A multimodality approach to improve oesophageal and gastric cancer treatment

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01 INTRODUCTION
GENERAL INTRODUCTION AND OUTLINE OF THE THESIS

Over the past decades, oesophageal and gastric cancer treatment has improved. Nevertheless, survival is still poor, leaving considerable room for further optimisation. From a clinical perspective, this can be done by improving patient selection (finding the right patient for the right treatment), by improving current treatment, or by adding new treatment strategies to the available armamentarium.

Studying the outcomes of various subgroups of patients who were treated according to current standards enables the identification of new patient categories for whom alternative treatment strategies might be beneficial (Part I). Furthermore, areas of improvement in oesophagogastric cancer surgery are potentially revealed by analysing current outcomes (Part II). By exploring the safety and feasibility of innovative techniques and new treatment strategies the care for oesophageal and gastric cancer patients might be taken a step further (Part II).

Epidemiology and aetiology

Oesophageal and gastric cancer contribute considerably to the worldwide cancer burden. Both are in the top-10 of most common and lethal malignancies.1 Highest incidences of both oesophageal and gastric cancer are found in developing countries.4

As for oesophageal cancer, the incidence rates of the two major histological cancer types vary greatly per geographic region which highlights the differences in aetiology throughout the world.5 Squamous cell carcinoma (SCC) incidences are highest in Southern-eastern and Central Asia, whilst adenocarcinomas are more common in high-income countries.2 SCCs are predominantly located in the proximal and middle oesophagus and are associated with high alcohol consumption and tobacco smoking.45 Adenocarcinomas are related to gastro-oesophageal reflux disease, obesity and, to a lesser extent than SCCs, to tobacco smoking.45 Three quarters of all oesophageal adenocarcinomas are located in the distal oesophagus.4

The vast majority of gastric cancers are adenocarcinomas which can be subdivided in three histological subtypes according to Laurén: intestinal, diffuse and mixed types.47 Intestinal subtypes form glands and resemble adenocarcinomas of the large intestine.48 They arise in a background of chronic mucosal damage and are the predominant subtype in the proximal stomach.5 Diffuse types consist of poorly cohesive, small, single cells that barely form glands and may contain various proportions of signet ring cells.48 This phenotype is most likely the result of genomic aberrations in genes related to cell-matrix interaction. In rare cases familial aggregation is found which is based on an inherited predisposition syndrome: hereditary diffuse gastric cancer (HDGC).7,8 The mixed subtypes show characteristics of both intestinal and diffuse types.48

In the Netherlands, the incidence of oesophageal cancer has greatly increased in the past decades: from 1350 newly diagnosed cases in 1990 to 2500 in 2017.12,13 This is mainly the result of a threefold increase in male patients with adenocarcinomas.13 In contrast, gastric cancer incidence steadily declined from 1900 new patients in 1990 to 1200 in 2017.14,15

The prognostic value of the Laurén classification in gastric cancer is well-described, but not for oesophageal adenocarcinoma. Whether these histological subtypes are present in oesophageal adenocarcinoma and, whether they are clinically relevant in terms of treatment response and survival, was studied in Chapter 2.14 Additionally, with the increasing incidence of oesophageal adenocarcinomas in mind, incidence and survival trends for oesophageal and gastric adenocarcinomas were studied per histological subtype in Chapter 3.

Treatment and survival

For both oesophageal and gastric cancer, surgery is the key for potential cure. In combination with surgery, multimodality treatment is increasingly used as multiple trials proved its benefit in terms of locoregional disease control and survival.17–22 In the Netherlands, standard treatment for locally advanced oesophageal cancer (CT1N+, >cT2M0) consists of neoadjuvant chemo-radiotherapy followed by an oesophageal resection.18 Patients unfit for surgery may opt for definitive chemo-radiotherapy (a more intensive chemo-radiotherapy schedule, without subsequent surgery). For locally advanced gastric cancer (>cT2, cM0), standard treatment consists of perioperative chemotherapy and a (sub)total gastrectomy.19 Up to 40% of patients is diagnosed at an incurable stage of disease, 13,15,21 To date, no potentially curative treatment strategies exist for patients with advanced tumour stages at diagnosis (i.e., locally irresectable or metastatic disease). These patients are treated with palliative chemotherapy, palliative radiotherapy, or best supportive care.24,25

Overall five-year survival rates in Western patients with oesophageal or gastric cancer are below 20%.13,15,26,27 Despite improvements since the introduction of multimodality treatment, survival remains dismal for those eligible for potentially curative treatment.13,15,21,27,28 For oesophageal adenocarcinoma patients without metastatic disease, 5-year survival rates improved slightly from 12% in 1989 to 25% in 2008.13 In contrast, survival for patients with gastric cancer without metastatic disease remained stable around 30%.15

In Chapters 4 and 5, two subgroups of oesophageal cancer patients treated with curative intent were studied in relation to treatment-outcome in order to find a starting point for further individualising current treatment. In Chapter 4, the long-term outcomes of chemoradiotherapy with or without additional surgery were compared between patients...
older than 70 years and their younger counterparts. In Chapter 5, pre-treatment levels of tumour markers CEA and CA19–9 were studied in relation to early treatment failure and survival.

Progress in oesophagogastric cancer treatment

Patient selection might become more accurate by the standardisation of pre-treatment staging modalities. The outcomes after surgery have improved by (amongst all) standardisation of lymph node dissection and technical innovations such as minimally invasive techniques. In addition, there is a growing awareness of the importance of collaboration between all in-hospital disciplines involved in oesophagogastric cancer care (Figure 1). These developments gave rise to the implementation of multidisciplinary teams and the increasing use of care pathways. Fuelled by the centralisation of oesophageal and gastric cancer surgery (≥20 resections per year since 2011 and 2013, respectively) postoperative mortality decreased and survival improved.

On a macro level, the Dutch upper gastrointestinal cancer audit (DUCA) was initiated to improve the quality of surgery by continuously monitoring outcomes and returning benchmarked information to care-givers. The ultimate goal is to reduce hospital-variation and create a specialised well-structured health-care climate in which care is delivered with the right infrastructure and expertise within reach.

In Chapters 6 and 7, the outcomes of oesophagogastric cancer surgery were evaluated in order to detect potential areas for improvement. As quality measurement of a multidimensional process involving oesophagogastric cancer surgery cannot be captured in one single parameter, the DUCA developed a composite outcome measure called “Textbook outcome.” In Chapter 6, this measure was validated in a single centre patient series. In Chapter 7, the effectiveness and clinical outcomes of a prophylactic gastrectomy were evaluated in patients with HDGC. These patients carry a 60–80% life-time risk of developing diffuse type gastric cancer.

A technical development in oesophagogastric cancer surgery is described in Chapter 8. It involves the implementation of a new feature in minimally invasive oesophageal cancer resection: the introduction of the third dimension. In Chapters 9 and 10 the study design and initial results of the PERISCOPE study are presented. The acronym stands for PERitoneal dissemination in Stomach Cancer patients with cytOreductive surgery and hyperthermic intraPEritoneal chemotherapy (HIPEC). The PERISCOPE study is the first to explore the safety and feasibility of HIPEC using oxaliplatin and docetaxel in a series of gastric cancer patients with limited peritoneal carcinomatosis. A general discussion and implications of this thesis are given in Chapter 11. Altogether, in this thesis, a variety of possibilities to improve the multimodality treatment of oesophageal and gastric cancer patients was studied, with a focus on patient selection, surgical outcomes and innovative procedures.
REFERENCES


