.

4.4.2 Definition of outcomes
Dysphagia was assessed using patient-reported outcomes collected in the trial. Dysphagia was reported in the EORTC disease-specific instruments and three items assessing problems or ability to eat solid, semisolid or only liquids were used. The items have a four-graded response grade from 1, no problem, 2 to little problem, 3 quite a bit to 4 very much problem.
Patho-histological response The Chireac tumour regression grade was assessed as described in Paper II. However, all specimens in the NeoRes trial were examined by a group of expert pathologists at Karolinska University Hospital in Stockholm being blinded to the treatment allocation.

4.4.3 Statistical analysis
Data were transformed according to the EORTC manual[191] and also missing data were alos analysed according to the manual. Data are presented as mean with a 95 % confidence interval. A mean difference of at least 10 in mean scores was considered clinically relevant.[190] Data analysis regarding dysphagia outcomes, both the Mann-Whitney U-test and a linear regression, were used in two different settings. To compare outcomes with dysphagia relief and histological outcome, a chi-square test was used or, if appropriate Fischer's exact test. Multivariate regression (adjusted for possible confounders such as age, gender histology and T stage) was performed to assess whether relief of dysphagia was associated with histological response.

4.4.4 Ethics
The NeoRes trial was approved by the research ethics committees in Sweden and Norway. The trials were registered in EUDRACT and accepted by the Swedish Medical Agency.. The Swedish Research Ethics Committee in Stockholm, registration number 2006/738-32 and 2008/403-32, and in Norway; Central Norway Regional Health Authority with registration number 4.2008.416. The trial is registered in Clinical Trials Database (https://clinicaltrials.gov; registration number NCT01362127).

4.5 PAPER IV

4.5.1 Study design
Health-related quality of life assessments in the NeoRes Trial. Patients completed validated and tested EORTC HRQoL instruments at baseline before any treatment, after conclusion of neoadjuvant treatment and at one, three- and five-years follow-up after surgery.

4.5.2 Definition of outcomes

The European Organisation for Research and Treatment of Cancer (EORTC), the general cancer instrument QLQ-C30 and the oesophageal disease module QLQ-OES24/OG-25 with report of differences between treatment groups and also changes over time within groups.

4.5.3 Statistical analysis

Data were linearly transcribed according to the manual and missing data were reported according to recommendations. Over one half of the items need to be included in a scale. Data were reported with mean and mean differences and statistically tested with a linear mixed effect model with time interaction and linear regression. Graphs and group comparisons were analysed using panel data, allowing all subjects to be included. The presentation of data was according to intention to treat and unadjusted analysis. To reduce the risk of multiple-testing spurious results, only data with mean differences over or at least ten in accordance with a normally used standard were statistically tested and presented with mean differences and a 95% confidence interval with statistical significance assumed with a p-value <0.05.

4.5.4 Ethics

Signed informed consent was obtained from all subjects. The trials were registered in EUDRACT and accepted by the Swedish Medical Agency, as well as ethical approved and in both Sweden and Norway. The Swedish Research Ethics Committee in Stockholm, registration number 2006/738-32 and 2008-403-32, and in Norway: Central Norway Regional Health Authority with registration number 4.2008.416. The trial is registered in the Clinical Trials Database (https://clinicaltrials.gov; registration number NCT01362127).

5 RESULTS

5.1 PAPER I

During the study period between 2009 and to the end of 2017, 1,156 subjects responded to the questionnaires and were accessible for inclusion. In total 2,292 subjects were alive one year after diagnosis of oesophageal or GOJ carcinoma and were reported in the nation-wide Swedish registry for carcinoma in the oesophagus (NREV) (Figure 5).

Characteristics of the included subjects are presented in Table 2. In general, subjects were mainly diagnosed with adenocarcinoma with location in the distal oesophagus and diagnosed with a tumour stage T2–T3. The highest frequency of WHO performance status is 0–1 and ASA comorbidity grade 1–2, though in the palliative cohort more subjects were reported with worse WHO performance status and ASA comorbidity grade. The groups were found balanced between responders and none responders. In total HRQoL formulas were completed by more than 55% of the curative patients while only 40% of those treated with palliative management intention (Table 2, Figure 5).

Description of the reference population and the cohort of subjects with oesophageal cancer
The majority of the subjects included in this study reported lower mean levels in functions and a higher degree of symptoms compared to a Swedish reference population in almost all items and scales reported within the QLQ-C30 instrument. Regarding function scales, cognitive function was lower in both the curative and palliative cohort, but the other included function scales were even lower (physical, role, emotional and social). Among symptom scores, all scores reported are higher in subjects with oesophageal cancer one year after diagnosis compared to the reference population (Table 3).

HRQoL comparisons between the curative and the palliative intent cohort
In analysis, between the curative and the palliative cohort, lower physical function was reported among subjects with palliative intent treatment (MD -11, 95 % ci: -14 to -7). However, subjects with curative intended treatment reported a more problems with diarrhoea (MD -9, 95% ci: -13 to -5) compared to the palliative cohort. Analyses of the oesophageal-specific module, dysphagia (MD 11, 95% ci: 7 to 15), anxiety of future health (MD 10, 95% ci: 6 to 15), eating with others (MD 12, 95% ci 8 to 17) and trouble with taste (MD 10, 95% ci 6 to 15) were reported with more problems among subjects receiving palliative intent treatment. All differences reported were both clinically relevant and statistically significant (Table 3).

HRQoL subgroup comparison within the curative intent cohort
Firstly, comparing early tumours (T0–T1) and advanced tumors (T2–T2), fewer problems with eating (MD 10, 95% ci 5 to 15) and weight loss (MD 18, 95% ci 11 to 25) were reported if early tumour diagnosis. All differences reported were both clinically relevant and statistically significant (Table 4).

Secondly, in comparisons between subjects with early tumour stage and dCRT. Subjects with early tumour stage reported more problem with diarrhoea (MD -10, 95% ci -17 to -3). However, more problems were reported regarding dysphagia (MD 16, 95% ci 8 to 25), choking when swallowing (MD 13, 95% ci 5 to 20) and talking (MD 13, 95% ci 6 to 20) in subjects treated with dCRT. All differences reported were both clinically relevant and statistically significant (Table 4).

Lastly, in comparisons between advanced tumours (T2–T4) and dCRT cohorts, more problems with diarrhoea was reported in the advanced surgery cohort (MD -14, 95% ci -20 to -8) compared to dCRT. In addition, dysphagia (MD 11, 95% ci 4 to 18) and choking (MD 10, 95% ci 4 to 16) were reported with more problems in subjects treated with dCRT. The differences reported were both clinically relevant and statistically significant (Table 4).

HRQoL sub-group comparison within the palliative intent cohort
All subjects diagnosed in the palliative stage were sub-grouped. Firstly, those diagnosed with metastasis (M1), secondly advanced tumour stage (T4) and lastly others (mainly fragile subjects with comorbidities or who did not want treatment). Only a few clinically relevant differences were reported in comparisons between groups. Subjects diagnosed with metastasis reported more problem with dry mouth (MD -24, 95% ci -45 to -4) compared to subjects with advanced tumour stage. More problems relating to hair loss were reported in subjects diagnosed with metastasis (MD -13, 95% ci -26 to 0) compared to advanced disease stage. Lastly, more problem with dysphagia is reported in subjects diagnosed with advanced locally tumour (MD -18, 95% ci -33 to -3) compared to subjects diagnosed with other reason. All differences reported were both clinically relevant and statistically significant (Table 5).

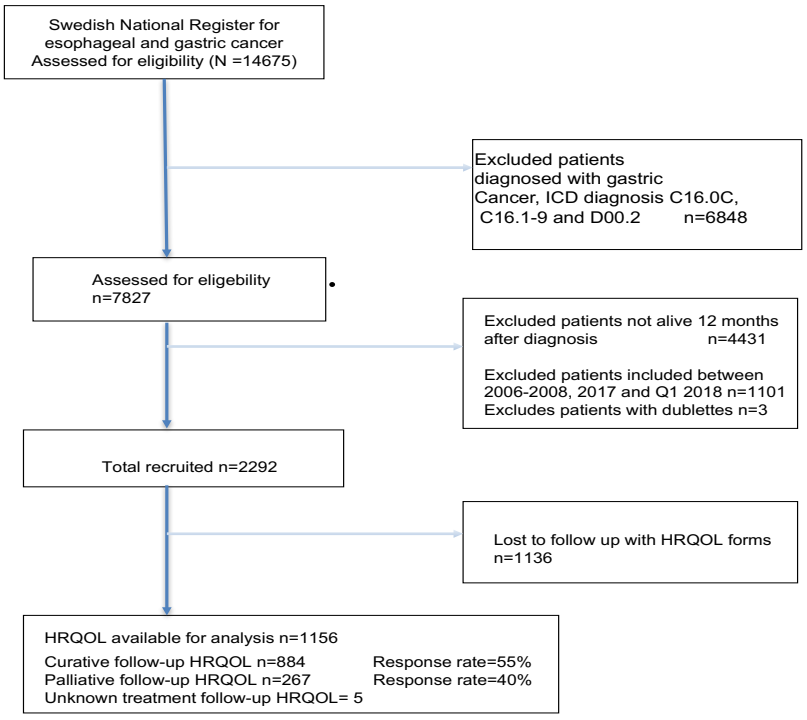


Figure 5. Flow-chart of the included patients who completed European Organisation for Research and Treatment of Cancer the general questionnaire QLQ-C30 and the oesophageal module QLQ-OG25

Table 2. Characteristics of all patients alive one year after oesophageal cancer diagnosis comparing those who completed European Organisation for Research and Treatment of Cancer the general questionnaire QLQ-C30 and the oesophageal module QLQ-OG25 and those who did not. Percentage within each category in brackets.

Table 2	**Curative intent**		**Palliative intent**	
	HRQoL[a] data		HRQoL[a] data	
	Yes	**No**	**Yes**	**No**
Total	884	709	267	411
Sex ratio (M: F)	683:201	559:150	193:74	299:112
Age (years)	66 (29–93)	65 (20–89)	72 (37–91)	70 (21–95)
WHO performance status	867	689	260	398
0	493 (57)	406 (59)	69 (27)	124 (31)
1	327 (38)	212 (31)	121 (47)	153 (38)
2	44 (5)	65 (9)	56 (22)	87 (22)
3	3 (0)	6 (1)	13 (5)	32 (8)
4	0	0	1 (0)	2
Missing	17	20	7	13
ASA fitness grade	871	697	259	400
1	297 (34)	236 (34)	49 (19)	75 (19)
2	443 (51)	338 (49)	107 (41)	163 (41)
3	126 (14)	114 (16)	86 (33)	143 (36)
4	5 (1)	9 (1)	17 (7)	19 (5)
Missing	13	12	8	11
Tumor location				
Proximal	53 (6)	45 (6)	14 (5)	33 (8)
Middle	81 (9)	78 (11)	25 (9)	45 (11)
Distal	643 (73)	502 (71)	169 (63)	237 (58)
Not specified	107 (12)	82 (12)	24 (9)	95 (23)
Tumor type	878	701	265	410
Adenocarcinom	614 (70)	464 (66)	175 (66)	260 (63)
SCC[b]	191 (22)	175 (25)	59 (22)	102 (25)
Other	73 (8)	62 (9)	31 (12)	48 (12)
Clinical T stage	884	708	267	410
T0-T1	145 (16)	132 (19)	40 (15)	46 (11)
T2-3	595 (67)	466 (66)	138 (52)	224 (55)
T4	36 (4)	54 (8)	38 (14)	69 (17)
Tx	108 (12)	56 (8)	51 (19)	71 (17)
Clinical N stage	884	708	267	410
N0	529 (60)	382 (54)	104 (39)	136 (33)
>N1	322 (36)	291 (41)	134 (50)	213 (52)
Nx	33 (4)	35 (5)	29 (11)	61 (15)
Clinical M stage	883	707	267	406
M0	851 (96)	673 (95)	155 (58)	214 (53)
M1	16 (2)	19 (3)	110 (41)	181 (45)
Mx	16 (2)	15 (2)	2 (1)	11 (3)

Abbreviations: a) HRQoL= health related quality of life, b) SCC= squamous cell carcinoma

Table 3. Mean, adjusted mean score difference (MD) and 95% confidence intervals (CI) in Health-Related Quality of Life scores at one-year follow-up from Swedish National Registry including oesophageal cancer in patients who completed European Organisation for Research and Treatment of Cancer QLQ-C30 questionnaire and oesophageal module QLQ-OG25 comparing patients with curative and palliative treatment intent and comparison in a Swedish reference population.

Table 3	**All* n=1156**	**Reference population n=4910**	**Curative treatment n=884**	**Palliative treatment n=267**	**Curative compared to palliative adjusted**
QLQ-C30	Mean (CI)	Mean (CI)	Mean (CI)	Mean (CI)	MD (CI)
Global health/QoL	60 (58 to 62)	76 (76 to 77)	61 (60 to 63)	55 (51 to 58)	-8 (-11 to -4)
Functions					
Physical function	73 (72 to 75)	88 (87 to 89)	76 (75 to 78)	64 (61 to 68)	**-11 (-14 to -7)**
Role function	64 (62 to 66)	88 (88 to 89)	66 (64 to 68)	56 (51 to 60)	-13 (-18 to -8)
Emotional function	75 (74 to 76)	86 (85 to 86)	76 (75 to 78)	71 (67 to 74)	-8 (-11 to -4)
Cognitive function	82 (80 to 83)	88 (88 to 89)	82 (81 to 84)	79 (76 to 82)	-4 (-7 to -1)
Social function	71 (69 to 72)	91 (91 to 92)	72 (70 to 74)	65 (61 to 69)	-10 (-14 to -6)
Symptoms					
Fatigue	43 (41 to 44)	19 (18 to 20)	41 (39 to 42)	49 (46 to 53)	10 (6 to 14)
Nausea and vomiting	17 (15 to 18)	3 (2 to 3)	16 (15 to 18)	18 (15 to 21)	2 (-8 to 5)
Pain	26 (25 to 28)	19 (18 to 20)	25 (23 to 27)	31 (27 to 35)	8 (4 to 12)
Dyspnoea	36 (34 to 38)	16 (16 to 17)	35 (33 to 37)	41 (37 to 45)	8 (4 to 12)
Insomnia	28 (26 to 30)	18 (17 to 18)	27 (25 to 29)	31 (27 to 35)	5 (1 to 10)
Loss of appetite	30 (28 to 32)	3 (3 to 4)	28 (26 to 30)	38 (33 to 43)	10 (5 to 15)
Constipation	14 (12 to 15)	5 (5 to 6)	11 (10 to 13)	22 (18 to 25)	10 (6 to 13)
Diarrhoea	21(19 to 22)	6 (5 to 6)	23 (21 to 25)	13 (10 to 16)	**-9 (-13 to -5)**
Financial	14 (12 to 16)	4 (4 to 5)	14 (13 to 16)	13 (10 to 16)	4 (0 to 7)
QLQ-OG25					
Function					
Body Image	72 (70 to 74)		74 (71 to 76)	67 (63 to 72)	-7 (-12 to -3)
Symptoms					
Dysphagia	24 (22 to 26)		22 (20 to 24)	32 (28 to 36)	**11 (7 to 15)**
Eating	33 (32 to 35)		32 (30 to 34)	37 (33 to 41)	6 (2 to 10)
Reflux	24 (22 to 25)		24 (23 to 26)	21 (18 to 25)	-2 (-6 to 2)
Odynophagia	20 (18 to 21)		19 (17 to 20)	23 (20 to 27)	6 (3 to 10)
Pain and discomfort	26 (25 to 28)		26 (24 to 28)	27 (23 to 31)	3 (-1 to 7)
Anxiety	46 (44 to 48)		44 (42 to 46)	52 (48 to 56)	**10 (6 to 15)**
Eating with others	21 (19 to 22)		18 (16 to 20)	29 (25 to 34)	**12 (8 to 17)**
Dry mouth	30 (28 to 32)		29 (26 to 31)	36 (32 to 40)	7 (2 to 11)
Trouble with taste	24 (22 to 26)		22 (20 to 24)	31 (27 to 36)	**10 (6 to 15)**
Trouble swallowing saliva	12 (11 to 14)		11 (10 to 13)	17 (13 to 20)	6 (2 to 9)
Choked when swallowing	18 (16 to 19)		17 (15 to 19)	20 (16 to 23)	3 (-1 to 7)
Trouble with coughing	31 (29 to 32)		30 (28 to 32)	31 (27 to 35)	1 (-3 to 5)
Trouble talking	12 (10 to 13)		11 (10 to 13)	14 (11 to 17)	3 (-1 to 6)
Weight loss	31 (29 to 33)		30 (28 to 33)	33 (29 to 38)	3 (-2 to 8)
Hair loss	21 (18 to 24)		22 (18 to 25)	19 (13 to 25)	-1 (-8 to 6)

Text in bold are clinically relevant and statistically significant

Table 4. Mean, adjusted mean score difference (MD) and 95% confidence intervals (CI) in Health-Related Quality of Life scores at one-year follow-up from Swedish National Registry including oesophageal cancer who completed European Organisation for Research and Treatment of Cancer QLQ-C30 questionnaire and oesophageal module QLQ-OG25 in patients stratified by clinical T-stage

Table 4	**cT0-T1**	**cT2-4 Surgery**	**cT2-4 dCRT**	**cT0-T1 compared to cT2-4 Surgery adjusted**	**cT0-T1 compared to T2-4 dCRT adjusted**	**cT2-4 Surgery compared to cT2-4 dCRT adjusted**
QLQ-C30	Mean (CI) **n (145)**	Mean (CI) **n (539)**	Mean (CI) **n (92)**	MD (CI)	MD (CI)	MD (CI)
Global health/QoL	64 (60 to 69)	61 (59 to 63)	58 (53 to 64)	-4 (-9 to 1)	-6 (-13 to 2)	-2 (-8 to 4)
Functions						
Physical function	79 (76 to 82)	76 (74 to 78)	72 (67 to 77)	-3 (-8 to 1)	-6 (-12 to 0)	-4 (-9 to 1)
Role function	71 (66 to 76)	66 (63 to 69)	65 (59 to 71)	-5 (-11 to 2)	-5 (-14 to 4)	-1 (-9 to 7)
Emotional function	76 (72 to 80)	76 (75 to 79)	75 (70 to 79)	0 (-5 to 5)	-3 (-10 to 3)	-2 (-7 to 3)
Cognitive function	83 (79 to 86)	83 (81 to 85)	79 (74 to 84)	0 (-4 to 4)	-5 (-11 to 1)	-4 (-9 to 0)
Social function	76 (71 to 80)	72 (70 to 74)	70 (64 to 76)	-4 (-9 to 2)	-7 (-14 to 1)	-3 (-9 to 4)
Symptoms						
Fatigue	35 (31 to 40)	41 (39 to 44)	45 (39 to 50)	6 (1 to 12)	9 (1 to 16)	3 (-3 to 9)
Nausea and vomiting	11 (8 to 15)	18 (16 to 20)	13 (9 to 18)	5 (0 to 9)	0 (-6 to 5)	-5 (-10 to 0)
Pain	27 (22 to 31)	25 (22 to 27)	25 (19 to 30)	-3 (-8 to 3)	-2 (-9 to 5)	2 (-4 to 8)
Dyspnoea	31 (27 to 36)	35 (32 to 38)	36 (30 to 42)	5 (-1 to 11)	6 (-2 to 14)	1 (-6 to 8)
Insomnia	24 (19 to 29)	29 (27 to 32)	23 (17 to 28)	3 (-3 to 9)	-2 (-10 to 6)	-6 (-13 to 1)
Loss of appetite	20 (15 to 25)	29 (26 to 32)	30 (22 to 37)	10 (3 to 16)	7 (-2 to 16)	0 (-8 to 8)
Constipation	12 (8 to 16)	11 (9 to 13)	14 (9 to 19)	-2 (-6 to 3)	1 (-6 to 8)	3 (-2 to 8)
Diarrhoea	21 (16 to 26)	26 (23 to 28)	11 (7 to 15)	3 (-3 to 8)	**-10 (-17 to -3)**	**-14 (-20 to -8)**
Financial	11 (7 to 16)	15 (13 to 17)	14 (8 to 19)	1 (-4 to 6)	2 (-5 to 9)	1 (-5 to 7)
QLQ-OG25						
Function						
Body Image	79 (74 to 84)	73 (70 to 76)	70 (63 to 78)	-7 (-13 to 0)	-9 (-18 to 0)	-1 (-9 to 7)
Symptoms						
Dysphagia	18 (13 to 23)	22 (19 to 24)	34 (27 to 42)	5 (-1 to 11)	**16 (8 to 25)**	**11 (4 to 18)**
Eating	24 (20 to 28)	34 (32 to 36)	34 (28 to 40)	**10 (5 to 15)**	8 (1 to 16)	-1 (-7 to 5)
Reflux	23 (18 to 28)	25 (23 to 28)	20 (14 to 25)	2 (-3 to 8)	-4 (-12 to 3)	-8 (-14 to -1)
Odynophagia	18 (13 to 22)	18 (16 to 20)	23 (18 to 29)	-1 (-6 to 4)	3 (-4 to 10)	5 (0 to 11)
Pain and discomfort	26 (22 to 31)	27 (25 to 29)	23 (17 to 28)	0 (-5 to 5)	-5 (-12 to 3)	-4 (-10 to 2)
Anxiety	40 (35 to 44)	44 (42 to 47)	47 (39 to 54)	4 (-2 to 10)	7 (-1 to 16)	3 (-4 to 10)
Eating with others	15 (10 to 20)	18 (16 to 21)	23 (17 to 29)	4 (-1 to 10)	9 (1 to 17)	4 (-3 to 11)
Dry mouth	27 (22 to 32)	28 (26 to 32)	28 (21 to 35)	3 (-3 to 9)	2 (-6 to 11)	-1 (-9 to 6)
Trouble with taste	18 (13 to 22)	22 (19 to 25)	28 (21 to 35)	4 (-2 to 10)	9 (1 to 18)	6 (-1 to 13)
Trouble swallowing saliva	8 (5 to 11)	12 (10 to 14)	14 (9 to 19)	3 (-2 to 7)	5 (-1 to 11)	2 (-4 to 7)
Choked when swallowing	14 (11 to 18)	16 (14 to 18)	27 (20 to 35)	3 (-2 to 8)	**13 (5 to 20)**	**10 (4 to 16)**
Trouble with coughing	28 (23 to 32)	31 (29 to 34)	32 (25 to 39)	3 (-3 to 9)	1 (-7 to 10)	0 (-7 to 7)
Trouble talking	9 (6 to 13)	11 (9 to 13)	19 (12 to 25)	5 (0 to 9)	**13 (6 to 20)**	5 (-1 to 10)
Weight loss	19 (14 to 24)	34 (31 to 37)	27 (20 to 34)	**18 (11 to 25)**	9 (1 to 17)	-8 (-16 to 0)
Hair loss	23 (12 to 36)	21 (17 to 26)	23 (11 to 36)	-5 (-18 to 9)	-9 (-28 to 10)	-3 (-15 to 10)

Text in bold are clinically relevant and statistically significant

Table 5. Mean, adjusted mean score difference (MD) and 95% confidence intervals (CI) in Health-Related Quality of Life scores at one year follow-up from Swedish National Registry including oesophageal cancer who completed European Organisation for Research and Treatment of Cancer QLQ-C30 questionnaire and oesophageal module QLQ-OG25 in patients stratified by reason for palliative intention.

Table 5	**Incurable due to**				**Mean score difference**	
	M1 n=110	Tumour stage T4 n=22	Non-tumour-related reasons[a] n=135	M1 compared to T4 adjusted	M1 compared to non-tumour-related reasons[a] adjusted	T4 compared to non-tumour-related reasons[a] adjusted
QLQ-C30	Mean (CI)	Mean (CI)	Mean (CI)	MD (CI)	MD (CI)	MD (CI)
Global health/QoL	54 (48 to 60)	49 (34 to 64)	56 (51 to 61)	-4 (-11 to 11)	2 (-6 to 11)	5 (-9 to 19)
Functions						
Physical function	65 (59 to 70)	62 (48 to 77)	65 (60 to 69)	0 (-14 to 15)	1 (-7 to 9)	1 (-12 to 15)
Role function	53 (46 to 60)	52 (36 to 69)	59 (53 to 65)	-1 (-19 to 18)	4 (-7 to 15)	3 (-15 to 21)
Emotional function	69 (64 to 74)	76 (65 to 87)	71 (67 to 75)	7 (-6 to 21)	0 (-8 to 7)	-8 (-20 to 4)
Cognitive function	79 (74 to 84)	81 (71 to 92)	79 (75 to 83)	3 (-9 to 15)	-1 (-7 to 6)	-2 (-13 to 9)
Social function	60 (54 to 66)	56 (40 to 73)	71 (66 to 76)	-3 (-19 to 13)	7 (-2 to 16)	10 (-4 to 24)
Symptoms						
Fatigue	50 (44 to 55)	51 (36 to 65)	49 (44 to 54)	0 (-15 to 15)	2 (-7 to 11)	1 (-13 to 16)
Nausea and vomiting	18 (13 to 23)	18 (7 to 29)	17 (13 to 21)	4 (-16 to 9)	-1 (-9 to 6)	3 (-8 to 15)
Pain	32 (25 to 38)	31 (17 to 45)	31 (26 to 36)	-2 (-19 to 14)	-1 (-10 to 8)	3 (-11 to 17)
Dyspnoea	42 (36 to 49)	44 (30 to 59)	40 (34 to 45)	4 (-13 to 21)	0 (-10 to 10)	-5 (-22 to 12)
Insomnia	30 (24 to 36)	38 (23 to 53)	30 (24 to 36)	7 (-9 to 23)	3 (-6 to 12)	-2 (-18 to 14)
Loss of appetite	38 (30 to 45)	44 (28 to 61)	37 (30 to 43)	1 (-19 to 21)	3 (-8 to 14)	1 (-17 to 19)
Constipation	20 (14 to 26)	20 (7 to 32)	23 (18 to 29)	-3 (-18 to 13)	4 (-6 to 13)	6 (-10 to 21)
Diarrhoea	12 (7 to 16)	12 (4 to 21)	14 (9 to 18)	0 (-12 to 11)	4 (-3 to 11)	3 (-8 to 15)
Financial	16 (11 to 21)	9 (-1 to 19)	11 (7 to 15)	-5 (-17 to 8)	1 (-7 to 8)	6 (-5 to 17)
QLQ-OG25						
Function						
Body image	64 (57 to 71)	67 (48 to 85)	70 (64 to 76)	2 (-17 to 21)	5 (-5 to 16)	4 (-13 to 21)
Symptoms						
Dysphagia	34 (27 to 40)	51 (34 to 67)	28 (23 to 33)	8 (-9 to 25)	-7 (-16 to 3)	**-18 (-33 to -3)**
Eating	38 (32 to 44)	45 (30 to 61)	35 (30 to 41)	2 (-14 to 18)	0(-9 to 9)	-5 (-20 to 10)
Reflux	22 (16 to 27)	23 (8 to 38)	21 (16 to 26)	-2 (-17 to 12)	-2 (-11 to 6)	1 (-13 to 15)
Odynophagia	22 (17 to 28)	27 (13 to 40)	24 (19 to 29)	0 (-14 to 14)	4 (-4 to 13)	4 (-10 to 18)
Pain and discomfort	26 (20 to 32)	29 (18 to 41)	28 (23 to 34)	3 (-13 to 18)	7 (-3 to 16)	7 (-8 to 22)
Anxiety	52 (46 to 59)	52 (36 to 67)	52 (46 to 57)	-3 (-21 to 14)	1 (-9 to 10)	3 (-13 to 19)
Eating with others	33 (26 to 40)	30 (14 to 46)	26 (20 to 32)	-7 (-26 to 11)	-5 (-16 to 6)	2 (-15 to 19)
Dry mouth	40 (32 to 48)	22 (6 to 38)	35 (29 to 40)	**-24 (-45 to -4)**	-5 (-16 to 5)	15 (-1 to 31)
Trouble with taste	37 (29 to 45)	32 (16 to 47)	26 (20 to 32)	-5 (-25 to 15)	-5 (-16 to 6)	-3 (-19 to 14)
Trouble swallowing saliva	20 (14 to 26)	14 (-1 to 29)	14 (10 to 19)	-11 (-27 to 4)	-9 (-18 to -1)	0 (-13 to 13)
Choked when swallowing	19 (13 to 25)	23 (10 to 36)	20 (15 to 25)	2 (-14 to 17)	3 (-6 to 9)	-1 (-15 to 13)
Trouble with coughing	27 (21 to 33)	29 (12 to 46)	35 (29 to 40)	-3 (-18 to 13)	7 (-2 to 16)	8 (-8 to 23)
Trouble talking	16 (11 to 22)	17 (5 to 28)	12 (8 to 16)	-3 (-17 to 10)	-5 (-13 to 3)	-3 (-14 to 9)
Weight loss	35 (28 to 42)	27 (10 to 44)	32 (26 to 39)	-15 (-33 to 4)	-1 (-12 to 10)	10 (-8 to 28)
Hair loss	27 (18 to 36)	18 (-3 to 39)	10 (3 to 17)	-5 (-29 to 18)	**-13 (-26 to 0)**	2 (-18 to 21)

Text in bold are clinically relevant and statistically significant

5.2 PAPER II

Patients included at diagnosis, during and after neoadjuvant treatment
During the study period, 43 patients were screened for inclusion and 35 patients were included and assessed at baseline and after the first cycle of chemotherapy. Because of side-effects during treatment, only 32 patients remained and were followed until surgery. In addition, 24 patients completed chemoradiotherapy versus 8 patients completed neoadjuvant chemotherapy (Table 6).

Comparisons of dysphagia, appetite and weight between baseline and first chemotherapy cycle
A statistically significant relief of dysphagia with both Ogilvie score (1.89 to 1.06) and Watson scale (27.03 to 16.46) was detected ($p<0.001$). Also, appetite scale (3.83 to 2.6, $p<0.03$) significantly improved already after first cycle of chemotherapy in the whole cohort. Patients remained weight stable after first chemotherapy cycle (77 kg, $p=1.00$) (Table 7).

Baseline assessment of dysphagia, meaning that the majority of the patients only being able to intake fluids and the rest restricted to eating minced food.
The relief of dysphagia after completion of cycle one, corresponded to being able to eat more solid food (vegetables, potatoes, fish, bread and pasta) and more than 40% of the patients were also able to eat meat (data not shown).

Comparisons of dysphagia, appetite and weight during treatment
Further statistically significant ($p<0.001$) relief of symptoms was detected after completed neoadjuvant therapy measured with both Ogilvie score (1.89 to 0.63) and Watson scale (27.03 to 9.41). However, appetite was not significantly improved in comparison with baseline (3.83 to 2.91, $p=0.11$) and after completion of neoadjuvant therapy before surgery, comparing the whole cohort. Patients remained weight stable during the treatment period (77 kg) (Table 7).

Also, after completion of neoadjuvant treatment before surgery patients reported that dysphagia was further relieved, with 60% of the patients studied being able to eat meat (data not shown).

Relief of dysphagia, appetite and weight in subgroups treated with nCT and nCRT
Only 8 patients completed neoadjuvant chemotherapy, and dysphagia was only improved significantly with Ogilvie score (1.7 to 0.62, $p=0.03$). Patients remained weight stable (77 kg) and appetite improved but not significantly during treatment period (3 to 1.5, $p=0.07$). However, in the neoadjuvant chemoradiotherapy group including 24 patients, both Ogilvie score (2 to 0.65, $p<0.001$) and Watson scale (29.27 to 8.75, $p<0.001$) significantly improved. No significance was detected regarding weight over time (77 kg, $p=0.71$) but appetite improved from 4.33 to 3.52 ($p=0.03$) (Table 7).

Dysphagia response and histological response
No association between the presence of histological response, the degree of response and relief of dysphagia was detected. (Watson, $p=0.466$ and Ogilvie, $p=0.181$) (Fig 6).

Table 6. Characteristics of 35 patients included in the analysis

Characteristics	n (%)
Included	35(100)
Gender	
Male	32 (91)
Female	3 (9)
Histology	
Adenocarcinomas	29 (83)
Squamous cell carcinoma	6 (17)
Tumor location	
Oesophagus	22(63)
Gastroesophageal junction	13(37)
Neoadjuvant treatment	
Chemotherapy	10 (29)
Chemoradiotherapy	25 (71)
Clinical T-stage	
T2	5 (14)
T3	30 (86)
Clinical N-stage	
N0	14 (40)
N1	16 (46)
N2	5 (14)

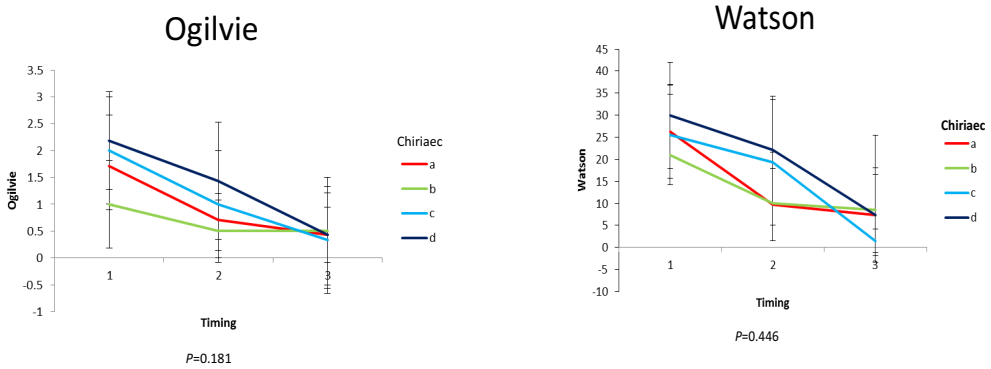


Fig. 6 Correlation between dysphagia development during and after neoadjuvant therapy (Watson, Ogilvie) and histological tumor response according to Chirieac. A-7, B-4, C-3, D-16.

Table 7. Development of dysphagia, weight, and appetite during neoadjuvant therapy

	Baseline	After Chemo-therapy cycle 1	P-value[a]	After completed neoadjuvant therapy	P value[b]	P-value [c]
All patients						
Included Patients	35	35		32		
Weight (mean)	77.33	77.38	**1,00**	76.79	**0.84**	**0.94**
Appetite score	3.83	2.6	0.03	2.91	1	0.11
Dysphagia score						
Ogilvie	1.89	1.06	<0.001	0.63	0.081	<0.001
Watson	2.,03	16.46	<0.001	9.41	0.06	<0.001
Chemoradiotherapy						
Included Patients	25	25		24		
Weight (mean)	77.4	77.5	**1.00**	76.6	**0.45**	**0.70**
Appetite score	4.33	2.7	0.03	3.52	0.59	0.03
Dysphagia score						
Ogilvie	2	1	<0.01	0.65	0.27	<0.001
Watson	29.27	16.45	<0.01	8.75	0.01	<0.001
Chemotherapy						
Included Patients	10	10		8		
Weight (mean)	77.2	76.9	**1.00**	77.3	**1.00**	**1.00**
Appetite score	3	2.6	1	1.5	0.48	0.07
Dysphagia score						
Ogilvie	1.7	1.1	0.14	0.62	0.38	0.03
Watson	22.55	14.55	0.19	9.87	0.87	0.11

a) p-value for difference between baseline and after cycle one, **b**) p-value for difference between after cycle one and after completed neoadjuvant therapy, **c**) p-value for whole treatment period from baseline to after complete neoadjuvant therapy. Repeated measurement analysis of variance was used for significance testing.

5.3 PAPER III

This paper presents dysphagia analysis in the NeoRes trial, a secondary endpoint outcome measurement. A total of 181 patients were randomised between 2006 and 2013, 91 patients were allocated to neoadjuvant chemotherapy and 90 patients to neoadjuvant chemoradiotherapy. In this study 134 patients were included at baseline and 98 patients at the end of treatment. The aim was to evaluate dysphagia response during neoadjuvant treatment, thus patients with stent insertion were excluded (20 patients) from the primary analysis (Figure 7). Assessment of dysphagia were extracted by use of validated questionnaires applied in the trial. Characteristics of the included patients is presented in table 8, and considered to be balanced between subjects that responded versus not responded to dysphagia questionnaires.

Changes of swallowing problems within treatment groups

In comparison within treatment allocation, among patients with dysphagia at baseline treated with nCT, they reported relief of dysphagia after completion neoadjuvant treatment. This was detected both clinically relevant and statistically significant (MD -16, 95% ci: -29 to -4, p=0.012). In patients without dysphagia they reported no changes. In addition, patients reported improved ability to eat solid food and minced food, both detected with clinical relevance and statistical significance. In patients treated with nCRT they also reported relief of dysphagia after completion of neoadjuvant therapy, both clinically relevantly and statistically significantly (MD -13, 95% ci: -25 to -1, p=0.039) improvement. In addition, improved ability to eat solid food were reported, this was both clinically relevant and statistically significant. However, in patients treated with nCRT and who reported no dysphagia at baseline deterioration were reported after completion of nCRT treatment. This was detected both clinically relevant and statistically significant (MD 17, 95% ci: 8 to 25 p<0.001) (Table 9).

Differences of dysphagia in comparisons between nCT and nCRT

No significantly difference were reported in comparison between allocated groups in patients who reported dysphagia at baseline. However, in comparison between groups among patients without dysphagia at baseline, a clinically relevant and statistically significant difference were reported with more dysphagia after ended nCRT treatment (MD 14, 95% ci: 3 to 25, p=0.014) (Table 10).

Nutritional considerations

Patients treated with nCT were weight stable when compared between baseline and before surgery (81 kg), while patients treated with nCRT loosed three kilograms when measured at baseline and before surgery (80 versus 77 kg). Nutritional treatment differed significantly between the groups, patients treated with nCRT were provided with more gastrostomies compared to those treated with nCT (20 versus 8, p=0.05). Also, management with orally feeding only was lower in patients with nCRT (56% versus 77%, p=0.05) compared to nCT (Table 11).

Comparisons between responses of dysphagia and histological responses

When investigated whether any correlation was detected between histological response and clinical T-stage, using histopathological stage and dysphagia scoring prior and after ended treatment, no statistically significant association between dysphagia response and histological response (p=0.204) were reported. In addition, dysphagia did not differ among those with complete response (TRG1) versus those with lack of any response (TRG4) (p=0.583) (Table 12).

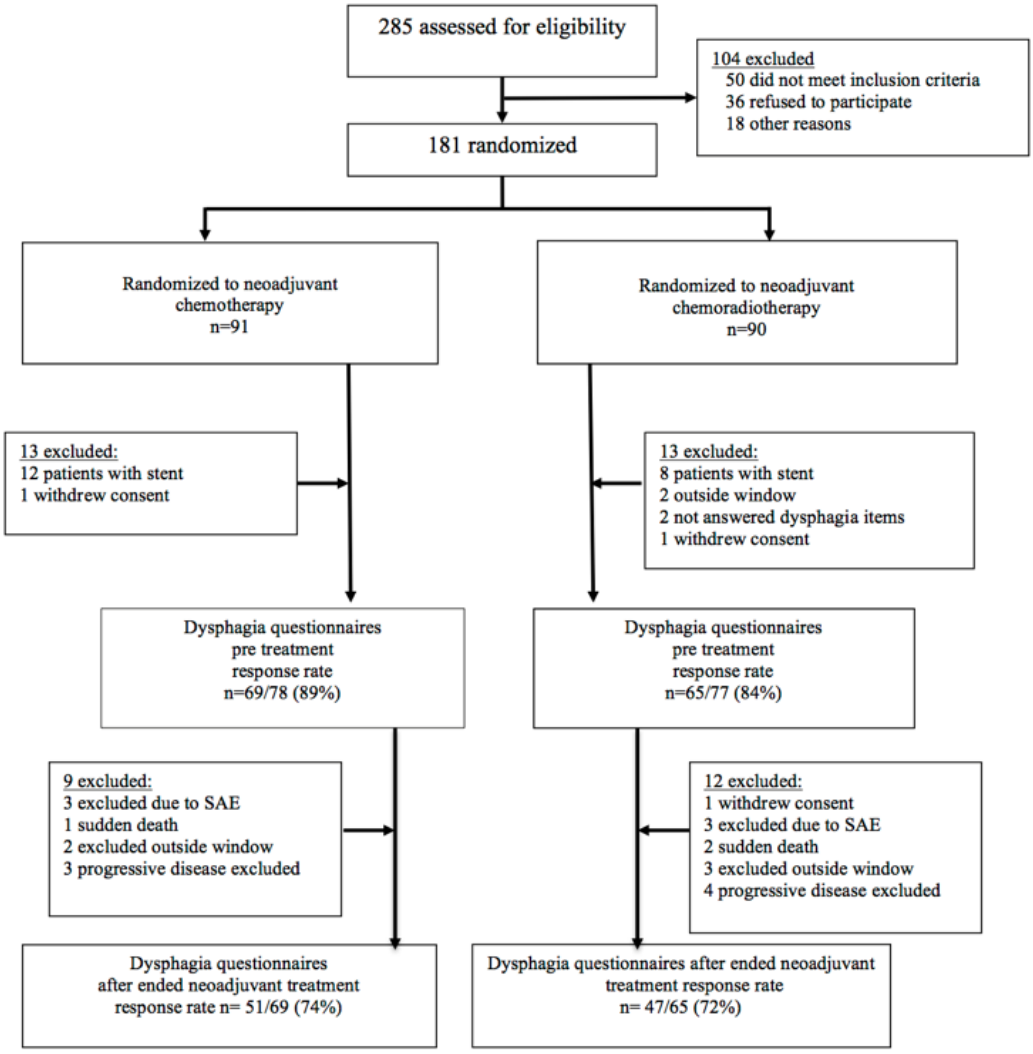


Figure 7. CONSORT all patients included in the NeoRes trial and completed dysphagia questionnaires

Table 8. Characteristics were similar in comparison with the whole cohort and between treatment allocations

Table 8	All patients randomised		Subgroup of patients who completed dysphagia questions	
	nCT (%)	**nCRT (%)**	**nCT (%)**	**nCRT (%)**
Eligible	91(100)	90(100)	69(89)	65(85)
Gender				
Female	14(15)	18(20)	10(14)	14(22)
Male	77(85)	72(80)	59(86)	51(78)
Age in years median (Range)	63(37–75)	63(38–74)	62(39–75)	63(42–74)
Histology at diagnosis				
Adenocarcinoma	66(73)	65(72)	51(74)	47(72)
SCC	25(27)	25(28)	18(26)	18(28)
Clinical TN-Stage [a]				
T1	1(1)	1(1)	1(1)	0(0)
T2	31(34)	31(34)	22(32)	20(31)
T3	59(65)	58(64)	46(67)	45(69)
N0	34(37)	33(37)	26(38)	21(32)
N-positive	57(63)	57(63)	43(62)	44(68)
WHO performance status[b]				
0	77(85)	75(83)	59(86)	53(82)
1	14(15)	15(17)	10(14)	12(18)

All patients who completed European of Research and Treatment of Cancer (EORTC) dysphagia questions in QLQ-OES24/OG25, and excluded patients with stent
a) Clinical tumor stage, T refers to the size and extent of the main tumor and N refers to the number of nearby lymph nodes that have cancer b) WHO performance status range 0-4
nCT= neoadjuvant chemotherapy, nCRT= neoadjuvant chemoradiotherapy

Table 9. EORTC QLQ OES24/OG25, self-reported dysphagia symptom score, both before and after neoadjuvant treatment by allocated treatment among patients with cancer of the oesophagus and GOJ returning questionnaires at both timepoints

Table 9	Number of patients	Before neoadjuvant treatment mean score (ci)	After neoadjuvant treatment mean score (ci)	Mean score difference (ci)	p-value
Neoadjuvant chemotherapy					
No dysphagia at baseline	17	0 (0–0)	3 (-2-7)	3 (-5-10)	0.216
Dysphagia at baseline	29	42 (32–51)	25 (12–39)	-16 (-29--4)	0.012
Problem to eat solid food [a]	29	60 (49–71)	31 (16–47)	-29 (-43--14)	<0.001
Problem to eat minced food [a]	28	44 (32–56)	27 (12–43)	-18 (-34- -2)	0.030
Problem to drink [a]	29	22 (10–33)	18 (5–31)	-3 (-18-11)	0.630
Neoadjuvant chemoradiotherapy					
No dysphagia at baseline	14	0 (0–0)	17 (5–28)	17 (8–25)	<0.001
Dysphagia at baseline	31	41(31–50)	28 (17–39)	-13 (-25--1)	0.039
Problem to eat solid food [a]	30	58 (47–68)	36 (23–49)	-22 (-36--8)	0.003
Problem to eat minced food [a]	30	37 (24–49)	28 (13–42)	-9 (-24-6)	0.242
Problem to drink [a]	29	22 (10–33)	18 (9–27)	-5 (-19-10)	0.521

The European Organization for Research and Treatment of Cancer (EORTC) Esophageal modules QLQ-OES24/OG25. Data is presented with means and mean score differences and 95% confidence (ci) intervals. All data analyzed with linear regression with prediction by arm. Scores are between 0-100 a high score= high level of symptoms. A mean score difference of 10 points or more was defined as a clinically relevant difference. Patients supported with stents are excluded from analysis. Self-reported comparison of dysphagia before and after neoadjuvant treatment in all study participants who completed dysphagia items both before and after treatment and reporting dysphagia at baseline. a) Items included in dysphagia scale.

Table 10. Comparison of dysphagia score between arms, regarding mean score difference between before and after neoadjuvant treatment

Table 10. Comparison of dysphagia scores between arms, regarding mean score difference between before and after neoadjuvant treatment					
	Number of patients	nCT[b] mean score difference	nCRT[b] mean score difference	Difference between arms	p-value
No dysphagia	31	3 (-2-7)	17 (8-25)	14 (3-25)	0.014
Dysphagia	60	-16 (-29-- 4)	-13 (-25--1)	4 (-14-21)	0.686
Problem to eat solid food [a]	59	-29 (-43--14)	-22 (-36- -8)	7 (-14-27)	0.519
Problem to eat minced food [a]	56	-18 (-34--2)	-9 (-24-6)	9 (-13-31)	0.415
Problem to drink [a]	58	-3 (-18 -11)	-5 (-19 -10)	-1 (-21-19)	0.910

Self-reported comparison of dysphagia before and after neoadjuvant treatment in all study participants who completed dysphagia items both before and after treatment and reporting dysphagia at baseline. a) Items included in dysphagia scale. Trial allocations b) nCT= neoadjuvant chemotherapy and nCRT= neoadjuvant chemoradiotherapy.

Table 11. Nutritional support and weigh changes among 152 patients with cancer of esophagus or GOJ and randomised in the NeoRes trial who completed EORTC QoL-OES24/OG25 baseline dysphagia questionnaire

Table 11	nCT	nCRT	p-value
152 patients:			
Albumin baseline mean (range)	40 (17–50)	40 (30–66)	0.516
Weight (kg) baseline mean (range)	81 (50–117)	80 (42–122)	0.559
Weight (kg) presurgery mean (range)	81 (48–122)	77 (42–121)	0.363
BMI baseline	26 (17–38)	26 (17–34)	0.477
BMI after treatment	26 (18–38)	25 (16–34)	0.455
Nutritional treatment from baseline until surgery:			**0.012**
Oral	61 (77)	40 (56)	0.005
Gastrostomy	8 (10)	20 (28)	0.005
Clinifeeding tube	4 (5)	8 (11)	0.231
Parenteral	6 (8)	4 (6)	0.433
Stent	11(14)	7(10)	0.426

Data are presented as mean and numbers. Discrepancies between the arms in patients with Gastrostomy (PEG) is primarily because of when the trial started in 2006, at one site the patients allocated with nCRT were prepared with PEG before treatment. Patients treated with stents included in the table. Albumin and nutritional treatments are analysed by Chi-square test and Fischer Exact Test. Weight (kg) and BMI is analysed using Mann Whitney U Test

Table 12. Comparison between histological response and clinical T-stage (cT), histopathologic (pT)-stage and dysphagia scoring prior to and after neoadjuvant treatment among patients with cancer of the esophagus or GOJ

All patients with surgery	n obs	TRG1 n (%)	TRG2 n(%)	TRG3 n(%)	TRG4 n(%)	p-value TRG1 vs TRG4
cT-stage [a]						0.262
T2	56	9 (31)	5 (21)	6 (32)	36 (43)	
T3	100	20 (69)	17 (79)	13 (68)	48 (57)	
pT-stage [b]						<0.001
ypT0	29	29 (100)	0 (0)	0 (0)	0 (0)	
ypT1	27	0 (0)	11 (46)	4 (21)	12 (14)	
ypT2	23	0 (0)	4 (17)	4 (21)	15 (18)	
ypT3	70	0 (0)	8 (33)	11(58)	51 (61)	
ypT4	7	0 (0)	1 (4)	0 (0)	6 (7)	
Prior to therapy dysphagia mean score (CI)	119	25 (15 - 34)	29 (12 - 45)	37 (19 - 55)	26 (19 - 33)	0.803
Post therapy dysphagia mean score (CI)	88	20 (6 - 34)	23 (8 - 38)	18 (-1 - 37)	20 (12 - 28)	0.583

a) cT-stage is Clinical T-stage, comparing, Chi square test used to compare TRG1 and TRG4
b) pT-stage is histopathologic T-stage defined by tumour regression grade according to Chireac (TRG), comparing The Chi-square test used to compare TRG1 and TRG4
Health Related Quality of Life (HRQoL), the dysphagia items on the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-OES24/OG25 before and after neoadjuvant treatment among patients with surgery. Wilcoxon rank sum test used to compare TRG1 and TRG4 CI=confidence interval

5.4 PAPER IV

A total of 285 patients were screened for eligibility in the NeoRes trial between October 2006 and February 2013. Of these, 181 met the inclusion criteria and signed informed consent forms to participate in the trial. At randomisation, patients were allocated to either neoadjuvant chemotherapy (n=91) or to neoadjuvant chemoradiotherapy (n=90) plus surgery. Baseline characteristics were balanced between the allocated groups. (See table 13) In total 165 patients were included in HRQoL analysis, and 154 patients completed baseline questionnaires and 113 patients after ended neoadjuvant treatment, see CONSORT (Figure 8), regarding HRQoL completion rates during follow up in the trial.

HRQoL before neoadjuvant treatment

At inclusion, patients reported lower scores in several functions (especially role, emotional and social), global health/QoL was low and several symptoms were scored high (fatigue, insomnia, loss of appetite, dysphagia, eating problems, odynophagia and anxiety of future health) (Table 14).

HRQoL after ended neoadjuvant treatment before surgery

Differences in comparison between allocation, was that patients reported more problems with appetite loss and this were clinical relevantly higher when given nCRT, but did not reach statistical significance. While problems of pain when swallowing (odynophagia) were relieved both clinically relevant and statistically significant when treated with nCT (MD 11, 95% ci: 0 to 22, p=0.047) compared to nCRT (Table 15).

Changes were reported within groups in comparisons with baseline. Patients reported several functions were further decreased after neoadjuvant treatment. However, clinically and statistically significant changes were observed regarding global health/QoL, physical, role and social function when treated with nCRT, but this was not reported in the nCT group. In addition, after neoadjuvant treatment especially some oesophagus related symptoms were relieved after neoadjuvant treatment in both groups. Especially, treatment with nCT reported changes with fewer troublesome eating problems, odynophagia and anxiety of future health, in contrast other symptoms deteriorated (fatigue, dry mouth and trouble with taste). Also, in the nCRT group symptoms were relieved (problems with choking and odynophagia), while other symptoms worsen (fatigue, nausea and vomiting, dyspnoea, appetite loss, financial difficulties and trouble with taste). All reported symptoms were changed both clinically relevant and statistically significant (Figure 9a).

HRQoL one year after surgery

In comparison between allocation no clinically or statistically significantly differences were revealed at one-year follow-up after surgery. However, between treatment groups patients treated with nCRT reported more clinically relevant more problem with dry mouth (MD 11, 95% ci: -3 to 25, p=0.123), but without statistical significance (Table 15).

Changes were reported within both groups in comparisons with baseline. Patients treated with nCT reported decreased physical function. Regarding symptoms patients reported improvements (trouble with sleeping and constipation) and conversely (dyspnoea, diarrhoea, reflux and trouble with talking) became worse. In addition, patients treated with nCRT reported decreased physical function. Among symptoms odynophagia improved, but dyspnoea and dry mouth became worse. All reported symptoms and physical function were detected with clinically relevance and statistically significance in both groups (Figure 9b).

HRQoL three years after surgery

Differences were reported between allocations at three years follow up, with better HRQoL in several aspects if treated with nCT compared to nCRT. Social functioning was clinically lower when treated with nCRT (MD -10 (95% ci: -23 to 4, p=0.159)) compared to nCT, but did not reach statistically significance. In addition, more problems were reported with dyspnoea (MD12 (95% ci: -1 to 27, p=0.067)) and problems with coughing (MD 17 (95% ci: 4 to 30, p=0.011)) both being clinically more affected when treated with nCRT compared to nCT. Although, coughing was also statistically significant (Table 15).

Changes were reported within both groups in comparisons with baseline. Patients treated with nCT reported no change in functions, while symptoms (insomnia, constipation and anxiety of future health) were improved. Reflux was the only reported problem that remained at three years follow up compared to baseline. Although, in the nCRT group patients reported lower levels of physical function and several worsen symptoms (dyspnoea, diarrhoea, reflux and trouble with cough) at three years follow up. In addition, patients also reported improved problems (dysphagia and odynophagia) when treated with nCRT. All reported symptoms and physical function were both with clinically relevant and statistically significant in both allocated treatment groups (Figure 9c).

HRQoL five years after surgery

In direct comparison between treatment allocation, several clinically relevant differences were reported but neither were statistically significant. Patients treated with nCRT they reported worsen functions and symptoms compared to nCT. Firstly, both role function (MD -12, 95% ci: -33 to 9, p=0.237) and social function (MD -11, 95% ci: -27 to 7, p=0.246) were lower compared to nCT. Secondly, among known treatment related side-effects more problems with fatigue (MD 10, 95% ci: -7 to 26, p=0.244) and dyspnoea (MD 16, 95% ci: -2 to 34, p=0.085) were reported. Lastly, among known oesophageal side-effects troubles with swallowing saliva (MD 13, 95% ci: -5 to 30, p=0.165), dry mouth (MD 18, 95% ci: -2 to 37, p=0.075) and trouble with taste (MD 10, 95% ci: -8 to 27, p=0.271) were more severe compared to nCT (Table 15).

Few changes were reported at five years follow up in comparisons with baseline. In functions no changes were reported in either group. Although, patients reported worsen problems with dyspnoea and reflux when treated with nCRT and both were clinically relevant and statistically significant (Figure 9d).

CONSORT diagram health-related quality of life in NeoRes trial

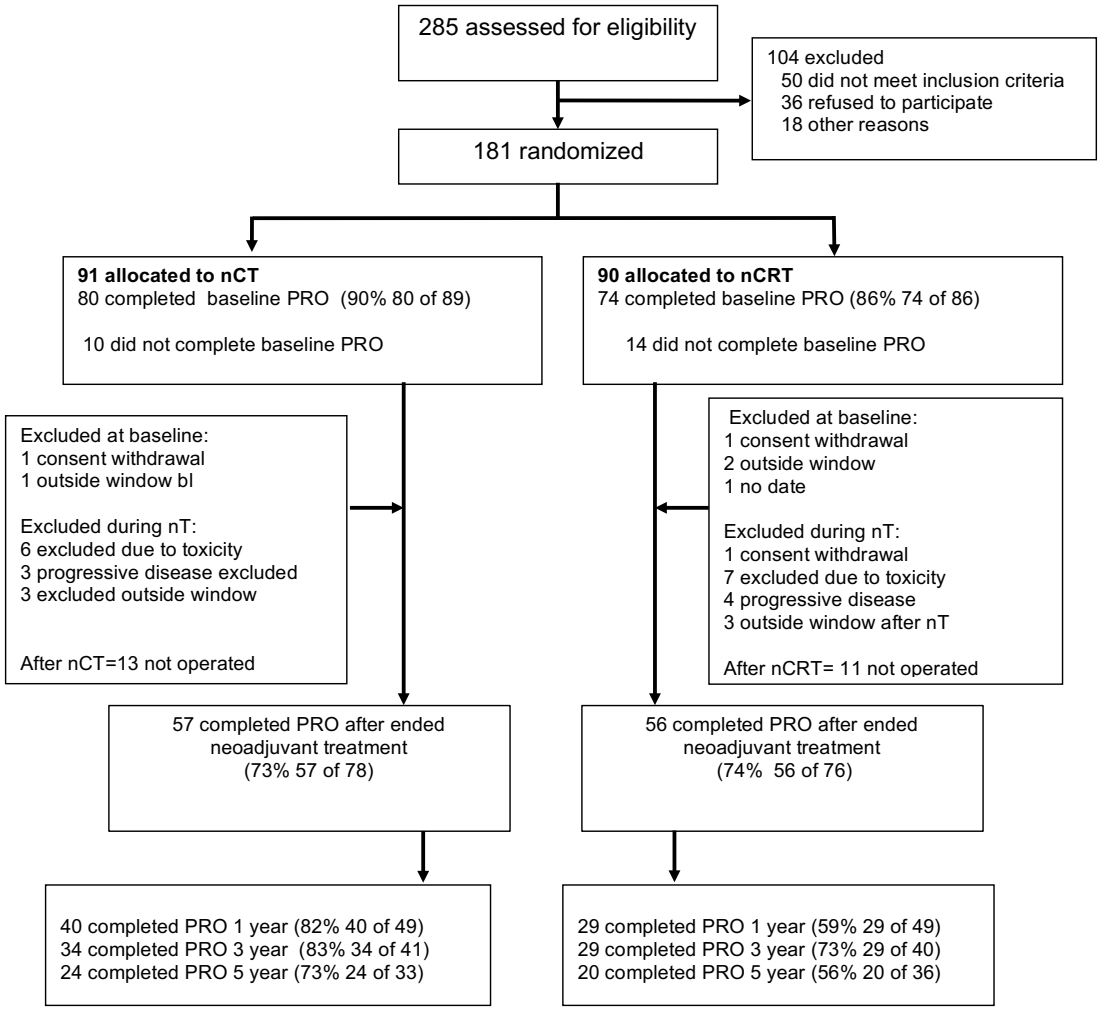


Figure 8. CONSORT diagram included patients in NeoRes trial and completed follow-up of patient reported outcomes using the European Organisation for Research and Treatment of Cancer (EORTC) core questionnaire QLQ-C30 and the esophageal module. Abbreviations: nCT=neoadjuvant chemotherapy, nCRT= neoadjuvant chemoradiotherapy

Table 13. Baseline characteristics overall between neoadjuvant chemotherapy (nCT) and neoadjuvant chemoradiotherapy (nCRT) and of the subgroup of patients who completed health related quality of life instruments (HRQoL) the European Organisation for Research and Treatment of Cancer (EORTC) core questionnaire QLQ-C30 and the oesophageal module.

Table 13	**All patients randomised**		**Subgroup of patients who completed HRQoL**	
	nCT (%)	**nCRT (%)**	**nCT (%)**	**nCRT (%)**
Total	91 (100)	90 (100)	80 (90)	74 (85)
Male gender	77 (85)	72 (80)	68 (85)	60 (81)
Age in years median (Range)	63 (37–75)	63 (38–74)	63 (37–75)	64 (38–74)
Histology at diagnosis				
Adenocarcinoma	66 (73)	65 (72)	59 (74)	54 (73)
SCC	25 (27)	25 (28)	21 (26)	20 (27)
Clinical T and N-Stage				
T1	1 (1)	1 (1)	1 (1)	1 (1)
T2	31 (34)	31 (34)	24 (30)	23 (31)
T3	59 (65)	58 (64)	55 (69)	50 (67)
N0	34 (37)	33 (37)	26 (32)	25 (34)
N-positive	57 (63)	57 (63)	54 (68)	49 (66)
Tumor location				
Proximal	2 (2)	2 (2)	1 (1)	1 (1)
Middle	13 (14)	13 (14)	11 (14)	11 (15)
Distal	59 (65)	61 (68)	51 (64)	51 (69)
GOJ	17 (19)	14 (15)	16 (20)	11 (15)
WHO performance status [a]				
0	77 (85)	75 (83)	67 (84)	61 (82)
1	14 (15)	15 (17)	13 (16)	13 (18)

a) WHO performance status from 0-4, the lower score denotes a better functional status.

Table 14. Baseline HRQoL mean scores by allocated treatment and mean differences between groups. Mean differences (MD), 95% confidence intervals (ci) and p-value for all patients who completed the European Organisation for Research and Treatment of Cancer (EORTC) core questionnaire QLQ-C30 and the oesophageal module.

Table 14	Neoadjuvant chemotherapy	Neoadjuvant chemoradiotherapy	Mean difference
QLQ-C30	Mean (95% ci) n (80)	Mean (95% ci) n (74)	MD (95% ci) n (154)
Global health/QoL	67 (62 to 72)	69 (63 to 74)	2 (-6 to 9)
Function			
Physical functioning	88 (84 to 92)	90 (87 till 93)	3 (-4 to 7)
Role functioning	73 (66 to 80)	77 (69 to 84)	4 (- 6 to 14)
Emotional functioning	72 (67 to 77)	78 (73 to 82)	5 (-1 to 12)
Cognitive functioning	87 (83 to 91)	88 (84 to 92)	1 (-5 to 7)
Social functioning	78 (72 to 84)	76 (70 to 83)	-2 (-10 to 7)
Symptoms			
Fatigue	29 (23 to 34)	27 (22 to 33)	-1 (-9 to 7)
Nausea and vomiting	10 (6 to 14)	12 (7 to 16)	2 (-4 to 8)
Pain	24 (18 to 29)	19 (13 to 24)	-5 (-13 to 3)
Dyspnoea	17 (11 to 23)	13 (7 to 19)	-4 (-13 to 4)
Insomnia	30 (23 to 36)	27 (21 to 34)	-2 (-12 to 7)
Loss of appetite	29 (22 to 36)	29 (21 to 36)	0 (-11 to 10)
Constipation	21 (15 to 26)	15 (9 to 21)	-6 (-14 to 2)
Diarrhoea	10 (5 to 16)	10 (4 to 15)	-1 (-9 to 7)
Financial difficulty	14 (8 to 20)	8 (2 to 14)	-6 (-14 to 3)
QLQ-OES24/OG25			
Dysphagia	28 (22 to 34)	31 (25 to 37)	3 (-5 to 12)
Eating	37 (31 to 43)	39 (33 to 45)	2 (-6 to 11)
Reflux	11 (6 to 16)	15 (10 to 20)	4 (-3 to 11)
Trouble swallowing saliva	14 (8 to 20)	15 (9 to 22)	2 (-7 to 10)
Choking	18 (13 to 23)	19 (13 to 25)	1 (-7 to 9)
Dry mouth	15 (8 to 21)	21 (15 to 28)	7 (-2 to 16)
Trouble with taste	8 (2 to 14)	10 (4 to 16)	2 (-6 to 10)
Trouble with coughing	14 (8 to 19)	19 (13 to 25)	5 (-3 to 13)
Trouble talking	3 (-1 to 7)	7 (3 to 11)	4 (-2 to 9)
Odynophagia	32 (25 to 38)	36 (29 to 43)	5 (-5 to 14)
Anxiety health in future	61 (54 to 68)	53 (46 to 61)	-8 (-18 to 2)

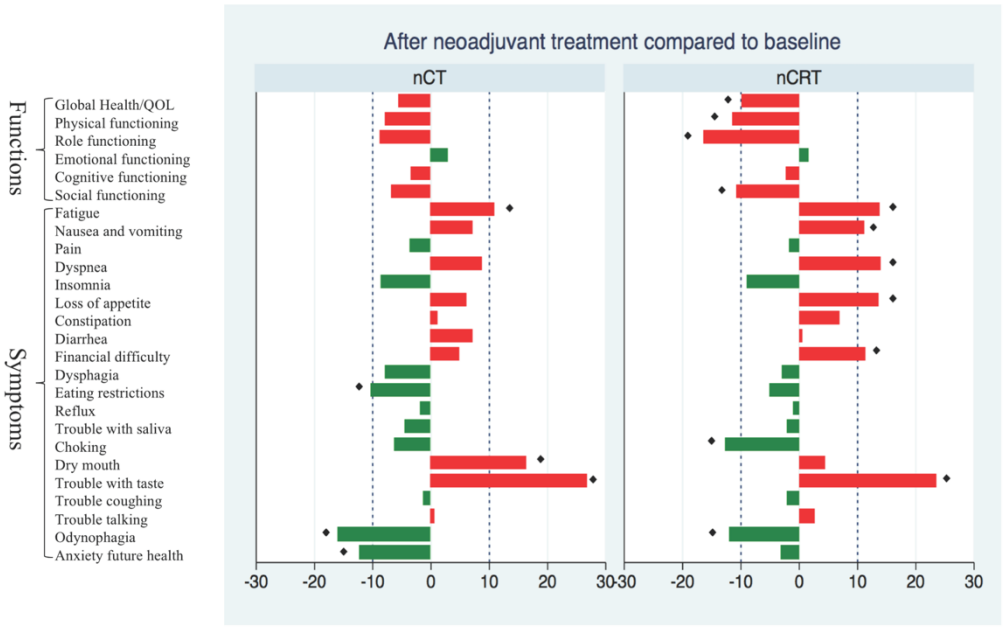
Data are presented as mean scores scores with 95% confidence intervals (ci) with a mean score differece (MD) between allocation before start of treatment. HRQoL scores indicators in the range of 0 to 100, with higher scores in function/symptoms indicating a better/worse state

Table 15. Mean differences (MD), 95% confidence intervals (ci) and p-value for all patients who completed the European Organisation for Research and Treatment of Cancer (EORTC) core questionnaire QLQ-C30 and the oesophageal module after neoadjuvant treatment and one, three and five years after surgery compared between allocated groups. A negative score indicates better function/worse symptoms among patients treated with nCT and a positive score indicates better function/worse symptoms among patients treated with nCRT

Table 15	After neoadjuvant treatment		1 year after surgery		3 years after surgery		5 years after surgery	
QLQ-C30	MD (95% ci) n (112)	p-value	MD (95% ci) n (68)	p-value	MD (95% ci) n (63)	p-value	MD (95% ci) n (44)	p-value
Global health/QoL	1 (-7 to 10)	-	-6 (-16 to 5)	-	-2 (-13 to 9)	-	- 8(-23 to 7)	-
Function								
Physical functioning	0 (-7 to 6)	-	4 (-4 to 13)	-	-6 (-15 to 2)	-	-4 (-16 to 8)	-
Role functioning	-3 (-14 to 9)	-	-1 (-16 to 14)	-	-9 (-25 to 6)	-	-12 (-33 to 9)	0.273
Emotional functioning	8 (0 to 16)	-	-6 (-17 to 4)	-	-6 (-16 to 5)	-	-8 (-22 to 7)	-
Cognitive functioning	4 (-3 to 11)	-	-3 (-12 to 6)	-	0 (-10 to 9)	-	-6 (-19 to 7)	-
Social functioning	-3 (13 to 7)	-	0 (-13 to 13)	-	-10 (-23 to 4)	0.159	-11 (-29 to 7)	0.246
Symptoms								
Fatigue	-3 (-12 to 6)	-	2 (-10 to 14)	-	9 (-3 to 21)	-	10 (-7 to 26)	0.244
Nausea and vomiting	2 (-6 to 9)	-	0 (-10 to 9)	-	5 (-5 to 15)	-	4 (-10 to 17)	-
Pain	-5 (-14 to 5)	-	-6 (-19 to 6)	-	5 (-7 to 18)	-	-2 (-19 to 15)	-
Dyspnoea	1 (-9 to 10)	-	6 (-7 to 18)	-	12 (-1 to 27)	0.067	16 (-2 to 34)	0.085
Insomnia	-7 (-18 to 4)	-	-2 (-16 to 12)	-	9 (-5 to 24)	-	4 (-16 to 24)	-
Loss of appetite	10 (-3 to 22)	0.121	-7 (-22 to 9)	-	5 (-12 to 21)	-	5 (-17 to 27)	-
Constipation	-4 (-14 to 5)	-	-6 (-18 to 7)	-	-2 (-15 to 11)	-	-2 (-19 to 15)	-
Diarrhoea	-3 (-13 to 6)	-	-9 (-21 to 3)	-	0 (-12 to 13)	-	6 (-11 to 22)	-
Financial difficulty	3 (-6 to 13)	-	5 (-8 to 17)	-	6 (-7 to 19)	-	8 (-10 to 25)	-
QLQ-OES24/OG25								
Dysphagia	7 (-3 to 17)	-	-8 (-22 to 5)	-	-4 (-18 to 10)	-	-7 (-26 to 11)	-
Eating	5 (-5 to 15)	-	-1 (-14 to 12)	-	-1 (-14 to 13)	-	3 (-15 to 20)	-
Reflux	4 (-4 to 12)	-	-7 (-14 to 8)	-	-2 (-14 to 10)	-	2 (-13 to 17)	-
Trouble swallowing saliva	-2 (-12 to 8)	-	-4 (-17 to 9)	-	-1 (-15 to 12)	-	13 (-5 to 30)	0.165
Choking	-7 (-16 to 2)	-	-4 (-15 to 8)	-	-6 (-18 to 7)	-	2 (-14 to 18)	-
Dry mouth	-8 (-19 to 2)	-	11 (-3 to 25)	0.123	5 (-10 to 20)	-	18 (-2 to 37)	0.075
Trouble with taste	-1 (-10 to 9)	-	-4 (-17 to 9)	-	4 (-9 to 18)	-	10 (-8 to 27)	0.271
Trouble with coughing	7 (-2 to 16)	-	5 (-7 to 18)	-	**17 (4 to 30)**	**0.011**	4 (-13 to 21)	-
Trouble talking	2 (-4 to 9)	-	0 (-8 to 8)	-	-1 (-10 to 8)	-	0 (-12 to 12)	-
Odynophagia	**11 (0 to 22)**	**0.047**	-5 (-19 to 10)	-	0 (-15 to 15)	-	4 (-16 to 24)	-
Anxiety health in future	-9 (-22 to 4)	-	3 (-13 to 18)	-	10 (-7 to 26)	-	6 (-16 to 28)	-

Values in bold are both clinically relevant and statistically significant.
Abbreviations: nCT = neoadjuvant chemotherapy and nCRT= neoadjuvant chemoradiotherapy. Clinical and statistical significance are assumed as MD over 10 and p-value <0.05. Longitudinal linear mixed effect models with the time interaction term was used to compare HRQoL between the treatment arms at each timepoint

a



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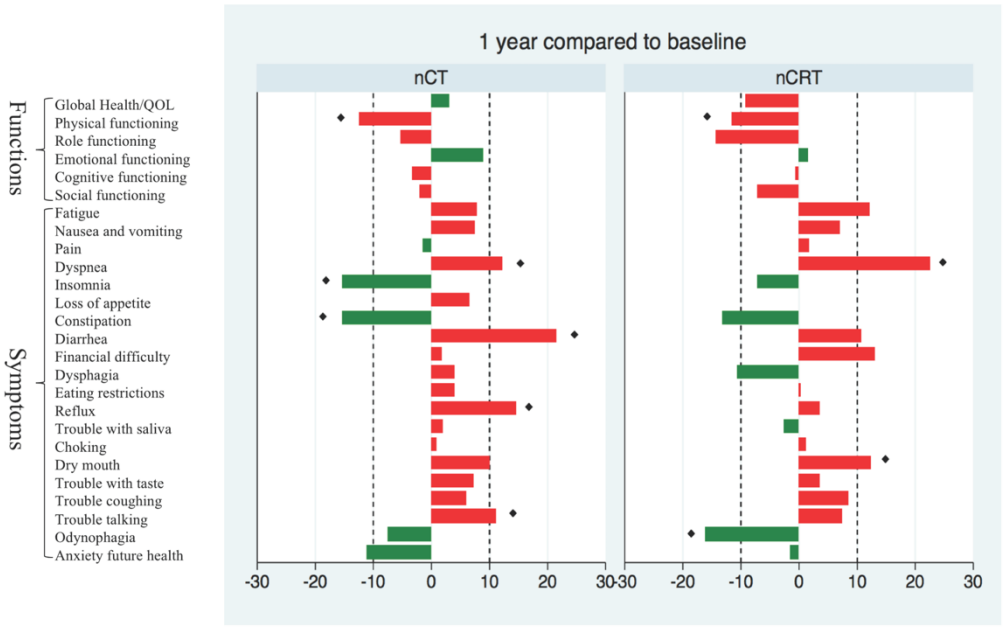
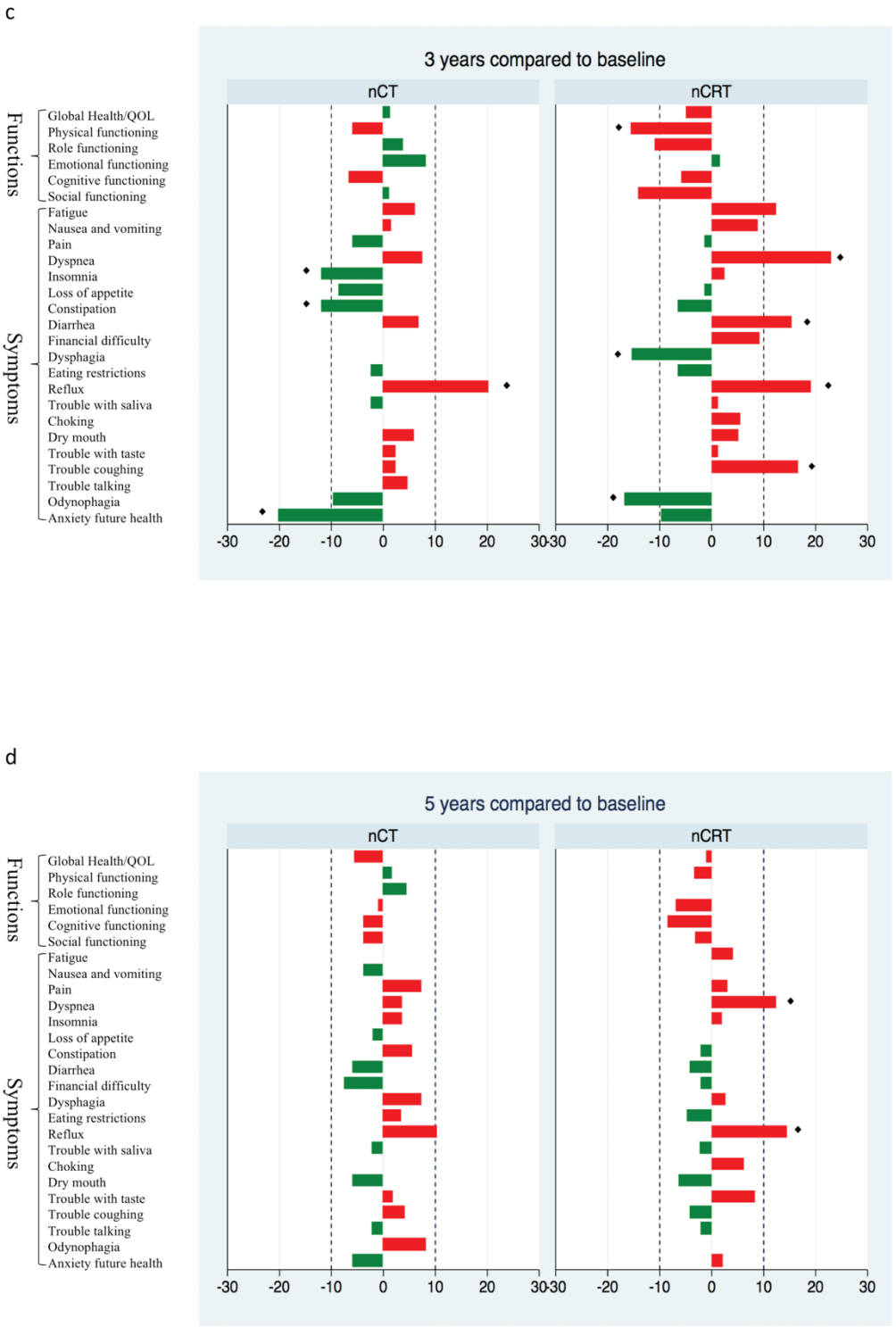


Function/symptom worse compared with baseline (before treatment)
Function/symptom better compared with baseline (before treatment)



Function/symptom worse compared with baseline (before treatment)
Function/symptom better compared with baseline (before treatment)

Figure 2. Health-related-quality of life comparing changes after neoadjuvant treatment (a), one (b), three (c) and five (d) years with baseline in each arm and each timepoint using linear regression and mean changes described with waterfall plots

◆ = (p-value<0.05 and 95% confidence interval ≠ 0). The dashed vertical line at ± 10 indicates the prespecified level for clinically meaningful change from baseline.

Abbreviations: nCT=neoadjuvant chemotherapy, nCRT=neoadjuvant chemoradiotherap

6 DISCUSSION

6.1 METHODOLOGICAL DISCUSSION

6.1.1 Study design

There are methodological aspects that needed to be considered in this thesis, which reports four papers using three different designs. The field of public health includes epidemiology with the study of the occurrence of illness. Studies of illnesses within epidemiology are often conducted using cohorts studies, with the broad definition of " any designated group of individuals who are followed of traced over a period of time" [192,193] and are therefore considered to be an archetype of studies within epidemiology. In research, different designs can be used depending on the research question and the hypothesis of the outcome investigated. When comparing outcomes with an experimental design, for example, using randomisation of the defined interventions, the main types are clinical trials, in which the investigated subject is diagnosed with a specific disease, although the disease is not the event being studied. Clinical trials are considered to be closed cohort studies[192] and regarded as the gold standard when comparing interventions.

A clinical trial needs a well-defined study protocol, containing well-defined exclusion and inclusion criteria's to detect whether one treatment is superior or inferior to the other. To gather high credibility, it is also considered important with a multicentre design although multicenter randomised controlled trials are time-consuming and expensive, and follows strict rules in order to guarantee the safety of the patients being investigated. In clinical trials, survival or disease-free survival is often investigated and, with these primary endpoints, there is a need for a high number of subjects to be randomised. Instead, with rare diseases it is possible to use surrogate variables as histological responses or other defined treatment responses as primary outcomes, as used in the NeoRes trial. Nowadays, it is also common to use HRQoL as primary outcomes within trials. Additionally, it is considered a golden rule to analyse the primary outcomes of randomised clinical trials using intention to treat analysis, since it is debated whether per protocol analysis is truthful. In this thesis, papers (II), III and IV is reporting data from the randomised NeoRes trial.

Nationwide cohort studies are a necessary balance for the outcomes of randomised trials. Nationwide data collection that is often initiated by governments in order to gain statistics of health outcomes in countries – which in Sweden is conducted via national registries – does not consume as many resources as randomised controlled trials. The Nordic countries have a history of registries within several areas, thus a structure exists. The superiority of using nationwide registries, also called "open cohort studies"[192], is that of they provide a real-world picture of all patients within the field being investigated. In this thesis, Paper I examines data from a nationwide population-based registry cohort.

Beyond, randomised trials or a nationwide registry are several prospective and retrospective designs when new hypotheses, treatments, outcomes etc. are being tested, as well as a use of a more detailed understanding with both quantitative and qualitative research outcomes. In this thesis, we present studies designed as prospectively collected data from a single centre cohort study in Paper II to a multicentre phase II, open, randomised controlled trial involving patients with oesophageal cancer in surgical and oncological centres in Sweden and Norway in 2006 to randomisation ending in 2013 and conclusion of a five-year follow-up in 2018. Paper I involve prospectively collected nation-wide registry data from NREV. The data have been collected from 2006 and is ongoing. This paper presents patient-reported outcomes in patients diagnosed between 2009 and 2016.

Other designs considered are case-control studies. This design investigates subjects who have a disease and may also be matched with subjects without a disease as a reference group. Often, the relationship of a suspected risk factor or an attribute of the disease is examined by comparison of diseased and non-diseased groups. This is usually called a

retrospective design, because it investigates the onset of the disease and backwards to the causal factors. Nowadays, cases and controls are collected prospectively, with meaning that collection of data starts before any cases have been diagnosed.

6.1.2 Validity

Two main sources of error in quantitative research needs to be considered. One is the systematic error, often referred to as bias, and this may affect the validity of the results. Second, is the random error affecting the precision of the results. The validity of the findings in research is named internal validity and it depends on the level of systematic error. When performing studies efforts are to minimize biases.

Validity is considered to be the relative absence of bias or systematic errors, and expresses of the degree to which a measurement measures what it is intended to measure, called *construct validity*. Furthermore, *content validity* concerns the content for which the measurement incorporates the domain of the phenomena of the study. Lastly, *criterion validity*, measures the extent to which the measurement correlates with an external criterion of the phenomenon being studied. There are two aspects of criterion validity to be considered: firstly, *concurrent validity,* meaning that the measurement and other criterion refer to the same point in time. Secondly, *predictive validity*, meaning that the measurement's validity is expressed in terms of its ability to predict the criterion. In this thesis, the validity of the outcomes is considered strong regarding Papers I, III and IV because these instruments have been tested and retested within several settings. Paper II used other measurements to evaluate dysphagia. The instruments have previously been used within other settings and in clinics but both measurements using Ogilvie score and Watson scale have recently been validated and published confirming its validity in Swedish settings. However, when comparing between instruments, the EORTC oesophageal instrument QLQ-OG25 was considered better at evaluating dysphagia compared to Watson and Ogilvie.[175] To enhance validity, in Paper I we adjusted for potential known confounders while in Papers III and IV, because of the randomised design, we suggested that validity was high because of the multicentre design, the randomisation and the stratification of histology.

6.1.3 Bias in design

A bias is a systematic error introduced at any stage that may interfere with the results. *Selection bias* is important to consider in the design of trials with properly inclusion and exclusion criteria. Such bias may be reduced through rigorous criteria to avoid confounding the results. During the trial there were several other biases to consider that could impact the outcome, such as *performance bias and misclassifications*. Papers III and IV may be biased due to missing data collection of HRQoL questionnaires. However, by use of well validated instruments we may have reduced misclassification for HRQoL outcomes. *Misclassification* is a type of systematic error and is also defined as an *information bias*. There are two types of misclassification. Differential misclassification may both overestimate or underestimate the true value. In differential misclassification, the errors are related to either exposure or outcome. In non-differential misclassification, the errors are related to both exposure and outcome. In Paper II the patients reported dysphagia and appetite via phone or at meetings and the interviewer recorded the answers. It is important to consider *interviewer bias* regarding how information is solicited, recorded and interpreted, together with the knowledge of the interviewers.

Attrition bias is incomplete outcome data and is especially important to consider in clinical trials reporting HRQoL. The missingness of data is the source of trustworthiness of the

results. Paper III and IV report the outcomes of NeoRes trial, and data is missing. Also, an important consideration is why the HRQoL follow-ups have been missed, although this was not recorded in the trial. Trials with significant PRO differences between arms, had greater completeness of reporting. This requires future attention.[113] Also, with a low rate of collected HRQoL questionnaires in Paper I, attrition bias is important to consider.

6.1.4 Random errors

Random errors are described as the variability or degree of precision of any measurement related to sample size, often described in statistics as type I and type II errors. The outcome of a statistical test is a decision to either accept or reject the null hypothesis (H_0) in favour of an alternative hypothesis (H_1). It is never possible to know the truth, but an objective truth is measured. Type I error or alpha error is an incorrect rejection. For example, if a 95% confidence is claimed, then there is a 5% probability, if there is no bias or incorrect assumption, to make a wrong assumption about your tested hypothesis. If the test hypothesis is false but is not rejected, the incorrect decision not to reject is called a type II error, or beta error. Thus, it is important to consider the power, by considering the alpha level and the actual magnitude of the population, relative to the amount of noise in your data called effect size and, lastly, sample size. In Paper II we have considered the possibility of producing a type II error, because of the small sample size.

6.1.5 Reliability

Reliability or the internal validity refers to the accuracy of the study results. An estimate that has little random errors is precise and both precision and validity are components of accuracy. The internal validity refers to the subjects inside the population investigated. Three violations to internal validity is categorized; namely confounding, selection bias and information bias. Furthermore, the reproducibility of a study and tests whether a consistency exists to the instruments used to measure the outcome of interest. Reliability of research is the agreement of using the same measurement technique and agreement of the replicate measurement at different points in time. A reliable test measure something in a consistent, repeatable and reproducible manner. In statistical terms the reliability of a scale in an instrument is increased by inclusion of and average a number of items, and each item is associated with an independent random error term. In HRQoL research, Cronbach's coefficient alpha is a measure of reliability in multi-item scales. There are also ongoing discussions regarding whether a single item is reliable.[93]

6.1.6 Confounding

A confounder is a systematic error, and may interfere with both the exposure and the outcome, making it difficult to know what is being measured. Often described as a " confusion of effects" and it leads to a bias. This may be controlled at analysis or by restriction. The confounder is related to exposure and outcome, and is not an intermediate in the causal pathway from exposure to outcome. To minimise confounding, randomisation, restriction or matching is used. Papers III and IV in this thesis reports the secondary outcomes of a randomised controlled trial, while Paper I comprises data from a population-based register NREV. Here it is important to consider confounding, and a method to reduce confounders is to adjust for potential confounders using multivariate regression. Residual confounding is a misclassification of confounding variables, unknown confounders or adjustment in categories that are too wide. Confounding by indication is confounding that leads to a distorted estimate of the association between the uses of a drug (or class of drug). This is preferentially prescribed to subjects who have, a priori- a higher or lower risk of presenting the event, especially considered in observational studies. Unlike bias, which is primarily introduced by the investigator or study participants, there are two ways of dealing

with confounding in the analysis of data: stratification or the use of regression models. In Paper II confounding needs to be considered, because some patients needed support of parenteral nutrition, and this may to some extent confound the interpretation of weight-stability.

6.1.7 Generalisability

Generalisability, also named "external validity", is a measure of how well results may be applied to a larger population or similar others. An important consideration of external validity is whether your data have missingness at any stage of your research. This is important to consider in this thesis as both Papers I and IV report HRQoL in both a population-based study and in a randomised controlled trial. The, amount of missing HRQoL instruments, may question the external validity. The conclusions drawn may be carefully interpreted suggesting more knowledge needed in the field.

6.1.8 Interpretation of HRQoL scores

The instrument EORTC QLQ-C30, was adopted in Papers I and IV, while the oesophageal module QLQ-OG25 was added in Paper I. In addition, the oesophageal-specific modules QLQ-OES24 and QLQ-OG25 were adopted in Paper IV, and in Paper III the dysphagia scale in the oesophageal module was used. All items have a 4-point Likert scale from (1) "not at all", (2) "a little", (3) "quite a bit", and (4) "very much", with the exception of the global health/QoL scale having a seven-point scale ranging from (1) "very poor" to (7) "excellent". The assessment provides information about the multidimension scale global health/QoL, functions and symptoms related to the treatment and known oesophageal-specific symptoms. The responders are asked to provide a summarized information of experience over the last week. Raw scores from the responses are calculated and transformed into a scale of 0–100 points according to instructions from the EORTC scoring manual.[191] A higher score on the global health/QoL and functional scales indicated better function while on a symptom scale or a single item a higher score means worse symptoms.

When adapting information from HRQoL outcomes, it is important to consider whether baseline information is provided from a healthy reference population or baseline score from randomised controlled trials. The interpretation is very different. In population-based research, the recommendation is to provide information before the subject becomes ill Thus, a reference population of a general population is often adapted as a baseline comparison.[194] In trials, it is important to consider the subjects scores at baseline, to enable true subjective differences and changes of treatment over time.[93,195]

In HRQoL research, the clinically meaningful difference is important to consider and there is still a need for a clear method for determining the clinical meaningfulness of changes in scores and not only adopt statistical significance. This is especially useful when working with large datasets, in which a statistical significance is likely to be obtained.[196] The methodology of clinical significance is moving forwards, with the adaption of minimally important differences. However, discussion are ongoing regarding how much change is clinically important.[138] A guideline that analyses and interprets PRO data proposes that a change of 10 on a 0–100 scale is supported of clinical meaning.[190,197] It is said to be of the same magnitude as 0.5 standard deviation (SD) and is universally acceptable.[198] However, in some instruments, a lower SD may be more accurate. The magnitude of clinical significance may currently have to be determined on an each trial base, although with increased knowledge of HRQoL in trials, clinicians will gain more insight into the magnitude of change that is clinically important.[138]

In this thesis, two different approaches were used to aid the interpretation of clinically meaningful differences. In the first Paper, we both adopted the recently published paper from Cocks et al.[189] for EORTC QLQ-C30, while in the analysis of QLQ-OG25, we used the hitherto most commonly adapted method, by Osoba and Kings, their interpretation with a difference of 10 or more of being moderate clinically meaningful.[116,190] Cocks et al. used a meta-analysis approach and blinded expert opinions to suggest clinically relevant changes within each subscale of QLQ-C30. In Papers II and IV, we used the interpretation of 10 as being clinically meaningful. The interpretation of HRQoL in this thesis is considered from an anchor-based approach and does not use the effect size interpretation.

6.2 DISCUSSION

6.2.1 Paper I

The main findings in this paper comparing HRQoL within a Swedish population-based cohort one year after diagnosis of oesophageal or GOJ cancer, generally low global health/QoL, deteriorated functions and more symptoms were reported, especially in comparison with the gender and age matched reference population. Patients managed with palliative treatment intention reported, as expected, lower function scores and higher symptom scores compared to those with intended curative management. With more pronounced differences regarding physical function, dysphagia, anxiety of future health, problems eating with others and trouble with taste. In addition, within the curative cohort, patients treated with dCRT reported more problems with dysphagia, eating problems and choking compared to the curative surgical cohort. Conversely, subjects treated with surgical resection reported more problems with diarrhoea compared to those treated with dCRT. High levels of anxiety for future health and low general health/QoL scores were reported in total in the cohort compared to the reference population.

Considerations of methodology needs to be discussed, it is a strength to report nation-wide prospectively collected HRQoL within a population-based registry. This limits selection and recall-bias, also reflect a true unselected population with a more reliable representation in decision-making. The use of globally validated instruments strengthens the outcomes. However, limitations need to be considered, and especially collection of HRQoL data at only one time-point it is not possible to report changes over time. In addition, the definition of the sub-cohort is based on treatment decision at MDT one year earlier, and this may not reflect the true given treatment and especially among subjects with curative treatment that during the first year may have recurrence and therefore treated as palliative at the timepoint of data collection. Missingness of data is considerable and this may further limit interpretation of data. The missingness of formulas are probably lower than reported, mainly because some regional cancer centres did not collect PRO outcomes during the first years of HRQoL in NREV. Also, data from some subjects may have been reported into the register later than one year after diagnosis. This will probably further affect the response rates of PROM data collection.

When reporting HRQoL outcomes it is important to consider that the responders have probably gone through personal changes during treatment and time, and especially one year after diagnosis all subjects have to some extent changed their personal values, internal standards or meaning of HRQoL. This is named response shift, [67,126] and important in interpretation of HRQoL outcomes, especially by use of guidelines when interpreting clinical relevance. In this paper we considered that response shift was similar in all subgroups.

The findings of this paper suggest improvements and especially need of more psychological support because of the high levels of anxiety reported one year after diagnosis among both curative and palliative subjects. Distress and anxiety have previously been highlighted in oesophageal cancer and other cancer diagnoses as an important symptom to be aware of.[153,199] Identifying distress and anxiety is recognised as a sixth vital sign in cancer care, and needs to be monitored routinely, to identify individuals experiencing high levels of anxiety and distress as a significant burden.[199] It has earlier been recognised that patients one year after diagnosis within several cancer diagnosis report high levels of distress.[133,199]

In addition, the oesophageal problems, particularly problems with dysphagia, have been found to be a causative distressing factor among surgically treated subjects with oesophageal cancer, and this may also be considerable in palliative settings.[153] One earlier paper have also addressed that dysphagia, uncertainty and fatigue influenced the subject's everyday life and that need of support and information is important.[182] Therefore, to investigate the underlying causes of why patients report problems of dysphagia one year after diagnosis in palliative subjects and those treated with dCRT is crucial. To decrease dysphagia is one of the main objectives in palliative treatment. It has earlier been addressed that dysphagia may recurrence with treatment with stents [142,162] and in comparison between palliative modalities it is also known that treatment of brachytherapy is considered with longer relief of dysphagia compared to stenting.[143] Also, treatment of dysphagia it is common with stenting in palliative patients and when treated with dCRT insertion of PEG to secure nutrition are widely used, thus not actually addressing swallowing ability. Although, deeper knowledge of the management of dysphagia is not available in this study.

The problem of diarrhoea is a well-known side-effect that is reported after oesophageal cancer surgery, probably to a large extent influenced by the vagotomy usually performed as an inherent part of the dissection.[47,129,137] Currently, early tumours with T0-T1 stage is mostly offered only endoscopic treatment, while in the beginning of this study cohort a large proportion were treated with oesophagectomy.

It is important to focus on the care that is needed to return persons to their fullest possible function in society after a cancer diagnosis. Both curative survivorship and palliative care require a holistic approach in order to address the physical, emotional, and social needs of patients with oesophageal cancer. This is an essential component of care from the time of diagnosis and throughout the person's life.[39,40,200]

6.2.2 Paper II

The main findings of this prospective cohort pilot study were that treatment with platin-5-Fluorouracil chemotherapy with or without the addition of radiotherapy, significantly reduces dysphagia, in patients diagnosed with locally advanced oesophageal or GOJ carcinoma. The relief was clearly significant already after the completion of first treatment with neoadjuvant chemotherapy with platins. In addition, no correlation was detected between the alleviation of dysphagia and histological response.

The main weakness of this paper is the small sample and that data was collected only at one centre, at Karolinska University Hospital. This study may introduce type II error, but since the findings were so clear we consider this to not fully explain our findings. A strength of this study is the use of PRO to assess dysphagia and also the main outcomes were prospectively collected.

Two previous reported papers have investigated HRQoL during neoadjuvant treatment, the first paper reported relief of dysphagia after two cycles of chemotherapy [172] and the second

paper reported stable dysphagia or relief of dysphagia after ended neoadjuvant treatment before surgery.[126] Although, these papers have not reported any intervention with stenting or other possible procedures to relive or support dysphagia, therefore a chance of bias may be considered in those papers. Recently also Cools-Lartigue et al, also explored dysphagia during neoadjuvant therapy in and investigating whether invasive tube placement either surgically or radiographically could be avoided, since it causes significant morbidity. Treatment given in this study was three- or four modalities of chemotherapy. Patients with dysphagia over 2 with at least 10% weight loss, received a fast track with start of first cycle of chemotherapy one week of presentation. Their findings suggested that patients experienced sufficient relief of dysphagia permitting the patients to start eating adequately and patients remained weight stable, after completion of several chemotherapy modalities containing platins.[171] In addition, within palliative treatment also relief of dysphagia have been described with chemotherapy of platins and 5-FU and addition of radiotherapy. [74]

In this paper we did not note that any patients receiving addition of radiotherapy reported deterioration of appetite or swallowing discomfort after completion of nCRT. It has been reported that amongst 15% –28% of the patients receiving radiotherapy develop radiation-induced oesophagitis [15]. A reason for not reporting this, is that the measurement was before surgery approximately 3-6 weeks after completion of nCRT. It is reported that the effect of radiotherapy induced oesophagitis, will recover after a few weeks after completion of radiotherapy.[201]

This paper is important in clinical-decision making, with increased knowledge of how patients should be managed regarding dysphagia and nutritional considerations at diagnosis, during neoadjuvant treatment and until surgery. Moreover, earlier papers have reported that neoadjuvant treatment may significantly worsen nutritional parameters compared to patients undergoing resection upfront,[158,167,202] while other recently published papers report that with professional support during neoadjuvant treatment patients may keep weight-stability and continue oral intake without stent or gastrostomy placement.[163,171] Stenting is also reported having a negative outcome impact on oncology.[159]

6.2.3 Paper III

The main findings of patient-reported dysphagia in the NeoRes trial comparing baseline and at completion of neoadjuvant treatment, was firstly that patients reported relief of dysphagia with improved ability to eat solid food in both groups. Secondly, radiotherapy induced oesophagitis may increase symptoms of swallowing problems. Thirdly, no correlation was detected between relief of dysphagia and histological tumour response in the NeoRes trial.

The weaknesses of this paper are the missing HRQoL formulas at both baseline and after neoadjuvant treatment, this reduces the power of secondary endpoint observations and also possibly introduce a risk of selection bias. Also, the lack of timing when questionnaires were returned after neoadjuvant treatment will probably influence the results. Another consideration is that it is not recommended to only analyse single scales and not reporting the other outcomes collected. However, the individual items and the scale added important information in this paper as the subanalysis of each separate item enabled us to better understand the degree of swallowing problems and to which degree relief of dysphagia was improved by neoadjuvant treatment. The major strength, is the randomised procedure with similar groups and with inclusion criteria's, enabling true comparisons between groups.

Previous literature supports the findings with relief of dysphagia during neoadjuvant therapy.[171,203] [172] In addition, the management of nutrition in oesophageal cancer,

especially when patients also suffer from dysphagia, is a challenge during and after completion of neoadjuvant therapy. At diagnosis, dysphagia with associated weight loss and malnutrition is the main clinical manifestation of oesophageal cancer and in order to tolerate curative treatment it is important to succeed in the management of symptoms at diagnosis and during neoadjuvant treatment.[167,171 178,204]
One side-effect reported is radiotherapy induced oesophagitis, which is associated with increased dysphagia and odynophagia.[15,158,201] The dynamics of oesophagitis are not well documented, but it is reported to peak approximately three to five weeks into treatment and, in some patients it may take several weeks after termination before it resolves.[204] To assess symptoms and the effectiveness of symptom management strategies, patient-reported outcomes are an important component in combination with the clinical judgement.

The lack of correlation between relief of dysphagia and pathohistological tumour response has been well-described in previous literature. [172,187,201,203,205] However, the findings of an increased ability to eat solid food should be explained by the debulking effect of tumour being enhanced by neoadjuvant treatment. Why this effect cannot explain the tumour response is unresolved.

Since 2010, by law (Patient law 2014:281), all cancer patients in Sweden shall be offered a contact nurse. This is to enhance information, improve communication with health-care, increase safety, continuity and patient-centeredness during treatment trajectory. This further increase safety when patients is introduced to new treatment strategies and the patients need for specialised support at diagnosis, during treatment and long-term follow up after ended treatment is addressed in several papers in oesophageal cancer. [85,86,181,184,186]

6.2.4 Paper IV

The main findings in this paper reporting patient-reported HRQoL outcomes in the NeoRes trial, was that in comparison between treatment groups patients reported clinically relevant and statistically significantly more problem with odynophagia after completion of nCRT compared to those who received nCT. Also, at three years follow-up after surgery patients allocated to nCRT reported clinically relevantly and statistically significantly more problems with coughing, compared to those treated with nCT. In longitudinal analysis within treatment allocation and in comparison, with baseline, the overall finding was that patients treated with nCRT reported more symptoms, lower global health/QoL and functions after completion of neoadjuvant treatment. In addition, at five years follow-up after surgery patients reported worsen problems with reflux and dyspnoea when treated with nCRT in comparison with nCT. However, some oesophageal symptoms improved, especially after completion of neoadjuvant treatment but also over time, and this was reported in both arms.

Methodological considerations to be discussed is the major strength of HRQoL analysis of randomised multicenter trial comparing neoadjuvant treatments and surgery in oesophageal cancer. A randomised comparison provides the best validity in comparison between treatments. Also, the use of globally validated HRQoL instruments is considered a strength, especially when validated to compare oncological and surgical settings in cancer and oesophageal cancer treatment. A limitation is the multi-testing of all HRQoL outcomes, with no specific primary or secondary outcome predefined. Another limitation is the lack of reporting the reason for and the number of missing HRQoL questionnaires particularly during follow-up. However, no difference was found when responders and non-responders

were compared. Also, the criteria of patients included with WHO score 0-1 limit the generalizability.

This is the first trial reporting HRQoL comparing nCRT and nCRT in oesophageal and GOJ carcinoma before surgery. Therefore, our findings are novel contribution within the area, but it is known that neoadjuvant therapies are followed by deterioration of several symptoms and functions especially shortly after completion of neoadjuvant therapies. In addition, it is acknowledged that oesophageal cancer surgery is associated with short- and long-term deterioration of HRQoL.[61,121,126,129,137] Many studies have reported huge detrimental effect of surgery but with partially recovery over time, although some functions impaired and symptoms never recovered or being chronic.[63,69,71,121] Also, outcomes from population based studies reported HRQoL and compared with a reference population, they reported no recovery after oesophageal cancer surgery at 6 months, 3 years and up to 10 years in several aspects. [47,62,121,130] Our findings are in line with other studies, reporting a detrimental effect of HRQoL outcomes after completion of neoadjuvant treatment, but we also detected improvement especially in some oesophageal reported symptoms.

One observational study has reported outcomes comparing neoadjuvant chemotherapy and neoadjuvant chemoradiotherapy before surgery and the authors reported detrimental effect during neoadjuvant treatment with both nCT and nCRT, but before surgery HRQoL recovered to baseline levels. Also, after surgery the same study concluded that neoadjuvant treatment did not hamper HRQoL outcomes compared to surgery alone and patients recovered in six months after surgery to baseline measurements.[126]

In addition, the CROSS trial comparing nCRT and surgery alone, reported deterioration in all aspects of HRQoL one week after termination of nCRT while at follow-up during the first year and a long-term follow-up at eight to nine years after surgery, they reported no difference in HRQoL outcomes when comparing surgery alone and nCRT + surgery. Although, physical function and fatigue was impaired at one year and in the long-term follow-up after surgery and they never restored to baseline levels in any of the allocated groups.[69,71] Our results in the NeoRes trial, detected that physical function was significantly impaired after neoadjuvant treatment in the nCRT group, while at one year follow-up after surgery physical function worsen in both allocated groups, although at three years follow-up changes were only detected among patients treated with nCRT.

In comparison with a Swedish reference population at six months and three years after surgery, functions deteriorated (role and social) and several problems with symptoms were reported (fatigue, appetite loss, diarrhoea, dyspnoea and reflux).[47,129] Long-lasting deterioration in social functioning, fatigue and coughing have also earlier been reported in a meta-analysis comparing HRQoL up to one year after surgery.[137] In the NeoRes trial, fatigue is only reported with significant results after completion of neoadjuvant therapy in both groups and also in comparison between groups at five years follow-up fatigue were to some extent more severe among patients treated with nCRT compared to nCT. Patients reported that role and social function, were also to some extent worsen when treated with nCRT at long-term follow-up compared to nCT. In addition, problem with dyspnoea and coughing were worsened when treated with nCRT at long-term follow-up compared to nCT. This is also detected when longitudinally changes from baseline were analysed within especially the nCRT group, long-term deterioration of dyspnoea were reported and problem with coughing at three years follow-up. Reflux were impaired at three years follow up in both groups and at five years follow-up only in the nCRT group. Loss of appetite were improved or stable compared with baseline and over time in both groups while diarrhoea

were reported with problems at one- and three-years follow-up in respectively nCT and nCRT group.

Restoration to baseline level at six months after completion of treatment have also been reported in trials comparing dCRT therapies.[122,123] Rees et al. reported HRQoL within the SCOPE-1 trial comparing dCRT therapies, at follow-up one year and 104 weeks, they reported that scores were similar or better than before treatment.[123] However, patients reported HRQoL outcomes in the NeoRes trial were not restored at one year after surgery and differences were detected between treatment allocation in both short and long-term follow up. The CROSS trial reported no difference over time between nCRT plus surgery and surgery alone, an explanation may be the different methodology adapted in analysis of the results, with use of multiple corrections in the CROSS trial.

The different methods adapted in interpretation of HRQoL results within trials, have recently been discussed. A review was published on advanced breast cancer describing standards and quality of reporting outcomes from randomised trials.[206] This review looked at statistical issues and considerations. Their conclusion was that the reporting of the outcomes of trials did require consensus because of a wide spread of reporting and consequently complicate the interpretation of PRO. Although, most of the trials have baseline data, and linear mixed effect models was the most used statistical model together with ANOVA/Linear regression and Wilcoxon and T-tests in comparison between patient groups.

The implication of HRQoL outcomes in the NeoRes trial with report of more symptoms especially over time in the nCRT group, needs to be confirmed in larger trials. Earlier results in the NeoRes trial have though reported more severe complications after surgery with nCRT treatment [41] and no survival benefit of either treatment is reported.[18] The NeoRes trial do not have statistical power to compare long-term outcomes, but it is the largest trial hitherto comparing nCRT and nCT with surgery.

7 CONCLUSIONS

- The overall HRQoL in patients with oesophageal cancer one year after diagnosis is much lower in comparison with an age and gender matched reference group from the general population.
- Anxiety is a major concern for oesophageal cancer patients one year after diagnosis.
- Patients with up-front palliative treatment intent, and patients recommended to receive dCRT at MDT, report high scores for dysphagia and other eating related symptoms, one year after diagnosis.
- Diarrhoea is a significant symptom one year after diagnosis in patients treated with curative intent surgery.
- During neoadjuvant treatment patients reported relief of dysphagia already after the first cycle of chemotherapy, followed by further relief after completed neoadjuvant treatment.
- In comparisons between nCT and nCRT, relief of dysphagia and improved ability to eat was experienced after both treatments, although patients initially without dysphagia who received nCRT reported some deterioration of eating ability after treatment, possibly due to radiation therapy-induced oesophagitis.
- No correlation was detected between dysphagia response and histological tumour response after neoadjuvant therapy.
- Only minor HRQoL differences were detected in the direct comparison between patients treated with nCT and nCRT, with less odynophagia immediately after completed nCT and more problems with cough and dyspnoea at long term follow-up after nCRT.
- In longitudinal, long-term analyses, patients reported severe deterioration of HRQoL after surgery both after nCT and nCRT, with gradual long-term recovery after both treatment types, but with more long-term symptoms remaining, compared to baseline, in patients treated with nCRT.

8 POPULÄRVETENSKAPLIG SAMMANFATTNING

Cancer i matstrupen (esofagus) är en tumörsjukdom med relativt dålig prognos jämfört med andra cancerdiagnoser, men prognosen har förbättrats det senaste decenniet med kombinerade behandlingar, som inkluderar framsteg inom onkologi och kirurgi. I Sverige, diagnosticeras cirka 450–500 personer årligen med esofaguscancer och sjukdomen är vanligast förekommande hos män. Två huvudtyper dominerar, körtelcancer (adenocarcinom) och skivepitelcancer. Kända riskfaktorer för adenocarcinom är rökning, övervikt och halsbränna och för skivepitelcancer är de dominerande orsakerna rökning och alkohol. Sväljsvårigheter, även kallad dysfagi är kardinal symptomet för 70%-90% av individerna vid diagnos, men på grund av matstrupens elasticitet uppkommer inte symptomet innan tumören har växt så att 75% av matstrupens lumen är täckt av tumören, därav en avancerad sjukdom vid diagnos.

En viktig del av forskningen idag är fokuserad på överlevnad, biverkningar, komplikationer och respons på behandling, men de senaste decennierna så har även personers subjektiva rapportering (PRO) om den egna hälsan med rapportering om livskvalitet, funktionsförmåga, samt symptom av sjukdomen eller behandlingen, blivit viktiga att undersöka. Syftet med denna avhandling är att utvärdera person rapporterad hälsorelaterad livskvalitet och dysfagi hos patienter som har diagnosticeras med cancer i esofagus.

Vid diagnos av esofaguscancer så finns flera behandlingsalternativ att tillgå, beroende på tumörstadium och individens hälsa. Vid botande behandling, så är i dagsläget förbehandling (neoadjuvant) med kemoterapi eller kemoradioterapi innan kirurgi vanligast. Kirurgisk behandling räknas idag som den enda botbara behandlingen. Studier pågår dock för att undersöka om definitiv kemoradioterapi kan vara botande behandling framförallt för personer diagnosticerade med skivepitelcancer i esofagus. Med neoadjuvant behandling har det påvisats att tumörbördan minskas och även minskad risk för spridning till lymfkörtlar, dock med ökad risk för toxiska symptom och komplikationer vid kirurgi. På grund av de sena symptomen vid diagnos är 70% av individerna palliativa redan vid diagnos, och om möjligt ges då onkologisk behandling för att främst lindra symptom och förlänga överlevnad.

Fyra delarbeten ingår i avhandlingen, två arbeten presenterar personrapporterad HRQoL och två arbeten utvärderar sväljförmåga under, före och efter onkologi. Tre av arbetena II (delvis), III och IV är delarbeten i en randomiserad kontrollerad studie, utfört mellan 2006 och 2013 i Sverige och Norge. NeoRes som studien kallas, inkluderade 181 personer som randomiserades mellan neoadjuvant kemoterapi eller neoadjuvant kemoradioterapi före kirurgi. HRQoL samlades in före, under behandling och upp till fem år efter kirurgi. För att utvärdera behandling är den bästa metoden att jämföra inom en randomiserad kontrollerad studie, dock är det viktigt att konkludera de uppnådda resultaten med data från nationella kvalitetsregister då det kan spegla en sannare bild av populationen jämfört med randomiserade studier.

Arbete I är en sammanställning av HRQoL formulär som har registrerats i det nationella kvalitetsregistret för esofaguscancer och ventrikelcancer (NREV). Totalt inkluderades 1156 personer med esofaguscancer som har registrerats mellan 2009 till 2016 och som har fått hemskickat frågeformulären ett år efter diagnos. Syftet var att beskriva HRQoL på alla individer som har blivit registrerade i NREV och jämföra med en ålders- och könsjusterad referenspopulation, samt att analysera HRQoL mellan den palliativa och kurativa kohorten och inom varje subkohort. Huvudresultaten visar att i jämförelse med referenspopulationen så rapporterade personerna med både kurativ och palliativ diagnos, lägre global

hälsa/livskvalitet, lägre funktioner och mer symptom ett år efter diagnos. Analyser mellan individer som har fått palliativ diagnos och de som har fått kurativt syftande behandling visade att HRQoL är sämre hos gruppen som har fått palliativa diagnos, framförallt sämre fysisk förmåga och mer sväljsvårigheter rapporterades. I tillägg så rapporterade de individer som fått enbart kemoradioterapi mer sväljsvårigheter jämfört med de kurativa kirurgiska kohorterna, medan kohorterna som har genomgått kirurgi rapporterar mer problem med diarré. Mycket symptom på ångest för den framtida hälsan och lågt skattad global hälsa/livskvalitet rapporterades i hela NREV kohorten.

Arbete II är en kohortstudie på patienter som har behandlats på Karolinska Universitetssjukhuset. Syftet var att undersöka dysfagi före behandling, under neoadjuvant behandling och före kirurgi. Resultaten visade att dysfagi efter första kur med cytostatika minskade så att förmågan att äta fast föda ökade och sväljsvårigheterna minskade ytterligare innan kirurgi. Studien visar att man skall vara ytterst selektiv vid behandling med stent eller att sätta gastrostomier på patienter inför neoadjuvant behandling och kirurgi.

I arbete III utvärderades dysfagi med en skala från HRQoL instrumentet. Resultatet visade att båda neoadjuvanta behandlingarna i NeoRes minskade dysfagi problemen efter avslutad behandling jämfört med innan behandling. Även att vissa patienter troligen får biverkningar av strålbehandlingen i form av inflammation i matstrupen (esofagit), som därmed kan försämra sväljförmågan under en tid. Inget samband påvisades mellan respons på dysfagi och patologisk respons på de givna neoadjuvanta behandlingarna.

I arbete IV analyserades HRQoL i NeoRes där data insamlades före behandling, efter neoadjuvant behandling, samt ett, tre och fem år efter kirurgi. Resultaten visade i jämförelse mellan behandlingsgrupperna att behandling med kemoradioterapi gav något mer signifikant symptombörda jämfört med enbart kemoterapi, med mer smärta vid sväljning (odynofagi) efter avslutad neoadjuvant behandling och mer problem med hosta vid tre års uppföljning efter kirurgi. Mätningar över tid visade att patienter som har fått neoadjuvant kemoradioterapi rapporterade mer symptom med reflux och dyspne vid femårsuppföljningen.

Sammanfattningsvis så visar avhandlingen att den rapporterade HRQoL är lägre jämfört med en referenspopulation ett år efter diagnos i NREV och det inkluderar lägre global hälsa, lägre rapporterad funktionsförmåga och mer symptombörda. Ångest inför den framtida hälsan rapporterades i hela kohorten och även problem med dysfagi rapporteras hos individer med palliativ behandlings intention och kurativ definitiv kemoradioterapi ett år efter diagnos. Vidare så minskar problem med dysfagi med neoadjuvant behandling av antingen cytostatika enbart eller i kombination med strålning innan kirurgi och redan efter första cytostatika kuren förbättras sväljförmågan så att förmågan att äta fast föda förbättrades. Inget samband mellan respons på dysfagi och histologisk respons har kunnat påvisas. HRQoL i NeoRes visade att patienter som har fått neoadjuvant kemoradioterapi rapporterade en högre signifikant symptombörda jämfört med patienter som enbart har fått kemoterapi före kirurgi, med mer rapporterade symptom på odynofagi efter avslutad neoadjuvant behandling, och problem med hosta, dyspne och reflux efter kirurgi.

9 FUTURE PERSPECTIVES

It is important to improve completion of PRO outcomes. This is needed both in future randomised controlled trials and in the national quality registry for oesophageal cancer, NREV. A strategy to improve completion of HRQoL questionnaires may be to use modern technology and centralization of such data collection in future trials. In NREV, we need to improve and investigate how we can improve collection of PRO data.

Dysphagia problems in long term follow-up needs to be addressed, especially among subjects diagnosed as palliative and among subjects treated with definitive chemoradiotherapy. A deeper knowledge of how palliative and dCRT treatment affect dysphagia is important. In addition, it is important to screen symptoms of recurrence or early and late side-effects of therapy and also to address the psychological effects enhanced by the cancer treatment. High levels of anxiety of future health have been reported in a majority of the subjects alive one year after diagnosis, this have earlier been acknowledged in other papers as well and this is a concern.

To further increase person centeredness in health-care, the patient's subjective report of their general health, functions and symptoms from treatment and disease by use of HRQoL instruments in clinical-decision making, will probably improve symptom management and person centeredness.

Recently a genome atlas in oesophageal cancer has reported that both adenocarcinoma and squamous cell carcinoma are different cancer types and with further sub classifications within each type. In future it would be interesting to investigate whether PRO will differ depending on the different subtypes of oesophageal cancer. To further improve HRQoL after treatment of oesophageal cancer it is important to investigate whether it exists any differences regarding social disparities, economic status, gender differences, age differences in Sweden among patients diagnosed with oesophageal cancer. This is should be possible with the large number of HRQoL responders within the curative cohort.

Future HRQoL research should also include other important questions regarding known side-effects from oesophageal cancer surgery, particularly knowledge of the patients' experiences of both early and late dumping syndrome, a well-known side-effect after gastrointestinal surgery. My experience is that dumping may affect the individual's daily life substantially, although how this is specifically manifested and actually influences the patient's daily life is not well investigated. In addition, with more patients becoming survivors, other HRQoL measurement is needed, since the instruments used today only measure known side-effects from treatment and tumour related symptoms from oesophageal cancer in short-term.

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