Oesophagogastric cancer: exploring the way to an individual approach

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Citation for published version (APA):

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Worldwide, oesophageal and gastric cancer account for 1.5 million new cancer cases each year. Both are in the top-10 leading causes of cancer death.\textsuperscript{1} In several Western countries, including the Netherlands, the incidence of oesophageal adenocarcinoma has significantly increased over the last decades.\textsuperscript{2-4} In contrast, the incidence of gastric cancer has been declining\textsuperscript{5,6} which holds especially true for non-cardia gastric cancer.\textsuperscript{5} Despite improvements in the treatment of oesophagogastric cancer, the prognosis remains poor in Western countries, with a 5-year survival rate of approximately 20%.\textsuperscript{4,5,7} About 40 – 50% of patients with this cancer present with incurable, stage IV disease.\textsuperscript{4,5,8} Furthermore, the majority of patients who are eligible for potentially curative treatment have locally advanced, lymph node positive disease. In order to improve survival rates after surgical resection, several (neo)adjuvant treatment regimens have been studied in recent years.\textsuperscript{9-11} Following the results of several trials and meta-analyses, preoperative chemoradiotherapy (CRT) followed by surgery is currently the preferred treatment of locally advanced oesophageal cancer in the Netherlands.\textsuperscript{11,12} For gastric cancer patients, both perioperative chemotherapy in combination with surgery and surgery followed by CRT are accepted multimodality approaches.\textsuperscript{9,10} Both these treatment regimes have been shown to increase survival, but there is still much room for improvement. An important strategy to improve treatment results is appropriate patient selection for different treatment modalities. Evaluating the outcome of subgroups based on pathological, radiological or genetic tumour characteristics can identify patients who might benefit from additional or alternative treatment regimes. It can also avoid mortality or morbidity in patients who gain little or have no benefit from a particular treatment. In the studies described in this thesis, the focus has been on improving the outcome of oesophagogastric cancer patients by exploring ways to individualize multimodality treatment in this patient group.

OUTLINE OF THIS THESIS

Part I. Surgical treatment and patient selection
Surgery is the cornerstone of potentially curative treatment of oesophageal and gastric cancer. Both oesophagectomy as well as gastrectomy are high-risk surgical procedures associated with a postoperative mortality rate which can be as high as 10% in nationwide registries.\textsuperscript{13,14} In an effort to improve these treatment results, oesophageal and gastric cancer surgery is increasingly performed in specialized centers. This centralization is observed throughout European countries, including the Netherlands.\textsuperscript{15} More recently, surgical audits for oesophagogastric cancer treatment have been initiated in the United Kingdom, Denmark, and the Netherlands.\textsuperscript{16-18} These auditing programs provide surgeons with the opportunity to learn from their own results by comparing these to the results of others. Also, differences between hospitals can be closely monitored. As described in Chapter 2, a systematic review of the literature is performed with the aim to define a minimum set of evidence-based quality of care indicators for the surgical treatment of locally advanced gastric cancer. Despite improvements in gastric cancer treatment,
the survival rate remains poor and has even worsened in Western patient series.\textsuperscript{19,20} One explanation might be the declining incidence of intestinal type tumours (according to Laurén\textsuperscript{21}), whereas the incidence of the more aggressive diffuse type tumours has remained stable or has even increased.\textsuperscript{22,23} In **chapter 3**, the surgical treatment results of gastric cancer patients is evaluated, with specific attention to differences in outcome between intestinal and diffuse type tumours.

The increasing use of neoadjuvant chemoradiotherapy (CRT) in oesophageal cancer treatment has added more complexity to the selection of patients for subsequent surgical resection. Patients who develop distant metastasis during or shortly after CRT have little or no benefit of surgical resection. The added value of oesophagectomy in patients with a major pathological response has also been questioned.\textsuperscript{24} The effect of re-staging patients after CRT using 18F-fluorodeoxyglucose positron emission tomography and computed tomography (FDG-PET/CT) is insufficiently investigated. Recent studies suggest that changes in metabolic parameters can identify patients with a major pathological response to CRT with a high accuracy.\textsuperscript{25,26} In **chapter 4**, the value of FDG-PET/CT for the selection of oesophageal cancer patients for surgical treatment is evaluated.

Gastrointestinal stromal tumours (GISTs) are rare tumours that can occur throughout the digestive system. Surgery is the standard of care for patients with localised disease. The response to additional chemo- and radiotherapy is very limited, and the prognosis of patients with locally advanced or metastatic disease used to be poor. The introduction of tyrosine-kinase inhibitor imatinib has significantly improved the prognosis of locally advanced and metastatic GISTs. The role of surgical treatment needs to be redefined with the availability of imatinib. In **chapter 5**, the outcome of patients who underwent surgical resection for a gastric GIST with or without preoperative imatinib treatment is analysed.

**Part II. Multimodality treatment**

In an attempt to improve the outcome of oesophageal and gastric surgery, several clinical trials of combined modality therapy have been performed. In 2001, the results of the US Intergroup 0116 trial were published and showed a benefit for postoperative chemoradiotherapy in gastric cancer patients who had undergone a radical (R0) resection.\textsuperscript{9} In the British MAGIC study, perioperative chemotherapy was associated with an improved 5-year overall survival (36%) compared to surgery alone (23%) in patients with gastric or lower oesophageal adenocarcinoma.\textsuperscript{10} In the CROSS trial, the addition of preoperative chemoradiotherapy to surgery increased the R0 resection rate in patients with oesophageal or oesophagogastric junction cancer, which lead to an improved disease-free and overall survival.\textsuperscript{11} Following the results of this trial, chemoradiotherapy followed by surgery is currently the preferred treatment of potentially curable oesophageal cancer in the Netherlands. For gastric cancer patients, perioperative chemotherapy or surgery followed by chemoradiotherapy are accepted multimodality approaches.\textsuperscript{9,10} In **chapter 6**, trends in the multidisciplinary treatment of oesophageal and gastric cancer patients in the Netherlands over the last decade are shown.
A microscopically irradical (R1) resection is a well-known adverse prognostic factor after gastric cancer surgery.\textsuperscript{27-30} However, the prognostic impact of an R1 resection in patients treated with postoperative CRT is unclear. In chapter 7, the prognostic significance of an R1 resection in gastric cancer patients treated with postoperative chemoradiotherapy is evaluated. Following this single institution study, the survival of a large Dutch cohort of R1 resected gastric cancer patients treated with or without postoperative chemoradiotherapy is analysed in chapter 8.

Part III. Genetic profiling

Over the last decade, there has been an enormous increase in studies on gene expression profiling of different tumour types. One of the landmark studies was done with breast cancer patients.\textsuperscript{31} Using microarray analysis with RNA from breast tumours, a prognostic gene expression profile consisting of 70 genes was identified. This 70-gene signature classified patients into a low or high-risk category for distant metastasis. A prospective validation study confirmed its use in clinical practice by identifying a group of patients in whom adjuvant treatment can be safely withheld.\textsuperscript{32} Also, in other cancer types, genetic profiling has been shown to provide prognostic information in addition to clinicopathological features such as TNM classification.\textsuperscript{33} In chapter 9, a review of the literature on gene expression profiling in oesophageal cancer is presented. A prerequisite for the success of studies aimed at genetic tumour profiling is high quality tumour tissue and detailed clinicopathological data. Due to the use of neoadjuvant CRT in potentially curable oesophageal cancer patients, the availability of untreated tumour tissue is limited to endoscopically obtained biopsy samples. Little is known about the success rate and possible pit-falls in the work-up of these small samples. Chapter 10 provides a detailed description of the work-up of fresh-frozen endoscopic biopsy samples of oesophageal adenocarcinoma towards DNA and RNA libraries suitable for next-generation sequencing. In current literature, the number of studies aimed at genetically characterize oesophageal adenocarcinoma is limited. Only recently, a large study in which whole-exome sequencing was used on 149 oesophageal adenocarcinoma resection specimens showed a high rate of genomic aberrations.\textsuperscript{34} The prognostic impact of these aberrations was not reported in this study, likely due to the absence of follow-up data. In chapter 11, DNA copy number aberrations and gene expression profiles of pre-treatment tumour samples from patients with oesophageal adenocarcinoma are analysed for the existence of genetically different subgroups and candidate therapeutic targets. Finally, the results of this thesis and future perspectives are discussed in chapter 12.
REFERENCES