Prognostication in esophageal cancer
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Citation for published version (APA):

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Summary
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In Western countries, the incidence of adenocarcinomas of the esophagus and gastro-esophageal junction has been steadily rising over the past decades. The treatment of patients with esophageal cancer is highly complex and needs an interdisciplinary approach. The recent development in several fields of medicine, ranging from targeted therapy for diverse molecular factors to the treatment of early cancers with endoscopic resection (ER), makes tailoring of treatment strategies to individual patients of pivotal importance. Accurate knowledge of predictive factors (standard pathological factors as well as genetic factors) for cancer recurrence might lead to improved prognostication and individually tailored therapeutic options.

For advanced lesions, surgery is still the best curative treatment, but it is associated with high morbidity and substantial mortality. Individual patients may have a higher or lower chance of experiencing complications depending on patient and treatment related factors. Models that take into account these differences and predict these outcomes for the individual patient might be used in treatment decisions, in comparing hospital performance and in informing patients about their risks associated with esophagectomy.

The studies described in this thesis intend to provide a better insight in the prognostication of survival and complications. Furthermore, implications on informing patients about their individual risk are described. The results of the present thesis will be discussed in more detail in three parts, PART I entitled “Prognostication of survival”, PART II entitled “Prognostication of postoperative complications” and PART III entitled “Preferences for prognostic information”.

PART I – Prognostication of survival

The purpose of a conventional cancer staging system is to predict survival on the basis of the anatomic extent of the tumor. This information can be used to estimate prognosis (post-treatment) of the patient and to direct tailored therapy (mainly pre-treatment). The current TNM system for esophageal carcinoma is based primarily on patients with squamous cell carcinoma of the cervical and thoracic esophagus. As is reviewed in chapter 1, more than a dozen conventional pathological factors with prognostic impact have been described in patients with adenocarcinoma of the esophagus and gastroesophageal junction. Although many of these factors have an important prognostic effect, these factors have not been incorporated in the TNM classification of the esophagus. This indicates that, most probably, additional factors can improve postoperative staging. In future, staging systems should be more dynamic and should reflect the increasing knowledge of cancer and its treatment. The rising problem is that the more variables a model contains the less practical it becomes. However, with the wide-spread use of computer programs and web-based engines this problem might be easily overcome. In this light, adenocarcinoma of the esophagus may
play an important role in the development of new computer based staging systems, since it is mainly a disease of the west, where the use of computers is getting more and more integrated in daily clinical practice.

One important factor which is often overlooked in patients with gastrointestinal cancers is the strong prognostic impact of extracapsular lymph node involvement. The biological significance of extracapsular lymph node involvement is described in chapter 2. The presence and extent of extracapsular lymph node involvement is an independent prognostic factor and identifies a subgroup of patients with a significantly worse long-term survival. Its presence reflects a particularly aggressive biologic tumor behavior and detection and quantification of extracapsular LNI in the surgical resection specimen might be helpful to individualize postoperative therapeutic strategies in the adjuvant setting. To facilitate a tailored approach in the neoadjuvant setting it would be necessary to discriminate preoperatively between positive nodes with and without extracapsular LNI, which is unreliable with the current diagnostic modalities.

The clinical relevance of positive nodes in the proximal field of the chest in patients with an adenocarcinoma of the cardia is also unknown, because in most hospitals patients with gastric cardia cancer undergo resection without intrathoracic lymphadenectomy. In Chapter 3 the incidence of these positive proximal nodes is described in patients who underwent an extended transthoracic esophagectomy as part of a randomized trial, and evaluates their prognostic significance. It was shown that lymph node metastasis in the proximal field of the chest is a not uncommon phenomenon and an indicator of poor prognosis in these patients. Preoperative detection of these nodes in the proximal field changes the treatment strategy since a transhiatal esophagectomy is insufficient under these circumstances. In order to resect these positive lymph nodes an extended transthoracic procedure should be performed. However, even after extended transthoracic resection, long-term survival is poor.

In a consecutive series of patients with adenocarcinoma of the esophagus and gastro-esophageal junction, treated in the Academic Medical Center in Amsterdam, pTNM-staging alone had moderate prognostic capabilities, as is described in chapter 4. More accurate estimates of survival for individual patients were possible by adding other clinicopathological prognostic factors to the model. To allow easy clinical use, a nomogram was developed based on the three strongest prognostic factors (depth of tumor infiltration, lymph node ratio and extracapsular lymph node involvement). This nomogram has the advantage that it estimates individual recurrence probability at three different time points after operation. To enhance applicability in other hospitals, the validity of the nomogram was externally tested in an independent series in chapter 5. Also in a consecutive series of patients treated at a foreign high volume center for esophagectomy, nomogram predictions discriminated better than pTNM-staging. The nomogram may be used to supply the patient with more reliable prognostic information, to offer tailored follow-up schedules and / or novel therapeutic strategies for the individual patient.

Nomogram predictions with use of clinicopathological predictors were not perfect, because our knowledge of prognostication is still incomplete. Increased knowledge of patient and
tumor related genetics may improve prognostication. Although we are still scratching the surface of knowledge about tumor and patient biology, molecular biology has revealed an overwhelming number of genes and molecules, which are related to tumor invasion and metastasis (lymphatic and hematogenous dissemination). The current knowledge of the prognostic impact of these genes and molecules in patients with adenocarcinoma of the esophagus is reviewed in chapter 6. A better knowledge of these factors may not only improve prognostication but may also offer new individually tailored options for targeted molecular therapy. In Chapter 7 the prognostic impact of C-MET expression in esophageal adenocarcinomas which developed in a Barrett’s segment is analyzed. Patients with high Met expression had significantly reduced overall and disease specific 5-year survival rates. Expression of Met was recognized as an independent prognostic factor by multivariate analysis. These findings support the concept of Met tyrosine kinase inhibition as (neo-)adjuvant treatment.

Dissemination is a complex, multistep process, during which tumor cells spread from the primary tumor mass to lymph nodes and more distant sites. Probably it is not one genetic factor that accounts for the development of dissemination. Therefore, gene expression profiling with use of microarrays was used to analyze the signatures of tumors which comprised genes of the whole genome. In Chapter 8 it is shown that with use of gene expression profiling of the primary tumor, it is possible to predict the presence of lymph node dissemination significantly better than with random classification. However, the predictive profile does not outperform current clinical practice to predict the presence of lymphatic dissemination in patients with adenocarcinoma of the esophagus. Several new genes and genetic pathways which are important in the development of lymphatic dissemination in esophageal adenocarcinoma were identified. The microarray technique was also used to predict the development of hematogenous dissemination after potentially curative surgery. This is described in Chapter 9. In esophageal adenocarcinoma it is not possible to predict the development of hematogenous dissemination with use of gene expression analysis. However with use of genetic profiling, several unknown genetic pathways which are important in the development of hematogenous dissemination were identified.

PART II – Prognostication of complications

In this part, the long-term impact of postoperative complications is described and diverse factors which are related with the individual risk for postoperative complications after esophagectomy for cancer are analyzed. In Chapter 10, the relation between postoperative complications and survival is described. It is shown that the relation between postoperative complications and cancer recurrence per se is not causal. However, postoperative complications were significantly associated with a short time-interval until death due to cancer recurrence in multivariate analysis. A possible explanation for this phenomenon is
that disturbed immunological host factors enhance microscopic residual disease to develop more rapidly into fatal recurrence.

In Chapter 11 the validation of the O-POSSUM model is described. The O-POSSUM overpredicted in-hospital mortality threefold and could not identify patients with a higher risk for in-hospital mortality. Therefore it can not supply individualized risk estimates and can not be used to compare the performance of different hospitals. Models like O-POSSUM are based on predicting in-hospital mortality, which is a relatively rare event in high volume centers performing esophageal cancer surgery. In Chapter 12 the development of a risk model that focuses on the severity of complications is described. With use of a nomogram it was possible to predict the occurrence and severity of complications of patients in daily clinical practice. Although calibration of the model is reasonably good, this model also suffers from a low discriminative ability. One of the reasons may be that the nomogram uses only preoperative variables. This means that unexpected complexities during surgery and during the early postoperative period (e.g. accidental aspiration, malfunctioning epidural analgesia) are not taken into account.

PART III – Preferences for prognostic information

This part of the thesis focuses on the implications of individualized risk estimates in terms of communication with patients. It is not only a challenge to accurately estimate individual prognosis, but also to inform patients about their prognosis, especially when prognosis is dismal. In Chapter 13 it is described that after potentially curative esophagectomy for cancer, the majority of patients wants detailed prognostic information and wants their specialist to begin the prognostic discussion. The majority of patients preferred their doctor to be realistic and words and numbers were preferred over figures and graphs. However, still there is a substantial proportion of patients that does not want to be fully informed, or is at least ambivalent about what their preferences are. The challenge for clinicians is to recognize when patients are ready to hear prognostic information, because forcing information on patients who would rather not know might be harmful. In Chapter 14 it is explored which psychological factors predict the preferences for prognostic information. It is shown that the more fear of recurrence, the more information patients want about their prognosis. Post hoc analyses showed that patients with worse quality of life reported more fear of recurrence.