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ASPECTS ON PROGNOSIS OF CANCERS OF THE OESOPHAGUS AND GASTRIC CARDIA

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ABSTRACT

Oesophageal cancer is an aggressive form of cancer with a poor prognosis. The two main histological types are squamous-cell carcinoma and adenocarcinoma. In the Western world the incidence rate of adenocarcinoma of the oesophagus, previously rather rare, has shown a dramatic increase in recent decades. Despite improvements in staging and treatment modalities, the 5-year survival rate remains around 10% overall and 25-30% for patients treated with curative intent. Identification of prognostic factors is important in an attempt to improve the outcome for oesophageal cancer patients.

In the first study we evaluate prognostic trends of oesophageal cancer in Sweden. The Swedish Cancer Register was used to identify all cases of oesophageal adenocarcinoma or squamous-cell carcinoma between 1961 and 1996. We found a significantly improved observed survival for oesophageal adenocarcinoma during 1990-1996 (10.5%) compared to previous decades (4%) and also a corresponding slightly improved survival for squamous-cell carcinoma by each decade (from 3.8% in 1961-1969 to 7.0% in 1990-1996).

Prognostic factors were studied in Papers II and III. In Paper II the effects of surgical prognostic factors on short and long-term outcome after tumour resection were studied, while in Paper III the influence of patient demographic characteristics and lifestyle factors on prognosis was studied. The 757 cases of adenocarcinoma of the oesophagus and gastric cardia, and squamous-cell carcinoma of the oesophagus, reported to the Swedish Esophageal and Cardia Cancer (SECC) study were used as study base. In Paper II, 232 patients out of the total 757 were resected and became the study cohort. In Paper III, 580 patients (356 non-resected and 224 resected) out of the 618 interviewed patients were the study cohort. Overall observed survival during the time period was 12% and for the resected patients 25%. Patients treated in a high-volume setting, defined as $\geq$10 oesophagectomies per year within the study period, had a modestly improved survival compared to patients treated in a low-volume setting. Need for post-operative ventilator support was a significant negative predictor of survival. Smoking and low educational level were negative predictors of survival in patients with squamous-cell carcinoma whilst obese patients diagnosed with adenocarcinoma of the oesophagus had a significantly improved survival compared to normal weight patients.

In the final study, palliation of dysphagia by placement of expandable metal stents was studied. During January 1993 to May 2005, 149 patients treated at a single institution were evaluated with regard to factors influencing morbidity, procedure-related mortality and symptom relief in terms of dysphagia. The procedure-related mortality was 3% and the complication rate 26%. Pre-treatment dysphagia improved in 70% of subjects ($p<0.0001$). Tumour length, tumour location, histology, age, gender or prior dilatation did not affect the outcome in terms of procedure-related morbidity or symptom relief.

Keywords: Oesophagus, adenocarcinoma, squamous-cell carcinoma, gastric cardia, prognosis, lifestyle factors, palliation, dysphagia

LIST OF PUBLICATIONS

I. Martin Sundelöf, Weimin Ye, Paul.W.Dickman and Jesper Lagergren
Improved survival in both histologic types of oesophageal cancer in Sweden
Int J Cancer, 2002, 99, 751-754

II. Martin Sundelöf, Jesper Lagergren, Weimin Ye
Surgical Factors Influencing Outcomes in Patients Resected for Cancer of the Esophagus or Gastric Cardia in Sweden in 1995-1997
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III. Martin Sundelöf, Jesper Lagergren, Weimin Ye
Patient Demographics and Lifestyle Factors Influencing Long-Term Survival of Esophageal Cancer and Gastric Cardia Cancer in a Nationwide Study in Sweden
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IV. Martin Sundelöf, Daniel Ringby, Dag Stockeld, Lars Granström, Eduard Jonas and Jacob Freedman.
Palliative treatment for malignant dysphagia with self-expanding metal stents: a 12-year experience
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CONTENTS

LIST OF ABBREVIATIONS

AOG	Adenocarcinoma of the oesophago-gastric junction
BMI	Body mass index
CI	Confidence interval
CT	Computed tomography
EMR	Endoscopic mucosal resection
EUS	Endoscopic ultrasound
GOJ	Gastro-oesophageal junction
HR	Hazard ratio
ICD	International classification of diseases
OGD	Oesophago-gastro-duodenoscopy
OGJ	Oesophago-gastric junction
ICU	Intensive care unit
PET	Positron emission tomography
SCCA	Squamous-cell carcinoma
SECC	Swedish Esophagus and Cardia Cancer study
TNM	Tumour node metastasis
UICC	International Union against Cancer

1 INTRODUCTION

Oesophageal cancer is mainly of two histological types, squamous-cell carcinoma (SCCA) and adenocarcinoma. Worldwide it is the 8th most common cancer form and the 6th most common cause of cancer death. Globally SCCA is the dominant histological type. However, in the Western world the incidence of adenocarcinoma has been increasing rapidly in recent decades. In the United States adenocarcinoma of the oesophagus has the most rapidly increasing incidence rate of all cancer forms. Also adenocarcinoma of the gastroesophageal junction (GOJ) has an increasing incidence rate, although not as steep as that of oesophageal adenocarcinoma. In Western societies tobacco smoking and a high level of alcohol consumption are known risk factors for SCCA, whereas the presence of Barrett´s oesophagus, gastro-oesophageal reflux and obesity are the strongest risk factors for adenocarcinoma.

Oesophageal cancer is usually aggressive with a notorious lack of symptoms during the early stages. The overall 5-year survival rate is around 10%. The majority of patients present with an already disseminated disease where treatment is limited to palliation. Surgery, often in combination with neo-adjuvant therapy, is the treatment of choice when cure is intended. However, despite the fact that the 5-year survival rate after surgery with intent to cure has improved over the last decade, the long-term survival rates are still as low as 25-30%.

This thesis addresses aspects on prognosis of both oesophageal cancer and cancer of the gastric cardia in Sweden and aims to identify factors that may influence survival and prognosis.

2 BACKGROUND

2.1 EPIDEMIOLOGY AND ETIOLOGY

2.1.1 Histological types

The mucosa of the oesophagus is lined by a squamous cell epithelium. Worldwide, SCCA is by far the most common histological type of oesophageal cancer and accounts for approximately 90% of all cases [1]. Adenocarcinoma, which is more common in the industrialised part of the world, commonly develops from Barrett's oesophagus [2]. Barrett's oesophagus is a columnar cell metaplasia replacing the squamous-cell epithelium in the distal part of the oesophagus [3]. Out of the three main types of Barrett's oesophagus, namely specialised intestinal-like, junctional type, and fundic type, only the intestinal-like type is associated with development of adenocarcinoma [4-8]. Cancer of the gastric cardia is with few exceptions adenocarcinoma, the remainder being SCCA or other more rare cancer forms. The fact that adenocarcinoma of the gastric cardia shares many characteristics with adenocarcinoma of the oesophagus has led to the hypothesis that the two cancer forms are variants of the same disease [9, 10]. Other histological types, including melanomas, carcinoids, leiomyosarcomas and lymphomas, are rarities and fall outside the scope of this thesis[1].

2.1.2 Geographical distribution and incidence trends

Worldwide approximately 462 000 new cases of oesophageal cancer are diagnosed each year, causing 386 000 deaths annually [11]. On a global scale there are striking variations in geographical distribution. The so-called "oesophageal cancer belt", stretches from northern Iran to north-central China with an incidence rate of around 200 per 100 000 persons / year. High-risk areas also include southern and East Africa, south-central Asia, eastern South America, and parts of western Europe [11, 12]. Even more marked is the variability of geographic distribution when smaller areas such as countries or areas within countries are compared [12-14].

As already mentioned, globally the most frequent histological subtype of oesophageal cancer is SCCA. The incidence rates for oesophageal SCCA have remained stable or even decreased in Western countries in recent decades [15, 16]. Adenocarcinoma, on the other hand, has shown a dramatic increase, especially in the United States and United Kingdom, but also in other countries of the industrialised part of the world, including Sweden [9, 10, 13, 17-24]. In the United States and the United Kingdom the incidence rates of oesophageal adenocarcinoma are currently higher than those for SCCA. There have been reports of annual incidence rate increases of around 20% among white males in the United States, which, in that population is higher than for any other malignancy [25, 26].

The incidence trends of gastric cardia adenocarcinoma are much more difficult to determine. This is due to the fact that the site classification differs between different registers [9, 21, 23, 27-29]. There are several reports indicating an increase in the incidence of gastric cardia adenocarcinoma [18, 21, 22, 30]. Some Western studies, on the other hand, report stable or even decreasing trends [16, 31]. Simultaenously, incidence rates of distal

gastric cancer seem to be decreasing. Therefore, the site classification becomes critical in efforts to determine the exact incidence trend for gastric cardia adenocarcinoma.

2.1.3 Risk factors

The etiological factors for oesophageal cancer and cancer of the gastric cardia are multifactorial. The geographical variation in incidence is closely related to a number of environmental factors. Oesophageal SCCA, oesophageal adenocarcinoma and gastric cardia adenocarcinoma share increasing age and male sex as risk factors.

2.1.3.1 Oesophageal squamous-cell carcinoma

Many studies have been performed in high-risk areas to investigate potential environmental and dietary risk factors. A number of these factors seem to be specific to the geographic region. Drinking hot beverages, consumption of opium residues and chewing tobacco, nutritional deficiencies and exposure to nitrosamines in nitrosamine-rich food are all risk factors found in specific geographic regions with high incidences of SCCA [1, 11].

In the Western part of the world the most pronounced risk factors are tobacco smoking and excessive use of alcohol [32-35]. Other risk factors suggested are low socio-economic status, low intake of vegetables and fruits, and low body mass index (BMI). The male sex predominates with 3:1 [33, 35-38].

2.1.3.2 Oesophageal adenocarcinoma

Since the incidence of oesophageal adenocarcinoma is increasing rapidly, intense efforts have been directed to identifying risk factors associated with the increase. While the majority of adenocarcinomas derive from Barrett's oesophagus [4], gastroesophageal reflux has been studied extensively and proven to be the strongest known risk factor for adenocarcinoma of the oesophagus [39-41]. Approximately 10% of all patients with chronic gastroesophageal reflux develop Barrett's oesophagus during their life-time [5]. The actual Barrett's oesophagus is usually asymptomatic [42]. Barrett´s oesophagus is associated with a 60 to 90-fold increased risk of oesophageal adenocarcinoma [43]. Contradictory results have been reported concerning drugs relaxing the lower oesophageal sphincter, with supposed consequent gastroesophageal reflux, as risk factors [44, 45]. Overweight is also associated with an increased risk (two to eightfold) and obesity, BMI > 30 kg/m^2, has a 16-fold increased risk of developing oesophageal adenocarcinoma [46]. Smoking seems to be a moderate risk factor while alcohol consumption and heredity do not seem to be risk factors [33, 34, 47, 48]. Infection with *Helicobacter pylori* has shown an inverse relation with development of adenocarcinoma of the oesophagus. Theoretically, the infection causes atrophic gastritis with resultant reduced acidity of the refluxed matter. This relationship is however questioned [49]. The male predominance of 7:1 is not fully explained.

2.1.3.3 Gastric cardia adenocarcinoma

Gastric cardia adenocarcinoma shares several of the known risk factors for oesophageal adenocarcinoma. The associations however, are not as strong as for oesophageal adenocarcinoma. Gastroesophageal reflux [40, 50], obesity [46, 51] and tobacco smoking [33, 34]

are associated with cardia cancer risk but not excessive alcohol consumption [34]. There is a male predominance of 6:1.

2.2 CLINICAL CONSIDERATIONS

2.2.1 Anatomy

2.2.1.1 Oesophagus

The oesophagus is an approximately 25 cm long tube that stretches from the hypopharynx, at the level of the sixth cervical vertebra, to the stomach. It consists of an inner mucosal layer, a submucosa which is the strongest layer, and a muscular layer (an inner circular and an outer longitudinal layer). The oesophagus lacks a serosa with the muscularis layer covered by an adventitia. The oesophagus is divided into a cervical, and thoracic upper, middle and lower parts. The *cervical part* is about 4 cm long and starts at the lower border of the cricoid cartilage ending at the thoracic inlet, approximately 18 cm from the maxillary incisors. The *upper thoracic part,* about 6 cm long, stretches from the thoracic inlet to the tracheal bifurcation about 24 cm from the maxillary incisors. The *mid-thoracic part* (proximal half of the oesophagus between the tracheal bifurcation and the OGJ) is 8 cm long and extends to about 32 cm from the maxillary incisors. The *lower part* of the thoracic oesophagus is the distal half of the oesophagus between the tracheal bifurcation and the OGJ, usually 40 cm from the maxillary incisors. The oesophagus is positioned in close anatomical relation to a number of vital structures, including the trachea, the heart, the lung and major intrathoracic vessels[52].

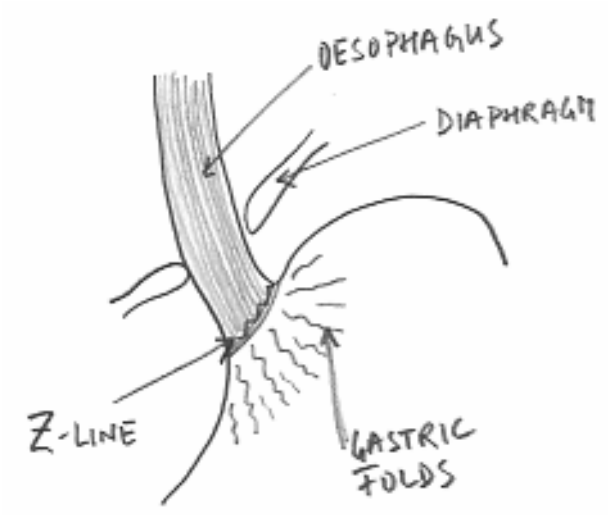
The arterial blood supply of the oesophagus is derived from six pathways: inferior thyroid artery, bronchial arteries, left gastric artery, branches from the descending aorta, right intercostal arteries and the left inferior phrenic artery. The venous drainage of the upper two-thirds of the oesophagus is into the systemic veins whereas the lower third is into the portal venous system. The submucosa contains a large plexus of veins that communicates with an external venous plexus. These veins drain into the portal venous system via the left gastric vein. There is a rich network of lymphatic vessels that form plexuses in the mucosa, the submucosa, the muscularis and the adventitia. The lymph vessels run longitudinally and anastomose within and between levels[52]. Whether or not lymph nodes are defined as *regional,* depends on the location of the primary tumour [53]. For the cervical oesophagus the regional lymph nodes include the scalene, internal jugular, upper and lower cervical, peri-oesophageal, and supraclavicular nodes. For the intrathoracic portion of the oesophagus, the upper peri-oesophageal (above the azygos vein), subcarinal, lower peri-oesophageal (below the azygos vein), mediastinal and perigastric (excluding celiac) lymph nodes, are defined as regional.

2.2.1.2 Oesophago-gastric junction, gastro-oesophageal junction, gastric cardia

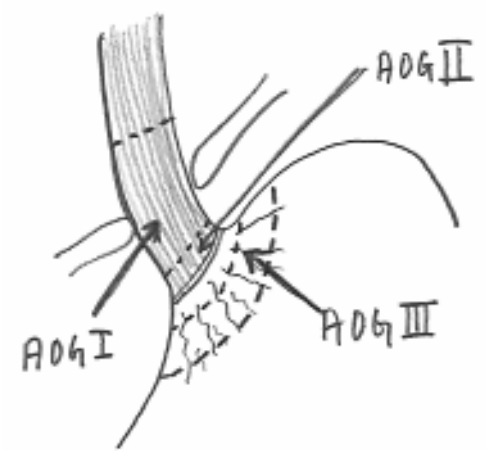
As seen in the legend, there are different terminologies used for describing the gastric cardia. The gastric cardia is said to be “the anatomical borderland between the oesophagus and the stomach” [54]. The junction (Figure1) can be defined from the external anatomical view, or the internal histological junction. Accurate definition of

the OGJ is complicated by the fact that the mucosa is not fixed to the muscular layer and can move freely. The lack of consensus regarding the OGJ has added to the controversy regarding the most appropriate way of classifying carcinomas of the OGJ/ gastric cardia. The fact that carcinomas of the cardia share features of both oesophageal and gastric cancers adds to the confusion. The classification system most commonly used from a surgical perspective is the Siewert classification [55]. Siewert defines the anatomical cardia as the superior margin of the gastric folds and adenocarcinoma of the oesophago-gastric junction (AOG) as a carcinoma where the center of the tumour lies within 5 cm proximal or distal from the anatomical cardia [54]. There are three types of AOG. A Type 1 AOG is located 5cm to 1cm proximal from the anatomical cardia and is regarded as an adenocarcinoma of the distal oesophagus. Type 2 tumours, located from 1 cm proximal to 2 cm distal from the anatomical cardia, are regarded as true cardia carcinomas. Type 3 tumours lie from 2 to 5 cm distal of the anatomical cardia and are regarded as subcardiac gastric cancers (Figure1).

The arterial blood supply of the gastric cardia is via the left inferior phrenic and left gastric arteries. The venous drainage is through the left inferior phrenic vein into the left suprarenal vein, but can also have a portal component via the left gastric vein. Patterns of lymphatic drainage of the gastric cardia mirror those of the distal part of the oesophagus with the exception that celiac lymph nodes are considered as regional.



a.



b.

Figure 1a. Anatomy (transsection) of the OGJ (A), with the oesophagus, the diaphragm, the squamocolumnar junction, and the gastric folds. The Z-line / squamocolumnar junction moves orally when Barrett´s oesophagus is present while the gastric folds do not. The classification of adenocarcinomas of the oesophagogastric junction according to Siewert and Stein is shown in Figure 1b.

2.2.2 Symptoms

Most patients (>70%) develop dysphagia as the first symptom of the disease [1, 26]. The oesophagus is very elastic and distensible resulting in late occurrence of swallowing-related symptoms. At the time of diagnosis more than 50% of patients have unresectable tumours or metastatic disease [1]. Progressive narrowing of the oesophageal lumen by the cancer leads to the typical symptom complex starting with difficulty in swallowing solid food progressing to inability to swallow liquids and eventually even their own saliva. Some patients also experience oesophageal pain, odynophagia, accompanying the dysphagia. More than 70% of patients present with a history of non-volontary weight loss [1]. Dyspnea, coughing, hoarseness and pain (retrosternal, back, right upper abdomen), rare as initial symptoms, usually indicate advanced disease.

2.2.3 Diagnostic principles and staging

2.2.3.1 Diagnosis

Upper endoscopy, oesophago-gastro-duodenoscopy (OGD) and biopsy are used to confirm the diagnosis. OGD gives important information regarding tumour stage, tumour location, tumour length and local growth patterns (circumferential or stricturing). Circumferential tumours are more likely to be transmural and the majority (80%) of these tumours are associated with lymph node metastases [56]. Adenocarcinoma diagnosed on random biopsies from Barrett's oesophagus seldom have lymph node metastases [57]. In Sweden oesophagogram (barium-swallow examination) is seldom used as the first diagnostic modality.

2.2.3.2 Pre-treatment staging

Investigations following OGD and biopsy are aimed at pre-treatment staging of the tumour and assessment of the general health status of the patient. The primary tumour, nodal, and metastatic status as depicted in the Tumour-Node-Metastasis (TNM) classification is essential to predict prognosis and for individualised treatment planning. Since both surgery and chemoradiotherapy for oesophegeal cancer are associated with significant complications, it is crucial to know whether patients are fit enough to tolerate treatment.

The combination of computed tomography (CT) of the abdomen and chest with intravenous contrast medium, endoscopic ultrasound (EUS), with or without fine needle aspiration of the tumour and lymph nodes, gives an accuracy of almost 80% in the assessment of primary tumour stage. This protocol gives an accuracy of more than 80% in assessing lymph node involvement but only 60-65% for determining systemic disease [26, 58]. Positron emission tomography (PET) using ^{18}F-fluoro-deoxy-D-glucose as isotope can be used for detection of especially solid organ systemic metastases, wheras CT-PET seems to have value in assessing regional lymph node involvement [59]. These modalities can also be used to measure response after induction of chemotherapy [60]. Studies have shown that PET can detect distant metastatic disease in 15% of patients where CT and EUS failed to do so [61, 62].

Thoracoscopy and laparoscopy, highly accurate for local staging (>90%), are invasive and therefore not used routinely. [63]. Bronchoscopy may be of value if involvenment of the tracheo-bronchial tree is suspected.

Assessment of the general health status of the patient includes, apart from a meticulous clinical investigation, electrocardiogram (ECG), stress ECG, spirometry, renal function tests, audiograms and routine blood samples.

2.2.3.3 TNM-classification and staging

Oesophageal cancer and cancer of the gastric cardia are staged according to the 2002 American Joint Committee on Cancer TNM classification [53], or the International Union Against Cancer (UICC) classification [64]. Oesophageal cancer (Table 1) and cancer of the gastric cardia are classified separately, as cancer of the GOJ is still included in the classification system for gastric cancer (Table 2). Staging of oesophageal and cardia cancers according to the TNM system is shown in Tables 3 and 4. The current division of oesophageal and cardia cancers in two TNM systems is controversial. Seemingly similar incidence trends, risk factors and anatomical proximity have raised the issue of creating a separate classification system for cardia cancer [54]. Oesophageal cancers seem to predominantly spread into the lower mediastinum and paracardiac nodes, while gastric cancers tend to spread within the abdominal compartment, but this is controversial [54, 65]. Type 1 cardia cancers behave more like distal oesophageal cancers whereas Types 2 and 3 are more similar to proximal gastric cancers [54, 55].

T- Primary tumour

TX- Primary tumour cannot be assessed
T0- No evidence of primary tumour
Tis- Carcinoma in situ
T1- Tumour invades lamina propria or submucosa
T2- Tumour invades muscularis propria
T3- Tumour invades adventitia
T4- Tumour invades adjacent structures

N- Regional lymph nodes

NX- Regional lymph nodes cannot be assessed
N0- No regional lymph node metastasis
N1- Regional lymph node metastasis

M- Distant metastasis

MX- Distant metastasis cannot be assessed
M0- No distant metastasis
M1- Distant metastasis

For tumours of lower thoracic oesophagus
M1a- Metastasis to celiac lymph nodes
M1b- Other distant metastasis

For tumours of upper thoracic oesophagus
M1a- Metastasis to cervical lymph nodes
M1b- Other distant metastasis

For tumours of mid-thoracic oesophagus
M1a Not applicable
M1b Non-regional lymph node or other distant metastasis

Table 1. TNM-classification of oesophageal cancer according to UICC[64]

T- Primary tumour

TX- Primary tumour cannot be assessed
T0- No evidence of primary tumour
Tis- Carcinoma in situ: intraepithelial tumour without invasion of the lamina propria
T1- Tumour invades lamina propria or submucosa
T2- Tumour invades muscularis propria or subserosa
    T2a- Tumour invades muscularis propria
    T2b- Tumour invades subserosa
T3- Tumour penetrates serosa without invasion of adjacent structures
T4- Tumour invades adjacent structures

N- Regional lymph nodes

NX- Regional lymph nodes cannot be assessed
N0- No regional lymph node metastasis
N1- Metastasis in 1 to 6 regional lymph nodes
N2- Metastasis in 7 to 15 regional lymph nodes
N3- Metastasis in more than 15 regional lymph nodes

M- Distant metastasis

MX- Distant metastasis cannot be assessed
M0- No distant metastasis
M1- Distant metastasis

Table2. TNM-classification of stomach cancer according to UICC[64]

Stage grouping	T- primary tumour	N- regional lymph nodes	M- distant metastasis
Stage 0	Tis	N0	M0
Stage 1	T1	N0	M0
Stage 2A	T2, T3	N0	M0
Stage 2B	T1, T2	N1	M0
Stage 3	T3	N1	M0
	T4	Any N	M0
Stage 4	Any T	Any N	M1
Stage 4A	Any T	Any N	M1a
Stage 4B	Any T	Any N	M1b

Table 3. Stage grouping of oesophageal cancer according to UICC[64]

Stage grouping	T- primary tumour	N- regional lymph nodes	M- distant metastasis
Stage 0	Tis	N0	M0
Stage 1A	T1	N0	M0
Stage 1B	T1	N1	M0
	T2 a/b	N0	M0
Stage 2	T1	N2	M0
	T2 a/b	N1	M0
	T3	N0	M0
Stage 3A	T2 a/b	N2	M0
	T3	N1	M0
	T4	N0	M0
Stage 3B	T3	N2	M0
Stage 4	T4	N1, N2, N3	M0
	T1, T2, T3	N3	M0
	Any T	Any N	M1

Table 4. Stage grouping of stomach cancer according to UICC[64]

2.3 PROGNOSIS AND TREATMENT

2.3.1 Prognosis in general

Oesophageal cancer and cancer of the gastric cardia have an extremely poor prognosis. For the greater part of the 20th century, palliation was the primary goal of treatment and cure was considered a chance phenomenon [66]. In 1941 Ochsner and DeBakey reviewed the literature and reported a postoperative mortality after oesophagectomy of 72% [67]. Dismal results were the rule and Earlam et al reported in 1980 an overall 5-year survival of 4 %, in-hospital mortality after oesophagectomy of 13% and 5-year survival after oesophagectomy of 10% [66]. Given its grim prognosis, oesophageal cancer is the 6th leading cause of cancer death worldwide [11]. Five-year survival rates of 5-10% still hold today [68]. However, several studies have recently reported an improved prognosis [69-74]. The reason for the improvement is probably multifactorial.

2.3.2 Treatment

2.3.2.1 Surgery

Surgical resection has remained the standard treatment for oesophageal and cardia cancer [26, 75, 76]. For oesophageal cancer, either a transhiatal approach (Orringer), with blunt dissection of the oesophagus via a laparotomy and a neck incision [77], or a transthoracic approach via laparotomy and right thoracotomy (Ivor-Lewis) is used [78]. There is also a more rare, but still sometimes used, third approach using abdominal, thoracic and cervical access (McKewan). For cardia cancer the optimal surgical approach is still a matter of controversy. There is some consensus that a Siewert 1 cardia cancer should be treated as a distal oesophageal cancer with oesophagectomy while cardia cancers of Siewert 2 and 3 subtypes should be treated with a gastrectomy and a transhiatal resection of the distal part of the oesophagus [79, 80]. The stomach is used more frequently as a substitute than the colon or jejunum. Oesophageal resections are major surgical procedures resulting in high numbers of postoperative complications [81-83].

2.3.2.2 Neo-adjuvant and adjuvant therapy

As most patients present with advanced non-resectable disease and since about 50% of patients assumed to have resectable disease turn out to have Stage 3 disease [1], new multimodality treatment options have been developed. Chemotherapy, radiotherapy and combination chemoradiotherapy have been used [84-88]. The results are controversial [26, 69]. Despite the fact that most randomised trials performed have been unable to show a survival benefit when using pre-operative neo-adjuvant therapy, some studies have shown a significantly improved survival after oesophagectomy combined with neo-adjuvant treatment protocols [69, 73, 89]. In these studies the use of neo-adjuvant therapy combined with a R0 resection was the strongest predictor of increased survival.

One out of seven randomised trials comparing neo-adjuvant chemotherapy followed by surgery, with surgery alone found a survival advantage [26]. Of the five reported randomised trials on neo-adjuvant radiotherapy followed by surgery compared to surgery alone, one reported a survival benefit when using the combined modality. However, a meta-analysis of all the trials failed to show a survival benefit [26]. Regarding

neo-adjuvant chemoradiotherapy followed by surgery compared to surgery alone, one out of seven reported randomised trials showed a survival benefit [26]. However, this study has been criticised. In a meta-analysis of the seven trials a significant survival benefit was shown if using neo-adjuvant chemotherapy in combination with surgery compared to surgery alone [90]. The most prominent effect on long-term survival was in the group of patients with a complete pathologic response to chemoradiotherapy. However, it has been stated that patients with a complete response to chemoradiation often have node-negative disease and that patients with node-positive disease seldom show a complete pathologic response to treatment [91]. Despite the fact that the results of neo-adjuvant therapy are not conclusive, several centres use individualised stage-specific neo-adjuvant treatment protocols in efforts to downstage locally advanced tumours [26, 69]. In the five randomised trials that have compared surgery followed by adjuvant chemotherapy, radiotherapy or chemoradiation with surgery alone, no survival benefit has been proven. However, in the group of patients with a high risk of recurrence there is evidence that adjuvant therapy can improve survival [92, 93].

2.3.2.3 Palliative therapy

Since most patients with newly diagnosed oesophageal cancer have disease too advanced for curative resection, palliation of symptoms and improvement in quality of life is the main goal in the majority of patients [94]. Dysphagia, the most prominent symptom, is nowadays often treated by placement of expandable metal stents [95, 96]. Local radiotherapy, photodynamic therapy and laser ablation are also used [97-99]. Results of laser and ethanol injection treatment are comparable to stent results, whereas photodynamic therapy and argon plasma coagulation seem to be less effective [100]. Some studies have reported that compared to brachytherapy, stent treatment achieves a faster palliation at the cost of more complications, while some but not all studies show a longer duration of palliation achieved by brachytherapy [99, 101-109].

In the group of patients that suffer from tracheo-bronchial fistulas, symptom relief is often dramatic when stents are used [110-114]. Combinations of the above-mentioned modalities can be used. Improvement and maintainance of nutritional status are important and may necessitate feeding through a percutanous gastrostomy (PEG).

2.3.3 Prognostic factors

2.3.3.1 Tumour Stage

The stage of oesophageal cancer is the strongest prognostic factor with survival rates of 95% for Stage 0, 50-80% for Stage 1, 30-40% for Stage 2A, 10-30% for Stage 2B, and 10-15% for Stage 3 disease. For Stage 4 (patients with distant metastases) the median survival is less than one year [1]. Diagnosis at an early stage will improve the overall prognosis. Several retrospective studies have shown improving trends in prognosis after oesophagectomy. These improved results may partially be due to a selection bias, as more early cancers are detected in surveillance programs for Barrett's oesophagus [70]. However, some authors also show improved survival after oesophagectomy for SCCA [74].

2.3.3.2 Tumour location and histological type

Tumour location and histological type of oesophageal cancer have both proven to be prognostic factors in resected patients. Adenocarcinoma seems to have a significantly better prognosis in all stages compared to SCCA [69, 115]. This finding may partly be explained by tumour location. Adenocarcinomas are more likely to develop in the distal part of the oesophagus while SCCA are more widely spread. Due to the anatomical features of the cervical and upper parts of the oesophagus, including its close relation to many vital structures, resection is more challenging compared to the lower part of the oesophagus [76]. A positive correlation between tumour length and T-stage has been shown. Tumours longer than 3.5 cm have a worse prognosis, most likely due to a higher T-stage [116].

2.3.3.3 Tumour differentiation and lymphatic vessel invasion

A low grade of tumour differentiation and histopathologic lymphatic vessel invasion are negative predictors of survival [117-119]. Interestingly however, lymphatic invasion seems to influence survival more negatively in Siewert 2 and 3 cardia cancers compared to subtype 1 [119].

2.3.3.4 R0-resection, lymphadenectomy and surgical technique

The goal of curatively intended oesophagectomy for oesophageal cancer and resection of gastric cardia tumours is complete (R0) resection of the tumour and surrounding lymph nodes. This has been confirmed as the most important prognostic factor for long-term survival in patients with localised oesophageal cancer [26, 74, 120, 121]. The possibility to treat small mucosal tumours (<1.5 cm) without lymph node metastases with endoscopic mucosal resection (EMR), emphasises the importance of pre-operative staging. In addition, resected specimens will give more information regarding the depth of tumour involvement [122]. Whether or not the extent of lymphadenectomy influences survival after oesophageal cancer resection is still controversial [123]. Therefore, both transhiatal and transthoracic approaches are still used. A slight survival advantage in favour of the transthoracic approach has been reported. Others have only shown an improved 5-year survival when comparing patients resected for tumours with less than 9 positive lymph nodes [124-126].

2.3.3.5 High- and low-volume centre or surgeon

In recent years several studies have addressed the outcome of major surgery with regard to the number of cases treated per year per treating centre as well as individual surgeons. There is now clear evidence that short term morbidity and mortality of oesophageal resection can be reduced if patients are treated within a high-volume centre or by high-volume surgeons [83, 127-131]. The effect on long-term survival, however, is uncertain [132]. The effect seen on long-term survival may be explained by the reduced post-operative/ in-hospital mortality.

The number of cases that would constitute a high-volume centre or surgeon with a presumed lower postoperative mortality morbidity is still a point of hot debate. Several different definitions of high- and low-volume centres and surgeons have been used [133]. In a meta-analysis by Metzger et al [133], a very low volume was defined as < 5 oesophagectomies, a low volume as 5-10 oesophagectomies, medium volume as 11-20 oesophagectomies and high volume as >20 oesophagectomies per year. In a population-based study in Sweden low volume was defined as <5 resections, intermediate 5-15 resections and high volume >15 resections per year. In this study a significantly better short- and long-term prognosis was seen when comparing high with low volume hospitals [129]. Birkmeyer et al defined <2 procedures per year as low volume, 2-6 as intermediate and >6 as high volume[128, 134]. The definitions and the results might also depend on the geographic area and health care system in which the studies are performed.

3 AIMS OF THE STUDIES

3.1 OVERALL AIMS

- The overall aim of the thesis was to study the prognosis of oesophageal cancer and cancer of the gastric cardia in Sweden, and to identify factors that might influence survival.

3.2 SPECIFIC AIMS

- To study survival trends over time of adenocarcinoma and SCCA of the oesophagus in Sweden.

- To study the influence of surgical factors on both short- and long-term survival after oesophagectomy for SCCA of the oesophagus and adenocarcinoma of the oesophagus and gastric cardia.

- To study the influence of patient demographics and lifestyle factors on long-term survival of patients with oesophageal or cardia cancers.

- To assess predictors of outcome after placement of metal stents in patients with irresectable disease, in terms of improvement of dysphagia and procedure related mortality and morbidity.

4 SUBJECTS AND METHODS

4.1 PAPER I

4.1.1 Design

A Swedish population-based, cohort study based on data from the Swedish Cancer Register.

4.1.2 The Swedish Cancer Register

The register was founded in 1958 and became national in 1960. All physicians in Sweden, including pathologists and cytologists, are obliged to report all new cases of cancer to the register. Pathologists and cytologists report cancer diagnoses based on autopsies, surgically resected tissue, cytologic specimens and biopsies, whereas physicians in clinical disciplines report cases both verified and not verified by biopsy. This results in double verification of most cases. Data entered into the register include the birth date-based 10-digit unique personal number assigned to all Swedish residents, gender, date of diagnosis, age at diagnosis, basis of diagnosis, specification of cancer found only at autopsy, specification of first or second cancers, and histological type. The Swedish Cancer Register has used the 7th version of the International Classification of Diseases (ICD) coding scheme during the entire study period. It has been estimated that the Swedish Cancer Register is 98% complete [135].

4.1.3 Patients and exclusions

All cases of oesophageal cancer (ICD-7 code 150) from 1961 to 1996 were identified from the register. Cases where the histological subtype (adenocarcinoma, code PAD=096 or squamous-cell carcinoma, code PAD=146) could not be verified, were excluded as were cases found incidentally at autopsy and secondary cancers. To determine the vital status of the patients, data were linked to the Swedish Death Register and the Total Population Register. Furthermore, data were correlated with the Swedish Emigration Register to correct for emigration. The National Registration numbers were used in all registers to ensure correct matching. If a personal number was not found in any of the records the case was excluded from the analysis.

4.1.4 Statistical analyses

Cases were followed from date of diagnosis to death, emigration or 31 December 1997, whichever occurred first. Survival rates, using the life-table method, were calculated for calendar periods 1961-1969, 1970-1979, 1980-1989, and 1990-1996 for the histological subtype of oesophageal cancer. Since life expectancy has improved over time, not only observed survival but also relative survival was calculated. Relative survival was calculated as the ratio of the observed to the expected survival in the entire population, matched for age, gender, and the calendar period. To test equality of survival between patients in different time periods, maximum likelihood tests were used. To determine effects of patient characteristics on survival with regard to time period, relative survival models were used. In this model sex, 4 groups of age at diagnosis and calendar period were used. Patients were divided into age groups <60, 60-69, 70-79 and 80+ years at diagnosis and calendar periods as described above. Results were expressed as relative

hazards of dying of a specific histological type of cancer of the oesophagus with a 95% confidence interval (CI). Standard errors of the estimates were adjusted for overdispersion.

4.2 PAPER II AND PAPER III

4.2.1 The Swedish Esophageal and Cardia Cancer study

The Swedish Esophageal and Cardia Cancer study (SECC), a nationwide case-control study addressing risk factors for oesophageal and cardia cancer, was used in both Papers II and III. The study design of the SECC study has been presented in detail elsewhere [40]. In brief, an organisation consisting of contact persons at all 195 hospital departments involved in the diagnosis and treatment of oesophageal and cardia cancer was created in collaboration with the six regional tumour registries in Sweden. All cases of oesophageal or cardia adenocarcinoma and half of those with oesophageal SCCA (born on even-numbered dates), in individuals less than 80 years old that were born and were still living in Sweden, were identified shortly after diagnosis during the period December 1, 1994 through December 31, 1997. In total, 757 individuals with oesophageal or cardia cancer were identified of whom 618 (82%) were interviewed.

4.2.2 Design Paper II and Paper III

Both Paper II and Paper III consist of Swedish nationwide retrospective observational studies.

4.2.3 Data collection Paper II

For Paper II the SECC files of the 757 patients were re-examined. For almost all resected cases (97%), the surgical specimen had been re-evaluated by a single pathologist. However, in order not to miss any resected case, hospital charts of patients in whom there was any indication that surgery could have been performed, but for whom no pathological specimens were registered, from the departments of general surgery, thoracic surgery, pathology and oncology where the patient initially was treated were obtained and reviewed. Out of a total of 306 patients, potentially eligible for resection, 32 who had only an explorative laparotomy due to disseminated disease, were excluded from the analysis. Furthermore, 42 patients for whom case records were incomplete were excluded. The remaining 232 cases formed the study cohort of resected patients as included in the study (Figure 3). Data collected for each patient included the treating hospital, date of surgery, co-morbid diseases, tumour histology, tumour location, tumour length, pre-operative tumour stage, pre-operative investigations, post-operative pathological tumour staging, tumour stage as assessed by the surgeon at surgery, histopathological grade of tumour differentiation, treatment other than surgery, proximal resection margin, result of lung function tests, result of cardiac work load test, surgical approach, substitute of the oesophagus, extent of lymphadenectomy, anastomotic technique (hand sutured vs stapled), operative blood loss, operating time, the surgeon's experience of oesophageal resection, complications (anastomotic leakage, severe bleeding, paresis of the recurrent laryngeal nerve, cardiovascular insufficiency, respiratory failure, serious infectious complications), re-operation, need for intensive care unit (ICU) treatment, ventilatory support, and duration of hospital stay.

The complications mentioned were defined as follows:

Anastomotic leakage was defined as clinically significant or radiologically detected leakage. S**evere bleeding** was defined as bleeding in excess of 2 liters during the first 24 hours or need of reoperation for bleeding. **Paresis of the recurrent laryngeal nerve** was clinical after examination by an otorhinolaringologist. **Cardiovascular insufficiency** was defined as myocardial infarct according to standard accepted criteria, and postoperative debute of atrial fibrillation requiring treatment. **Respiratory insufficiency** was defined as the need for re-intubation and mechanical ventilation. **Severe infectious complications** included intra-abdominal or intrathoracic abscesses, larger than 3x3 cm detected on imaging or sepsis with bacteraemia.

Hospitals were defined as high-volume centres if an annual number of 10 or more resections had been performed during the study period. Similarly, surgeons were defined as high volume if they had performed 10 or more resections annually during the study period.

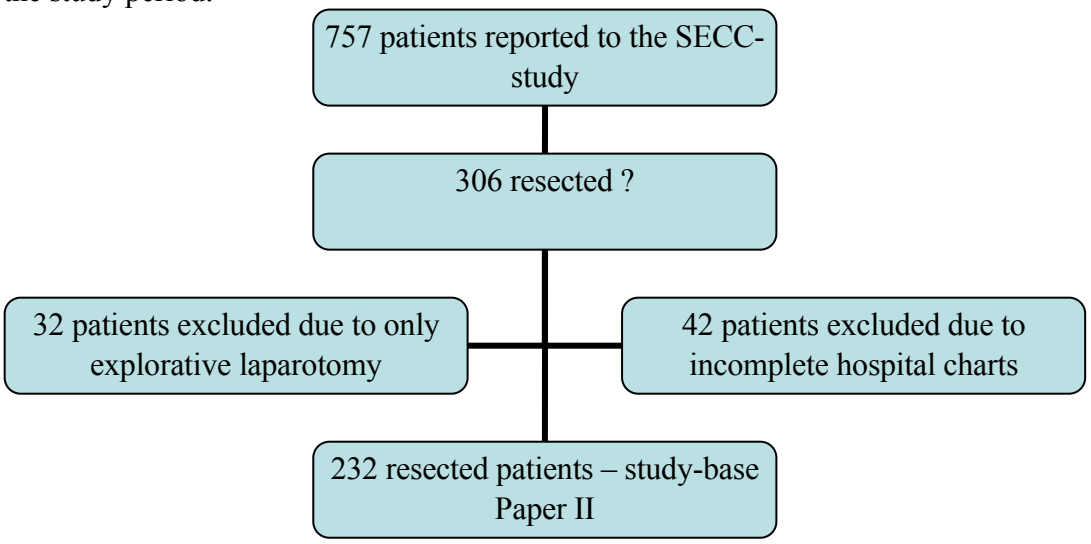


Figure 3. Inclusion and reasons for exclusion of patients in Paper II

4.2.4 Staging

The TNM-classification (2002) [53] was used for staging. Modifications were made regarding nodal stage (N) of gastric cardia tumours. During the study period pathologists classified the cancers according to the 1992 system. The number of lymph nodes in cardia cancers classified as Siewert Type 2 or 3 was often too few to obtain a true N-stage according to the UICC system of 2002. We therefore used the reported number of lymph node metastases for N-stage, regardless of the total amount of lymph nodes identified. Furthermore, Type 1 AOG [136] was regarded as distal oesophageal cancer and the TNM-staging system for oesophageal cancer was used. For Types 2 and 3 AOG the TNM-system for gastric cancer was used with the modification described above. Tumours were staged into four groups: Stage 1 included Stage 0 and Stage 1 (oesophageal cancer) or 1A and 1B (cardia cancer); Stage 2 included Stage 2A and 2B (oesophageal cancer) or Stage 2 (cardia cancer); Stage 3 included Stage 3 (oesophageal cancer) or Stage 3A and 3B (cardia cancer); and Stage 4 included Stage 4A and 4B (oesophageal cancer) or Stage 4 (cardia cancer).

4.2.5 Data collection Paper III

In Paper III the 618 interviewed patients were followed to determine survival. Out of the 42 cases described in Paper II where hospital charts were incomplete 38 were interviewed in the SECC study. These 38 cases were excluded from the study. The remaining 580 patients, 356 not resected and 224 resected, were analysed (Figure 4).

We used the interview data retrieved from the original SECC study. The following variables were used:

Symptomatic reflux was defined as recurrent reflux symptoms, i.e. heartburn or regurgitation, reported at least once per week for one year or more. Subjects were divided into four **BMI groups according to BMI** 20 years before the interview. **Physical activity was** categorised into four levels, using a combination of 12 variables, including usual activities such as standing, walking and climbing stairs, as well as physical activity during leisure time and at work. A lifetime history of **tobacco use** was recorded where smokers were defined as individuals smoking regularly at least one cigarette per day or at least one cigar or pipe per week during a period of at least six months, and previous smokers as individuals who stopped smoking two years or more before the interview. **Alcohol consumption was** assessed with separate questions regarding consumption of beer, wine and liquor 20 years before the interview. The amount of alcohol was calculated as pure alcohol in grams per week, and categorised into four groups.

Cancer stage for the 224 cases interviewed and resected was retrieved from the data collected in Paper II. For the remaining 356 patients cancer stage was unknown, but the survival curve was more or less identical to the survival curve of Stage 4 tumours in the resected group, indicating that these patients probably suffered from advanced disease.

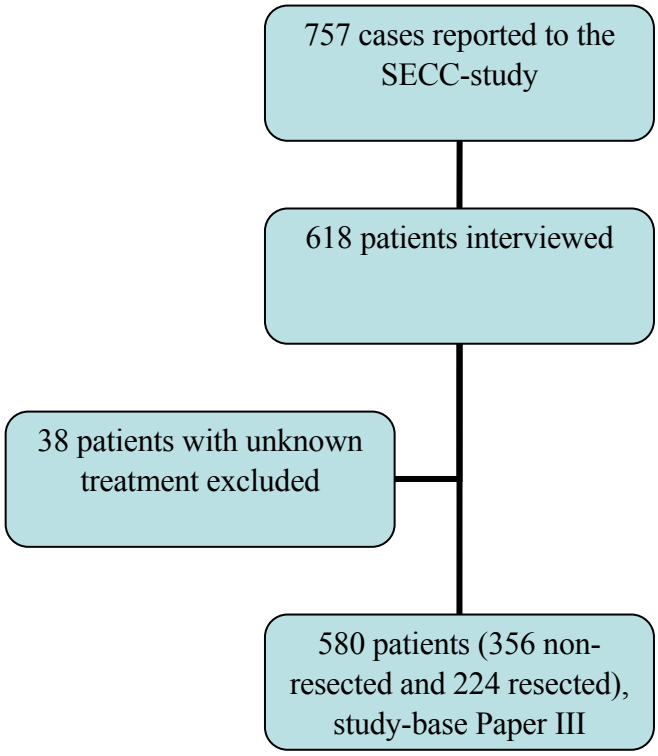


Figure 4. Inclusion and reasons for exclusion of patients in Paper III

4.2.6 Statistical analysis

The Wilcoxon test was used to compare medians of continuous variables between high- and low-volume hospitals or high- and low-volume surgeons, for example operative blood loss, while Fisher's exact test was used to evaluate differences in the distribution of categorised variables, for example percentages of post-operative complications between two groups. Through linkage to the Swedish National Death Register, patients were followed up for mortality until 31 December 2004. Survival curves were estimated by the Kaplan-Meier method and the curves were compared using the log-rank test. The entry date in Paper II was the date of surgery, while the entry date in Paper III was the date of diagnosis. The impact of the prognostic factors was further evaluated using multivariate analysis with the Cox proportional hazards regression model from which hazard ratios (HRs) with their corresponding 95% CIs were derived. The data conformed to proportional hazards assumptions as verified by the method of Schoenfeld's partial residuals. Interaction between oesophagectomy and other demographic and lifestyle factors was tested by including cross-production terms in the regression models.

4.3 PAPER IV

4.3.1 Design

A retrospective observational clinical study of consecutive patients with malignant dysphagia, treated with self-expandable metal stents at a single institution during a 12 year period.

4.3.2 Data collection

A search of computerised medical records for patients palliatively treated with oesophageal stents between December 1993 and May 2005 in the Division of Surgery, Danderyd Hospital, was performed. Date of death was obtained through linkage to the Swedish National Death Register. The following data were retrieved from medical records and pathology reports: gender, age, date of diagnosis, date of stent placement, tumour length, tumour location, tumour histology, health status at stent placement, use of medication, procedure-related complications, complications within 30 days of stent placement, weight, height, dysphagia score before and after treatment, and eventual other treatments.
A standard five-grade scale was used to evaluate dysphagia (Table 5). The score was determined before and after stent placement, the post-treatment assessment being performed within two days of stent placement. Ability to eat in terms of the solidity of food was documented. The data on dysphagia were retrieved mostly from the documentation in the medical records by the treating nursing staff.

Severity of dysphagia	**Score**
Inability to swallow saliva	5
Difficulty to swallow liquids	4
Difficulty to swallow soft food	3
Difficulty to swallow solid food	2
Ability to eat a normal diet	1

Table 5. Dysphagia scoring system

4.3.3 Stent insertion

Wallstents (Boston scientific, Galway, Ireland) or Ultraflex stents (Olympus, Seoul, Korea) were used. Stent placement techniques differed in accordance with the introducer and release mechanisms of the different stents and instructions from the manufacturers. All procedures were performed under conscious sedation with midazolam, 1-5 mg intravenously and morphine 2.5 – 10 mg intramuscular. OGD was performed to establish the extent of the tumour and the state of the rest of the upper gastro-intestinal tract. If needed, dilatation of the tumour was performed using a Rigiflex© balloon (Olympus, Seoul, Korea) (12-14 mm) to permit passage of the gastroscope. Fluoroscopy was used to map the longitudinal extent of the tumour placing skin markers. Stents were placed over a guidewire positioned via the gastroscope and under fluoroscopic guidance. Endoscopic verification of stent placement and expansion was only performed when there was doubt about the result.

4.3.4 Statistical analyses

Descriptive statistics of the dataset were reported as frequencies and percentages. The Kaplan-Meier method was used to calculate survival, using time of stent placement as entry date and date of death, or 31 September 2005, if patients were alive, as exit date. The Wilcoxon rank-sum test was used to evaluate differences in pre- and post-treatment dysphagia scores. Logistic regression was used to evaluate the effect of age, gender, tumour length, tumour location and histology on relief of dysphagia and early and late complications. Stratification for age was <60, 60-69, 70-79 and ≥80 years, for tumour length <5 cm, 5-8 cm and >8cm, for histology adenocarcinoma, SCCA or other and for dilatation yes or no.

4.4 PAPERS I, II, III, AND IV

Statistical analyses in all papers were performed using either STATA® 9.1 or 9.2 (StataCorpLP,Collage Station,Texas,USA) or SAS® (SAS Institute Inc., SAS Campus Drive, Cary, NC 27513, USA) version 6, 8 or 9.

5 RESULTS

5.1 PAPER I

5.1.1 Patients

In total, 10820 records of patients with oesophageal cancer were found through the Swedish Cancer Register during the period 1961 through 1996. After excluding 480 cases found first at autopsy, 918 secondary oesophageal cancer cases, and 70 invalid records, 9,352 patients with oesophageal cancers remained for final analyses. The number of patients diagnosed with adenocarcinoma was 1441 while 6395 had SCCA. There was a strong male predominance in both histological types, 80% in the adenocarcinoma group and 69% in the SCCA group. The median age at diagnosis for adenocarcinoma patients increased from 67.5 in 1961-1969 to 70.0 in 1990-1996, while the median age for patients with SCCA was stable (69 years) during the study period.

5.1.2 Survival trends of adenocarcinoma

Curves of relative survival of patients diagnosed with adenocarcinoma of the oesophagus are shown in Figure 5. Among patients with adenocarcinoma of the oesophagus, both the observed and the relative survival increased during the recent decade, compared to all previous decades studied. The 5-year observed survival was lowest during 1970-1979 (2.7%) and increased to 10.5% in 1990-1996. The 5-year relative survival was stable around 5% during the first three decades and increased to 13.7% during the most recent study period (1990-1996). The improvement in survival during the entire follow-up duration for patients diagnosed during 1990-1996 was statistically significant (p value < 0.001) as compared to that during 1961-1989.

5.1.3 Survival trends of squamous cell carcinoma

Curves of relative survival of patients diagnosed with SCCA of the oesophagus are shown in Figure 6. The long-term survival improved slightly and gradually for each decade during the study period. The 5-year observed survival increased from 3.8% to 7.0%, and the 5-year relative survival increased from 5.0% to 8.9% during the four decades of observation. The comparison of the 5-year survival between the time periods 1990-1996 and 1961-1989 revealed a statistically significant improvement (p value< 0.001).

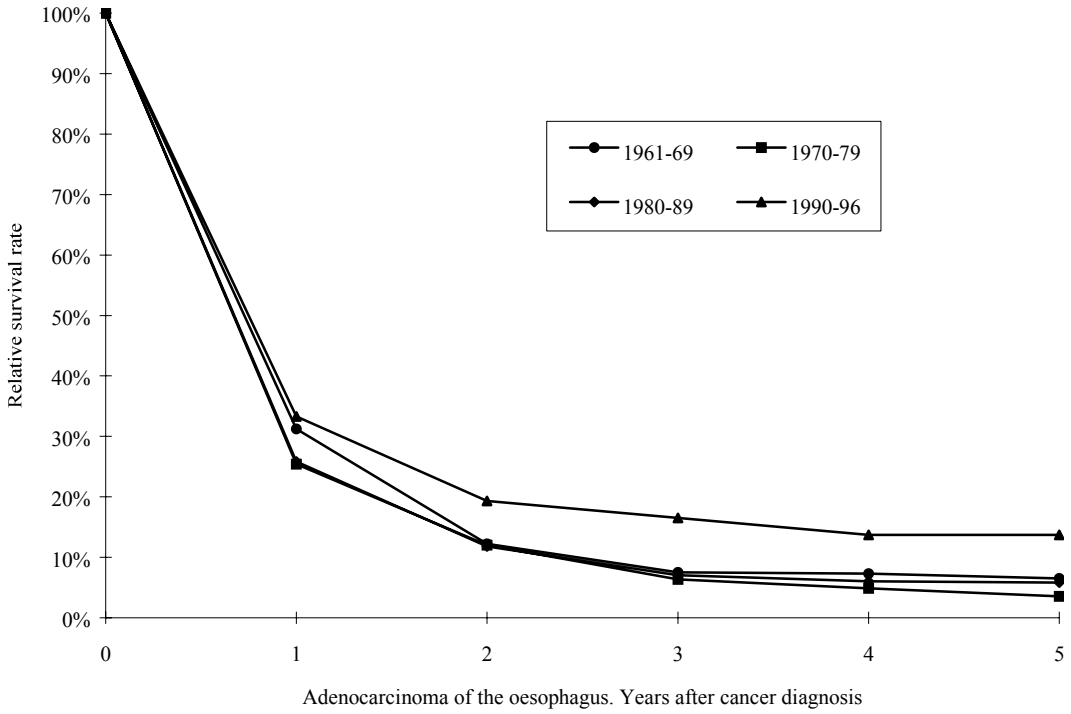


Figure 5. The relative survival of oesophageal adenocarcinoma diagnosed in Sweden during 4 calendar periods

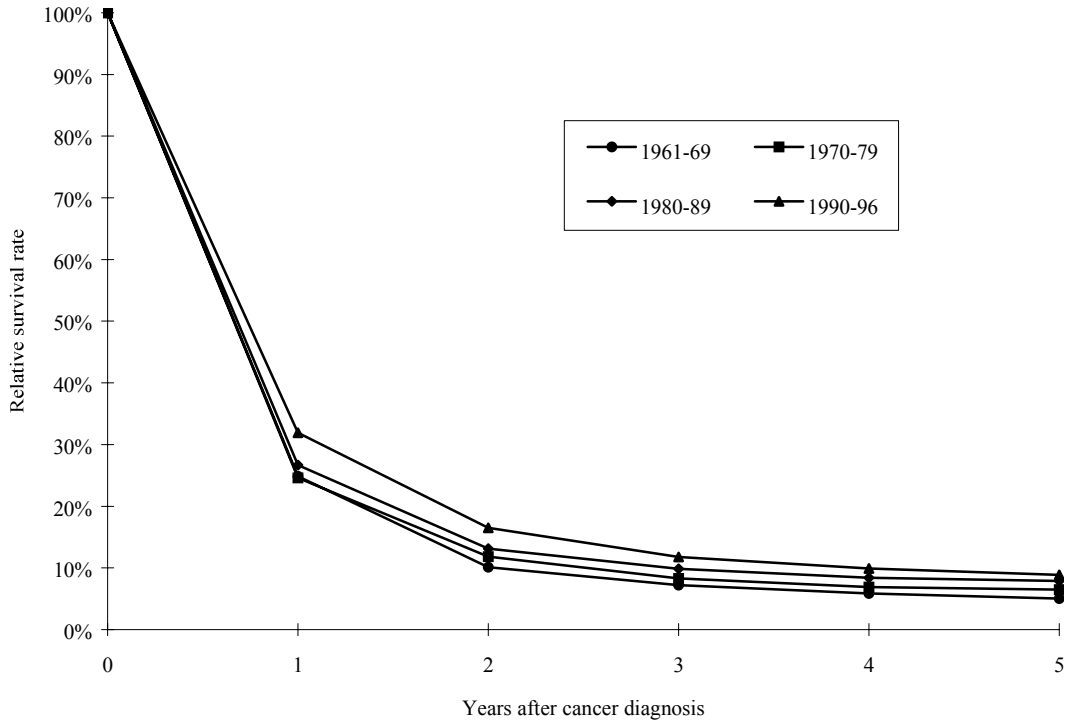


Figure 6. The relative survival of oesophageal SCCA diagnosed in Sweden during 4 calendar periods

5.1.4 Multivariate analysis of gender, age and period of diagnosis

Multivariate analyses of adenocarcinoma and SCCA are presented in Table 6 and Table 7 respectively. For the adenocarcinoma patients there was no significant difference in the 5-year relative survival between sexes. Patients where the diagnoses were made after 80 years of age had a significantly increased mortality as compared to those diagnosed at ages younger than 60. There was a 19% deficit in relative hazard of dying of oesophageal adenocarcinoma in the first 5-year period after diagnosis among those diagnosed during the 1990s as compared to those diagnosed in the 1960s after correcting for effects of sex and age at diagnosis.

Multivariate analysis of the SCCA patients showed that in the first 5-year follow-up period after diagnosis, women had a significantly decreased mortality as compared to men. Patients who were diagnosed at age older than 80 years had a significantly increased mortality as compared to those diagnosed at age younger than 60. After correcting for effects of gender and age at diagnosis, the relative hazard decreased with more recent calendar period.

	Adenocarcinoma
	Relative Hazard, (95% CI)
Period of diagnosis	
- 1961-1969	1.0 Reference
- 1970-1979	1.14 (0.83-1.57)
- 1980-1989	1.07 (0.79-1.45)
- 1990-1996	0.81 (0.59-1.10)
Age at diagnosis	
- < 60	1.0 Reference
- 60-69	1.29 (1.00-1.65)
- 70-79	0.97 (0.73-1.28)
- 80+	1.82 (1.33-2.48)
Gender	
- Male	1.0 Reference
- Female	0.95 (0.74-1.22)

Table 6. Relative hazard of dying of oesophageal adenocarcinoma during the first 5-year period after diagnosis. The multivariate models included all variables listed in the table

	SCCA
	Relative Hazard, (95% CI)
Period of diagnosis	
- 1961-1969	1.0 Reference
- 1970-1979	0.92 (0.72-1.19)
- 1980-1989	0.83 (0.65-1.06)
- 1990-1996	0.79 (0.60-1.03)
Age at diagnosis	
- < 60	1.0 Reference
- 60-69	1.14 (0.92-1.41)
- 70-79	0.88 (0.68-1.13)
- 80+	1.59 (1.20-2.11)
Gender	
- Male	1.0 Reference
- Female	0.68 (0.56-0.82)

Table 7. Relative hazard of dying of oesophageal SCCA during the first 5-year period after diagnosis. The multivariate models included all variables listed in the table

5.2 PAPER II

5.2.1 Patients, tumours and treatment

In total 232 patients underwent resection for oesophageal cancer or cancer of the gastric cardia. Tumours originated almost evenly from the oesophagus and gastric cardia. In 221 patients (95%) tumour stage was available, 22% had a Stage 1 and 16% had a Stage 4 tumour. A majority of tumours had a low grade of differentiation (56%), while high grade of differentiation was uncommon (7%) (Table 8).

In Table 8 patient demographics and treatment characteristics are shown. The median age at surgery was 67 years with a nearly 7:1 male predominance. About 40% of patients had at least one co-morbid disease defined before surgery. Twenty three percent of patients received pre-operative neo-adjuvant therapy. The surgical technique differed depending on the surgeon, the tumour location and preoperative staging of the tumour. Most patients (84%) underwent a laparatomy and right-sided thoracotomy or a three-phase oesophagectomy also including a neck anastomosis, while the rest were operated via a transhiatal approach. The stomach was used as the oesophageal substitute in most cases (72%). Among the 64 gastrectomies performed, the colon was used as substitute in 7 cases. The gastrectomies and transhiatal approach were mainly used for patients with gastric cardia cancer. The hand sutured anastomoses were usually sutured in two layers, while a circular stapler was preferred for the stapled anastomoses. The resection margin was greater than 5 cm in a fourth of the patients, less than 2 cm in a similar proportion, while information was missing in a quarter of the patients. The main differences between adenocarcinoma and SCCA of the oesophagus were that SCCA more often originated proximally, were more often operated with a transthoracic approach and more often treated with neo-adjuvant therapy (Table 9).

Characteristics, in number (%)	**Total (n=232)**	**Adenocarcinoma (n=188)**	**SCCA (n=44)**
	n (%)	**n (%)**	**n (%)**
Tumour location			
Proximal/middle oesophagus	18 (8)	2 (1)	16 (36)
Distal oesophagus	96 (41)	71 (38)	25 (57)
Cardia	118 (51)	115 (61)	3 (7)
Tumour stage			
Stage1 (0,1,1A,1B)	52 (22)	42 (22)	10 (23)
Stage2 (2,2A,2B)	61 (26)	47 (25)	14 (32)
Stage3 (3,3A,3B)	70 (30)	63 (34)	7 (16)
Stage4 (4,4A,4B)	38 (16)	29 (15)	9 (20)
Unknown	11 (5)	7 (4)	4 (9)
Grade of tumour differentiation (according to postoperative histopathology report)			
High	17 (7)	14 (7)	3 (7)
Medium	76 (33)	63 (34)	13 (30)
Low	130 (56)	107 (57)	23 (52)
Unknown	9 (4)	4 (2)	5 (11)

Table 8. Tumour characteristics of 232 cases resected for cancer of the oesophagus or cardia in Sweden, 1 December 1994 – 31 December 1997

Characteristics, in number (%)	Total (n=232) n (%)	Adenocarcinoma (n=188) n (%)	SCCA (n=44) n (%)
Age at surgery, years			
< 59	55 (24)	46 (24)	9 (20)
60-65	46 (20)	36 (19)	10 (23)
66-70	61 (26)	46 (24)	15 (34)
> 70	70 (30)	60 (32)	10 (23)
Gender			
Male	193 (83)	161 (86)	32 (73)
Female	39 (17)	27 (14)	12 (27)
Co morbidity			
None	139 (60)	115 (61)	24 (55)
Prior surgery within the operating field	32 (14)	21 (11)	11 (25)
Respiratory diseases	17 (7)	14 (7)	3 (7)
Cardiovascular diseases	37 (16)	32 (17)	5 (11)
Combined co morbidity	7 (3)	6 (3)	1 (2)
Treatment			
Surgical resection only	178 (77)	154 (82)	24 (55)
Surgical resection and neo-adjuvant therapy	54 (23)	34 (18)	20 (45)
Surgical approach			
Transthoracic	195 (84)	152 (81)	43 (98)
Transhiatal	37 (16)	36 (19)	1 (2)
Conduit			
Stomach	168 (72)	129 (69)	39 (88)
Jejunum	57 (25)	55 (29)	2 (5)
Colon	7 (3)	4 (2)	3 (7)
Anastomosis			
Stapled	124 (53)	104 (55)	24 (55)
Hand sutured	108 (47)	84 (45)	20 (45)
Proximal resection margin			
< 2 cm	57 (25)	45 (24)	12 (27)
2-5 cm	68 (29)	55 (29)	13 (30)
> 5 cm	51 (22)	43 (23)	8 (18)
Unknown	56 (24)	45 (24)	11 (25)

Table 9. Patients' demographics and procedure-related factors of 232 cases resected for cancer of the oesophagus or cardia in Sweden, 1 December 1994 – 31 December 1997

5.2.2 Short-term outcome and prognostic factors

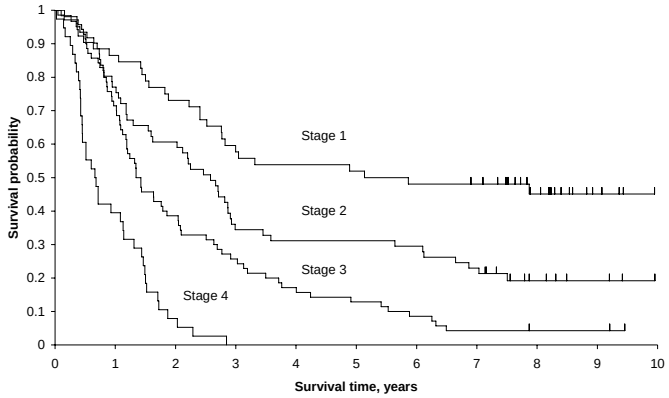
In total 76 patients (33%) suffered severe complications. Seventeen (8%) had an anastomotic leak, 3 (1%) suffered severe postoperative bleeding, 3 (1%) had a paresis of at least one of the recurrent laryngeal nerves, 21 (9%) suffered from severe respiratory failure and 13 (6%) from severe sepsis. When comparing occurrence of specific complications between high- and low-volume centres and high- and low-volume surgeons, significant differences were found regarding operating time, need for post-operative ventilator support, postoperative ICU stay and number of patients with severe sepsis. The median operating time in high-volume hospitals was longer than that in low-volume hospitals ($p < 0.0001$). The median operative blood loss was about 1 liter, independent of the surgery volume. The observed frequency of postoperative complications was higher (36%) in low-volume hospitals than in high-volume hospitals (28%), but this difference was not statistically significant (Table 10). Analyses of specific types of complications suggested an increased occurrence of anastomoses leak in low-volume hospitals compared to high-volume hospitals ($p = 0.06$), while sepsis occurred more often in high-volume hospitals ($p = 0.03$). Patients operated at low-volume hospitals more often required respirator support, and stayed longer in ICU compared to high-volume hospitals, but there was no difference in median of days of hospitalisation (Table 10). About 12 percent of the patients required a secondary operation, with an indication of lower frequencies in high-volume centres. This difference was not statistically significant. There were 4 patients who died within 30 days after operation, all operated at low-volume hospitals. The results regarding surgeon volume were generally similar to those from analyses by hospital volume. There was clear overlap of these two variables (Spearman rank correlation coefficient = 0.82).

	Hospital volume		
	High* **(n=81)**	**Low†** **(n=151)**	**P value‡**
Operating time (minutes), median (range)	525 (150-830)	360 (145-780)	< 0.001
Operative blood loss (ml), median (range)	1100 (250-5200)	1100 (200-6500)	0.78
Post-operative complications, number (%)	23 (28)	54 (36)	0.31
Post-operative ventilator support, N (%)	14 (17)	57 (38)	< 0.001
Days in ICU, median (range)	1 (1-17)	2 (1-72)	< 0.001
Days in hospital, median (range)	19 (9-57)	17.5 (7-102)	0.28
Required secondary surgery, number (%)	8 (10)	19 (13)	0.67
30-day mortality, number (%)	0 (0)	4 (3)	0.30
In-hospital mortality, number (%)	1 (1)	4 (3)	0.66

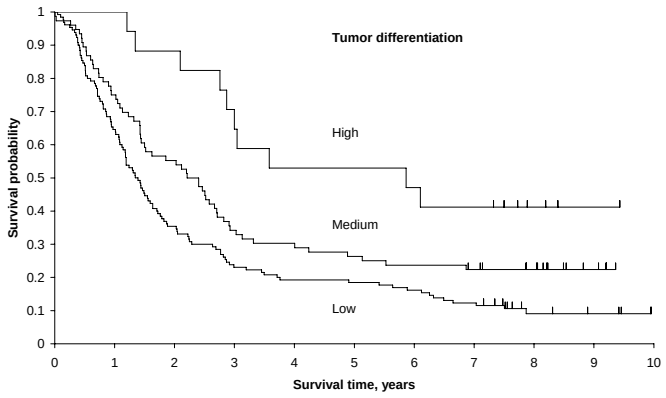
Table 10. Per-operative and short term post-operative outcome of 232 cases resected for cancer of the oesophagus or cardia in Sweden, 1 December 1994 – 31 December 1997, stratified by volume of hospital

5.2.3 Long-term outcome, univariate analysis

The overall 1-, 2-, 3-, 4-, and 5-year survival rates were 71%, 47%, 31%, 27%, and 25%, respectively. Tumour stage, tumour differentiation, surgery volume, and need of postoperative ventilator support were shown in univariate analyses to be statistically significant prognostic factors. The 5-year survival rates for Stage 1, Stage 2, Stage 3, and Stage 4 were 52%, 31%, 13% and 0%, respectively (Figure 7A). Survival based on grade of tumour differentiation is presented in Figure 7B. A higher grade of differentiation was associated with a better survival. Patients who required post-operative ventilator support had a poorer prognosis compared to those who did not (Figure 7C). Patients operated at a high-volume hospital or by a high-volume surgeon had a better prognosis compared to low-volume surgery (Figures 8A and 8B). Age at operation, gender, tumour location, pre-operative co-morbidity, post-operative complications, neo-adjuvant treatment, surgical approach or proximal resection margin, did not statistically significantly influence the long-term prognosis.



A.



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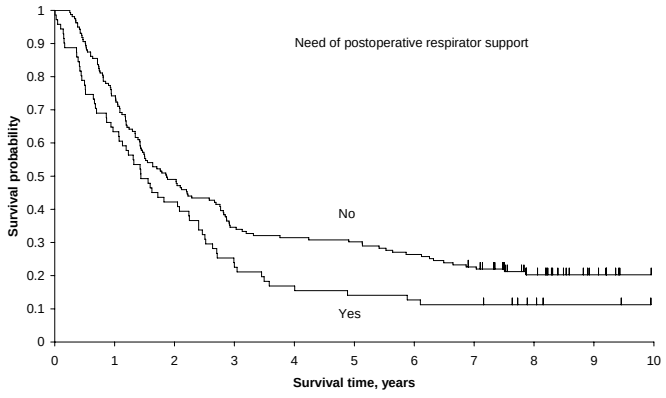
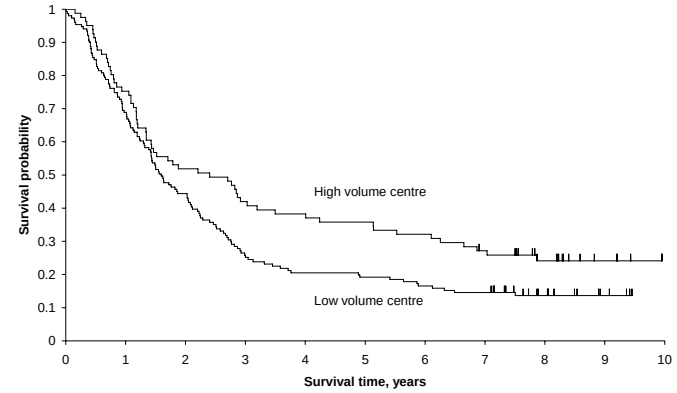
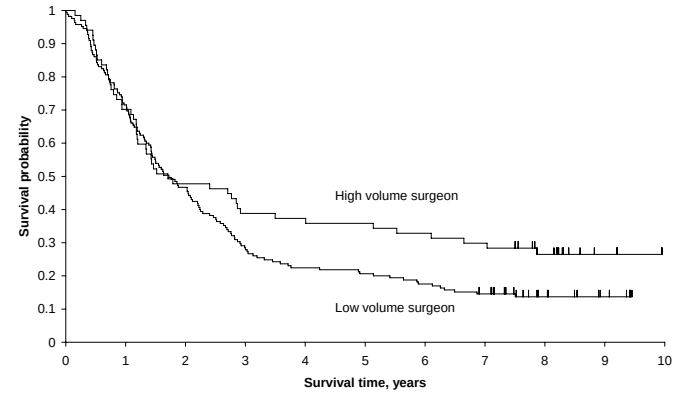


C.

Figure 7. Survival curves (univariate analysis) of patients resected for cancer of the oesophagus and gastric cardia, 1 December 1994- 31 December 1997 in Sweden, by tumour stage for the 221 patients with tumour stage defined (A) p-value by log-rank test <0.0001, by grade of tumour differentiation for the 223 patients with tumor differentiation defined (B) p-value by log-rank test <0.001, and by need forpost-operative ventilator support for 232 patients (C) p-value by log-rank test =0.02



A



B

Figure 8. Survival curves (univariate analysis) of patients resected for cancer of the oesophagus and gastric cardia, 1 December 1994- 31 December 1997 in Sweden, by volume of centre (A), p-value by log-rank test = 0.02, and by volume of surgeon (B) p-value by log rank test = 0.07

5.2.4 Long-term outcome, multivariate analysis

Multivariate analysis is presented in Table 11. Statistically significant prognostic factors identified in the univariate analyses were mutually adjusted for in Cox proportional hazards regression models. Due to the high correlation between volume of hospital and volume of surgeon, these two factors were included in models exclusively. Tumour stage appeared to be the single most important prognostic factor, while low-volume surgery and need for post-operative ventilator support modestly increased the risk of mortality. Grade of tumour differentiation did not have significant influence after multivariate adjustments. Patients operated in low-volume centres had a 30 percent (95% CI, 0-90%, P=0.07) higher risk of mortality, compared to those operated in high-volume centres (Table 10). Separate multivariate analysis by including volume of surgeon in the model showed similar results - patients operated by low-volume surgeons had a 40 percent (95% CI, 0-100%, P = 0.05) higher risk of mortality, compared to those operated by high-volume surgeons.

Variable	HR	95% CI
Tumour stage		
Stage1 (0, 1, 1A and 1B)	Referent	
Stage2 (2, 2A and 2B)	1.8	(1.1-2.9)
Stage3 (3, 3A and 3B)	3.0	(1.9-4.8)
Stage4 (4, 4A and 4B)	7.7	(4.4-13.5)
Treating hospital		
High-volume hospital	Referent	
Low-volume hospital	1.3	(1.0-1.9)
Need for post-operative ventilator support		
No	Referent	
Yes	1.4	(1.0-1.9)

Table 11. Multivariate analyses of effects of prognostic factors on long-term prognosis in 232 cases resected for cancer of the oesophagus or gastric cardia in Sweden, 1 December 1994 - 31 December 1997. Cox proportional hazards regression model was used. The 17 cases with missing information on tumour stage or grade of tumour differentiation were excluded. Tumour differentiation was also included in the analysis

5.3 PAPER III

5.3.1 Patients

The study base consisted of 580 patients, 177 diagnosed with oesophageal adenocarcinoma, 159 with oesophageal SCCA and 244 with gastric cardia adenocarcinoma. A majority of patients were male and older than 65 years. Symptomatic gastro-oesophageal reflux and overweight were over-represented among patients with oesophageal adenocarcinoma, and tobacco smoking and excessive alcohol use were more frequently reported among patients with SCCA, compared to patients with other types of tumours. The rate of oesophagectomy was higher among patients with oesophageal or cardia adenocarcinoma, compared to patients with oesophageal SCCA (Table 12). Other selected characteristics and lifestyle factors of the patients are shown in Tables 12 and 13.

Characteristics	Oesophageal adenocarcinoma (n=177) n (%)	Oesophageal SCCA (n=159) n (%)	Gastric cardia adenocaricnoma (n=244) n (%)
Sex			
Male	153 (86)	115 (72)	208 (85)
Female	24 (14)	44 (28)	36 (15)
Age, years			
<60	32 (18)	36 (23)	71 (29)
60-65	30 (17)	39 (25)	36 (15)
66-70	42 (24)	31 (20)	49 (20)
>70	73 (41)	53 (33)	88 (36)
Educational level, years			
0-6	44 (25)	39 (25)	42 (17)
7-10	91 (51)	73 (46)	119 (49)
>10	42 (24)	47 (30)	83 (34)
Symptomatic gastroesophageal reflux			
Yes	107 (60)	25 (16)	67 (27)
No	70 (40)	134 (84)	177 (73)
BMI (20 years before interview)			
<22	10 (6)	45 (29)	45 (18)
22-24.9	59 (33)	63 (40)	95 (39)
25-29.9	86 (49)	40 (25)	81 (33)
≥30	22 (12)	10 (6)	23 (9)
Esophagectomy			
No	102 (58)	115 (72)	139 (57)
Yes	75 (42)	44 (28)	105 (43)

Table 12. Patient characteristics, of 580 patients diagnosed with cancer of the oesophagus or gastric cardia in Sweden 1 December 1994 to 31 December 1997

Characteristics	Oesophageal adenocarcinoma (n=177) n (%)	Oesophageal SCCA (n=159) n (%)	Gastric cardia adenocaricnoma (n=244) n (%)
Smoking			
Never	54 (31)	20 (13)	39 (16)
Ex-smoker	81 (46)	44 (28)	117 (48)
Current smoker	42 (24)	95 (60)	88 (36)
Alcohol intake (grams / week, 20 years before interview)			
Never	38 (21)	15 (9)	30 (12)
1-15	50 (28)	32 (20)	69 (28)
16-70	50 (28)	37 (23)	75 (31)
>70	39 (22)	75 (47)	70 (29)
Physical activity			
1st low	41 (23)	35 (22)	53 (22)
2nd	53 (30)	59 (37)	71 (29)
3rd	42 (24)	37 (23)	63 (26)
4th high	41 (23)	28 (18)	57 (23)

Table 13. Selected lifestyle factors of 580 patients diagnosed with cancer of the oesophagus or gastric cardia in Sweden 1 December 1994 to 31 December 1997

5.3.2 Long-term outcome

The observed 1-, 3-, and 5-year survival rates by histological subtype are presented in Table 14. The observed overall 5-year survival rate was 12% (95% CI 10-15%). No major differences were found between the histological subtypes. The prognosis was better, for all three types of cancer, among resected patients, and was strongly related to the tumour stage. Figure 9 shows the survival curves for the surgically resected patients, stratified by tumour stage, and for patients not resected. The survival curve of non-resected patients was similar to that of the resected patients with advanced tumour stage (Stage IV).

Time	Total	Oesophageal adenocarcinoma		Oesophageal SCCA		Gastric cardia adenocarcinoma	
		Non-resected	Resected	Non-resected	Resected	Non-resected	Resected
1-year	51 (47-55)	39 (30-49)	73 (62-82)	30 (22-39)	68 (52-80)	38 (30-46)	77 (68-84)
3-year	19 (16-22)	10 (5-16)	37 (27-48)	9 (4-15)	32 (19-46)	9 (5-14)	32 (24-41)
5-year	12 (10-15)	2 (0.3-6)	28 (18-38)	4 (2-9)	30 (17-43)	5 (2-10)	22 (15-30)

Table 14. Observed 1-, 3-, and 5-year survival rates in percent (95% CI) for patients diagnosed with cancer of the oesophagus and gastric cardia, 1 December 1994 to 31 December 1997 in Sweden, estimated by Kaplan-Meier method

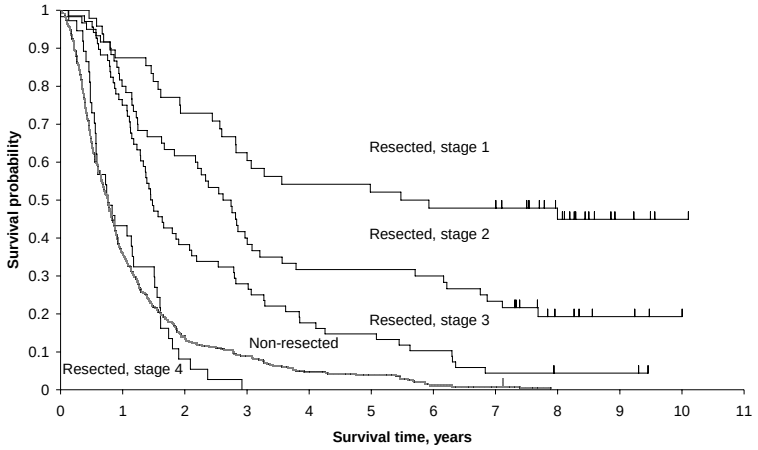


Figure 9. Survival curves of the 224 surgically resected patients, stratified by tumour stage and 356 patients not resected

5.3.3 Prognostic factors, multivariate analysis

5.3.3.1 Oesophageal adenocarcinoma

Among patients with oesophageal adenocarcinoma, obese patients (BMI ≥ 30 kg/m^2) had a 40% decreased risk of death (HR=0.6, 95% CI 0.3-1.0), compared to those with normal weight (BMI 22-24.9 kg/m^2) 20 years before interview. Sex, age, educational level, smoking, reflux symptoms, physical activity and alcohol intake did not statistically significantly affect the risk of mortality.

5.3.3.2 Squamous-cell carcinoma

Among patients with oesophageal SCCA, lean patients had a more favorable prognosis (HR=0.6, 95% CI, 0.4-1.0), compared to those with a normal BMI, while ex-smokers had a poorer prognosis compared to non-smokers (HR=2.1, 95%CI 1.0-4.4). Patients with a low educational level had a worse prognosis (HR=1.7 and 1.9 for those with 7-10 years and <7 years education, respectively), compared to those with a higher education level (>10 years). Sex, age, reflux symptoms, physical activity and alcohol intake did not statistically significantly affect the risk for mortality.

5.3.3.3 Gastric cardia adenocarcinoma

No significant influence on long-term survival was found for any of the tested variables in the multivariate analysis.

5.3.3.4 Interaction

Tests of interaction between oesophagectomy and demographic and lifestyle factors revealed a statistically significant interaction between educational level and surgical treatment among patients with oesophageal adenocarcinoma. Stratified analyses revealed that among non-resected patients, a lower educational level was associated with a more favorable prognosis, while among resected patients, the lowest educational level was associated with a more than 2-fold increased risk of death.

5.4 PAPER IV

5.4.1 Patients

One hundred and seventy-four stents were placed in 149 patients. Ninety-one (61%) were male and 58 (39%) female. The median age of patients treated was 74 years, with a range between 44 and 93 years. Only in 2 cases was the tumour location proximal. The rest of the tumours were more or less evenly distributed between the middle oesophagus (55%) and distal oesophagus / gastric cardia (44%). There was an equal distribution of adenocarcinoma and SCCA. Tumour length was documented in 113 cases. The median length of tumours was 6 cm with a range between 2 and 15 cm. BMI was known in 99 cases resulting in an average BMI of 20.3 (range 13.3 - 32.3). The median hospital stay was 7 days (range 1 - 45).

The majority of patients (n=125, 84%) received one stent, while 20 patients received two stents and 3 patients received 3 stents. In 1 patient 4 stents were inserted. Only three uncovered stents were used. Indications for stent placement were dysphagia in 137 patients (92%) and tracheo-bronchial fistulae in 12 (8%). The latter group all received covered stents. No patient was alive at the end of follow-up.

Adjuvant treatment was administered before or after stent placement in 60 patients (40%) (radiotherapy in 35, chemotherapy in 11, and chemo-radiation therapy in 14 patients). Endoscopic dilatation as a separate procedure before stent placement was performed in 54 patients (36%). Endoscopic dilatation during the stent placement procedure was performed in 42 patients (22%). One hundred and twenty-four patients (83%) received a PEG for nutritional support. PEG placement was prior to the stenting procedure in 109 patients, while 15 patients received a PEG during the stent session, but before actual stent placement. There were no PEG-related complications.

5.4.2 Morbidity and Mortality

The primary stent insertion was uneventful in 132 patients. The 30-day morbidity rate was 24%. Four deaths (3%) were related to stent placement (severe aspiration pneumonia, perforation diagnosed day 1 leading to a fatal mediastinitis, myocardial infarction combined with pulmonary embolism and severe tumour bleeding). Early and late complications are shown in Table 13. Early complications (≤7 days) were observed in 42 patients and occurred at a median of 3 days (Table 15). Retrosternal pain and pharyngeal discomfort were frequently observed and not regarded as complications. Pain requiring intravenous administration of opoids on more than 3 occasions within 12 hours of stent placement was regarded as a complication. Late complications (>7 days) were observed in 45 patients (Table 15). Recurrent or increasing dysphagia dominated these complications. Re-stenting, usually due to inadequately positioned previous stents, was performed in 33 patients.

Complication	Early complications, ≤7 days after stent placement, n=42 (24%) n (%)	Late complications, >7 days after stent placement, n=45 (26%) n (%)
Pain	11 (6%)	0
Pneumonia	6 (3%)	0
Perforation	2 (1%)	0
Bleeding	2 (1%)	2 (1%)
Non-optimal placement	7 (4%)	0
Migration	7 (4%)	0
Food impaction	3 (2%)	6 (3%)
Myocardial infarction/ pulmonary embolism	1 (1%)	0
Technical failure	3 (2%)	0
Dysphagia - tumour overgrowth	0	35 (20%)
Fistulation	0	2 (1%)

Table 15. Early and late complications after stent placement in 149 consecutive patients treated at a single centre between March 1993 and May 2005

5.4.3 Improvement in dysphagia

The dysphagia scores before and after the primary stent insertion were available in 139 stent placements. In 35 placements there were insufficient data to calculate the scores. The dysphagia score significantly improved after stent placement ($p < 0.0001$). In a number of cases the dysphagia score had not changed but patients expressed subjective improvement in swallowing ability. We could not find any differences or trends indicating that age, gender, tumour location, tumour length, histology or dilatation prior to stent placement influenced the outcome.

6 DISCUSSION

6.1 FINDINGS AND IMPLICATIONS

6.1.1 Prognosis in general

Results shown in Paper I show a statistically significant improvement in the long-term survival of both histological types of oesophageal cancer in Sweden during the 1990s compared to the three previous decades. Particularly, the long-term relative survival among patients with adenocarcinoma of the oesophagus has improved during 1990-1996. The general observed survival matches the total observed survival shown in the study in Paper III.

The overall prognosis of oesophageal cancer, however, remains very poor. A population-based study on prognosis of oesophageal cancer patients in Sweden during 1961 to 1987 did not show any clear improvement in survival rates. A slightly improved survival among patients with oesophageal adenocarcinoma who were diagnosed in the 1980's compared to previous decades has been observed in the US [137]. Also in a study by our group comparing outcome after surgery over time a statistically significant improvement in prognosis was shown [72].

To be able to control for the fact that the general survival in the Swedish population has increased over time, we calculated the observed survival as well as the relative survival. It is, however, the observed survival that is of interest in clinical practice. The small difference between the relative survival at 3 years and 5 years after the diagnosis indicates that most recurrences of oesophageal cancer occur shortly after the treatment has been completed and it underlines the aggressive nature of these tumours. Patients who have survived 3 years after diagnosis are likely to have been cured.

This study, however, fails to clarify the reason for the improved survival. Previous studies indicate that an earlier discovery of oesophageal cancer is an important predictor of long-term survival. The general introduction of endoscopy as a diagnostic tool during the 1980's could explain earlier detection of tumours. One would, however, expect that the effect would already be visible for adenocarcinomas diagnosed during the 1980's. The introduction of endoscopic surveillance programs for Barrett's oesophagus might explain the more pronounced improvement in survival among patients with adenocarcinoma as compared to patients with squamous-cell carcinoma during the 1990's. Furthermore, improvements in surgical treatment techniques, with reduced operative mortality and more radical resection margins might have contributed to the increased survival seen for both histological types of oesophageal cancer during recent years. Adjuvant treatment might have influenced results. A limited number of hospitals in Sweden used adjuvant therapy during the study period. Another hypothesis is that an improved awareness of early disease symptoms in the general population might also have contributed to our results. Additionally an increased awareness of the disease by treating physicians may lead to earlier detection of tumours with resultant improved survival.

6.1.2 Surgical prognostic factors

In Papers I and II the influence of surgical factors on prognosis were evaluated in an attempt to explain the improved survival. The general 5-year survival of 25% among

our cohort of patients operated during the mid 1990's is in line with the Swedish study by our group that revealed a gradually improved survival after oesophageal cancer surgery performed between 1987 and 2000 [72]. The strongest prognostic factor in the current study was, as expected, tumour stage, which even more emphasises the importance of early detection.

Another independent prognostic factor was the duration of post-operative ventilator support. This may not be surprising, as patients in need of post-operative ICU care, frequently including ventilation support, often are in poor health due to other systemic diseases, influencing long-term survival.

In a recent review summarising 312 papers concerning mortality after oesophagectomy, a general short term postoperative mortality of 6.7% was reported [81]. In our study the 30-day mortality was only 2%, but this figure could be an underestimation due to selection bias.

During recent years, highly specialised surgery has increasingly been centralised to high-volume centres, since it has been proposed that the early post-operative outcome is better in such centres and among high-volume surgeons [69, 83, 127, 132, 134, 138, 139]. The strong correlation between hospital volume and surgeon volume in this study prohibited valid analyses that could distinguish between the effect of hospital volume and surgeon volume. All 4 early postoperative deaths recorded in our study, occurred at low-volume centres and among less experienced oesophageal cancer surgeons. In contrast, the occurrence of post-operative complications was only slightly higher at low-volume centres or among less experienced surgeons, possibly explained by the referral of more difficult cases with a higher risk of complications to high-volume centres. However, no differences in co-morbidity or tumour stage were detected between the cases resected at low- and high-volume hospitals.

Improvement in long-term survival has also been noted for patients operated in high-volume centres or by high-volume surgeons. However, few such studies have been published and available studies give contradictory results [129, 132, 139, 140]. In Paper II, we provide some evidence of a modestly improved long-term survival when the patients were operated at a high-volume hospital or by an experienced oesophageal cancer surgeon.

The previously reported differences in prognosis between gender [72], tumour histology [115], lymphatic invasion [141], extent of lymphadenectomy [142] and multimodality treatment could not be verified in Paper II, although our sample size is moderate. The relevance of the extent of the resection margins can be discussed. We did not find any significant influence of the length of the proximal resection margin on survival. In conclusion, cancer stage remains the strongest prognostic factor, while a modest positive prognostic trend for patients operated in high-volume centres is shown.

6.1.3 Patient characteristics and lifestyle-related factors

There is limited knowledge on whether risk factors for oesophageal cancer also influence long-term survival of the disease. There is, to our knowledge, only one previous study that has addressed the potential influence of etiologic risk factors on the prognosis of patients with oesophageal cancer [143]. In this study, predictors of longer

survival for oesophageal cancer include overweight in oesophageal adenocarcinoma patients, a high income in both histologic types, and female sex in oesophageal SCCA. Compared to this paper, our study included additional information regarding treatment and for resected patients tumour stage.

6.1.3.1 Sex

The finding in Paper I that female patients, diagnosed with SCCA, had an improved survival, compared to men is in agreement with findings by Trivers et al[143]. Papers II and III, however, failed to show a difference. The number of female patients may be too low to ensure sufficient statistical power. Biologically it is hard to explain why females have an improved survival for oesophageal cancer. Hitherto the difference has not been shown in studies concerning oesophageal adenocarcinoma. It could be a confounding factor in squamous-cell carcinoma patient characteristics with regard to, for example, smoking.

6.1.3.2 Age

In neither Paper II, nor Paper III did age affect outcome. However, the analyses in these studies were made on patients younger than 80 years. The results are similar to a previous Swedish study comparing outcome after oesophagectomy in patients younger and older than 70 years [144]. In Paper I, however, we found a negative effect on long-term survival in the group of patients that were older than 80 years compared to younger patients and the general age-matched population. Complications related to co-existing age-related diseases might explain this phenomenon.

6.1.3.3 Body mass index

Studies on obesity as a predictor of long-term survival have been undertaken in patients with breast cancer and prostate cancer. The results are contradictory in prostate cancer, but in breast cancer patients' obesity seems to be a negative predictor of survival [145-150]. We found similar results concerning overweight as in the study by Trivers et al. [143], contrary to the findings in breast and prostate cancer patients. It is speculated that overweight patients may have an increased risk of developing Barrett's oesophagus or are more prone to undergoing endoscopic examination for reflux symptoms, and thus have a higher chance of early detection of oesophageal adenocarcinoma. Although we adjusted for tumour stage in our analysis, the possibility of residual confounding can not be totally excluded. Moreover, the commonly occurring severe malnutrition among patients diagnosed with oesophageal cancer might reduce their chance of survival after the treatment, compared to overweight patients. However, in SCCA patients, lean patients had a better survival compared to normal weight patients.

6.1.3.4 Smoking

A study on lifestyle factors and prognosis among patients with laryngeal and hypopharyngeal cancers reported that cigarette smoking, and to a limited extent, excessive alcohol consumption, negatively influenced the overall survival, whereas high intakes of vegetables and vitamin C favourably affected the prognosis [151]. A Japanese cohort study also reported a negative effect of combined excessive use of alcohol and smoking on oesophageal cancer prognosis [152]. The finding of smoking as a negative predictor of survival has also been found in other cancer forms, including lung

and breast cancer [153-155]. In our study, previous smoking had a significant negative effect on survival in patients with oesophageal SCCA, while no such effect was evident for adenocarcinoma. A possible explanation for the effect of tobacco smoking is that other smoking-related diseases can contribute to earlier deaths. However, we did not find any significant effects of smoking on the prognosis of oesophageal and cardia adenocarcinoma. Obviously, more detailed studies are needed to understand the underlying mechanism.

6.1.3.5 Alcohol consumption and physical activity

Alcohol consumption and physical activity did not influence survival in any of the studied histological cancer types. However, difficulties in the grading of physical activity and the risk of recall bias may affect the results. When the total group of patients, irrespective of histological subtype, were divided in resected and non-resected patients, resected patients had a clear trend towards better survival, the higher the level of physical activity was. The highest level of physical activity was a significant positive predictor of survival, compared to the lowest level of physical activity. A high level of physical activity probably contributes to a better physique, enabling better tolerance of major surgery and neo-adjuvant therapy. One must emphasise that the data, although statistically significant, may be tainted by bias.

6.1.3.6 Educational level

Income, often used as indicator of socio-economic status, was not assessed in our study. Educational level was used instead. Our results indicate that a low educational level is associated with a poorer prognosis for oesophageal SCCA patients. We believe that this is probably a reflection of the characteristics of the SCCA patient, e.g. residual confounding by tobacco smoking, rather than the quality of the health care. In Sweden the public health care system is tax-funded, prohibiting treatment of different socio-economic groups differenctly. The lack of effects of educational level among the oesophageal and cardia adenocarcinoma patients lends further support to this hypothesis.

6.1.3.7 Summary

In summary, obesity, low socio-economic status as measured by educational level, and tobacco smoking might independently influence the long-term survival in oesophageal cancer patients. The effect seems to be different between patients with adenocarcinoma and SCCA. Further studies are needed to investigate these findings, especially in terms of underlying mechanisms.

6.1.4 Palliative treatment with expandable metal stents

As mentioned before and shown in Papers II and III, the majority of patients diagnosed with oesophageal cancer already have disseminated disease. The goal of treatment of these patients should be optimal management of symptoms as non-invasive and with as few complications as possible, rather than attempts to prolong life, often with methods associated with incapacitating side effects. To evaluate the effect of expandable metal stents on dysphagia, and to determine whether patient characteristics and tumour related factors influence the outcome, the study in Paper IV was undertaken.

The study shows that good palliation of malignant dysphagia can be achieved with oesophageal stenting in the majority of patients. Complications and procedure-related mortality are uncommon. The rate of complications and 24% 30-day mortality rate in our study are comparable to figures reported in the literature [97, 156-159]. The rate of re-intervention in our material (17%) is in line with previously reported results [160]. In a recent study, it was shown that there is no difference in outcome when comparing low-volume centres (<10 procedures during a 4 year period) with high-volume centres (≥10 procedures during a 4 year period) [161].

Findings similar to ours, indicating that age, gender, tumour location, tumour length, histology, and dilatation immediately prior to the stent placement do not influence outcome in terms of complication rate or relief of dysphagia have previously, to our knowledge, only been reported once [162].

In conclusion, expandable metal stents are successful in reducing malignant dysphagia and control of malignant fistulation. Complications are few and necessity for re-intervention infrequent. Demographics and tumour characteristics do not seem to influence outcome. Larger, randomised studies are needed to evaluate the success of different treatment modalities in the group as a whole as well as in demographic and tumour-specific sub-groups.

6.2 METHODOLOGICAL CONSIDERATIONS

Some methodological aspects of the studies in this thesis need more detailed discussion. For the readers' convenience the definitions of some specific systematic and random errors will be presented first, followed by comments on the study design and methodology for each paper.

6.2.1 Definitions

6.2.1.1 Confounding

A confounding factor is defined as a factor that is associated with both the exposure and the outcome, and therefore affects the results, if not adjusted for. For example, if for patients SCCA is the exposure and time of death the outcome, results will be affected by the tumour stage. Stage is a confounder and must be adjusted for. To be able to adjust for potential confounders, regression models are used as in all papers included in this thesis.

6.2.1.2 Selection bias

Selection bias is a systematic error and means that the data (e.g, patients/cases in all papers) are collected in a manner that leads to analyses of a non-representative population instead of the "true" population that was intended to be studied. For example, only the patients in a cohort that participated in interviews are included in a dataset, or a population of patients at a single institution is studied but results are presented as representative of a group larger than the actual study cohort.

6.2.1.3 Information bias

Information bias is another example of a systematic error and means that the data collected on exposures and outcome are incorrect. For example, if physicians are obliged to report all of their own complications there is a risk that not all complications will be reported. Another example of information bias is when a definition of an exposure (e.g, high-volume centre) made by the investigator, does not accurately express what is true. Information bias includes so-called recall bias. Information on exposure that is documented is untrue due to the fact that the patient does not remember correctly. This bias is hard to correct for, especially when dealing with cancer disease since the newly diagnosed patient might be misled by symptoms or present beliefs that will influence answers to questions regarding exposures.

6.2.1.4 Random errors

Type I and Type II errors are examples of random errors. Type I error occurs when a false positive finding reaches the level of significance. In all studies where multiple testing is performed, there is a risk for a Type I error. To avoid so-called "fishing expeditions", where a large number of exposures are tested and all positive findings are reported, with a high probability of false positive findings, hypothesis must be carefully defined before the analyses of the study, and the most plausible findings reported. Type

II errors mean that a non-significant result is false. This is often the case when the sample size is too small.

6.2.1.5 Testing of hypothesis

In summary, extreme caution must be exercised when interpreting positive significant findings in clinical research. Often, the sample size is small and the quality of data regarding possible confounders insufficient. Therefore, conclusions solely based on statistically significant findings must be avoided. Sometimes trends that reflect the hypothesis but, due to small sample size, for example, do not reach significance, are more relevant.

6.2.2 Paper I

Strengths of our study in Paper I include the nationwide and population-based design, the length of the observation, the completeness of follow-up, and the precision due to the large number of cases. With this design, selection bias is avoided and high precision with a reduced risk of Type II error is achieved. Another potential source of selection bias is the level of completeness of the register. The Swedish Cancer Register is assessed to be 98% complete from 1961 and therefore we chose this year as starting point as opposed to 1958 when the register was not national. To avoid confounding when comparing the trends of prognosis, the relative survival was calculated. As mentioned before, the observed survival is the most interesting information in a clinical setting, but when comparing trends of survival over time it is more appropriate to use the relative survival since the changes of survival in the general population over time will act as a confounder if it is not controlled for. By calculating the ratio between observed and expected survival for each decade and age-group strata, this source of error is avoided.

Weaknesses include the lack of data concerning tumour stage which unfortunately prohibited analyses of the stage-specific survival. Furthermore, we did not have data regarding treatment and could therefore not differentiate between patients treated with palliative intent and those treated with curative intent.

6.2.3 Paper II and Paper III

Strengts of Papers II and III include the nationwide and population-based study design with almost complete case ascertainment, limiting the risk of selection bias. Our case ascertainment has been shown to be more complete and cases are more accurately classified than in the Swedish Cancer Register [27]. Moreover, the setting in Sweden with the use of unique personal registration numbers and continued updated population registries, ensured an almost 100% complete follow-up. However, since the eligible cases were limited to individuals of native Swedish descent and ages below 80 years, our results may not apply to the entire Swedish population, including immigrants and octogenarians and beyond.

The exclusion of 42 individuals due to incomplete medical records presents a potential risk of selection and misclassification bias, as does underreporting of resected cases. Data on the date of diagnosis and death of these 42 individuals exist. Missing some

resected cases that died early can account for the low postoperative mortality that we reported. If date of diagnosis and date of death or 60 days, whichever occurred first, were used as entry and exit dates for the 42 patients, another 3 cases can be added to the already known 4 cases that died within 30 days. However, we do not know whether these individuals were resected.

It would have been more appropriate to have linked all 757 cases to the Swedish In-patient Register as a double check on resected cases, but the latency of that register was at least 2 years. However, 97% of all surgical specimens were re-examined by a second pathologist and these reports separately filed. Meticulous review of medical records revealed 32 cases that were initially thought to have undergone oesophagectomy, but only had an explorative laparotomy. Another source of selection bias is the fact that 50% of cases of squamous-cell carcinoma are not included, as the SECC study focused on adenocarcinoma and the SCCA cases were used as controls. Furthermore, patients that were included in the SECC study needed to be able to take part in interviews. To avoid selection bias in Paper II, and to reduce the risk of not including some patients that were too sick due to primary disease or major surgery to participate in interviews, all 757 cases were used as source. However, in Paper III only those who participated in interviews were used as cases. Further disadvantages include the partly retrospective data collection and the limited sample size that prohibited the detection of weak or moderate associations or valid evaluation of rare outcomes, notably 30-day mortality.

As with other studies addressing surgery volume, the choice of cut-off point for the centre and surgeon volume was based on weak grounds. There is no general definition of high volume and those studies reported have chosen cut-off points arbitrarily. From a methodological point of view, the most important consideration regarding choice of cut-off is to make this decision ahead of the initiation of any analyses. Otherwise the fishing for a "better" cut-off might be tempting. In one published study by our group on complications and quality of life after oesophageal cancer surgery, the cut-off point of 5 was used [82]. The cut-off point was chosen according to the definition by Birkmeyer et al, but reduced from 6 to 5 due to the sample size. In another study on long-term survival after oesophageal cancer surgery the cut-off point of 10 was used [140], and since the study in Paper II also studied long-term survival we chose 10 as cut-off point. However, this led to a very small number of surgeons that in our study in Paper II qualified as high-volume surgeons. An almost perfect correlation was seen between high-volume centre and surgeon, implying similarities in the exposure.

Due to the relatively small sample size, we were forced to study oesophageal and gastric cardia adenocarcinoma as single entity in Paper II. In Paper III, however, as all cases, regardless of treatment were used, numbers permitted division into sub-groups. This inconsistency might have affected results.

We chose to categorise cancer stage into 4 stages. This categorisation is not optimal. Stage 1B (cardia) and Stage 2B (oesophagus) indicate more advanced disease compared to 1 and 1A, and 2 and 2A, respectively. This might lead to underestimation of differences in observed survival between stages as a result of our grouping. We furthermore believe that AOG Type 1 should be regarded as a distal oesophageal adenocarcinoma. This subtype was therefore classified according to the UICC system

for oesophageal cancer and not gastric cancer. Thus by having a consistent, although arbitrary, grouping of cancer stage, we were able to adjust for stage in all analyses, reducing the effect of confounding factors. In Paper III, however, information on the tumour stage for non-resected patients was not available. The similar survival curves among non-resected and the resected patients with Stage IV tumour imply that most of the non-operated patients had advanced disease.

In Paper III recall bias for some exposure variables, e.g. alcohol intake and physical activity might exist. Moreover, the survival rates might have been overestimated since those who were not interviewed, and thus not included in the study, might have had more advanced disease. Yet, the observed survival rates of the current study are in line with previously reported results [72, 163].

There is a risk for random errors in both Papers II and III, due to the relatively small sample size. To avoid the risk of random errors influencing conclusions, hypotheses were carefully set in the beginning of the studies. We believe that the studies are more likely to be tainted by Type II than Type I errors.

6.2.4 Paper IV

The retrospective nature of the study and the fact that treatment was at a single institution are weaknesses. Such design is prone to selection and information bias. Prospective collection of information would have been desirable, preferably in a randomised setting. The grade of dysphagia might be a source of information bias as it was not collected in a standard manner but transferred from hospital charts, mainly from documentation by nursing staff.

Strengths of the study are the relatively large number of patients that was included and the completeness of follow-up, reducing the risk of selection bias. To reduce the risk of information bias, all patient records were evaluated by one individual (the author). Only three of the patients included were treated by the author.

The risk of Type I and particularly Type II errors exists. Even in this study the hypothesis was carefully set in the beginning of the study. Results were comparable with previous literature reports. A similar multivariate analysis was, to our knowledge, done only once before. We did not uncover any positive findings but do not believe it to be the result of a Type II error.

7 CONCLUSIONS

- The prognosis of oesophageal cancer has improved in Sweden during the 1990s for both adenocarcinoma and SCCA.
- Tumour stage is the strongest prognostic factor.
- Patients who have undergone oesophagectomy at a high-volume centre have a modestly improved long-term survival compared to patients that are treated in a low-volume centre.
- Postoperative respirator support is a prognostic predictor after oesophagectomy.
- Females, diagnosed with SCCA, have a better survival compared to men
- Patients above 80 years with oesophageal cancer have a lower survival compared to patients in lower age groups and compared to tumour-free controls in the same age group.
- Obese patients diagnosed with adenocarcinoma seem to have a better long-term survival compared to patients with normal weight.
- Patients diagnosed with oesophageal SCCA who have a low educational level have a worse prognosis compared to patients with a high educational level.
- Smoking is a negative predictor of survival in patients diagnosed with oesophageal SCCA but not in patients diagnosed with oesophageal adenocarcinoma or cardia cancer.
- The use of metal stents as palliative treatment for malignant dysphagia is safe and significantly reduces dysphagia.
- Age, gender, tumour location, tumour length, prior dilatation and histological type of cancer do not influence outcome of stent placement with regard to improvement in dysphagia or the rate of complications.

8 FUTURE RESEARCH

Some of the results of the investigations included in this thesis raise questions that have to be addressed in future research.

Our findings in Paper II warrant larger, preferably prospective studies, including data on oncological treatment.

Our findings in Papers I and III, indicating that the overall prognosis is still extremely poor and that stage is the strongest prognostic factor, underline the need to find serological or genetic markers for both early detection and detection of recurrence and disseminated disease. The role of obesity must be studied, especially in the light of contradictory results compared to other cancer forms.

More emphasis on research regarding palliation is still relevant in an age where the majority of patients are diagnosed with advanced disease.

9 SAMMANFATTNING PÅ SVENSKA

9.1 INLEDNING

9.1.1 Epidemiologi

I Sverige är cancer i matstrupen eller övre magmunnen (cardia) ovanliga cancerformer. Årligen diagnostiseras ca 500 nya fall av matstrups- och övre magmunscancer i vårt land. Globalt sett, upptäcks omkring 462 000 nya fall av matstrupscancer årligen, vilket gör matstrupscancer till den 8:e mest vanliga cancerformen världen över. Samtidigt är matstrupscancer den 6:e vanligaste orsaken till död på grund av cancer, globalt sett. Matstrupscancer är huvudsakligen av två skilda typer, adenocarcinom eller skivepitelcancer. Namnen på cancerformerna återspeglar helt i vilken typ av slemhinna cancern har uppstått. Världen över är skivepitelcancer den vanligaste cancerformen, och utgör ungefär 90% av alla nyupptäckta fall. Framför allt är skivepitelcancer vanlig inom det så kallade ”matstrupscancer-bältet” som sträcker sig från norra Iran till de nordliga och centrala delarna av Kina. Här är andelen nyupptäckta fall per 100 000 invånare 40-50 ggr så hög som i exempelvis Sverige. Även andra delar i världen såsom delar av Syd-Amerika, sydöstra delarna av Afrika samt mindre områden i västra Europa (Frankrike och Schweiz) uppvisar fler fall av skivepitelcancer i matstrupen jämfört med övriga delar i världen. Orsaken till den ytterst klara geografiska skillnaden har förstås inneburit extensiv forskning beträffande riskfaktorer till denna cancerform. Numera kända riskfaktorer till skivepitelcancer i matstrupen är bl a intag av nitrosamin-innehållande livsmedel, exponering för nedbrytningsprodukter av opium och intag av mycket heta drycker, vanligtvis olika former av te. I den industrialiserade delen av världen är tobaksrökning, överkonsumtion av alkohol och undernäring de starkaste riskfaktorerna för utvecklande av skivepitelcancer i matstrupen.

Adenocarcinom, som är den andra typen av matstrupscancer och som också är den typ av cancer som vanligtvis uppträder i övre magmunnen har en helt annan geografisk utbredning och följdaktligen också helt andra riskfaktorer. Fram till för drygt två decennier sedan var adenocarcinom i matstrupen ytterst ovanligt. På senare tid har dock denna cancerform ökat kraftigt. I USA är adenocarcinom i matstrupen numera den cancerform som ökar hastigast av alla cancerformer. I både Storbrittannien och USA är adenocarcinom i matstrupen numera vanligare än skivepitelcancer. De starkaste riskfaktorerna för utvecklande av adenocarcinom i matstrupen är så kallad Barretts matstrupe, ett tillstånd där slemhinnan i nedre delen av matstrupen omvandlas till magsäcksslemhinna pga av kontinuerlig exponering för surt maginnehåll, frekventa besvär av sura uppstötningar (reflux), och övervikt. Rökning är till viss del en riskfaktor medan alkoholkonsumtion och ärftlighet inte är förenade med ökad risk för adenocarcinom i matstrupen.

För båda cancerformerna gäller att de är vanligare hos män, ffa adenocarcinom, och blir vanligare med stigande ålder. Medelåldern hos patienter som diagnostiseras med matstrupen är knappt 70 år.

9.1.2 Symtom och diagnostik

9.1.2.1 Symtom

Matstrupen är ett mycket elastiskt och rörformat organ som sträcker sig från bakre delarna av svalget ned till övre maggropen. Att matstrupen just innehar denna elastiska egenskap leder också till att symtom på tumörsjukdom uppträder sent. En tumör som växer kommer successivt göra öppningen i röret trängre och följdaktligen leder detta till sväljningssvårigheter. Sväljningssvårigheter (dysfagi), eller att matbitar fastnar eller ”hakar upp sig” är det absolut vanligaste symtomet på sjukdomen. Mer än 70% av alla patienter med nyupptäckta fall av matstrupscancer har dysfagi. Förloppet är ofta långdraget med långsamt tilltagande sväljningssvårigheter, initialt endast med hårdsmält mat, senare även med passerad mat, och ännu senare, i värsta fall, oförmåga att svälja sin egen saliv. Andra symtom kan vara smärta vid sväljning (odynofagi), ofrivillig viktnedgång, förstås som en följd av sväljningssvårigheterna och smärta i ryggen, bakom bröstbenet, i övre delen av buken mm. Denna typ av smärta är dock ovanlig som symtom och avspeglar, när den existerar, oftast en redan avancerad, spridd cancersjukdom.

9.1.2.2 Diagnostik

Matstrupscancer diagnostiseras genom en kameraundersökning av matstrupen, en sk gastroskopi. Vid denna undersökning kan man inspektera matstrupe, magsäck och tolvfingertarm. Via kamerainstrumentet tas också prover från den misstänkta tumören och skickas för mikroskopisk analys. Visar det sig att det finns en verifierad cancer genomgår patienten sedan en noggrann omfattande utredning där målet är att kartlägga cancern och bestämma om den är botbar eller inte. Man kallar detta för, stadiumindelning eller ”staging” av cancerformen. Utifrån tumörens lokalisation i matstrupen, dess storlek och växtsätt, om det finns lymfkörtlar som misstänks innehålla cancerceller i närheten av tumören eller på längre avstånd i från tumören och om det finns så kallade dottersvulster i tex lever eller lungor bestäms vilket cancerstadium som patienten har. För att kunna göra detta genomgår patienten bl a skitröntgenundersökningar av bröstkorgen och buken, samt ultraljudsundersökning på insidan av matstrupen. I utredningen ingår också att bestämma patientens allmänna hälsotillstånd och om det är möjligt för patienten att genomgå de behandlingsalternativ som finns.

9.1.3 Prognos och behandling

Cancer i matstrupen oavsett subtyp har en mycket dålig prognos. Generellt sett (oavsett behandlingsprincip) överlever ungefär 10% av alla patienter fem år. I den grupp som behandlas med intentionen att bota cancern överlever ca 25% av dessa patienter fem år. Sedan lång tid och än idag är kirurgi med avlägsnande av tumören och närliggande lymfkörtlar det sätt som används för att bota patienten. Detta ingrepp är ett extremt omfattande ingrepp där matstrupen avlägsnas och ersätts med magsäck, tjocktarm eller tunntarm. För att detta skall vara möjligt måste man först operera i buken för att friställa/fridissikera det organ som skall användas som substitut. Därefter öppnas bröstkorgen och matstrupen med tumör avlägsnas och sedan dras det organ som valts som substitut upp i bröstkorgen och skarvas ihop med den lilla rest av matstrupe som lämnats kvar. På detta sätt skapas en ny matstrupe och patienten skall härefter kunna

äta på vanligt sätt igen. Operationen tar allt från 4 till 12 timmar. På grund av denna omfattande kirurgi följer att det är vanligt med allvarliga komplikationer. Minst 30% av patienter som genomgår denna operation drabbas av åtminstone en allvarlig komplikation till ingreppet, och 2-6% dör inom 30 dagar efter ingreppet på grund av bieffekter eller komplikationer. På senare tid har man med hjälp av onkologiska alternativ, cellgifter och strålbehandling, försökt förbättra prognosen. Många gånger används förbehandling med en kombination av cellgifter och strålbehandling för att minska storleken på cancern för att möjliggöra ett fullständigt borttagande av tumören vid operation. Det är fortfarande livligt debatterat om detta behandlingssätt har en vinst på lång sikt för överlevnaden men fler och fler studier talar för detta, åtminstone vid vissa stadium av sjukdomen. Den omfattande behandlingen innebär förstås en lång rehabiliteringstid och generellt är inte patienter som genomgått en matstrupscanceroperation återställda på ett tillfredsställande sätt förrän ett år efter operationen. Med tanke på den urusla prognosen är det därför viktigt att man dels hittar fall tidigt men också att de som opereras är väl utvalda. I Sverige opereras numera ca 30% av alla nyupptäckta fall, medan resten av patienterna redan har en spridd sjukdom och behandlas istället med olika alternativa palliativa metoder.

9.2 SYFTE MED STUDIERNA

Syftet med studierna i denna avhandling har varit att:

- studera hur prognosen av matstrupscancer har förändrats över tid i Sverige.
- om man kan finna faktorer inom det kirurgiska behandlingssättet i Sverige som påverkar både korttidsöverlevnad och långtidsöverlevnad.
- om livsstilsfaktorer och patientkaraktäristika styr överlevnad på något sätt.
- utvärdera en av de metoder som finns för symtomlindring av de patienter som är för sjuka för att genomgå operation.

9.3 STUDIER

9.3.1 Studie I

Syftet med delarbete 1 var att studera hur prognosen förändrats med tiden i Sverige. Vi analyserade alla fall av matstrupscancer i Sverige mellan 1961 och 1996. Genom användning av Canceregistret, Dödsorsaksregistret, Emigrationsregistret samt Folkbokföringsregistret, studerades 1-, 3- och 5-årsöverlevnad för skivepitelcancer och adenocarcinom i matstrupen. I det Svenska Cancer Registret finns alla (98%) fall av cancer som upptäckts i landet sedan 1960 registrerade. Vi kunde jämföra prognostiska skillnader mellan respektive decennium (60-, 70-, 80-, och 90-tal). Både observerad samt relativ överlevnad studerades. Med relativ överlevnad menas att man relaterar den funna observerade överlevnaden till den förväntade överlevnaden för respektive åldersgrupp och cancergrupp. Detta görs eftersom den generella överlevnaden hos befolkningen successivt förbättrats med tiden. Ingen uppgift om typ av behandling fanns i denna studie.

Resultaten visade att prognosen förbättrats för både skivepitelcancer samt adenocarcinom med tiden så att den signifikant var bättre 1991-1996 jämfört med de tre tidigare decennierna. Då specifik behandling samt tumörstadium saknades i studien kunde vi endast spekulera i att orsaken till den förbättrade prognosen kan bero på förbättrat multidisiplinärt omhändertagande och bättre utvecklad behandlingsteknink

samt att man också, genom större tillgänglighet och mer frekvent användande av endoskopisk diagnostik, upptäcker fler fall tidigare, det vill säga i ett gynnsammare tumörstadium ur prognos och behandlingsaspekt.

9.3.2 Studie II och Studie III

Syftet med studie II var att studera hur olika faktorer, relaterade till den kirurgiska behandlingen av matstrupscancer, påverkar komplikationsfrekvensen, överlevnad de närmsta 30 dagarna efter operation samt 5-års överlevnaden. Syftet med studie III var att studera om livsstilsfaktorer och patientkaraktäristika påverkar långtidsöverlevnaden.
Till både studie II och studie III användes ett patientmaterial som var en del av en tidigare studie, SECC-studien (svenska esofagus och cardia cancer studien), där riskfaktorer för adenocarcinom i matstrupen studerades. I denna studie rapporterades alla nyupptäckta fall av adenocarcinom i matstrupe och övre magmun, samt hälften av alla nyupptäcta skivepitelcancerfall i matstrupe, under tiden 1 dec 1994- 31 dec 1997 till institutionen för epidemiologi på Karolinska Institutet. Dessa patienter blev sedan tillfrågade om de kunde delta i djupintervjuer med avseende på alla tänkbara riskfaktorer. Sammanlagt rapporterades 757 nyupptäckta fall till institutionen från hela Sverige. Av dessa intervjuades 618 stycken. Genom att samla in journaler på alla som opererats och i detalj studera dessa erhölls ett material för opererade patienter, sammanlagt 232 stycken. I studie III använde vi oss av alla patienter som hade genomgått intervjuer. Av dessa använde vi 580 stycken då vi saknade uppgifter på 38 stycken huruvida de opererats eller inte.
Fem-årsöverlevnaden efter kirurgisk resektion var 25%. Av de 232 patienterna drabbades 77 stycken (33%) av en eller flera svårare komplikationer. Fyra patienter dog inom 30 dagar efter operationen på grund av de komplikationer de drabbats av. Cancerstadium var den starkaste prognostiska faktorn. De patienter som behandlats på ett sjukhus som, inom denna studie, opererat 10 eller fler patienter (högvolym), hade en bättre långtidsöverlevnad och också färre komplikationer, jämfört med sjukhus som opererat färre än 10 patienter (lågvolym) inom studien. Liknande resultat erhölls när kirurger jämfördes på samma sätt. Patienter som hade en mer fördelaktig mikroskopisk aggressivitetsgrad av tumören (hög differentieringsgrad) hade en bättre långtidsöverlevnad jämfört med låg differentieringsgrad. De patienter som behövde kvarstanna på intensivvårdsavdelning och erhålla respiratorvård hade en sämre långtidsöverlevnad jämfört med patienter som ej var i behov av respiratorvård efter operationen. För att korrekt studera dessa faktorer kontrollerade vi för sk störfaktorer i statistiska regressionsmodeller. Efter detta visade det sig att tumörstadium var en starkt signifikant prognostisk faktor. Högvolymsjukhus, högvolymkirurg och respiratorbehov var också signifikant positiva prognostiska faktorer men precis på gränsen till signifikanta. Tumördifferentieringsgrad var inte en signifikant prognostisk faktor

I studie III var fem-årsöverlevnaden i hela materialet 12%. 39%(224 patienter) av totalt 580 opererades. Resten, 356 patienter, genomgick andra behandlingar förmodligen pga redan spridd sjukdom. Vi studerade hur kön, ålder, refluxsymtom, kroppskonstitution (20 år före intervjun), alkoholkonsumtion, rökning, fysisk aktivitet (20 år före intervjun) och utbildningsnivå påverkade långtidsöverlevnaden. Patienter med adenocarcinom i matstrupen som varit överviktiga 20 år tidigare hade en bättre överlevnad jämfört med normalviktiga, till skillnad från patienter med skivepitelcancer

i matstrupen där de som varit magra 20 år före intervjun hade en bättre överlevnad jämfört med normalviktiga. Rökning hade en negativ effekt på patienter med skivepitelcancer men inte på patienter med adenocarcinom. De patienter med skivepitelcancer som hade en låg utbildningsgrad (<7 år), hade en sämre långtidsöverlevnad jämfört med patienter med övriga utbildningsnivåer.

Tumörstadium är den starkaste prognostiska faktorn. Patienter som behandlas kirurgiskt på högvolymsjukhus, och av högvolymkirurger, enligt vår definition, verkar ha en bättre chans till långtidsöverlevnad och mindre risk för komplikationer.
Kroppskonstitution (BMI), rökning och utbildningsnivå påverkar långtidsöverlevnaden men effekten skiljer sig åt beroende på subtyp av matstrupscancer.

9.3.3 Studie IV

Syftet med studien var att studera faktorer som påverkar komplikationsfrekvens, korttidsöverlevnad och symtlindring av dysfagi när expanderbara metallstent används som palliativ behandlingsmetod av patienter med matstrupscancer.
Alla patienter som erhållit stent på kirurgkliniken, Danderyds Sjukhus mellan mars 1993 och maj 2005 studerades. Sammanlagt 149 patienter inkluderades. Dysfagigrad enligt en specifik dysfagiskala noterades före och efter behandling. Alla journaler granskades med avseende på komplikationer och dödsfall som kunde relateras till behandlingen. Tumörens längd, lokalisation, histologisk subtyp, ålder på patienten, kön och om man var tvungen att ballongvidga tumörområdet studerades med avseende på utfall enligt ovan, med hjälp av regressionsmodell.
Komplikationsfrekvensen var 26%. Fyra dödsfall med relation till behandlingsmetoden inträffade. Dysfagigraden kunde signifikant förbättras. Tumörlängd, lokalisation, histologisk subtyp, ålder, kön och ballongvidgning påverkade inte utfallet av komplikationer eller om dysfagin kunde förbättras eller inte.

Behandling med expanderbara metallstent är en säker behandlingsmetod som i majoriteten av behandlade fall momentant leder till en förbättring av dysfagigraden. Utfallet påverkas inte av tumör- och/eller patientrelaterade faktorer.

9.3.4 Slutsatser

Studie I-IV visar att:

- Trots det faktum att prognosen hos matstrupscancerpatienter fortfarande är dålig, har den förbättrats under 90-talet.
- Cancerstadium är den starkaste prognostiska faktorn.
- Kirurgisk behandling på högvolymsjukhus, behov av respirator efter operation, kön, ålder, kroppskonstitution, utbildningsgrad, och rökning är faktorer som kan påverka långtidsöverlevnaden hos patienter med matstrupscancer.
- De patienter som har en spridd sjukdom och dysfagisymtom kan säkert och, med avseende på symtomlindring av dysfagi, effektivt behandlas med expanderbara stent.

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