

Aspects on the Management of Patients with Esophageal Cancer

Henrik Bergquist

GU LOGGAN

**Department of Otorhinolaryngology, Head and Neck Surgery,
the Sahlgrenska Academy, Göteborg University, Sweden**

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Correspondence to:

Dr Henrik Bergquist
Department of Otorhinolaryngology / Head & Neck Surgery
Sahlgrenska University Hospital
SE- 413 45 Göteborg, Sweden
henrik.bergquist@vgregion.se

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*To my grandfathers for inspiring me to become a doctor,
to my parents, my brother and sisters for supporting me in doing so,
and finally, and most importantly, to my wife Philippa,
my solid rock and love.*

Abstract

Cancer of the esophagus is the 8th most common cancer form in the world, with approximately 460.000 new cases annually. It is often diagnosed at a late stage, associated with severe morbidity and a poor prognosis, why treatment frequently has a palliative aim to control the main symptom, i.e. dysphagia. The present thesis aims to explore some of the questions related to and eventually improving the management of these patients.

The two most common palliative strategies today, i.e. stent-treatment and brachytherapy, were compared in a randomised trial enrolling 65 patients with incurable cancer of the esophagus or gastro-esophageal junction (GEJ). Stent-treatment was found to offer a more prompt effect on dysphagia and was more cost-effective than brachytherapy. On the other hand, brachytherapy offered a less pronounced deterioration of health-related quality of life (HRQL) and an equal relief of dysphagia after 3 months, why it gives a viable alternative in patients with a longer survival (Paper I+II).

To evaluate if survival can be better predicted, 96 patients with newly diagnosed incurable cancer of the esophagus or GEJ were included and their clinical variables and HRQL data analyzed. In a univariate analysis, Karnofsky Index, M-stage, tumor-stage, CT derived size assessment of the primary tumor and 10 of 25 scales and items of the HRQL questionnaires (EORTC QLQ-C30 and QLQ-OES18) were found to relate to survival. However, in a multivariate analysis, only M-stage, physical functioning, fatigue and reflux scale were found to be independent predictors. Internal validation of the established predictors showed a high level of reliability (Paper III).

Psychiatric morbidity in patients with cancer of the esophagus or GEJ was screened at diagnosis and during one year thereafter. We observed anxiety disorder and depression in 94 patients in all stages of the disease using the HADS questionnaire. Anxiety and/or depression were found to be common at diagnosis (42% of the patients), regardless of sociodemographic background, tumor-stage or therapy given. The proportion of patients with anxiety disorder decreased during the first two months compared to at diagnosis (34%), while the proportion of patients with depression was comparatively stable over time (29% at diagnosis). Depression was, however, more common among patients who died during the study period compared to the survivors (Paper IV).

The long-term clinical and functional outcomes of radical surgery with pharyngolaryngoesophagectomy and jejunal transposition following chemoradiotherapy in patients with proximal esophageal or hypopharyngeal cancer were evaluated. Promising long-term results with regard to survival were observed. In addition, a generally good HRQL and mild dysphagia was found, in spite of a generally poor speech valve function and disturbed bolus-passage according to radiological evaluation (Paper V+VI).

Key words: brachytherapy, dysphagia, esophageal neoplasms, free jejunal graft, health economic evaluation, palliative care, prediction, psychiatric morbidity, radiographic evaluation, stent, survival, quality of life, voice prosthesis.

List of papers

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

- I. Bergquist H, Wenger U, Johnsson E, Nyman J, Ejnell H, Hammerlid E, Lundell L and Ruth M.
Stent insertion or endoluminal brachytherapy as palliation of patients with advanced cancer of the esophagus and gastroesophageal junction. Results of a randomized, controlled clinical trial.
Diseases of the Esophagus. 2005;18(3):131-9.
- II. Wenger U, Johnsson E, Bergquist H, Nyman J, Ejnell H, Lagergren J, Ruth M and Lundell L.
Health economic evaluation of stent or endoluminal brachytherapy as a palliative strategy in patients with incurable cancer of the oesophagus or gastro-oesophageal junction: results of a randomized clinical trial.
European Journal of Gastroenterology and Hepatology. 2005 Dec;17(12):1369-77.
- III. Bergquist H, Johnsson Å, Hammerlid E, Wenger U, Lundell L and Ruth M.
Factors predicting survival in patients with advanced esophageal cancer – a prospective multicenter evaluation.
Submitted Alimentary Pharmacology & Therapeutics.
- IV. Bergquist H, Ruth M and Hammerlid E.
Psychiatric morbidity among patients with cancer of the esophagus or the gastro-esophageal junction – a prospective, longitudinal evaluation.
Accepted for publication Diseases of the Esophagus.
- V. Bergquist H, Ejnell H, Fogdestam I, Mark H, Mercke C, Lundell L and Ruth M.
Functional long-term outcome of a free jejunal transplant reconstruction following chemoradiotherapy and radical resection for hypopharyngeal and proximal oesophageal carcinoma.
Digestive Surgery 2004;21(5-6):426-31.
- VI. Bergquist H, Andersson M, Ejnell H, Hellström M, Lundell L and Ruth M.
Functional and radiological evaluation of free jejunal transplant reconstructions after radical resection of hypopharyngeal or proximal esophageal cancer.
Accepted for publication World Journal of Surgery.

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Abbreviations

AJCC	American Joint Committee on Cancer
CI	Confidence Interval
CT	Computer Tomography
EORTC	European Organisation for Research and Treatment of Cancer
EUS	Endoscopic Ultrasound
GEJ	Gastro-Esophageal Junction
GERD	Gastro-Esophageal Reflux Disease
Gy	Gray
HADS	Hospital Anxiety and Depression Scale
HDR	High Dose Rate
HPV	Human Papilloma Virus
HRQL	Health Related Quality of Life
ITT	Intention-To-Treat
KPSSI/KPS	Karnofsky Performance Status Scale Index
LES	Lower Esophageal Sphincter
MRI	Magnetic Resonance Imaging
PEJ	Pharyngo-Esophageal Junction
PET	Positron Emission Tomography
PLE	Pharyngo-Laryngo-Esophagectomy
PP	Per-Protocol
SEMS	Self-expandable Metal Stent
SD	Standard Deviation
TNM	Tumor, Node, Metastases
QoL	Quality of Life
QLQ-C30	Quality of Life Questionnaire-Core 30
QLQ-OES18	Quality of Life Questionnaire-Oesophageal module 18
UICC	Union Internationale Contre le Cancer
WDS	Watson Dysphagia Score

Introduction

Cancer is the Latin word for crab. The word has been used to depict malignancy since ancient times, possibly because of the crab-like persistence a malignant tumor sometimes shows in grasping the tissues it invades, or because of the form of some cancerous lesions that actually reminds of the form of a crab. Hippocrates (Figure 1), who described cancer in detail, used the Greek terms "*carcinos*" and "*carcinoma*" to refer to chronic ulcers or growths that seemed to be malignant tumors¹. Later on, a Roman physician by the name Celsus (28 BC - 50 AC) translated the Greek word "*carcinos*" into the word "*cancer*". Hence, the word "*cancer*" is very old. However, it is used for a large number of different diseases with a variety of etiologies and appearances that require different cares and treatments.

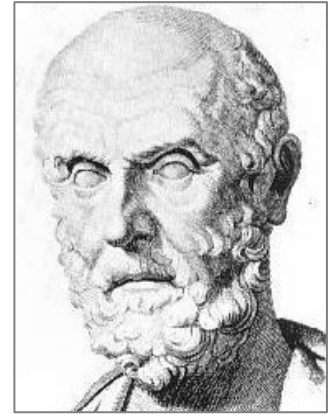


Figure 1. Hippocrates (460-370 BC)

That cancer can emerge also in the esophagus has been known since centuries and was recognized as a cause of dysphagia by the Chinese about 2000 years ago². Surgical treatment of esophageal cancer has been performed since the end of the 19th century, and initially, the goal was mainly to achieve palliation through “by-passing” the site of the tumor so that nutrition could be preserved. More sophisticated methods were developed during the 20th century, also aiming at eradicating the tumor burden and finding suitable substitutes for the removed part of the esophagus. Several prominent surgeons have contributed to this progress, among those Dr César Roux (1857-1934) who in 1906 described the use of the jejunum as a replacement for the esophagus³ and Dr Iwor Lewis (1895-1982) who in 1948 described gastric mobilization and jejunostomy followed by a right thoracotomy and immediate anastomosis as a one stage procedure⁴.

The advancement within the oncological field has resulted in chemo- and radiotherapy as optional treatment strategies for cancer of the esophagus or in addition to surgery. Radiation therapy has been practiced in cancer treatment ever since Wilhelm Conrad Röntgen (1845-1923) discovered the x-rays in 1895, and the modern era of chemotherapy can be traced back to the discovery of nitrogen mustard during World War II⁵. During the last decades, development of new cytotoxic agents as well as modification of radiation schedules, e.g. hyperfractionation, with better tumor-specific distinctiveness and milder side effects, have greatly contributed to a wider use in esophageal cancer treatment. The start of use of high dose rate (HDR) endoluminal brachytherapy in the end of the 1980s has resulted in an optional treatment strategy for palliation of these patients⁶. Self-expandable metal stents (SEMS) became commercially available in the beginning of the 1990s and has revolutionized the treatment of malignant strictures within the esophagus⁷.

Nevertheless, in spite of this progress, esophageal cancer is still often diagnosed at a much too late stage, is related to severe morbidity and a poor prognosis with an overall 5-year survival rate between 10 and 15%⁸. In the majority of cases, distant metastases are already present at diagnosis and, as a consequence, palliative treatment is the only option available⁹. Hence, much effort still has to be done to improve the situation for these patients.

Epidemiology and risk factors

Today, cancer of the esophagus is assessed to be the 8th most common cancer form in the world, with approximately 460.000 new cases annually¹⁰. The incidence varies between different geographical regions, with especially high rates in Asia, Africa and South-America, and in some parts the rates are as high as 200

per 100.000 inhabitants and year. For Western Europe and Northern America, the incidence rates are around 5-10 per 100.000, with prevalence rates close to this number indicating a short survival time after diagnosis. Globally, esophageal cancer is the sixth cause of cancer-related death¹⁰.

There are mainly two different types of esophageal cancer, i.e. adenocarcinoma and squamous cell carcinoma, and even though they share many characteristics, the risk factors for the two types have proved to be rather diverse. Adenocarcinoma of the esophagus and the gastro-esophageal junction (GEJ) has demonstrated a rapid increase in incidence during the last decades, especially among white males within Western Europe and Northern America¹¹. The reasons for this are still ambiguous, however, a connection to an increased prevalence of known risk factors such as gastro-esophageal reflux-disease (GERD), Barrett's esophagus and obesity has been proposed^{9,12,13}. Furthermore, the reduced prevalence of *Helicobacter pylori* infections (mainly due to medical eradication therapy), as well as an augmented use of medications that affect the tonus of the lower esophageal sphincter (LES) (e.g. anticholinergics and benzodiazepines), have been suggested as potential causes of an increased incidence of esophageal adenocarcinoma⁹. The observed male predominance is, however, not explained by these hypotheses.

Squamous cell carcinoma of the esophagus, on the other hand, has demonstrated relatively stable incidence rates within most geographical regions during the last decades and, what is more, a tendency towards declining rates has been reported for several countries including Sweden during the last few years¹⁴. Established risk factors for this type of cancer are smoking, excessive alcohol consumption, dietary factors, low socioeconomic status and a previous history of head-and-neck cancer⁹. Moreover, a recent field of investigation is the association between human papilloma virus (HPV) infections and squamous cell cancer of the esophagus. However, high risk HPV-types detection rates are greatly variable in different geographical areas of the world and may have a conjunction with socioeconomic status¹⁵. As for adenocarcinoma and many other cancer forms, high age is a risk factor also for squamous cell carcinoma of the esophagus. In addition, esophageal cancer is three times more common in men than in women¹⁶.

Symptoms, diagnosis and staging

Approximately 90% of patients with esophageal cancer present with dysphagia⁹. Many patients also have a history of weight loss, anemia, and/or retrosternal pain, while hoarseness and dyspnea may be a sign of overgrowth to adjacent structures. Frequently, symptoms have been present for 6 months or more, possibly due to a poor awareness among the general population of dysphagia as a symptom of a potentially lethal disease¹⁷. Endoscopy with biopsy for histological examination verifies the diagnosis and computerized tomography (CT) scans of the neck, thorax and abdomen, endoscopic ultrasound examination (EUS) and in some cases bronchoscopy and/ or laparoscopy of the abdomen are part of the staging procedure. Determination of the exact length, invasiveness and localization of the tumor is important for a correct decision upon treatment-strategy (Figure 2)¹⁸.

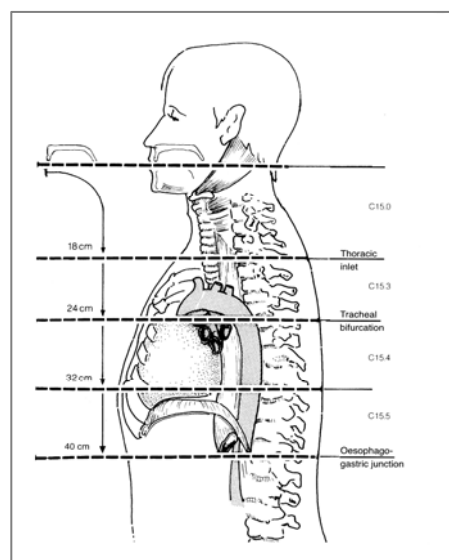


Figure 2. Localization of esophageal cancer (UICC, TNM Atlas, 5th ed, 2004).

Table 1a. TNM classification of esophageal cancer (*UICC, TNM Classification of Malignant Tumors, 6th ed, 2002*).

Primary tumor (T-stage)	
T _x	Primary tumor can not be assessed
T ₀	No evidence of primary tumor
T _{is}	Carcinoma in situ
T ₁	Tumor invades lamina propria or submucosa
T ₂	Tumor invades muscularis propria
T ₃	Tumor invades adventitia
T ₄	Tumor invades adjacent structures
Regional lymph nodes (N-stage)	
N _x	Regional lymph nodes can not be assessed
N ₀	No regional lymph node metastasis
N ₁	Regional lymph node metastasis
Distant metastases (M-stage)	
M _x	Distant metastases can not be assessed
M ₀	No distant metastases
M ₁	Distant metastasis

Table 1b. Staging of esophageal cancer (*UICC, TNM Classification of Malignant Tumors, 6th ed, 2002*).

UICC-stage	T	N	M
Stage 0	T _{is}	N ₀	M ₀
Stage I	T ₁	N ₀	M ₀
Stage IIA	T ₂ T ₃	N ₀ N ₀	M ₀ M ₀
Stage IIB	T ₁ T ₂	N ₁ N ₁	M ₀ M ₀
Stage III	T ₃ T ₄	N ₁ N _{x-1}	M ₀ M ₀
Stage IVA	T ₁₋₄	N _{x-1}	M _{1a}
Stage IVB	T ₁₋₄	N _{x-1}	M _{1b}

Staging is performed according to the TNM-classification and the UICC (Union Internationale Contre le Cancer) or AJCC (American Joint Committee on Cancer) staging system (Table 1a+b)¹⁹. For T- and N-stage, EUS has proved to be the most reliable staging technique to date, with an accuracy between 80 and 90%²⁰. However, the development of other non-invasive staging modalities, such as high-resolution CT, magnetic resonance imaging (MRI) and positron emission tomography (PET) may result in a diminishing use of EUS as a staging-tool for esophageal cancer. Although the TNM-staging has many values and is currently considered “the golden standard” for classification of esophageal cancer, its reliability as a predictor for survival has repeatedly been questioned^{21,22}. Whether this eventually will result in a novel classification system with better clinical implications is, however, a matter of speculation.

Treatment with a curative intent

Patients without metastases or tumor-invasion into adjacent structures (T₁₋₃N_{x-1}M₀) are normally offered treatment with a curative intent. Giving that sufficient outcomes on a bicycle exercise test and a spirometry test have been achieved, this treatment typically consists of radical surgery including lymphadenoidectomy with or without preoperative chemoradiotherapy⁹. Depending on the tumor-location, different surgical approaches are practiced. Tumors of the proximal intrathoracic or mid-thoracic part of the esophagus can be handled by total esophagectomy including thoracotomy and substitution with gastric tubularization or colonic transposition.

Distal tumors including the GEJ are usually treated by partial esophagectomy, including substitution with gastric tubularization or by an esophago-jejunostomy (Roux-en-Y). The latter intervention is mainly used for cancers of the GEJ type III (subcardial)²³ and often performed by a transhiatal approach²³. Although survival rates are

unsatisfactory even after curatively intended therapy, recent data suggest an improvement for both histological types for Sweden in the last few years. For adenocarcinoma, the 5-year relative survival rate during 1990-96 was 13.7%, while the corresponding figure for squamous cell carcinoma was 8.9%²⁴. A better selection of surgical candidates, as well as an enhancement of the entire treatment arsenal including the surgical procedures, has been emphasized as potential explanations to this trend.

Palliative treatment

Palliation is the primary aim in the majority of patients with advanced cancer of the esophagus and the GEJ. However, as these patients have a complex symptomatology, multiple aspects have to be considered to comprehensively address the patient’s overall situation^{6,7}. The relief of dysphagia, with a minimum of side

effects and interventions, is an objective of high priority and a variety of palliative procedures have been advocated. Endoscopic placement of SEMS (Figure 3) has become the most widely practiced treatment, in part due to the comparatively simple technique and rapid effect on dysphagia^{7,25}. Complications are reasonably infrequent and mainly consist of stent-migration, food impaction, perforations and fistulae²⁶. Stent occlusion, due to tumor or granulation tissue growth, is, however, a matter of concern and re-intervention rates has been described in as much as 27% of patients²⁷. Endoluminal brachytherapy (Figure 4) is an alternative with some promising results²⁸, but requires access to rather sophisticated equipment, e.g. a radiation source, and is normally available at high-volume centers only²⁹. A drawback for laser therapy as a palliative regime has been the transitory effect on dysphagia and need for repeated interventions³⁰, whereas photodynamic therapy (PDT) is rather costly and associated with side effects such as photosensitivity³¹. The use of external radiotherapy alone or in combination with chemotherapy has been questioned due to the delay in relief of dysphagia and severe side effects⁶.

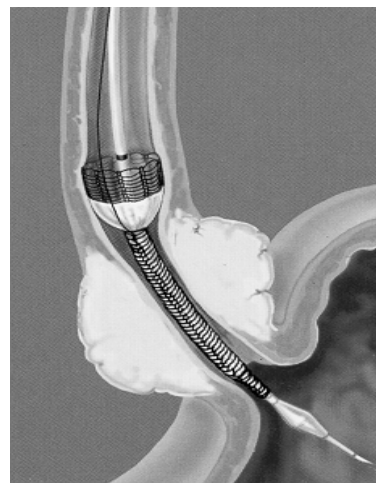


Figure 3. Self-expandable metal stent (SEMS).

Aspects on patient's quality of life may be considered to be of special importance when the treatment regime is strictly palliative. Apart from the direct effects of the dysphagia-relieving interventions, such factors as pain therapy, nutritional support and psychological care from both health care providers and family members are important to the quality of the patient's remaining life. In recent years, health-related quality of life (HRQL) questionnaires have been developed to enable longitudinal evaluation of patient's quality of life during and after treatment for cancer³², including patients with esophageal cancer³³. The value of utilizing these instruments, not only for aims of research but also as a tool in clinical practice, has been emphasized by many³⁴⁻³⁷. Another topic of interest, especially when considering treatment strategies with similar clinical outcomes, is the health economic consequences. There is a constant need for controlled randomized clinical trials, including all these aspects, to offer guidance for the clinician in the choice between various palliative therapeutic modalities³⁸.

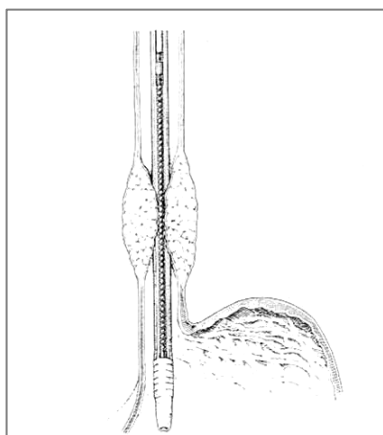


Figure 4. High-dose rate (HDR) brachytherapy.

Cancer of the pharyngo-esophageal junction

Cancer of the hypopharynx and the proximal part of the esophagus are often considered together due to their equivalent clinical characteristics and therapeutic problems. Histologically, in the vast majority of cases, they are both squamous cell carcinomas and also share the same main risk factors, i.e. excessive alcohol consumption and smoking⁹. Rather frequently, cancer is present at both sites either due to continuous overgrowth or due to two synchronous primary tumors. Hence, cancer of the hypopharynx and the proximal part of the esophagus are often referred to as cancer of the pharyngo-esophageal junction (PEJ)³⁹.

For patients with non-disseminated disease, radical surgical intervention with or without the addition of chemoradiotherapy is to date considered the first line of treatment by many⁴⁰⁻⁴³. Nevertheless, surgical treatment of patients with cancer of the PEJ remains a great challenge and several different techniques have

been applied throughout the years, including the use of myocutaneous flaps, colon transposition and reversed gastric tubes^{40,43-49}. Circumferential pharyngo-laryngo-esophagectomy (PLE) and reconstruction with a free vascularized jejunal transplant has gained a wide acceptance world-wide, in part due to improvements in the microsurgical technique, an acceptable procedure-related morbidity and mortality and in many cases a promising functional long-term outcome^{41,43,45,46,50,51}.

Non-surgical treatment of these patients, such as chemoradiotherapy alone, may be associated with several disadvantages such as; severe toxicity, insufficient eradication of the primary tumor, a high rate of tumor recurrence, persisting dysphagia and no survival gain^{52,53}. By-pass surgery as an option for palliation, associated with high rates of perioperative mortality and morbidity⁶, has to a great extent been replaced by stent placement. Although complications and technical difficulties exist also for the latter strategy, recent studies report encouraging results⁵⁴⁻⁵⁶. However, the majority of studies performed on patients with cancer of the PEJ are retrospective analyses consisting of a broad mixture of different tumor-sites, tumor-stages and therapeutic interventions (Table 2). Consequently, as long as no results from randomized controlled trials between various treatment options for these patients exist, it is difficult to emphasize the superiority of one regime compared to the other.

Table 2. Retrospective studies presenting results after pharyngo-laryngo-esophagectomy (PLE) and reconstruction with a visceral interposition.

Ref	No pat	Main Site	Reconstruction	C/RT	Postop mortality	Graft failure	Strictures	Fistula	1yr surv	3yrs surv	5yrs surv
Timon ⁴⁴	51	H+E	Sto/Col	Mix	25%				36%		8%
Triboulet ⁴²	209	H+E	Sto/Jej/Col	Mix	5%	6%	8%	22%	62%	32%	24%
Nakatsuka ⁴⁶	70	H+E	Jejunum	RT	2%	7%	9%	4%			
Shilling ⁴⁰	18	H	Stomach	RT	11%			6%	82%	72%	60%
Ullah ⁴⁷	26	H+E	Stomach	-	12%		19%	15%	65%	35%	26%
Oniscu ⁴⁸	20	H	Jejunum	Mix	0%	0%	30%	5%	52%	33%	18%
Laterza ⁴⁹	167	H+E	Sto/Jej/Col	Mix	9%	2%		18%			17%
Jones ⁴¹	90	H	Jejunum	RT	4%	19%	12%	11%	70%	50%	42%
Ferguson ⁵¹	18	H+E	Jejunum	RT		6%	11%	33%	22%	11%	0%
Shirakawa ⁴³	54	H+E	Jejunum	-	0%	9%					47%

H=hypopharynx; E=proximal esophagus; Sto=stomach; Jej=jejunum; Col=colon; C/RT=chemo/radiotherapy; Surv=survival

Cancer of the gastro-esophageal junction

Tumors which have their center within 5 cm proximal or distal to the anatomical cardia are usually categorized as cancers of the gastro-esophageal junction (GEJ). Although some controversies still exist, epidemiological, clinical and pathological data support a sub-classification of these cancers. Such a sub-classification, today considered as the golden standard, was presented by Siewert and Stein in 1998⁵⁷.

Adenocarcinoma of the distal esophagus (cancer of the GEJ Type I) usually arises from an area with specialized intestinal metaplasia (Barrett's esophagus) and typically infiltrate the GEJ from above. This type of cancer has been associated with, as opposed to the other types, a significantly marked male preponderance, the common presence of a hiatal hernia and a long history of GERD. True carcinoma of the cardia (cancer of the GEJ Type II) arises from the cardiac epithelium or short segments with intestinal metaplasia at the GEJ, while subcardinal gastric carcinoma (cancer of the GEJ Type III) infiltrates the GEJ and distal

esophagus from below²³. The latter type is associated with a higher extent of diffuse tumor growth and a worse outcome after surgical resection compared to Type I, while Type II has characteristics somewhere in between the two other tumor types. For cancer of the GEJ Type I, II and III, the 5-year survival rates after surgical resection are approximately 45%, 40% and 25%, respectively⁵⁸.

Apart from the localization, the three types of cancer of the GEJ also shows different patterns of lymphatic spread and are accordingly treated with different approaches. The optional surgical strategies consist of abdomino-thoracic en bloc esophago-gastrectomy, subtotal esophagectomy with resection of the proximal stomach, total gastrectomy with transhiatal resection of the distal esophagus or a more limited resection of the GEJ. Consequently, various extent of lymphadenoidectomy is performed²³.

Palliation of patients with cancer of the GEJ constitutes a particular problem. Higher complication rates after stent insertion has been reported for these patients compared to patients with cancer of more proximal parts of the esophagus²⁵. Such complications typically consist of stent-migrations, problems with reflux, ulcerations and bleedings. In addition, the quality of swallowing after stent-insertion has been reported to be inferior. This has partly been explained by an angulation of the stent at the GEJ resulting in a disturbed bolus-passage²⁵.

Health-related quality of life

During the last three decades, an increasing awareness of the importance of evaluating the cancer patient's quality of life has been observed. This has been facilitated by the development of various validated questionnaires that focus both on the general health issues as well as cancer specific and tumor-site specific problems. General questionnaires typically deal with physical, psychological and social functioning and can be applied to any patient group or to the general population. One of the most used general questionnaire is the 36-item short-form health survey (SF-36), first presented in 1992⁵⁹. Cancer specific questionnaires mainly focus on functions, symptoms and various side effects of treatment. Examples of such well-established questionnaires are the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30)³² (Appendix 1) and the Functional Assessment of Cancer Therapy scale (FACT-G)⁶⁰. Tumor-site specific questionnaires, such as the EORTC esophageal module (EORTC QLQ-OES18)³³ (Appendix 2), aim to measure functional problems, as well as side effects of treatment, for a specific cancer type of interest.

The prognostic value of various clinical data at diagnosis, such as patient's age, performance status or tumor-characteristics, varies between different cancer types and has been questioned^{21,22}. The outcome of HRQL questionnaires has, however, been found to own predictive properties on survival, both in patients with early and advanced cancer^{36,61}, and also in patients with esophageal cancer³⁵. Self-reported quality of life data from individual cancer patients have shown not only to harmonize with the disease course but even better reflect the functions and problems/symptoms than other biomedical indicators³⁷. This could be due to, for instance, the occurrence of micrometastatic disease states that is not detected by radiological examination³⁵. Some authors even suggest that HRQL outcomes better outlines the disease states than what the patient actually tells the doctor³⁷. In addition, others have found doctors to be systematically too optimistic when predicting survival in terminally ill patients⁶¹. Consequently, HRQL instruments offer a large variety of implications and should be generously incorporated in clinical trials involving cancer patients.

Psychiatric morbidity

Psychiatric morbidity among cancer patients has also attracted an increasing interest in recent years. This has been promoted by the development of new therapeutic modalities for both curative and palliative treatment, increasing awareness of the importance of cancer patients' quality of life, but also by the development of more sophisticated methods for screening for mental distress⁶²⁻⁶⁴. Most of the available screening questionnaires have been developed to screen for anxiety and depression disorders. In 1983, Zigmond and Snaith presented one of the most used instruments so far, the Hospital Anxiety and Depression Scale (HADS) questionnaire⁶³ (Appendix 3).

Anxiety disorders encompass several subgroups, e.g. panic disorders, obsessive-compulsive disorders, post-traumatic stress disorders and different phobias, including social anxiety disorder. In the general population, the lifetime prevalence rate for anxiety disorders ranges between 3 and 12 percent and is approximately twice as common among women as among men⁶⁵. Major depressive disorders account for more than 4 percent of the overall global disease burden, have a lifetime prevalence rate between 5 and 10 percent and is highly associated with recurrent episodes⁶⁶. Among patients with cancer, a high prevalence of anxiety disorder and depression has been found in several cross-sectional and longitudinal studies, e.g. in patients with cancer located in the head and neck, breasts and the gastro-intestinal tract⁶⁷⁻⁷⁴.

A recent register study, performed by the Swedish National Board of Health and Welfare, found an increased risk for suicide among patients with cancer compared to the general population⁷⁵. A correlation between cancer type with a poor prognosis and an increased risk for suicide was reported, and cancer of the esophagus was found to be among the forms of cancer associated with the highest risk of all sites investigated. Moreover, the occurrence of psychiatric morbidity and hence the potential need for psychological support may vary over time after diagnosis. Great concern and attention is thus warranted for these patients' mental health, not only at diagnosis but also during treatment.

Health-economics

Health economics is a branch of economics concerned with issues related to the scarcity in the allocation of health and health care. Preferably, health economic evaluation should be carried out alongside clinical trials in order to build in appropriate data as an integrated part of the study^{76,77}. Topics related to various aspects of health economics include the measurement of health status, the production of health care, the demand for health services, health economic evaluation, health insurance and the analysis of health care markets, health care financing, and hospital economics. However, the costs can be assessed in many different ways and thus with different health economic results.

A matter of importance is to determine from whose viewpoint an economic evaluation is to be carried out. It may be based on the individual patient's, the hospital's, the government's or the society's point of view⁷⁶. The latter is usually preferred since this will include all the costs and benefits, no matter to whom they accrue. Secondly, the costs can be assessed from consumed resources or from charges. The former assessment, also known as "micro-costing", includes detailed measurements of hospital investments, maintenance of equipment, salaries, material-costs, housing, overhead costs etc., and is perhaps the most accurate approach⁷⁷. It is, however, relatively work- and time-consuming and is mainly used in large clinical trials. When costs are assessed from charges, the costs are calculated from bills from the providers of health care services. For this approach to be consistent, the gap between the costs of consumed resources and the charges has to be small.

Four main approaches to health economic evaluation exist. These include cost-minimization analysis (used when the clinical outcome is believed to be the same between groups), cost-effectiveness analysis (the outcome is measured in natural units, e.g. life years gained), cost-utility analysis (the outcome is linked to subjective data, e.g. HRQL) and cost-benefit analysis (the outcome is valued in monetary terms)⁷⁶. Each of these approaches involves identification, measurement and, where appropriate, evaluation of the costs and consequences of the options under review. The appropriate method of economic evaluation will depend on the context in which choices need to be made.

General and specific aims of this thesis

The general comprehensive aim of this thesis was to explore questions related to the management of patients with esophageal cancer.

To achieve this, the following specific aims were defined:

- To compare endoluminal brachytherapy with endoscopic stent placement over time in newly diagnosed patients with advanced cancer of the esophagus or the GEJ. The patient's HRQL, psychiatric morbidity and health-economic aspects were the primary outcomes and, secondly, other parameters relevant to the management of these patients were addressed, such as the level of dysphagia control, adverse events and survival.
- To assess the value of clinical data, CT-derived tumor size assessment and HRQL data at diagnosis for prediction of the remaining lifetime in patients with newly diagnosed incurable cancer of the esophagus or the GEJ.
- To prospectively and longitudinally screen for psychiatric morbidity in a group of patients with all stages of newly diagnosed cancer of the esophagus or the GEJ. A secondary aim was to explore potential relationships between the patients' mental health and their sociodemographic and clinical data, as well as the treatment regime applied.
- To evaluate functional long-term outcomes in patients who have undergone circumferential PLE due to hypopharyngeal or proximal esophageal cancer and reconstruction with a free vascularized jejunal transplant combined with a voice prosthesis.

Methodological considerations

This thesis summarizes six studies incorporating different groups of patients, treatment modalities and investigational methods. Study I and II evaluated different aspects on treatment in a group of 65 patients with incurable cancer of the esophagus and the GEJ, while study III analyzed potential factors predictive of survival in 60 of the 65 patients included in study I and II plus 36 patients from another trial with the same inclusion-criteria. In study IV, we screened for psychiatric morbidity in 94 other patients with all stages of cancer of the esophagus or the GEJ and in study V and VI, the long-term results of the first 16 patients treated with radical surgery due to cancer of the PEJ were evaluated.

Study-designs

In study I and II, a prospective, randomized, parallel group, multicenter study was conducted to compare SEMS-treatment and fractionated HDR brachytherapy in patients with incurable cancer of the esophagus or the GEJ. Randomization was performed in a 1:1 fashion by a validated computer-based algorithm stratifying for age, sex, grade of dysphagia, tumor histology and site, and was conducted by The Regional Cancer Register of Göteborg. Primary outcomes were patient's HRQL (study I) and health economy (study II). Secondary outcomes were effect on dysphagia, adverse events and survival. A per-protocol (PP) and an intention-to-treat (ITT) analysis were performed in study I and II, respectively. The patients were followed until death.

In study III, prospectively collected data from two randomized controlled trials on patients with incurable cancer of the esophagus or the GEJ were analyzed in order to evaluate factors predictive of survival. In the first trial, patients were randomized to treatment with either SEMS or endoluminal brachytherapy (study I+II). In the second trial, patients were randomized to treatment with SEMS either with or without an antireflux valve⁷⁸. Analyzes incorporated various clinical data, HRQL data at inclusion from the EORTC QLQ-C30 and QLQ-OES18 questionnaires and results from CT derived tumor size assessment. The latter was, however, done from routine CT examinations obtained for staging purposes before treatment.

In study IV, a prospective cohort study was set up to screen for psychiatric morbidity by means of the HADS questionnaire in patients with newly diagnosed, untreated cancer of the esophagus or the GEJ. Potential relationships between the patients' mental health and their sociodemographic and clinical data, as well as the treatment regime applied were explored. The HADS questionnaire was completed at inclusion and 1, 2, 3, 6 and 12 months later.

In study V, a retrospective, case-series evaluation of the long-term results of the first 7 patients who underwent PLE due to cancer of the PEJ at the Sahlgrenska University Hospital was performed, along with a presentation of pre-, per- and postoperative data including histopathological examination of the specimens. In study VI, a cross-sectional study including assessment of HRQL (EORTC QLQ-C30 and QLQ-OES18), voice quality and dysphagia (including Watson Dysphagia Score and radiological examination with an inter-observer evaluation) of 10 survivors after PLE (partly the same patients as in study IV) was carried out.

Comments

This thesis includes several different study-designs indeed, including retrospective, cross-sectional and prospective ones. In the hierarchy of research designs, the results of randomized controlled trials are considered to be evidence of the highest grade, whereas observational studies are viewed as having less validity because they reportedly overestimate treatment effects⁷⁹. Even so, different study-designs fulfill

different purposes. A major advantage of a randomized controlled clinical trial is the control over unknown confounders, i.e. factors that cannot be adjusted for since they are unknown. The outcomes can thereby often give direct implications in clinical practice. However, a drawback for a randomized control trial could be a low degree of generalizability, mainly due to the strict inclusion and exclusion criteria predetermined.

Retrospective and cross-sectional studies mainly fulfill hypothesis-generating purposes, but are nonetheless important. In addition, it has been shown that no fundamental difference exist in conclusiveness between randomized and non-randomized trials as long as they are relatively small⁸⁰. These aspects are relevant for many non-randomized studies performed in patients with esophageal cancer, since these patients are typically in a poor condition; have a short survival time and frequently, only a limited number of patients are available for inclusion.

The pros and cons of PP- and ITT-analyses depend on the object of interest in a study, but normally, the ITT-principle is considered to be the most accurate way to present data. Both analyses were performed in study I, however, only the PP-analysis was presented in order to best describe the effects of the actual treatment given. No statistically significant differences in HRQL outcomes were found between the two methods of analysis. Accordingly, an ITT-analysis was preferred in study II in order to evaluate the health economic effects of a decision upon treatment with either SEMS or brachytherapy.

Treatment procedures

In study I and II, patients allocated to stent treatment were given a self-expandable Ultraflex® (Micro-vasive®, Boston Scientific Corp.) metal stent with a length from 10 to 15 cm depending on the length of the tumor (Figure 3). The vast majority were covered with an upper flare diameter of 23 mm and a shaft diameter of 17 mm. In cases where the stent had to be located with its lower margin below the GEJ, non-covered SEMS were often used to prevent migration. All stents were inserted by use of standard techniques with or without pre-dilatation of the stricture²⁵. The insertion was performed as an in-patient procedure under conscious sedation or under general anesthesia.

The endoluminal brachytherapy was performed using a high-dose-rate Iridium¹⁹² source (Figure 4). A 10 mm applicator was used if possible, otherwise a 1.7 mm applicator carried the radiation source (only used in a minority of patients). The target was defined as the macroscopic tumor to which was added a 1 cm therapeutic margin in distal and proximal directions. The dose was prescribed at 10 mm depth from the surface of the applicator. Three fractions of 7 Gy were delivered with an interval of one to two weeks.

In study V and VI, the surgery was performed as a joint venture between upper gastrointestinal-, ENT- and plastic reconstructive surgeons. In addition to lymphadenoidectomy, the larynx, hypopharynx and proximal esophagus were resected en-bloc with the intention to get a tumor free margin of ≥ 2 cm. A jejunal segment, 15-20 cm of length with a suitable long mesenteric pedicle was harvested via a midline abdominal incision and subsequently used as an interposition (Figure 5). The proximal end of the jejunal segment was closed by staplers and the pharyngo-jejunostomy was constructed either end-to-side or end-to-end by use of interrupted invaginated absorbable sutures. The distal jejuno-esophagostomy was sutured accordingly end-to-end, again with absorbable suture material. Micro-vascular end-to-end and/or end-to-side anastomoses were performed to recipient vessels in the neck. The jejunal segment was harvested in combination with a shorter jejunal segment, 2-3 cm long. This segment, positioned outside the adjacent skin area in order to monitor viability of the transplant, was removed 3-6 days later. Approximately three months after initial surgery, a secondary tracheo-jejunal puncture using a speech valve (Provox I) was established.

Comments

The previously advocated non-expandable plastic prostheses have to a great extent been replaced by SEMS, mainly because of a better technical success rate, fewer complications and lower mortality rates⁸¹. Consequently, the latter type was used in study I and II. Several types of SEMS exist on the market today, however, with slightly varying characteristics and clinical outcomes^{26,82}. In order to reduce an observed risk of migration, uncovered stents were previously recommended for cancers of the distal esophagus and the GEJ⁸¹. Today, covered stents are used throughout the entire esophagus, mainly because these recommendations could not be supported by more recent studies and because the covering prevents ingrowth of tumor and granulation tissue into the stent^{27,83}. Only a minority of the stents used in study I and II were uncovered, why a possible influence on outcome may be considered as unlikely.

Reflux symptoms have been reported in up to 95% of patients where the stent has been placed across the GEJ⁸⁴. Consequently, an anti-reflux valve has been established in some stent-types. These antireflux stents have shown good results concerning acid exposure in the lower esophagus as measured by 24h-pH monitoring⁸⁵, however, the clinical benefit of antireflux stents for patients with cancer of the distal esophagus or the GEJ has yet to be confirmed⁷⁸. Moreover, they were not commercially available at the time of study I and II, and hence not used.

Low-dose rate brachytherapy schedules have today been replaced by the less time-consuming and more effective HDR concept⁸⁶. The latter has been given as a single dose treatment or as fractionated sessions²⁹. The fractionation allows a higher radiation dose and, according to some studies²⁸, leads to better dysphagia and tumor control without a corresponding increase in side effects. Others have found an equally good relief of dysphagia after single session HDR brachytherapy and with an equal prevalence of side effects^{38,87}. The brachytherapy given in study I and II were in accordance with recommendations by the American Brachytherapy Society⁸⁸.

Radical surgery including PLE and substitution with a free vascularized jejunal transplant in patients with cancer of the PEJ has been emphasized by many surgeons^{41,42,46} and is, since 1995, considered to be the first line of treatment at the Sahlgrenska University Hospital. The advantage of using a tubularized transplant for interposition, as opposed to myocutaneous flaps, is the reduced risk of strictures and fistula formation⁴⁶. Moreover, this intervention is performed as a one-stage procedure. This reduces the peroperative time and shortens the hospital stay³⁹.

In study VI, pouches at the pharyngo-jejunostomy were found to induce a significant retardation of bolus transit in some patients. Despite the fact that this was not clearly related to clinical symptoms, it is reasonable to suggest that, if technically possible, the formation of such a pouch should be avoided.

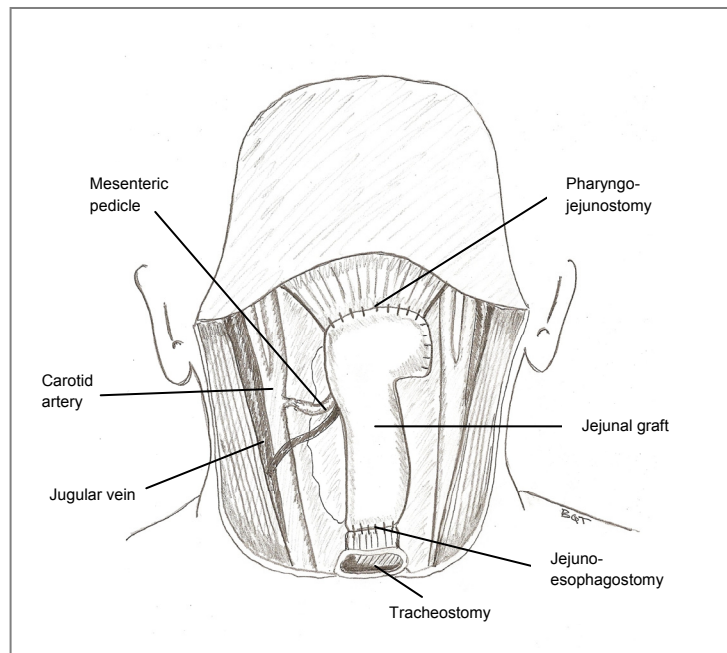


Figure 5. Jejunal interposition after pharyngo-laryngo-esophagectomy (PLE) (Paper V+VI).

Modifications of the pharyngo-jejunal anastomosis, e.g. to an end-to-end anastomosis, could therefore be of value. Such an approach was recently suggested by Okazaki *et al.*, who also, in order to avoid strictures and fistula formation, used a “z-plasty-like” anastomosis- technique for the jejuno-esophagostomy in 20 patients undergoing PLE⁸⁹.

Clinical evaluations

In study I and II, clinical evaluation was performed by a physician at the time of inclusion and 1, 3, 6, 9 and 12 months later. The evaluation included recording of the Karnofsky Performance Status Scale Index (KPSSI)⁹⁰ (Appendix 4), the grade of dysphagia according to Ogilvie *et al.*⁹¹, the patient’s weight and the occurrence of adverse events. In study IV, participating patients answered questions read by a physician from a standardized questionnaire on sociodemographic background, co-morbidity, weight loss and tumor-related symptom duration before diagnosis. The physician also registered the KPSSI and Body Mass Index (BMI). In study VI, ten survivors were evaluated with regard to their KPSSI, grade of dysphagia according to Ogilvie *et al.*⁹¹ and their Watson Dysphagia Score (WDS). In addition, the patients’ speech valve and/or electrolarynx (Servox) speech functions were assessed.

Comments

The KPSSI allows the physician to classify the patient according to the patient’s ability to perform normal activity, to do active work and the need for assistance rated on a scale from 0 to 100. It is established in clinical practice, is easy to estimate and can be used to compare the effectiveness of different therapies. Moreover, its interrater reliability and validity are considered to be good⁹⁰.

A scale for estimating the grade of dysphagia in patients with cancer of the esophagus or the GEJ was described by Ogilvie and co-workers in 1982⁹¹. The scale has been used in many studies as well as in clinical practice, and describes the severity of the disorder. However, the grade of dysphagia is rated on a rather rough scale from 0 to 4 (0=no dysphagia; 1=some dysphagia, but no dietary limitations; 2=can drink, but only eat semisolid food; 3=can only drink; 4=total dysphagia) and has, to the best of our knowledge, not been validated in cancer patients. A more detailed description of the patient’s swallowing difficulties can be captured by estimating his or her WDS. This score was presented by Dakkak and co-workers in 1992 and ranges from 0 (no dysphagia) to 45 (severe dysphagia) on a 9-items scale (from liquids to solid food)⁹². The latter score has partly been validated in patients with various grades of esophageal strictures.

Factors including gender, social functioning, a history of alcoholism and co-morbidity have previously been suggested to be related to psychiatric morbidity and were thereby a matter of interest in study IV^{67,69,75}. Due to the limited number of patients and declining survival rates over time, imbalanced factors and small subgroups were, however, difficult to compare and evaluate. For some questions, there was also a certain risk of recall biases as suggested by the fact that none of the patients reported a previous history of an anxiety disorder or depression episode. The difficulty in obtaining a reliable estimate of a person’s alcohol consumption is also well-known.

Several different methods of how to evaluate the voice quality after the establishment of a speech valve in patients surgically treated due to cancer of the PEJ have previously been described^{93,94}. Most of them are, however, not validated and rather insensitive. A more advanced method, including spectrographic analysis of acoustic parameters, were described by Benazzo and co-workers in 2001⁵⁰. The speech valve assessments made in study V and VI were solely based on clinical grounds (mainly with regard to intelligibility, syllables per breath and degree of speech valve use), graded as good, average or poor and performed by a speech

pathologist and a surgeon in concordance. The main reasons for not doing a more sophisticated analysis was that the patients were relatively few in study V and the results generally poor in study VI.

Evaluation with questionnaires

All six studies comprising this thesis contained evaluation with questionnaires. In study I, III, V and VI, the EORTC QLQ-C30 (version 3.0) was used (Appendix 1). This questionnaire is tumor-specific and designed for self-administration. It has been used extensively in different HRQL-studies and its cross-cultural validity and psychometric properties are considered satisfactory³². The questionnaire comprises five functioning scales; physical-, role-, emotional-, cognitive- and social functioning. There are three symptom scales; fatigue, nausea/vomiting and pain and six single items relating to dyspnea, insomnia, loss of appetite, constipation, diarrhea and financial difficulties. It also includes a global health status/QL scale (2 questions). A one-week time frame is employed. All scales and single-item scores are transformed into a score from 0 to 100. A high score for a functional scale and for the global health status/QL scale represents a high/healthy level of functioning/high QL, while a high score for a symptom scale or single item represents a high level of symptoms/problems. The QL scores are calculated according to the EORTC QLQ-C30 scoring manual⁹⁵.

In study I, III and VI, the EORTC QLQ-OES18 was used (Appendix 2). This questionnaire consists of questions related to problems due to the specific tumor location and treatment³³. The questionnaire comprises four scales: dysphagia-, eating-, reflux-, and local pain scale. There are 6 single items relating to problems with swallowing saliva, choking when swallowing, problems with dry mouth, problems with taste, problems with coughing, and problems with speech. Both the scales and single items are scored according to the same scoring system as the EORTC QLQ-C30⁹⁵. Good psychometric and clinical validity for the questionnaire has been demonstrated in previous studies³³.

The HADS questionnaire was used in study I and IV (Appendix 3). It has been designed to screen for psychiatric morbidity in patients with somatic illness and comprises two scales, one for depression (seven questions) and one for anxiety (seven questions). Each item is rated on a four-point Likert scale. Cut-offs have been established for when to regard a patient as a probable (>10 points, on one scale) or possible (>7 points, on one scale) case of psychiatric illness⁶³. Scores indicating psychiatric morbidity (HADS total score) were defined as >7 points on either scale, i.e. a score indicating possible anxiety disorder and/or depression. The HADS questionnaire has been shown to perform well in assessing the symptom severity and caseness of anxiety disorders and depression in both somatic, psychiatric and primary care patients and in the general population⁹⁶.

Comments

All of the above mentioned HRQL questionnaires has in common that they are filled in directly by the patient. The questions are answered on a multiple-choice scale (i.e. a Likert scale), and a certain time frame (i.e. one week) is employed. Matters of importance for a reliable interpretation of the HRQL data are that the compliance is high (i.e. the proportion of patients that answers the questionnaire) and that the amount of missing data is low (i.e. single questions that are not answered). It should be reasonably brief (i.e. preferably less than 10 minutes to complete) and easily understood. In addition, the occurrence of a response shift should always be kept in mind (i.e. the patient changes its perspective of his or her HRQL over time as a result of coping strategies, change in internal standards or increased knowledge). The latter phenomenon is, however, considered to be a natural adaptation to a disease and its treatment.

A disadvantage with written questionnaires is the inflexibility with regard to the response format and thereby the inability to further explore the responses. However, the questionnaires are easy to analyze, less time-consuming than face-to-face interviews and reference data to the general population and other cancer populations exist^{78,97-100}. Recent findings that certain questions of the HRQL questionnaires are more important than others¹⁰¹, and the subsequent development of shorter questionnaires¹⁰², further support this investigational method as being suitable in patients with low performance status and rapid deterioration, e.g. patients with advanced cancer of the esophagus.

For the HADS questionnaire, we used the cut-off levels for possible and probable affective disorder suggested by Zigmond and Snaith⁶³. In a recently published overview, including 10 studies of cancer patients (n=1803), the mean optimal cut-off score for caseness on HADS-anxiety was 8.8 with a mean sensitivity of 0.72 and a mean specificity of 0.81⁹⁶. For HADS-depression, the mean cut off was 8.3 with a mean sensitivity of 0.66 and specificity of 0.83. Moreover, the cut-off levels used here have previously been shown to have a high validity in Scandinavian patients with head and neck cancers⁶⁷.

Health economic evaluation

In study II, internal hospital debits from the administration charts of 2003 at the Sahlgrenska University Hospital were used to assess the costs and the health economic view of the health care system was used. Cost assessment was started from the day of randomization and continued until death in order to estimate the total lifetime cost. The initial treatment cost was obtained by assessing all the costs from randomization until discharge from the hospital after cessation of treatment, i.e. after SEMS insertion or the last brachytherapy session. In addition, a health economic questionnaire was given to the patients at the various follow-up visits. In this questionnaire, patients were asked to report any contacts with the health care system since the last visit. However, to minimize the obvious risk of recall bias, a secondary data evaluation was performed by surveying the records in the hospital administration systems from the area where the patient lived. A sensitivity (threshold) analysis was performed to assess the degree of difference in costs between the two comparators.

Comments

The “micro-costing” approach was not used, mainly because it was deemed to be work and time-consuming and the gap between costs of consumed resources and charges was considered to be small since the Swedish health care system is non-profitable. Cost-minimization analyses were carried out since there were no significant differences in outcome variables that could be used for a cost-effectiveness analysis. The costs were assessed from inclusion until death in order to capture the health economic effects, not only of the initial treatment, but also of re-intervention, late complications, hospice care etc.

CT derived tumor size evaluation

In study III, CT derived assessments of the tumors were performed on a diagnostic radiological workstation (CentricityTM RA600, GETM, Milwaukee, USA) and all measurements were performed on a high resolution screen (Coronis 3 MP, BarcoTM). The examinations were made at local hospitals with helical CT technique with a slice thickness of 5-10 mm. All measurements were done on series with intravenous contrast. If primary digital images were not available, previously printed images were digitalized using a scanner (Diagnostic Pro, VidarTM) with a resolution of 150 dpi. The length of the tumor was calculated as the number

of images in which the tumor could be localized multiplied by the slice thickness. To obtain the tumor volume, the cross sectional area was measured in each of these slices by manual outlining of the tumor on the screen using a mouse controlled cursor. In case of a visible lumen, this was also outlined and the luminal area was subtracted from the area calculated from the outer limit of the tumor (Figure 6). The cross sectional areas were multiplied by the slice thickness and the total volume calculated by the summation of these volumes (summation-of-area technique). The maximal tumor diameter was also measured.



Figure 6. Outlining of an esophageal tumor on a computerized tomography (CT) image (Paper III)

Comments

Factors like slice thickness, image resolution, high quality multi-planar reformation, the use of intravenous and/ or oral contrast media and antispasmodic drugs have been suggested to influence size assessment^{103,104}. Great potentials thus exist for further refinement of this technique. Moreover, some reports state that more than 80% of volume measurement errors are due to the inter-observer variability¹⁰⁵. All radiological measurements in study III were hence performed by one single consultant thoracic radiologist. Intra-observer variability in CT derived tumor size assessment has, on the other hand, been reported to be satisfactory¹⁰⁶. The radiologist was, at time when the measurements were performed, unaware of the survival times of the patients.



Figure 7. Barium examination showing the emptying of a jejunal graft with retention in a pouch (lateral projection) (Paper VI).

Barium examinations

The barium examinations in study VI were carried out in patients fasted for at least 6 hours. The study included both dynamic examination of motility with videofluoroscopy and a series of spot films, to evaluate morphology and emptying of the jejunal graft (Figure 7). The patients were asked to take 5 ml of barium (“High-Density”, Astratech, Sweden) from a cup and then hold it in the mouth to test for adequacy of containment. They were then asked to swallow on command. Additional swallows of 15 ml “High-Density” contrast and of 5 ml of barium paste were recorded. Spot films of the jejunal interponate and the native esophagus were exposed, so that the localization of the anastomoses as well as any morphological abnormalities could be determined as accurately as possible. The transit of

a bolus of 20 ml of barium through the jejunal segment and the remaining native esophagus was videotaped.

The video recordings of swallowing were analyzed in slow motion and the findings recorded on a data sheet (Excel, Microsoft, Ca, USA) by two reviewers in consensus. Another data sheet was completed by a third, independent reviewer, to allow for calculation of inter-observer variability. Oral and/or pharyngeal dysfunction was graded as none, mild, moderate or severe. In addition to this qualitative assessment, a quantitative frame-by-frame analysis of the pharyngeal phase of the swallowing was performed. The function of the jejunal graft was assessed in relation to the degree of delay in bolus transit. The degree of intrinsic activity in the graft, as well as any localized delay or hold-up in transit of bolus, was also noted. The motility

in the remaining native esophagus was evaluated with regard to the presence of non-propulsive, tertiary contractions, delayed esophageal emptying and impaired LES relaxation.

Comments

The value of radiographic evaluation, as opposed to techniques such as scintigraphy, lies in a better ability to differentiate between structural and functional disturbances¹⁰⁷. This is of importance when assessing patients with esophageal cancer, especially after substitution with a jejunal graft where endoscopic surveillance may be associated with difficulties. Moreover, although experienced radiologists were involved, a radiological assessment is a subjective thing with observer variability. Consequently, in study VI, effort was put on estimating the degree of inter-observer variability regarding the radiological evaluations.

Statistics and ethics

The majority of the statistical analyses in this thesis were performed by Statistiska Konsultgruppen, Göteborg. All 6 studies were approved by the local ethics committees and informed consent was obtained from each participating patient before inclusion.

Paper I and II

A sample size of 75 patients in each treatment arm was calculated from 30% difference in dysphagia score with a power of 80% at a 0.05 significance level. An interim analysis was planned after 60 enrolled patients. After this analysis, the inclusion was stopped since significant differences between the groups were observed. The presented data refers to a PP-analysis in Paper I and an ITT-analysis in Paper II. In Paper I, for comparison between groups, Fisher's non-parametric permutation test¹⁰⁸ was used for continuous variables, Mantel-Haenszel's Chi-square test for ordered categorical variables and Fisher's exact test for dichotomous variables. For comparison over time within groups, Fisher's non-parametric permutation test for matched pairs¹⁰⁸ was conducted. A difference of 10 points in the QoL scores was regarded as clinically relevant^{109,110}. In Paper II, Mann-Whitney test was used for numerical variables and chi-square and Fischer's exact test for comparisons for categorical variables as appropriate between groups. Survival analysis was performed with Kaplan-Meier estimates and formally tested with Log-Rank-test. All tests were two-tailed and conducted at a 5% significance level. Data were expressed as means and SD if not stated otherwise.

Paper III

For descriptive purposes, frequencies and percent were computed for categorical and dichotomous variables and mean, SD, median and range for continuous variables. Mann-Whitney U-test was used for test between two groups with respect to continuous variables. The effect of a predictor on time to death was described with Hazard Ratio. The survival analysis was performed by using Cox Proportional Hazard Model. For survival analysis of dichotomous and non-ordered categorical variables as predictors, the Log-rank test was used. For description of survival analyses, Kaplan-Meier graphs were used. To control for possible confounding effects of established prognostic factors and associations between CT derived size assessment of the primary tumor as well as HRQL scores, multivariable models using a stepwise Cox regression procedure were performed. Variables that were not significant on a 5% level in the univariate analysis, that were too unevenly balanced, had a high percentage of missing data or showed a high correlation with other potential prognostic variables were not included into the multivariate procedure. Univariate and multiple stepwise logistic regression were used to select independent predictors for probability of death before and after 3 months. Bootstrapping techniques were used for internal validation of the multivariate model. Bootstrap samples were drawn with replacement and with the same size as the original sample. Cox Proportional Hazard model was created within each bootstrap sample and best sets of independent variables were defined. This procedure was repeated 1000 times to obtain stable estimates of the optimism of the model, i.e. how much the model performance was expected to decrease in new patients. All tests were two-tailed and conducted at a 5% significance level. To control for multiple significance, the upper limit of the expected number of false significances was calculated. The upper limit of expected number is calculated by $\alpha * (N - n(\alpha)) / (1 - \alpha)$, where N = number of tests, $n(\alpha)$ = number of significances on level α and α = significance level.

Paper IV

For descriptive purposes, frequencies and percent were computed. Between group comparisons were performed using the Pitman's nonparametric permutation test for all correlation analyses¹⁰⁸, along with Pearson's correlation coefficient for descriptive purposes. Fisher's non-parametric permutation test was used when comparing ordered and continuous variables between groups¹⁰⁸. Change over time was tested for ordered categorical variables (HADS scores) using the sign test. Mantel-Haenszel's Chi-square test was used for measuring changes between groups. For survival analyses, the Log-rank-test was used for binomial or non-ordered categorical variables and Cox's PH-regression was used for ordered or continuous variables. All tests were two-tailed and conducted at a 5 % significance level.

Paper V and VI

Inter-observer agreement of the radiological findings was assessed by calculation of the weighted kappa-value¹¹¹.

Results and comments

Paper I and II

Out of the 65 patients randomized, 28 patients completed the SEMS treatment and 24 patients the brachytherapy and were hence eligible for the PP-analysis in study I. 5 patients chose to withdraw their consent after randomization and consequently, 60 patients (30 patients in each arm) were eligible for the ITT-analysis in study II. Six patients died before having or completing the stipulated treatment and 2 were excluded due to technical difficulties (both patients being allocated to brachytherapy) (Figure 8). Mean time from inclusion until start of treatment was 10.9 days for the SEMS group and 17.3 days for the brachytherapy group.

Compliance for the HRQL questionnaires was adequate (>80%) at all measurement-points and missing data were few (2%). Mean global QL scores at inclusion were 43 for the SEMS group and 44 for the brachytherapy group. The group of patients treated with SEMS reported significantly better HRQL scores for dysphagia at the one-month follow-up than at inclusion, but most other HRQL scores, including functioning and symptom scales, deteriorated over time. Among brachytherapy-treated patients, improvements were found for the dysphagia-related scores at the three-month follow-up, whereas other significant changes of HRQL scores over time were few and hence more stable than in the SEMS group. Psychiatric morbidity, as assessed by the HADS questionnaire, was common (>60% of patients at inclusion) with no preponderance to either treatment strategy.

A statistically significant improvement in the dysphagia score according to Ogilvie *et al.*⁹¹ was reported for the SEMS group at the 1-month follow-up (Figure 9). This difference was, however, not seen at the

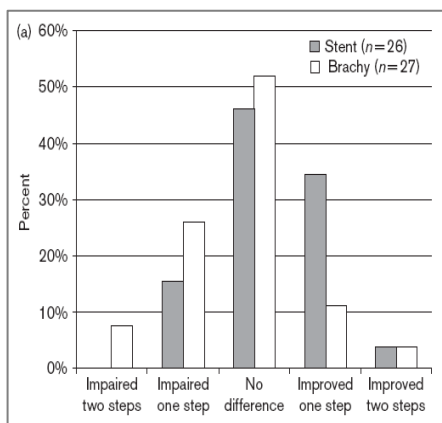


Figure 9. Significant (p=0.03) change in dysphagia scores between inclusion and the 1 month follow-up in favour of the stented patients (Paper II).

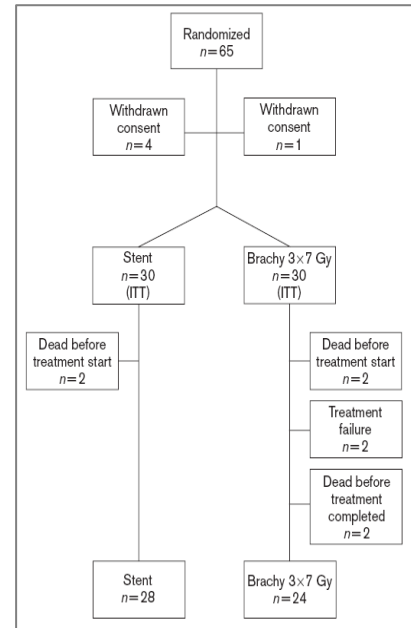


Figure 8. Number of randomized patients, withdrawals before start of treatment, number of patients available for the intention-to-treat (ITT) analysis and number of patients completing the treatment (available for the per-protocol (PP) analysis), for the two treatment groups (Paper I+II).

subsequent follow-up at 3-months. No significant differences for KPSSI, weight loss or the occurrence of adverse events were found between the two groups and the survival times were comparable (median survival time around 120 days) (Figure 10).

The median total lifetime cost and initial treatment cost for brachytherapy were significantly higher compared to those for SEMS treatment (€33171 vs. €17690 and €23857 vs. €4615, respectively). This difference was mainly due to higher costs for the therapeutic procedure and for in-hospital stay (Table 3). Sensitivity analyses showed that the charge for a brachytherapy session had to be reduced from €6092 to €4222 to make this therapeutic concept cost-competitive. Consequently, stenting was found to be more cost-effective compared to brachytherapy.

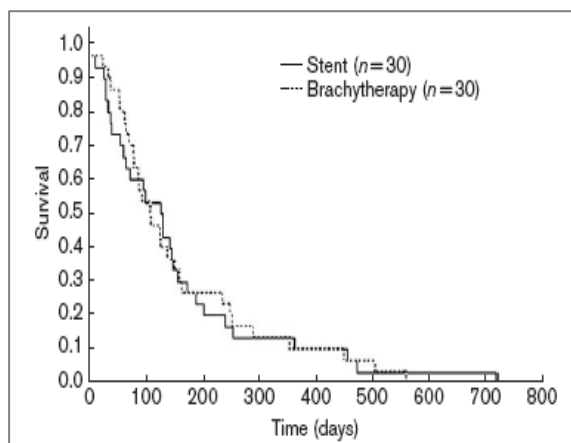


Figure 10. Cumulative survival rate from inclusion plotted as Kaplan-Meier estimates (Paper II).

Comments

HRQL proved to be generally poor in patients evaluated, both at inclusion and over time. Global QL-scores were considerably lower than in the general population¹⁰⁰ and also compared to other cancer populations^{97,98,112}. In addition, the survival time was very limited in both groups, emphasizing the obvious need for a rapid effect of treatment. The immediate mechanical effect of the SEMs offered a more prompt effect on dysphagia than fractionated HDR brachytherapy. In addition, time from inclusion until start and end of initial treatment varied between the two comparators and was in favor of the SEMs treatment. Consequently, these patients reported

improved dysphagia scores at the one-month follow-up. A reduced delay from inclusion until the start of brachytherapy, possibly given as a single session with a higher dose⁸⁷, could level out some of this discrepancy. However, others report a similar outcome as in our study with the latter brachytherapy schedule³⁸.

An overall improvement of dysphagia was only found in 40% of the patients regardless of treatment, inferior to that reported by others^{26,38,87}. An explanation for this could be that the scoring of dysphagia in our study was done by a physician, in contrast to others that have used diary cards³⁸. Another possible way to better investigate the effect on dysphagia would have been to measure HRQL including the dysphagia scale of the EORTC QLQ OES18 at tighter intervals during the first months, but this could severely have hampered the compliance in these vulnerable patients.

The fact that HRQL showed a less pronounced deterioration over time in the brachytherapy group is somewhat surprising in view of the more prompt effect on dysphagia with SEMs treatment. This finding, which has also been confirmed by others³⁸, may in part be explained by initially more frequent contacts with the health care system in the brachytherapy group. Another field, that is open for speculations, is to what extent the psychological effects of a treatment directed towards the uncontrolled neoplastic growth could contribute to a better outcome. Nevertheless, the results indicate that SEMs is the more favorable modality in patients with a short expected survival (< 3 months), while brachytherapy might be preferable in patients with a longer ditto.

Table 3. Total lifetime costs divided into used resources (Paper II).

	Stent (n=30)	Brachytherapy (n=30)
In-hospital stay (€)	13 667/9379 (961–53 391)	13 122/13 218 (0–39 895)
Primary treatment (€)	1985/2126 (0–2127)	15 232/18 278 (0–18 278)
Outpatient visits (€)	366/183 (0–1465)	464/366 (0–2014)
Upper gastrointestinal endoscopy with or without dilatation (€)	383/0 (0–2372)	317/0 (0–330)
Secondary stent treatment (€)	709/0 (0–4254)	638/0 (0–4254)
Percutaneous endoscopic gastrostomy (€)	58/0 (0–582)	78/0 (0–582)
Additional costs for endoscopic procedure under general anaesthesia (€)	331/355 (0–1065)	142/0 (0–1065)
Central venous catheters and total parenteral nutrition (€)	595/0 (0–3975)	363/0 (0–2914)
Rehabilitation and hospice care (€)	5856/0 (0–38 155)	4422/0 (0–44 810)
Radiology (€)	482/211 (0–2647)	446/270 (0–2060)
Other costs (€)	132/0 (0–1778)	190/0 (0–4820)
Total lifetime cost (€)	24 564/17 690 (3088–76 233)	35 414/33 171 (4322–67 414)

Data presented as the mean/median (range).

Health economic analyses must include both costs and outcome measurements to be meaningful⁷⁶. While differences between other endpoints were comparatively modest, our study showed an overwhelming difference between costs for SEMS and brachytherapy in favor of the former treatment. Consequently, stenting was found to be the most cost-effective concept. One should, however, bear in mind that this conclusion is only valid in the present setting, i.e. a Swedish non-profitable health care system with the majority of the initial treatments being performed under general anesthesia and with 3 sessions of brachytherapy. In fact, in a Dutch study using a “micro-costing” approach, Homs *et al.* found a health economic outcome that was comparable between SEMS and brachytherapy when the latter treatment was given as a single session of 12 Gy and both SEMS and brachytherapy were performed under sedation as an out-patient procedure³⁸.

Paper III

In the univariate analysis, KPSSI, M-stage and UICC-stage were found to be significantly related to survival (Table 4). A larger CT-derived tumor volume, as well as a wider maximal diameter, was found to be associated with a shorter survival time. In addition, 10 of the 25 scales and single items of the EORTC QLQ-C30 and QLQ-OES18 were also found to predict survival.

Factors significantly correlated to survival were also tested in a Cox multivariate model. The fatigue scale from the EORTC QLQ C-30 questionnaire, as well as the reflux scale from the esophageal module, were found to add prognostic information to the strongest predictor, i.e. M-stage, and were thus independent predictors of survival (Table 5). A higher score of 10 points for a patient was found to increase the likelihood of death, at any given time, with 10% for the fatigue scale and with 11% for the reflux scale. In patients without metastases (M0-stage), the reflux scale was found to be the strongest independent predictor of survival, with a 33% higher likelihood of death, at any given time, for a patient that scored 10 points more than another patient. The physical functioning scale was found to be the strongest independent predictor in patients with metastatic disease (M1-stage), with a corresponding figure of 16%.

A subgroup analysis of the single questions comprising the scales was also performed. Question no 4 (“Do you need to stay in bed or a chair during the day?”) in the physical functioning scale and question no 12 (“Have you felt weak?”) in the fatigue scale of the EORTC QLQ-C30 questionnaire, as well as question no 44 (“Have you had acid indigestion or heartburn?”) in the reflux scale of the EORTC QLQ-OES18 questionnaire were found to be the most important questions for prediction of survival.

To confirm the established prognostic model, a risk group validation was performed by dividing the patients into two groups. The groups consisted of those who died prior to 3 month after inclusion (n=47) vs. those who lived longer (n=49). A logistic regression analysis was then performed to evaluate potential

Table 4. Univariate Cox analysis (Paper III).

Variable	Hazard Ratio* (95% CI)	p Value
KPSSI	0.98(0.96-0.99)	0.002
M-stage	1.89 (1.21-2.91)	0.004
UICC-stage	1.44 (1.05-1.96)	0.03
CT-volume pr. tum. (cm ³)	1.005(1.001-1.009)	0.025
CT-max diameter pr. tum. (cm)	1.026(1.009-1.043)	0.002
EORTC QLQ-C30:		
Physical function	0.91(0.85-0.99)	0.02
Role function	0.92(0.86-0.97)	0.004
Cognitive function	0.92(0.86-0.99)	0.03
Fatigue	1.12(1.05-1.21)	0.001
Pain	1.10(1.03-1.17)	0.006
Dyspnea	1.08(1.02-1.14)	0.014
Appetite loss	1.07(1.01-1.13)	0.016
EORTC QLQ-OES18:		
Eating scale	1.10(1.01-1.19)	0.031
Reflux scale	1.15(1.05-1.25)	0.002
Trouble with speech	1.08(1.00-1.16)	0.038

*Hazard ratio for HRQL scores provides the likelihood of death at any given time for a patient with a score of 10 points more than another patient; KPSSI=Karnofsky Performance Status Scale Index; UICC=Union Internationale Contre le Cancer; pr. tum.=primary tumor

predictive factors. M-stage was again found to be the strongest predictor of survival, followed by fatigue, physical functioning and the reflux scale. A bootstrapping re-sampling analysis further confirmed the replication stability of the final model.

Comments

Traditionally, much focus has been on the definition and evaluation of prognostic factors for patients with tumor states enabling therapy for cure¹¹³. In Study III, we shifted this focus to the larger group, i.e. those where palliative treatment is the only option. The issue of how to best palliate patients with advanced cancer of the esophagus and GEJ is pivotal since the clinician has to choose between therapeutic options with a range of pros and cons. Study III consequently offers guidelines for the selection of patients for stenting and others in who more advanced palliative therapeutic modalities, e.g. brachytherapy, shall be considered.

While the found predictors of survival showed a high level of reliability, it must be remembered that the analyses were performed on data from patients included in two different randomized trials. Even though the inclusion and exclusion criteria were mainly the same for the two trials, fusion of data could result in biases. As a consequence, the final model was tested on subgroups with patients included in one trial only, as well as in patients treated with either SEMS or brachytherapy, with an outcome that confirmed its reliability. In spite of this, care should be taken when interpreting the results and before applying them in clinical practice.

The findings that M-stage, as well as the EORTC QLQ-C30 physical functioning and the fatigue scale, are predictors of survival in cancer patients have been confirmed in several other studies^{34,35,114,115}. An unexpected finding was, however, that the reflux scale also turned out to be an independent predictor of survival, not only in patients without metastases, but for the whole study-group. Why the degree of acid indigestion or heartburn would be related to the patient's remaining life-span is not easy to understand, but this symptom appears to be related to a more aggressive type of tumor or disease state.

Although a relation to survival for two of the CT derived tumor size parameters could be confirmed, they could not be established as independent predictors. However, it is important to remember that, for various reasons, size assessment could be performed in only 58% of the patients. In 20 patients, a CT had not

Table 5. Final Cox multivariate models (Paper III).

Variable	Hazard Ratio* (95% CI)	p Value
Whole study group (n=96)		
M-stage	2.15 (1.35-3.43)	0.0013
Fatigue	1.10 (1.02-1.19)	0.016
Reflux scale	1.11 (1.00-1.22)	0.040
Patients with M0-stage (n=36)		
Reflux scale	1.33 (1.11-1.61)	0.0026
Patients with M1-stage (n=52)		
Physical functioning	0.84 (0.75-0.93)	0.0012

*Hazard ratio for HRQL scores provides the likelihood of death at any given time for a patient with a score of 10 points more than another patient.

been performed at all or was not performed within a reasonable time-frame. The CT examination had been destroyed in 12 patients, and in 8 patients, with distally located tumors, the tumor margins could not clearly be delineated from ordinary gastric tissue. One criterion for excluding a variable in a multivariate analysis is a high amount of missing data. Hence, the question whether CT derived tumor size parameters are independent predictors of survival in patients with incurable cancer of the esophagus or not remains unanswered.

Paper IV

At inclusion, 42% of the 90 patients evaluated had HADS-scores indicating psychiatric morbidity (i.e. either probable or possible anxiety disorder and/or depression) (Figure 11). No statistically significant change in the HADS total score over time was found; neither for any sociodemographic subgroup, nor for any clinical

subgroup. However, the majority (73%) of patients with scores indicating depression at inclusion also reported scores indicating anxiety disorder, demonstrating a high degree of co-variation for the two disease states evaluated. This trend was seen in patients treated both with curative and palliative intent and was maintained over time.

During the study year, the proportion of patients with scores indicating possible/probable anxiety disorder (>7 points on the anxiety scale) ranged between 16% and 34% and was highest at inclusion. At all follow-ups, except at 3 months, this proportion was significantly lower than at inclusion. After an initial decrease in both treatment groups, anxiety score levels similar to those reported at inclusion was again found at the 3 month follow-up for those treated with curative intent. A positive correlation was found between HADS anxiety scores at inclusion and the duration of tumor-related symptoms prediagnosis. Moreover, a larger proportion of patients with a duration of tumor-related symptoms prediagnosis exceeding 6 months scored worse than the other patients on anxiety at the 1- and 6-month follow-ups. Compared to male patients, a significantly larger proportion of female patients had possible/ probable anxiety disorder at the 1-, 2- and 3 month follow-ups. No other significant change over time in HADS anxiety scores was found; neither for the whole study group, nor for any subgroup.

Regarding depression, the proportion of patients with HADS scores >7 points ranged between 27% and 44% during the study year, with a tendency (ns) to increase over the first 6 months. A significantly larger proportion of patients with scores indicating depression was found at inclusion among patients treated with palliative intent compared to those treated with curative intent. A negative correlation was also found between depression scores and KPSSI scores at inclusion. Moreover, a tendency was found towards a lower

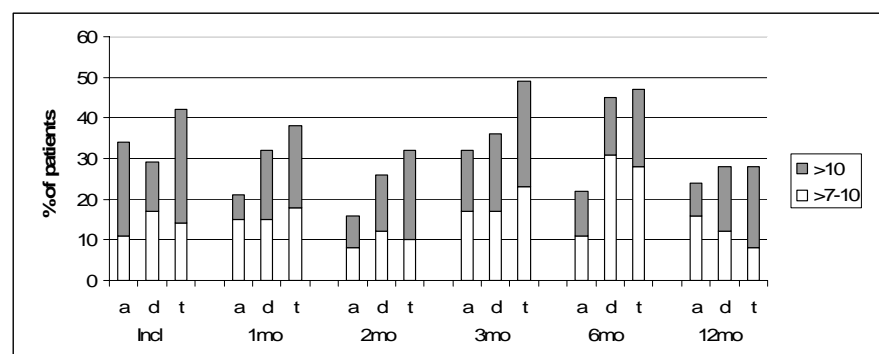


Figure 11. Percentage of all patients that completed the questionnaire with scores indicating possible (>7-10 points) or probable (>10 points) anxiety (a), depression (d) anxiety and/or depression (t). Incl=inclusion; mo=month (Paper IV).

proportion of patients with depression scores >7 points among survivors compared to patients who died. No other statistically significant differences were found between the two treatment groups over time, nor for the sociodemographic subgroups or the other clinical subgroups analyzed. No correlations between HADS scores and survival were found.

Comments

About 25-30% of all cancer patients are reported to develop clinically significant anxiety disorder and depression within 2 years of diagnosis⁶⁷. The present study showed that a large proportion of patients with newly diagnosed esophageal cancer suffer from symptoms of anxiety and/or depression as measured by the HADS questionnaire. In addition, the present findings are in line with previous reports from studies of cancer with a poor prognosis^{116,117}.

The occurrence of anxiety at inclusion was significantly related to the duration of symptoms pre-diagnosis. An explanation for this could be that patients with a pre-morbid anxiety disorder tend to suppress their symptoms more than do others and thus seek medical care at a later stage. In contrast to these results, and to some previous observations among head and neck cancer patients⁷¹, we did not find a relationship

between anxiety and TNM-stage, KPSSI score or treatment regime. Our findings also contrast with results that females score worse than males on the anxiety scale at diagnosis^{67,74}. On the other hand, our female patients scored worse at the 1-, 2- and 3-month follow-ups, but the proportion of females was fairly low.

In contrast to what has been reported for instance regarding lung cancer patients¹¹⁸, we could not verify that lower social functioning, e.g. living alone, and more physical symptoms or co-morbidity predict depression, although many of our patients had a relatively advanced tumor burden with a low survival rate, and at least 9 patients suffered from excessive alcohol consumption. However, depression was less common among patients who were eligible for treatment with curative intent, a group which in this study contained less subjects living alone and with a lower degree of co-morbidity compared to those who received palliative treatment.

A time pattern, similar to that reported by Shepherd *et al.*⁷⁰, with highest anxiety scores at diagnosis and highest depression scores during treatment, was observed. A possible explanation could be that as the patients gradually become more aware of the implications of their diagnosis and prognosis, the more depressed they get. The dampening effect on anxiety over-time, on the other hand, could be associated with the care and treatment the patients receive. It is also possible that the information given regarding the expected outcome may have an impact, as suggested by the fact that patients who received treatment with palliative intent scored worse for depression compared to those who survived the whole study period, as well as by the observation that those in the “curative group” who died scored relatively low on the depression scale. However, the results must be interpreted bearing in mind that this study had a strictly descriptive purpose and that factors not accounted for in the study might be involved, such as post-operative morbidity, change in medication but also the decreasing patient sample size due to mortality, especially for patients that received palliative treatment. Compliance, which was very high in contrast to previous reports of patients with a relatively advanced disease¹¹⁸, was, on the other hand, less likely to be a factor of importance.

Paper V and VI

Between June 1995 and October 2005, three patients with hypopharyngeal cancer and 13 consecutive patients with proximal esophageal cancer (15 males and 1 female) underwent circumferential PLE to which was added a free vascularized jejunal transplant (n=14), colonic transposition (n=1) or a gastric tube (n=1) at the Sahlgrenska University Hospital. All patients underwent surgery with curative intent. The patients with hypopharyngeal cancer received initial treatment with full-dose radiotherapy (64 Gy), but due to remaining tumor growth, they were offered rescue surgery. Patients with a tumor site in the proximal esophagus were treated with preoperative chemoradiotherapy (cisplatinium, 5-FU and 40.8 Gy), except for one patient that 7 years prior to the operation had received radiotherapy (58 Gy) due to a laryngeal carcinoma. All operations had a per- and postoperative uneventful course and postoperative examination in study V showed histopathological down-staging in all cases. The duration of the operations presented in study V ranged between 7h 20 min and 13h. By the time of the follow-up in study

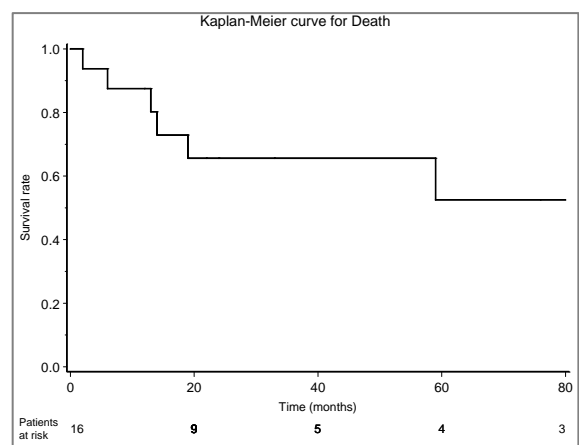


Figure 12. Cumulative survival rate from the time of initial surgery plotted as Kaplan Meier estimates for the 16 patients who have undergone pharyngo-laryngo-esophagectomy at the Sahlgrenska University Hospital since 1995 (Paper VI).

VI, four of the 16 patients had died due to metastatic disease and two patients had died due to myocardial infarction (Figure 12). In addition, two patients were recently diagnosed with local recurrence.

At the various follow-ups, KPSSI ranged from 70-90 (Paper V) and 60-90 (Paper VI), respectively. For the 10 survivors evaluated in Paper VI (mean follow-up time 54 months), Global QoL was generally good (mean 74), and the degree of dysphagia according to Ogilvie *et al.*, the mean WDS (Figure 13) and the dysphagia related scales and items of the EORTC QLQ OES-18 indicated a comparatively good ability to swallow. In spite of this, radiographical signs of disturbed bolus transport through the jejunal transplant and the remaining native esophagus were found in all patients examined. No correlation was, however, found

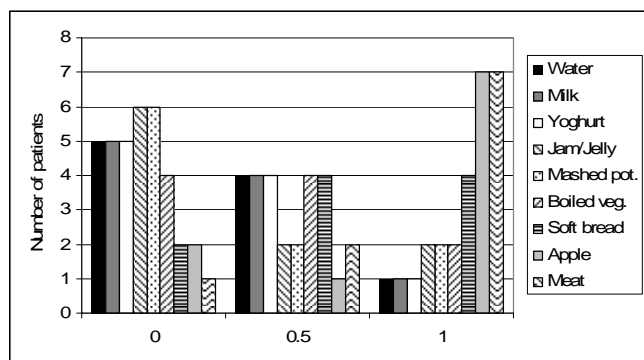


Figure 13. Watson Dysphagia Scores (WDS) for the 10 survivors that underwent pharyngo-laryngo-esophagectomy (PLE) (Paper VI).

between radiographic findings and clinical assessment or outcome from the HRQL questionnaire. The inter-observer agreement concerning the various radiological findings was high (weighted kappa = 0.81).

The speech valve function was initially assessed as good in one patient, average in two patients and poor in one patient (Paper V). At the later follow-up (Paper VI), all patients with a speech valve were considered to have a poor function. All patients learned how to use Servox speech, however, and could thereby maintain an acceptable way of communication.

Comments

Only a few reports exist describing the outcome after neoadjuvant chemoradiotherapy followed by PLE including substitution with a free jejunal transplant and the subsequent establishment of a speech valve. Hence, study V and VI substantially contributes to the knowledge within this field and, in addition, present an exceptional long-term follow-up. Our results, including no cases of perioperative deaths, no cases of graft necrosis, down-staging after chemoradiotherapy in all cases examined, an acceptable morbidity and a promising outcome in terms of survival, gives further support to the feasibility of this strategy and to its maintenance in the therapeutic arsenal.

Most patients examined in study VI demonstrated adequate oro-pharyngeal swallowing, despite radiological signs of disturbed bolus passage through the jejunal graft. Based on the clinical assessments and the results from the HRQL questionnaires, dysphagia was, however, relatively mild in those patients who were free of tumor recurrence, with a high rate of full oral nutrition in accord with previously reported series^{41,45,46,50}. This discrepancy undoubtedly suggests a variety of different reasons behind dysphagia in these patients. Furthermore, the mean global health status/QoL score was 74, which compares well to the general Swedish population¹⁰⁰.

The mean Watson Dysphagia Score was in the vicinity of that seen in patients surgically treated for achalasia¹¹⁹, whereas the EORTC QLQ OES-18 based dysphagia scale was close to that reported by Viklund *et al.* in patients surgically treated due to cancer of the intrathoracic esophagus or GEJ⁹⁹. Whether this is due to a lack of perception in a denervated tissue is open for speculation, but a poor correlation between symptoms of dysphagia and motility patterns has previously been reported also in non-operated patients examined by manometry¹²⁰. It must also be remembered that the pre-surgical expectations on the swallowing

ability after the operation might have influenced the self-assessed scoring, contributing to a response shift in the HRQL parameters. Thus, low expectations may have contributed to a relatively good score in a patient with a jejunal transplant, while an otherwise healthy person would have scored the same swallowing difficulties as more severe.

In contrast, the assessment of patients' speech valve functions revealed rather discouraging results. After some hopeful outcomes, at least initially, following intense training lead by a speech pathologist (Paper V), the apprehension at the later follow-up (Paper VI) was that the speech valve functions in our patients were generally poor. One of the main reasons for this poor outcome was frequent problems with leakage and thereby an inability to produce intelligible speech. As opposed to the native esophageal wall, the jejunal graft is comparatively sensitive why an erosive effect of the collars of the speech valve easily occurs. Broader collars that reduce the pressure on the jejunal wall could possibly be a feasible solution to this problem.

General discussion and future perspectives

For a disease associated with such a dismal prognosis as cancer of the esophagus, several aspects exist regarding the management of the patients concerned. The aim of this thesis is to put focus on some of those. Comprising the majority of patients, the centre of attention has to a great extent been those with an incurable disease destined for palliative care. Questions related to morbidity, adverse events, quality of life, mental illness and health economy have been emphasized; factors of special importance when handling patients with a limited life-span. However, cancer of the esophagus constitutes a wide specter of different disease states, including various tumor-stages, localizations, subtypes and the eligibility for curative treatment or not. Hence, the perspective on the management of these patients can be immensely widened.

Esophageal cancer remains a significant public health problem worldwide and prevention is of utmost importance. The vast majority of cases of squamous cell carcinoma can be explained by the use and abuse of tobacco products and alcohol, but a diet lacking in fresh fruits and vegetables may also play a role¹²¹. Another field of recent interest is the role of HPV infections in squamous cell carcinoma and the suggested benefit of vaccination schedules¹⁵. Thus, there is no shortage of potential targets for primary prevention efforts. For adenocarcinoma, on the other hand, the conditions are more ambiguous. Even though some risk factors are known, the benefit of strategies such as weight reduction, treatment of GERD or long-term surveillance of Barrett's esophagus have not yet been clearly established¹²¹. Nevertheless, chemoprevention has recently been suggested for patients at risk¹²². A daily intake of a non-steroidal anti-inflammatory drug, e.g. aspirin, may have a risk-reducing effect in some patients¹²³.

Although slightly improved survival rates have been observed in some countries during the last decade²⁴, the overall outcome in patients with esophageal cancer, even after treatment with a curative intent, is still disappointing. While there is still room for improvements of surgical procedures and radiation schedules, major steps towards better results will probably appear within the field of chemotherapy and targeted agents. Several classes of novel targets for the latter approach has been described, which include interference with growth regulatory signals, inhibition of angiogenesis, interference with uncontrolled replication, promotion of apoptosis and inhibition of invasion, metastasis and inflammation¹²⁴.

Today, the two most viable strategies for relief of dysphagia in patients with incurable cancer of the esophagus are SEMS treatment or brachytherapy. We, and others^{38,114}, have showed that both concepts have a place on the therapeutic arena and that careful selection of candidates are important to obtain a satisfactory outcome. Predictors of survival could be a help in this selection. An interventional study, performed in a new set of patients, which utilizes the found predictors in the choice of therapy could be a way to verify the generalizability and usefulness of our findings. Another approach, recently undertaken by our team, would be to combine the advantages of the two comparators. Consequently, this concept consists of SEMS insertion followed by immediate brachytherapy given as a single session. When testing such a novel strategy, careful monitoring of the occurrence of adverse events is of course an important aspect.

Other fields of interest, when considering strategies for relief of dysphagia and palliation in patients with esophageal cancer, are the development of new types of stents and new combinations of cytotoxic drugs. The enhancement within stent-designing, including development of biodegradable stents, stents with a radioactive coating as well as cytotoxic drug-eluting stents, is one promising route to achieve progress⁷. The combination of epirubicin, cisplatin and 5-FU (ECF) was recently found to offer better HRQL after 3 and 6 months compared to another scheme of chemotherapy in patients with advanced esophagogastric cancer, and could hence be an alternative for patients with a longer remaining life-expectancy¹²⁵.

The findings of a correlation between CT derived size assessment of the primary tumor and survival in study III is interesting, especially since no correlation between T-stage and survival was found. Although not confirmed in our study, the actual volume, length or diameter of the primary tumor could prove to be a better prognostic factor than the level of invasion into the esophageal wall as traditionally assessed by EUS²⁰. The CT scans in our study consisted of axial images only, but the use of thin collimation, that allows high quality multiplanar reformation, would significantly improve the three-dimensional measurements. The use of positive or negative oral contrast media just before the CT examination, with or without antispasmodic drugs (e.g. *N*-butylscopolamine) to distend the esophagus and stomach¹⁰³, would allow a better delineate of the limits of tumors. The use of MRI may also be a feasible alternative since it may be superior to CT in tumor size evaluation due to better multiplanar imaging and better contrast between soft-tissues¹⁰⁴. Consequently, this topic needs further investigation. As the technical development advances, numerous interesting findings and applications could be expected within this field.

Since the life time risk for a person to have an anxiety disorder or depression is reasonably high^{65,66}, as well as the fact that several studies report an increased prevalence of psychiatric morbidity within cancer populations^{67,71-73}, screening for these disease states are of great importance to offer adequate treatment and enhance compliance. Although none of the patients in study IV reported a previous or on-going episode of anxiety disorder or depression at inclusion, there was an obvious risk of recall biases when collecting these data. In addition, many psychiatric diseases are under-diagnosed and not always obvious to the patient⁶⁶. A more active interview at inclusion, with questions especially focusing on these aspects, could possibly have resulted in more reliable information at baseline.

The feasibility of the HADS questionnaire as a valid and reliable tool for detection of a possible or probable anxiety disorder and/or depression has been confirmed by many^{67-69,96}. However, most studies done so far, including our own, have all aimed to screen for illness and describe the prevalence within a certain population. Only a few studies have incorporated interventional procedures and thereby given guidelines for using the questionnaire as an instrument in clinical practice. An example of the latter kind of study was recently performed in breast cancer patients with results that further support the usefulness of the HADS questionnaire¹²⁶. Accordingly, the next step for researchers that share our field of interest would be to set up similar studies in patients with esophageal cancer.

Radical surgery for cancer of the PEJ involves huge resources in terms of adequate preoperative investigations, time in the operating theatre, collaboration between different professions, accurate monitoring of the patients per- and postoperatively and preparedness in the case of urgent complications. Consequently, PLE is mainly performed in high-volume centers. The relative scarcity of candidates suitable for this kind of intervention, as well as the constant need for maintenance of surgical skills, give further support to this centralization¹²⁷. Nevertheless, there is always room for improvements.

Several studies report inferior results for speech valve function among patients operated with a free jejunal transplant reconstruction due to cancer of the PEJ compared to patients with laryngeal cancer that has undergone laryngectomy alone^{93,94}. It has been proposed that the reason for this might be the intrinsic motility, the lack of muscle layers of the transplant or the absence of the pharyngo-esophageal segment^{50,94}. The function of the speech valves assessed in study VI was indeed rated as generally poor, and HRQL scores for trouble with speech reached a mean value of 47. Some studies have reported a better outcome^{48,50,93}, while others have suggested preservation of the larynx even with the use of free jejunal transplant reconstruction^{43,128}. The obvious reasons for this would be maintenance of the patient's own voice and, as a consequence, a better quality of life. However, there are two obvious risks associated to this surgical

strategy; one is to offer incomplete radicality. Secondly, the present findings of frequent oro-pharyngeal regurgitations suggest that larynx-sparing surgery may as well be burdened by aspirations to the respiratory tract as has frequently been observed in patients operated with gastric pull up¹²⁹.

The task to find the optimal curative treatment for patients with cancer of the PEJ remains. While many centers recommend a similar concept as described in Paper V and VI⁴¹⁻⁴³, others propose a more conservative strategy with chemoradiotherapy alone^{52,130,131}. The pros and cons in terms of the chances to relieve dysphagia, maintain an acceptable voice quality, reduce the risk for complications and, most importantly, to maximize the chances for survival must carefully be considered before choice upon therapy. However, today the lack of prospective studies gives the decision-maker little guidance. To conduct a randomized controlled trial, comparing neoadjuvant chemoradiotherapy followed by PLE with chemoradiotherapy alone, would be the next important step to gain more knowledge within this field and would, furthermore, be ethically motivated.

General conclusion

- Patients with incurable cancer of the esophagus or the GEJ have a severely deteriorated HRQL, both at inclusion and over time.
- Insertion of a self-expandable metal stent offers a more instant relief of dysphagia compared to endoluminal brachytherapy. In addition, stent treatment is currently more cost-effective than fractionated brachytherapy.
- Deterioration of HRQL was less pronounced in patients that receive brachytherapy, and after 3 months, relief of dysphagia was equal for the two comparators. Consequently, brachytherapy is a viable alternative in patients with a longer remaining life-expectancy.
- KPSSI, M-stage, UICC-stage, CT-derived tumor size parameters and 10 of the 25 scales and single items of the EORTC QLQ-C30 and QLQ-OES18 questionnaires correlate to survival in patients with incurable cancer of the esophagus or the GEJ.
- The physical functioning, fatigue and reflux scales are independent predictors of survival in patients with incurable cancer of the esophagus or the GEJ, while M-stage is the strongest predictor.
- Psychiatric morbidity is common among esophageal cancer patients, both at inclusion and over time regardless of the cancer-therapy given.
- Reconstruction after radical resection for cancer of the PEJ can be carried out with low peroperative mortality, acceptable morbidity and a promising functional outcome.
- HRQL was generally good after surgical treatment due to cancer of the PEJ, with mild dysphagia but a poor speech valve function. Radiological signs of disturbed bolus passage were common but the clinical impact of this seems to be low.

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Sammanfattning på svenska

Matstrupscancer beräknas vara den åttonde vanligaste cancerformen i världen, med över 460 000 nya fall per år. Sjukdomen diagnostiseras ofta i ett sent skede, är förknippad med stort lidande för den enskilda patienten och en allmänt dålig prognos. På grund av dessa omständigheter har behandlingen oftast en lindrande inriktning istället för en botande sådan. Huvudsyftet med lindrande behandling är framförallt att minska patienternas sväljningsbesvär. Denna avhandling omfattar olika frågeställningar kring behandling och omhändertagande av dessa patienter.

De två vanligast förekommande lindrande behandlingsmetoderna idag, stentbehandling och brachyterapi, jämfördes i en randomiserad studie där 65 patienter med obotbar matstrupscancer deltog. Vi fann att stentbehandling gav en snabbare minskning av sväljningsbesvären jämfört med brachyterapi, samt att denna dessutom var mer kostnadseffektiv. Brachyterapi, å andra sidan, gav en mindre uttalad försämring av patienternas upplevda livskvalitet i övrigt och en likvärdig effekt vad gäller sväljningsbesvär från tre månader och framåt. Detta innebär att denna behandlingsmetod kan vara ett bättre alternativ för patienter med en längre förväntad överlevnadstid efter diagnos (Arbete I+II).

För att utvärdera om patienternas överlevnadstid efter diagnos kan förutsägas analyserade vi kliniska data och livskvalitetsformulär (EORTC QLQ-C30 och QLQ-OES18) hos 96 patienter med obotbar matstrupscancer. I en univariat analys visade sig flera faktorer ha ett samband med överlevnadstiden. Dessa var Karnofsky Index, eventuell förekomst av metastaser, tumörstadium, datortomografiberäknad storlek av primärtumören samt 10 av de 25 skalorna och enskilda frågorna från livskvalitetsformulären. Då vi gick vidare med en multivariat analys fann vi dock att endast förekomst av metastaser samt fysisk funktion-, trötthets- och refluxskalorna var oberoende prediktorer för överlevnadstid. En intern validering av de funna prediktorena visade en hög grad av tillförlitlighet hos den funna prognostiska modellen (Arbete III).

Eventuell förekomst av psykisk ohälsa hos patienter med matstrupscancer har inte tidigare utvärderats. Med hjälp av HADS frågeformulär undersökte vi förekomsten av ångest- och depressionssjukdom hos 94 patienter med olika tumörstadiet av matstrupscancer, både vid diagnos och under ett års tid. Ångest- och/eller depressionssjukdom visade sig vara vanligt förekommande vid diagnos (42 % av patienterna), oavsett vad patienterna hade för sociodemografisk bakgrund, vilket tumörstadium de hade, eller vilken behandling de fick. Andelen patienter med ångestsjukdom minskade under de två första månaderna jämfört med vid diagnos (34 %), medan andelen patienter med depressionssjukdom var mer stabil över tiden (29 % vid diagnos). Depressionssjukdom visade sig vara mer vanligt förekommande hos dem som dog under studieåret jämfört med hos de som överlevde (Arbete IV).

Slutligen gjorde vi en långtidsutvärdering av kliniska och funktionella parametrar hos patienter som genomgått strålning- och cytostatikabehandling följt av kurativt syftande operation med faryngo-laryngo-esofagektomi och substitution med ett fritt jejunuminterponat. Resultaten vad beträffar överlevnad visade sig vara lovande jämfört med tidigare behandlingsalternativ. Patienterna uppgav överlag en relativt god livskvalitet samt lindriga sväljningsbesvär, trots att deras röstförmåga med hjälp av talventil bedömdes vara dålig och att röntgenundersökning visade nedsatt bolustransport genom interponatet (Arbete V+VI).

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Appendix 1



EORTC QLQ-C30 (version 3)

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

Please fill in your initials:

--	--	--	--	--

Your birthdate (Day, Month, Year):

--	--	--	--	--	--	--	--	--	--

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

31

--	--	--	--	--	--	--	--	--	--

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

During the past week:

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

Please go on to the next page

During the past week:

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

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

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

1 2 3 4 5 6 7

Very poor

Excellent

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

1 2 3 4 5 6 7

Very poor

Excellent

Appendix 2



EORTC QLQ – OES18

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

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

Appendix 3

The Hospital Anxiety and Depression Scale (HADS) Questionnaire

Instructions: Doctors are aware that emotions play an important part in most illnesses. If your doctor knows about these feelings he or she will be able to help you more. This questionnaire is designed to help your doctor know how you feel. Read each item and place a firm tick in the box opposite the reply which comes closest to how you have been feeling in the past week. Don't take too long over your replies: your immediate reaction to each item will probably be more accurate than a long thought out response.

I feel tense or 'wound up':	A	I feel as if I am slowed down:	D
Most of the time	3	Nearly all of the time	3
A lot of the time	2	Very often	2
Time to time, occasionally	1	Sometimes	1
Not at all	0	Not at all	0
I still enjoy the things I used to enjoy:	D	I get a sort of frightened feeling like 'butterflies in the stomach':	A
Definitely as much	0	Not at all	0
Not quite so much	1	Occasionally	1
Only a little	2	Quite often	2
Not at all	3	Very often	3
I get a sort of frightened feeling like something awful is about to happen:	A	I have lost interest in my appearance:	D
Very definitely and quite badly	3	Definitely	3
Yes, but not too badly	2	I don't take as much care as I should	2
A little, but it doesn't worry me	1	I may not take quite as much care	1
Not at all	0	I take just as much care as ever	0
I can laugh and see the funny side of things:	D	I feel restless as if I have to be on the move:	A
As much as I always could	0	Very much indeed	3
Not quite so much now	1	Quite a lot	2
Definitely not so much now	2	Not very much	1
Not at all	3	Not at all	0
Worrying thoughts go through my mind:	A	I look forward with enjoyment to things:	D
A great deal of the time	3	A much as I ever did	0
A lot of the time	2	Rather less than I used to	1
From time to time but not too often	1	Definitely less than I used to	3
Only occasionally	0	Hardly at all	2
I feel cheerful:	D	I get sudden feelings of panic:	A
Not at all	3	Very often indeed	3
Not often	2	Quite often	2
Sometimes	1	Not very often	1
Most of the time	0	Not at all	0
I can sit at ease and feel relaxed:	A	I can enjoy a good book or radio or TV programme:	D
Definitely	0	Often	0
Usually	1	Sometimes	1
Not often	2	Not often	2
Not at all	3	Very seldom	3

Appendix 4

Karnofsky Performance Status Scale

100	Normal, no complaints, no evidence of disease
90	Able to carry on normal activity, minor symptoms of disease
80	Normal activity with effort, some symptoms of disease
70	Cares for self: unable to carry on normal activity or active work
60	Requires occasional assistance but is able to care for needs
50	Requires considerable assistance and frequent medical care
40	Disabled, requires special care and assistance
30	Severely disabled, hospitalisation is indicated, death not imminent
20	Very sick, hospitalisation necessary, active treatment necessary
10	Moribund, fatal processes progressing rapidly
0	Dead