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## Quality assurance in the surgical treatment of gastric cancer

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# CHAPTER 1

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## GENERAL INTRODUCTION AND OUTLINE OF THIS THESIS

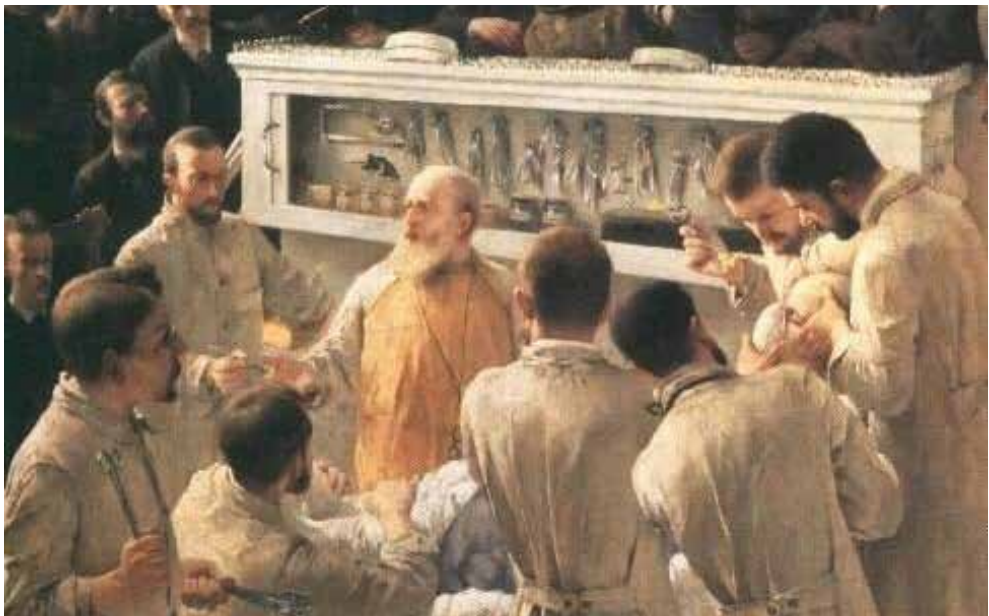
## **INTRODUCTION**

### *Epidemiology*

Despite declining incidence, gastric cancer remains the fourth most common malignancy worldwide accounting for an estimated number of one million new cases per year, and the third leading cause of cancer death with an estimated 723,000 deaths in 2012.<sup>1</sup> Large geographic differences are observed in the incidence of gastric cancer between the Western and the Eastern world with a peak in South Korea (incidence 33,000 per year).<sup>2</sup> In Europe, it is the sixth most common type of cancer and survival remains poor with only 25% of all gastric cancer patients surviving the first five years.<sup>3</sup> Even after gastric cancer surgery with adequate lymph node dissection, only 50% of the patients is still alive after 5 years.<sup>4</sup>

### *Surgical treatment*

Since Theodor Billroth was able to perform the first successful gastric resection in 1881, major changes have been made in the treatment of gastric cancer in the Western world (*Figure 1*).<sup>5</sup> Nevertheless, until today, surgery remains the cornerstone of the treatment of gastric cancer. The extent of lymph node dissection during a gastrectomy has shown to be a crucial factor associated with survival.<sup>6</sup> However, different extent of lymph node dissection regimens are employed across the world. In the Asian world extended lymph

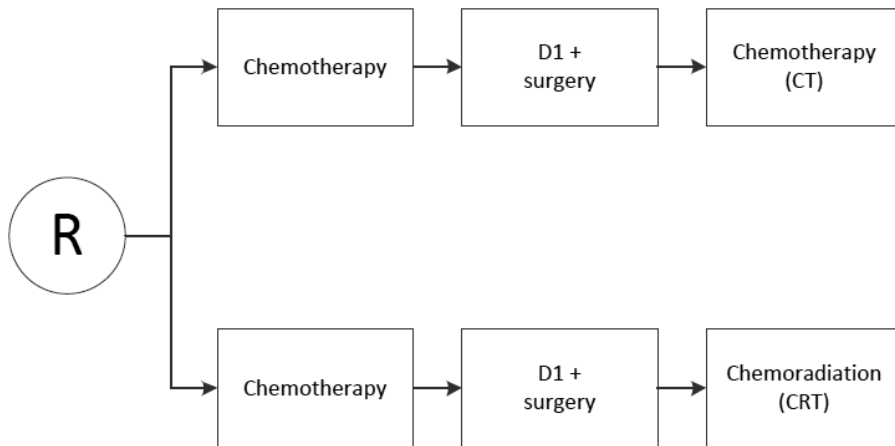


***Figure 1. 'Billroth im Hörsaal', painting by A.F. Seligmann in 1880. The first successful gastrectomy by Theodor Billroth in the auditorium of Vienna General Hospital.***

node dissection (D2 dissection; removal of lymph node stations 1-11) is common practice, whereas in Western countries limited lymph node dissection (D1; removal of lymph node stations 1-6) was standard procedure until recently.<sup>7</sup> The long term follow up results of the Dutch Gastric Cancer trial showed a survival benefit for the extended lymph node dissection, especially if surgical morbidity and mortality could be minimized.<sup>8</sup>

### *Multimodality treatment*

Several trials studied the benefit of (neo)adjuvant chemotherapy and/or radiotherapy in addition to surgery in locally advanced gastric cancer. The US Intergroup 0116 trial and the British MAGIC trial changed current clinical practice for resectable gastric cancer in the Western world.<sup>9,10</sup> In the Intergroup 0116 trial the addition of adjuvant chemoradiotherapy (45 Gy combined with 5-FU) improved survival, whereas in the MAGIC trial a survival benefit was shown of peri-operative chemotherapy (epirubicin, cisplatin, and 5-FU). As a result, adjuvant chemoradiotherapy became standard treatment in the United States, whereas perioperative chemotherapy has become the therapy of choice in Europe – including the Netherlands – for locally advanced gastric cancer.<sup>7,11</sup> Due to different inclusion criteria and study design of the Intergroup 0116 trial and the MAGIC trial, a direct comparison between these two practice changing trials is not possible. To determine the optimal approach for adjuvant therapy after gastrectomy in patients with locally advanced gastric cancer, the CRITICS (ChemoRadiotherapy after Induction chemotherapy In Cancer of the Stomach) trial was initiated (*Figure 2*). In this international randomised controlled multicentre trial, patients with resectable



**Figure 2. Study design of the CRITICS trial**

Abbreviations; R: randomization; Chemotherapy = epirubicin, cisplatin/oxaliplatin, and capecitabine (ECC/EOC); D1+ surgery: surgery including a D1+ lymphadenectomy; Chemoradiotherapy: 45 Gy/25 fractions + capecitabine + cisplatin

gastric cancer were treated with three cycles of preoperative chemotherapy (epirubin, cisplatin/ oxaliplatin, and capecitabine (ECC/EOC)), followed by surgery with an adequate lymph node dissection (D1+ dissection: removal of station 1-9 and 11, *Figure 3*), followed by either three cycles of chemotherapy (ECC/EOC, *standard arm*) or concurrent chemoradiation (45 Gy with capecitabine and cisplatin, *experimental arm*). Patients were randomised before start of treatment.

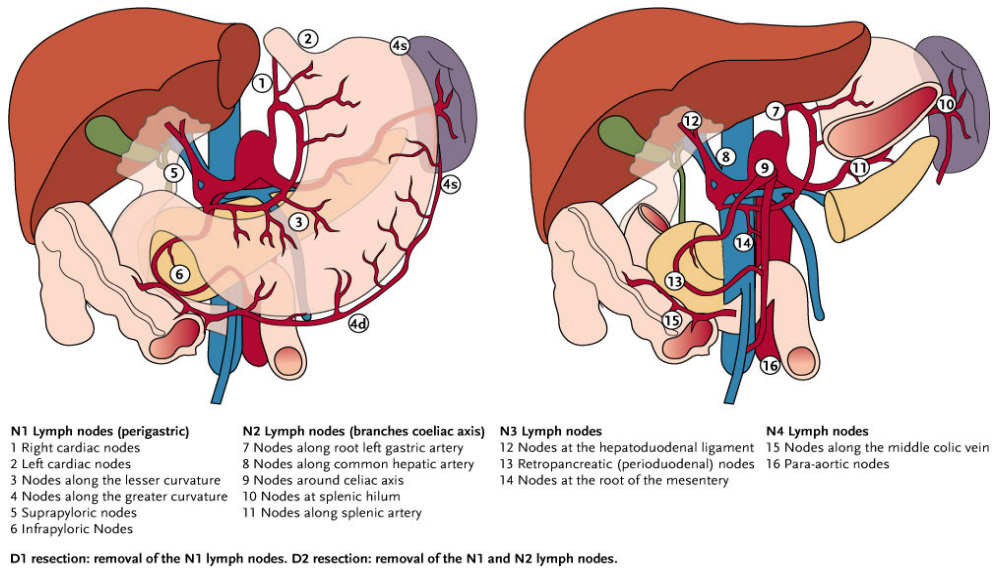
#### PART I – SURGICAL QUALITY ASSURANCE IN THE CRITICS GASTRIC CANCER TRIAL

High surgical quality is essential in gastric cancer multimodality trials. However, protocol adherence for lymphadenectomy remains often a point of debate. In the Dutch Gastric Cancer Trial, surgical quality assurance was strictly monitored. For instance, participating surgeons were instructed by an expert gastric cancer surgeon in the operating theatre and after a 4 months instruction period the supervising surgeons kept monitoring the technique and the extent of lymphadenectomy. Nevertheless, final analysis of the Dutch Gastric Cancer Trial showed that due to lack of adherence to the study protocol, survival benefit of the D2 group in the first results may have been obscured. Non-compliance occurred in 81% and 82% in the D1 and D2 group, respectively. After excluding the patients who did not had a resection according the protocol, there was a survival difference in favor of the D2 group. Furthermore, the Intergroup 0116 trial was highly criticized by the fact that only 10% of the patients underwent the intended D2 lymph node dissection and raised the question whether the chemoradiotherapy benefit was in fact compensation for the poor quality of surgery.<sup>9</sup> It can be concluded, that high surgical quality in multimodality gastric cancer trials is crucial for the reliability of the primary outcomes of these trials. Therefore, in **Chapter 1**, surgicopathological quality control and protocol adherence to lymphadenectomy in the CRITICS trial were studied and described.

Although improvements have been made in the last decades regarding the surgical procedure of gastric cancer, it is still considered high-risk surgery. Actual surgical morbidity and mortality rates are around 39% and 5%, respectively.<sup>12,13</sup> In **Chapter 2** surgical morbidity and surgical mortality in the CRITICS trial are investigated and factors associated with postoperative complications are identified.

Timing of randomization in multimodality gastric cancer trials is often a point of discussion. In the Intergroup 0116 trial, randomization between adjuvant chemoradiotherapy versus no adjuvant treatment was performed after surgery.<sup>10</sup> Critics argued that the choice of this moment of randomization, after pathology results, might have led to selection bias. In the CRITICS trial, randomization took place before start of preoperative chemotherapy. Opponents considered this as a limitation, as the quality of surgery might be influenced by the knowledge of the surgeon of the adjuvant treatment form that would follow for the patient. A surgeon could decide to

perform a less extended lymph node dissection – as the extent of lymph node dissection is associated with increased morbidity – in case a patient was randomized for adjuvant chemoradiotherapy. To evaluate the possible influence of upfront randomization for postoperative treatment on the quality of surgery in the CRITICS trial, surgical quality parameters in both study arms were compared and evaluated in **Chapter 3**.



**Figure 3. Lymph node locations and numbering according to the Japanese Research Society for the study of Gastric Cancer**

## PART II – INFLUENCE OF HOSPITAL VOLUME ON OUTCOMES OF GASTRIC CANCER SURGERY

Hospital volume has become a hot topic in gastric cancer surgery in the last decades. Consensus is growing that the complex care of gastric cancer surgery should take place in high volume hospitals. Many studies have investigated the relationship between hospital volume and short-term outcomes, such as postoperative mortality. However, this short term outcome may not be the optimal way to assess quality of cancer surgery. Studies investigating the relation between hospital volume and quality of surgery are scarce, as detailed information regarding surgical quality is often lacking in retrospective studies. In **Chapter 4**, the effect of hospital volume of gastric cancer surgery on quality of surgery was evaluated using data of the CRITICS trial linked with data of annual hospital volume of the Netherlands Cancer Registry. To investigate whether hospital volume also results in improved long-term outcomes, the effect of hospital volume of gastric cancer surgery on recurrence and survival in the CRITICS trial was investigated and described in **Chapter 5**.

### PART III – OPTIMAL TREATMENT STRATEGY FOR SUBGROUPS OF GASTRIC CANCER PATIENTS

Improving quality of care for patients with gastric cancer in the Western world is a great challenge. This is especially the case for certain subgroups, among them older gastric cancer patients and patients with metastatic disease. Older gastric cancer patients are very often excluded from randomized clinical trials, as most of the time the upper limit of age for inclusion does not exceed 75 years. Additionally, older gastric patients are a heterogeneous group of patients, with (more) comorbidity, an increased risk of postoperative complications, and increased mortality.<sup>14</sup> In short, the optimal treatment strategy for older gastric cancer patients remains unclear. Therefore, more insight is needed in current treatment strategy and survival outcomes for this growing group of patients. In **Chapter 6** a study is described which aimed to provide an overview of treatment strategies and survival outcomes of older gastric cancer patients in five European countries, based on population-based data. For gastric cancer patients with metastatic disease at presentation, choosing the optimal treatment strategy is challenging as well. More than two thirds of patients have metastatic disease (stage IV) at time of diagnosis.<sup>15</sup> These patients are generally treated with chemotherapy and have a poor prognosis with a median survival of 10 months.<sup>16,17</sup> In the Dutch Gastric Cancer Trial it was shown that a palliative resection might be beneficial for high risk patients but the role of a palliative resection in metastatic patients remained debatable.<sup>18</sup> Recently, the results of the REGATTA trial, the first randomized clinical trial investigating the value of a palliative resection in patients with a single non-curable factor without obstruction or bleeding, were published. No survival benefit was shown for a palliative resection with chemotherapy over chemotherapy alone in patients with non-curable advanced gastric cancer.<sup>18</sup> To obtain an overview of treatment strategies, and especially the role of a palliative resection in daily practice, a study was conducted with population-based data of five European countries and presented in **Chapter 7**.

### PART IV – DIRECTIONS FOR THE FUTURE

Despite improvements with respect to surgical techniques, perioperative care, and extension of multimodality regimens, survival for Western gastric patients remains poor. Although the CRITICS trial showed no difference in overall survival between the chemotherapy study arm and the chemoradiotherapy study arm, new insights are given.<sup>19</sup> In the CRITICS trial only 47% of the patients in the chemotherapy study arm and 52% in the chemoradiotherapy study arm were able to complete treatment according to protocol. These results indicate that the current multimodality treatment regimens after surgery are very demanding for Western gastric cancer patients. Therefore, a shift from adjuvant towards neo-adjuvant treatment strategies should be considered for future treatment. In **Chapter 8**, an overview is given of the current evidence regarding neoadjuvant treatment of gastric cancer in the Western world.



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