Prognostication in esophageal cancer
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General introduction and outline of the thesis
General introduction

Esophageal cancer
World wide, esophageal cancer is sixth on the list of cancer related mortalities. It is an aggressive disease with early lymphatic and hematogenous dissemination. The incidence of cancer of the esophagus is rapidly rising in Western Europe and North America, mainly due to the increase in adenocarcinomas around the gastro-esophageal junction in the past decades.

Surgery is currently seen as the best curative treatment option. However, in the Netherlands approximately 40% of the 1500 patients that present annually can not undergo surgery due to distant metastasis or local irresectability. Despite comprehensive preoperative staging to select patients for potentially curative surgery, many patients present with recurrences within two years after surgery and even in specialized high volume centers, 5-year survival rates rarely exceed 40%.

Individualized treatment of patients with esophageal cancer
The treatment of patients with cancer of the esophagus and gastroesophageal junction is highly complex and needs an interdisciplinary approach. In recent years the treatment of patients with esophageal cancer became more and more tailored to the individual patient. Recent advances in endoscopy have changed the indications for surgical treatment in patient with lesions which are limited to the mucosa. These lesions can now be diagnosed and treated with endoscopic resection (ER) in experienced centers. In selected patients lesions can be removed by ER with a low rate of severe complications. The role of surgery in patients with locally advanced esophageal carcinoma has also evolved. Recent research indicated that patients with an adenocarcinoma located in the (distal) esophagus might have a survival advantage when they undergo more extensive surgery (transthoracic esophagectomy with extended lymphadectomy). Patients with tumors located at the junction might be better off with a transhiatal resection since they do not have a survival benefit after a more extensive procedure, while a transhiatal approach is associated with less morbidity.

Despite comprehensive preoperative staging to select patients for potentially curative surgery, many have unrecognized metastatic disease at the time of first presentation and later present with locoregional, hematogenous and pleural / peritoneal recurrences within two years after potentially curative surgery. Novel diagnostic modalities, such as FDG-PET have been used to enhance patient selection for curative esophagectomy. However, the diagnostic yield of FDG-PET is limited after extensive state-of-the-art conventional staging.

In future, treatment will probably become more individualized. It is important to focus on distinctive clinical and biological characteristics of patients with esophageal cancer with the aim of increasing efficacy of treatment and decreasing harms.
Staging of esophageal cancer

Esophageal cancer is generally staged according to the TNM-staging system\textsuperscript{17,18}. For the esophagus, the staging system originally designed for squamous cell carcinoma is now also applied for adenocarcinoma, despite their potentially different biological behavior. For adenocarcinoma of the GEJ, staging systems for cancer of both the esophagus and the stomach are used\textsuperscript{17,18}. The T-stage represents the depth of tumor ingrowth, the N-stage stands for the presence (N1) or absence (N0) of regional lymph node metastases, while the M-stage describes the presence (M1) or absence (M0) of distant metastases (lymphatic and hematogenous). However, this classification is poorly predictive for the individual patient\textsuperscript{19-21}. Tumors with comparable type and stage show a large heterogeneity in clinical outcome. Throughout the years, many additional factors have been described which may have an important prognostic impact such as the number of positive lymph nodes and the radicality of resection\textsuperscript{6,19,22,23}. Inclusion of these factors is recommended, but definitive useful solutions are not available. Surgical staging according to findings in the resection specimen are seen as the gold standard. The preoperative staging of esophageal cancer remains difficult because errors in predicting T, N and M stage frequently occur with the current imaging techniques, especially in low-volume centers for EUS\textsuperscript{24,25}. Better surgical staging based on findings in the resection specimen can be clinically helpful to guide the development or to guide the improvement of preoperative diagnostic modalities. Furthermore, it is helpful to supply tailored follow-up schedules, to target novel adjuvant strategies and to supply more reliable prognostic information for the individual patient. Finally, it might even have a future role in comparing hospitals.

Molecular biology of esophageal cancer

Compared to other cancers of the gastrointestinal tract, lymphatic and hematogenous dissemination occurs relatively early during the development of esophageal cancer\textsuperscript{26}. It has been suggested that this early lymphatic dissemination is due to the extensive lymphatic network in the submucosa of the esophagus, which is less developed elsewhere in the digestive tract\textsuperscript{26}. However, the potential for lymphatic and hematogenous dissemination greatly varies between tumors with comparable stages. These differences in biological behavior of esophageal adenocarcinomas have been explained by the role of molecular tumor biology and patient genetics.

So far, the molecular analysis of esophageal cancer has mainly focused on the prognostic significance of alterations in single candidate genes like COX-2 and HER-2/neu\textsuperscript{27-30}. These single candidate genes do not have sufficient prognostic power in the clinical setting to justify clinical implementation for staging purposes, however these factors may offer new individually tailored therapeutic options, such as selective COX-2 inhibitors (e.g. celecoxib) and selective inhibitors of HER2 (e.g. herceptin)\textsuperscript{31,32}. The completion of the sequencing of the human genome in 2003 marked the dawn of a new era of human biology and medicine\textsuperscript{33}. With the development of DNA microarray technologies it has been made possible to analyze the expression of thousands of genes.
simultaneously. The principle of a microarray experiment is illustrated in Figure 1. mRNA from one condition (e.g. mRNA of an esophageal adenocarcinoma of a patient who died from hematogenous dissemination) is labeled with a fluorescent dye and mixed with the same amount of mRNA from another condition (e.g. mRNA of an esophageal adenocarcinoma of a patient who survived), labeled with a reverse-color dye. Next, the fluorescently labeled mRNA is hybridized on an oligonucleotide microarray. The hybridization intensities of each spot can be measured and analyzed which results in an mRNA profile.

The broad analysis of gene expression in esophageal adenocarcinoma may have several advantages: genes with a previously unknown role in carcinogenesis may be recognized, relationships between genes may be characterized and patterns for prognosis may be identified. In several cancers, (e.g. breast and colon cancer) genomic profiling was able to predict survival. In esophageal adenocarcinoma only limited data are available and so far microarray research mainly focused on the progression of Barrett’s esophagus into early cancers.

**Prediction of the risk for complications**

Surgery is currently the best curative treatment option for esophageal cancer. However, esophagectomy is accompanied by a high operative risk. Advances in surgical techniques together with improvements in perioperative care have reduced the operative morbidity- and mortality risk and in most high-volume centers in-hospital mortality is below 5%. The crude operative mortality rate is an objective and robust measure of outcome that can be used to inform patients and to compare quality of care between hospitals, but does not correct for risk factors of individual patients. Risk-adjusted models have been developed to correct for the so-called case mix (age, general health and comorbidity), but in esophageal cancer surgery, these models have never been externally validated and/or have a low discriminative value.
While in-hospital mortality in high-volume centers has steadily decreased to an acceptable level, esophagectomy is still associated with significant morbidity. Early postoperative complication rates vary between 40 and 80%, depending on the applied criteria\textsuperscript{3,43}. As is the case with in-hospital mortality, the risk of developing complications in the early postoperative period is probably dependent on patient related risk factors. Predictive models for complications that were previously developed, mainly focused on the presence of complications per se (without any grading of severity) and appeared to lack any predictive power in esophageal surgery\textsuperscript{44-46}. Recently a classification system was developed to grade the severity of complications. This classification system is based on the therapeutic consequences of complications and is significantly correlated with length of hospital stay\textsuperscript{47}. With use of this model it might be possible to predict the severity of complications in patients who undergo esophagectomy for cancer.

**Informing patients about prognosis**

In line with current notions about autonomy, patients should be adequately informed about their disease status and prognosis. Improving individualized prognostication of survival is a challenge. However, another challenge is to inform patients about their (often poor) individual prognosis. After potentially curative esophagectomy (which is often accompanied by substantial morbidity and impact on quality of life) it may be difficult to discuss ‘poor’ prognoses with sensitivity and honesty\textsuperscript{3,43,48}. In developed countries, cancer patients increasingly express a preference for more detailed information and involvement concerning their disease. The majority of patients seek full information regarding their diagnosis, treatment options and side effects of treatment. Evidence for the preferences concerning disclosure of prognosis, though, is limited to breast cancer patients and cancer patients with metastatic disease\textsuperscript{49-51}. The clear majority of these patients want information regarding their prognosis. However, information preferences concerning prognosis in patients after potentially major surgical treatment, such as esophagectomy are unknown. It is not clear which patients want detailed information and which patients want more general information. Moreover, it is unknown which (medical and psychological) factors are associated with certain preferences.

**Outline of the thesis**

The studies in this thesis address issues concerning prognostication in esophageal cancer, and focus on those patients who received potentially curative treatment. The thesis is divided into three parts, PART I - Prognostication of survival focuses on possible improvement of staging after potentially curative surgery for adenocarcinoma of the esophagus and gastroesophageal junction. Attention is paid to standard clinicopathological factors and novel molecular factors. PART II - Prognostication of complications focuses on morbidity after
esophagectomy and the identification of patients who have a higher risk for complications after surgery for malignant disease. Finally, PART III - Preferences for prognostic information focuses on the preferences of patients in the communication of prognosis.

PART I – Prognostication of survival

TNM cancer staging systems predict survival on the basis of the anatomic extent of the tumor. However, numerous other prognostic factors have been described, but are not included in this system. Chapter 1 reviews established pathological determinants found in the resection specimen, aspects of operative technique, response to preoperative chemoradiation therapy and the occurrence of complications and their prognostic impact. Furthermore, this chapter reviews different proposed adaptations of esophageal cancer staging to improve postoperative staging in patients with adenocarcinoma of the esophagus and gastroesophageal junction.

One of the pathological determinants which is often overlooked in patients with adenocarcinoma of the esophagus and gastroesophageal junction is the presence of extracapsular lymph node involvement. In Chapter 2, the incidence of extracapsular lymph node involvement and its relation with other pathological parameters is evaluated. Furthermore, its prognostic impact in patients with adenocarcinoma of the esophagus and gastroesophageal junction is evaluated.

In Chapter 3 patients are described with an adenocarcinoma of the cardia and lymph node metastases in the proximal field of the chest. The incidence of these relatively distant lymph node metastases and their prognostic significance are evaluated.

The accuracy of the TNM system is questioned repeatedly. More accurate estimates of survival for individual patients may be possible by using a different approach, such as nomograms. The development of a nomogram for patients with adenocarcinoma of the esophagus or gastroesophageal junction is described in Chapter 4. Nomograms are easy to use in clinical practice and can predict survival at different time-points with better accuracy than conventional TNM-staging. Nomograms taking into account diverse pathological parameters make it possible to predict individual prognosis. To test generalizability, Chapter 5 describes the validation of the prognostic nomogram in an independent series of patients treated in a Belgian high volume center.

The above mentioned chapters all describe prognostic factors which can be found with routine pathology and do not need specific immunohistochemical staining, nor genetic analyses. However, molecular pathology has revealed an overwhelming number of genes and molecules, which are related to tumor invasion and dissemination. Many of these genes and molecules have prognostic impact. Chapter 6 reviews the recent advances in our understanding of genetic and molecular changes related to adenocarcinoma of the distal
esophagus and GEJ with special emphasis on their specific prognostic value and possibilities for (future) targeted therapy in the clinical setting.

The hepatocyte growth factor receptor, C-Met, is related with COX-2 expression in esophageal cancer and has oncogenic properties. In Chapter 7 the prognostic value of C-Met is determined. Furthermore, its relation with other important proteins involved in cancer progression is described.

Although the presence and extent of lymphatic dissemination is one of the most important predictors of survival in patients with adenocarcinoma of the esophagus, it remains difficult to determine preoperatively, because errors frequently occur with the current diagnostic modalities. Also, the molecular analysis of esophageal cancer has mainly focused on the prognostic significance of alterations in single candidate genes and these genes have limited additional power. In Chapter 8 the gene expression of the entire human genome is analyzed to identify a specific genetic signature for the development of lymphatic dissemination.

Despite comprehensive preoperative staging to select patients for potentially curative surgery, many have unrecognized metastatic disease at the time of first presentation and later present with recurrent disease after esophagectomy. The gene expression profiles of patients with and without hematogenous dissemination are analyzed with use of the microarray technique in Chapter 9. The prognostic impact of genetic signatures and the relation of genetic pathways in the development of hematogenous dissemination are described.

**PART II – Prognostication of complications**

After esophagectomy for adenocarcinoma of the distal esophagus, the majority of patients develops an early recurrence and dies within two years. It has been suggested that potent immunosurveillance is of pivotal importance to eradicate microscopic residual disease after surgery. Esophagectomy is frequently accompanied by substantial complications with secondary disturbance of the immune system. These complications might have a negative impact on immunosurveillance and thus on the time interval until tumor recurrence. The effect of complications on the time interval until death due to recurrence is described in Chapter 10.

The operative mortality rate is an objective and robust measure of outcome that can be used to inform patients and to compare quality of care between hospitals. However, direct comparison of mortality rates between hospitals can be misleading. Crude rates do not take into account the differences in physiological condition (age, general health and comorbidity) between patients of the patient population. The O-POSSUM score predicts in-hospital mortality based on a combination of patient related parameters. In Chapter 11 the external validation of the O-POSSUM score is described. It is analyzed how well the model, originally developed in the United Kingdom, fits on the patients operated on in a high volume center for esophageal surgery.
The severity of complications was never taken into account in predictive models. Previously developed predictive models include also peroperative findings such as blood loss and operation time or focus only on in-hospital mortality. In Chapter 12 a new model is described to predict the severity of complications with use of conventional and widely available preoperative risk factors for patients who underwent potentially curative esophagectomy for cancer. To enhance clinical applicability of a model with more than two outcomes, a nomogram is developed.

PART III – Preferences for prognostic information

It is a challenge to accurately estimate individual prognosis, but it is another challenge to inform patients about their prognosis. In Western countries, cancer patients increasingly express a preference for more detailed information concerning their disease. The preferences of esophageal cancer patients for content, style and format of prognostic information are analyzed in Chapter 13. Also, diverse clinico-pathological predictors of these preferences are studied.

Apart from clinico-pathological factors, probably also psychological factors are associated with certain preferences for information. In Chapter 14 the relation of various psychological predictors for preferences regarding prognostic information are explored.

References


