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## Gastric cancer : staging, treatment, and surgical quality assurance

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# CHAPTER I

General introduction and outline of this thesis



Figure 1. Theodor Billroth operating in the auditorium of Vienna General Hospital (Allgemeine Krankenhaus). Painting entitled *Billroth im Hörsaal*, by Adalbert Franz Seligmann, approximately 1890



## INTRODUCTION

Since Theodor Billroth (Figure 1) performed the first successful gastrectomy in 1881, many improvements have been made in the treatment of gastric cancer.<sup>1</sup> Postoperative mortality has dropped from nearly a 100% in the early days to below 1% nowadays in experienced hands.<sup>2</sup> Japanese surgeons developed the standardized lymph node dissection.<sup>3</sup> Many trials have been performed on different surgical techniques, including the extent of lymph node dissection.<sup>4</sup> And over the past decade, surgery combined with multimodality therapy has become standard of care for advanced gastric cancer.<sup>5</sup> Another recent development is the introduction of nationwide quality assurance programs and population-based studies investigating the effects of these programs in gastric cancer treatment.<sup>6,7</sup>

Although these improvements have contributed to an increased quality of care, gastric cancer remains the second cause of cancer death worldwide, and yearly approximately one million new patients are diagnosed with gastric cancer.<sup>8</sup> In the Western world, recent survival figures remain dismal. For the approximately 75,000 newly diagnosed European gastric cancer patients each year, 5-year survival is only 24%.<sup>9-10</sup> In the Netherlands, yearly approximately 1,800 patients are diagnosed with gastric cancer, and 5-year survival is 22%.<sup>11</sup> This makes gastric cancer a challenging disease, appealing for maximum effort to improve care. The studies as described in this thesis reflect on several recent developments in the staging and treatment of gastric cancer.

Research as described in part I of this thesis was performed at the *Department of Surgery at Memorial Sloan-Kettering Cancer Center in New York, USA*. Research described in part II and III was performed at the *Leiden University Medical Center, Leiden, and the Netherlands Cancer Institute - Antoni van Leeuwenhoek Hospital, Amsterdam, the Netherlands*.

## PART I - STAGING AND PROGNOSTICATION

For over 50 years, the TNM classification has been a standard in classifying the anatomic extent of disease.<sup>12</sup> In 2010, the 7<sup>th</sup> edition of the International Union Against Cancer (UICC) and the American Joint Committee on Cancer (AJCC) TNM staging system was presented.<sup>13</sup> In **Chapter 2**, changes between the 6<sup>th</sup> and 7<sup>th</sup> edition of the TNM classification for gastric cancer are evaluated, and both staging systems are compared with regards to complexity and predictive accuracy.

In the 7<sup>th</sup> edition TNM classification, tumors of the gastroesophageal junction (GEJ) are considered esophageal cancers.<sup>14</sup> Furthermore, for esophageal and GEJ cancers, tumor grade was introduced as an independent determinant of stage grouping in early stage tumors. With the significantly worse prognosis of poorly differentiated early stage adenocarcinomas, these tumors might become candidate for preoperative therapy, given the accurate identification of these tumors with preoperative staging. In **Chapter 3**, preoperatively determined tumor grade is compared to postoperative tumor grade in patients who were treated with surgery alone for adenocarcinoma of the esophagus or

GEJ, in order to assess the feasibility of clinical decision making based on the 7<sup>th</sup> edition TNM classification for these tumors.<sup>15</sup>

**Chapter 4** describes the development of a nomogram - a tool for individual patient prognostication - predicting survival for patients who already have survived a certain period in time after surgery. Another aim of this study was to explore whether variables available with follow-up, such as weight loss and performance status, would improve the predictive accuracy of this nomogram in the follow-up setting. In **Chapter 5**, the performance of the previously published gastric cancer nomogram was assessed in patients who received postoperative chemoradiotherapy.<sup>16</sup>

## **PART II - MULTIMODALITY TREATMENT**

Surgery is the primary curative treatment for locally advanced gastric cancer. A D2 dissection is the recommended type of surgery in Western countries, while in the East at least a D2 lymph node dissection is performed.<sup>17,18</sup> Despite the effort to improve surgical quality, the locoregional relapse rate remains high with consequently a poor prognosis.<sup>19,20</sup> Since publication of the results of the US Intergroup 0116 study, indicating a benefit in survival for postoperative chemoradiotherapy compared to surgery alone, and the British MAGIC study, in which improved survival was found for patients who were treated with perioperative chemotherapy, surgery alone is no longer standard of care for patients with advanced gastric cancer.<sup>21-23</sup>

In **Chapter 6**, an overview of the literature on treatment of resectable gastric cancer is presented, including surgery and multimodality therapy.

In **Chapter 7**, recurrence and survival patterns of patients who received surgery followed by chemoradiotherapy are compared with recurrence and survival patterns of patients who were treated with surgery alone, separately analyzing the effect of the extent of lymph node dissection and whether resection margins were free of tumor cells.<sup>24</sup>

**Chapter 8** focuses on another question regarding multimodality therapy use. While it is suggested that more than 15 lymph nodes (LNs) should be evaluated for accurate staging of gastric cancer, LN yield in Western countries is low.<sup>25,26</sup> The effect of preoperative chemotherapy on LN yield in gastric cancer is unknown. The aim of the study described in this chapter is to determine whether preoperative chemotherapy is associated with any difference in the number of LNs obtained from specimens of patients who underwent curative surgery for gastric adenocarcinoma.

In **Chapter 9** the outline of the currently accruing CRITICS trial is described in detail.<sup>27</sup> In this study, patients receive three cycles of preoperative ECC (epirubicin, cisplatin, and capecitabine), followed by D1+ surgery (D2 dissection without splenectomy or pancreatectomy). Postoperative therapy consists of another three cycles of ECC, or chemoradiotherapy with capecitabine and cisplatin.

### PART III - SURGICAL QUALITY ASSURANCE

Improving quality of care for patients with resectable gastric cancer is a major challenge, as postoperative mortality is generally high and long term survival leaves room for improvement. In Japan, postoperative mortality rates of 0.8% have been reported.<sup>2</sup> However, in Western countries where the incidence of gastric cancer is much lower, and gastrectomies are performed in lower volume hospitals, mortality rates vary between 2% for specialized centers to above 10% for nationwide cancer registries.<sup>28,29</sup> Although performing randomized studies can significantly improve outcome over a longer period,<sup>30</sup> increasing surgeon and hospital exposure is the key to improvement of treatment results after low volume high-risk surgery such as gastrectomy. Many studies have explored the relation between hospital volume and outcome and found that increasing surgeon and hospital volume are associated with lower postoperative mortality and higher survival rates, both in the Western world and in Asia.<sup>6</sup> Centralization of gastric cancer surgery is currently implemented in the United Kingdom, Sweden, Finland, and the Netherlands. An additional instrument for improvement of care is auditing. With auditing, surgeons can improve their results by learning from their own outcome statistics benchmarked against their peers. Among other variables of interest, in gastric cancer surgery auditing provides the opportunity to analyze differences in hospital mortality, the extent of lymph node dissection, and the use of laparoscopic techniques. Auditing has proven its value in rectal cancer treatment in Europe,<sup>31</sup> and audits for gastric and esophageal cancer are currently present in Denmark, the United Kingdom, and the Netherlands.

As an introduction to part III of this thesis, **Chapter 10** describes the results of a systematic review of the literature on quality of care indicators for gastric cancer surgery. In **Chapter 11** and **Chapter 12**, trends in incidence and survival of gastric, GEJ, and esophageal cancer in the Netherlands are described.

During the past decade, multimodality therapy has become standard of care for the treatment of resectable gastric cancer.<sup>23</sup> In the Dutch guidelines for the treatment of gastric cancer, the use of perioperative chemotherapy is recommended.<sup>32</sup> However, it is unknown how well these evidence-based recommendations are implemented in daily clinical practice. This question is discussed in **Chapter 13**, where the results of a population-based study on the type of treatment for gastric cancer in the Netherlands are described, looking at resection rates and the use of multimodality treatment.

In **Chapter 14**, the results of a study on hospital volumes, mortality, and survival for esophagogastric cancer surgery in the Netherlands are presented. This study also focuses on the relation between annual hospital volume and outcomes after esophagogastric cancer surgery. Another related question is whether the type of hospital where surgery is performed affects outcomes after esophagogastric cancer surgery. This issue is addressed in **Chapter 15**, where outcomes after esophagectomy and gastrectomy are separately analyzed for university, teaching non-university, and non-teaching non-university hospitals in the Netherlands.

In **Chapter 16**, resection rates, outcomes, and annual hospital volumes for esophagogastric cancer surgery in the Netherlands are compared with several other European countries. Furthermore, the relation between annual hospital volume and outcomes is explored in the large dataset used for this study. This study provides the initial step towards a European upper gastrointestinal cancer audit.

Finally, the results of this thesis and future perspectives are discussed in **Chapter 17**.



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