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Quality of Life after Esophageal Cancer Surgery

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To all esophageal cancer patients

ABSTRACT

The principal aim of this research was to find ways to improve the quality of life of esophageal cancer patients after surgical treatment and to reduce persisting symptoms that often occur after that procedure. Since esophageal cancer surgery is extensive and carries a poor long-term prognosis, it is relevant to assess quality of life and complications as outcome measures. In three of four studies, we used a nationwide, population-based, prospective design to evaluate the patients' quality of life and symptoms, and the relation between surgery-related factors and quality of life and complications. We used the Swedish Esophageal and Cardia Cancer Register, where most surgically treated esophageal cancer patients in Sweden are registered. Details about tumor characteristics and stage, surgical procedures, and complications were collected prospectively. Medical records and specific charts from surgical procedures, histopathology reports, and intensive care unit reports were continuously scrutinized. Six months after surgical treatment the patients received a self-administered written quality of life questionnaire, developed by the European Organisation for Research and Treatment of Cancer (EORTC), namely a core questionnaire, QLQ-C30, with an esophageal-specific module, QLQ-OES18. In the fourth study we used a hospital-based design where all patients who had been in contact with the specialist nurse at the clinic received two study-specific questionnaires, for evaluation of the patients' appraisal of given support and supportive care. Further, the medical records were reviewed to assess the reasons for contact with the specialist nurse.

Patients who undergo esophageal cancer resection still suffer greatly from a reduced quality of life and several general and esophageal-specific symptoms six months postoperatively. The global quality of life was considerably reduced compared with a general Swedish reference population. The most affected functions were role and social functioning, and the worst general symptoms were fatigue, appetite loss, diarrhea, and dyspnea, and among the esophageal-specific symptoms eating difficulties, reflux, and dysphagia were most frequently reported.

Among surgery-related factors, the occurrence of major complications importantly reduced the global quality of life, the physical functioning and the role functioning after the surgery. There was a statistically significant dose-response relation between number of complications and all these outcomes.

Almost every second operation (44%) entailed at least one severe complication within 30 days postoperatively. Esophageal resections conducted by low-volume surgeons (<5 operations per year) increased the risk of anastomotic leakage compared to those performed by surgeons with a higher volume (OR 7.9, 95% CI 2.1-29.0). Transthoracic esophageal surgery carried an increased risk of respiratory complications compared to a transhiatal (abdominal only) approach.

Support given by a specialist nurse was found to be important through the entire care pathway, particularly during the follow-up phase, as compared with that given by other health care professionals. Specialist nurse support was appraised by the patients as being both satisfactory and highly important, and the most frequent contact reason was nutritional problems.

In conclusion, patients who undergo esophageal cancer resection suffer greatly from reduced quality of life and several persistent symptoms six months postoperatively. The occurrence of surgery-related complications is a predictor of reduced quality of life, and esophageal cancer surgery conducted by low-volume surgeons carries an increased risk of anastomotic leakage. A specialist nurse who provides support to patients with esophageal cancer and coordinates the care pathway is a valuable resource.

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LIST OF PAPERS

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

- I.** Pernilla Viklund, Yvonne Wengström, Ioannis Rouvelas, Mats Lindblad, Jesper Lagergren. Quality of life and persisting symptoms after esophageal cancer surgery.
European Journal of Cancer (In press)
- II.** Pernilla Viklund, Mats Lindblad, Jesper Lagergren. The influence of surgery-related factors on quality of life after esophageal or cardia cancer resection.
World Journal of Surgery 2005;29(7):841-848
- III.** Pernilla Viklund, Mats Lindblad, Ming Lu, Weimin Ye, Jan Johansson, Jesper Lagergren. Risk factors for complications after esophageal cancer resection: A nationwide and prospective population-based study in Sweden.
Annals of Surgery 2006;243(2):204-211
- IV.** Pernilla Viklund, Yvonne Wengström, Jesper Lagergren. Supportive care for patients with esophageal and other upper gastrointestinal cancers: The role of a specialist nurse in the team.
European Journal of Oncology Nursing (In press)

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LIST OF ABBREVIATIONS

BI	Barthel Index of Disability
BMI	Body Mass Index
CI	Confidence interval
CT	Computerized tomography
EORTC	European Organization for Research and Treatment of Cancer
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30
EORTC QLQ-OES18	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Oesophageal 18
EUS	Endoscopic ultrasound
FACT-E	Functional Assessment of Cancer Therapy-Esophageal
FACT-G	Functional Assessment of Cancer Therapy-General
HADS	Hospital Anxiety and Depression scale
MPQ	McGill Pain Questionnaire
NICE	National Institute for Clinical Excellence
OR	Odds ratio
ORC	Oncological Rehabilitation Center
PEG	Percutaneous endoscopic gastrostomy
PET	Positron emission tomography
QPP	Quality from the Patient's Viewpoint
SECC register	Swedish Esophageal and Cardia Cancer register
VIPS	Well-being, Integrity, Prevention, and Secrecy
WHO	World Health Organization
WHOQOL	World Health Organization Quality of Life Group

INTRODUCTION

Esophageal and cardia cancer is relatively rare in the western world. Esophageal cancer is the sixth most frequent cause of death from cancer worldwide,¹ a rank that is higher than the incidence (eighth).² In Sweden, esophageal and cardia cancer are less common, with approximately 650 new cases annually.³ Since the esophageal and cardia sites of cancer share most characteristics and the treatments are very similar, in this thesis, I include cardia cancer in the concept esophageal cancer. There is a male predominance in western societies, with a sex ratio of approximately 7 to 1.^{2, 4} The overall prognosis is poor, with a 5-year survival of 5-15% in Europe.^{5, 6} The patients usually suffer from troublesome symptoms such as dysphagia, weight loss, fatigue and pain. The only established treatment that can offer a possibility of cure is surgical removal of the tumor. The operation usually involves extensive surgery both of the abdomen and the chest and in some cases also of the neck. After the surgical treatment many patients suffer from complications that typically require long postoperative convalescence period. During recent years, the population-based survival after esophageal cancer surgery has improved, but the 5-year survival rate after radical surgery is still only 31%.⁷ While most of the previous studies of outcome of esophageal cancer surgery have concerned post-surgical survival, few studies have examined the patients' quality of life and persisting symptoms after such surgery. Several questions need to be addressed, for example "What is the quality of life of these patients after surgery?", "What symptoms do the patients suffer from after their surgical treatment?", "Are there any specific surgery-related factors that influence the quality of life in a particularly negative way?". The answers to such questions might help to identify interventions that can improve the situation and facilitate life for these patients. During my clinical work with esophageal cancer patients, I have found this topic very important and interesting. This interest prompted the current doctoral work, which might contribute to answering some of the above mentioned questions. It is hoped that this thesis will be the start of continued and intensified research.

BACKGROUND

ESOPHAGEAL CANCER

Epidemiology

There are two main histological types of esophageal cancer, squamous cell carcinoma and adenocarcinoma. Squamous cell carcinoma is the most common histological type, with tobacco smoking and high alcohol intake as the main risk factors in western populations,^{8, 9} especially in combination. During the last decades, the incidence of adenocarcinoma of the esophagus has, for uncertain reasons, increased in the western world and in the early 1990s it surpassed the incidence of squamous cell carcinoma in some countries.¹⁰⁻¹² The strongest known risk factors for adenocarcinoma are gastroesophageal reflux,¹³ Barrett's esophagus (a columnar metaplasia of the distal part of the esophagus linked with chronic reflux),¹⁴ and a high body mass.^{15, 16}

Prognosis

Esophageal cancer is an aggressive cancer, independent of histological type. The overall prognosis is poor with a 5-year survival of 5-15% in Europe, including Sweden.^{5, 6} The long-term survival is highly dependent on the tumor stage, with a survival rate of 95% for stage 0 disease, 50-80% for stage I, 30-40% for stage IIA, 10-30% for stage IIB, and 10-15% for stage III. Patients who have stage IV disease, i.e., distant metastases, and receive palliative chemotherapy have a median survival of less than one year.¹ During recent decades the survival after a radical esophageal resection has improved, and in Sweden the current 5-year population-based survival is 31%.⁷ As another consequence of the aggressiveness, tumor recurrences usually occur at an early stage after surgical treatment, and in view of the low rate of late recurrences, a patient who survives three years after a radical esophageal cancer resection can be considered cured.⁶

Symptoms

Cancer of the esophagus typically causes strictures that result in dysphagia, which is the dominating symptom that occurs as an initial clinical manifestation in approximately 80-90% of the patients. Dysphagia causes problems with swallowing solid food and in the long run also beverages, and it is often accompanied by odynophagia, i.e., "esophageal pain". Most of the patients (60-75%) also experience weight loss,^{1, 17, 18} mainly due to the obstructive effect of the

tumor. The dysphagia is often a slow process, and by the time the patients seek medical advice they might have had these symptoms for several months and have altered their diets considerably. Chest pain or discomfort is another symptom that occurs in approximately 25% of esophageal cancer patients. Other common symptoms include vomiting, hoarseness (due to cancer overgrowth of the laryngeal nerve), cough, and bleeding.¹⁸

THE CARE PATHWAY

The Specialist Nurse

The current care pathway for patients with esophageal cancer is multidisciplinary and increasingly complex. At the Department of Surgery of Karolinska University Hospital, Solna, a *specialist nurse* is the central person in the care pathway. In Figure 1, the care pathway of the patients in this hospital is presented as a flow chart. Initially, the referrals come directly to the nurse, who then contacts one of the esophageal cancer surgeons to review the referral and plan for further investigations. Thereafter, the nurse contacts the patient to inform him or her that the referral has been received and to give the patient information about the plan for further diagnostic examinations, and what these examinations involve.

The nurse has a responsibility to get the care pathway to run without delays, to see that all examinations are done in the correct order, and to be at hand for the patients so that they can feel secure and have someone to turn to with their questions and problems. The nurse works in close collaboration with the esophageal cancer surgeons, the health care professionals in the surgical ward and at the outpatient clinic, at the departments of radiology, endoscopy, pathology, anesthesiology and oncology, and at the operating department, as well as with caregivers outside the hospital. Together with a multidisciplinary team, the specialist nurse takes part in the planning of the treatment. During the time that the patient is hospitalized in the surgical ward, the nurse visits him or her. To further maintain the continuity, the specialist nurse is present with the patient at all follow-up appointments with the surgeon and is the person that the patient first contacts if there are any uncertainties or problems.

Diagnostic Procedures

The aim of the diagnostic procedures is to ascertain the patients' tumor stage (TNM stage), i.e., the depth of the wall invasion of the primary tumor (T), the occurrence of any lymph node metastases (N), and finally, the occurrence of any distant metastases (M).¹⁹ Each of the specific examinations included among the

diagnostic procedures contributes to assessment of different parts of the TNM stage, and the patient therefore has to undergo several examinations before surgical resection is considered.

Often the patient has undergone a *gastroscopy with biopsies* as an outpatient through referral from the general practitioner, and the diagnosis is then usually confirmed when the patient is referred to the hospital. Otherwise, at Karolinska University Hospital, the patient undergoes this procedure as a first examination, conducted by one of the upper-gastrointestinal surgeons.

Next, a *computerized tomography (CT) scan* within ten days from the date of referral, and preferably before the patient has the first appointment with the surgeon. The CT allows a broad (less detailed) overall assessment of the tumor stage through visualization of the local tumor and potential regional or distant metastases.^{20, 21} The result of the CT scan is important for the patient's further examinations. If it does not show any signs of metastases, the patient undergoes a number of more precise radiological procedures and physical examinations (described below), which in combination usually provide valid information on whether or not the tumor can be treated with a curative intent, i.e., with surgical resection.

Even if the patient has undergone gastroscopy through a referral from the general practitioner, the esophageal surgeon conducts this procedure again to ascertain the exact site and size of the tumor before the surgical treatment. If the patient has lost 10% or more of the average body weight, a *percutaneous endoscopic gastrostomy* (PEG) is considered for nutritional support, with the aim of improving the patient's body weight and nutritional status prior to surgery. The PEG procedure is carried out at the same time as the second gastroscopy, by the esophageal surgeon. An *endoscopic ultrasound* (EUS) examination is performed to further investigate the tumor stage, particularly the local tumor stage (T) and the node status (N). The EUS procedure together with an ultrasonically guided fine-needle aspiration allows direct puncture of the tumor or, more importantly, the lymph nodes, which increases the diagnostic accuracy.²¹⁻²³ To add more information regarding the need to seek for specific potential metastases, the CT scan is carried out before the EUS, and a *trans-abdominal ultrasound* is performed at the time of the EUS. If the EUS identifies a close relation between the tumor and the airways, or if the esophageal cancer is located proximally, i.e., usually close to the trachea, a *bronchoscopy* is conducted to assess any tumor ingrowth into the airways. To obtain objective information as to whether the patient is fit enough for the extensive surgical treatment, the patient also undergoes an *exercise treadmill test* (bicycle ergometer test) to evaluate the heart function and general physical capacity during a work load. Based on previous research,^{24, 25} the patient should

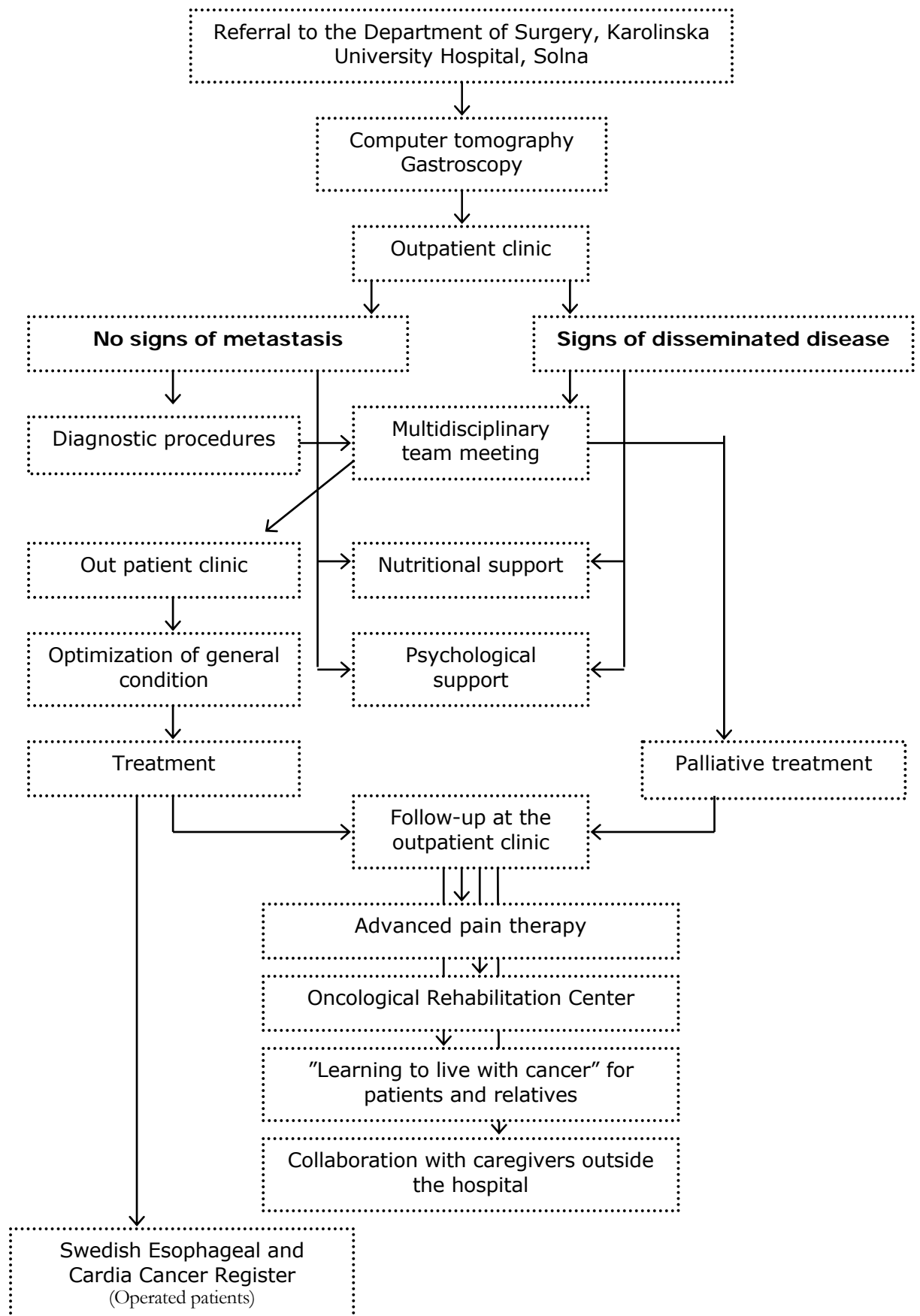


Figure 1. Flow chart of the care pathway coordinated by the specialist nurse.

have a working capacity equivalent to at least 100 W in that test to be reasonably fit for an esophageal resection. During the thoracic part of the surgical procedure, the patient's right lung is shut off from ventilation to achieve better surgical access. For this reason the function of the lungs is tested by *spirometry*.

The last investigation performed before surgery is considered is a *positron emission tomography* (PET) *scan*. PET is a noninvasive imaging technique that involves distribution of radioactively labeled molecules in the body. Glucose, labeled with a radioactive isotope, is often used.²⁶ This technique makes use of the fact that the tumor and any metastases arising from it often require much energy for its metabolism and therefore are visible on the PET image. This examination is internationally well established as the most sensitive means of detecting distant metastases in patients with esophageal cancer.²⁷ In Sweden, however, PET is only available at a limited number of hospitals and clinical routine use of PET in esophageal cancer patients is, to the best of my knowledge, currently only established at the Karolinska University Hospital.

After completion of the examinations summarized above, the patient is discussed at a *multidisciplinary team meeting* where surgeons, oncologists, radiologists, pathologists, specialist nurses, dietitians, and sometimes also other specialists, e.g., oto-rhino-laryngologists and gastroenterologists, participate. The multidisciplinary treatment is subsequently presented to the patient at a follow-up appointment with the surgeon and the specialist nurse. The treatment decision is taken in agreement with the patient.

Virtually all of the patients experience weight loss, at least to some extent. Irrespective of whether the treatment has a curative or palliative intent, the patients usually face continuous nutritional difficulties. All patients therefore have contact with a *dietitian* from the beginning of the care pathway. Some patients need nutritional support prior to surgical treatment. To reduce the risk of complications the patients receive immunonutrition five days prior to surgery. Such nutrition is continued postoperatively for about 7 days given through a jejunal catheter.^{28, 29}

Before the surgical treatment can be performed, the patient has to be examined by an *anesthesiologist* for consideration of any further operability tests, medications, or other measures required to optimize the patient's general condition before surgery.

Prior to surgery, the patient is referred to a physician (anesthesiologist) who is a *specialist in the treatment of pain* to plan for optimal treatment analgesia during and after the surgical procedure. The pain specialist participates in the treatment of

the patient in the surgical ward in the postoperative phase and during the follow-up, whenever necessary.

For physical preparation prior to the surgical procedure and to facilitate recovery during the postoperative period, the patient meets with the *physical therapist*. There is also a possibility to have contact with a *hospital social worker* whenever needed.

Finally, *blood samples* have to be taken, for examinations including blood chemistry, electrolyte status, liver status, blood grouping, and serological tumor markers.

Treatment

The treatment options for patients suffering from esophageal cancer are broad, but the only truly established treatment that can offer possibility of cure is an extensive surgical procedure alone. Combined oncological therapies, i.e., chemotherapy and/or radiotherapy, together with surgery with curative intention, have been studied in randomized trials, but still without overall survival results promising enough to establish any change in clinical practice.^{20, 23}

Surgery with curative intention

Historically, the first esophageal cancer resection with a transthoracic approach was performed by Franz Torek (1861-1938) in 1913, the surgeon in the photograph to the right. The patient was a 67-year-old woman who surprisingly lived for another 13 years after the procedure.³⁰ Today, surgery is the standard treatment for patients with localized esophageal cancer who are fit enough to undergo an esophageal resection. The two most common surgical approaches for esophageal cancer resection are transthoracic and transhiatal esophagectomy.^{1, 20, 21} The transthoracic approach, which is by far the most common procedure in Sweden, combines a laparotomy with a thoracotomy, typically a right-sided one. For esophageal cancer, the transhiatal procedure usually involves a blunt dissection of the esophagus in the middle and upper part in the chest, and the anastomosis is placed through a separate incision in the neck. The transthoracic approach allows better visualization of the tumor and a better possibility of lymph node removal in the chest, compared to the transhiatal method. The transhiatal approach has the advantage of an anastomosis outside



Franz Torek (1861-1938)³⁰

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the thorax, thus avoiding life-threatening mediastinitis in the event of an anastomotic leakage, and a reduced risk of pulmonary complications.^{20, 21} The most commonly used substitute for the removed esophagus is the stomach, but in some cases the small bowel or the colon is used. During surgery the stomach is usually constructed as a tube, pulled-up through the diaphragm, and sutured to the proximal esophageal remnant.

At our surgical unit, the patient is registered by a nurse in the surgical ward the day before the surgical treatment. Preoperative information is given and the patient's case history is documented. A laxative is given to clear the large intestine, as sometimes the bowel is used as the substitute for the removed esophagus. During the night, a glucose infusion is given intravenously. During surgery, several drainages are placed, e.g., one or two pleural drainages, a urine catheter, an epidural catheter for pain relief, and central and peripheral venous catheters for intravenous infusions. In addition, a nutritive jejunal catheter is placed in the proximal part of the small bowel. This catheter is used to give immediate enteral nutrition, and is left in the position until the patients can completely support themselves with food orally. After the surgical procedure the patient is treated in the intensive care unit during the first days. To relieve the anastomosis in the esophagus naso-gastric drainage is applied for a few days. After the period in the intensive care unit, the patient returns to the surgical ward for continued observation, treatment and rehabilitation. The patient is primarily cared for by the health care professionals in the surgical ward, but has contacts with several other health care professionals whenever needed, e.g., with the physiotherapist for professional help with physical rehabilitation, the dietitian for help and support with nutritional planning, the social worker, and the pain specialist. The patient usually remains in the surgical ward for approximately 10 to 14 days if no serious complications occur.

Complications, problems, or symptoms are common after the surgical procedure for esophageal cancer. Approximately, 26-41% of the patients suffer from at least one severe complication postoperatively.¹ The expected convalescence time is long. It can take one to two years before the cured patient is back on a baseline level of general well-being, i.e., to the condition before the manifestation of the disease. The patient often suffers from nutritional problems such as loss of appetite, weight loss, dysphagia, and other difficulties with eating. Fatigue, esophageal pain, diarrhea, cough, and dry mouth are other symptoms and problems that may occur. Moreover, various more or less long-standing psychological problems are frequently disclosed.

Palliative treatment

In about 25 - 50% of patients with esophageal cancer the disease is already incurable when it is first detected, or the patients are not fit enough for surgery.^{1, 31} For these large proportions a wide variety of palliative treatments are currently available.^{21, 32} Some of the principle aims of such palliative treatment are to rapidly relieve dysphagia, maintain the swallowing ability, and avoid complications from invasive treatment options. One of the most important goals of the palliative treatment is to preserve the patient's overall quality of life.³³ The most widely used local palliative treatments used to relieve dysphagia are endoscopic insertion of an esophageal stent, endoscopic laser therapy, and brachytherapy (intraluminal radiotherapy). A stent is a self-expanding tube, which is most often made of a metal net. The stent is placed over the area of the obstructing esophageal tumor as part of a gastroscopy procedure and it usually offers rapid relief of the dysphagia.^{21, 32, 34} Laser therapy is a form of local endoscopic treatment in which laser acts directly on the tumor tissue. Brachytherapy is local short-wave radiotherapy given in the esophagus directly on the tumor to reduce the obstructing tumor mass. Other palliative treatments in esophageal cancer include external radiotherapy, chemotherapy, nutritional support (sometimes including feeding through a gastrostomy or jejunal catheter), psychological support, and symptomatic treatment of pain, vomiting, fatigue, and appetite loss.³²

Follow-up after Surgery

At our unit, the surgically treated patient is followed up for up to three years, with regular appointments with the surgeon and the specialist nurse as well as extra appointments on demand. During the entire care pathway and after the planned follow-up, the patient is able to contact the specialist nurse at any time. Thus, the specialist nurse is the patient's key contact person at the hospital.

One week after the patient is discharged from hospital the specialist nurse contacts him or her to check on the general status, answer any questions, and find out if any problems have arisen and need to be rapidly taken care of. The first appointment with the surgeon at the out patient clinic takes place approximately one month after discharge. Thereafter, the patient is followed up every third month during the first postoperative year, every sixth month during the second year, and finally yearly. After the 3-year follow-up, the patient can make additional appointments on demand, and the specialist nurse remains the contact person.

To facilitate the physical and psychological recovery after the treatment, the patient may be referred to the *Oncological Rehabilitation Center* (ORC) at the hospital, where professional and organized support can be given individually or in groups.

On a regular basis the patient and his or her relatives can be offered an established educating program for rehabilitation, information, and support entitled “*Learning to live with cancer*”.³⁵⁻³⁷ This course is led by the specialist nurse and several lecturers are invited. The program focuses on cancer diagnoses and includes eight meetings covering areas such as the human body and cancer disease, diagnostic procedures, treatment options, nutritional information, the society’s recourses, trials of relaxation therapy and painting therapy, and alternative treatment options.

QUALITY OF LIFE

Definitions

There is no generally accepted definition of the concept “Quality of life”. In 1946 the World Health Organization (WHO) defined health as “a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity”, a definition which was signed by representatives of 61 states.³⁸ This statement generated a broader concept of health that included not only physical and mental dimensions but also social dimensions. As a concept, quality of life is broader than the health concept. Quality of life is considered to be multidimensional, in that it covers a wide range of aspects including physical, functional, emotional and social well-being, satisfaction, and relationships, for example. It is also subjective, as it can only be understood from the patients own point of view.³⁹⁻⁴³ Most people define their quality of life in terms, for example, of having good physical and mental health and the physical ability to do the things they want to do, having a positive psychological outlook and emotional well-being, having good relationships with their family and friends, being part of social activities, having enough money, and being independent.⁴³ The lack of one single accepted definition of quality of life has led to the construction of several definitions by different opinion leaders. Calman⁴⁴ defined quality of life in cancer patients as the difference, or the gap, between the patient’s expectations and achievements, the smaller the gap the higher being the quality of life. Cella and Cherin⁴⁵ have proposed a definition of quality of life that incorporates individual preferences into level of impairment, stating that quality of life “refers to patients’ appraisal and satisfaction with their current level of functioning compared to what they perceive to be possible or ideal”. WHO has a definition of quality of life provided by their working party, the World Health Organization Quality of Life Group (WHOQOL), which includes aspects such as the individual’s perception, expectations, standards and concerns, physical health, psychological state, level of independence, social relationship, and relationship to the environment.⁴¹

Health-related quality of life has been distinguished from quality of life in its wider concept, and is more specific and probably more appropriate for use in clinical research and practice, as it focuses on aspects of life that are affected by health care interventions.^{42, 43, 46} Cella⁴⁷ suggested that the health-related quality of life concept should be applied with reference to the extent to which one's usual or expected physical, emotional and social well-being is affected by a medical condition or its treatment. A broader definition of health-related quality of life has been proposed by Shumaker and Naughton:⁴⁶ "Health-related quality of life refers to people's subjective evaluations of the influence of their current health-status, health care and health promoting activities on their ability to achieve and maintain a level of overall functioning that allows them to presume valued life goals and that is reflected on their general well-being". Thus, there are many definitions of quality of life, a fact which seems to contribute to the difficulties in the assessment and interpretation of this outcome in clinical research. In this thesis, I have used the term quality of life to refer to health-related quality of life.

Measurement of Quality of Life

The currently most common way of measuring quality of life is by the use of written questionnaires that are constructed so that the patient himself/herself can fill them in. A good quality of life questionnaire should show reliability, validity, and responsiveness to clinically significant changes over time.^{33, 42, 48-50} The patient is the person who is best suited to judge his/her quality of life and should be the one who completes a quality of life questionnaire.^{33, 40, 42, 43, 48, 51, 52} Some patients, however, are unable to complete a questionnaire for reasons such as cognitive impairment, communication deficits, or severe distress, and in such cases the information given from proxies can be valuable.⁵³

A large number of seemingly well-constructed and psychometrically valid quality of life questionnaires have been developed. Generic tools measure the broadest aspects of physical, emotional, and social function and are intended for general use, irrespective of the illness or condition of the patient.^{33, 50} An example is the SF-36, developed by Ware et al.⁵⁴ These tools are also often applicable to healthy people and provide an overall picture of the respondent's state of health, but they fail to assess clinically important aspects of the patients' health.^{33, 50} This has led to the development of disease-specific questionnaires that address symptoms and psychosocial complaints that often occur within a particular subset of patients. Such questionnaires may be diagnosis-specific or suitable for a larger group of diseases, e.g., cancer. One of the two most widely used disease-specific questionnaires has been developed by the European Organisation for Research and Treatment of Cancer (EORTC), the EORTC Quality of Life Questionnaire-

Core 30 (EORTC QLQ-C30).⁵⁵ The other one is the Functional Assessment of Cancer Therapy-General (FACT-G) scale.⁵⁶ Both these questionnaires have an additional esophageal-specific module, the EORTC Quality of Life Questionnaire-Oesophageal 18 (EORTC QLQ-OES18)^{57, 58} and the FACT-Esophageal (FACT-E), respectively.⁵⁹⁻⁶¹ In a comparison of EORTC QLQ-C30 with FACT-G,⁶² it was found that these two questionnaires cover slightly different aspects of the quality of life and that the subscales are not directly comparable. Another group of tools is the group of domain-specific questionnaires that concentrate on one particular aspect of the quality of life,^{33, 50} such as the Barthel Index of Disability (BI),⁶³ which measures the physical function, the Hospital Anxiety and Depression scale (HADS),⁶⁴ which measures anxiety and depression, and the McGill Pain Questionnaire (MPQ)⁶⁵ which assesses pain. In the current studies, we have used the cancer-specific and esophageal-specific questionnaires developed by the EORTC.

SUPPORTIVE CARE

Definitions

Supportive care is another broad general concept. This concept brings together all those aspects of the management of the cancer patients that are not aimed at the control of the tumor, e.g., control of symptoms, nutritional support, and psychosocial support.⁶⁶ Together with the National Institute for Clinical Excellence (NICE),⁶⁷ the National Council for Palliative Care⁶⁸ suggests that “Supportive care helps the patients and their family to cope with their condition and treatment of it – from pre-diagnosis, through the process of diagnosis and treatment, to cure, continuing illness or death and into bereavement. It helps the patient to maximize the benefits of treatment and to live as well as possible with the effects of the disease. It is given equal priority alongside diagnosis and treatment”. Whelan et al⁶⁹ have defined supportive cancer care as “Those health services and related activities designed to help patients and their families with their cancer experience during the diagnostic, treatment, follow-up, and palliative phases”. Coluzzi et al⁷⁰ state that supportive care comprises not only physical and symptom support, but also instrumental and social care, provision of information, psychological support, and attention to spiritual needs. In my thesis, I have used the above presented broad definition of supportive care proposed by both Whelan⁶⁹ and Coluzzi.⁷⁰

Supportive care may be said to be an “umbrella” term for all services, provided by both generalists (e.g., general practitioners and district nurses) and specialists (e.g., health care staff with specific training and qualifications), that may be required to

support patients with cancer and their care-givers.⁶⁷ In this doctoral research the function of the specialist nurse has been evaluated, as the central coordinator of the supportive care for esophageal cancer patients during their entire care pathway.

AIMS OF THE STUDIES

The overall aim of these studies was

to find ways to improve the quality of life of esophageal cancer patients after surgical treatment, and to reduce persisting symptoms that often occur after the surgical procedure, i.e., to facilitate the patient's life after the treatment.

The specific aims were

- to assess and describe the quality of life of esophageal cancer patients and persisting symptoms after surgical treatment, and to compare the situation of these patients with that of a general Swedish reference population (paper I).
- to identify any factors related to esophageal cancer surgery that might influence the patients' quality of life after the operation and long-term postoperative symptoms (paper II).
- to identify any factors related to esophageal cancer surgery that might influence the risk of postoperative complications (paper III).
- to elucidate and evaluate the role of a specialist nurse as a key person in the care pathway for patients with esophageal cancer (paper IV).

MATERIALS AND METHODS

DESIGN

The studies described in this thesis were conducted to evaluate the quality of life and persisting symptoms after esophageal cancer surgery with the aim of obtaining further knowledge that can facilitate the future patients' life after treatment. The limited incidence of this cancer in Sweden makes clinical research at individual hospital units difficult, and selection of patients and retrospective data collection are methodological threats to the aims of the studies. For these reasons, nationwide, population-based prospective designs were adopted in studies I-III (papers I-III). In study IV (paper IV) a cross-sectional and hospital-based design was used.

DATA COLLECTION

Patients registered in the Swedish Esophageal and Cardia Cancer (SECC) register were eligible for studies I-III. In study IV, patients with esophageal or any other upper gastrointestinal cancer who had been admitted to the Department of Surgery at the Karolinska University Hospital, Solna, participated.

The Swedish Esophageal and Cardia Cancer Register (studies I-III)

In studies I-III, we used data collected from the SECC register. The register is based on a nationwide and all-encompassing Swedish network of hospital departments and clinicians involved in the diagnosis or treatment of patients with esophageal or cardia cancer. The network was initially developed for a population-based case-control study concerning risk factors for esophageal and cardia cancer.¹³ The SECC register started in April 2nd 2001 with the aims of being a resource for clinical research, improving the quality of the surgical treatment of the esophageal cancer patients, and thereby improve the prognosis for the patients suffering from this fatal disease. Out of 179 hospital departments, representing general surgery, thoracic surgery, oto-rhino-laryngology, oncology, and pathology, 174 (97%) participate in this register and at each participating department there is a contact physician and often yet another contact person. Each contact physician is responsible for the local registration in the register. This network makes it possible to rapidly identify and register newly diagnosed cases throughout Sweden. The SECC register is coordinated by a central project administrator who is a key person in the registration and data collection. The coordinator receives the histopathology report from the pathology department

when an esophageal or cardia cancer diagnosis is confirmed, and then she reminds the contact physicians to register the patient and starts the collection of information required. Informed consent is obtained from each living patient before inclusion in the SECC register. Because of the need for informed consent, there was a slight reduction of registered patients despite the fact that the register has a national coverage of approximately 90%. The registry also collaborates with all six Swedish regional tumor registries to ensure optimal completeness of the registration.

Information coverage

In the SECC register detailed data are collected, including tumor characteristics, i.e., histological type, specific site and stage (TNM), preoperative physical examination results, neo-adjuvant treatments, surgical procedures, radicality of the surgical treatment, complications, length of hospital stay, and whether the patient has been discharge home or to other places for care. All this information is collected and validated through manual review of each individual case record as part of the registry routine.

Validity and quality of the register

The high national coverage of the SECC register, the detailed and prospective data collection, and the objective manual review of each case record ensure that the data entered in the register are of good quality and validity. This high quality is also attributable to the important function of the project administrator, who has repeated contacts with the responsible contact physicians at each hospital department until the medical records from each patient have been completely collected.

Unit of Upper Gastrointestinal Surgery (study IV)

In study IV, all patients with cancer of the upper gastrointestinal tract who had ever been in contact with the specialist nurse at the Unit of the Upper Gastrointestinal Surgery at the Department of Surgery at Karolinska University Hospital in Stockholm during the period November 1, 2001 to January 31, 2004 were eligible for participation. Of these patients, all who were alive at the time of the start of the data collection were eligible to receive the study questionnaires (described below). Furthermore, the medical records of all patients with esophageal or gastric cancer who had been in contact with the unit and the specialist nurse were reviewed. The aim of this review was to ascertain the reasons for contacts with the specialist nurse and to determine what kind of problems predominated in the selected group of patients.

QUESTIONNAIRES

In studies I and III, questionnaires developed by EORTC were used (the EORTC QLQ-C30 and EORTC QLQ-OES18). In study IV, study-specific questionnaires were used. Each questionnaire is presented below.

EORTC Questionnaires (studies I and III)

EORTC QLQ-C30

The first-generation core questionnaire was developed by EORTC in 1987 and contained 36 questions (EORTC QLQ-C36). The questionnaire was designed to be cancer-specific, multidimensional in structure, appropriate for self-administration and applicable across a range of cultural settings.^{55, 71} Since then, the questionnaire has been tested and continuously developed. Today, the EORTC QLQ-C30 (version 3.0) is the version that is used and it contains 30 items.⁵⁵ The questionnaire incorporates five functional scales (physical, role, cognitive, emotional, and social), three symptom scales (fatigue, pain, and nausea or vomiting), and a global health-status/quality of life scale. This questionnaire also contains six single items addressing further symptoms that commonly occur among cancer patients, such as dyspnea, appetite loss, insomnia, constipation and diarrhea, and finally, a question addressing the perceived financial impact of the disease. Each item has four response alternatives: 1) “Not at all”, 2) “A little”, 3) “Quite a bit”, and 4) “Very much”, except for the global health-status/quality of life scale, which has the response alternatives based on a marking on a categorical scale ranging between 1) “Very poor” and 7) “Excellent”. The time frame covered in the questionnaire is the past week.

The QLQ-C30 has been tested for both reliability and validity.^{55, 72-77} Reliability testing is used to assess the extent to which a questionnaire is free of measurement errors,^{42, 49, 78} and to evaluate how reliable, consistent, repeatable, and reproducible a questionnaire is.⁵⁰ Validity testing is an assessment of the extent to which a measurement method truly detects what it is designed to detect, the most fundamental consideration in developing and evaluating questionnaires.^{49, 50, 78, 79} Although the results of the questionnaire testing indicated good validity and reliability, further improvements are warranted.^{55, 72-77}

EORTC QLQ-OES18

The EORTC QLQ-OES18 is a disease-specific module that supplements the core QLQ-C30 questionnaire with assessment of specific esophageal cancer symptoms.^{57, 58} QLQ-OES18 comprises four symptom scales (eating, reflux, esophageal pain, and dysphagia) and six single items addressing the symptoms

cough, dry mouth, taste, choking, speech, and trouble swallowing saliva. This questionnaire has the same four response alternatives and the same time frame as the core questionnaire presented above.

Both the reliability and the validity of QLQ-OES18 have been tested. The results indicated that this questionnaire was valid, but further improvement of this tool is warranted, since some of the correlations were poor.^{57, 58}

Scoring

Scores were derived from the two EORTC questionnaires on the basis of the response alternatives presented above. These scores were linearly transformed into a 0 to 100 scale in accordance with the EORTC Scoring Manual.⁸⁰ A high score in the functional and global health-status/quality of life scales represented a higher level of function and better global quality of life, whereas a high symptom score represented a greater degree of symptoms, i.e., more problems with symptoms.

Clinical relevance

Based on previous results,^{81, 82} a difference in mean scores of 10 or more on the 0 to 100 scale was considered to be of clinical relevance. Osoba et al⁸² found that in patients who reported “a little” change either for the better or for the worse, the mean score change was 5 to 10, for a “moderate” changes it was about 10 to 20 and for change reported as “very much” it was greater than 20. This approach has previously been applied in other quality of life studies.⁸³⁻⁸⁵

Time frame of assessment

Our assessment was made six months after the esophageal cancer surgery. This time frame was based on previous observations that the quality of life had generally returned to a stable preoperative baseline value about six months after such surgery, indicating that acute problems after the operation had subsided.^{59, 86-88} Moreover, among patients who have undergone radical surgery, tumor recurrence is unlikely to cause symptoms so rapidly after the operation.⁸⁶ Both in study I and study III, a total of up to three letters to remind the candidate participants about the questionnaires were sent out.

Reference population (study I)

In study I, the mean scores in the esophageal cancer resection group were compared with the corresponding mean scores derived from a study of a large sample of the Swedish general population.⁸³ In this comparison study,⁸³ a random

sample of 3069 individuals was evaluated with the EORTC questionnaire QLQ-C30 only. Sociodemographic characteristics and health conditions were also addressed. From the comparative study, we used the scores from specified groups, i.e., individuals without any health problems and individuals with any cancer, and the total scores for men and women.

Study-specific Questionnaire (study IV)

First questionnaire - support

The study-specific questionnaire used in study IV was constructed to address the question how patients with esophageal or other upper gastrointestinal cancer perceived the support provided by a specialist nurse and how this support was judged in comparison with that provided by other professionals in the team, including physicians, nurses at the surgical outpatient clinic, and nurses in the surgical ward. A further aim of the questionnaire was to evaluate the patients' experience of the support that was given and to obtain their options of the importance of this support. The assessment was based on principles of a previously established and validated questionnaire entitled "Quality from the Patient's Perspective" (QPP).⁸⁹⁻⁹¹

The questionnaire contained 12 statements which were presented separately for three phases of the care pathway (see below), with references to each of the professional categories involved. Each statement had four alternative responses regarding support: 1) "completely agree", 2) "mainly agree", 3) "partly agree", and 4) "disagree". Each initial statement was followed by a question with the purpose of assessing the perceived importance of this support to the individual patient, with another four alternative answers: 1) "most important", 2) "important", 3) "rather important", and 4) "not important".

An example of a statement with response alternatives: *"The specialist nurse at the department of surgery supported me during the diagnostic phase of my disease"*

"P":

- 1) "Completely agree",
- 2) "Mainly agree",
- 3) "Partly agree",
- 4) "Disagree"

"For me, this support was":

- 1) "Most important"
- 2) "Important"
- 3) "Rather important"
- 4) "Not important"

The questionnaire separately assessed three phases of the care pathway: First, the diagnostic phase (before any decision was made about the treatment), second, the treatment phase (from the date of the decision regarding treatment to the first

outpatient follow-up contact), and finally, the follow-up phase (beginning with the first outpatient contact after the treatment).

Second questionnaire – supportive care

A second self-administered study-specific questionnaire, containing nine statements, was developed to collect more specific information about the supportive care provided by the specialist nurse. This questionnaire was sent out 4 to 6 months after the first questionnaire to the patients who had responded to the first questionnaire. The questionnaire had a construction similar to that of the first questionnaire (see description above).

Example of a statement with response alternatives:

“I have got in contact with the specialist nurse when I have called her on the phone or pager or visited her”

- 1) “Completely agree”
- 2) “Mainly agree”
- 3) “Partly agree”
- 4) “Disagree”

“It has been of importance to me that I have got in contact with the specialist nurse when I have called her on the phone or pager or visited her”

- 1) “Most important”
- 2) “Important”
- 3) “Rather important”
- 4) “Not important”

These two study-specific questionnaires were piloted by asking two patients to read and answer the questions and make comments whenever there were any difficulties or uncertainties in the questionnaires, but neither of these patients found them difficult to fill in. Together with each of the two questionnaires, a letter of information about the study and a response envelope were enclosed. For each of the two questionnaires, two reminders were sent to patients who did not reply.

STATISTICAL METHODS

In Table 1, all statistical methods used in studies I-IV are listed. Various analyses were conducted in the studies summarized in this thesis. Descriptive statistics were used and numbers and percentages are presented to describe the distribution of patients and some of their characteristics in each study. In all statistical analyses

the statistical software SAS 9.1 or SAS 8.2 for Windows was used. The statistical methods applied in the different studies are described below.

Table 1. Overview of statistical methods used in studies I-IV.

	Study I	Study II	Study III	Study IV
Mann-Whitney	X	X		
t test	X			
Jonckheere-Terpstras		X		
Logistic regression		X	X	
Fisher's exact				X
Content analysis				X

Study I

The responses in the EORTC questionnaire were linearly transformed into a 0 to 100 scale in accordance with the EORTC Scoring Manual.⁸⁰ Mean scores and standard deviations (SDs) were calculated. Based on previous research,^{81, 82} we considered a difference in mean scores of 10 or more on the 0 to 100 scale to be of clinical relevance. When mean scores differed by at least 10 between groups of patients in our study, the Mann-Whitney test was used to determine whether the difference was statistically significant at the 5% level ($\alpha = 0.05$). The Mann-Whitney test is a non-parametric method that is recommended if the data do not have a normal distribution.⁹² Results of comparisons with a general Swedish reference population were tested with the two-sample *t* test whenever sample size, mean scores, and standard deviations were available for the reference group and when the mean scores differed by at least 10. The two-sample *t* test is a test used for comparison of two independent groups of data.⁹²

Study II

As in study I, the responses in the EORTC questionnaire were linearly transformed into a 0 to 100 scale in accordance with the EORTC Scoring Manual.⁹³ All exposure variables were categorized on the basis of biological or distributional criteria. A reference category was selected for each variable. Thereafter, the other categories were compared with the reference category within that variable. The non-parametric Mann-Whitney test was used for comparing the outcome variables with the reference category within each variable. Two-sided *p* values were calculated at the 5% significance level in all tests, and the calculations included the possibility that a difference could be of the same magnitude but in an opposite direction.^{92, 94} The Jonckheere-Terpstras test was used for calculation of *p* values for trend in variables where a dose-response association was deemed to be biologically plausible and when the estimates from the Mann-Whitney test revealed statistically significant differences. The Jonckheere-Terpstras test is a

non-parametric test that can be used to detect dose-related trends for continuous data.⁹⁵ The statistically significant findings were also analyzed in a logistic regression model in which adjustments were made for potential confounding by age (in three categories: <60, 60-69, >69 years), sex, and tumor stage (in four stages: 0-I, II, III, and IV).

Study III

In this study, an unconditional logistic regression model was used to estimate the relative risk of complications, with comparisons of exposed and unexposed groups of patients, in the form of odds ratios (ORs) with 95% confidence intervals (CIs). In multivariable modeling, our basic model included adjustments for age (categorized into three groups: <60, 60-69, or ≥ 70 years), sex, and tumor stage (four groups: 0-I, II, III, or IV). We also analyzed the variables in a more extensive model in which we adjusted the results for the above covariates as well as for several other covariates, including histological cancer type (categorized into two groups: adenocarcinoma or squamous-cell carcinoma), neoadjuvant treatment (two groups: yes or no), peroperative bleeding volume (three groups: < 500, 500-1000, or ≥ 1000 ml), surgical approach (two groups: transhiatal (abdominal only) or transthoracic), surgeon volume (three groups: <5, 5-10, or >10 operations per year), type of hospital (two groups: university or non-university), and type of anastomosis (two groups: stapled or hand-sewn). We defined two separate main outcome variables: 1) occurrence of any pre-defined complications and 2) occurrence of anastomotic leakage. Regarding complications, this outcome variable was analyzed in three levels: 1) occurrence of any pre-defined complication, 2) occurrence of at least two complications, and 3) occurrence of at least three complications.

Study IV

Fisher's exact test was used for testing of statistical significance ($\alpha = 0.05$) of differences between the specialist nurse and other health care staff members on group levels. This type of test can be performed when the sample size is small and when comparing percentages of distributions.⁹² Quantitative content analysis of the textual data, i.e., analysis where documentation is categorized and classified, was used to identify and organize the nursing documentation.^{96, 97} The documentation was categorized under the headings nutrition, knowledge/development, pain, psychosocial, skin, respiration/circulation, medications, activity, elimination, sleeping, and communication, according to a generally accepted Swedish nursing documentation style, entitled VIPS (which

stands for well-being, integrity, prevention, and secrecy).⁹⁸ Under each heading, the reasons for contacts were divided into more detailed categories.

RESULTS

PATIENT CHARACTERISTICS

Some characteristics of the patients in each study are presented in Table 2.

Table 2. Characteristics of patients participating in studies I-IV.

	Study I	Study II	Study III	Study IV
Total number of patients	282	100	275	73
Median age (years)	67	65	67	64
Sex, number (%)				
Male	224 (79)	76 (76)	218 (79)	40 (55)
Female	58 (21)	24 (24)	57 (21)	33 (45)

STUDY I

In Table 3, selected mean scores are presented for the total study group, for male and female study patients, and for subgroups of a general Swedish reference population. Compared to the entire reference population and to the reference subgroup diagnosed with any form of cancer, the scores for global quality of life, functional scales, and general symptoms, particularly fatigue, appetite loss, and diarrhea, were considerably worse among the study patients. Compared to a sample of the reference population who had no chronic health problems, the mean scores for the quality of life, functioning scales, and general symptoms among the study patients were even worse (data not shown). The mean scores in all scales and items were virtually similar between genders. Concerning age groups, the patients in the youngest category (<60 years) were more affected in the emotional functions than older patients ($p<0.01$). The patients in the youngest age group also reported more trouble with insomnia ($p<0.05$) and greater financial difficulties ($p<0.001$), compared to older groups.

Regarding the esophageal-specific scores, no comparison population was available, but most people in the population at large have no esophageal symptoms, and therefore our general reference population would have a mean symptom score very close to 0. In Table 3 some mean scores from the esophageal-specific questionnaire are presented. Eating difficulties were the single worst problems among the persisting esophageal-specific symptoms, followed by reflux and dysphagia. There were no clinically relevant differences in esophageal-specific symptoms between males and females, and these mean scores were in general evenly distributed between age groups (data not shown).

Patients in whom the resection was not macroscopically radical were both clinically and statistically significantly more negatively affected in the global quality of life scale, all functioning scales, and the general symptom scales (except for the nausea and vomiting scale), compared to patients in whom the resection was macroscopically radical. The patients with macroscopically non-radical resection also had higher mean scores (more severe symptoms) for dyspnea, financial difficulties, reflux, cough, dry mouth, choking, and speech (data not shown).

Table 3. Quality of life, and general and esophageal-specific symptoms, presented as mean scores (range 0 to 100) with standard deviations (SD) in 282 esophageal cancer patients treated surgically, compared to a general Swedish reference population, including a subgroup with a cancer diagnosis.

	Total study patients n=282	Cancer reference group n=134	Male reference group n=1,450	Male study patients n=224	Female reference groups n=1,619	Female study patients n=58
Scales and items						
QLQ-C30						
Global QoL scale [†]	59 (23)	73	78 (21)	59 (24) [†]	75 (22)	60 (21) [†]
Role function [†]	63 (34)	82	87 (24)	62 (35) [†]	87 (24)	64 (31) [†]
Social function [†]	71 (29)	88	91 (19)	71 (29) [†]	90 (20)	73 (28) [†]
Emotional function [†]	72 (25)	82	84 (20)	73 (24) [†]	78 (22)	69 (28) [*]
Fatigue scale [§]	44 (28)	27	19 (21)	44 (28) [†]	23 (22)	43 (25) [†]
Appetite loss [§]	35 (35)	-	4 (14)	34 (36) [†]	5 (15)	39 (33) [†]
Diarrhea [§]	33 (32)	-	5 (15)	33 (32) [†]	5 (16)	33 (33) [†]
Dyspnea [§]	33 (32)	25	20 (28)	32 (31) [†]	16 (24)	33 (33) [†]
Scales and items						
QLQ-OES18						
Eating scale [§]	35 (26)	-	-	34 (26)	-	36 (24)
Reflux scale [§]	26 (29)			24 (28)		32 (31)
Dysphagia scale [§]	25 (27)			25 (27)		25 (26)

* p value <0.05. [†] p value <0.001. [‡] Score range 0 to 100. Higher score represents a better quality of life or a higher level of functioning. [§] Score range 0 to 100. Higher score represents more severe symptoms.

STUDY II

Some mean scores for measures of global quality of life, functioning, and symptoms in relation to some surgery-related factors are presented in Table 4.

The mean scores for global quality of life after surgery did not differ significantly between sexes or age groups. The mean global quality of life scores were worse among patients with tumors in the proximal esophagus than among those with distal tumors, but the difference was not statistically significant. Although patients with early tumor stages (0 to I) on average reported better scores than patients with advanced (stage IV) disease, the limited number of patients with stage IV disease seemed to prevent the difference from reaching statistical significance. But

the mean score difference between stage IV and the other group of tumor stages was of clinical relevance (data not shown).

Wider resection margins resulted in better mean scores for global quality of life, and the results were of clinical relevance, with mean a score difference of more than 20. The difference did reach statistically significant levels for physical and role functioning, but after adjustment for confounding by age, sex, and tumor stage, the difference did not remain significant for physical functioning ($p=0.13$) (Table 4).

The use of a gastric tube as the esophageal substitute appeared to result in more problems with indigestion than when the small bowel was used (Roux-en-Y reconstruction). The mean score difference was of both clinical relevance and statistical significance. Other potentially relevant surgery-related factors, e.g., the degree of radicality of the surgical procedure with regard to lymph node dissection and proximal resection margins, the amount of blood loss during surgery, the length of the operation, or the type of hospital (university or not), did not strongly affect the mean scores measuring quality of life.

The occurrence of complications statistically significantly reduced the mean scores of global quality of life, physical functioning, and role functioning. There were significant dose-response relations for all these outcomes. These associations remained statistically significant after adjustment for confounding variables, except for the relation to physical functioning ($p=0.10$). With the exception of anastomotic strictures, the major types of complications, i.e., anastomotic leakage, infections, cardio-pulmonary complications, and cardiac complications, each contributed to a reduction in the scores of quality of life.

Table 4. Surgery-related factors and global quality of life, physical and role functions, and esophageal-specific symptoms among 100 patients who had undergone esophageal cancer resection.

	QLQ-C30			QLQ-OES18		
	Global quality of life scale [¶]	Physical function scale [¶]	Role function scale [¶]	Dysphagia scale [#]	Reflux scale [#]	Swallowing [#]
Proximal resection margin						
>49 mm (ref)	64 (19)	87 (15)	76 (20)	10 (11)	25 (28)	14 (27)
11-49 mm	59 (22)	78 (22)	67 (34)	20 (22)	26 (33)	19 (20)
0-10 mm	55 (27)	68 (23) ^{*,†}	47 (40) [*]	33 (30) ^{*,†}	28 (28)	14 (20)
Esophageal substitute						
Stomach	61 (22)	77 (21)	64 (34)	19 (22)	29 (30)	19 (21)
Small-bowel	59 (22)	77 (22)	62 (36)	27 (20)	17 (30) [*]	13 (19)
Colon	58 (38)	82 (20)	72 (35)	19 (17)	6 (10)	17 (0)
Postoperative complications						
None (ref)	65 (21)	82 (19)	74 (30)	21 (21)	23 (31)	15 (22)
1-2	54 (23) [*]	73 (22) [*]	54 (35) [*]	21 (23)	29 (29)	21 (18) [*]
> 2	51 (24) [†]	62 (24) ^{*,†}	33 (18) ^{†,§}	11 (14)	25 (29)	19 (19) [†]
Groups of complications[¶]						
Re-operation	56 (26)	63 (23) [*]	37 (31) [†]	-	-	-
Anastomotic leakage	53 (16)	65 (19) [*]	38 (32) [†]	-	-	-
Infections	48 (23) [*]	62 (25) [*]	43 (32) [*]	-	-	-
Respiratory insufficiency	51 (26)	68 (22) [*]	48 (31) [†]	-	-	-
Cardiac complications	49 (22) [*]	71 (25)	53 (29)	-	-	-

* p value <0.05. † p value <0.01. ‡ p for trend <0.05. § p for trend < 0.01. ¶ Scores compared to the group of patients with no postoperative complications. ¶ = Score range 0 to 100. Higher score represents a better quality of life or a higher level of functioning. # Score range 0 to 100. Higher score represents more severe symptoms.

STUDY III

This study showed that almost every second esophageal resection for cancer, i.e., 122 out of 275 (44%), was followed by at least one severe complication within 30 days after the procedure. With a few exceptions, the patients with esophageal cancer underwent a transthoracic esophageal resection with a gastric tube pulled up as esophageal substitute. The overall 30-day mortality rate was 3.6% (10 patients), the in-hospital mortality was 7.3% (20 patients), and the 90-day mortality was 8.4% (23 patients). The most frequent complications were respiratory insufficiency, severe pneumonia, heart complications, and serious infections. In analyses using the occurrence of at least two complications as the outcome, we found that higher age might be associated with an increased risk, and when at least three complications were used as the outcome, an age above 70 years carried a statistically significantly increased risk (OR 4.3, 95% CI 1.4-13.5). Moreover, the trend with increasing age was significant ($p = 0.004$). Low-volume surgery, preoperative chemo- or radiotherapy, and a high peroperative bleeding volume, were associated with increased point risk estimates of complications, but these tendencies did not reach the level of statistical significance. No influence of sex or tumor stage was found.

The frequency of anastomotic leakage among patients operated on by low-volume surgeons (<5 operations per year) and by surgeons with a higher volume (≥ 5 operations annually) is presented in Figure 2. Esophageal resections conducted by low-volume surgeons were associated with a nearly eight-fold increase in the risk of anastomotic leakage, compared to those performed by surgeons with a higher volume (Table 5). No difference in the risk of anastomotic leakage was found between hand-sewn and stapled anastomoses (data not shown).

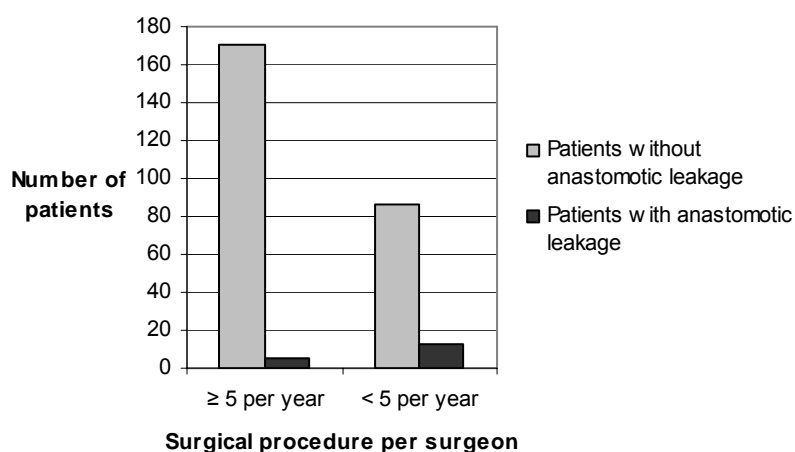


Figure 2. Occurrence of anastomotic leakages related to number of surgical procedures performed annually per surgeon.

Cardia cancer patients ran a higher risk of respiratory complications after surgery with a transthoracic approach than after a transhiatal (abdominal only) approach (OR 4.8, 95% CI 1.7-13.8).

Table 5. Risk of anastomotic leakage among low-volume surgeons and surgeons with a higher volume expressed in odds ratios with 95% confidence intervals (CI).

	Odds Ratio (95% CI) Basic model*	Odds Ratio (95% CI) Multivariable model†
Surgical procedure per surgeon		
≥ 5 / year	1.0 (reference)	1.0 (reference)
< 5 / year	5.6 (1.9-16.8)‡	7.9 (2.1-29.0)‡

* = Adjusted for age, sex, and tumor stage. † = Adjusted for age, sex, tumor stage, tumor location, histological type of tumor, neoadjuvant and adjuvant treatment, type of surgery, surgical approach, and substitute for the esophagus. ‡ = *p* value < 0.01

STUDY IV

The patients' appraisal of the importance of support during the three phases of the care pathway, i.e., the diagnostic, treatment, and follow-up phase, is illustrated in figures 3, 4, and 5. During the diagnostic phase, the support given by the specialist nurse and the physicians was appreciated most compared with that given at the outpatient clinic and in the surgical ward and was deemed to be most important (Fig. 3). During the treatment phase, the support given by the specialist nurse was experienced as being just as satisfactory as during the diagnostic phase (data not shown). The support from the physicians was given the highest praise during the treatment phase of the care pathway. The support from the health care staff in the surgical ward was judged to be more important during the treatment phase (fig. 4) than in the other phases of the care pathway (Figs 3-5), and was experienced as being almost as satisfactory as that of the specialist nurse during the treatment phase. Compared with the support given by the specialist nurse, no statistically significant differences were found between the health professional groups during the treatment phase. Based on the distribution of the answers, the support from the specialist nurse was deemed more important than that from all the other groups of professionals in the team during the follow-up phase (Fig. 5), but the differences did not reach statistical significance.

The majority (range 71-94%) of the participating patients "completely agreed" that all parts of the supportive care given by the specialist nurse were satisfactory. The patients reported that the information given by the specialist nurse was possibly easier to understand and that they found it easier to put questions to the

nurse than to the physicians. While 10% of the patients had difficulty in understanding the information about the disease and its treatment given by the physicians, none of them had problems in understanding what they were told by the specialist nurse. However, the information given by the physicians was considered to be more important than that given by the specialist nurse.

Among documented contacts between the specialist nurse and patients with esophageal or gastric cancer, nutritional problems and problems or questions regarding knowledge or development predominated during the follow-up phase.

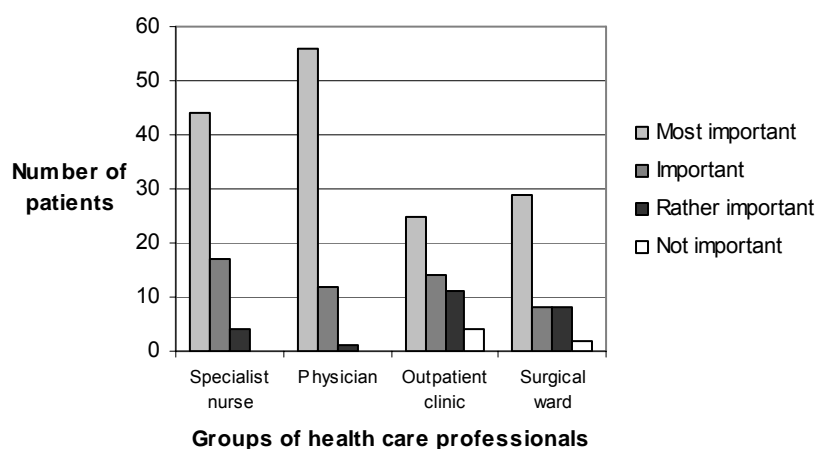


Figure 3. Patients' appraisal of the importance of support provided by groups of health care professionals during the diagnostic phase.

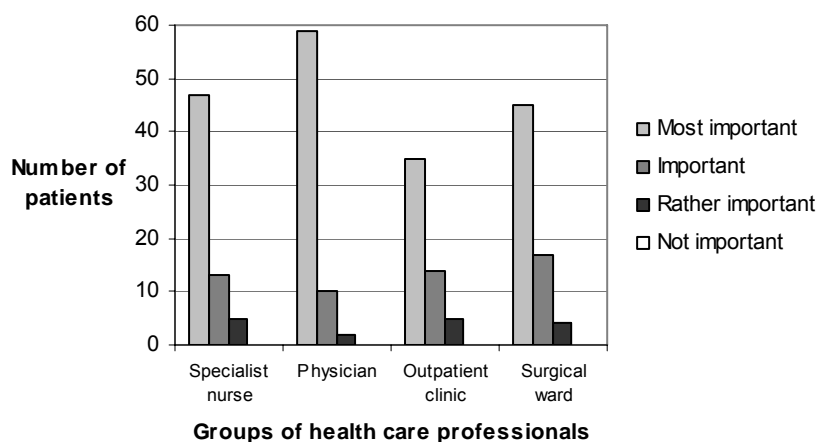


Figure 4. Patients' appraisal of the importance of support provided by groups of health care professionals during the treatment phase.

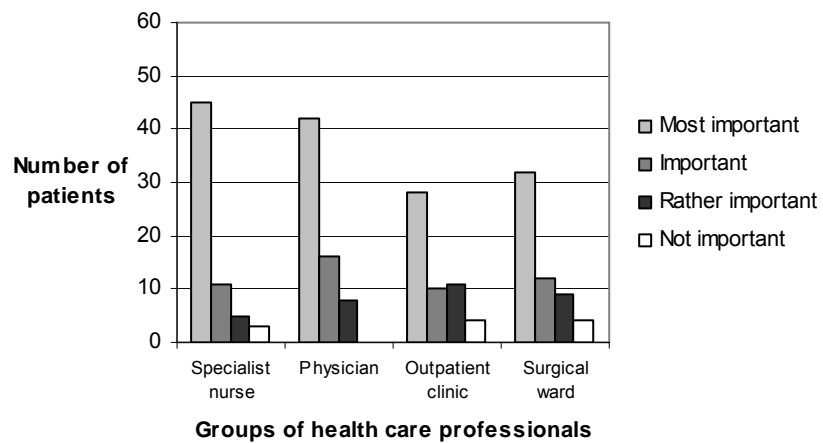


Figure 5. Patients' appraisal of the importance of support provided by groups of health care professionals during the follow-up phase.

DISCUSSION

METHODOLOGICAL CONSIDERATIONS

Some methodological aspects of the studies described in this thesis deserve particular attention.

Systematic errors

Selection bias

Studies I-III had a basically similar design, since the data were collected from the same source, the SECC register. An advantage of these studies is the nationwide population-based design, which reduced the risk of selection bias and facilitated generalization. Remaining sources of selection bias were non-participation in the registration and the mortality that occurred between registration and the six-month follow-up. During the different study periods, the number of surgically treated patients may seem low despite the nationwide extent of the data collection, but the resection rate has decreased over the years, probably reflecting new or improved diagnostic techniques for detection of advanced disease not amenable to surgery. Moreover, during the initial phase of the registration in the SECC register, the registration frequency was less complete. Furthermore, all hospital departments that conducted esophageal cancer surgery did not participate. In addition, some patients died before registration and some did not wish to participate in the registration or in the individual studies. Despite these sources of non-participation, however, the frequency of registered patients corresponded well with the current approximately 25% resection rate in Sweden, as was recently reported from our group in a complete nationwide, retrospective and population-based study based on the Swedish In-patient Register,⁷ indicating that the SECC register, and thus the current studies I-III had good nationwide coverage. The non-participation is probably therefore not a major concern and is not likely to severely affect the internal or external validity of the study.

In study IV, non-participation is a potential source of selection bias. It is possible that patients who chose not to participate in this study could have had less positive experiences of their care, compared to participating patients. Any such selection bias should, however, be limited in view of the high participation frequency. The retrospective design is a disadvantage. The high mortality rates of these cancers meant that the majority of the patients who had been in contact with the specialist nurse had died, a fact that strongly reduced the sample size and

increased the risk of selection bias in that survivors might have been more likely to report positive experiences of their care.

Information bias

An advantage of studies I-III was that all the exposure data were collected prospectively, i.e., before the endpoint (or outcome) was assessed. This would circumvent the risk of information bias and would also further reduce the risk of selection bias.⁹⁹

The assessment of all exposures and outcomes was conducted in a relatively objective manner. The medical records were collected through a project administrator, and were thoroughly reviewed by a small number of persons in the core group of the SECC register (including myself). Moreover, during this review, data were collected in a structured manner, on the basis of an extensive study protocol, which should have counteracted selective data collection. Self-reported data from participating hospital departments were disregarded, including for example complications; this was of particular relevance for the validity of study III, since collection of self-reported complications is prone to be biased through selection. Also, the assessment of quality of life was relatively objective, in the sense that we (the research group) used validated tools and we did not to any degree interfere or participate during the completion of the questionnaires.

In study IV, the quality of the data might have been reduced by the retrospective data collection. For instance the retrospective nature of the data collection might have caused recall bias, i.e., patients might have had difficulty in recalling their previous experiences. Furthermore, the experience of past contacts with persons involved in the patient's care pathway might be difficult to remember, implying a risk of non-differential misclassification. The life threatening disease and the importance of each of these contacts should, however, act against such recall difficulties. The high motivation of the patients and their ability to recall past contacts with health care professionals was also objectively demonstrated by the fact that their written responses were generally thorough and complete. Another potential problem in study IV is that in the review of the medical records only the contacts documented in those records could be assessed. A number of less formal contacts were never documented, e.g., contacts with the specialist nurse during appointments with the physicians, as well as telephone booking of appointments with the physician.

Another source of information bias is the choice of cut-off for the surgeon volume, which was a particular concern in study III. Few studies have addressed surgeon volume in relation to outcomes of esophageal cancer surgery. Most

studies have focused on hospital volume. In study III, we defined low-volume surgeons as surgeons performing fewer than 5 esophageal cancer resections annually. Importantly, this cut-off was defined at the planning stage of the study, i.e., before any analyses had begun. Thus, no so called “fishing expedition” was allowed. The choice of cut-off was based on a previous study in combination with our own pre-defined choice of a clinically relevant cut-off. Birkmeyer et al¹⁰⁰ used <2 operations per year as a cut-off for low-volume surgeons, 2-6 operations as medium volume, and >6 as high-volume surgeons. Since our database was limited with regard to sample size, we finally used only one cut-off (+/- 5 operations per year). In this way, we did not compare low-volume surgeons with high-volume surgeons, but instead compared low-volume surgeons with non-low-volume surgeons, which is important to emphasize. As recorded in our study protocol, we also tested the use of two cut-offs, and assessed the volume of >10 operations annually, but we found no major differences in the results compared with the use of ≥ 5 operations, but the number of surgeons with a considerably higher volume was too small to allow valid comparisons. We therefore only used the cut-off at 5 operations annually in the final analyses.

Misclassification of the outcomes quality of life and complications is another source of error in studies I-III. The pros and cons of assessment of quality of life through the use of written questionnaires are discussed in more detail below. Since the definitions of complications were all pre-established and the assessment of such complications was made prospectively and objectively, we believe that the misclassification would be reduced. Moreover, any remaining misclassification should be non-differential, and bias the positive findings against the null, i.e., dilute any associations.

Confounding

In the SECC register, much information is collected and the data are detailed in many respects. Data regarding age, sex, tumor stage (TNM stage), histological tumor type, neoadjuvant treatment, type of surgical approach, peroperative bleeding volume, type of anastomosis, operation time, individual surgeons, and type of hospital are examples among the many data collected. This type of extensive data collection makes it possible to adjust for potential confounding by such variables as part of the analyses. The definition of a confounder is that this factor is associated both with the exposure (e.g., hospital volume in study III) and the outcome under study (e.g., complications), and is not in the causal pathway.⁹⁹ In studies II and III we adjusted for potential confounding factors in various logistic regression models (see methods section). Nevertheless, in the SECC register some possibly important confounding factors are still lacking, such as

comorbidity, alcohol intake, tobacco smoking habits, and body mass index (BMI). Squamous-cell carcinoma of the esophagus is linked with tobacco smoking and high alcohol intake,⁹ while esophageal adenocarcinoma is linked with reflux¹³ and obesity.^{15, 16} We were therefore able to adjust for histological types of esophageal cancer in order to assess indirectly any confounding by alcohol intake, tobacco smoking habits, and BMI. Since our adjustment for histological type did not materially influence the crude results, it provides some evidence against confounding by these factors. Biased influence of comorbidity remains a possibility that we could not address in the studies, however.

We aimed to avoid confounding by acute postoperative problems and tumor recurrences in the studies. The choice of one time window that we considered “stable” for the assessment of quality of life in studies I and II, i.e., six months after surgery, was carefully considered. In previous studies it was found that the quality of life had returned to a stable preoperative baseline approximately six months after esophageal cancer surgery, indicating that acute problems after surgery had subsided.^{59, 86-88} On the other hand, among patients who have undergone a macroscopically and microscopically radical resection, tumor recurrence is an unlikely cause of symptoms occurring so quickly after the operation. The vast majority of tumor recurrences after such surgery occur later, but the aggressiveness of these tumors means that most recurrences nevertheless occur within 1-2 years. In study I, we stratified for radicality by dividing the study patients into two groups, with tumors macroscopically radically resected and with those macroscopically non-radically resected, and we found that the latter patients had a considerably worse quality of life and suffered from more symptoms. These results support the finding by Zieren et al⁸⁶ that tumor recurrence is the single strongest negative factor for quality of life. Thus, to reduce the risk of influence of recurrent disease when comparing different surgery-related factors, in study II, we only included patients in whom the resection was both macroscopically and microscopically radical.

Random error

Type I error

A threat to all studies that include several analyses, i.e., multiple testing, is the occurrence of false positive findings reaching the level of statistical significance (type I error). In the studies included in this thesis, no adjustments for multiple comparisons were made. We decided at the planning stage of the studies that instead we would avoid or reduce effects of multiple testing as part of the study design. Thus, all hypotheses were formulated before any analyses were conducted,

and no analyses that were not defined in the study protocol were allowed. We also limited the number of study hypotheses to those that we considered to be of highest clinical relevance and most biologically plausible. Similarly, the categorization and models used were all predefined. Moreover, in study I we only tested for statistical significance when differences between the scores for quality of life between groups were of clinical relevance. Such a study design approach is probably the most effective means of preventing errors from multiple testing, but such errors cannot be entirely ruled out in the studies.

Type II error

In studies II and III, there was a risk that a of type II error might occur, i.e., that a statistically non-significant result would be false, and that in fact there was an association (a “false negative” finding); this is often due to a small study sample.⁹²
⁹⁹ Our comparatively large sample sizes diminished the risk of such error, however. But although the sample size in study II was larger than that in most previous studies in this field, the study had only limited power to identify weak differences in the mean scores for quality of life, indicating a need for larger studies in the future.

Testing of hypotheses

Statistical tests for significance are often over-interpreted in human research. A lack of perfectly fitting statistical models, varying sample sizes, multiple testing, and “fishing expeditions” are examples of problems that can occur in research, and thus, all results of test for statistical significance must be interpreted with caution. Other factors also need to be evaluated in any attempts to consider causality (true associations), e.g., dose-response associations, biological plausibility, strengths of any associations, time sequences, and so on. For example, dose-response effects might be more relevant than single p values.

Quality of life measurements

In clinical research on the treatment of cancer patients quality of life is an outcome measure that has been explored only to a very limited extent, despite the obvious relevance for the treated patients. As a result of the recent advances in the development of well-constructed and psychometrically valid quality of life questionnaires that are easy to use and understand, and more disease-specific, a large number of good tools are currently available. In studies I and II, the EORTC quality of life questionnaires (QLQ-C30 and QLQ-OES18) were selected. This choice was based mainly on the following reasons: 1) the core questionnaire has been developed specifically for cancer patients, 2) there is a

special esophageal-specific module, 3) the questionnaires are well validated, and 4) the use of these questionnaires throughout Europe meant that our results could be compared with findings in previous and future studies. Since the first version of the EORTC core questionnaire was introduced in 1987, it has been further developed and QLQ-C30 version 3 is the last version. During these years the questionnaire has been tested with good results for validity and reliability in several validation studies.^{55, 72-77} There is, however, a need for further improvement, especially regarding the scale of role functioning. The first version of the EORTC esophageal-specific module contained 24 questions, and after further tests of validity and reliability, the last version, QLQ-OES18, contains 18 questions. Even if the tests indicated that this questionnaire is valid, further improvement of this tool is nevertheless warranted.

The EORTC questionnaires have been found to be easy to fill in, with a time to completion of 10 to 15 minutes. In our studies, the patients' written responses were generally thorough and complete, supporting the view that the questionnaires are easy to use. The advantage of written questionnaires over structured interviews is that the patients can complete the questionnaire whenever they have time to do it, they can do it in privacy, and they can do it at their own pace, without any feeling of stress. It is important, however, that with the questionnaire or in the attached letter of information the name of a contact person is given who can be reached by telephone if the respondent has any uncertainties about the questionnaire. On the other hand, if the questionnaire is completed during a telephone interview the risk of missing values is reduced.

The most widely used format for response alternatives in quality of life questionnaires is categorical ordinal data which resemble the Likert scale, or summated rating scale,¹⁰¹ which contains a limited number of ordered responses that have a descriptive label associated with each level, e.g., 1) "Not at all", 2) "A little", 3) "Quite a bit", and 4) "Very much". The responses in a multi-item scale, i.e., a scale including several items that measure the same dimension, are summated to a score. Multiple-item scales improve reliability and allow random errors of measurement to average out.¹⁰¹ For example, if there is a scale containing five questions about physical function, and the patient by mistake marks the "wrong" response alternative in one question, this would not seriously influence the summated score. The more questions a scale contains the fewer the random errors. The EORTC questionnaires contain several multiple-item scales. Five out of the eight scales currently included in the QLQ-C30 and one of the four scales in the QLQ-OES18 contain only two items, which can introduce problems with random error. But, since the questionnaires have been thoroughly

tested for validity and reliability with promising results, this does not seem to be a serious concern.

We followed the Scoring manual⁸⁰ in all parts of the linearly transformation of the categorical ordinal data, i.e., “not at all” to “very much” (see description above), to numerical continuous data, i.e., a scale from 0 to 100. The scaling technique is based on the Likert method of summated scales. Several assumptions that might not be entirely true are made, e.g., that it is appropriate to give equal weight to each item and to grade each item on a linear interval scale. This lack of giving weight to any of the scales might rather be an advantage. The linear scale allows for comparisons more easily across scales compared to raw scores. It has been shown by Dawes et al,¹⁰² however, that such simple linear scoring systems are robust.

The use of linearly transformed scores might be difficult to interpret. For example, what does a mean score of 70 in the functional scales mean? and what is meant by a difference in mean scores of 15 between groups of patients? One way to facilitate the interpretation of the results is to report the raw scores in addition to the transformed ones. Another way is to compare the data with previously published results,⁸⁰ e.g., results for the general Swedish population⁸³ that we used in study I. Moreover, the linear scale is pragmatic and clinicians are becoming familiar with this (personal communication with Jane Blazeby). However, there are no firm scientific grounds for stating that a mean score in one scale is equal to that of another scale. The significance to patients of changes in their quality of life might be important to take into account, but again the interpretations are often hazardous. A mean score changes of 10 or more is considered by many, however, to be of clinical relevance,^{81, 82} The clinical relevance might be more important than the statistical significance in quality of life research. A change that reaches statistical significance does not necessarily imply that it has any clinical relevance. If the sample size is large, one may find a difference between two measurements that is of statistical significance, but such difference might not affect the patients. In study I, therefore, where our sample size was considerable, we only tested for statistical significance when the mean score difference was of clinical relevance.

FINDINGS, INTERPRETATIONS AND IMPLICATIONS

Study I

In study 1, the low scores in the global quality of life scale and in the function scales six months after esophageal cancer surgery are most likely explained at least to a major part by the magnitude of the surgical procedure, resulting in

considerable morbidity. Another possible explanation is recurrent disease, which is exemplified by the poor scores in the group of patients with macroscopic signs of residual cancer in the surgical specimen, but our choice of time window for the assessment of these scores should argue against such influence (see discussion above). The mean score in the global quality of life scale in our study was just as low as that found for incurable esophageal cancer patients scheduled for palliative treatment in another study,¹⁰³ but comparisons between studies are hampered by differences in study design and between populations, and it has been reported from another study that patients treated with surgery had a better quality of life than palliatively treated patients.¹⁰⁴ Nevertheless, such comparisons indicate the problems that the surgically treated patients encounter postoperatively. Among the functioning scales, scales assessing role and social functions were particularly affected among our study patients. The poor scores in these functioning scales are also likely to be closely linked with persistence of postoperative symptoms, i.e., problems with fatigue, appetite loss, diarrhea, eating, and cough. Among the general symptoms, loss of appetite severely affected the patients, and is probably explained by the extensive surgical reconstruction of the upper gastrointestinal tract. Problems with diarrhea are likely to be due to the mandatory division of the vagal nerve during surgery. As expected, among esophageal-specific symptoms, the eating scale scores were particularly high, which is probably accounted for by the need for changes in the distribution, frequency, and size of their meals. Dysphagia was not an unexpected postoperative symptom, since the stomach or bowel is never as good as a substitute as the normal esophagus. Regular contact with an experienced dietitian would seem a good recommendation to reduce eating and dysphagia problems. Use of PEG or of a nutritional jejunal catheter could further improve the nutritional status. Postoperative dysphagia is often caused by an anastomotic stricture, and is usually readily dealt with by endoscopic dilatation. Since anastomotic strictures occur rather late after the surgical procedure (most often 3 months postoperatively),¹⁰⁵ dysphagia due to such strictures might often be feared by the patients to be due to a recurrent cancer. Reflux is a well-known clinical problem in this group of patients, and is due to changes in the anatomy of the gastro-esophageal junction, including loss of function of the lower esophageal sphincter. Some limited data indicate that this problem might be prevented in some cases by a modified fundoplication during the surgical procedure.¹⁰⁶

The poor quality of life after esophageal cancer surgery must be kept in the minds of the persons who decide upon the treatment, and in situations where the surgery is highly likely to offer only palliation, the anticipated reduction in the quality of life should be a factor to be considered in the decision-making.

Moreover, some studies suggest that a poor quality of life might be a valuable predictor of a reduced chance of survival after such surgery.¹⁰⁷⁻¹¹⁰ Patients who are treated with a curative intent might accept a reduction in their quality of life, since the principle aim of their treatment is cure, while among patients who can only be offered palliation, any improvement of the quality of life is the main goal of the treatment.⁸¹ Nevertheless, the results of this study strongly point to the need to consider any preventive actions during surgery that might increase the chances of a relatively improved quality of life, e.g., operations by high-volume surgeons,¹⁰⁰ an antireflux procedure,¹⁰⁶ and use of jejunal catheters.^{111, 112} There are also several possible early interventions that might be more relevant and are easy to perform. Information given to the patients before surgery might be one key factor to facilitate and speed up intervention actions. Moreover, the patients might benefit from contact with a specialist nurse during the care pathway for support and to facilitate early interventions.¹¹³⁻¹¹⁵ Furthermore, any measures that can prevent the occurrence of postoperative complications can reduce the negative impact of esophageal cancer surgery on the quality of life.¹¹⁶ It has also been suggested that the development of minimally invasive surgery might result in less severe postoperative problems.¹¹⁷

Study II

The occurrence of major surgery-related complications seems to considerably reduce the quality of life as assessed six months after esophageal cancer surgery. The obvious conclusion from this finding is that complications should be avoided as far as possible, but it is similarly obvious that the surgeons already do their best to prevent such complications. Possibly, however, the mere knowledge of this finding may in some way help to remind the surgeons to make every effort to carry out the surgery as safely as possible. Surgeon volume is another objective factor that needs to be considered in the future surgical treatment of these patients.¹⁰⁰ But it is notable that several potentially relevant factors during surgery did not appear to have a detrimental effect on the subsequent quality of life. It is particularly interesting that a more extensive lymph node dissection or longer operation time did not have a negative influence on the assessed postoperative quality of life. However, there are probably many other surgery-related factors that might be relevant to consider in the prevention of impairment of the quality of life after esophageal cancer surgery. This study, therefore, needs to be followed by several others. The limited statistical power of this study also emphasizes the need for collaborative research. In a randomized study the possible differences between neck and chest anastomoses after esophageal cancer resection were addressed. Although these appear to be equally safe, the limited

additional esophageal resection in the neck group did not increase the tumor removal or survival.¹¹⁸ Since some data indicate more problems with reflux in patients with neck anastomoses,¹¹⁹ one additional possible surgical intervention might be to avoid neck anastomoses, if not required.

The high frequency of severe complications together with the low short-term mortality rate observed in the current studies shows that the management of such complications is usually successful regarding survival alone, but study II underlines the fact that quality of life is another important outcome to be considered.

Study III

The frequency of complications observed in this study was higher than that in most previous reports (26-41%),¹ possibly as a result of selection bias in studies that are not population-based. Several studies have shown that factors that reduce short-term mortality after esophageal cancer resection are a high hospital volume and high surgeon volume,¹²⁰⁻¹²³ and that surgeon volume had a greater impact.¹⁰⁰ In line with this finding, our study indicates that the surgeon volume was more important than the hospital volume with regard to anastomotic leakage. We found no decreased risk of overall complications at university hospitals compared to non-university hospitals, however. This might be due to selection bias, in that in Sweden, operations requiring extensive dissection and advanced reconstructions are usually carried out at university hospitals, and such procedures more frequently entail complications, compared to less advanced cases that can be operated on at smaller hospitals. Moreover, patients with more comorbidity might more readily be selected for surgery at university hospitals than at smaller hospitals. Such selection bias might explain the lack of improvement of short-term results with regard to occurrence of complications at university hospitals in our study.

Our study suggests that transthoracic esophageal surgery is associated with an increased risk of respiratory complications compared to a transhiatal (abdominal only) approach, a finding in line with previous results.¹²⁴ However, there might be a survival advantage in the transthoracic group that cannot be neglected,¹²⁴ and the only way to perform an optimal radical tumor dissection with the intention to cure in the case of esophageal cancer includes a transthoracic approach.¹²⁵ Hence, the increased risk of respiratory complications should not prevent the use of a transthoracic approach whenever this procedure is possible and the surgery has a curative intent. For palliative resections, however, this increased risk of complications should be taken into consideration.

To further improve the patients' quality of life, all possible means of counteracting complications are warranted.

Study IV

The results from this study indicate that a specialist nurse with supportive and coordinating functions is a valuable complement in the care of patients with esophageal cancer. Previous studies of the support provided by a specialist nurse in the care pathway for patients with esophageal cancer are lacking, but similar functions for patients with some other cancer types have been evaluated with positive results.¹²⁶ In agreement with our results, the contribution of specialist nurses has been reported to be essential to the process of coordination of the treatment of cancer, and nurse-led services for cancer patients may ensure high-quality care and improve patient experiences.¹²⁷ Close collaboration with all health care professionals participating in the care pathway is a basic prerequisite, particularly with the physicians.

Interestingly, in our study information given by the specialist nurse was considered by some patients to be easier to understand than that given by the physicians. Our results support previous observations that patients with a newly diagnosed cancer,^{69, 128} as well as patients with advanced tumors,¹²⁹ have a substantial need for information about disease-specific issues as well as extra written information that can well be given by a specialist nurse.¹²⁹ Additional or repeated information is possibly even better given by the nurse than by the physicians. The built-up confidence between the specialist nurse and the patient should facilitate their communication, and the specialist nurse might have more time for the patients.

Contacts regarding nutritional difficulties predominated among patients with esophageal cancer, a finding indicating that specialist nurses should develop specific skills that fit well with the specific needs for supportive care in particular types of cancer. The unique tasks of these nurses for specific diseases should be developed on the basis of future research. Specialist nurses might be of particular relevance for patients with esophageal cancer in view of the complexity of the diagnostic procedures, the extensive surgical treatment, and the reduced quality of life after surgery, as well as the poor prognosis in these cancers. A specialist nurse who supports the patients in different ways should be of considerable comfort for these suffering patients and can maintain the efficiency of the care pathway.

CONCLUSIONS

Patients who undergo esophageal cancer resection suffer greatly from impairment of their quality of life and several general and esophageal-specific symptoms six months postoperatively.

Occurrence of surgery-related complications is a major predictor of reduced quality of life six months after esophageal cancer resection.

Esophageal cancer surgery conducted by low-volume surgeons increases the risk of the severe complication anastomotic leakage.

A specialist nurse with supportive and coordinating functions is a valuable complement in the care of patients with esophageal cancer.

FUTURE RESEARCH

The results from these studies point to a need for more focused research on quality of life to address specific risk factors associated with esophageal cancer surgery that it might be possible to prevent. Studies with larger sample sizes that have the statistical power to detect moderate or weak risk factors would be valuable, since even less strong associations might be of clinical importance. Moreover, prospective and longitudinal follow-up of quality of life and symptoms in large registers are warranted. One important aim of such an approach would be to identify differences between short-term symptoms and long-term effects with chronic symptoms. By identifying risk factors for reduction of quality of life and for short-term and long-term problems, it might be possible to avoid such factors through preventive actions and early interventions.

Specialist nurses with a supportive and coordinating function seem to be of importance for esophageal cancer patients, but more studies are warranted to develop this type of function, and extensive disease-specific knowledge is needed to further improve this role. In addition, a randomized study in which patients in one arm receive the support of a specialist nurse and those in the other arm have the traditional contacts with the health care system would allow a more valid assessment of the function.

In general, further development of the scientific methods in quality of life research would be of interest. For example, written questionnaires could be extended to the use of personal interviews, preferably conducted by unbiased, professional interviewers. Furthermore, it would be interesting to conduct validation studies using more objective measurements to compare with the data collected, e.g., estimation of eating problems by endoscopy and radiologic time barium swallow examination, or assessment of reflux by 24-hour pH measurements. The area of research that uses quality of life or symptoms as the outcome under study is probably only in the beginning of a long era of further development and improvement.

POPULÄRVETENSKAPLIG SAMMANFATTNING (POPULAR-SCIENTIFIC SUMMARY IN SWEDISH)

BAKGRUND

Cancer i matstrupe (esofagus) och övre magmun (cardia) är relativt ovanligt i västvärlden. Dessa tumörer har många likheter och behandlas likartat, varför övre magmuncancer i fortsättningen införlivas i begreppet matstrupscancer. Årligen drabbas sammanlagt cirka 620 personer i Sverige. Antalet insjuknande i adenocarcinom (körtelcancer) i matstrupen har under de senaste decennierna ökat snabbt i USA och Europa, inklusive Sverige. Med en 5-årsöverlevnad i hela diagnosgruppen på endast 5-15 % i Europas länder är prognosen sämre än för de flesta tumörsjukdomar. De dominerande symtomen är sväljningssvårigheter och viktnedgång vilka oftast uppkommer sent i sjukdomsförloppet. Den enda etablerade och dokumenterade behandling som kan leda till bot är radikal operation, men även majoriteten av de opererade patienterna avlider i sin sjukdom (31 % 5-årsöverlevnad). Operationen tillhör de mest avancerade och påfrestande ingrepp som överhuvudtaget genomförs, vilket avspeglas i att den efterföljs av en komplikationsfrekvens på hela 30-50 % och en dödlighet inom 30 dagar på 5-15 %. Standardingreppet innebär som regel en hel dags omfattande operation i både bukhåla och brösthåla och ibland även på halsen vid ett och samma tillfälle. Vårdkedjan för denna patientgrupp är dessutom ovanligt komplicerad. Tidigare forskning avseende resultat efter matstrupscanceroperation har fokuserat på överlevnad, medan livskvalitet och stödbehov efter en sådan operation är påtagligt bristfälligt studerade. Denna avhandling fokuserar främst på situationen för patienter som opererats för matstrupscancer. Avhandlingen belyser livskvalitet och kvarstående symtom, vilka faktorer som kan påverka livskvaliteten samt patienternas behov av stöd. Huvudsyftet är att finna vägar som kan förbättra livssituationen för denna utsatta patientgrupp.

METODER

Avhandlingen är uppbyggd kring fyra delarbeten (vetenskapliga uppsatser). I delarbete I, II och III, användes data från Svenska Esofagus- och CardiaCancerregistret (SECC-registret) där nästan alla patienter som opererats för matstrupscancer är registrerade. I SECC-registret insamlas fortlöpande uppgifter om patient- och tumörkaraktistika, operationer, operatörer, komplikationer och vårdtid sedan den 2 april 2001. Medicinska journaler, operationsjournaler, tumörpreparatsvar, och intensivvårdsjournaler granskades av SECC-registrets

medlemmar (däribland jag). Mätning av livskvalitet och olika symtom gjordes sex månader efter operationen, en tidpunkt som valdes för att akuta problem då som regel är överståndna samtidigt som inverkan av tumöråterfall är osannolik. Patienterna besvarade två väl utprovade skriftliga livskvalitetsenkäter, utarbetade av en europeisk cancerorganisation (European Organisation for Research and Treatment of Cancer = EORTC). En enkät mätte allmän livskvalitet och generella symptom (QLQ-C30) och en mätte matstrupsspecifika symptom (QLQ-OES18). Patienternas svar omvandlades till poäng på en skala mellan 0 och 100. I delarbete I definierades, i enlighet med tidigare forskning, en poängskillnad på minst 10 som kliniskt betydelsefull. Genomsnittlig livskvalitetspoäng analyserades och jämfördes med enkätsvaren från en svensk normalbefolkning. I delarbete II bestämdes en jämförelsekategori (referenskategori) för varje variabel som studerades (t.ex. blödning, operationstid och komplikationer). Ett statistiskt test (Mann-Whitney) användes för att undersöka om övriga kategorier i variabeln avvек från jämförelsekategorin på ett statistiskt signifikant sätt eller inte (statistiskt signifikanta p-värden). Resultaten justerades dessutom för effekter av möjliga störfaktorer (confounders) som ålder, kön och tumörstadium i en mer avancerad analys. I delarbete III studerades faktorer som kunde påverka risken för förutbestämda komplikationer hos opererade patienter. En analysmetod, s.k. logistisk regressionsanalys, användes för att beräkna relativ risk (odds ratio) för komplikationer med 95 % konfidensintervall (KI). Resultaten justerades, dels i en basmodell för ålder, kön och tumörstadium, och dels i en mer omfattande modell för en rad möjliga störfaktorer för att renodla effekter av den studerade faktorn. I delarbete IV studerades specialistsjuksköterskans roll för patienterna utgående från tre aspekter: patienternas upplevelse av stöd, patienternas upplevelse av sjuksköterskans funktioner samt patienternas dokumenterade omvårdnadsbehov. Alla patienter med cancer i övre mag-tarmkanalen som varit i kontakt med specialistsjuksköterskan på Kirurgiska kliniken på Karolinska Universitetssjukhuset, Solna fick besvara två studiespecifika enkäter. En första enkät utvärderade patienternas upplevelse av stöd från olika personalkategorier, dvs. specialistsjuksköterska, läkare, avdelningspersonal och mottagningspersonal under tre olika faser i vårdkedjan: utredning, behandling och uppföljning. En uppföljande enkät utvärderade specifikt specialistsjuksköterskans funktion. Den tredje delen av datainsamlingen utfördes för att kartlägga patienternas dokumenterade omvårdnadsbehov och detta skedde via journalgranskning av alla patienter med matstrups- eller magsäckscancer som varit i kontakt med specialistsjuksköterskan.

RESULTAT

Delarbete I: Patienter som genomgått operation för matstrupscancer lider av starkt nedsatt livskvalitet och allmänna och matstrupsspecifika symtom fortfarande sex månader efter operationen. Den allmänna livskvaliteten var klart nedsatt jämfört men en normal svensk befolkning. De mest påverkade funktionerna gällde arbete och fritids samt social funktion. De i jämförelse med jämförelsebefolkningen mest dominerande generella symtomen var utmattning/trötthet, aptitlöshet, diarré och andnöd, alla med både kliniskt relevanta och statistiskt signifikanta skillnader. Problem att äta, hosta, reflux, matstrupssmärta och torr mun var de vanligaste matstrupsspecifika symtomen efter operationen.

Delarbete II: Förekomst av komplikationer efter operationen var den faktor som starkast påverkade livskvaliteten negativt ($p=0,03$). Komplikationer som innan studien hade definierats som kliniskt betydande (reoperation, läckage i skarven mellan matstrupsrest och matstrupens ersättningsorgan, djup infektion, andningssvikt, hjärt- eller blodkärlskomplikationer och kirurgtekniska komplikationer) bidrog alla till denna livskvalitetsnedsättning. Patienter vars matstrupe ersatts med tarm hade mindre besvär av att vätska rann upp mot munnen (reflux) än de där magsäcken använts ($p=0,04$). Grad av kirurgisk radikalitet, operationstid eller blödning under operationen påverkade inte livskvaliteten statistiskt signifikant. Ingen inverkan av tumörens läge, typ eller stadium, eller patientens kön eller ålder påvisades.

Delarbete III: Nästan hälften (44 %) av de patienter som opererades för matstrupscancer fick minst en allvarlig komplikation. Patienter som opererades av kirurger som opererade få patienter (<5 operationer/år) hade en nästan 8 gånger ökad risk för läckage i skarven mellan matstrupsrest och dess ersättningsorgan jämfört med kirurger som opererade fler patienter (≥ 5 operationer/år) (odds ratio 7.9, 95 % KI 2.1-29.0). Ingen skillnad i risk för skarvläckage påvisades mellan handsydd och maskinsydd (staplade) skarvar. Patienter med övre magmuncancer som opererades via både bukhåla och bröstorg (transthorakalt) hade högre risk för andningsrelaterade komplikationer jämfört med dem som enbart opererades via buksnitt (transhiatalt) (odds ratio 4.8, 95 % KI 1.7-13.8). Hög ålder, tilläggsbehandling med strålning och cytostatika, och större blödningsmängd under operation medförde en antytt ökad risk för komplikationer, men dessa resultat nådde inte statistisk signifikans. Ingen inverkan av kön eller tumörstadium identifierades.

Delarbete IV: Stöd som ges av en specialistsjuksköterska med samordnings- och stödfunktion värderades av patienterna som både tillfredsställande och mycket viktigt genom hela vårdkedjan, speciellt i uppföljningsfasen efter behandling, jämfört med andra personalkategorier. Medan 10 % hade svårt att förstå information från läkaren hade inga patienter problem att förstå information given av specialistsjuksköterskan. Dokumenterade kontakter var vanligast under uppföljningsfasen och nutritionsproblem var den dominerande kontaktorsaken hos patienter med matstrups- eller magsäckscancer.

SLUTSATSER

Matstrupscancerpatienter som genomgår en stor matstrupsoperation lider av avsevärt nedsatt livskvalitet och flertalet generella och matstrupsspecifika symtom fortfarande sex månader efter operationen. Förekomst av komplikationer efter matstrupscanceroperation är den starkast negativa operationsrelaterade faktorn för nedsatt livskvalitet. Operationer utförda av kirurger med låg mängd operationer verkar öka risken för läckage i skarven mellan matstrupsrest och matstrupens ersättningsorgan. Specialistsjuksköterskor med samordnings- och stödfunktion kan rekommenderas som kontaktsjuksköterskor för patienter med cancer i övre mag-tarmkanalen samt som koordinatörer av deras vårdkedja.

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