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# Esophageal Cancer Surgery – Factors Influencing Survival

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*To the memory of my beloved grandmother, γιαγιά Νόρα.*



# Abstract

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The principal aim of this thesis was to address factors that may affect survival after esophageal cancer surgery. Surgical resection remains the only established potentially curative treatment for patients with resectable esophageal cancer. It is an extensive surgical procedure that often combines surgery of the abdomen, chest, and neck and is associated with a considerable risk of major postoperative complications and in-hospital mortality. Moreover, even after successful esophageal resection, only a minority of the patients are cured.

In this research project, we have conducted nationwide, population-based studies to evaluate the short-term and long-term postoperative outcomes in relation to possible effects of calendar period, neoadjuvant therapy, hospital volume, and surgeon volume. In studies I-III we identified all residents in Sweden diagnosed with primary esophageal cancer and treated with esophageal resection during the period January 1, 1987 through December 31, 2000 by means of data from the Cancer Register and In-patient Register. Data regarding tumor characteristics and preoperative treatment were collected retrospectively through manual reviews of histopathological records. The patients were followed up with respect to death or emigration through population registers. In study IV, details regarding tumor and patient characteristics, and surgical procedures were collected prospectively during the period April 2, 2001 to December 31, 2005, by using the Swedish Esophageal and Cardia Cancer Register, where most surgically treated esophageal cancer patients in Sweden are registered. The patients were followed up in the Total Population Register until April 2, 2006.

According to study I, the long-term and short-term survival after esophageal cancer surgery has improved substantially in Sweden since 1987. The short-term mortality has been significantly reduced and is currently lower than 5%. The 5-year survival improved from 20% during the period 1987-1991 to 31% during the period 1997-2000, an improvement that was not explained by changes in patient or tumor characteristics.

In study II, the overall postoperative survival was found to be similar in patients with and without neoadjuvant therapy (HR 0.99, 95% CI 0.86-1.16). Only patients with a complete histopathological response after neoadjuvant treatment (27% of all patients in the neoadjuvant group) had an improved prognosis (HR 0.71, 95% CI 0.53-0.94).

The impact of hospital volume on long-term survival after esophageal cancer surgery was addressed in study III. After adjustment for several confounders, including tumor stage and comorbidity, no difference in long-term survival was found between patients operated on at high-volume and low-volume hospitals (HR 0.99, 95% CI 0.84-1.18).

In study IV, the short-term prognosis after esophageal cancer surgery seemed to be more favorable in patients operated on by higher-volume surgeons compared to those operated on by low-volume surgeons (30-day mortality OR 0.39, 95% CI 0.09-1.70, 90-day mortality 0.42, 95% CI 0.10-1.80). There was no tendency, however, to further survival improvement with increasing surgical workload among the experienced esophageal cancer surgeons.

In conclusion, the chance of cure after surgery for localized esophageal cancer has increased during recent years. Since neoadjuvant treatment and hospital volume seem to have no or only limited influence, the reasons for the improved prognosis remain to be identified. Patients operated on at high-volume hospitals by experienced esophageal cancer surgeons have a better short-term prognosis.



# LIST OF PAPERS

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The thesis is based on the following papers, which will be referred to by their Roman numerals:

- I. Rouvelas I, Zeng W, Lindblad M, Viklund P, Ye W, Lagergren J.  
**Survival after surgery for oesophageal cancer: a population-based study.**  
*Lancet Oncology* 2005, 6:864-870.
- II. Rouvelas I, Zeng W, Lindblad M, Viklund P, Ye W, Lagergren J.  
**Survival after neoadjuvant therapy compared with surgery alone for resectable esophageal cancer in a population-based study.**  
*World Journal of Surgery* 2006 Sep 4; [Epub ahead of print]
- III. Rouvelas I, Lindblad M, Zeng W, Viklund P, Ye W, Lagergren J.  
**Impact of hospital volume on long-term survival after esophageal cancer surgery.**  
*Archives of Surgery (In press).*
- IV. Rouvelas I, Jia C, Viklund P, Lindblad M, Lagergren J.  
**Surgeon volume and postoperative mortality after oesophagectomy for cancer.**  
*European Journal of Surgical Oncology* [Epub ahead of print]

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# List of Abbreviations

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BMI	Body mass index
CI	Confidence interval
CT	Computerized tomography
EUS	Endoscopic ultrasonography
HR	Hazard ratio
HVH	High-volume hospital
HVS	High-volume surgeon
ICD	International classification of disease
LVH	Low-volume hospital
LVS	Low-volume surgeon
MVS	Medium-volume surgeon
NSAID	Non-steroidal anti-inflammatory drugs
OR	Odds ratio
PET	Positron emission tomography
SECC register	Swedish Esophageal and Cardia Cancer Register
THE	Transhiatal esophagectomy
TNM	Tumor, Nodal, and Metastasis classification
TTE	Transthoracic esophagectomy
UICC	Union Internationale Contre le Cancer



# Introduction

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Cancers arising from the esophagus, including the gastroesophageal junction (gastric cardia), are relatively uncommon in the western world, but worldwide esophageal cancer is the eighth most common form of cancer<sup>1,2</sup> and the sixth leading cause of death from cancer. In Sweden, the incidence of esophageal and cardia cancer is low, with approximately 600 new cases reported per year.<sup>3</sup> Since esophageal and cardia carcinomas share most characteristics and treatment options, these tumors will be considered in combination within the concept esophageal cancer for the remainder of this thesis. Esophageal cancer is an aggressive disease with overall long-term survival rates below 15% in western countries.<sup>4,5</sup> In the absence of medical contraindications to surgery, resection is the mainstay of treatment for patients with localized esophageal cancer.<sup>1,6</sup> Esophagectomy is, however, one of the most demanding and traumatic surgical procedures undertaken in elective general surgery, often involving surgery of the abdomen,

chest, and neck, and the postoperative in-hospital mortality is considerable.<sup>6-11</sup> However, advances in non-invasive imaging, preoperative staging, anesthesia, and postoperative pain control combined, with refinements in the surgical technique and pre- and postoperative care, have contributed to the reduction of operative mortality rates to below 5% in experienced centers.<sup>12-14</sup> Unfortunately, esophageal cancer rarely causes early symptoms, which means that most of the patients have unresectable or metastatic disease at the time of presentation and only a minority of the patients are eligible for curatively intended treatment.<sup>15</sup> Moreover, even after apparently successful esophageal resection, fewer than 40% of the patients are cured.<sup>1,6</sup>

Esophageal cancer surgery is still a major challenge for the surgical team. This thesis, based on four original articles, addresses and aims at shedding light on different factors that may be involved in the outcome after such surgery.



# Background

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## Esophageal cancer

### ***Incidence and geographical distribution***

Esophageal cancer is the eighth most common cancer worldwide and the sixth most common cause of cancer death.<sup>1, 16</sup> In the year 2002, 462 000 new cases were diagnosed, and 386 000 deaths were reported.<sup>16</sup> There are striking variations in the geographical distribution of esophageal cancer. The parts of the world with the highest risk are in central Asia, China, southeastern Africa, and eastern South America, with estimated incidence rates as high as 200 per 100 000.<sup>2, 17</sup> Further characteristic findings are the major differences in incidence between ethnic groups within the same country and within the same ethnic group residing in different countries.<sup>17-20</sup> In Sweden, about 400 new cases of esophageal cancer, and about 200 cases of gastric cardia cancer, are diagnosed every year.<sup>3</sup>

More than 90% of esophageal cancers are either squamous cell carcinomas or adenocarcinomas.<sup>21</sup> On rare occasions, other tumors may develop in the esophagus in addition, e.g., small cell carcinoma, gastrointestinal stroma cell tumor, melanoma, leiomyosarcoma, carcinoid, and lymphoma. In a global perspective, squamous cell carcinoma is the dominating histological subtype.<sup>16</sup> However, during the past two decades and for still uncertain reasons, an epidemiological shift has occurred and adenocarcinoma has surpassed squamous cell carcinoma as the most common histological type of esophageal cancer both in the USA and in several countries in western Europe.<sup>18, 22-25</sup> An increasing incidence of adenocarcinoma of the esophagus is a strik-

ing feature of the industrialized world and this increase is more rapid than that of any other solid tumor in some populations. The same pattern, but in a more moderate grade, has also been observed in Sweden (Fig 1).

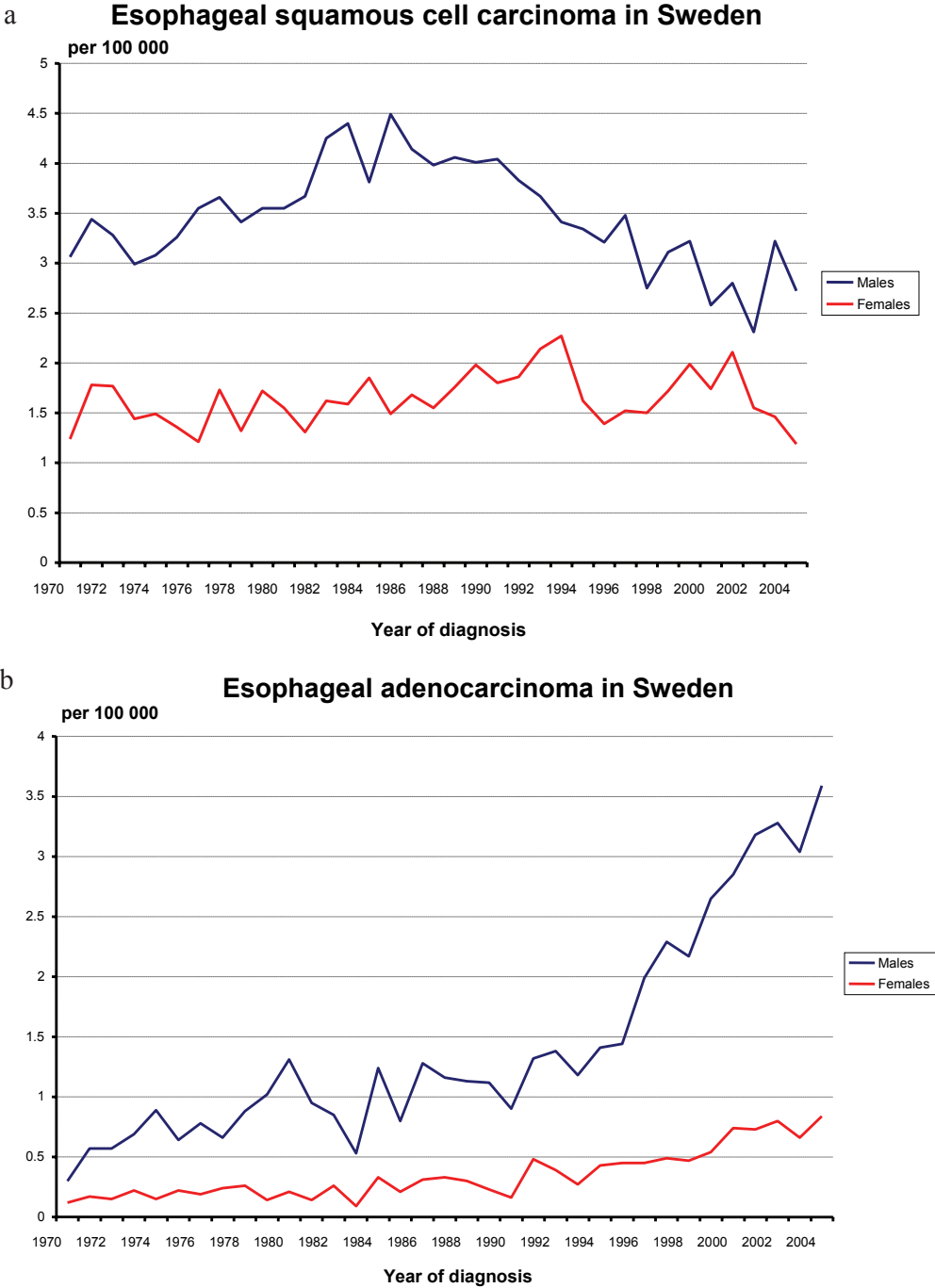
### ***Risk factors***

The etiology of esophageal cancer is multifactorial, and differences in exposure to a range of environmental risk factors are believed to account to a large extent for the striking variations in the incidence rates of this disease observed over time and between populations.<sup>17, 22, 24, 26</sup> In general the incidence of esophageal cancer rises with increasing age, with most patients diagnosed between the ages of 55 and 85,<sup>17</sup> and the disease is characterized by a male predominance.

### ***Esophageal squamous cell carcinoma***

In a global perspective, males of all ages are more affected by esophageal squamous cell carcinoma than are females, with a male/female sex ratio of about 3 to 1.<sup>27</sup>

***Tobacco smoking*** and substantial ***alcohol intake***, especially in combination, greatly increase the risk of squamous cell carcinoma, and may account for more than 90% of all cases of this type of carcinoma in the industrialized world and may explain the male predominance.<sup>28, 29</sup> The risk of developing squamous cell carcinoma is directly correlated with the number of cigarettes smoked per day and the duration of smoking.<sup>28-30</sup> Other established risk factors include ***socioeconomic deprivation***<sup>31</sup> and ***low***



**Figure 1.** Incidence of esophageal squamous cell carcinoma (a) and esophageal adenocarcinoma (b) in Sweden between 1970 and 2004.<sup>3</sup>



*consumption of fruit and vegetables.*<sup>32, 33</sup>

Generally, factors that cause chronic irritation or inflammation of the esophageal mucosa appear to increase the risk of developing squamous cell carcinoma. Some conditions that can give rise to such chronic irritation and consequently increase the risk for the disease include *achalasia*,<sup>34, 35</sup> *frequent consumption of extremely hot beverages*,<sup>36, 37</sup> and *caustic injury of the esophagus*.<sup>38, 39</sup>

Furthermore, although it was found that heredity seemed to play a limited role in a population-based prospective study,<sup>40</sup> the rare condition of *Plummer-Vinson syndrome*<sup>41</sup> and also genetic factors seen in familial clustering such as *Tylosis*,<sup>42, 43</sup> have been reported to be linked with an increased incidence of esophageal squamous cell carcinoma.

### Esophageal adenocarcinoma

As already mentioned, the increasing incidence of adenocarcinoma has been a striking feature in many parts of the industrialized world during the last few decades.<sup>18, 24, 26</sup> There is a strong and unexplained male predominance of this form of esophageal carcinoma of about 6-8:1 in most Western societies.<sup>18, 26</sup> A hypothesis that sex hormones are an explanatory factor for this gender difference has been tested, but the results have been conflicting.<sup>44, 45</sup>

*Barrett's esophagus*, a columnar metaplasia replacing the normal squamous cell epithelium in the distal esophagus, associated with gastroesophageal reflux,<sup>46</sup> is the strongest known risk factor for development of adenocarcinoma of the esophagus.<sup>47</sup> The occurrence of Barrett's esophagus has been found to be associated with an at least 60-90-fold increase in the risk of esophageal adenocarcinoma.<sup>48, 49</sup> *Gastroesophageal reflux*, one of the most prevalent conditions in the Western world,<sup>50</sup> is *per se* a strong and independent risk factor for esophageal adenocarcinoma.<sup>51-53</sup> *Use of medications that re-*

*lax the lower esophageal sphincter* might be linked with a risk of tumor development, but the results of different studies of this issue have been contradictory.<sup>54, 55</sup>

*High body mass index (BMI)* is a strong and independent risk factor for esophageal adenocarcinoma, with risk increases varying between 2- and 8-fold among overweight (BMI 25-30) and 3- and 16-fold among obese persons (BMI>30).<sup>52, 56, 57</sup> *Tobacco smoking* moderately increases the risk of disease development,<sup>28, 31</sup> while no positive association has been identified with *alcohol consumption*.<sup>28, 31</sup>

*Low dietary intake of fruits, vegetables, and antioxidants* and a *low socioeconomic status* seem to be associated with esophageal adenocarcinoma.<sup>58-60</sup> *Non-steroid anti-inflammatory drugs (NSAID)* may decrease the risk of developing this disease.<sup>61</sup> Infection with *Helicobacter pylori* seems to reduce the risk of esophageal adenocarcinoma.<sup>62, 63</sup>

## Diagnosis

### Clinical presentation

As mentioned in the introduction, esophageal cancer rarely causes early symptoms, and most of the patients therefore have advanced disease at the time of symptom presentation and only a minority of the patients are eligible for treatment with a curative intent.<sup>15</sup> Dysphagia is the most common first symptom (80-90%), followed by odynophagia, i.e., pain on swallowing food and liquids (20-50%).<sup>21</sup> Up to 70% of the patients have experienced anorexia and weight loss. Dyspnea, cough, hoarseness, and pain (retrosternal, back, or right upper abdominal) occur less often but may indicate the presence of advanced disease.

<sup>1</sup> Physical examination usually shows nothing remarkable. Lymphadenopathy, particularly in the left supraclavicular fossa (Virchow's node), pleural effusion, and hepatomegaly are indicators of metastatic disease.

### Diagnostic studies, staging

Nowadays, *upper endoscopy* is the primary mode of investigation in patients presenting symptoms of esophageal malignancy. Flexible endoscopy allows a macroscopic and through biopsies, a histological diagnosis. *Barium-swallow examination* is no longer commonly used for investigation of patients with suspected esophageal cancer. Once the diagnosis is confirmed, further investigations are performed with the aim of determining the tumor stage, i.e., the depth of wall invasion of the primary tumor (**T**), the occurrence of any lymph node metastasis (**N**), and the occurrence, if any, of distant metastasis (**M**) (Table 1).<sup>64</sup> Accurate tumor staging is decisive for selection of the optimal mode of treatment for the individual patient.

*Computerized tomography (CT scan)* of the chest, abdomen, and pelvis with intravenous contrast medium is important for evaluating the presence of any distant metastasis. In the absence of distant metastasis further investigation with *endoscopic ultrasonography (EUS)* is beneficial for more accurate evaluation of locoregional spread of the tumor, i.e., the depth of primary tumor invasion, regional lymph node involvement, and possible overgrowth on adjacent organs.<sup>65</sup> Furthermore, EUS enables ultrasonographically guided fine-needle aspiration of suspicious lymph nodes, which has a diagnostic accuracy of more than 90%.<sup>66</sup> *Positron emission tomography (PET)*, often in combination with CT, is being increasingly used in assessment of early distant spread of the tumor that cannot be detected by CT or EUS.<sup>67,68</sup>

*Bronchoscopy* may be of value when tracheal overgrowth is suspected. Moreover, *thoracoscopic* or *laparoscopic* staging is highly accurate for detection of metastases,<sup>69</sup> but these procedures have the disadvantage of being invasive and are therefore less commonly used nowadays. *CT-PET* might obviate such procedures in the future.

### Treatment and prognosis

The overall prognosis in esophageal cancer is poor, with a 5-year survival below 15% in western countries, including Sweden.<sup>4,5,70</sup> The long-term prognosis and treatment options are highly dependent on the tumor stage. The tumor stage also determines whether the therapeutic intention is for cure or palliation.

### Surgery

To date, radical surgical resection remains the only established potentially curative treatment for patients with resectable esophageal cancer.<sup>1,6</sup> More than 50% of patients have unresectable or metastatic disease at the time of presentation. Among patients with resectable tumors, more than 50% have stage III disease.<sup>71,72</sup>

Esophagectomy is an extensive surgical procedure that usually combines surgery of the abdomen and chest, and sometimes also of the neck, and is associated with a considerable risk of major postoperative complications and in-hospital mortality.<sup>9-11</sup> Moreover, even after successful esophageal resection, fewer than 40% of the patients are cured.<sup>6,10</sup> However, advances in non-invasive imaging, preoperative staging, anesthesia, and postoperative pain control, combined with refinements in the surgical technique and pre- and postoperative care, have enabled experienced centers to reduce short-term postoperative mortality below 5%,<sup>12-14</sup> and also to improve long-term survival.<sup>6,10</sup>

After radical surgical resection of the tumor, the 5-year survival rate exceeds 95% for stage 0 disease, and is 50-80% for stage I disease, 30-40% for stage IIA, 10-30% for stage IIB, and 10-15% for stage III disease.<sup>73-75</sup> Patients with metastatic (stage IV) disease, who are treated with palliative measures only, have a median survival of less than one year.<sup>76</sup>

Centralization of esophageal cancer surgery has become general praxis nowadays since it has been established that this reduces the

**Table 1. 2002 American Joint Committee on Cancer (AJCC) Staging System for Esophageal Carcinoma**

**Definition of TNM**

*Primary tumor (T)*

TX Primary tumor cannot be assessed

T0 No evidence of primary tumor

Tis Carcinoma *in situ*

T1 Tumor invades lamina propria or submucosa

T2 Tumor invades muscularis propria

T3 Tumor invades adventitia

T4 Tumor invades nearby structures

*Regional lymph nodes (N)*

NX Regional lymph nodes cannot be assessed

N0 No regional lymph node metastasis

N1 Regional lymph node metastasis

*Distant metastasis (M)*

MX Distant metastasis cannot be assessed

M0 No distant metastasis

M1 Distant metastasis

Tumors of the lower thoracic esophagus:

M1a Metastasis in celiac lymph nodes

M1b Other distant metastasis

Tumors of the midthoracic esophagus:

M1a Not applicable

M1b Nonregional lymph nodes and/or other distant metastasis

Tumors of the upper thoracic esophagus:

M1a Metastasis in cervical nodes

M1b Other distant metastasis

---

**STAGE GROUPING**

Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage IIA	T2	N0	M0
	T3	N0	M0
Stage IIB	T1	N1	M0
	T2	N1	M0
Stage III	T3	N1	M0
	T4	Any N	M0
Stage IV	Any T	Any N	M1
Stage IVA	Any T	Any N	M1a
Stage IVB	Any T	Any N	M1b

---

risk of short-term mortality and morbidity. Previous studies have repeatedly demonstrated an inverse correlation between hospital volume and postoperative mortality, expressed either as in-hospital mortality or as 30-day mortality, after surgery for esophageal cancer.<sup>77-83</sup> This beneficial association has also been confirmed in a meta-analysis.<sup>84</sup> Correspondingly, there is an inverse association between annual surgeon workload and early postoperative outcome, expressed either as postoperative mortality or complications after surgery.<sup>11, 85-88</sup> However, only two studies have addressed the association between hospital volume and long-term prognosis after esophageal cancer surgery, and their results have been conflicting.<sup>89, 90</sup>

### **Transthoracic and transhiatal esophagectomy**

A number of approaches to esophageal resection have been described. Each has its supporters and opponents. The two most commonly used are *transthoracic (TTE)* and *transhiatal esophagectomy (THE)*.

The *transthoracic approach*, described by Ivor Lewis in 1946,<sup>91</sup> is performed through an upper abdominal incision and a right posterolateral thoracotomy with an esophagogastric anastomosis in the upper thorax (Fig 2). Its supporters point out the excellent visualization and possibilities for thorough dissection of perigastric and peri-esophageal nodal tissue and thoracic esophagus, thereby ensuring complete tumor removal and minimizing the risk of tumor spillage. *Transhiatal esophagectomy*, advocated by Orringer,<sup>92</sup> is accomplished through upper abdominal and cervical incisions, i.e., without thoracotomy (Fig 3). The esophagus is bluntly dissected from both above and below and a cervical anastomosis is performed.

Proponents of THE claim that it is oncologically equivalent to TTE, minimizes respiratory complications of thoracotomy, reduces the lethal complications of mediastinitis caused by intrathoracic anastomotic leakage, and shortens the duration of the operation. However, the results of both retrospective and prospective trials regarding differences in number of complica-

tions, operative mortality, and survival rates, have been conflicting.<sup>93-96</sup>

Irrespective of whether TTE or THE is performed, the most commonly used substitute for the removed esophagus is the stomach, constructed as a tube, but in some cases the small bowel or the colon is used.

### **Extent of surgery**

An additional area of controversy has been the extent of the lymph node dissection necessary to provide the best long-term outcome.<sup>97, 98</sup> *Extended lymphadenectomy*, including the cervical region, is widely practiced in Japan. Advantages of this method are that it allows better tumor staging and reduces the risk of locoregional recurrence of the disease.<sup>99-101</sup> However, tests for any potential long-term survival benefit has been made in two randomized trials and the results have been conflicting.<sup>102, 103</sup> Moreover, more extended surgery is associated with an increased risk of morbidity and adverse effects on the long-term quality of life.<sup>103, 104</sup>

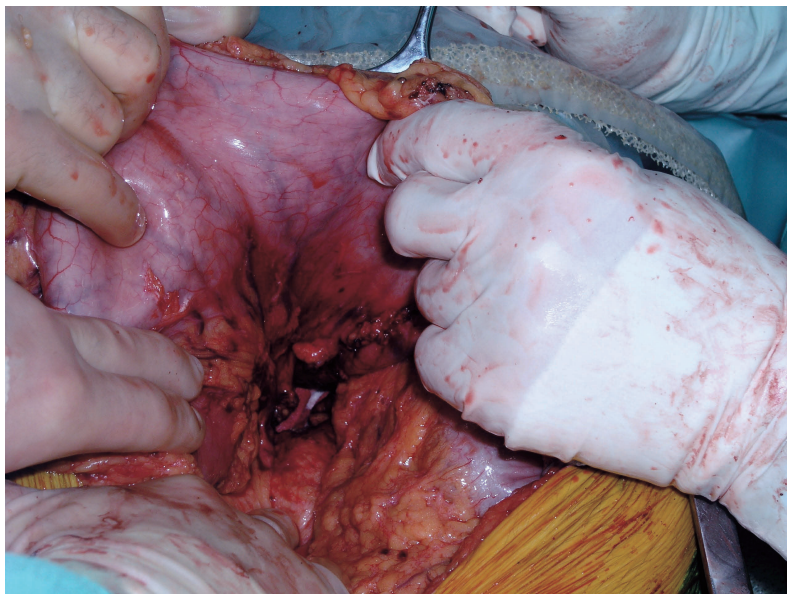
### **Minimally invasive esophagectomy**

During the last decade, several centers have begun to explore the role of *minimally invasive esophagectomy* with the hope of obtaining an equivalent long-term outcome while reducing morbidity and short-term mortality. Currently, techniques have been developed for both a laparoscopic and a combined thoracoscopic/laparoscopic approach.<sup>105</sup> These techniques have been proven safe and effective in a large series of patients,<sup>105-107</sup> but numerous issues remain unsolved regarding their clinical usefulness.

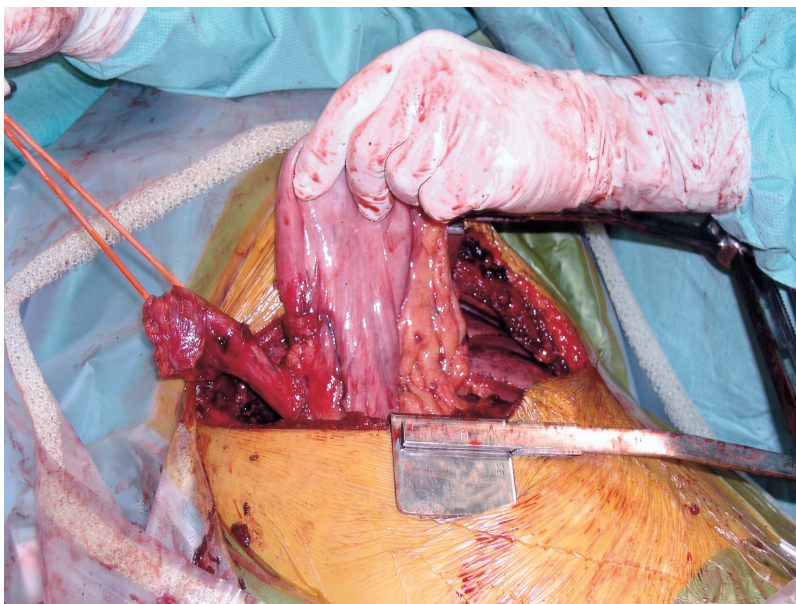
### **Oncological treatment**

Given the poor outcome after surgery, despite the improved results in recent years, different therapeutic strategies have been investigated as a means of enhancing local control and improving survival among patients with localized esophageal cancer. In these trials, oncological modalities have played a central role.

a

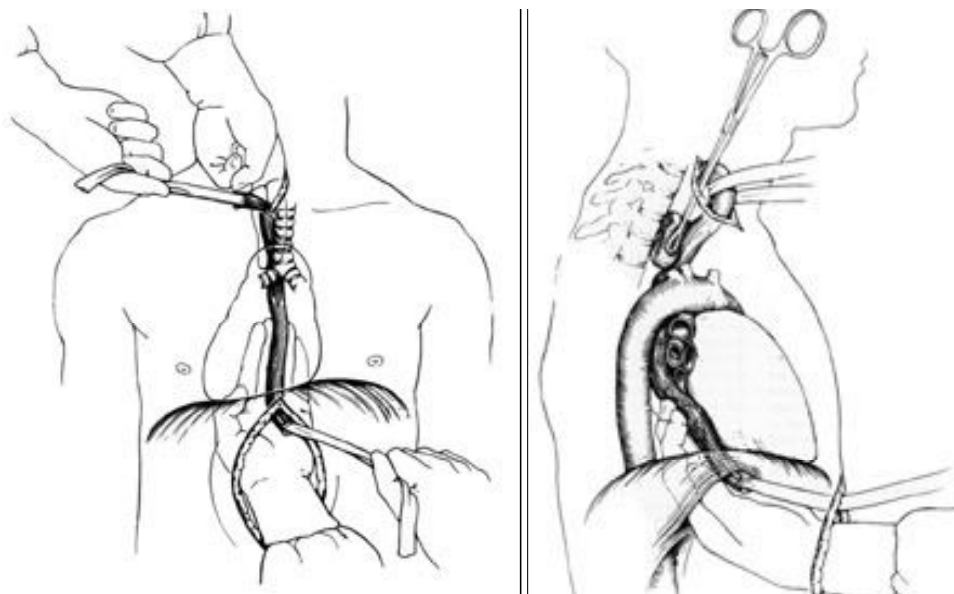


b



**Figure 2.** Ivor-Lewis esophagectomy. (a) Laparotomy where the stomach has been mobilized. (b) Right posterolateral thoracotomy where the lower third of the esophagus and the stomach are demonstrated, and the gastric tube is to be constructed.





**Figure 3.** Transhiatal dissection of the lower esophagus through the diaphragmatic hiatus. The fingers are closely applied to the esophagus during the dissection. Mobilization of the upper thoracic esophagus is achieved similarly through a limited cervical incision.<sup>92</sup> Reprinted with permission from the American Association for Thoracic Surgery.

### Radiotherapy and chemoradiotherapy without surgery

The use of primary **radiotherapy** as an alternative to surgery has been investigated, but with disappointing results.<sup>108, 109</sup> Thus, use of radiation alone is not recommended for curative treatment of esophageal cancer.

**Combinations of radiotherapy and concurrent chemotherapy** have shown results superior to those of radiotherapy alone, and equivalent to those of surgery alone in some studies.<sup>110, 111</sup> However, the risk of persistent or recurrent local disease was high (40%). Nevertheless, large randomized trials comparing chemoradiotherapy and surgery as monotherapy are warranted.

### Neoadjuvant treatment

The use of neoadjuvant treatment, i.e., use of any kind of oncological modality prior to surgery, has been evaluated extensively in recent years.

#### Neoadjuvant radiotherapy

Five randomized trials of **neoadjuvant radiation** compared to surgery alone have been published.<sup>112-116</sup> With the exception of one study,<sup>112</sup> no improvement in survival was demonstrated. These negative findings were also confirmed in a meta-analysis.<sup>117</sup>

#### Neoadjuvant chemotherapy

In seven randomized prospective trials **neoadjuvant chemotherapy** has been compared with surgery alone.<sup>112, 118-123</sup> Only in one of them<sup>123</sup> was a survival advantage found among patients treated with **neoadjuvant chemotherapy**, but there has been some criticism regarding the preoperative staging and surgical technique in this trial. Thus, any possible beneficial effect of preoperative **chemotherapy** remains questionable.

### *Neoadjuvant chemoradiotherapy*

Several randomized studies have been conducted to address the potential benefit of **neoadjuvant chemoradiotherapy** compared to surgery alone in patients with resectable esophageal cancer.<sup>124-129</sup> Only one study showed that preoperative *chemoradiotherapy* offered a statistically significant survival benefit compared with surgery alone.<sup>128</sup> However, this study has been criticized for its suboptimal preoperative staging and an extremely poor outcome in the surgery alone group (6% 3-year survival). Thus, no firm conclusions can be reached regarding *neoadjuvant chemoradiotherapy*. Large multi-institutional trials are required to resolve these conflicting results.

A consistent finding among the trials addressing the potential value of preoperative chemoradiotherapy is that about 25% of the patients show a complete pathological response to the oncological treatment, i.e., with no residual tumor in the resected specimen. This group of patients seems to have a significant survival benefit.<sup>6</sup> However, there are doubts as to whether surgery after such a complete response further improves the chance of cure for this particular group of patients or whether esophagectomy should be conducted only among patients with residual tumor.

### **Postoperative adjuvant therapy**

Only in few randomized studies has surgery alone been compared with surgery combined with postoperative adjuvant radiotherapy, chemotherapy, or chemoradiotherapy, and none of them has documented any difference in survival in the absence of residual disease.<sup>130-132</sup>

### **Palliative treatment**

At least 50% of the patients with esophageal cancer have an unresectable tumor or metastatic disease at the time of presentation.<sup>1</sup> For this large number of patients a wide variety of palliative treatments are available.<sup>96,133</sup> The most important goal of such treatment is to preserve the patient's overall quality of life.<sup>134</sup> Some of the principal aims of palliation are to rapidly relieve dysphagia, maintain the swallowing ability, and avoid complications of invasive treatment options. Generally fit patients with dysphagia and a resectable tumor could possibly benefit from a **palliative surgical resection**.<sup>133</sup> On the other hand, patients with unresectable disease can be palliated by less invasive treatment options, e.g., a **self-expandable metallic stent**, **laser therapy**, **intraluminal or external radiation**, or **chemotherapy**.<sup>1,133</sup>





# Aims of the Studies

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The overall aim of this research was to identify and investigate factors that might have an impact on long-term and short-term survival after surgery for resectable esophageal cancer in large, population-based cohort studies with complete follow-up.

The specific aims were:

- To determine whether the short-term or long-term survival after surgery for esophageal cancer has improved since 1987 in Sweden, using a population-based design with complete follow-up and access to all relevant potentially confounding factors (Study I, Paper I).
- To evaluate the influence of neoadjuvant treatment for resectable esophageal cancer on the long-term postoperative survival in a population-based setting (Study II, Paper II).
- To assess the population-based effect of hospital volume on the long-term survival after curatively intended surgery for esophageal cancer, taking into account potential confounding by tumor or patient characteristics (Study III, Paper III).
- To examine the association between surgeon volume and early postoperative mortality after esophagectomy for cancer and to address the question whether postoperative mortality rates differ between individual experienced surgeons depending on their annual surgical workload (Study IV, Paper IV).



# Materials and Methods

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## Design

The studies described in this thesis were conducted to address factors that may influence the long-term and short-term survival after surgery for resectable esophageal cancer. The limited incidence of this cancer in Sweden makes clinical research at individual hospital units difficult and a risk of selection bias in combination with poor statistical power is a methodological threat. For these reasons, we adopted nationwide, population-based designs in all the studies included in this thesis. In Table 2, an overview of the materials and methods used in the four studies is presented.

### **Cohort, studies I-III**

All Swedish residents who had undergone resection alone for primary esophageal cancer during the period January 1, 1987 through Dec 31, 2000, were included in study I. Eligible for studies II and III were all the patients who during the same time period had been treated with esophagectomy, with or without neoadjuvant therapy.

### **Cohort, study IV**

All Swedish residents diagnosed with primary esophageal or cardia cancer and treated with esophagectomy during the period April 2, 2001 through December 31, 2005, were eligible for inclusion.

### **Follow-up, studies I-IV**

A complete follow-up of all patients was achieved through linkage to the nationwide, complete registers of Death and Emigration by use of the patient's national registration number, a unique identification number assigned to every resident in Sweden. It was necessary to get information

about emigration, since information on death in the population registers is not available for cohort members who emigrate. For further validation of these linkages, the cohort was also linked to the Total Population Register, which rapidly and continuously records the vital status and addresses of all Swedish citizens who are living in Sweden. The patients were followed up from the date of surgery to death, emigration, or the end of the study (October 18, 2004 [studies I-III], April 2, 2006 [study IV]), whichever occurred first.

## Data collection

Studies I-III were based on data from the Swedish Cancer Register and the Swedish Inpatient Register, i.e., two large nationwide, population-based registers, and on review of histopathological records. Study IV was based on data from the Swedish Esophageal and Cardia Cancer (SECC) Register.

### **Studies I-III**

#### **The Swedish Cancer Register**

The Swedish Cancer Register was established in 1958 and since that time both physicians and pathologists in Sweden have been obligated to report all newly detected cancer cases to the register. The register has been estimated to be at least 98% complete.<sup>135</sup> During the past 20 years about 100% of all cases of esophageal cancer notified to the register have been verified histologically.<sup>136, 137</sup> Through all the years the 7<sup>th</sup> version of the International Classification of Diseases (ICD) has been used in the register. Furthermore, during the period 1987-1992, the 9<sup>th</sup> version (ICD-9; codes 150.0-150.9) has

been used, and during the period 1993-2000 the 10<sup>th</sup> version (ICD-10; codes C153-C159). Only patients with primary esophageal cancer of the histological type adenocarcinoma or squamous cell carcinoma were included in the study. Patients with other, rare esophageal tumors were excluded, since such tumors are not comparable with esophageal cancer in terms of treatment or survival.

### The Swedish In-patient Register

The Swedish In-patient Register contains data on all in-hospital care, including codes for diagnoses and surgical procedures, throughout Sweden. Data regarding esophageal cancer surgery, i.e., type and date of surgery, and hospital in which

the procedure took place, were collected from this register. The In-Patient register has had complete nationwide coverage since January 1, 1987, and this date was therefore chosen as the starting date for our study. The 6<sup>th</sup> edition of the Swedish version of the Classification of Surgical Procedures was used for identification of esophageal resections (codes 2820, 2821, 2822, 2829) during the period 1987-1996 and the 7<sup>th</sup> version was used during the period 1997-2000 (codes JCC00, JCC10, JCC11, JCC20, JCC30, JCC96, and JCC97).<sup>138</sup> In the register up to eight discharge diagnoses are documented for each occasion of in-hospital care. Thus, we were also able to collect data regarding diseases that represented comorbidity diagnoses recorded prior to surgery.

**Table 2.** Overview of the four studies included in this thesis.

	<i>Studies I-III</i>	<i>Study IV</i>
<b>Register/Other data sources</b>	Swedish Cancer Register, Swedish In-patient Register, histopathological records	Swedish Esophageal and Cardia Cancer Register
<b>Design</b>	Retrospective, nationwide population-based cohort study	Prospective population-based cohort study
<b>Cohort</b>	<p><u>Study I:</u> All residents in Sweden diagnosed with esophageal cancer and treated only with surgery.</p> <p><u>Study II:</u> All residents in Sweden diagnosed with esophageal cancer and treated with surgery or combination of neoadjuvant treatment and surgery.</p> <p><u>Study III:</u> All residents in Sweden diagnosed with esophageal cancer and treated with surgery.</p>	All Swedish residents diagnosed with esophageal or cardia cancer and treated with surgery.
<b>Data collection, time period</b>	Jan 1, 1987 - Dec 31, 2000	April 2, 2001 – Dec 31, 2005
<b>Follow-up</b>	Jan 1, 1987 - Oct 18, 2004, via register linkages	April 2, 2001 – Apr 2, 2006, via register linkages
<b>Outcomes</b>	Short-term and long-term survival	30- and 90-day mortality
<b>Adjustments</b>	<p><u>Study I:</u> age, sex, comorbidity, tumor stage, tumor location, tumor histology.</p> <p><u>Study II:</u> age, sex, comorbidity, tumor location, tumor histology, hospital volume, and calendar period.</p> <p><u>Study III:</u> age sex, comorbidity, tumor stage, tumor location, tumor histology, and calendar period.</p>	Age, sex, comorbidity, tumor stage, tumor location, tumor histology, preoperative oncological treatment, and curative intention
<b>Statistical analyses</b>	Kaplan-Meier, log-rank test, Cox proportional hazards regression model, hazard ratios.	Unconditional logistic regression, odds ratios, Spearman test, Fisher's exact test

### Histopathological records

All departments of pathology in Sweden were asked to send a copy of the histopathological record to the study secretariat for record review of every patient in the study cohort. We received this report for 94.7% of all patients. From these records, data regarding tumor characteristics, i.e., stage (studies I and III), location, and histology, were collected. The tumor stage was defined according to the TNM classification of the Union Internationale Contre le Cancer (UICC), 6<sup>th</sup> edition.<sup>139</sup> Moreover, through scrutiny of these records combined with information on the referral notes we were able to collect data regarding the occurrence and type of any neoadjuvant treatment, i.e., radiotherapy, chemotherapy, or chemoradiotherapy, given prior to surgery. If such treatment was given, the tumor response to that preoperative therapy was assessed. A complete histopathological response was defined as no residual tumor identifiable in the resected specimen. Information regarding tumor stage prior to neoadjuvant therapy was not available.

These records were reviewed objectively and in detail by one investigator (the author, IR), who was kept blinded to the patient's survival time. In addition, two other investigators checked a random sample (n=100) of this classification and found it to be highly valid (i.e., >90% concordance).

### Study IV

#### The Swedish Esophageal and Cardia Cancer (SECC) Register

The SECC Register is based on a nationwide, all-encompassing Swedish network of hospital departments and clinicians involved in the diagnosis or treatment of patients with esophageal cancer. The network was initially developed for a population-based case-control study concerning risk factors for esophageal cancer.<sup>140</sup> The SECC Register was initiated on April 2, 2001 with the aims of being a resource for clinical research and improving the quality of the surgical

treatment of the esophageal cancer patients in Sweden. Out of 179 hospital departments, representing general surgery, thoracic surgery, otorhinolaryngology, oncology, and pathology, 174 (97%) participated in this register and at each participating department there was a contact physician and often another contact person. Each contact physician was responsible for the local registration in the register. This register makes it possible to rapidly identify and register newly diagnosed cases throughout Sweden. The SECC register is coordinated by a central administrator who is a key person in the registration and data collection (Eja Fridsta). This coordinator received the histopathology report from the pathology department when a new case of esophageal cancer was confirmed. Thereafter, the coordinator reminded the contact physician about the registration of the patient and the collection of data required. Informed consent was obtained from each living patient prior to inclusion in the register. The register also collaborated with all six Swedish regional tumor registries to ensure optimal completeness of the registration.

In the SECC register detailed data are collected regarding patient characteristics, i.e., age, sex, and comorbidity, as well as tumor characteristics, i.e., tumor stage, location, and histology, neoadjuvant/adjuvant oncological treatments, hospital, surgical procedures, radicality of the surgical treatment, and occurrence and type of postoperative complications. The Siewert classification was used for the definition of the site of adenocarcinomas near the gastroesophageal junction.<sup>141</sup> The tumor stage was classified according to the UICC system.<sup>139</sup> All this information was collected and validated through manual scrutiny of each individual case record as part of the register routine. The high national coverage, the detailed and prospective data collection, and the objective manual review of each case record, including evaluation of internal validity, ensure good quality and validity of the register.

## Statistical analyses

### *Studies I-III*

Survival rates were estimated by the Kaplan-Meier method and for comparison the log-rank test was used. Short-term survival was defined as survival up to 30 days after surgery, and long-term survival was defined as survival up to 1, 3, and 5 years after surgery. The 30-day definition of short-term survival was preferred to in-hospital mortality, since it was considered less susceptible to different discharge policies and inequalities regarding the availability of suitable intermediate care facilities in our population-based design. Differences in survival between different patient groups were also determined by using different Cox proportional hazards regression models with various adjustments. Thus, hazard ratios (HRs) with 95% confidence intervals (CI) were estimated. The possible confounders for which our different models were adjusted, were categorized as follows: age (<55 years, 55-65 years, 66-75 years, and >75 years), concurrent diseases (none, one, two or more, and missing data), tumor stage (0-I, IIA-IIB, III, IVA-IVB, and undefined), tumor location (upper, middle, and lower esophagus, and not defined), histological type (squamous cell carcinoma, adenocarcinoma, and uncertain distinction between these two types), and time of surgery (1987-1991, 1992-1996, and 1997-2000).

*In study I*, observed survival rates in relation to tumor stage were analyzed by age, sex, comorbidity, tumor location, histological type, and time of surgery. Two models were adopted to evaluate differences in survival after surgery between the calendar periods: (1) a “basic model” with adjustments for age, sex, and tumor stage, and (2) a “fully adjusted model” including additional adjustments for comorbidity, tumor location, and tumor histology. The earliest period of surgery was used as a reference category in the regression analyses.

*In study II*, observed survival rates were analyzed separately for patients who were treated with surgery alone and for those treated with a combination of neoadjuvant therapy and surgery. In addition, we estimated short-term and long-term survival stratified into two groups according to the response to neoadjuvant treatment: (1) patients with a complete histopathological response and (2) patients without a complete histopathological response. We also stratified the type of neoadjuvant treatment into two groups: (1) radiotherapy and (2) chemoradiotherapy. The group that received preoperative chemotherapy only was too small to evaluate separately. We used two models for comparisons in these analyses: a “basic model” with adjustment for age and sex, and a “multivariable model” with additional adjustments for comorbidity, tumor location, tumor histology, hospital volume ( $\leq 5$ , 6-10, and  $>10$  operations annually), and calendar period. The group of patients treated with surgery alone was used as a reference category.

*In study III*, the hospitals performing surgery for esophageal cancer were divided into two predefined categories based on annual number of esophagectomies conducted there. Low-volume hospitals (LVH) were defined as hospitals that performed fewer than 10 esophageal resections annually during the 14-year study period 1987-2000, and high-volume hospitals (HVH) were those performing 10 or more resections per year during that period. Short-term and long-term survival rates among patients operated on in hospitals of these two categories were assessed. Moreover, we measured the tumor stage-specific survival rates among the patients treated with esophagectomy without preoperative oncological therapy in the two hospital volume categories. Two models were adopted to estimate differences in survival between patients operated on in HVH and those operated

on in LVH. In the “basic model” included adjustments for age and sex, while the “adjusted model” adjustments were made for age, sex, comorbidity, tumor location, histological type, preoperative oncological treatment (yes or no), and calendar period.

#### **Study IV**

To evaluate effects of surgeon volume, prior to the analyses we used the same cut-off level as has been applied in previous research.<sup>88</sup> That is the participating surgeons were divided into three categories on the basis of their average annual workload as recorded in the SECC register: Low-volume surgeons (LVS) performed <2 esophagectomies, medium-volume surgeons (MVS) performed 2-6 esophagectomies, and high-volume surgeons (HVS) performed >6 esophagectomies annually. Unconditional logistic regression was used to examine associations between surgeon volume and 30- and 90-day mortality, expressed in odds ratios (OR) with 95% CI. We used a “basic model” with adjustments for age (<55 years, 55-65 years, 66-75 years, and >75 years), sex, and tumor

stage (0, I, II, III, IV), and a “full multivariable model” in which we adjusted the results for the above covariates and several others, including occurrence of preoperative comorbidity (none, 1-2, and >2), tumor location (upper esophagus, middle esophagus, lower esophagus, and cardia), histological type (squamous cell carcinoma of the esophagus, adenocarcinoma of the esophagus, adenocarcinoma of the cardia), preoperative oncological treatment (no or yes), and surgical intent (curative or palliative). We had also intended to adjust the surgeon volume results for hospital volume, but the Spearman test showed too strong a correlation between surgeon volume and hospital volume to allow valid analysis. Thus, this covariate was excluded from the final model.

Furthermore, to assess the hypothesis that the outcome would improve further with increasing workload among HVS, we compared the individual results of each HVS with those for the surgeon with the highest volume by using Fisher’s exact test. In addition, a nonparametric test for trend was conducted.





# Results

## Patient and tumor characteristics

An overview of the patient characteristics of the patients included in the four studies, and of the tumors is presented in Table 3.

**Table 3.** Overview of patient and tumor characteristics in studies I-IV.

	Study I	Study II	Study III	Study IV
<b>Total number of patients</b>	764	1155	1199	607
<b>Median age, years</b>	66	65	66	66
<b>Sex, no (%)</b>				
Male	558 (73)	831 (72)	862 (72)	489 (81)
Female	206 (27)	324 (28)	337 (28)	118 (19)
<b>Concurrent diseases, no (%)</b>				
None	504 (66)	801 (69)	835 (70)	190 (31)
One/ (One or two, study IV)	199 (26)	183 (16)	189 (16)	359 (59)
Two or more/(three or more, study IV)	61 (8)	140 (12)	144 (12)	58 (10)
Missing data	-	31 (3)	31 (2)	-
<b>Tumor stage, no (%)</b>			*	
Stage 0	-	-	-	25 (4)
Stage I	117 (15)	-	117 (15)	90 (15)
Stage II	292 (38)	-	292 (38)	179 (29)
Stage III	254 (33)	-	254 (33)	245 (41)
Stage IV	87 (11)	-	87 (11)	68 (11)
Missing data	14 (2)	1155 (100)	14 (2)	-
<b>Tumor location, no (%)</b>				
Upper esophagus	26 (3)	59 (5)	59 (5)	17 (3)
Middle esophagus	163 (21)	265 (23)	265 (22)	80 (13)
Lower esophagus	568 (74)	813 (70)	815 (68)	231 (38)
Cardia (Siewert II/Siewert III)	-	-	-	279 (46)
Missing data	-	18 (2)	60 (5)	-
<b>Tumor histology, no (%)</b>				
Squamous cell carcinoma of esophagus	447 (59)	736 (64)	737 (61)	149 (24)
Adenocarcinoma of esophagus	291 (38)	337 (29)	338 (28)	171 (28)
Adenocarcinoma of cardia	-	-	-	278 (46)
Dysplasia	-	-	-	9 (1)
Not defined	26 (3)	82 (7)	124 (11)	-

\* The tumor stage could be assessed only in patients treated with surgery alone (n=764, study I)

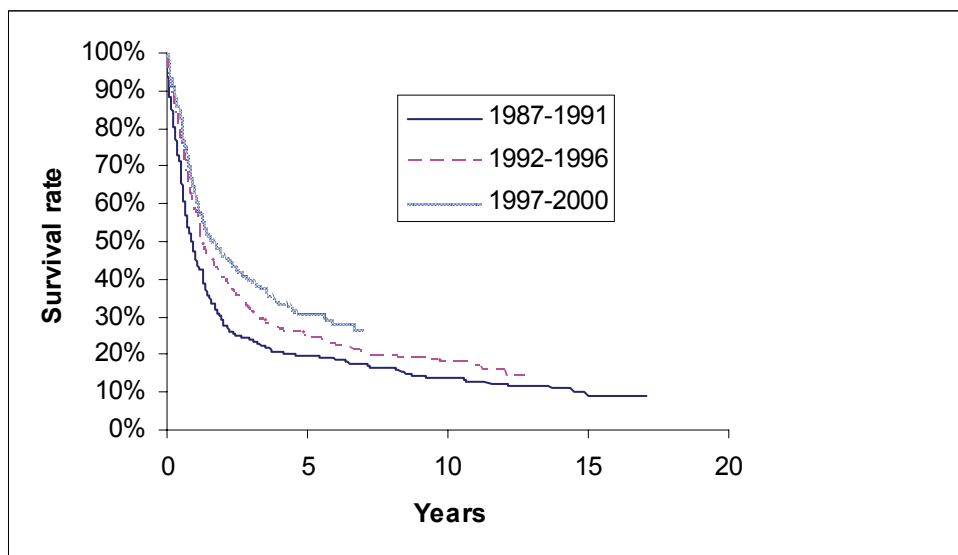
## Study I

From the cancer register, we identified 4904 patients who were diagnosed with primary esophageal cancer between 1987 and 2000. Every fourth of these patients, i.e., 1199/4904 (24%) had undergone esophagectomy. After exclusion of 391 (33%) patients who had received neoadjuvant treatment and 44 (4%) patients with missing data, 764 (64%) patients who had undergone esophageal resection alone remained for final analysis. As shown in Table 3, most patients had stage II or stage III tumors. The lower third of the esophagus was the most common tumor location, and squamous cell carcinoma was the most common histological type.

In Table 4, selected observed short-term and long-term survival rates are presented by age, comorbidity, tumor stage, and calendar period. Worse short-term survival was associated with increasing age and occurrence of comorbidity, while long-term survival was highly dependent

on tumor stage at diagnosis. Furthermore, the overall survival after surgery improved significantly during the study period (1992-1996,  $p=0.0062$ , and 1997-2000,  $p<0.0001$ , compared to 1987-1991; Table 4 and Fig 4). In the last study calendar period, the observed 30-day mortality decreased to below 5% (4.9%), while the 5-year survival increased from 20% in 1987-1991 to 25% in 1992-1996, and to 31% in 1997-2000. Women had an overall better prognosis than men, whereas the survival did not differ with tumor location or histological type.

Regarding hazard ratios for death in relation to time period of surgery, we found that the risk of death decreased significantly during 1997-2000 compared with 1987-1991 (Table 5). This statistically significant difference was observed both in the “basic” and the “fully adjusted” model and implied a 43% decrease in the risk of mortality in patients operated on in the last calendar period (HR 0.57, 95% CI 0.45-0.71).



**Figure 4.** Observed survival after esophagectomy in patients with esophageal cancer in Sweden during three calendar periods: 1987-1991, 1992-1996, and 1997-2000.

**Table 4.** Observed short-term and long-term survival in 764 patients with esophageal cancer in Sweden treated with surgery alone in 1987-2000 in relation to age, comorbidity, tumor stage, and calendar period.

	Number of patients (%)	Number of patients (Survival rate in %)			
		30 days	1 year	3 years	5 years
<b>Total</b>	764 (100)	708 (93)	427 (56)	245 (32)	194 (25)
<b>Age (years)</b>					
<55	104 (14)	103 (99)	63 (61)	37 (36)	29 (27)
55-65	218 (29)	205 (94)	121 (55)	71 (33)	57 (26)
66-75	302 (40)	276 (91)	170 (56)	96 (32)	76 (25)
>75	140 (18)	124 (89)	67 (52)	41 (29)	32 (23)
<b>Concurrent diseases</b>					
None	504 (66)	475 (94)	298 (59)	179 (35)	145 (29)
One	61 (8)	51 (84)	28 (46)	16 (26)	12 (20)
Two or more	61 (8)	51 (84)	28 (46)	16 (26)	12 (20)
<b>Tumor stage</b>					
Stage 0-I	117 (15)	112 (96)	100 (86)	83 (71)	74 (63)
Stage II	292 (38)	269 (92)	187 (64)	112 (38)	86 (29)
Stage III	254 (33)	238 (94)	107 (42)	36 (14)	22 (8)
Stage IV	87 (11)	79 (91)	29 (33)	13 (15)	11 (13)
Unknown stage	14 (2)	10 (71)	4 (29)	1 (71)	1 (71)
<b>Calendar period</b>					
1987-1991	228 (30)	205 (90)	106 (46)	55 (24)	45 (20)
1992-1996	293 (38)	272 (93)	171 (58)	93 (32)	73 (25)
1997-2000	243 (32)	231 (95)	150 (62)	97 (40)	76 (31)

**Table 5.** Adjusted hazard ratio (HR) of mortality after esophagectomy in relation to calendar period, with 95% confidence intervals (CI) and p values.

	Basic HR (95% CI) *	p value	Adjusted HR (95% CI) †	p value
<b>Calendar period</b>				
1987-1991	1.00 (reference)		1.00 (reference)	
1992-1996	0.83 (0.69-1.01)	0.0637	0.76 (0.62-0.92)	0.0062
1997-2000	0.67 (0.54-0.82)	0.0002	0.57 (0.45-0.71)	<0.0001

\* The basic model included adjustments for age, sex, and tumor stage

† The full model included adjustments for age, sex, comorbidity, tumor stage, tumor location, and tumor histology

## Study II

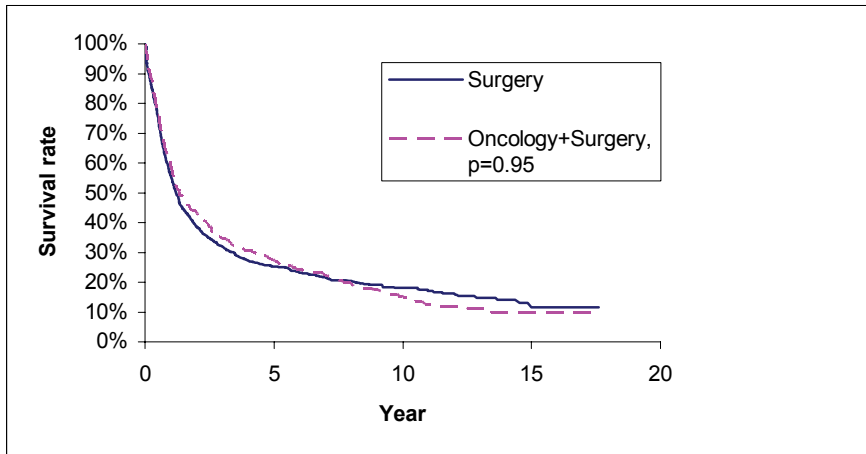
From the Swedish cancer register we identified, 1155 patients with esophageal cancer who had undergone esophageal resection with or without neoadjuvant therapy. There were 764 patients (66%) in the surgery only group and 391 (34%) in the neoadjuvant group. The distribution of treatment was similar during the study period. Of those patients who received preoperative oncological therapy, 28% (n=108/391) displayed a complete histopathological response to the treatment. Such a complete response became more common during the more recent calendar periods.

The observed short-term and long-term survival rates indicated no overall survival advantage for

patients treated with neoadjuvant therapy compared to those who had undergone surgical resection alone (p=0.95; Table 6, Fig 5). This lack of association between preoperative oncological treatment and survival benefit was also confirmed in both our “basic” and “multivariable” models (Table 7). However, patients with a complete histopathological response to neoadjuvant treatment showed an overall improvement in survival compared to the surgery only group (Table 6). The “multivariable” model (Table 7) indicated a statistically significantly 29% lower overall mortality risk among patients with a complete histopathological response compared to those treated with surgery alone (HR 0.71, 95% CI 0.53-0.94).

**Table 6.** Observed survival rates among esophageal cancer patients treated with surgery only and with neoadjuvant therapy combined with surgery. Data are given for groups with and without a complete response to neoadjuvant therapy.

Treatment	Number of patients (Survival rate in %)			
	30 days	1 year	3 years	5 years
Surgery only	708 (93)	426 (56)	244 (32)	193 (25)
Any neoadjuvant treatment and surgery	370 (95)	230 (59)	135 (35)	107 (27)
Not complete histopathological response	266 (94)	150 (53)	78 (28)	56 (20)
Complete histopathological response	103 (96)	79 (73)	56 (52)	49 (46)



**Figure 5.** Survival curves for esophageal cancer patients treated with surgery only and with neoadjuvant therapy combined with surgery.

**Table 7.** HR with 95% CI of mortality among esophageal cancer patients treated with surgery only and surgery combined with neoadjuvant therapies. Data for groups with a complete response to neoadjuvant therapy are given.

Treatment	Overall mortality			
	Basic HR (95% CI) <sup>†</sup>	p value	Multivariable HR (95% CI) <sup>‡</sup>	p value
Surgery only	1.00 (reference)		1.00 (reference)	
Any neoadjuvant treatment and surgery	1.00 (0.88-1.15)	0.95	0.99 (0.86-1.16)	0.96
Complete response	0.68 (0.53-0.86)	0.002*	0.71 (0.53-0.94)	0.017*

\* p value < 0.05, i.e., statistically significant HR, <sup>†</sup> Adjusted for age and sex, <sup>‡</sup> Adjusted for age, sex, co-morbidity, tumor location, tumor histology, hospital volume and calendar period.

### Study III

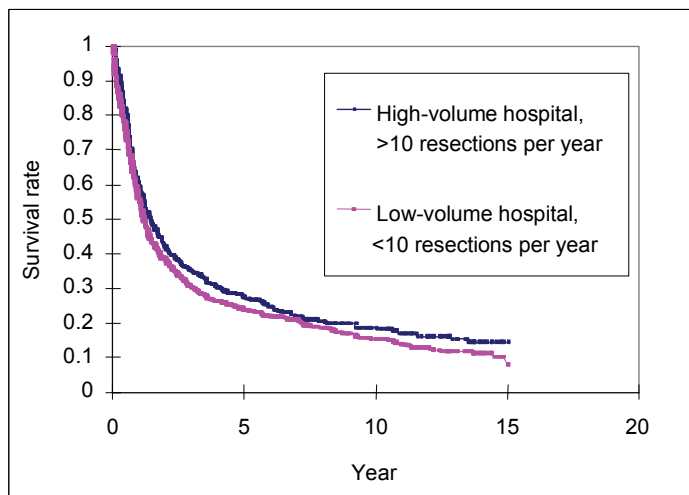
During the study period 1987-2000, we identified 1199 patients diagnosed with primary esophageal cancer and treated with esophagectomy. Among 53 hospitals that contributed with these esophagectomies, only two hospitals were classified as HVH. The majority of the patients ( $n=731$ , 61%) underwent surgery at an LVH. The patient and tumor characteristics were similarly distributed between the two groups.

The observed 30-day mortality was more than twice as high at LVH (9%) as at HVH (4%), but this difference did not reach the level of statistical significance. The overall observed postoperative survival was slightly better among the patients operated on at HVH (Table

8, Figure 6). The basic hazard ratios, adjusted for age and sex only, showed a statistically significant decrease in overall mortality by 22% among patients operated on at HVH (HR 0.88, 95% CI 0.77-0.99), but after additional adjustments for other covariates, but without adjustment for tumor stage, this difference was attenuated and no longer statistically significant (HR 0.90, 95% CI 0.79-1.04). Furthermore, when our calculations were restricted to patients without preoperative oncological therapy, for whom data on tumor stage were therefore available, the adjusted hazard ratio showed no difference between LVH and HVH (HR 0.99, 95% CI 0.84-1.18) (Table 9).

**Table 8.** Short-term and long-term survival among all 1199 patients who underwent esophageal cancer resection, by hospital volume category.

Hospital category	Number of patients (Survival rate in %)			
	30 days	1 year	3 years	5 years
Low-volume hospital ( $n = 731$ )	667 (91)	402 (55)	221 (30)	174 (24)
High-volume hospital ( $n = 468$ )	448 (96)	272 (58)	163 (35)	128 (27)
p value	0.085	0.459	0.150	0.101



**Figure 6.** Observed survival in all 1199 study patients with esophageal cancer treated with esophagectomy, in relation to hospital volume.

**Table 9.** Basic and adjusted HR of mortality after esophagectomy by hospital volume with 95% CI and p values.

Hospital category	All patients (n = 1199)		Patients without preoperative oncological therapy (n = 764)	
	Basic HR (95% CI) *	p value	Basic HR (95% CI) *	p value
	Adjusted HR (95% CI) †		Adjusted HR (95% CI) ‡	
Low-volume hospital	1.00 (reference)		1.00 (reference)	
High-volume hospital	0.88 (0.77-0.99)	0.047	0.91 (0.77-1.07)	0.258
	0.90 (0.79-1.04)	0.157	0.99 (0.84-1.18)	0.987

\* The basic models included adjustments for age and sex. † The adjusted model included adjustments for age, sex, comorbidity, tumor location, tumor histology, preoperative oncological treatment, and calendar period. ‡ The adjusted model included adjustments for age, sex, comorbidity, tumor stage, tumor location, tumor histology, and calendar period.

# Study IV

From the SECC register, we identified 607 patients who were operated on for esophageal cancer. The majority (58.8%) were operated on by HVS. In Table 10, selected surgical details regarding the esophagectomy procedure are presented in relation to surgeon volume category. As shown in the table, LVS performed abdominal procedures with an intra-abdominal anastomosis more frequently than did HVS. Furthermore, HVS performed longer operations but with lower peroperative blood loss compared to LVS.

The overall 30-day mortality was 3%, while the corresponding 90-day mortality rate was 7.9% (Table 11). The basic odds ratios for 30-day mortality indicated a 72% and 67% lower risk of death among patients operated on by MVS and HVS, respectively, compared to those treated by LVS, but these differences were not statistically

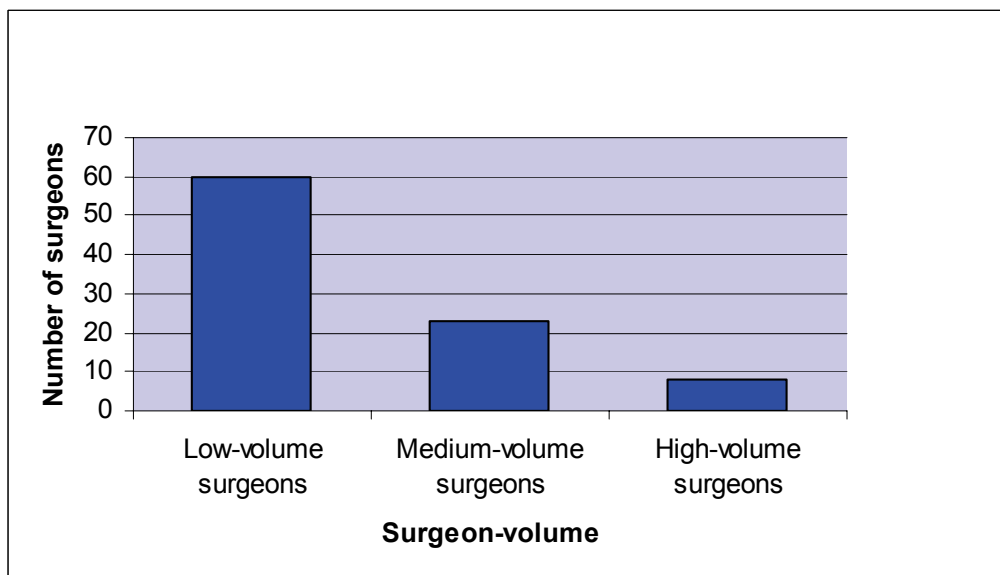
significant. After further adjustments in our “multivariable” model, the differences became more attenuated (Table 11). The odds ratio indicated a 52% statistically non-significant decrease in the risk of death within 90 days after the operation in patients operated on by MVS compared to LVS, but only a corresponding 14% decrease in patients operated on by HVS (Table 11).

Eight surgeons were defined as HVS in our study (Fig 7). We compared the observed 30- and 90-day mortality rates among these individual surgeons and found considerable individual differences, particularly regarding 90-day mortality. Moreover, there was no trend of improved results with increasing annual workload among the individual HVS (p value for trend; 0.84 and 0.80 for 30- and 90-day mortality, respectively).

**Table 10.** Surgical details of 607 esophagectomies for esophageal or cardia cancer performed during the period April 2, 2001 through December 31, 2005, by surgeon volume category.

Surgical details of esophagectomies	Number of patients (%)			
	Total	Low-volume Surgeon	Medium-volume Surgeon	High-volume Surgeon
<b>Approach</b>				
Transthoracic	499 (82.2)	48 (68.6)	153 (81.8)	298 (85.1)
Abdominal	108 (17.8)	22 (31.4)	34 (18.2)	52 (14.9)
<b>Location of anastomosis</b>				
Cervical	56 (9.2)	1 (1.4)	12 (6.4)	43 (12.3)
Intrathoracic	460 (75.8)	50 (71.4)	142 (75.9)	268 (76.6)
Intra-abdominal	91 (27.1)	19 (27.1)	33 (17.6)	39 (11.1)
<b>Operation time</b>				
5 hours	131 (22.1)	20 (31.2)	36 (19.3)	75 (21.8)
5-9 hours	378 (63.6)	43 (67.2)	137 (73.7)	198 (57.6)
> 9 hours	85 (14.3)	1 (1.6)	13 (7.0)	71 (20.6)
<b>Peroperative bleeding</b>				
500 ml	157 (26.6)	12 (19.1)	41 (22.4)	104 (30.1)
500-1000 ml	216 (36.5)	23 (36.5)	69 (37.7)	124 (35.9)
1000 ml	218 (36.9)	28 (44.4)	73 (39.9)	117 (33.9)





**Figure 7.** Number of surgeons (registered in the SEEC Register) performing esophagectomies, by annual surgical workload.

**Table 11.** Risk of mortality within 30 days and 90 days after esophagectomy for esophageal and cardia cancer among 607 patients, expressed as OR with 95% CI, by surgeon volume category.

Mortality	Total No. (%) of patients	Low-volume Surgeon		Medium-volume Surgeon		High-volume Surgeon	
		No.	Basic OR	No.	Basic OR	No.	Basic OR
		(%) of	(95% CI) *	(%) of	(95% CI) *	(%) of	(95% CI) *
		Multivariable OR (95% CI)†	Multivariable OR (95% CI)†	Multivariable OR (95% CI)†			
All patients (n=607)							
30 days	18 (3.0)	5 (7.1)	1.00 (reference)	4 (2.1)	0.28 (0.07-1.13) 0.39 (0.09-1.70)	9 (2.6)	0.33 (0.09-1.26) 0.42 (0.10-1.80)
90 days	48 (7.9)	8 (11.4)	1.00 (reference)	9 (4.8)	0.41 (0.15-1.11) 0.48 (0.16-1.38)	31 (8..9)	0.77 (0.28-2.15) 0.86 (0.31-2.38)

\* The basic model included adjustments for age, sex, and tumor stage, † The multivariable model included adjustments for age, sex, co-morbidity, tumor stage, tumor location, tumor histology, preoperative oncological treatment, and curative intention.



# Discussion

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## Methodological considerations

### *Study design*

Epidemiology is defined as a study of the distribution and determinants of disease in human populations.<sup>142</sup> There are two types of epidemiological studies, experimental and observational. In theory, the best empirical evidence regarding disease causation should come from randomized trials in humans.<sup>143</sup> However, this can sometimes be unethical if the exposure is harmful, or it can be impractical or impossible for the reason that the incidence of most diseases is low and their latencies long. A decreased risk of confounding and bias in experimental studies distinguish them from observational type. Thus, an important limitation of the present investigation is the general use of observational study designs. To establish new treatment strategies, large randomized trials would be the preferable method.

The problem with randomized trials is the inability to address several specific hypotheses simultaneously. Two-armed randomized studies can mainly focus on one single surgical factor. The limited scientific literature available consists mainly of clearly under-powered case series from single hospital departments. This fact makes it impossible, or at least very difficult, to identify a single surgical factor that can attract a sufficiently large number of surgical units in the joint effort that is needed for a focused, well-designed clinical trial. The observational design, on the other hand, makes it possible to analyze various surgical variables at the same time. An important objective of this research was to identify factors that seem to contribute to

an improved surgical outcome with results that are convincing enough to lay the foundation for clinical trials. Moreover, Sweden can offer virtually unique opportunities to conduct observational research in a population-based nationwide setting with a limited risk that bias or chance will affect the results. In addition, the large differences in the surgical treatment between hospital departments in Sweden further facilitate observational research (and complicate randomized studies).

One of the main types of epidemiological analytical studies is the *cohort study*. This is defined as a group of designated individuals who are followed up or traced over time regarding the occurrence of a disease.<sup>142</sup> It can be either *prospective* or *retrospective*. A prospective cohort study is one in which the exposure information is recorded at the beginning of the follow-up and where the period of time at risk for disease occurs during the conduct of the study. In contrast, in a retrospective cohort study the cohorts are identified from recorded information and the time during which they were at risk for disease occurred before the study began. As a retrospective cohort study has to rely on existing records, important information may be missing or may be unavailable. Nevertheless, when a retrospective cohort study is feasible, it offers the advantage of providing information that is usually much less costly than that obtained from a prospective one, and it may produce results much sooner or with a longer follow-up, as there is no need to wait for the event to occur.

In any cohort study, the acquisition of outcome data involves tracing or following up all study participants from the point of a defined exposure over a period of time, to determine whether they develop the disease of interest. Failure to obtain such outcome information, i.e., loss to follow-up, is the major source of bias in most cohort studies. Thus, in view of the often large number of participants in cohort studies, follow-up represents the major challenge in terms of validity and consumption of time and money.

In Sweden, the national registration numbers in combination with nationwide and virtually complete registers, i.e., Cancer Register, In-patient Register, Death Register, Emigration Register, and Total Population Register, provide a unique opportunity to conduct large and valid cohort studies, with complete follow-up, at a reasonable speed and cost.

In *studies I-III* we used a retrospective, nationwide population-based cohort design where the data were collected from the Swedish cancer register and In-Patient register, whereby the members of the exposed cohort were defined. Our aims in these three studies were to test the hypothesis that survival after esophageal cancer surgery has improved during the years and to further assess the possibility that preoperative oncological therapy has a beneficial effect on long-term survival after esophagectomy in case of preoperative oncological therapy; also, to examine the relation of this survival to hospital volume. Advantages of this design include complete, nationwide recruitment of patients which has the important effects of counteracting selection bias, allowing good statistical power and ensuring generalizability of the findings, factors that often constitute serious obstacles for single hospital and institutional studies. Furthermore, completeness and length of follow-up are other strengths of our setting that were made possible through linkages to the nationwide and updated registers named above.

In *study IV* we adopted a prospective, nationwide population-based cohort design with collection

of the data from the SECC Register. The same advantages as mentioned above for the study setting of studies I-III are also applicable to this design. Moreover, the prospective data collection offered us the advantage of minimizing the risk of information bias and further reduced the risk of selection bias.<sup>142</sup>

### **Sources of error**

The primary concern in the design of any research study should not be generalizability, but validity. Determining the validity of a study involves consideration of alternative explanations for an observed association before claiming the existence of a true relationship. Two sources of error afflict epidemiological studies and need to be investigated: systematic error and random error. Not until the validity has been assessed can the generalizability of the results be considered.

### **Systematic error**

Systematic error, i.e., bias, is an error that cannot be reduced by increasing the sample size of the study; it can further be classified into selection bias, information bias, and confounding.

### **Selection bias**

Selection bias in a study stems from the procedures used to select subjects and from factors that influence study participation.<sup>142</sup> Such error is a most cumbersome problem in observational clinical research and this is particularly evident in the area of surgical research and even more so regarding the relatively infrequent esophageal cancer surgery. The population-based approach with the high participation rates strongly reduces the risk of selection bias in the current project, however. All studies included in this thesis have had a nationwide, population-based design, which is a clear advantage compared to single hospital and institutional studies. In *studies I-III*, selection should be of no major concern, since active participation of the patients was not a requirement. All patients who had ever undergone esophageal cancer resection in a Swedish hospital during the study period were included without exception. However, in *study*

**II**, one of the main problems was the lack of information regarding tumor stage prior to neoadjuvant treatment, which introduced a risk of imbalance regarding tumor stage between the treatment groups and thus an obvious risk of selection bias, since neoadjuvant therapy is administered mostly for advanced esophageal cancer (stages III and IV). The lack of preoperative tumor staging did not allow any valid subgroup analyses, since we did not know how the tumor stage contributed to selection for treatment.

In **study IV**, the data were collected prospectively, i.e., before the outcome was established, a procedure that further reduces the risk of selection bias. On the other hand, non-participation in the SECC Register was a greater source of bias in that study. During the initial phase of registration in the SECC Register, the registration frequency was less complete. Furthermore, all hospital departments that were involved in diagnosis and treatment of esophageal cancer did not participate or some departments might have chosen to register patients with the best outcome. In addition, some patients died prior to registration and some patients did not wish to participate in the study. Regardless of these potential sources of bias, the relatively small number of esophagectomies can be explained by the low frequency of resections in Sweden (25% of all cases of esophageal cancer according to unpublished data from the SECC Register and in agreement with the findings from paper I). The observed low overall mortality might also indicate selection bias, but on the other hand this idea is not supported by the high frequency of complications among the registered patients, reported from a recent study by our group using the same register.<sup>11</sup> Moreover, the 30-day mortality in the current study was in line with that in other western studies.<sup>6,10</sup>

### Information bias

Information bias can arise when information collected about or from study subjects is erroneous.<sup>142</sup> In **study IV** the prospective

collection of data reduced the risk of information bias, but in **studies I-III** the data were collected retrospectively, entailing risk of such error. Weaknesses of **studies I-III** include the lack of data regarding details of oncological and surgical procedures; that is, we did not have access to given doses or to information on completion of given therapies, but on the other hand analyses of such details were not the aim of our studies and they were not included in the hypothesis. Moreover, there was no access to information on potential treatment given after the esophageal resection. However, postoperative treatment after esophageal cancer was rarely given in Sweden during the study period, and this lack of information should therefore not have affected our findings. Finally, since coverage by the In-Patient register was not complete until 1987, we did not have data for comorbidity that necessitated admission to hospital or outpatient visits before that time.

Regarding **study II** and to some extent **study III**, the lack of data regarding tumor stage was a potential source of differential misclassification of disease, i.e., the misclassification is related to the exposure. In **study III**, the availability of information on tumor stage for a large subset of patients made it possible to evaluate the influence of this important prognostic variable and limited the risk of such misclassification. However, the risk of such error in **study II** is obvious (risk for exaggeration or underestimation of an association) and must be taken into account when interpreting the results.

In all four studies, the exposures and the outcomes were assessed objectively. The medical and histopathological records and the operation notes were reviewed manually, in a structured manner, on the basis of an extensive study protocol. Moreover, uniform staging of tumors according to modern standards was performed. In addition, a random sample of protocols was checked by two other investigators and high accuracy was confirmed, a decisive factor for the internal validity of the study. Our ability to collect all relevant data from

medical records covering most aspects of the surgical procedure, complications, and tumor and patient characteristics would have reduced the risk of information bias from exposure misclassification. Misclassification of surgical variables was minimized by the thorough review not only of operation records, but also in **study IV**, of the operation charts and the records from intensive care units after the operations. Moreover, all histopathological records were re-reviewed. We were able to assess the outcome mortality with high quality. The short-term and long-term survival was objectively and reliably confirmed in two independent Swedish population registers

### Confounding

Confounding is a central issue for every epidemiological study design. It is defined as a mixing of effects.<sup>142</sup> A confounder must be associated with the disease and the exposure and must not be an effect of the exposure, i.e., an intermediate step in the causal pathway from exposure to disease.

In all the studies included in this thesis, we had the possibility through our nationwide registers and review of histopathological records to collect a large amount of important data regarding both patient characteristics (age, sex, comorbidity) and tumor characteristics (stage, location, histology). Furthermore, we had access to data regarding preoperative treatment, surgical details, postoperative complications, the hospital where the operation took place, and the surgeon who performed the procedure. This extensive data collection enabled us to adjust for a large number of potential confounders in multivariable regression models. On the other hand, the lack of a randomized design prohibited adjustment for any unknown confounding factors.

In **study II** and to some extent in **study III** it was not possible to adjust for tumor stage, one of the most important prognostic variables, since this information was not available prior

to neoadjuvant treatment. However, in study III we managed to overcome this limitation by including tumor stage in the regression model for the subset of the patients who had undergone esophagectomy alone without preoperative treatment, for whom information regarding tumor stage was accessible.

### Random error

Random error refers to the variability, or the degree of precision, of any measurement, and is related to the sample size of the study, approaching zero as the sample size increases.

### Type I error

A type I error occurs when an association between exposure and disease appears to be statistically significant when in fact no causal relationship exists (chance). This is a major threat to all studies that include several analyses, i.e., multiple testing. In the studies described in this thesis, no adjustments for multiple comparisons were made. We already decided in the planning stage of the studies, as part of the study design, to avoid or reduce effects of multiple testing. Thus, all hypotheses were formulated before the initiation of the analyses and the study protocols were thoroughly written and followed. Furthermore, we limited the number of study hypotheses to those we considered to be of highest clinical relevance. In addition, the categorization and the models used were predefined.

### Type II error

A type II error occurs when no statistical association is found, but a causal relationship does in fact exist. This kind of error may result from flawed disease or exposure data, or from an inappropriate study design. The most common cause, however, is insufficient statistical power. In **studies I-III** the size of the studies, owing to the nationwide, population-based setting, allowed good statistical power, an issue that has been a serious problem in single-institutional studies. However, in **paper IV**, although the study was nationwide, the limited occurrence

of postoperative deaths and the decreasing frequency of esophagectomies conducted in Sweden lowered the statistical power. It was therefore not possible to establish relative risk estimates with statistical significance.

## Findings and implications

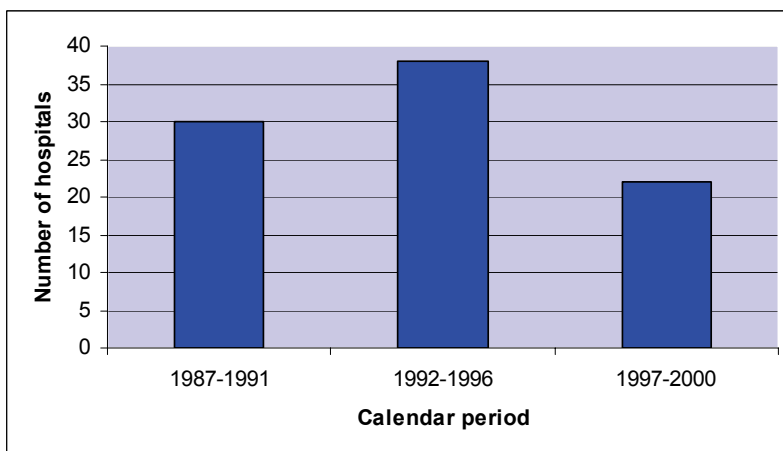
### ***Survival after surgery for esophageal cancer over the years***

The findings in *study I* indicates that both short-term and long-term survival after surgery for esophageal cancer in Sweden has improved since 1987. Our results showed that the short-term mortality has been decreased significantly and is currently lower than 5%. Moreover, the long-term survival after surgery improved substantially over the last few years of the study, an improvement that could not be explained by any changes in patient or tumor characteristics.

The improved overall survival over time could be explained by earlier detection of disease as a consequence of advances in non-invasive imaging and preoperative staging, allowing surgery of less advanced tumors. However, our results remained significant even after adjustment for tumor stage, and we found no evidence of a shift in tumor stage at diagnosis

during the study period. But another explanation of our findings could be misclassification of tumor stage. Over the years surgeons might have become more thorough and extensive regarding lymph node dissection and pathologists might have become more careful in examining the specimens. Such changes in practice could have biased our results and explain the positive trend in our study despite the fact that our statistical models were adjusted for tumor stage. Moreover, better preoperative staging over the years might have led to differences in the selection of cases suitable for surgery or adjuvant treatment, i.e., in later periods patients chosen for adjuvant treatment could have had more advanced disease compared to those chosen for surgery alone. However, the proportion of patients who received adjuvant treatment did not change over the calendar periods in our study. Furthermore, we found no tendency over the years indicating that patients who were more fit and in better general health had a greater chance of undergoing surgery.

Our data confirm previous results from non-population-based studies, adding support to indications of a true effect.<sup>6, 10</sup> Advances in preoperative staging and anesthesia combined with refinements in the surgical technique and postoperative care have probably contributed



**Figure 8.** *Number of hospitals in Sweden performing esophagectomies by calendar period*



to a reduction of operative mortality and consequently to an improvement in short-term survival. On the other hand, improvements in the surgical technique alone might explain the improved long-term outcomes. Such possible surgical factors remain unidentified, but one explanation might be the fact that fewer and more specialized units have performed esophagectomies during the recent years (Figure 8).

### **Neoadjuvant treatment and esophageal cancer surgery**

According to our findings in *study II*, the surgical outcomes with and without neoadjuvant therapy in patients with a resectable esophageal cancer were similar. Only patients with a complete histopathological response after neoadjuvant treatment had a significantly improved prognosis.

These results are in agreement with previous reports in the literature. Several randomized studies have addressed the potential benefit of neoadjuvant therapy in treatment of esophageal cancer, but the main problem in those studies was the difficulty in enrolling a sufficiently large number of patients to provide satisfactory statistical power. In five randomized studies preoperative radiotherapy was compared with immediate surgery,<sup>112-116</sup> and except in one study,<sup>112</sup> no improved survival was demonstrated. Furthermore, a meta-analysis confirmed this overall finding.<sup>117</sup> Moreover, in seven randomized studies preoperative chemotherapy was compared with surgery alone,<sup>112, 118-123</sup> but only one trial<sup>123</sup> showed a survival advantage associated with the use of neoadjuvant chemotherapy. However, there has been some criticism regarding several details in that study concerning limited preoperative staging (CT not required) and accomplishment of a relatively small number of complete surgical resections (54% of the sur-

gery alone group and 60% of the neoadjuvant group). Furthermore, 17% of the patients in the surgery alone group of that study left the operating room without a resection. Thus, the interpretation of this study is difficult.

A combination of preoperative chemotherapy and radiotherapy has been tested in several randomized trials in the hope of improving the outcome.<sup>124-129</sup> Only two of those studies had a statistical power that enabled statistically meaningful results, and neither of them showed an advantage of neoadjuvant chemoradiotherapy.<sup>125, 129</sup> A single-institutional study indicated better survival among patients in the neoadjuvant group, but many concerns have been raised regarding the reliability of the results of that trial.<sup>128</sup> Much of the concern has been focused on the suboptimal preoperative staging and the extremely poor outcome in the surgery only group (6% 3-year survival compared to 32% in the neoadjuvant group). Thus, there is still no convincing evidence that such a therapeutic strategy offers any survival benefit.

In our study, however, we identified a group of patients with a significantly better prognosis, namely the group with a complete histopathological response to neoadjuvant treatment. In line with the previous literature, the frequency of such a response was approximately 25%.<sup>6, 144</sup> This finding highlights the urgent need to improve our ability to identify factors that can predict or contribute to a complete histopathological response to preoperative oncological treatment. The higher frequency of complete response in the more recent calendar periods indicates a positive trend, probably as a result of more effective oncological modalities. However, there remain doubts as to whether surgery further improves the chance of cure after oncological therapy in this particular group.



### ***The impact of hospital volume on esophageal cancer surgery***

The main hypothesis in **study III** was that hospital volume influences the long-term outcome after esophageal cancer surgery. Previous studies have repeatedly demonstrated an inverse correlation between hospital volume and postoperative morbidity and mortality.<sup>11, 77-82</sup> These findings are strengthened by the results of our population-based study regarding 30-day mortality, although they did not reach the level of statistical significance.

To our knowledge, however, only two studies have previously addressed the impact of hospital volume on long-term survival after esophageal cancer surgery, and the results have been conflicting.<sup>89, 90</sup> In a retrospective case-note study in the West Midlands region of England, no relation between increasing hospital volume and improved long-term surgical outcome was found.<sup>89</sup> Problems of that study include failure to retrieve all the hospital notes and a relatively high 30-day mortality (10%) compared to that reported from other western studies.<sup>6, 10, 12</sup> On the other hand, a Swedish study indicated a 5-year survival advantage among patient operated on at HVH compared to LVH; but a major weakness of that study is a lack of information on potential significant confounders, including comorbidity and tumor stage.<sup>90</sup>

Our results, after adjustment for the most plausible potential confounders, including tumor stage, showed no relation between long-term survival and hospital volume. This finding, however, deserves cautious interpretation, since several additional studies are needed to establish this issue. If true, our finding indicates that tumor biology seems to have a much greater impact on the long-term outcome than does surgical volume. However, it is important to point out that specialized units with high volume and great experience in these extensive procedures should still be recommended, since it is well documented that serious postoperative complications and early postoperative mortality decreases with increasing volume.<sup>11, 81, 82</sup>

### ***Impact of surgeon volume on esophageal cancer surgery***

In **study IV**, we tested the hypothesis that a higher annual surgical workload is associated with lower postoperative mortality after esophageal cancer surgery. The results indicated that such an association exists. However, we found no trend of improved results among the eight experienced surgeons based on their individual annual volume alone.

Several studies have shown improved postoperative outcomes, expressed either as 30-day mortality, in-hospital mortality, or postoperative complications in relation to increased surgical volume.<sup>11, 86-88</sup> To facilitate comparisons with previous research with awareness of that the reality in the United States might be different from that in Europe, our cut-off for grouping of surgeon volume was based on a large population US study that had revealed a strikingly decreased postoperative mortality after esophagectomy when this was performed by HVS.<sup>88</sup> However, the study referred to differed considerably from ours regarding postoperative mortality (9.1% compared to 2.6% among patients operated on by HVS). Furthermore, there was a lack of data regarding tumor characteristics and surgical details in the US study, variables that are important for the interpretation of the results. Nevertheless, our results regarding 30-day mortality were well in agreement with the overall results of that study.

The beneficial effect of HVS was more evident regarding the 30-day than the 90-day mortality, a trend that adds weight to our speculation that tumor biology has a stronger impact on the long-term outcome compared to surgery. On the other hand, certain preoperative factors (tumor location and histology) and surgical details (approach) seemed to favor LVS and might explain why our improved short-term survival was not statistically significant. Another issue that deserves attention is the definition of HVS. The heterogeneity of the definition of surgeon volume is apparent in the literature and it is

difficult to identify minimum volume thresholds at which satisfactory performance is achieved.

<sup>145</sup> This fact further complicates the comparison of findings in different studies.

Finally, we found no further improvement in short-term mortality in association with increasing annual surgical workload among the

eight experienced esophageal cancer surgeons. This finding indicates that surgical volume is not the only relevant surgical factor with regard to short-term mortality. Certain individual skills of the surgeon might also have an important impact on the outcome, a possibility of which the patient should be kept aware.

# Conclusions

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- The short-term survival after esophageal cancer surgery is dependent on age and comorbidity, while the long-term survival is dependent on tumor stage.
- The short-term and long-term survival after surgery for esophageal cancer has improved significantly since 1987 in Sweden, probably as a result of improved surgery.
- The overall long-term survival after esophageal cancer surgery seems to be equivalent in patients with and without neoadjuvant treatment.
- Only patients with a complete histopathological response to neoadjuvant therapy seem to have a significant survival benefit after esophageal cancer surgery compared to patients treated with surgery alone.
- Patients with resectable esophageal cancer and operated on at a high-volume hospital seem to be at reduced risk of short-term mortality compared to those operated on at a low-volume hospitals.
- No association was found between hospital volume and long-term outcome after esophageal cancer surgery
- The short-term prognosis after esophageal cancer surgery seems to be better among patients operated on by higher-volume surgeons than among those operated on by low-volume surgeons.
- There was no tendency toward an improved surgical outcome with increasing annual volume alone among individual experienced esophageal surgeons.



# Future Research

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Several of the findings in these investigations, and the persistently low chance of cure in patients diagnosed with esophageal cancer, highlight the need of further research in this field.

Surgical factors that might have contributed to the improved survival after esophageal cancer surgery over the years should be clarified and investigated in details. Large population-based studies covering a long time period and with access to detailed operative notes and histopathological records could possibly contribute to a better understanding of this positive trend. Such a design would enable us to identify differences in surgical details and practice that might have played a role in the better surgical outcomes in recent years. The impact of different factors such as surgical approach, extension of surgical radicality, and type of substitute and anastomosis should be investigated thoroughly and with good statistical power. Such research is currently being planned within our research unit.

Moreover, as already mentioned in this thesis, there is significant heterogeneity regarding the definition of hospital volume and surgeon volume in the existing literature and it has been difficult to identify minimum thresholds for acceptable surgical outcomes. Further investigation on this matter is warranted. Nowadays, centralization of advanced surgical procedures, including esophagectomy, has become praxis in several countries, but the acceptable minimum number of procedures performed annually by a surgical team in such a specialized unit must be better defined. Large cohort studies, and if possible randomized studies, for comparing such specialized units with different thresholds would be of great value.

Although surgery remains the only established treatment with a curative intent for patients with resectable esophageal cancer, it offers only a limited chance of cure. It is apparent that the combination of surgery with different oncological modalities needs to be further investigated. A recently published randomized trial in the U.K. revealed a significant improvement in survival among patients who were treated with both preoperative chemotherapy and surgery for resectable gastroesophageal cancer compared to those treated with surgery alone.<sup>146</sup> Unfortunately, the number of patients with lower esophageal cancer was too small to allow conclusions for this group of patients. The only way to overcome the conflicting results of studies regarding the benefit of neoadjuvant therapy would be to design a large multi-institutional study where neoadjuvant chemotherapy, neoadjuvant chemoradiotherapy, with surgery alone are compared. Accordingly, large randomized trials comparing definitive chemoradiotherapy to surgery alone are also needed. Furthermore, it is important to identify factors that can predict or contribute to a complete histopathological response to neoadjuvant therapy, since this group of patients has the highest survival benefit.

Numerous issues remain unresolved regarding the clinical usefulness of minimally invasive esophagectomy. Further studies are needed to address the optimum approach, cost-effectiveness, applicability to general surgeons, and proof of possible advantages over open techniques.



# Sammanfattning på Svenska (Summary in Swedish)

**Bakgrund** Matstrupscancer (esofagus-cancer) är den åttonde vanligaste cancerformen globalt sett. Den generella prognosen vid matsrupscancer är sämre än för de flesta tumörssjukdomar och detta gäller de båda dominerande histologiska huvudtyperna, skivepitelcancer och adenocarcinom. Femårsöverlevnaden understiger 15 % i de flesta länder. Tumörstadium är den viktigaste prognostiska faktorn. Radikal kirurgisk borttagning av tumören är den enda etablerade botande behandlingen, vilken dock är förknippad med en 40-60 % förekomst av betydande postoperativa komplikationer och risk för tidig död. Utredningen inför beslut om kirurgi inleds i de flesta fall med datortomografi av bröstkor-gen och buk för att identifiera eventuella fjärrmetastaser, vilket är avgörande för valet mellan kurativ och palliativ behandling. I avsaknad av fjärrmetastaser kompletteras utredningen oftast med endoskopiskt ultraljud för att bättre kartlägga det lokala och regionala tumörstadiet samt avgöra eventuell tumöröverväxt på intilliggande organ. Det finns två olika kirurgiska huvudprinciper för dissektion av matstrupstumören, den transtorakala (via bröstkor-gen) och den transhiatala (via buken och halsen), utan någon dokumenterad skillnad beträffande långtidsöverlevnad. Tidiga komplikationer efter kirurgin påverkar starkast patientens livskvalitet även på sikt. Aktuell forskning pekar på att morbiditet och mortalitet kan minskas av en koncentration av kirurgin till högvolymscentra. I övrigt råder brist på etablerad kunskap om hur den kirurgiska behandlingen av matstrupscancer ska utföras med bästa möjliga resultat avseende både långsiktig överlevnad (bot) och korttidsöverlevnad. Denna brist på evidens gör att kirurgin varierar starkt mellan olika centra. Dessa variationer

ger bra underlag för värdefulla observationella studier av hur olika kirurgiska faktorer påverkar ovan nämnda resultat. Min avhandling fokuserar på faktorer som påverkar överlevnaden efter kurativt syftande matstrupscancerkirurgi och baseras på nationsomfattande svenska observationella studier.

**Metoder** Avhandlingen är uppbyggd kring fyra delarbeten. I *delarbete I-III* kunde alla patienter som behandlats med kirurgi för matstrupscancer i hela Sverige under perioden 1 januari 1987 till 31 december 2000 identifieras med hjälp av länkning mellan de nationellt heltäckande Cancerregistret och Patientregistret. Dessa patienter kunde följas upp fram till 18 oktober 2004 avseende överlevnad och utflyttning ur landet genom ytterligare länkning till det nationellt täckande dödsorsaksregistret, totala befolkningsregistret och emigrationsregistret. Bland totalt 4904 patienter med matstrupscancer diagnosiserade under studieperioden hade 1199 patienter (24.4 %) genomgått kirurgi. Information beträffande tumör- och patientegenskaper, preoperativ behandling samt sjukhus kunde insamlas genom manuell granskning av journalkopior i form av histopatologiska utlåtanden från operationspreparat (PAD-utlåtanden). Via Patientregistret erhöles dessutom information om annan sjuklighet.

I *delarbete IV*, samlades data in via Svenska Esofagus- och CardiaCancerregistret (SECC-registret). I SECC-registret insamlades fortlöpande (prospektivt) uppgifter om patient- och tumöregenskaper, operationer, sjukhus, operatörer och komplikationer sedan den 2 april 2001. Medicinska journaler, inklusive operationsberättelser, histopatologiska utlåtanden, och inten-

sivvårdsjournaler granskades av registrets medlemmar. Insamlingen av data avslutades den 31 december 2005 och patienterna följdes upp till och med den 2 april 2006.

**Delarbete I** påvisade en markant förbättrad överlevnad efter kirurgi för matstrupscancer sedan 1987 i Sverige. 30-dagarsdödligheten efter kirurgi minskade från 10.1% under perioden 1987-1991 till 4.9 % under perioden 1997-2000. Under perioden 1987-1991 var överlevnaden 46.5 % 1 år efter kirurgi, 24.1 % 3 år efter kirurgi och 19.7 % 5 år efter kirurgi. De motsvarande siffrorna under perioden 1997-2000 var 61.7 %, 39.9 % samt 30.7 %. Förbättringen kunde ej förklaras av skillnader i patient- eller tumörsegenskaper, vilket talar för att förbättringen beror av bättre kirurgi.

**Delarbete II** analyserade om onkologisk behandling inför matstrupscancerkirurgi förlänger överlevnaden. Den totala överlevnaden i grupperna med och utan onkologisk behandling var lika efter justering för potentiella störfaktorer (HR 0.99, 95 % CI 0.86-1.16). De 108 patienter (27.6 %) i den grupp som behandlades onkologiskt inför operation och hade komplett tumörrespons histopatologiskt, dvs det fanns inga tecken till kvarvarande tumör i samband med operation, hade dock en bättre prognos än patienter som enbart behandlats med kirurgi (HR 0.71, 95 % CI 0.53-0.94). Således verkar den preoperativa onkologiska behandlingen inte påverka den totala överlevnaden hos patienter med resektabel matstrupscancer, men den begränsade grupp patienter som får komplett respons efter onkologisk behandling har en bättre prognos.

**Delarbete III** undersökte relationen mellan sjukhusvolym och långtidsöverlevnad efter kirurgi för matstrupscancer. Studien visade ingen bättre långtidsprognos bland patienterna som genomgick operation vid högvolumcentra (>10 matsrupscanceroperationer/år) jämfört med sjukhus med lägre operationsvolym (<10 matsrupscanceroperationer/år). HR var statistiskt icke-signifikant 10 % lägre vid "högvolumsjukhus" justerat för alla störfaktorer utom tumörstadium (HR 0.90, 95 % CI 0.79-1.04). I kohorten begränsad till de 764 patienter (64 %) som behandlats enbart med kirurgi fanns även valida data om tumörstadium och justerat även för tumörstadium, påvisades ingen skillnad i överlevnad mellan "hög- och lågvolumsjukhus" (HR 0.99, 95 % CI 0.84-1.18).

**Delarbete IV** delade in de kirurger som genomför matstrupscancerkirurgi i tre grupper, beroende på antalet genomförda operationer årligen, för att studera eventuella samband mellan operatörens kirurgiska volym och korttidsöverlevnad. Patienterna som opererades av "högvolumkirurger" hade en lägre 30-dagarsdödlighet jämfört med patienterna som opererades av "lågvolymkirurger" (2.6 % jämfört med 7.1 %). Denna effekt var dock mindre uttalad avseende 90-dagarsöverlevnad (8.9 % respektive 11.4 %). När vi vidare jämförde resultaten bland de 8 mest erfarna esofaguscancer kirurgerna kunde vi inte identifiera något samband mellan ytterligare ökande kirurgisk volym och överlevnad, utan här verkar även andra faktorer vara av betydelse.



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