Quality assurance in the surgical treatment of gastric cancer

Claassen, Y.H.M.

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CHAPTER 1

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.[1] 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).[2] 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.[3] Even after gastric cancer surgery with adequate lymph node dissection, only 50% of the patients is still alive after 5 years.[4]

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*).[5] 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.[6] However, different extent of lymph node dissection regimens are employed across the world. In the Asian world extended lymph

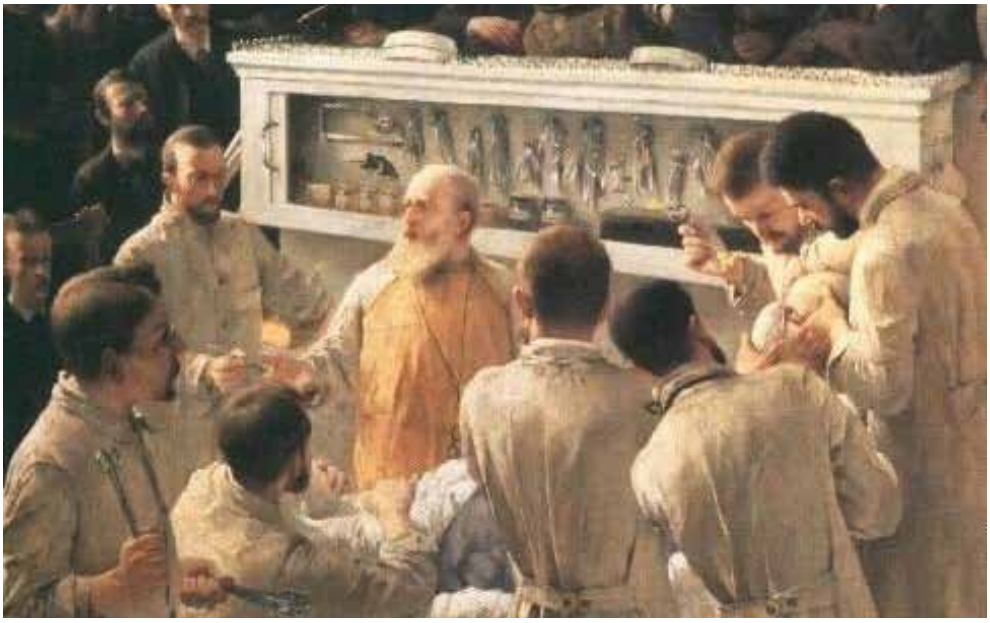


Figure 1. 'Billroth im Hörsal', painting by A.F. Seligmann in 1880. The first successful gastrectomy by Theodor Billroth in the auditorium of Vienna General Hospital.

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.[7] 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.[8]

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.[9,10] 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 (epirubin, 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.[7,11] 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

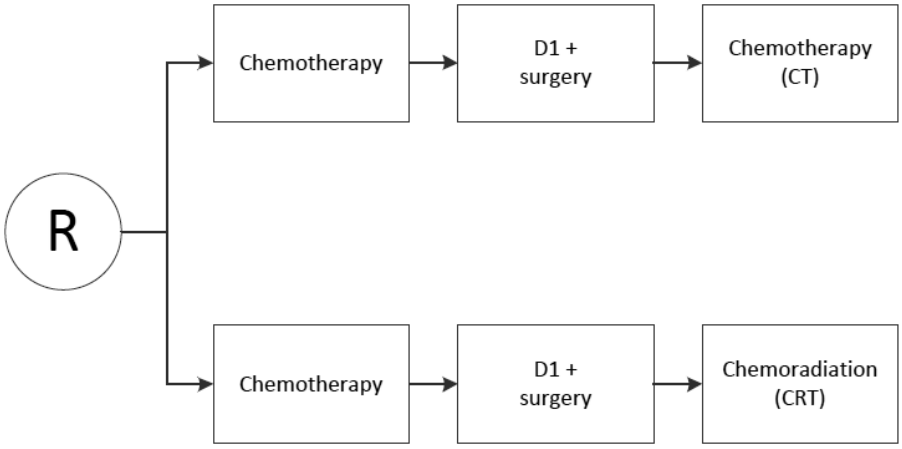


Figure 2. Study design of the CRITICS trial

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.

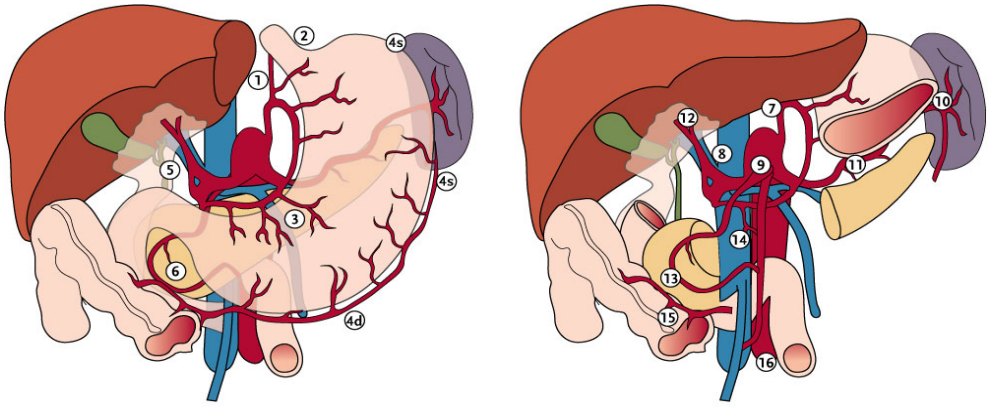
PART I – SURGICAL QUALITY ASSURANCE IN THE CRITICS GASTRIC CANCER TRIAL

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.[9] 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.[12,13] 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.[10] Criticists 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**.



N1 Lymph nodes (perigastric)
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D1 resection: removal of the N1 lymph nodes. D2 resection: removal of the N1 and N2 lymph nodes.

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.[14] 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.[15] These patients are generally treated with chemotherapy and have a poor prognosis with a median survival of 10 months.[16,17] 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.[18] 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.[18] 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.[19] 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.

REFERENCES

1. Ferlay J, Soerjomataram I, Dikshit R, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer 2015; 136(5): E359-86.
2. Yamamoto M, Rashid OM, Wong J. Surgical management of gastric cancer: the East vs. West perspective. J Gastrointes Oncol 2015; 6(1): 79-88.
3. De Angelis R, Sant M, Coleman MP, et al. Cancer survival in Europe 1999-2007 by country and age: results of EUROCARE--5-a population-based study. Lancet Oncol 2014; 15(1): 23-34.
4. Rosa F, Alfieri S, Tortorelli AP, et al. Trends in clinical features, postoperative outcomes, and long-term survival for gastric cancer: a Western experience with 1,278 patients over 30 years. World J Surg Oncol 2014; 12: 217.
5. Weil PH, Buchberger R. From Billroth to PCV: a century of gastric surgery. World J Surg 1999; 23(7): 736-42.
6. Gunderson LL. Gastric cancer--patterns of relapse after surgical resection. Seminars in radiation oncology 2002; 12(2): 150-61.
7. Bickenbach K, Strong VE. Comparisons of Gastric Cancer Treatments: East vs. West. J Gastric Cancer 2012; 12(2): 55-62.
8. Songun I, Putter H, Kranenbarg EM, et al. Surgical treatment of gastric cancer: 15-year follow-up results of the randomised nationwide Dutch D1D2 trial. Lancet Oncol 2010; 11(5): 439-49.
9. Cunningham D, Allum WH, Stenning SP, et al. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. New Engl J Med 2006; 355(1): 11-20.
10. Macdonald JS, Smalley SR, Benedetti J, et al. Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction. New Engl J Med 2001; 345(10): 725-30.
11. Landelijke richtlijn maagcarcinoom 2.2. 2017, [Available from: http://www.oncoline.nl/maagcarcinoom, accessed at 13-06-2017].
12. Bosing NM, Goretzki PE, Roher HD. Gastric cancer: which patients benefit from systematic lymphadenectomy? Eur J Surg Oncol 2000; 26(5): 498-505.
13. Bartlett EK, Roses RE, Kelz RR, et al. Morbidity and mortality after total gastrectomy for gastric malignancy using the American College of Surgeons National Surgical Quality Improvement Program database. Surgery 2014; 156(2): 298-304.
14. Pisanu A, Montisci A, Piu S, et al. Curative surgery for gastric cancer in the elderly: treatment decisions, surgical morbidity, mortality, prognosis and quality of life. Tumori 2007; 93(5): 478-84.
15. Dassen AE, Lemmens VE, van de Poll-Franse LV, et al. Trends in incidence, treatment and survival of gastric adenocarcinoma between 1990 and 2007: a population-based study in the Netherlands. Eur J Cancer 2010; 46(6): 1101-10.
16. Waddell T, Verheij M, Allum W, et al. Gastric cancer: ESMO-ESSO-ESTRO clinical practice guidelines for diagnosis, treatment and follow-up. Eur J Surg Oncol 2014; 40(5): 584-91.
17. Wagner AD, Unverzagt S, Grothe W, et al. Chemotherapy for advanced gastric cancer.

Cochrane Database Syst Rev 2010; (3): Cd004064.
18. Hartgrink HH, Putter H, Klein Kranenbarg E, et al. Value of palliative resection in gastric cancer. Br J Surg 2002; 89(11): 1438-43.
19. Cats A, Jansen EPM, van Grieken NCT, et al. Chemotherapy versus chemoradiotherapy after surgery and preoperative chemotherapy for resectable gastric cancer (CRITICS): an international, open-label, randomised phase 3 trial. Lancet Oncol 2018; 19(5): 616-628.

PART I

SURGICAL QUALITY ASSURANCE IN THE CRITICS GASTRIC CANCER TRIAL

CHAPTER 2

SURGICOPATHOLOGICAL QUALITY CONTROL AND PROTOCOL ADHERENCE TO LYMPHADENECTOMY IN THE CRITICS GASTRIC CANCER TRIAL

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ABSTRACT

Objective: The purpose of this study was to evaluate surgicopathological quality and protocol adherence for lymphadenectomy in the CRITICS trial.

Summary Background Data: Surgical quality assurance is a key element in multimodal studies for gastric cancer. In the multicenter CRITICS trial (ChemoRadiotherapy after Induction chemotherapy In Cancer of the Stomach), patients with resectable gastric cancer were randomized for preoperative chemotherapy, followed by gastrectomy with a D1+ lymphadenectomy (removal of stations 1-9 and 11), followed by either chemotherapy or chemoradiotherapy.

Methods: Surgicopathological compliance was defined as removal of ≥15 lymph nodes. Surgical compliance was defined as removal of the indicated lymph node stations. Surgical contamination was defined as removal of lymph node stations that should be left in situ. The Maruyama Index (MI, lower is better), which has proven to be an indicator of surgical quality and is strongly associated with survival, was analyzed.

Results: Between 2007 and 2015, 788 patients were randomized, of which 636 patients underwent a gastrectomy with curative intent. Surgicopathological compliance occurred in 72.8% (n=460) of the patients and improved from 55.0% (2007) to 90.0% (2015). Surgical compliance occurred in 41.1% (n=256). Surgical contamination occurred in 59.6% (n=371). Median MI was 1 (range 0-136).

Conclusions: Surgical quality in the CRITICS trial was excellent, with a MI of 1. Surgicopathological compliance improved over the years. This might be explained by the quality assurance program within the study and centralization of gastric cancer surgery in the Netherlands.

INTRODUCTION

High quality surgery is the cornerstone in the treatment of (locally advanced) resectable gastric cancer. Patient outcomes after gastric cancer surgery have improved over the last years with respect to postoperative morbidity, postoperative mortality, and survival.[1,2] In Asian countries, an extended lymph node dissection (D2) has been a standard procedure for many decades, whereas in Western countries a limited lymph node dissection (D1) was common practice until recently.[3] In contrast with the initially reported results of the Dutch Gastric Cancer Trial (DGCT), the long term follow up did show a benefit for a more extended lymph node dissection, especially if morbidity and mortality could be minimized.[4,5]

An important aspect in the debate on the extent of lymphadenectomy is the protocol adherence for lymphadenectomy. In the DGCT, strict surgical quality control was implemented and monitored. For instance, participating surgeons were instructed by an expert gastric cancer surgeon in the operating theatre. However, despite an intense quality assurance program, further analysis in the DGCT showed that a lack of compliance for the study protocol, may have obscured a difference in the first results of survival between the D1 and D2 group.[6]
The most important and best validated quality indicator for assessing the adequacy of lymphadenectomy in gastric cancer is the 'Maruyama Index of Unresected Disease' (MI), as shown in both the DGCT and in the Intergroup 0116 trial.[7,8] The MI is a quantitative estimate of residual nodal disease after gastric cancer surgery, based on eight characteristics of the tumor.[9] In contrast to the extent of the lymph node dissection (D0-D3), the MI proved to be an independent prognostic factor for survival as well; a MI of less than 5 has been associated with a significantly better survival when compared to a MI of 5 or greater.[7,8,10]

In order to improve survival for locally advanced gastric cancer, many studies with neo-adjuvant and adjuvant chemotherapy and/or radiotherapy have been performed. For Western patients, two studies, the Intergroup 0116 trial and the MAGIC trial, changed clinical practice for locally advanced resectable gastric cancer.[11,12] In the Intergroup 0116 trial, adjuvant chemoradiotherapy improved survival compared to surgery alone. That study, however, was criticized for a poor adherence to the surgical protocol, as only 10% of patients underwent the intended D2 lymph node dissection.[12] In the MAGIC trial, peri-operative chemotherapy improved survival over surgery alone, but details on surgical quality assurance were not reported.[11] Due to differences in both the study design and the eligibility criteria, a direct comparison of data between the aforementioned studies was not possible. Therefore, the international multicenter CRITICS trial (ChemoRadiotherapy after Induction chemotherapy In Cancer of the Stomach) was initiated. In this randomized clinical trial, patients with resectable gastric cancer were treated with three cycles of preoperative epirubicin, cisplatin/ oxaliplatin and capecitabine (ECC/EOC), followed by surgery with adequate lymph

node dissection. Adjuvant therapy was upfront randomized between either three cycles of ECC/EOC or concurrent chemoradiotherapy.[13] To avoid the discussion that peri-operative therapy would compensate for inadequate surgery, at least a D1+ lymph node dissection was mandatory and quality assurance was closely monitored. The purpose of the current study was to analyze surgicopathological quality and protocol adherence to lymphadenectomy in the CRITICS trial.

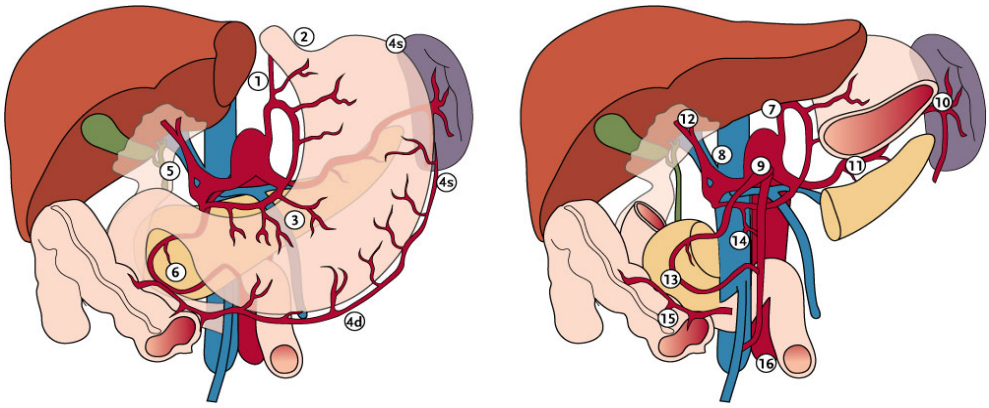
METHODS

CRITICS protocol

The study protocol of the CRITICS trial has been published previously.[13] In the CRITICS trial, patients with a histologically proven Ib-IVa (AJCC 6th edition) gastric adenocarcinoma were included.[14] The bulk of the tumor had to be located in the stomach, although extension into the gastro-esophageal junction (GEJ) was allowed. Inoperable patients, patients with distant metastases, and patients with a T1N0 tumor (determined with endoscopic ultrasound) were excluded.

Patients were treated with three cycles of epirubicin, cisplatin/oxaliplatin, and capecitabine (ECC/EOC) at three-weekly intervals preoperatively. Surgery was planned three-six weeks after the last chemotherapy cycle. Assessment of American Society of Anesthesiologists (ASA) classification was performed by an anesthesiologist. Only patients with ASA classification of 1 or 2 were included. The decision to proceed to surgery was based on the absence of signs of progressive disease as evaluated by CT-scan after 2 cycles of chemotherapy. Both open and minimally invasive surgery were allowed. Abdominal washing was advised. In case of ascites, this had to be examined for malignant cells. A gastric resection was not performed in patients with tumor infiltration of the head of the pancreas needing a Whipple procedure, para-aortic distant lymph node metastases, tumor positive cytology of abdominal fluid or peritoneal metastases.
The principle of surgery was a wide resection of the tumor bearing part of the stomach en bloc with the N1 and N2 lymph nodes according to a D1+ lymph node dissection (removal of stations 1-9 and 11, *Figure 1*) and with the removal of a minimum of 15 lymph nodes. A D1 lymph node dissection was defined as removal of station 3-6 during partial gastrectomy and station 1-6 during total gastrectomy. A D0 dissection was defined as less than a D1 dissection. A D2 lymph node dissection was defined as removal of station 1,3, 5-9 during partial gastrectomy and station 1-11 during total gastrectomy. A D3 dissection was defined as the removal of lymph node station 1-14. The extent of lymph node dissection performed was recorded in the Case Report Form (CRF). Splenectomy or resection of the pancreatic tail was not performed unless there was direct ingrowth into these organs. Other adjacent organs were only removed if there was suspicion of tumor involvement. The goal was to obtain a free margin on the frozen section. If possible, a macroscopic margin of 5 cm was obtained, both proximal as well as distal. For a tumor in the upper part of the stomach, a total gastrectomy was

performed. For tumors in the middle part of the stomach, a subtotal gastrectomy was performed, leaving a small portion of the stomach below the GE-junction. For tumors in the distal part of the stomach, a subtotal gastrectomy was performed, leaving lymph node stations 2 and 4s in situ. For tumors extending into the esophagus, either a transhiatal esophago-cardia resection with gastric tube reconstruction was performed or a total gastrectomy with distal esophagectomy and intrathoracic esophagojejunostomy. For the first group of patients, lymph node station 4d and 6 were left in situ.



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D1 resection: removal of the N1 lymph nodes. D2 resection: removal of the N1 and N2 lymph nodes.

Figure 1. Lymph node locations and numbering according to the Japanese Research Society for the study of Gastric Cancer

Surgical quality assurance

Before participation in the CRITICS trial, surgeons were instructed during a presentation which lymph node stations had to be removed according to the protocol. Surgeons received an instructional DVD and an instruction book as well. During the CRITICS trial continuous quality assurance took place since 2011. This consisted of regular feedback on the number of removed lymph nodes per patient in the trial to the participating surgeon and pathologist, together with the average of each surgeon, average of each participating hospital, and the average in the study at that moment. The number of removed lymph nodes was registered shortly after surgery. In case less than 15 lymph nodes were sampled, feedback as soon as possible after surgery was provided to the respective surgeon and pathologist and if possible, the surgical specimen was inspected for remaining lymph nodes.

Eligibility current study
For the current study, patients who underwent a gastric resection with curative intent were selected from the CRITICS database. Patients were excluded from the analyses of surgicopathological compliance if the total number of sampled lymph nodes was not reported by the pathologist. Patients were excluded from the analyses of surgical compliance, surgical contamination, and MI if the exact location of the lymph node stations was not extractable from the surgery report.

Central data review
To validate and to optimize the data for the extent of lymphadenectomy, two expert gastric surgeons revised the resected lymph node stations (1-16) and type of lymph node dissection (D0, D1, D1+, D2, or D3) based on surgery reports of all patients, supplementary to the data recorded in the CRF. In case the number of the removed lymph node station was not specifically mentioned, an assumption was made based on the anatomical structures mentioned in the surgery report if possible. For instance, as a given surgery report described removal of lymph nodes across the splenic artery, it was defined as removal of lymph node station 11. If no assumptions could be made, it was scored as unknown. In case all stations were unknown, the patient was excluded from analysis. In case a single lymph node station was unknown, the station was considered as not removed.

Surgicopathological compliance
Surgicopathological compliance was defined as sampling of a minimum of 15 lymph nodes and non-compliance as removal of less than 15 lymph nodes. Minor non-compliance was defined as removal of a minimum of 10 lymph nodes. Removal of less than 10 lymph nodes was considered as major surgicopathological non-compliance.

Surgical compliance and surgical contamination
Surgical compliance was defined as the removal of lymph node station 1-9 and 11, except for resections of distal gastric tumors where stations 2 and 4s were left in situ and esophago-cardia resections with gastric tube reconstructions where station 4d and 6 were left in situ. The definition of surgical non-compliance was no removal of one or more indicated lymph node stations. For the current analysis, the group of eligible patients who underwent surgery with curative intent was divided into two groups: compliance for all intended lymph node stations and non-compliance for one or more stations. The latter group was subdivided into minor non-compliance (1 or 2 of the intended lymph node stations not removed) and major non-compliance (≥3 of the intended lymph node stations not removed). The definition of surgical contamination was removal of one or more lymph node stations outside the intended extent of resection. Surgical contamination was divided in minor contamination (1 or 2 lymph node stations outside the extent of indicated stations removed) and major contamination (≥3 lymph node stations outside the extent of indicated stations removed).

Maruyama Index

The MI is a quantitative estimate of possible metastatic lymph nodes left behind after the operation. For some lymph node stations the chance to be metastatic is very low and leaving them behind does not much affect outcome. If however, the chance for a certain lymph node station to be metastatic is high, then not removing these nodes probably affect outcome. The MI in this study is determined by the Maruyama Program, similar to the Intergroup 0116 trial and the DGCT.[7,9,10] The MI is based on eight variables (sex, age, type of cancer, depth of tumor invasion, maximal diameter, location, position, and histological type) which can all be defined before or during the operation. To quantify the likelihood of unresected nodal disease, the MI is defined as the sum of Maruyama Computer Program predictions for the regional lymph node stations 1 to 12 which were not removed by the surgeon. For example, a given patient underwent a gastrectomy with removal of lymph node stations 1 to 9. The MI is calculated by adding up the likelihood of disease percentages of the unresected stations: station 10, 11, and 12.

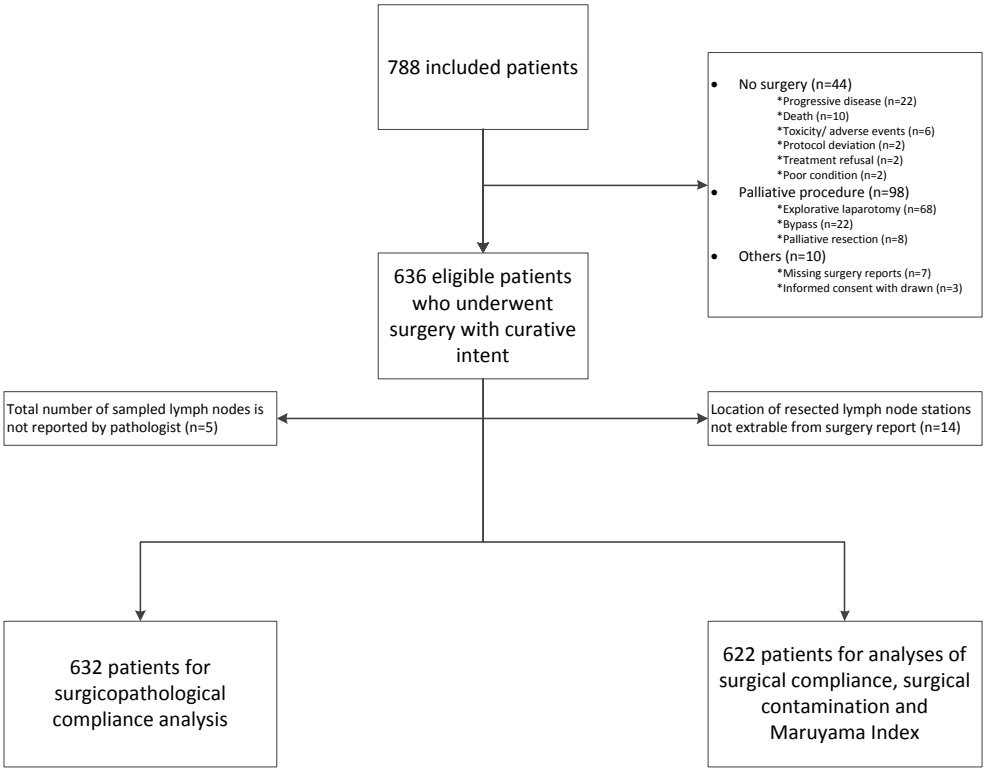

Figure 2. Study flow chart

RESULTS

Characteristics of the patients
From January 2007 to April 2015, 788 patients were included in the CRITICS trial in 56 centers in the Netherlands, Sweden, and Denmark (*Figure 2*). For the current analyses, data of 636 patients were available, 632 patients for the analyses on surgicopathological compliance and 622 patients for the analyses on surgical compliance, surgical contamination, and MI.

Patient characteristics are shown in *Table 1*. The location of the tumor was equally divided between proximal, middle, and distal tumors (37.1%, 28.8% and 34.1%, respectively). The majority of patients underwent a total gastrectomy (50.0%) or a subtotal gastrectomy (40.1%), whereas a small group underwent an esophago-cardia resection with gastric tube reconstruction (9.9%). The majority of patients (n=544, 87.5%) had at least a D1+ lymph node dissection. A splenectomy was performed in 38 patients (6.0%) and a distal pancreatectomy in 16 patients (2.5%). The majority of splenectomies was performed in combination with removal of lymph node station 10 (n=30, 78.9%) and lymph node station 11 (n=34, 89.5%). A splenectomy was most often performed with a total gastrectomy (n=33, 86.9%). For a subtotal gastrectomy and a gastric tube reconstruction splenectomy was performed in 4 (1.6%) and 1 patient (1.6%), respectively. In approximately two-thirds of all distal pancreatectomies (n=16) lymph node station 11 was removed (n=10, 62.5%). A distal pancreatectomy was most often performed in combination with a total gastrectomy (n=10, 62.5%).

Surgicopathological compliance
The surgicopathological compliance is shown in *Figure 3*. In the majority of patients (n=460, 72.8%) the lymphadenectomy was compliant, in 14.4% (n=91) the lymphadenectomy was minor non-compliant and in 12.8% (n=81) major non-compliant. Surgicopathological compliance increased over time (*Figure 4)* which started with 55.0% in 2007 and rose to 90.0% in 2015. A median of 20.0 lymph nodes were evaluated by the pathologist with a range of 0-72.

Surgical compliance and surgical contamination
Surgical compliance occurred in 256 patients (41.1%, *Table 2)*. Surgical compliance and minor non-compliance occurred in 476 patients (76.5%). The majority of the non-compliance group consisted of one missed lymph node station (n=135, 21.7%) or two missed lymph node stations (n=85, 13.7%). For proximal and middle located tumors, lymph node station 11 was the station most often not removed (64.3%), followed by lymph node station 2 (41.9%), and lymph node station 9 (36.1%). Of the distally located tumors, lymph node station 1 was most often not removed (71.2%), followed by station 11 (69.1%), and station 9 (43.9%). Lymph node station 5 was most often not removed in gastric tubes reconstructions (87.0%), followed by station 11 (54.3%) and station 8 (34.8%).

Table 1. Patient characteristics

	Total (n=636)
Median age (years)	62 (28-82)
Sex	
Male	429 (67.5)
Female	207 (32.5)
Tumor localization	
Proximal	236 (37.1)
Middle	183 (28.8)
Distal	217 (34.1)
Type of gastric resection	
Total	318 (50.0)
Subtotal	255 (40.1)
Esophago-cardiac resection	63 (9.9)
Tumor stage	
pT0/pTis/pT1	133 (20.9)
pT2	222 (34.9)
pT3	217 (34.1)
pT4	64 (10.1)
Node stage	
pN0	311 (48.9)
pN1	214 (33.7)
pN2	77 (12.1)
pN3	34 (5.3)
Type of LND*	
D0	4 (0.6)
D1	74 (11.9)
D1+	501 (80.6)
D2	40 (6.4)
D3	3 (0.5)
Splenectomy	
Yes	38 (6.0)
No	598 (94.0)
Distal pancreatectomy	
Yes	16 (2.5)
No	620 (97.5)

Age is presented as median (range), other data are presented as n (%)
Abbreviations; Type of LND: type of lymph node dissection
**Data available of n=622*

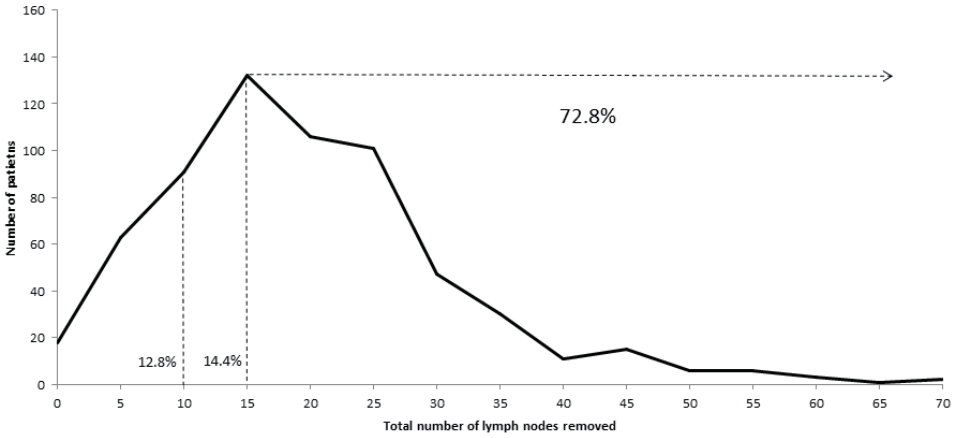

Figure 3. Surgicopathological compliance

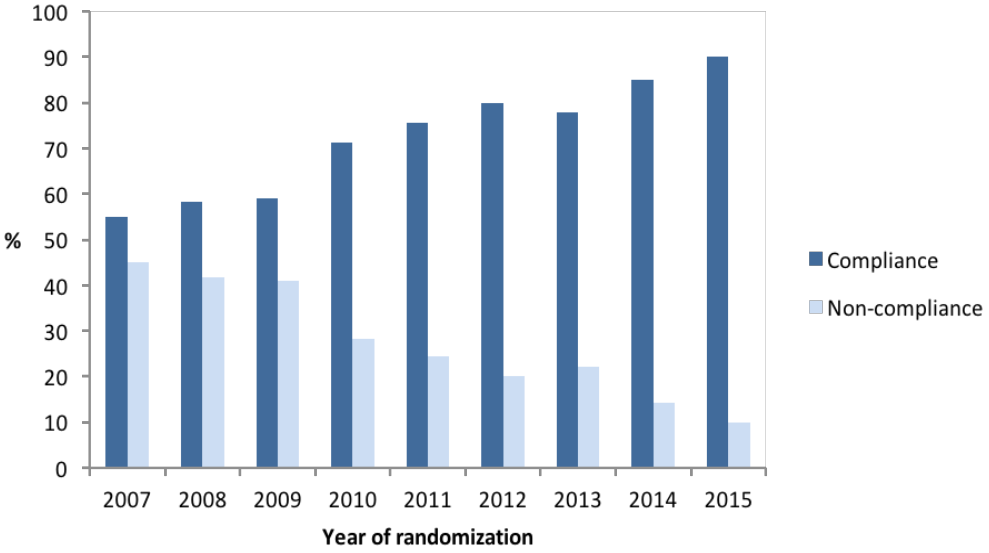

Figure 4. Surgicopathological compliance over time

Surgical contamination occurred in 371 of the 622 patients (59.6%, *Table 2*). The majority of this group consisted of minor contamination (n=336, 54.0%). Major contamination occurred in 35 patients (5.6%).

Table 2. Extent of surgical compliance and surgical contamination

	Total (n=622)
Compliance	256 (41.1)
Non-compliance	
Minor non-compliance*	220 (35.4)
1	135
2	85
Major non-compliance*	146 (23.5)
3	69
4	42
5	21
6	11
7	2
10	1
Non contamination	251 (40.4)
Contamination	
Minor contamination**	336 (54.0)
1	223
2	113
Major contamination**	35 (5.6)
3	28
≥4	7

**= Number of intended lymph node stations not removed.*

***= Number of lymph node stations too many removed.*

Data are presented as n (%)

Maruyama Index

Median MI was 1 (range 0-136), compared to median MI of 26 in the DGCT and 70 in the Intergroup 0116 trial (*Table 3*).[7,10]

Table 3. Overview of 'Maruyama Index of Unresected Disease' (MI) of the CRITICS trial in comparison with the DGCT and the Intergroup 0116 trial

	Median MI	**Range**	**N**	**Years of inclusion**
CRITICS	1	0-136	622	2007-2015
DGCT[10]	26	0-350	648	1989-1993
Intergroup 0116 trial[7]	70	0-429	556	1991-1998

N = number of analyzed patients for MI

Abbreviations; DGCT: Dutch Gastric Cancer Trial

DISCUSSION

In this study, surgicopathological quality was evaluated in the CRITICS trial, a multicenter randomized gastric cancer trial. Surgicopathological compliance strongly improved over the years and the vast majority of patients underwent at least a D1+ lymphadenectomy (87.5%) with corresponding high rates of surgical compliance.

Since the releases of the staging manuals of the American Joint Committee on Cancer (AJCC) in 1997, 2002, and 2010 for gastric cancer, removal of at least 15 lymph nodes during surgery is recommended.[14-16] Adequacy of lymph node assessment according to these guidelines was associated with better survival.[17] Neither the Intergroup 0116 trial nor the MAGIC trial addressed this important topic.[11] In the CRITICS trial, removal of at least 15 lymph nodes was achieved in 72.8% of patients. During the study period, a gradual increase of the surgicopathological compliance was observed: from 55.0% in 2007 to 90.0% in 2015. This is most likely the result of the surgical quality assurance program within the CRITICS trial which started in 2011. Moreover, since 2012, gastric cancer surgery in the Netherlands was centralized towards hospitals performing a minimum volume of at least 10 gastric resections per year. As of 2013, this was increased to 20 resections per year. This quality incentive might also be an explanation for increasing surgicopathological compliance during the CRITICS trial. A Danish study showed that surgicopathological compliance improved from 19% before centralization of gastric cancer surgery to 76% after centralization in that country.[18]

A "D1+" lymphadenectomy was a minimal requirement in the CRITICS trial. This term was determined with best insight at the start of this trial while the discussion of extent of lymphadenectomy was ongoing. About 87% of the patients underwent at least a D1+ lymphadenectomy in the CRITICS trial. Compared to earlier gastric cancer randomized trials, this rate of protocol adherence for lymphadenectomy is high. In the Intergroup 0116 trial where patients were randomized after surgery, only 10% of the patients underwent the intended D2 lymphadenectomy.[11] To exclude compensation of chemoradiation for inadequate surgery, in the ARTIST trial, the addition of radiotherapy to adjuvant chemotherapy alone was investigated in gastric cancer patients who underwent a D2 lymph node dissection. After 7 years of follow up, no difference was seen in disease free survival and overall survival.[19] The difference in outcome between the Intergroup 0116 trial and the ARTIST trial emphasizes the importance of adequate surgery. In the ARTIST trial, only in the subset of patients with node-positive disease, a significant improvement in disease free survival by adjuvant chemoradiation was found. Hence, the ARTIST 2 trial is currently being performed which will evaluate adjuvant chemotherapy and chemoradiation after a D2 lymph node dissection in patients with node-positive gastric cancer (ClinicalTrials.gov identifier: NCT0176146).

Surgical non-compliance for dissection of correct lymph node stations could influence the outcome of multicenter trials for gastric cancer. The MRC trial mentioned the

occurrence of non-compliance and contamination, though a quantification of both was not stated.[20] Previously, De Steur et al. determined the quality of lymph node station dissections in the DGCT and showed a surgical non-compliance of 80.5% in the D1 arm and 81.6% in the D2 arm.[6] In the CRITICS trial, surgical non-compliance occurred in 58.9% of patients, which was minor (1 or 2 lymph node stations not removed) in the majority of patients. The rate of surgical contamination of 59.6% in the CRITICS trial is higher than the contamination rates of 25.8% in the D1 group and 28.7% in the D2 group of the DGTC.[6] In further analysis of the DCTG it is shown that contamination led to a survival benefit.[6] Altogether, in comparison with the DGCT, both surgical compliance and surgical contamination rates were better in the CRITICS trial.

In the late eighties, Maruyama and colleagues constructed a computer program for determining the extent of lymphadenectomy in gastrectomies (Maruyama Computer Program), based on similar characteristics of 3843 patients with gastric cancer who underwent an extensive lymphadenectomy.[9] The high accuracy of the Maruyama Computer Program was evaluated in Japan, Germany, and Italy.[9,21,22] Hundahl et al. showed in both the Intergroup 0116 trial as well as in the DGCT that the 'Maruyama Index of Unresected Disease' (MI) based on the Maruyama Computer Program, is the most important quality indicator of lymph node dissection in gastric cancer surgery.[7,8] A MI of less than 5 appeared to be strongly associated with a better disease-free and overall survival in both trials.[7,8,10] Median MI in the DGCT and Intergroup 0116 trial were 26 and 70, respectively.[7,10] The median MI of 1 in the CRITICS trial was much lower, indicating a high quality of surgery. Median MI was 4 at the start of the CRITICS trial in 2007 and decreased to a median of 0 after 2012. This emphasizes that the quality of surgery improved over time during the study, in accordance with the improved surgicopathological compliance.

Above mentioned results of the surgical quality in the CRITICS trial show the high protocol adherence to lymphadenectomy and the success of the intended surgical quality assurance in this trial. Recently, a systemic review showed a wide range in gastro-esophageal randomized clinical trials in respect of lymph-node harvest, in-hospital mortality, and locoregional cancer recurrence.[23] To reduce this surgical variation between randomized clinical trials, standardization of surgical techniques and assessment of surgical performance in future gastric randomized clinical trials should be a component in the study protocol.

In conclusion, surgicopathological quality control and centralization of gastric cancer surgery have led to a very high protocol adherence for lymphadenectomy and consequently, a high surgicopathological compliance and a low MI in the CRITICS trial. Surgical quality control remains very important in multimodal trials with a surgical component.

REFERENCES

1. Papenfuss WA, Kukar M, Oxenberg J, et al. Morbidity and mortality associated with gastrectomy for gastric cancer. Ann Surg Oncol 2014; 21(9): 3008-14.
2. Jemal A, Siegel R, Xu J, et al. Cancer statistics, 2010. CA: a cancer journal for clinicians 2010; 60(5): 277-300.
3. Bickenbach K, Strong VE. Comparisons of Gastric Cancer Treatments: East vs. West. J Gastric Cancer 2012; 12(2): 55-62.
4. Hartgrink HH, van de Velde CJ, Putter H, et al. Extended lymph node dissection for gastric cancer: who may benefit? Final results of the randomized Dutch gastric cancer group trial. J Clin Oncol 2004; 22(11): 2069-77.
5. Songun I, Putter H, Kranenbarg EM, et al. Surgical treatment of gastric cancer: 15-year follow-up results of the randomised nationwide Dutch D1D2 trial. Lancet Oncol 2010; 11(5): 439-49.
6. De Steur WO, Hartgrink HH, Dikken JL, et al. Quality control of lymph node dissection in the Dutch Gastric Cancer Trial. Br J Surg 2015; 102(11): 1388-93.
7. Hundahl SA, Macdonald JS, Benedetti J, et al. Surgical treatment variation in a prospective, randomized trial of chemoradiotherapy in gastric cancer: the effect of undertreatment. Ann Surg Oncol 2002; 9(3): 278-86.
8. Hundahl SA, Peeters KC, Kranenbarg EK, et al. Improved regional control and survival with "low Maruyama Index" surgery in gastric cancer: autopsy findings from the Dutch D1-D2 Trial. Gastric Cancer 2007; 10(2): 84-6.
9. Kampschoer GH, Maruyama K, van de Velde CJ, et al. Computer analysis in making preoperative decisions: a rational approach to lymph node dissection in gastric cancer patients. Br J Surg 1989; 76(9): 905-8.
10. Peeters KC, Hundahl SA, Kranenbarg EK, et al. Low Maruyama index surgery for gastric cancer: blinded reanalysis of the Dutch D1-D2 trial. World J Surg 2005; 29(12): 1576-84.
11. Cunningham D, Allum WH, Stenning SP, et al. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. N Engl J Med 2006; 355(1): 11-20.
12. Macdonald JS, Smalley SR, Benedetti J, et al. Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction. N Engl J Med 2001; 345(10): 725-30.
13. Dikken JL, van Sandick JW, Swellengrebel HA, et al. Neo-adjuvant chemotherapy followed by surgery and chemotherapy or by surgery and chemoradiotherapy for patients with resectable gastric cancer (CRITICS). BMC Cancer 2011; 11: 329.
14. Green FL, Page DL, Fleming ID, et al. American Joint Committee on Cancer (AJCC) Staging Manual. 6th ed New York, NY: Springer 2002.
15. Fleming ID, Cooper JS, Henson DE, et al. AJCC Cancer Staging Manual. Philadelphia, PA: Lippincott-Raven, 1997.
16. Compton CC, Byrd DR, Garcia-Aguilar J, et al. AJCC Cancer Staging Manual. 7th ed New York: Springer-Verlag, 2010.
17. Coburn NG, Swallow CJ, Kiss A, et al. Significant regional variation in adequacy of lymph node assessment and survival in gastric cancer. Cancer 2006; 107(9): 2143-51.

18. Jensen LS, Nielsen H, Mortensen PB, et al. Enforcing centralization for gastric cancer in Denmark. Eur J Surg Oncol 2010; 36 Suppl 1: S50-4.
19. Park SH, Sohn TS, Lee J, et al. Phase III Trial to Compare Adjuvant Chemotherapy With Capecitabine and Cisplatin Versus Concurrent Chemoradiotherapy in Gastric Cancer: Final Report of the Adjuvant Chemoradiotherapy in Stomach Tumors Trial, Including Survival and Subset Analyses. J Clin Oncol 2015; 33(28): 3130-6.
20. Cuschieri A, Weeden S, Fielding J, et al. Patient survival after D1 and D2 resections for gastric cancer: long-term results of the MRC randomized surgical trial. Surgical Co-operative Group. Br J Cancer 1999; 79(9-10): 1522-30.
21. Bollschweiler E, Boettcher K, Hoelscher AH, et al. Preoperative assessment of lymph node metastases in patients with gastric cancer: evaluation of the Maruyama computer program. Br J Surg 1992; 79(2): 156-60.
22. Guadagni S, de Manzoni G, Catarci M, et al. Evaluation of the Maruyama computer program accuracy for preoperative estimation of lymph node metastases from gastric cancer. World J Surg 2000; 24(12): 1550-8.
23. Markar SR, Wiggins T, Ni M, et al. Assessment of the quality of surgery within randomised controlled trials for the treatment of gastro-oesophageal cancer: a systematic review. Lancet Oncol 2015; 16(1): e23-31.

CHAPTER 3

SURGICAL MORBIDITY AND MORTALITY AFTER NEOADJUVANT CHEMOTHERAPY IN THE CRITICS GASTRIC CANCER TRIAL

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ABSTRACT

Background: In order to determine the optimal combination of perioperative chemotherapy and chemoradiotherapy for Western patients with advanced resectable gastric cancer, the international multicentre CRITICS trial (ChemoRadiotherapy after Induction chemotherapy In Cancer of the Stomach) was initiated. In this trial, patients with resectable gastric cancer were randomised before start of treatment between adjuvant chemotherapy or adjuvant chemoradiotherapy following neoadjuvant chemotherapy plus gastric cancer resection. The purpose of this study was to report on surgical morbidity and mortality in this trial, and to identify factors associated with surgical morbidity.

Methods: Patients who underwent a gastrectomy with curative intent were selected. Logistic regression analyses were used to assess risk factors for developing postoperative complications.

Results: Between 2007 and 2015, 788 patients were included in the CRITICS trial, of whom 636 patients were eligible for current analyses. Complications occurred in 296 patients (47%). Postoperative mortality was 2.2% (n=14). Complications due to anastomotic leakage was cause of death in 5 patients. Failure to complete preoperative chemotherapy (OR=2.09, *P*=0.004), splenectomy (OR=2.82, *P*= 0.012), and male sex (OR=1.55, *P*=0.020) were associated with a greater risk for postoperative complications. Total gastrectomy and oesophago-cardia resection were associated with greater risk for morbidity compared with subtotal gastrectomy (OR=1.88, *P*=0.001 and OR=1.89, *P*=0.038).

Conclusion: Compared to other Western studies, surgical morbidity in the CRITICS trial was slightly higher whereas mortality was low. Complications following anastomotic leakage was the most important factor for postoperative mortality. Important proxies for developing postoperative complications were failure to complete preoperative chemotherapy, splenectomy, male sex, total gastrectomy, and oesophago-cardia resection.

INTRODUCTION

Gastric cancer is the fourth most common malignancy worldwide with nearly one million new cases per year, and the third leading cause of cancer death with an estimated 723.000 deaths in 2012.[1] Survival remains poor with only 25% of all gastric cancer patients surviving the first five years.[2]
Surgery is the only curative treatment for locally advanced gastric cancer. In the Western world, a gastrectomy is considered high-risk surgery with surgical morbidity rates of 39% and mortality rates of approximately 5%.[3, 4] Even after an adequate gastric resection with a D2 lymphadenectomy, survival remains poor with a 5-year survival around 50%.[5]

Several studies have been performed to improve survival for locally advanced gastric cancer with (neo-) adjuvant chemotherapy and/or radiotherapy. Two randomised studies, the Intergroup 0116 trial and the MAGIC trial, changed current clinical practice for resectable gastric cancer in the Western world.[6, 7] In the Intergroup 0116 trial, a survival benefit was shown with adjuvant chemoradiotherapy compared to surgery alone, whereas in the MAGIC trial peri-operative chemotherapy improved survival over surgery alone.[6, 7] A direct comparison of the results from these two trials was not possible due to the differences in study design and eligibility criteria. To determine the optimal approach for adjuvant therapy after gastrectomy in patients with gastric cancer, the CRITICS (ChemoRadiotherapy after Induction chemotherapy In Cancer of the Stomach) trial was initiated. In this multicentre trial, patients with resectable gastric cancer were treated with three cycles of preoperative chemotherapy, followed by surgery with adequate lymph node dissection, followed by either three cycles of chemotherapy (standard arm) or concurrent chemoradiation (experimental arm), according to the results of randomisation before the start of treatment.[8]
The purpose of the present analyses was to evaluate surgical morbidity and mortality in the CRITICS trial and to identify risk factors for postoperative complications.

METHODS

CRITICS protocol
The protocol of the CRITICS trial has been published previously.[8] Patients with a histologically proven stage Ib-IVa (AJCC 6th edition) gastric adenocarcinoma were eligible for inclusion.[9] The bulk of the tumour had to be located in the stomach (determined by gastroscopy and/or endoscopic ultrasound), although extension into the gastro-oesophageal junction (GEJ) was allowed. The most important exclusion criteria were medical inoperability, distant metastases, and an uT1N0 tumour (determined with endoscopic ultrasound). Randomisation was performed before start of treatment.
Prior to surgery, all patients received three cycles of epirubicin, cisplatin or oxaliplatin, and capecitabine (ECC/EOC) at three-weekly intervals. Surgery was planned three to six

weeks after the last chemotherapy cycle. The principle of surgery was a wide resection of the tumour bearing part of the stomach en bloc with the N1 and N2 lymph nodes according a so-called D1+ lymph node dissection (lymph node stations 1-9 and 11) and with a minimum of 15 lymph nodes removed.[10] For tumours in the upper part of the stomach, a total gastrectomy was recommended with removal of lymph node station of 1-9 and 11. For tumours in the middle or distal part of the stomach, a subtotal resection of the stomach was recommended with removal of lymph node station of 1-9 and 11 apart from lymph node stations 2 and 4s. A trans-hiatal oesophagus-cardia resection was defined as resection of the distal part of the oesophagus and the upper part of the stomach (cardia) through the abdominal cavity with removal of lymph node station of 1-9 and 11 apart from lymph node stations 4d and 6. This type of resection with gastric tube reconstruction was allowed for tumours extending into the oesophagus.
Adjacent organs were removed only in case of there was suspicion of tumour involvement. If possible, a macroscopic margin of 5 cm was obtained to the proximal as well as the distal end.
Within twelve weeks after surgery, patients were treated with either adjuvant chemotherapy (three courses of ECC/EOC) or adjuvant chemoradiotherapy (radiotherapy combined with capecitabine and cisplatin), according to the upfront randomisation.

Patient selection and comorbidity
Patients who underwent a gastric resection with curative intent were selected from the CRITICS patient cohort. Curative intention of the gastrectomy was reviewed by two expert gastric surgeons based on the surgery report.
Co-morbidity was recorded in the Case Report Form (CRF) and was defined as the presence of at least one disease of the cardiovascular system, the gastrointestinal system, the genitourinary system, the central nervous system, the endocrine system, allergies, any musculoskeletal diseases, or other medical diseases. Co-morbidity was divided into three subgroups: none, presence of 1 or 2 co-existing diseases, and presence of three or more co-existing diseases.

Postoperative complications and postoperative mortality
Postoperative complications were blinded reported in the CRF without registration of grading of the complications. Postoperative complications were categorised in the CRF as surgery related complications (such as anastomotic leakage, bleeding, and ileus), infectious complications (such as abscess, sepsis, and abdominal wound infection), and general complications (such as pulmonary, cardiovascular, and thrombo-embolic). No uniform definitions of surgery related, infectious complications, and general complications were described in the study protocol of the CRITICS trial. Re-intervention due to a complication was defined as a re-intervention done for the management of a postoperative complication and was recorded in the CRF. Re-intervention was the equivalent of a Clavien-Dindo IIIA or IIIB grade.[11] Postoperative mortality was defined as death within 30 days after surgery or during hospital stay, if this exceeded 30 days.

Statistical analyses

Uni- and multivariate logistic regression analyses were used to assess risk factors for developing a postoperative complication. The chi-squared test was used to compare categorical data between total gastrectomies, subtotal gastrectomies, and oesophagocardia resections and the non-parametric Kruskal-Wallis test was used for numerical data. For all statistical analyses SPSS program 21.0 was used. A $P < 0.05$ was considered statistically significant.

RESULTS

Patient and surgical characteristics

The CRITICS gastric cancer trial was a multicentre (56 centres) randomised clinical trial, conducted in the Netherlands, Sweden, and Denmark from January 2007 to April 2015. In total, 788 patients were randomised of whom 152 patients did not meet the selection criteria for the current analyses (*Figure 1*). Consequently, 636 patients who underwent gastric cancer resection with curative intent were selected for the current analyses.

In total, 87 patients (13.7%) were not able to complete neoadjuvant chemotherapy. The majority of these patients had problems due to toxicity (n=74, 85.1%), followed by intercurrent disease (n=5, 5.7%), stomach bleeding/ perforation (n=3, 3.4%), poor condition (n=2, 2.3%), progression of the disease (n=1, 1.1%), refusal of patient (n=1, 1.1%), or death (n=1, 1.1%).

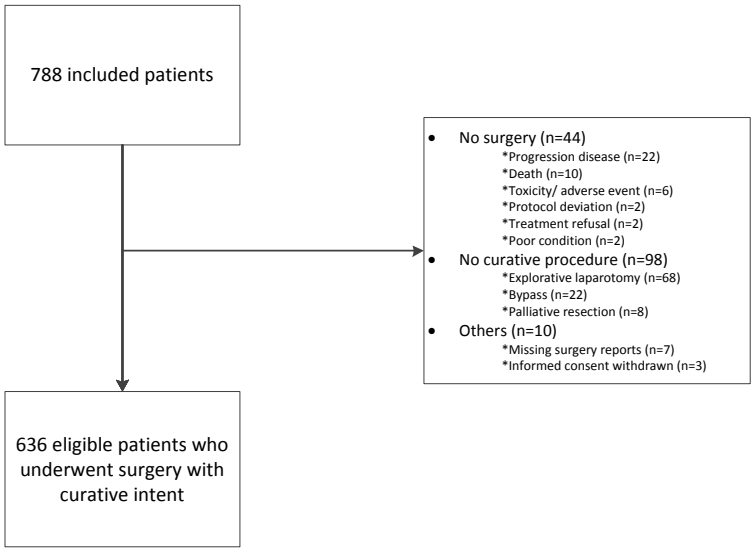

Figure 1. Study flow chart

Patient and surgical characteristics are shown in *Table 1*. Most patients underwent a total (n=318, 50.0%) or a subtotal gastrectomy (n=255, 40.1%), whereas a small group had an oesophago-cardia resection (n=63, 9.9%). Forty-nine patients with an antrum tumour had a total gastrectomy due to more extensive growth of diffuse type tumours. One patient with a proximal tumour underwent a proximal gastric resection. Usually, surgery was performed with an open approach (n=530, 83.3%); a laparoscopic procedure was performed in 101 patients (15.9%). The conversion rate was 11.9% (n=12). Reasons for conversion were direct tumour ingrowth in adjacent organs (n=9), perforation of meso-colon (n=1), perforation of duodenum (n=1), and hemodynamic instability (n=1). Thirty-eight patients underwent a splenectomy (6.0%) due to tumour ingrowth (65.5%), or bleeding (34.5%). Three patients in the subtotal gastrectomy group underwent a splenectomy, due to bleeding (n=2) or ingrowth of tumour (n=1). Sixteen patients underwent a distal pancreatectomy (2.6%) of whom half had a splenectomy as well. After excluding the patients of whom the location of the resected lymph node stations were not extractable from the surgery report (n=14), the majority of patients (n=544, 87.5%) underwent a D1+ lymph node dissection or more. In most of the patients (n=460, 72.8%) at least 15 lymph nodes were removed. A median of 20 retrieved lymph nodes were reviewed by the pathologist.

Table 1. Patient and surgical characteristics

	Total (n=636)
Age (years)	62 (28-82)
Sex	
Male	429 (67.5)
Female	207 (32.5)
BMI	
<18	15 (2.4)
18-24	306 (48.1)
≥25	315 (49.5)
Co-morbidity	
None	85 (13.4)
1-2	327 (51.4)
≥3	224 (35.2)
Completion preop chemo	
Yes	549 (86.3)
No	87 (13.7)
Tumour localisation	
Proximal	224 (35.2)
Middle	187 (29.4)
Distal	225 (35.4)

Table 1 continues

	Total (n=636)
Type of resection	
Total gastrectomy	318 (50.0)
Subtotal gastrectomy	255 (40.1)
Oesophago- cardia resection	63 (9.9)
Lauren classification	
Intestinal	175 (27.5)
Diffuse	206 (32.4)
Mixed	34 (5.3)
Missing	221 (34.8)
ypT stage	
ypT0/pTis/pT1	133 (20.9)
ypT2	222 (34.9)
ypT3	217 (34.1)
ypT4	64 (10.1)
ypN stage	
ypN0	311 (48.9)
ypN1	214 (33.7)
ypN2	77 (12.1)
ypN3	34 (5.3)
Radicality	
R0	515 (81.0)
R1	66 (10.4)
Unknown	55 (8.6)
Approach	
Open	530 (83.3)
Minimally invasive	89 (14.0)
Conversion	12 (1.9)
Missing	5 (0.8)
Splenectomy	
Yes	38 (6.0)
No	598 (94.0)
Pancreatectomy	
Yes	16 (2.6)
No	624 (97.4)

Age is presented as median (range), other data are presented as n (%).
Abbreviations; BMI = Body Mass Index; Completion preop chemo = completion of preoperative chemotherapy.

Postoperative complications and postoperative mortality
The overall complication rate was 46.5% (n=296, *Table 2*). Approximately 60% (n=52) of the patients who did not complete preoperative chemotherapy (n=87) developed a postoperative complication. Surgery related complications in the total study population occurred in 142 patients (22.3%). Anastomotic leakage was the most frequent surgical complication (n=45, 7.1%), followed by bleeding (n=18, 2.8%), and ileus (n=18, 2.8%). Reinterventions due to a complication occurred in 13.4% (n=85) of the total study population. Of the patients who developed a complication, 56.3% and 57.2% of the patients of the chemotherapy and chemoradiotherapy arm, respectively, did complete adjuvant treatment, compared to 60.0% and 67.6% of the patients who did not develop a complication (*P*<0.001 and *P*=0.036*)*. Data of complications of the different surgical subgroups are given in *Table 2*.

Table 2. (Three most frequently occurring) complications of subtotal gastrectomies, total gastrectomies, oesophago-cardia resections, and total study population

	Subtotal gastrectomy (n=255)	**Total gastrectomy (n=318)**	**Oesophago-cardia resection (n=63)**	***P***	**Total (n=636)**
Complication overall	93 (36.5)	170 (53.5)	33 (52.4)	*<0.001*	296 (46.5)
Surgery related complications	40 (15.7)	85 (26.7)	17 (27.0)	*0.004*	142 (22.3)
Anastomotic leakage*	5 (2.0)	32 (10.1)	8 (12.7)	*<0.001*	45 (7.1)
Bleeding*	5 (2.0)	13 (4.1)	0 (0.0)	0.112	18 (2.8)
Ileus*	6 (2.4)	11 (3.5)	1 (1.6)	0.597	18 (2.8)
Infectious complications	37 (14.5)	98 (30.8)	13 (20.6)	*<0.001*	148 (23.3)
Abscess*	8 (3.1)	28 (8.8)	1 (1.6)	*0.005*	37 (5.8)
Sepsis*	7 (2.7)	24 (7.5)	4 (6.3)	*0.038*	35 (5.5)
Abdominal wound inf*	9 (3.5)	15 (4.7)	2 (3.2)	0.705	26 (4.1)
General complications	53 (20.8)	103 (32.4)	24 (38.1)	*0.001*	180 (28.3)
Pulmonary*	15 (5.9)	48 (15.1)	15 (23.8)	*<0.001*	78 (12.3)
Cardiovascular*	7 (2.7)	25 (7.9)	5 (7.9)	*0.024*	37 (5.8)
Pulmonary embolism*	1 (0.4)	6 (1.9)	4 (6.3)	*0.004*	11 (1.7)
Reintervention due to complication	18 (7.1)	55 (17.3)	12 (19.0)	*0.001*	85 (13.4)
Hospital stay (days)	10 (8-14)	12 (10-17)	12 (10-16.3)	*<0.001*	11 (9-16.3)

Duration of surgery, blood loss, and hospital stay are presented as median (25 percentile – 75 percentile), other data are presented as n (%). Abbreviations; Abdominal wound inf = abdominal wound infection.
**three most frequently occurring complications, a patient can be registered for more than one complication*

Postoperative mortality was 2.2% (n=14) in the total group, and 8.0% (n=7) in the group that did not complete preoperative chemotherapy (n=87). Cause of death of the 14 patients were complications due to anastomotic leakage (n=5), followed by duodenal stump leakage (n=2), bleeding after abdominal infection (n=2), intestinal ischemia (n=1), tumour perforation (n=1), pancreatitis (n=1), complications following pulmonic complications (n=1), and sudden cardiac arrest (n=1). Two patients (5.3%) died in the group of splenectomies (n=38) and two patients (12.5%) in the group of distal pancreatectomies (n=16), of whom one had a splenectomy as well. After developing a complicated postoperative course, postoperative mortality was highest in the group aged 70+ (n=5, 7.4%), compared to 5.3% (n=6) and 2.6% (n=3) in the group of 60-69 years and in the younger than 60 years group, respectively.

Risk factors for postoperative complications

Univariate analysis showed that patients who failed to complete preoperative chemotherapy (OR=1.85; CI=1.16-2.92; *P*=0.009) were more likely to develop complications (*Table 3*). Furthermore, patients who underwent a splenectomy (OR=2.98; CI=1.45-6.13; *P*=0.003), male patients (OR=1.58; CI=1.13-2.21; *P*=0.008), patients who underwent a pancreatectomy (OR=3.23; CI=1.02-10.27; *P*=0.046), and patients who underwent a total gastrectomy (OR=2.01; CI=1.44-2.82; *P*<0.001) or an oesophago-cardia resection (OR=1.98; CI=1.13-3.47; *P*=0.017) were more prone to develop complications. In multivariate analyses, all of these remained statically significant, except the pancreatectomy group.

Table 3. Uni- and multivariate logistic regression analyses of risk factors for postoperative complications*

		Univariate analysis			**Multivariate analysis****		
		OR	*P*	CI	OR	*P*	CI
Age							
	<60 years	1			1		
	60-69 years	1.14	0.482	0.80-1.62	1.03	0.891	0.70-1.51
	≥ 70 years	1.24	0.317	0.82-1.87	1.08	0.744	0.68-1.73
Sex							
	Male	1.58	*0.008*	1.13-2.21	1.56	*0.020*	1.07-2.26
BMI							
	<18	1			1		
	18-24	1.22	0.709	0.43-3.52	0.87	0.809	0.27-2.81
	≥25	1.43	0.511	0.50-4.10	1.12	0.847	0.35-3.65
Co-morbidity							
	none	1			1		
	1-2	1.12	0.651	0.69-1.81	1.09	0.748	0.64-1.85
	≥3	1.40	0.192	0.85-2.32	1.27	0.404	0.72-2.23

Table 3 continues

		Univariate analysis			Multivariate analysis**		
		OR	*P*	CI	OR	*P*	CI
Lauren classification							
	Intestinal	1			1		
	Diffuse	0.84	0.391	0.56-1.26	0.90	0.655	0.57-1.42
	Mix	1.13	0.756	0.53-2.34	1.33	0.485	0.60-2.94
ypTstage							
	ypT0/pTis/ pT1	1			1		
	ypT2	1.30	0.241	0.84-2.00	1.01	0.962	0.62-1.65
	ypT3	1.18	0.453	0.76-1.83	0.88	0.623	0.52-1.48
	ypT4	1.28	0.427	0.70-2.32	0.82	0.579	0.40-1.67
ypNstage							
	ypN0	1			1		
	ypN1	1.30	0.141	0.92-1.85	1.25	0.275	0.84-1.86
	ypN2	1.57	0.080	0.95-2.60	1.41	0.249	0.79-2.53
	ypN3	1.34	0.420	0.66-2.72	1.03	0.952	0.44-2.40
Preop chemo not completed							
	Yes	1.85	*0.009*	1.16-2.92	2.09	*0.004*	1.27-3.43
Splenectomy							
	Yes	2.98	*0.003*	1.45-6.13	2.82	*0.012*	1.26-6.32
Pancreatectomy							
	Yes	3.23	*0.046*	1.02-10.27	1.41	0.636	0.34-5.80
Type of gastrectomy							
	Subtotal gastrectomy	1			1		
	Total gastrectomy	2.01	*<0.001*	1.44-2.82	1.88	*0.001*	1.30-2.72
	Oesophago-cardia resection	1.98	*0.017*	1.13-3.47	1.89	*0.038*	1.04-3.46
Blood transfusion							
	Yes	1.30	0.272	0.82-2.06	1.15	0.572	0.70-1.90

**Postoperative complication(s); surgery related and/or infectious and/or general complication.*
***Adjusted for age groups, sex, BMI, co-morbidity, Lauren classification, pTstage, pNstage, preop chemo not completed, splenectomy, pancreatectomy, type of gastrectomy, and blood transfusion.*
Abbreviations; OR = odds ratio; CI = confidence interval; BMI = Body Mass Index; Preop chemoth not completed = preoperative chemotherapy not completed.

DISCUSSION

In this study, postoperative morbidity and mortality in the CRITICS trial were evaluated and risk factors for postoperative morbidity identified.

Overall morbidity rate in the CRITICS trial was nearly 47%, with a reintervention rate of 13%. This percentage is slightly higher compared to other earlier practice changing randomised gastric cancer trials, as the Medical Research Council (MRC) trial and the Dutch Gastric Cancer Trial (DGCT) (MRC trial: 46%, DGCT: 43%), taking into account that in the CRITICS trial a D2 lymphadenectomy is performed without removal of the spleen, and the pancreatic tail, and lymph node station 10.[12, 13] In the Italian Gastric Cancer Trial, however, a considerable lower overall morbidity (17.9%) was registered.[14] Since the start of the Dutch Upper Gastrointestinal Cancer Audit (DUCA) in 2011, a complicated course after a gastrectomy of approximately 20% was registered which remained constant until 2015.[15]
Postoperative mortality rate in the CRITICS trial was 2.2%. Postoperative mortality rates in previous randomised clinical trials were 10% in the MRC trial, 13% in the DGCT, and 2.2% in the Italian Gastric Cancer Trial, respectively.[12-14] The postoperative mortality in the CRITICS trial was also low, compared to the postoperative mortality registered by the DUCA from 2011 to 2015, varying between 3.5% and 7.5%, and the British audit AUGIS (Association of Upper Gastrointestinal Surgeons of Great Britain and Ireland), varying between 1.9% and 4.5%.[15, 16]
Thus, the for current Western standards relative high morbidity rate did not result in a higher mortality rate. High accuracy of registering complications in the CRITICS trial and the more vulnerable status of patients due to preoperative chemotherapy could partly explain this postoperative complication rate. Furthermore, it might be explained by the relatively low severity of the complications and by the increasing quality of perioperative care over time.

In the current study postoperative mortality was most often caused by complications due to anastomotic and duodenal stump leakage. In literature anastomotic leakage after gastrectomy have been reported to occur in 1.2%-5.0% of the cases, with a related mortality rate of 21.1%.[17, 18] Recently it was shown that neoadjuvant chemotherapy prior to gastric resection was not associated with an increased risk of anastomotic leakage or short-term morbidity or mortality.[19] It could be, however, that the consequences, once an anastomotic leakage occurs, are greater in patients who underwent neoadjuvant chemotherapy than in patients who did not underwent neoadjuvant chemotherapy. At this moment the proven survival benefit of neoadjuvant therapy over surgery alone outweighs this possible disadvantage.[20]

In the CRITICS trial, registration of specific complications was recorded in the CRF whereby a detailed overview of complications was obtained. However, as a consequence of not registering aspects as severity of comorbidity, seriousness and grading of the

complications (e.g. with a Clavidien-Dindo classification), more detailed analyses were not possible and this is a major shortcoming of the current study. On the other hand, in the current study it was possible to investigate the influence of postoperative morbidity on the completion of the adjuvant treatment; either chemotherapy or chemoradiotherapy. In both study arms developing a complication was associated with a smaller chance to complete adjuvant treatment, emphasizing the long-term effect and the impact of a postoperative course in this group of patients.

The group that did not complete preoperative chemotherapy in the current study was more than twice as likely to develop postoperative complications (OR=2.15, *P*=0.003) and had a higher postoperative mortality rate (8.0%), findings of which surgeons should be aware. Results showed that not completing preoperative chemotherapy in the CRITICS trial was mainly due to toxicity (85.1%), which stresses the major clinical implications of side effects of the chemotherapy in this group of patients. Recently it was shown that sarcopenia is associated with toxicity in gastric cancer patients undergoing neo-adjuvant chemotherapy.[21] It is well known that sarcopenic and frail patients are vulnerable to experience severe problems once a complication occurs.[22] In this trial sarcopenia and frailty were not reported as such, but the ability not to complete preoperative chemotherapy mainly due to toxicity could indicate such a condition. Patients who were able to complete their chemotherapy could have been fitter, physically stronger, and therefore less likely to develop a complication.

Previously, splenectomy has been described as an important risk factor for a complicated postoperative course and hospital mortality with even a significant adverse effect on survival.[23, 24] In the Dutch Gastric Cancer Trial pancreatic resections and splenectomies were routinely performed for D2 dissections in proximal tumours to obtain proper removal of lymph node stations 10 and 11, which occurred in 23% of the patients in the Dutch Gastric Cancer Trial.[23] The increased morbidity and mortality caused by pancreatic resections and splenectomies probably have offset the difference in survival between the D1 and D2 groups.[23] Recently, the randomised JCOG-0110 trial has proven that routine removal of the spleen should be avoided, as it increases morbidity without improving survival.[25] In the CRITICS trial only 6% of the patients underwent a splenectomy. Unfortunately, for adequate removal of all tumour tissue the increased risk for complications could not be avoided in these patients.

In bowel surgery, several studies suggested that male sex is a risk factor for developing postoperative complications.[26, 27] With respect to gastric cancer surgery, opposite results are shown. In accordance with the results of a recent retrospective study, our results showed an increased risk of postoperative complications for male gender, whereas another study showed that females were at high risk.[28, 29] Without a clear biological explanation for these findings and with the absence of grading of postoperative complications in the current study, this finding should be interpreted with caution.

The postoperative complication rate was significantly higher in the total gastrectomy group compared with the subtotal gastrectomy group. In the last decade of the 20th century, a French and an Italian randomised trial were performed to analyse the

differences between a total and a subtotal gastrectomy, resulting in a similar long-term survival but with a higher morbidity rate, a higher mortality rate, and a decreased quality of life for patients who underwent a total gastrectomy. It was thus recommended to perform a subtotal gastrectomy when possible.[24, 30] According to the current guidelines, for diffuse type of tumours, due to their composition of poorly cohesive tumour cells and poor differentiation, a total gastrectomy is recommended.[31] Results in this study showed differences between the two types of procedures all in favour of a subtotal gastrectomy with regard to the development of postoperative complications, the reintervention rate, and hospital stay. This emphasizes the concept that total gastrectomy should only be performed if the extension or the type of the tumour dictates so.

Overall, compared to other Western studies, surgical morbidity in the CRITICS trial was slightly higher whereas mortality was low. Complications following anastomotic leakage was the most important factor for postoperative mortality. Important proxies for developing postoperative complications were failure to complete preoperative chemotherapy, splenectomy, male sex, total gastrectomy, and oesophago-cardia resection.

REFERENCES

1. Ferlay J, Soerjomataram I, Dikshit R, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer 2015;136(5):E359-86.
2. Jemal A, Siegel R, Xu J, et al. Cancer statistics, 2010. CA Cancer J Clin 2010;60(5):277-300.
3. Bosing NM, Goretzki PE, Roher HD. Gastric cancer: which patients benefit from systematic lymphadenectomy? Eur J Surg Oncol 2000;26(5):498-505.
4. Bartlett EK, Roses RE, Kelz RR, et al. Morbidity and mortality after total gastrectomy for gastric malignancy using the American College of Surgeons National Surgical Quality Improvement Program database. Surgery. 2014;156(2):298-304.
5. Rosa F, Alfieri S, Tortorelli AP, et al. Trends in clinical features, postoperative outcomes, and long-term survival for gastric cancer: a Western experience with 1,278 patients over 30 years. World J Surg Oncol 2014;12:217.
6. Macdonald JS, Smalley SR, Benedetti J, et al. Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction. N Eng J Med 2001;345(10):725-30.
7. Cunningham D, Allum WH, Stenning SP, et al. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. N Eng J Med 2006;355(1):11-20.
8. Dikken JL, van Sandick JW, Swellengrebel HA, et al. Neo-adjuvant chemotherapy followed by surgery and chemotherapy or by surgery and chemoradiotherapy for patients with resectable gastric cancer (CRITICS). BMC cancer. 2011;11:329.
9. Green FL, Page DL, Fleming ID, et al. American Joint Committee on Cancer (AJCC) Staging Manual. 6th ed New York, NY: Springer 2002.
10. Japanese Gastric Cancer Assocation. Japanese Classification of Gastric Carcinoma - 2nd English Edition. Gastric Cancer 1998;1:10-24.
11. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg. 2004;240(2):205-13.
12. Cuschieri A, Fayers P, Fielding J, et al. Postoperative morbidity and mortality after D1 and D2 resections for gastric cancer: preliminary results of the MRC randomised controlled surgical trial. The Surgical Cooperative Group. Lancet. 1996;347(9007):995-9.
13. Bonenkamp JJ, Songun I, Hermans J, et al. Randomised comparison of morbidity after D1 and D2 dissection for gastric cancer in 996 Dutch patients. Lancet. 1995;345(8952):745-8.
14. Degiuli M, Sasako M, Ponti A. Morbidity and mortality in the Italian Gastric Cancer Study Group randomized clinical trial of D1 versus D2 resection for gastric cancer. Br J Surg 2010;97(5):643-9.
15. https://www.dica.nl/media/332/DICA-jaarrapportage-2015.pdf.
16. http://content.digital.nhs.uk/catalogue/PUB21561/clin-audi-supp-prog-oeso-gast-2016-rep.pdf.
17. Tsou CC, Lo SS, Fang WL, et al. Risk factors and management of anastomotic leakage after radical gastrectomy for gastric cancer. Hepatogastroenterology 2011;58(105):218-23.

18. Kawamura Y, Satoh S, Suda K, et al. Critical factors that influence the early outcome of laparoscopic total gastrectomy. Gastric cancer 2015;18(3):662-8.
19. Haskins IN, Kroh MD, Amdur RL, et al. The effect of neoadjuvant chemoradiation on anastomotic leak and additional 30-Day morbidity and mortality in patients undergoing total gastrectomy for gastric cancer. J Gastrointest Surg 2017; epub ahead of print.
20. Jiang L, Yang KH, Guan QL, et al. Survival benefit of neoadjuvant chemotherapy for resectable cancer of the gastric and gastroesophageal junction: a meta-analysis. J Clin Gastroenterol 2015;49(5):387-94.
21. Tan BH, Brammer K, Randhawa N, et al. Sarcopenia is associated with toxicity in patients undergoing neo-adjuvant chemotherapy for oesophago-gastric cancer. Eur J Surg Oncol 2015;41(3):333-8.
22. Wagner D, DeMarco MM, Amini N, et al. Role of frailty and sarcopenia in predicting outcomes among patients undergoing gastrointestinal surgery. World J Gastrointest Surg 2016;8(1):27-40.
23. Hartgrink HH, van de Velde CJ, Putter H, et al. Extended lymph node dissection for gastric cancer: who may benefit? Final results of the randomized Dutch gastric cancer group trial. J Clin Oncol 2004;22(11):2069-77.
24. Bozzetti F, Marubini E, Bonfanti G, et al. Subtotal versus total gastrectomy for gastric cancer: five-year survival rates in a multicenter randomized Italian trial. Italian Gastrointestinal Tumor Study Group. Ann Surg 1999;230(2):170-8.
25. Sano T, Sasako M, Mizusawa J, et al. Randomized controlled trial to evaluate splenectomy in total gastrectomy for proximal gastric carcinoma. Ann Surg 2017; 265(2): 277-283.
26. Kirchhoff P, Dincler S, Buchmann P. A multivariate analysis of potential risk factors for intra- and postoperative complications in 1316 elective laparoscopic colorectal procedures. Ann Surg 2008;248(2):259-65.
27. Lipska MA, Bissett IP, Parry BR, et al. Anastomotic leakage after lower gastrointestinal anastomosis: men are at a higher risk. ANZ J Surg 2006;76(7):579-85.
28. Kang SC, Kim HI, Kim MG. Low serum albumin level, male sex, and total gastrectomy are risk factors of severe postoperative complications in elderly gastric cancer patients. J Gastric Cancer 2016;16(1):43-50.
29. Sah BK, Zhu ZG, Wang XY, et al. Post-operative complications of gastric cancer surgery: female gender at high risk. Eur J Cancer Care 2009;18(2):202-8.
30. Gouzi JL, Huguier M, Fagniez PL, et al. Total versus subtotal gastrectomy for adenocarcinoma of the gastric antrum. A French prospective controlled study. Ann Surg. 1989;209(2):162-6.
31. Van Cutsem E, Sagaert X, Topal B, et al. Gastric cancer. Lancet. 2016;388(10060):2654-64.

CHAPTER 4

IMPACT OF UPFRONT RANDOMIZATION FOR POSTOPERATIVE TREATMENT ON QUALITY OF SURGERY IN THE CRITICS GASTRIC CANCER TRIAL

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ABSTRACT

Background: Preoperative randomization for postoperative treatment might affect quality of surgery. In the CRITICS trial (ChemoRadiotherapy after Induction chemotherapy In Cancer of the Stomach), patients were randomized before treatment to receive chemotherapy prior to a D1+ gastrectomy (removal of lymph node station (LNS) 1-9+11), followed by either chemotherapy (CT) or chemoradiotherapy (CRT). In this analysis, the influence of upfront randomization on the quality of surgery was evaluated.

Methods: Quality of surgery was analyzed in both study arms using surgicopathological compliance (removal of ≥15 lymph nodes), surgical compliance (removal of the indicated LNS), and surgical contamination (removal of LNS that should be left in situ). Furthermore, the 'Maruyama Index of Unresected disease' (MI) was evaluated in both study arms, and validated with overall survival.

Results: Between 2007 and 2015, 788 patients with gastric cancer were included in the CRITICS study of whom 636 patients were operated with curative intent. No difference was observed between the CT and CRT group regarding surgicopathological compliance (74.8% vs 70.9%, *P*=0.324), surgical compliance (43.2% vs 39.2%, *P*=0.381), and surgical contamination (59.4% vs 59.9%, *P*=0.567). Median MI was 1 in both groups (range CT: 0-88 and CRT: 0-136, *P*=0.700). A MI below 5 was associated with better overall survival (CT: *P*=0.009 and CRT: *P*=0.013).

Conclusion: Surgical quality parameters were similar in both study arms in the CRITICS gastric cancer trial, indicating that upfront randomization for postoperative treatment had no impact on the quality of surgery. A Maruyama Index below five was associated with better overall survival.

INTRODUCTION

Timing of randomization in multimodality trials is often a point of debate. This is illustrated by the criticism on the timing of randomization in the Intergroup 0116 trial where randomization for adjuvant chemoradiotherapy versus no adjuvant treatment was done after surgery.[1] Opponents found that this moment of randomization may have led to selection bias, as pathology results were known at the time of selecting patients for the study. Preoperative randomization avoids this patients' selection for study participation after surgery.

The US Intergroup 0116 trial and the British MAGIC trial changed current clinical practice for resectable gastric cancer in the Western world, by showing a survival benefit with adjuvant chemoradiotherapy and peri-operative chemotherapy, respectively.[1,2] As the results of the Intergroup 0116 trial and the MAGIC trial were not directly comparable due to differences in study design and eligibility criteria, the CRITICS trial (ChemoRadiotherapy after Induction chemotherapy In Cancer of the Stomach) was initiated. In this multicenter trial, patients with resectable gastric cancer were treated with three cycles of preoperative chemotherapy and surgery with an adequate lymph node dissection, followed by either three cycles of chemotherapy (CT) or concurrent chemoradiotherapy (CRT). Randomization was done before the start of preoperative chemotherapy.[3] The moment of randomization has been criticized. It has been suggested that the quality of surgery in the CRITICS study might be influenced by the knowledge of the treatment that would follow, as surgeons were not blinded for the adjuvant therapy. To dispel this assumption, the possible influence of upfront randomization for the postoperative treatment on the quality of surgery in the CRITICS trial was investigated in the current analyses.

Surgical quality was assessed in both study arms using surgicopathological compliance (removal of at least 15 lymph nodes), surgical compliance (removal of the indicated lymph node stations), and surgical contamination (removal of lymph node stations that should be left in situ). Furthermore, surgical quality was analyzed by calculating the 'Maruyama Index of Unresected disease' (MI), the strongest quality indicator for determining the adequacy of lymphadenectomy in gastric cancer surgery. Additionally, the MI was validated with overall survival, as in both the Dutch Gastric Cancer Trial (DGCT) and the Intergroup 0116 trial, the MI proved to be strongly associated with survival, with a cut-off value below five for a favorable outcome.[4-6] By analyzing these surgical quality parameters in both study arms the aim of the current study was to evaluate the possible influence of upfront randomization for postoperative treatment on the quality of surgery in the CRITICS gastric cancer trial.

METHODS

CRITICS protocol

The study protocol of the CRITICS trial has been published previously.[3] Patients with a histologically proven stage Ib-IVa (AJCC 6th edition) gastric adenocarcinoma were included.[7] The bulk of the tumor had to be located in the stomach, though extension into the gastro-esophageal junction (GEJ) was allowed. Patients with ASA classification 1 or 2 were included. The most important exclusion criteria were inoperability, distant metastases, and T1N0 disease (determined with endoscopic ultrasound).

Prior to surgery, all patients were assigned to receive three cycles of epirubicin, cisplatin/oxaliplatin, and capecitabine (ECC/EOC) at three-weekly intervals. Surgery was scheduled three to six weeks after the last chemotherapy cycle. The principle of surgery was a wide resection of the tumor bearing part of the stomach with en bloc removal of lymph nodes at stations 1-9 and 11 (D1+ lymph node dissection) and with a minimum of 15 lymph nodes. A D1+ was chosen with best insight while the discussion regarding the extent of lymphadenectomy for gastric cancer in the Western world was still ongoing at the moment of designing the trial. A D1 lymph node dissection was defined as removal of stations 3-6 during subtotal gastrectomy and stations 1-6 during total gastrectomy. A D2 lymph node dissection was defined as removal of stations 1,3, 4sb, 4d, 5, 6, 7, 8a, 9, 11p, and 12a during subtotal gastrectomy and stations 1-7, 8a, 9, 10, 11p, 11d, and 12a during total gastrectomy.[8] Adjacent organs were only removed if there was suspicion of tumor involvement. If possible, a macroscopic margin of 5 cm was obtained, both to the proximal end and to the distal end. For tumors in the upper part of the stomach, a total gastrectomy was performed. For tumors in the middle or distal part of the stomach, a subtotal resection of the stomach was performed, leaving lymph node stations 2 and 4s in situ. A transhiatal esophagus-cardia resection with gastric tube reconstruction was performed for gastro-esophageal junction (GEJ) tumors extending into the esophagus, leaving lymph node stations 4d and 6 in situ. Both open and minimally invasive procedures were allowed.

After surgery, the study protocol dictated either another three courses of ECC/EOC (CT) or chemoradiotherapy (CRT; 45 Gy in 25 fractions combined with daily capecitabine and weekly cisplatin). Randomization of the adjuvant therapy occurred prior to the start of treatment (*Figure 1*).

Surgical quality assurance in the CRITICS trial

Before participation in the CRITICS trial, a presentation was given to instruct surgeons which lymph node stations had to be removed according to the study protocol. Participating surgeons also received a DVD and a book with instructions as well. Continuous quality assurance was carried out since 2011 and included regular feedback to the participating surgeon and pathologist on their average lymph node count in the trial, together with the average lymph node count in the study at that moment. Also, if the study coordinator received a report with a lymph node count below 15, feedback was provided within three months after surgery to the respective surgeon and pathologist and if possible, the surgical specimen was examined for remaining lymph nodes.

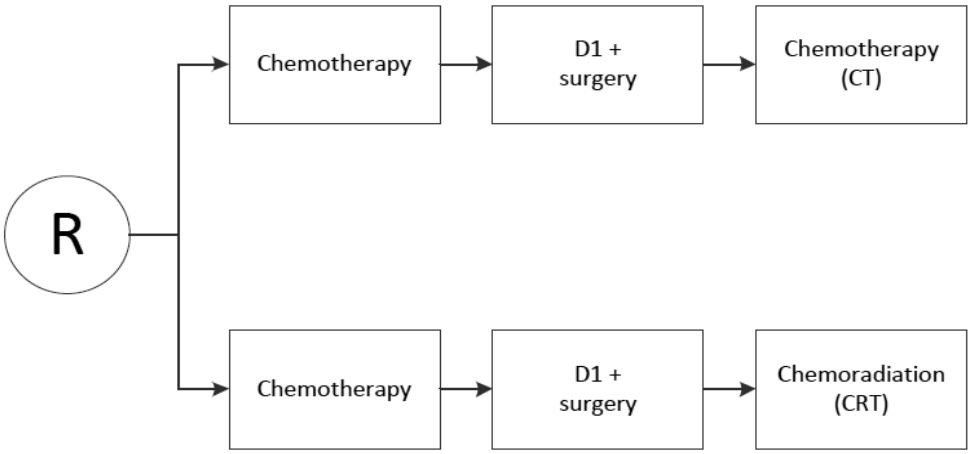


Figure 1. Design of the CRITICS trial
Abbreviations; R: randomization; Chemotherapy = epirubicin, cisplatin/oxaliplatin, and capecitabine (ECC/EOC); D1+ surgery: surgery including a D1+ lymphadenectomy; Chemoradiotherapy: 45 Gy/25 fractions + capecitabine + cisplatin

Eligibility current study
For the current analyses, patients were selected from the CRITICS database if the gastric cancer operation was performed with curative intent, based on the surgical report.
Patients were excluded from the surgicopathological analyses if the total number of sampled lymph nodes was not documented by the pathologist. Patients were excluded from the analyses of surgical compliance, surgical contamination, and MI, if the exact location of the directed lymph node stations was not extractable from the surgical report.
This study was reported according the CONSORT 2010 statement.[9]

Central data review
Data on the dissected lymph node stations (1-16) and type of lymph node dissection (D1+ or more) were extracted from the surgical reports, supplementary to the data recorded in the CRF. These data were validated and optimized by two experienced gastric surgeons. In case the number of removed lymph node stations was not explicitly stated in the surgical report, an assumption was made based on the mentioned anatomical structures in the surgical report, if possible. For example, when a given surgical report described removal of lymph nodes along the common hepatic artery, it was revised as removal of lymph node station 8. If assumptions were not possible, it was scored as unknown. In case all stations were unknown, patients were excluded from the analyses. In case a single lymph node station was unknown, the station was considered as not removed.

Surgicopathological compliance
Surgicopathological compliance was defined as the removal of a minimum of 15 lymph nodes and surgicopathological non-compliance as the removal of less than 15 lymph nodes. The latter group was divided into minor surgicopathological non-compliance, defined as removal of a minimum of 10 lymph nodes, and major surgicopathological non-compliance, defined as removal of less than 10 lymph nodes.

Surgical compliance and surgical contamination
Surgical compliance was defined as the removal of station 1-9 and 11, except for subtotal gastric resections where lymph node stations 2 and 4s were left in situ, and esophagus-cardia resections where lymph node stations 4d and 6 were left in situ. The definition of surgical non-compliance was not harvesting all indicated lymph node stations. The surgical non-compliance group was divided into minor non-compliance (1 or 2 of the intended lymph node stations not removed) and major non-compliance (≥3 of the intended lymph node stations not removed).
Surgical contamination was defined as removal of one or more lymph node stations outside the intended extent of resection. Surgical contamination was subdivided into minor contamination (1 or 2 lymph node stations that should be left in situ removed) and major contamination (≥3 lymph node stations that should be left in situ removed). Surgical compliance and surgical contamination were based on the data validated by two experienced gastric surgeons.

Maruyama Index
The MI is based on eight parameters: sex, age, type of cancer (early or advanced), depth of invasion, maximal diameter, location (upper third, middle third, lower third), position (lesser curvature, greater curvature, anterior, posterior, circular), and histological type. In the current study, the MI was determined by using the Maruyama Computer Program. To quantify the likelihood of unresected nodal disease, the MI is defined as the sum of Maruyama Computer Program predictions for the regional lymph node stations 1 to 12, which were not removed by the surgeon. When a given patient underwent a total gastrectomy with removal of lymph node stations 1 to 7 and 9, the MI was calculated by adding up the likelihood of unresected nodal disease at stations 8, 10, 11, and 12.

Statistics
The chi-squared test was used to compare categorical data between the CT and CRT group and the unpaired t-test was used for numerical data. Overall survival since surgery for both study arms was estimated by the Kaplan-Meier method and survival distribution of MI (<5 and ≥5) was assessed by the log-rank test. The effect of MI (<5 and ≥5) on survival in both groups was determined by an interaction test. A *P* lower than 0.05 was considered as statistically significant. SPSS program 21.0 was used for statistical analyses.

RESULTS

From January 2007 to April 2015, 788 patients were included at 56 centers in the Netherlands, Sweden, and Denmark. For current analyses, 636 patients were eligible; 632 patients for the analyses on surgicopathological compliance, 622 patients for the analyses on surgical compliance, surgical contamination, MI, and MI and survival (*Figure 2*).

Patient characteristics are shown in *Table 1*. The localization of the primary tumor (proximal, middle, distal stomach) was equally distributed in the CT group and in the CRT group. In both groups, the majority of patients underwent a total gastrectomy, followed by a subtotal gastrectomy, and an esophagus-cardia resection. In the CT group, 22 patients underwent a splenectomy (7.1%) compared to 16 patients (4.9%) in the CRT group. The rate of distal pancreatectomies was low in both groups, 6 patients (1.9%) in the CT group and 10 patients (3.1%) in the CRT group, respectively.

Table 1. Patient characteristics

	CT group (n=310)	**CRT group (n=326)**	***P***
Median age (years)	61.5(28-81)	63.0 (30-82)	0.240
Sex			
Male	214 (69.0)	215 (66.0)	0.359
Female	96 (31.0)	111 (34.0)	
Lauren classification			
Diffuse	101 (32.6)	105 (32.2)	0.712
Intestinal	88 (28.4)	87 (26.7)	
Mixed	13 (4.2)	21 (6.4)	
Unknown	108 (34.8)	112 (34.7)	
Tumor localization			
Proximal stomach	116 (37.8)	120 (36.8)	0.655
Middle stomach	95 (30.7)	88 (27.0)	
Distal stomach	99 (31.6)	118 (36.2)	
Type of resection			
Total gastrectomy	159 (51.3)	159 (48.8)	0.688
Subtotal gastrectomy	119 (38.4)	136 (41.7)	
Esophagus-cardia resection	32 (10.3)	31 (9.5)	
Tumor stage			
pT0/pTis/pT1	62 (20.0)	71 (21.8)	0.882
pT2	108 (34.8)	114 (35.0)	
pT3	110 (35.5)	107 (32.8)	
pT4	30 (9.7)	34 (10.4)	

Table 1 continues

	CT group (n=310)	CRT group (n=326)	*P*
Node stage			
pN0	150 (48.4)	161 (49.4)	0.846
pN1	109 (35.1)	105 (32.2)	
pN2	35 (11.3)	42 (12.9)	
pN3	16 (5.2)	18 (5.5)	
UICC Stage			
Stage 0	21 (6.8)	22 (6.7)	0.373
Stage 1	100 (32.3)	101 (31.0)	
Stage 2	65 (21.0)	84 (25.8)	
Stage 3	87 (28.1)	73 (22.4)	
Stage 4	37 (11.9)	46 (14.1)	
Splenectomy			
Yes	22 (7.1)	16 (4.9)	0.244
No	288 (92.9)	310 (95.1)	
Distal pancreatectomy			
Yes	6 (1.9)	10 (3.1)	0.489
No	304 (98.1)	316 (96.9)	
Approach			
Open	256 (82.6)	274 (84.0)	0.837
Minimally invasive	46 (14.8)	43 (13.2)	
Conversion	6 (1.9)	6 (1.8)	
Unknown	2 (0.7)	3 (1.0)	
Surgical complication			
Yes	70 (22.6)	72 (22.1)	0.880
No	240 (77.4)	254 (77.9)	
Median n# LN dissected	21 (0-72)	19 (0-71)	0.037
Radicality			
R0	248 (80.0)	267 (81.9)	0.828
R1	34 (11.0)	32 (9.8)	
Unknown	28 (9.0)	27 (8.3)	

Age and median n# of LN dissected is presented as median (range), other data are presented as n (%)
Abbreviations; CT group: chemotherapy; CRT group: chemoradiotherapy; median n# LN dissected: median number of lymph nodes dissected

Surgicopathological compliance occurred in 230 patients (74.8%) in the CT group and 232 patients (70.9%) in the CRT group (*P*=0.324, *Figure 3a*). Surgicopathological compliance improved over time both in the CT group (from 60.0% to 100%) and in the CRT group (from 50.0% to 80.0%). No significant difference was observed between the

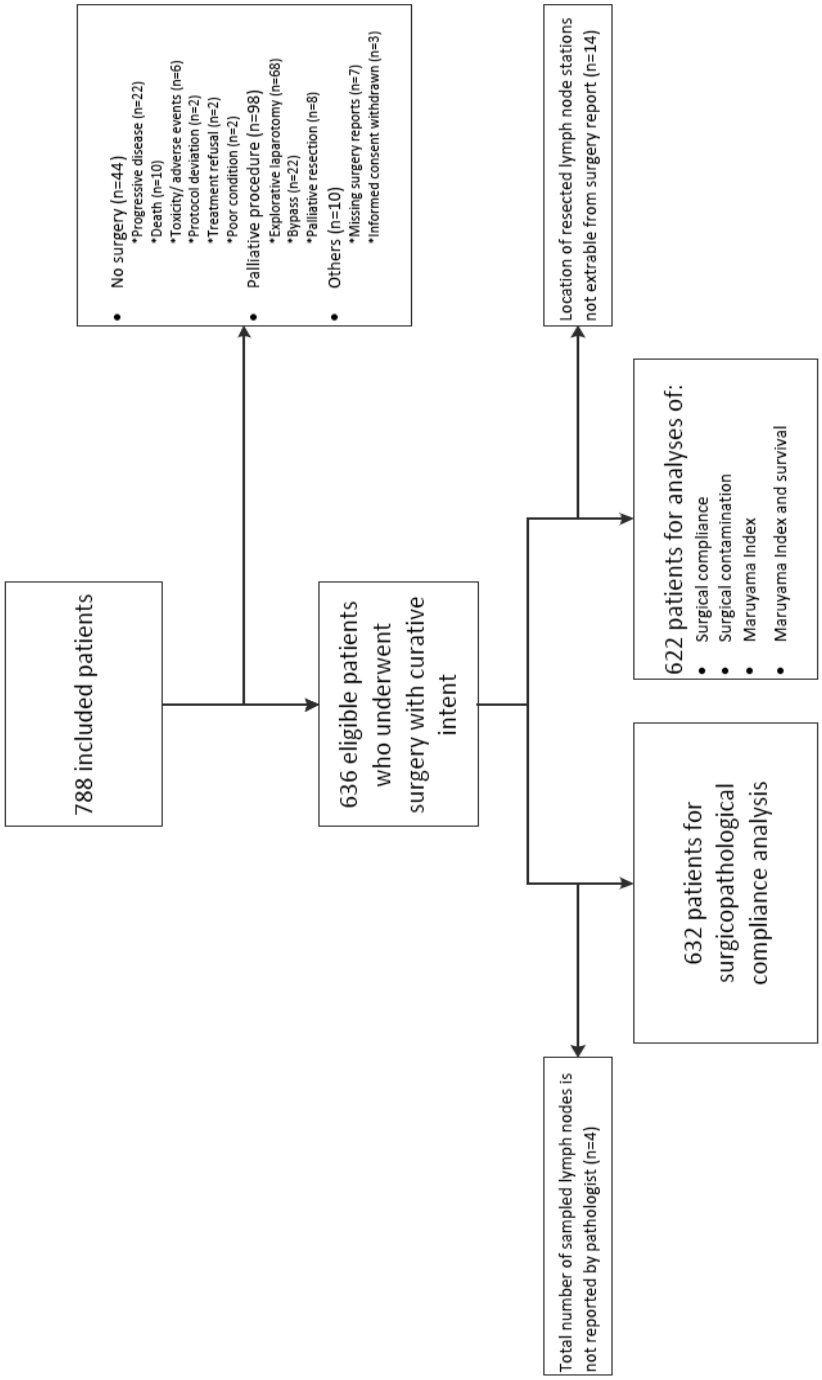


Figure 2. Study flow chart

CT group and the CRT group with respect to at least a D1+ lymphadenectomy performed (88.8% vs 86.2%, *P*=0.333). Complete surgical compliance occurred in 131 patients (43.2%) in the CT group and in 125 patients (39.2%) in the CRT group (*P*=0.381, *Figure 3b*). Similarly, surgical contamination was not different between the two study arms (*Figure 3c).*

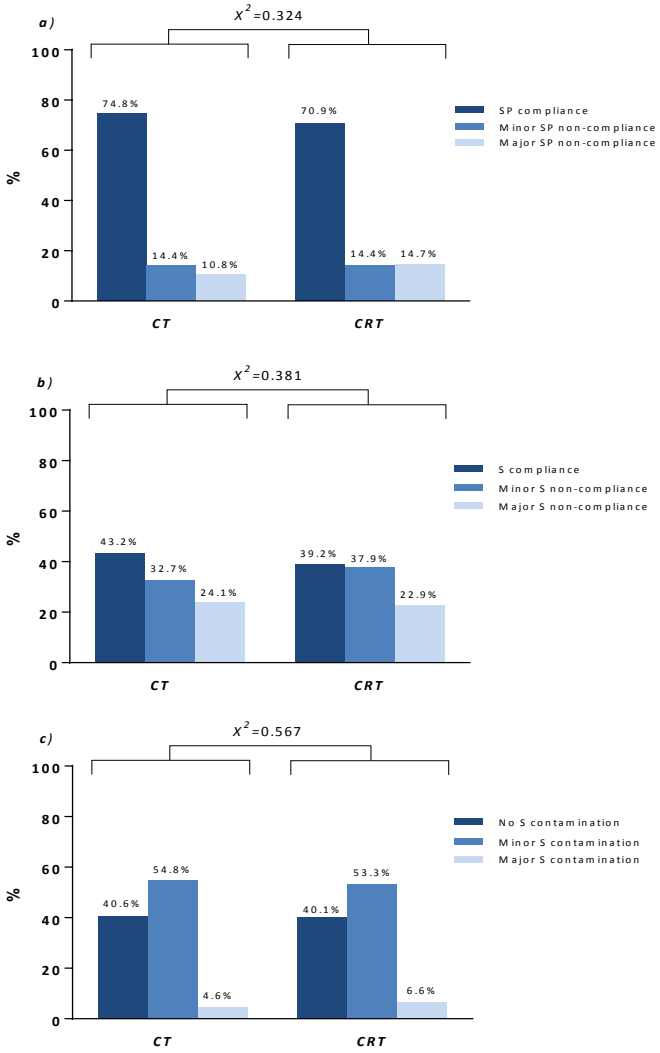
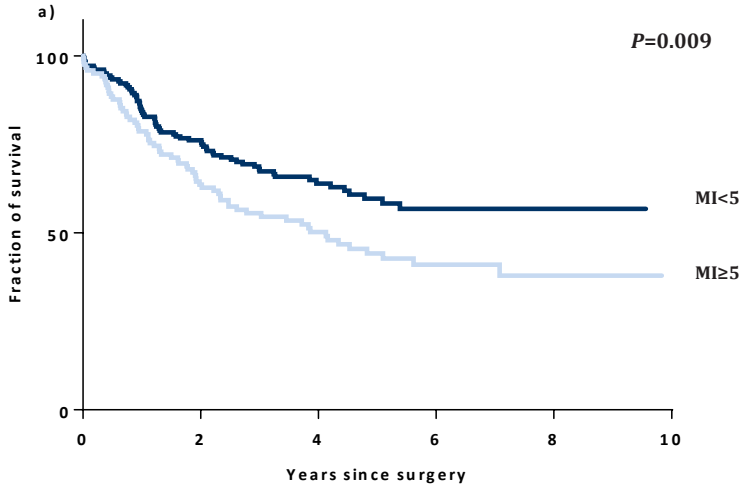
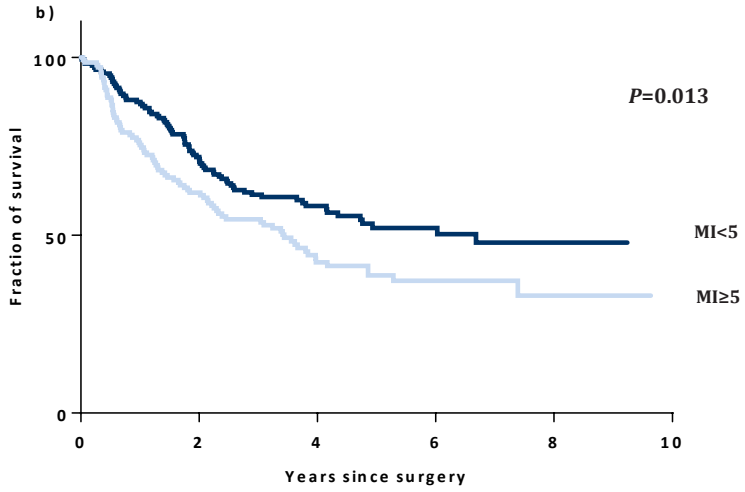


Figure 3. Comparison of the CT and the CRT group with regard to a) surgicopathological (SP) compliance (≥15 lymph nodes), b) surgical (S) compliance, and c) surgical (S) contamination
Abbreviations; CT: chemotherapy; CRT: chemoradiotherapy



MI<5	N at risk	181	126	64	30	9	0
MI≥5	N at risk	121	71	44	19	9	0



MI<5	N at risk	176	117	64	30	8	0
MI≥5	N at risk	143	85	41	16	6	0

Figure 4.The Maruyama Index (MI) showing a statistically significant difference in overall survival between MI<5 versus MI≥5, both in the CT group (a) and in the CRT group (b)
Abbreviations: CT: chemotherapy; CRT: chemoradiotherapy; N at risk: number of patients at risk

Median MI was 1 in both the CT group (range 0-88) and the CRT group (range 0-136, *P*=0.700). A MI <5 was associated with an improved overall survival in both groups (*Figure 4*). The effect of MI<5 on survival did not differ between the two groups (HR:1.06; 95% CI: 0.67-1.69; *P*=0.793).

DISCUSSION

In the CRITICS trial, gastric cancer patients were randomized before start of treatment between adjuvant chemotherapy (CT) versus adjuvant chemoradiotherapy (CRT) after preoperative chemotherapy and surgery. In the current study, the potential effect of upfront randomization for postoperative treatment on the quality of surgery was evaluated. No significant differences were observed between the CT and the CRT group with regard to a number of surgical quality parameters. A Maruyama Index, one of the most potent quality parameters in gastric cancer surgery, below 5 was associated with an improved overall survival in both groups.

The CRITICS trial was designed based on two randomized trials, the Intergroup 0116 trial and the MAGIC trial, that changed current clinical practice in the Western world for locally advanced resectable gastric cancer by showing an improved survival with postoperative chemoradiotherapy and perioperative chemotherapy, respectively.[1,2] In the Intergroup 0116 trial, patients were randomized 20-40 days after surgery, for postoperative chemoradiotherapy versus no adjuvant treatment. The study has been criticized for the fact that only 10% of the patients underwent the intended D2 lymph node dissection.[1] In the CRITICS trial in 73% of the patients at least 15 lymph nodes were removed and around 41% of the patients underwent the intended D1+ dissection (surgical compliance).[10] Although the latter finding is an improvement compared to the number of the Intergroup 0116 trial, surgical compliance in the CRITICS trial might have been expected to be higher due to the strict quality assurance program within the trial. However, when interpreting the surgical compliance rate in the CRITICS trial some aspects should be taken into account. First, surgical compliance is probably an underestimation, as a 'unknown lymph node station' was considered 'not removed'. Furthermore, in contrast to the Eastern world, lymph nodes of different lymph node stations in the Western world are *not* separately removed by the surgeon. As a consequence, removal of specific lymph node stations is less recorded in surgery reports and all lymph nodes together are offered to the pathologist instead of lymph nodes from each specific lymph node station. The number of lymph nodes is therefore probably of more value than the surgical compliance rate.

Postoperative randomization such as in the Intergroup 0116 trial harbors the risk of selection bias, as only a proportion of patients will be able to start postoperative treatment. These patients may reflect a selection of younger, physically more fit patients with a good performance status, leading to a possible overestimation of the survival

benefit. The extent of this selection will be considerable because it is known that after gastric cancer surgery a significant proportion of patients will never start, due to disease progression, postoperative complications, poor condition, refusal of patients, or even death. In the CRITICS trial, 61% of the patients in the CT group and 63% in the CRT group started postoperative treatment and 47% (CT group) and 54% (CRT group) was able to complete adjuvant therapy, respectively.[11] This is comparable to other gastric cancer trials as the Intergroup 0116 trial and the French FNCLCC and FFCD trial where 63% and 50% of the patients completed treatment according the study protocol, respectively.[1,12] In the MAGIC trial, 66% of the patients commenced with postoperative chemotherapy and 43% of the patients managed to complete adjuvant treatment.[2] In this trial, patients were randomly assigned to either perioperative chemotherapy and surgical resection or to surgical resection alone, six weeks prior to surgery. With this design, insight is gained in the whole chain of multimodal treatments, so more accurate information can be given to the patients' options. This applies for randomized clinical trials with multimodal treatment routes in general, however, in gastric cancer trials this is even more important because the proportion of patients who do not complete the whole chain is substantial.

In the CRITICS trial, as in the MAGIC trial, patients were randomized for postoperative treatment before the start of treatment; either three additional courses of chemotherapy or chemoradiotherapy. It was decided to randomize prior to preoperative treatment in order to prevent selection of patients after surgery, which might bias the inclusion. Opponents have considered the preoperative randomization as a possible limitation of the CRITICS trial for the reason that this could influence the quality of surgery. These assumptions suggest that the surgical performance was influenced by the knowledge of the result of the randomization, as participating surgeons were not blinded for the adjuvant treatment. For instance, a surgeon might decide to perform a more extended lymphadenectomy in case a patient was randomized for 'only' chemotherapy instead of chemoradiotherapy.
Results of the current study showed no significant differences between the CRT and the CT group with regard to surgicopathological compliance, number of adequate lymphadenectomies performed, surgical compliance, and surgical contamination. Both groups had a median MI of 1. Altogether, there are no indications that upfront randomization for postoperative treatment in the CRITICS trial was associated with differences in the quality of surgery. Thereby, the primary outcomes of the CRITICS trial, overall survival and progression-free survival, can be compared more reliably between both arms whereby more trustworthy conclusions can be drawn about the possible added effect of adjuvant therapy in patients with locally advanced resectable gastric cancer.

In the MAGIC trial, detailed information about the quality of surgery was lacking, and in the Intergroup 0116 trial, the proportion of adequate gastric cancer resections was low. The strength of the current study was the very detailed information on the quality

of surgery, and it shows the success of the surgical quality assurance within the CRITICS trial. The design of the CRITICS trial, including the upfront randomization, has its limitations. Inherent to this design, the number of randomized patients who completed the full multimodal treatment was around 50%, in both arms, leading to a possible underestimation of the treatment effect. On the other hand, this design provides insight in the entire chain of multimodal treatments for gastric cancer patients and reflects daily practice in treating Western gastric cancer patients.

In conclusion, our analyses indicate that upfront randomization for postoperative treatment did not influence the quality of surgery in the CRITICS trial. A Maruyama Index below five was associated with a better survival.

REFERENCES

1. Macdonald JS, Smalley SR, Benedetti J, et al. Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction. N Engl J Med. 2001;345(10):725-30.
2. Cunningham D, Allum WH, Stenning SP, et al. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. N Engl J Med. 2006;355(1):11-20.
3. Dikken JL, van Sandick JW, Swellengrebel HA, et al. Neo-adjuvant chemotherapy followed by surgery and chemotherapy or by surgery and chemoradiotherapy for patients with resectable gastric cancer (CRITICS). BMC cancer. 2011;11:329.
4. Peeters KC, Hundahl SA, Kranenbarg EK, et al. Low Maruyama index surgery for gastric cancer: blinded reanalysis of the Dutch D1-D2 trial. World J Surg. 2005;29(12):1576-84.
5. Hundahl SA, Macdonald JS, Benedetti J, et al. Surgical treatment variation in a prospective, randomized trial of chemoradiotherapy in gastric cancer: the effect of undertreatment. Ann Surg Oncol. 2002;9(3):278-86.
6. Hundahl SA, Peeters KC, Kranenbarg EK, et al. Improved regional control and survival with "low Maruyama Index" surgery in gastric cancer: autopsy findings from the Dutch D1-D2 Trial. Gastric Cancer. 2007;10(2):84-6.
7. Green FL , Page DL, FLeming ID, et al. American Joint Committee on Cancer (AJCC) Staging Manual. 6th ed New York, NY: Springer. 2002.
8. Degiuli M, De Manzoni G, Di Leo A, et al. Gastric cancer: Current status of lymph node dissection. World J Gastroent 2016; 22(10): 2875-93.
9. Schulz KF, Altman DG, Moher D. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. BMJ 2010; 340: c332.
10. Claassen YHM, de Steur WO, Hartgrink HH, et al. Surgicopathological Quality Control and Protocol Adherence to Lymphadenectomy in the CRITICS Gastric Cancer Trial. Ann Surg. 2017; epub ahead of print.
11. Cats A, Jansen EPM, van Grieken NCT, et al. Chemotherapy versus chemoradiotherapy after surgery and preoperative chemotherapy for resectable gastric cancer (CRITICS): an international, open-label, randomised phase 3 trial. Lancet Oncol 2018; 19(5): 616-28.
12. Ychou M, Boige V, Pignon JP, et al. Perioperative chemotherapy compared with surgery alone for resectable gastroesophageal adenocarcinoma: an FNCLCC and FFCD multicenter phase III trial. J Clin Oncol. 2011; 29(13): 1715-21.

PART II

INFLUENCE OF HOSPITAL VOLUME ON OUTCOMES OF GASTRIC CANCER SURGERY

CHAPTER 5

ASSOCIATION BETWEEN HOSPITAL VOLUME AND QUALITY OF GASTRIC CANCER SURGERY IN THE CRITICS TRIAL

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ABSTRACT

Background: Studies investigating the association between hospital volume and quality of gastric cancer surgery are lacking. In the present study, the effect of hospital volume on quality of gastric cancer surgery was evaluated by analysing data from the CRITICS (ChemoRadiotherapy after Induction chemotherapy In Cancer of the Stomach) trial.

Methods: Patients who underwent gastrectomy with curative intent in the Netherlands were selected from the CRITICS trial database. Annual hospital volume of participating centres was derived from the Netherlands Cancer Registry. Hospital volume was categorized into very low (1–10 gastrectomies per year per institution), low (11–20), medium (21–30) and high (31 or more), and linked to the CRITICS database. Quality of surgery was analysed by surgicopathological compliance (removal of at least 15 lymph nodes), surgical compliance (removal of indicated lymph node stations) and the Maruyama Index. Postoperative morbidity and mortality was also compared between hospital categories.

Results: Between 2007 and 2015, 788 patients were included in the CRITICS study, of whom 494 were analysed. Surgicopathological compliance was higher (86.7 *versus* 50.4 per cent; $P < 0.001$), surgical compliance was greater (52.9 *versus* 19.8 per cent; $P < 0.001$) and median Maruyama Index was lower (0 *versus* 6; $P = 0.031$) in high-volume hospitals compared with very low-volume hospitals. There was no statistically significant difference in postoperative complications or mortality between the hospital volume categories.

Conclusion: Surgery performed in high-volume hospitals was associated with better surgical quality than surgery carried out in lower-volume hospitals.

INTRODUCTION

Surgical resection remains the only curative treatment for locally advanced gastric cancer.[1] Despite improvements in surgical techniques and perioperative care, the mortality rate after gastrectomy in the Western world is still around 5 per cent.[2] The 5-year survival rate after gastrectomy with an adequate D2 lymph node dissection does not exceed 50 per cent.[3]

Since Luft and colleagues in 1979 suggested that high-volume hospitals have better outcomes for surgical procedures than low-volume hospitals, hospital volume has become a point of debate.[4] Studies have assessed the association between hospital volume and short- and long-term outcomes for a wide range of diseases including oesophageal and gastric cancer.[5–7] Postoperative mortality is often used as an outcome measure.[8–11] The relationship between hospital volume and improved short- and long-term outcomes has led to centralization of gastric cancer surgery in England in 2001 and in Denmark in 2003.[12,13] In the Netherlands, the Dutch Health Care Inspectorate incorporated a minimum volume of ten gastric resections per year per institution in 2012, and 20 per year per institution from 2013.

Studies investigating the relationship between hospital volume and quality of surgery are scarce, as detailed information regarding surgical quality is often lacking in retrospective studies. The present study aimed to assess the association between hospital volume and quality of gastric cancer surgery using data from a large international multicentre RCT, the CRITICS study. In this trial, patients with resectable gastric cancer underwent three preoperative cycles of epirubicin, cisplatin/oxaliplatin and capecitabine (ECC/EOC), followed by surgery and then either three further cycles of ECC/EOC or concurrent chemoradiotherapy. Information on surgical quality, including lymph node station removed during gastrectomy, was registered.

METHODS

Patients with a histologically proven stage Ib–IVa (AJCC 6th edition) gastric adenocarcinoma were included in the CRITICS trial. The bulk of the tumour had to be located in the stomach, although extension into the gastro-oesophageal junction was allowed. Inoperable patients, those with distant metastases, and patients with T1 N0 disease (determined by endoscopic ultrasonography) were not eligible. The study protocol for the CRITICS trial has been published previously.[14,15] For the present analysis, patients included in the CRITICS trial who underwent gastric resection with curative intent in a Dutch hospital were selected from the study database.

Hospital volume
Annual hospital volume was defined as the number of gastrectomies per hospital per

year. All participating hospitals in the CRITICS trial in the Netherlands gave permission to share the number of gastric resections per year during the study period of the CRITICS trial (2007–2015). Annual hospital volume was calculated from the Netherlands Cancer Registry. Gastrectomies included partial gastric resection, total gastric resection, gastrectomy with *en bloc* resection of surrounding organs/structures, and gastric resection not otherwise specified. Gastrectomies for benign diseases are not registered in the Netherlands Cancer Registry. Patients were categorized based on the date of primary resection. For patients who underwent multiple operations, the procedure that included the gastrectomy was used. Annual hospital volume was linked anonymously with data from the CRITICS trial.
Hospitals were ranked by annual hospital volume of gastrectomies ranging from very low (1–10), low (11–20), medium (21–30) to high (31 or more). As centralization of gastric cancer surgery took place during the study interval, hospitals could migrate between categories over the years, but each patient was categorized in one volume category based on the date of surgery.

Surgery
All patients were assigned to receive three cycles of ECC/EOC at 3-weekly intervals before operation. Surgery was performed 3–6 weeks after the last chemotherapy cycle. Both open and minimally invasive procedures were allowed. Total gastrectomy was performed for tumours in the upper part of the stomach. Subtotal resection of the stomach was advised for tumours in the middle or distal part of the stomach. Transhiatal oesophagus–cardia resection with gastric tube reconstruction was allowed for proximal tumours infiltrating the oesophagus. Lymph node dissection involving removal of lymph node stations 1–9 and 11 (lymph node locations and numbering according to the Japanese Research Society for the study of Gastric Cancer), with a minimum of 15 lymph nodes, a so-called D1+ lymph node dissection, was mandatory according the study protocol.[16] The definition of a D1 lymph node dissection was removal of stations 3–6 during partial gastrectomy and stations 1–6 during total gastrectomy. A D0 dissection comprised gastrectomy with a less than D1 dissection. A D2 lymph node dissection included removal of stations 1, 3, 5–9 for partial gastrectomy and stations 1–11 for total gastrectomy. The definition of D3 dissection was removal of lymph node stations 1–14. Splenectomy or resection of the pancreatic tail was not performed unless the tumour invaded these organs.

Central data review
The extent of lymphadenectomy was determined by two expert gastric surgeons. The resected lymph node stations (1–16) and type of lymph node dissection (D0, D1, D1+, D2 or D3) were scored based on the operative reports and the data recorded in the case report form. If the number of lymph node stations removed was not mentioned specifically, an estimate of the nodal stations removed was made based on the operative report, whenever possible. Removal of lymph nodes along the left gastric artery was defined as removal of lymph node station 7. If no assumptions could be made, the extent

of lymphadenectomy was scored as unknown. If all removed stations were unknown, the patient was excluded from the analysis. If information on removal was unknown for a single lymph node station, the station was scored as not removed. The proportion of patients with an estimated number of nodal stations resected was not recorded.

Outcome measures of surgical quality

Surgicopathological compliance was defined as the removal of a minimum of 15 lymph nodes, and surgicopathological non-compliance as the removal of fewer than 15 lymph nodes.

The Maruyama Index of Unresected Disease (MI) is based on eight variables (sex, age, type of cancer, depth of invasion, maximum diameter, tumour location (upper, middle or lower third of stomach), position (anterior, posterior, circular, around lesser or greater curvature) and histological type). In the present study, the MI was calculated with the Maruyama computer program, as in the Intergroup 0116 trial and the Dutch Gastric Cancer Trial.[17–19] The lower the MI, the better the surgical quality. The proportion of patients with a MI below 5 was also calculated as a MI lower than 5 has been associated with improved disease-free and overall survival.[18–20] To quantify the likelihood of unresected nodal disease, the MI is defined as the sum of Maruyama computer program predictions of lymph node stations 1–12 that were not removed by the surgeon. When a patient underwent gastric resection with removal of lymph node stations 1–8, the MI was calculated by adding up the likelihood that each of the other lymph node stations was affected (stations 9–12).

Surgical compliance was defined as the removal of lymph node stations 1–9 and 11, with exception of stations 2 and 4s in subtotal gastric resections, and stations 4d and 6 in gastric tube reconstructions. Surgical non-compliance was defined as no removal of the indicated lymph node stations.

The definition of surgical contamination was removal of one or more lymph node stations outside the intended extent of resection.

Postoperative complications and mortality

Complications were recorded in the case report form, and classified as surgery-related (such as anastomotic leakage, bleeding and ileus), infectious (for example abscess, sepsis and abdominal wound infection) and general complications (such as pulmonary, cardiovascular and thromboembolic). Postoperative mortality was defined as death within 30 days of surgery and/or during the hospital stay.

Missing data

Patients were excluded from the surgicopathological analyses if the total number of lymph nodes sampled was not reported by the pathologist. They were excluded from the analyses of surgical compliance, surgical contamination and MI if the exact location of the lymph node stations removed could not be retrieved from the surgery report.

Statistical analysis

Comparisons were done using the χ^2 test for categorical data, and the non-parametric Kruskal–Wallis test for numerical data. An independent-samples medians test was carried out to compare medians. To test whether type of hospital (academic *versus* community hospital) was a possible confounder, an interaction test was performed for categorical outcomes and a univariable general linear model for numerical outcomes. $P < 0.050$ was considered statistically significant. All analyses were carried out using SPSS® version 21.0 (IBM, Armonk, New York, USA).

RESULTS

Between January 2007 and April 2015, 788 patients were included in the CRITICS trial, of whom 631 were treated in Dutch hospitals (*Fig. 1*). Some 494 of 631 patients underwent a gastric resection with curative intent. Data were available from 492 patients for the analysis of surgicopathological compliance, and from 480 patients for the analyses of surgical compliance, surgical contamination and MI.

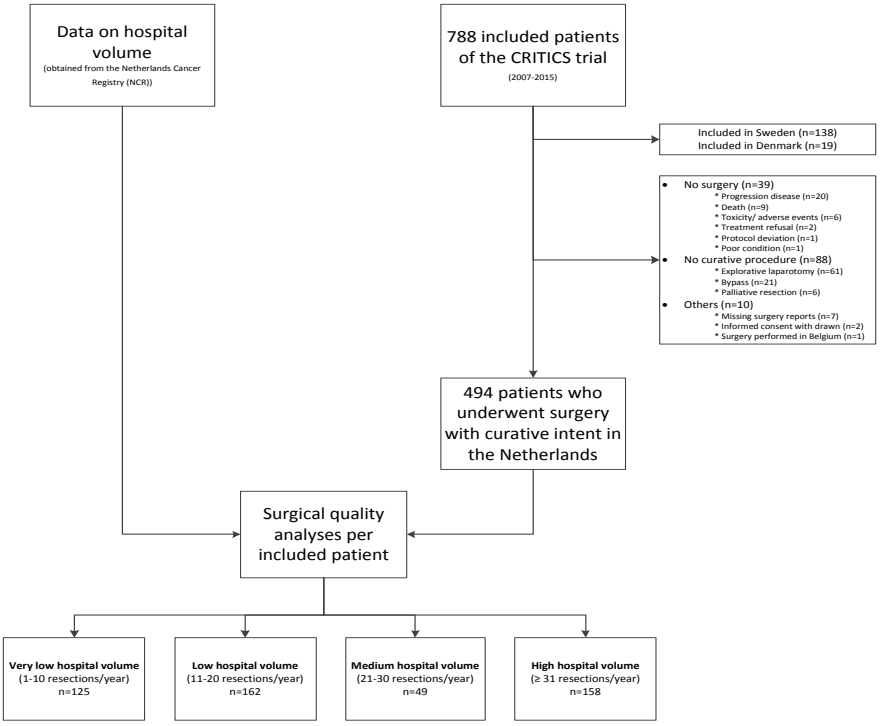

Fig. 1 Study flow chart. Data on hospital volume for patients who has surgery with curative intent in the Netherlands were obtained from the Netherlands Cancer Registry

The proportion of patients who completed preoperative chemotherapy was not statistically significantly different between the four categories of hospital volume, varying between 82.1 and 91.2 per cent (overall $P = 0.141$). Most patients underwent surgery in a low-volume (162, 32.8 per cent) or high-volume (158, 32.0 per cent) hospital, followed by a very low-volume (125, 25.3 per cent) or a medium-volume hospital (49, 9.9 per cent) hospital. *Table 1* shows patient, tumour and treatment related characteristics in relation to hospital type. The mean and median number of gastrectomies performed per hospital annually were 22.2 and 18.0 respectively.

Table 1. Patient, tumour and surgical characteristics according to hospital volume

	Very low volume (*n* = 125)	**Low volume (*n* = 162)**	**Medium volume (*n* = 49)**	**High volume (*n* = 158)**	***P*†**
Age (years)*	61 (35–81)	63 (28–82)	63 (37–78)	63 (33–78)	0.327‡
Sex ratio (M : F)	81 : 44	107 : 55	39 : 10	104 : 54	0.267
Co-morbidity					0.205
None	18 (14.4)	19 (11.7)	7 (14)	14 (8.9)	
1–2	70 (56.0)	81 (50.0)	21 (43)	73 (46.2)	
≥ 3	37 (29.6)	62 (38.3)	21 (43)	71 (44.9)	
Tumour location					0.005
Proximal stomach	32 (25.6)	63 (38.9)	18 (37)	59 (37.4)	
Middle stomach	35 (28.0)	40 (24.7)	11 (22)	59 (37.3)	
Distal stomach	58 (46.4)	59 (36.4)	20 (41)	40 (25.3)	
Type of resection					0.379
Total gastrectomy	48 (38.4)	71 (43.8)	27 (55)	74 (46.8)	
Subtotal gastrectomy	65 (52.0)	73 (45.1)	16 (33)	71 (45.0)	
Oesophagus–cardia resection	12 (9.6)	18 (11.1)	6 (12)	13 (8.2)	
Surgical approach					0.036
Open	111 (88.8)	128 (79.0)	35 (71)	122 (77.2)	
Minimally invasive	10 (8.0)	28 (17.3)	12 (24)	31 (19.6)	
Conversion	1 (0.8)	6 (3.7)	2 (4)	3 (1.9)	
Missing	3 (2.4)	0 (0)	0 (0)	2 (1.3)	
Tumour category					0.022
pT0/pTis/pT1	25 (20.0)	38 (23.5)	14 (29)	31 (19.6)	
pT2	59 (47.2)	65 (40.1)	9 (18)	58 (36.7)	
pT3	37 (29.6)	45 (27.8)	18 (37)	55 (34.8)	
pT4	4 (3.2)	14 (8.6)	8 (16)	14 (8.9)	

Table 1 continues

	Very low volume (*n* = 125)	Low volume (*n* = 162)	Medium volume (*n* = 49)	High volume (*n* = 158)	*P*†
Node category					0.625
pN0	64 (51.2)	76 (46.9)	26 (53)	79 (50.0)	
pN1	47 (37.6)	61 (37.6)	12 (24)	52 (32.9)	
pN2	12 (9.6)	21 (13.0)	8 (16)	21 (13.3)	
pN3	2 (1.6)	4 (2.5)	3 (6)	6 (3.8)	
Splenectomy					0.539
Yes	5 (4.0)	3 (1.9)	1 (2)	7 (4.4)	
No	120 (96.0)	159 (98.1)	48 (98)	151 (95.6)	
Distal pancreatectomy					0.462
Yes	4 (3.2)	4 (2.5)	1 (2)	1 (0.6)	
No	121 (96.8)	158 (97.5)	48 (98)	157 (99.4)	

*Values in parentheses are percentages unless indicated otherwise; *values are median (range). Very low-volume hospitals: one to ten gastrectomies per year; low-volume hospitals, 11–20 per year, medium-volume hospitals, 21–30 per year; high-volume hospitals, at least 31 per year. † χ^2 test, except ‡Kruskal–Wallis test.*

Surgical quality

Surgicopathological compliance was achieved in 50.4 per cent of patients in very low-volume hospitals, compared with 86.7 per cent in high-volume hospitals ($P < 0.001$) (*Fig. 2a*). The median number of resected lymph nodes was 24 (range 1–66) in high-volume hospitals; this decreased to 21 (5–57), 18 (0–71) and 15 (1–53) in medium-, low- and very low-volume hospitals respectively ($P < 0.001$).

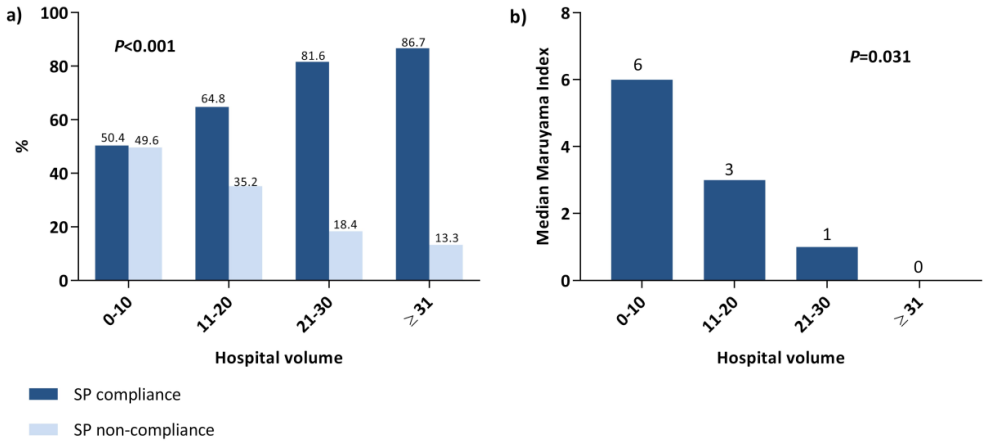

Fig. 2a) Surgicopathological (SP) compliance and b) Maruyama Index according to hospital volume. a P < 0.001 (χ^2 test), b P = 0.006 (independent-samples medians test)

D1+ lymph node dissection or more was performed in 69.0 per cent of the patients in very low-volume hospitals, compared with 87.3, 98 and 96.2 per cent of patients in low-, medium- and high-volume hospitals respectively. An inverse relationship between median MI and hospital volume was seen (*Fig. 2b*). The median MI was 6 (range 0–130), 3 (0–136), 1 (0–38) and 0 (0–93) in very low-, low-, medium- and high-volume hospitals respectively. A MI of 5 was achieved in 47.4 per cent (55 of 116 patients), 53.2 per cent (84 of 158), 57 per cent (28 of 49) and 68.2 per cent (107 of 157) respectively ($P = 0.004$). Type of hospital was not a confounder for surgicopathological compliance (interaction test $P = 0.536$) or for MI ($P = 0.545$).

Surgical compliance was noted in 23 of 116 patients (19.8 per cent) in very low-volume hospitals compared with 83 of 157 (52.9 per cent) in high-volume hospitals ($P < 0.001$) (*Fig. 3a*). There were no significant differences between hospital volume categories regarding surgical contamination ($P = 0.670$) (*Fig. 3b*).

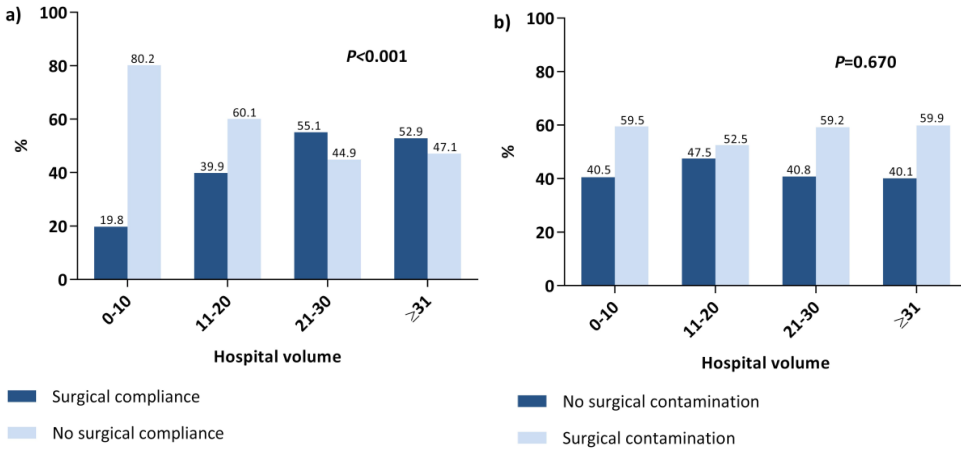

Fig. 3a) Surgical compliance and b) extent of surgical contamination according to hospital volume, a) P < 0.001, b) P = 0.670 (χ^2 test)

Postoperative complications and mortality

Postoperative complications were seen in 226 of the 494 patients (45.7 per cent) (*Table 2*). There were no differences in type of complications between hospital volume categories. The rate of reinterventions for complications was not statistically different. There were 11 postoperative deaths (2.2 per cent).

Table 2. Postoperative complications and mortality according to hospital volume

	Very low volume (*n* = 125)	**Low volume (*n* = 162)**	**Medium volume (*n* = 49)**	**High volume (*n* = 158)**	***P*†**
Complication overall	53 (42.4)	77 (47.5)	27 (55)	69 (43.7)	0.447
Surgery-related complication	23 (18.4)	40 (24.7)	14 (29)	33 (20.9)	0.418
Anastomotic leakage	11 (8.8)	11 (6.8)	6 (12)	8 (5.1)	
Bleeding	2 (1.6)	2 (1.2)	2 (4)	4 (2.5)	
Ileus	3 (2.4)	5 (3.1)	1 (2)	5 (3.2)	
Infectious complication	27 (21.6)	34 (21.0)	10 (20)	30 (19.0)	0.946
Abscess	6 (4.8)	9 (5.6)	2 (4)	8 (5.1)	
Sepsis	6 (4.8)	9 (5.6)	1 (2)	5 (3.2)	
Abdominal wound infection	8 (6.4)	7 (4.3)	2 (4)	4 (2.5)	
General complication	35 (28.0)	53 (32.7)	15 (31)	39 (24.7)	0.455
Pulmonary	15 (12.0)	23 (14.2)	7 (14)	15 (9.5)	
Cardiovascular	4 (3.2)	10 (6.2)	4 (8)	8 (5.1)	
Thromboembolic	1 (0.8)	3 (1.9)	0 (0)	0 (0)	
Reintervention*	15 (12.0)	26 (16.0)	7 (14)	18 (11.4)	0.636
Postoperative death	2 (1.6)	7 (4.3)	1 (2)	1 (0.6)	0.149

*Values in parentheses are percentages unless indicated otherwise. *For management of a postoperative complication. Very low-volume hospitals: one to ten gastrectomies per year; low-volume hospitals, 11–20 per year, medium-volume hospitals, 21–30 per year; high-volume hospitals, at least 31 per year. †χ^2 test.*

DISCUSSION

In this study, gastrectomy for cancer performed in high-volume hospitals was associated with better surgical quality parameters compared with surgery undertaken in lower-volume hospitals.

Large multicentre studies investigating the association between hospital volume and surgical quality of gastric resections are scarce. Specific surgical information, such as removal of lymph node stations, is not usually available in national registries, although this is one of the essential parameters for evaluation of the quality of surgical care. Data from the CRITICS trial were used in the present study. No significant difference in overall survival between the two study arms was found in the intention-to-treat analysis in this RCT.[21] The strength and the uniqueness of the present study lie in the detailed data available. In an analysis of data from the Intergroup 0116 trial in 2007, Enzinger and colleagues observed no impact of hospital volume on overall long-term survival.[22]
However, the proportion of patients with an adequate lymph node dissection was limited, which may have obscured a potential benefit of high-volume surgery, as noted

by the authors.[22] The present authors recently showed that at least 15 lymph nodes were removed in 87 per cent of the patients in the CRITICS trial and that approximately 80 per cent underwent an adequate lymph node dissection.[23] The high surgical standard in the CRITICS trial support the present results.

Removal of 15 lymph nodes or more has been defined as a surgical quality parameter with proven impact on survival.[24] The cut-off point of 15 lymph nodes is currently under debate, as several studies have reported longer disease-free survival when a greater number of lymph nodes was removed.[25] However, the cut-off point of 15 lymph nodes is still widely used today. In the Intergroup 0116 trial, the number of resected lymph nodes did not differ between low-volume (0–5 gastrectomies per year), moderate-volume (6–13) and high-volume (at least 14) hospitals, whereas the present study showed a significant increase in number of lymph nodes sampled with increasing hospital volume.[22] In this context, it should be acknowledged that the proportion of total gastrectomies was greater in the higher-volume categories than in the very low-volume hospital in the present study. Furthermore, the awareness and dedication of the pathologist may play a role. The pathology technician is an important healthcare-related factor influencing the total number of lymph nodes reported, and *ex vivo* dissection of lymph nodes during gastrectomy optimizes lymph node yield.[26,27] In the CRITICS trial, gastrectomy specimens with *en bloc* lymph node stations were sent directly to the pathology department for processing. Awareness of the pathologist or technician was raised by giving feedback when fewer than 15 nodes were reported during the course of the trial. This emphasizes that lymph node yield is a quality indicator for the whole team and not only for the surgeon.

In the CRITICS trial, an adequate gastric resection was defined as a D1+ lymphadenectomy or more, determined more than 10 years ago at a time when the debate about the superiority of D2 dissection was still ongoing. An adequate gastric resection was performed in 98 and 96.2 per cent of the patients in medium- and high-volume hospitals, but in only 69.0 per cent in very low-volume hospitals. This is better than the adequacy in hospitals participating in the Intergroup 0116 trial, where even in high-volume hospitals (at least 14 resections/year), half of the patients underwent a D0 dissection and only 10 per cent had the intended D2 dissection.[22]

The MI is one of the most important surgical quality indicators in gastric cancer surgery, as shown in the Intergroup 0116 study and Dutch Gastric Cancer Trial.[19,20] The MI was strongly related to survival: a MI lower than 5 was associated with improved disease-free and overall survival.[18–20] In the Intergroup 0116 trial, the MI was less than 5 in only 13.6 per cent of patients in high-volume hospitals, compared with 68.2 per cent in high-volume hospitals in the present study.[22]

Postoperative complication rates were not significantly different between the hospital volume categories. It was expected that complication rates may be lower in high-volume

hospitals. This expected difference may be counteracted by the higher percentage of patients with a co-morbidity score of 3 or more and the larger proportion who had a total gastrectomy in high-volume hospitals compared with lower-volume hospitals.[28] Postoperative mortality was low for each hospital volume category compared with rates in a retrospective French study that reported the impact of centre volume on postoperative mortality after gastric cancer surgery.[29] In that study, the postoperative mortality rate ranged from 4.3 to 10.2 per cent, and was 7.9 per cent in very high-volume hospitals (at least 60 resections/year); it should be noted that the majority of patients had a cardia tumour.

The experience of the surgeon rather than hospital volume as such is of importance. Recently it was shown that mortality after gastrectomy decreased as surgeon volume increased to 30 patients per year.[30] Although the surgeon still plays an important role in the curative treatment of gastric cancer, multimodal treatment and multidisciplinary teams including radiation oncologists, medical oncologists, gastroenterologists, pathologists and anaesthesiologists are key nowadays. Moreover, it should be noted that hospital volume was defined by operated patients only, which represents less than half of the patients with gastric cancer.

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REFERENCES

1. Van Cutsem E, Sagaert X, Topal B, et al. Gastric Cancer. Lancet 2016; 388(10060): 2654-2664.
2. Songun I, Putter H, Kranenbarg EM, et al. Surgical treatment of gastric cancer: 15-year follow-up results of the randomised nationwide Dutch D1D2 trial. Lancet Oncol 2010;11(5): 439-449.
3. Rosa F, Alfieri S, Tortorelli AP, et al. Trends in clinical features, postoperative outcomes, and long-term survival for gastric cancer: a Western experience with 1,278 patients over 30 years. World J Surg Oncol 2014;12: 217.
4. Luft HS, Bunker JP, Enthoven AC. Should operations be regionalized? The empirical relation between surgical volume and mortality. N Engl J Med 1979;301(25): 1364-1369.
5. Birkmeyer JD, Sun Y, Goldfaden A, et al. Volume and process of care in high-risk cancer surgery. Cancer 2006;106(11): 2476-2481.
6. Birkmeyer JD, Sun Y, Wong SL, et al. Hospital volume and late survival after cancer surgery. Ann Surg 2007;245(5): 777-783.
7. Gori D, Tedesco D, Goggi R, et al. Relationship between surgical volumes and 30-day mortality in patients with oesophagus and stomach cancer: a review of the literature and metanalysis. Epidemiol Prev 2014;38(3-4): 167-175.
8. Damhuis RA, Meurs CJ, Dijkhuis CM, et al. Hospital volume and post-operative mortality after resection for gastric cancer. Eur J Surg Oncol 2002;28(4): 401-405.
9. Sabesan A, Petrelli NJ, Bennett JJ. Outcomes of gastric cancer resections performed in a high volume community cancer center. Surg Oncol 2015;24(1): 16-20.
10. Anderson O, Ni Z, Moller H, et al. Hospital volume and survival in oesophagectomy and gastrectomy for cancer. Eur J Cancer 2011;47(16): 2408-2414.
11. Coupland VH, Lagergren J, Luchtenborg M, et al. Hospital volume, proportion resected and mortality from oesophageal and gastric cancer: a population-based study in England, 2004-2008. Gut 2013;62(7): 961-966.
12. Association of Upper Gastrointestinal Surgeons of Great Britain and Ireland (AUGIS), Guidance on minimum surgeon volumes [Available from: http://www.augis.org/wp-content/uploads/2014/05/AUGIS_recommendations_on_Minimum_Volumes.pdf , accessed at 05-06-2017].
13. Jensen LS, Nielsen H, Mortensen PB, et al. Enforcing centralization for gastric cancer in Denmark. Eur J Surg Oncol 2010;36 Suppl 1: S50-54.
14. Green FL, Page DL, Fleming ID, et al. American Joint Committee on Cancer (AJCC) Staging Manual. 6th ed New York, NY: Springer 2002.
15. Dikken JL, van Sandick JW, Swellengrebel HA, et al. Neo-adjuvant chemotherapy followed by surgery and chemotherapy or by surgery and chemoradiotherapy for patients with resectable gastric cancer (CRITICS). BMC cancer 2011;11: 329.
16. Kampschoer GH, Maruyama K, van de Velde CJ, et al. Computer analysis in making preoperative decisions: a rational approach to lymph node dissection in gastric cancer patients. Br J Surg 1989;76(9): 905-908.

17. Peeters KC, Hundahl SA, Kranenbarg EK, et al. Low Maruyama index surgery for gastric cancer: blinded reanalysis of the Dutch D1-D2 trial. World J Surg 2005;29(12): 1576-1584.
18. Hundahl SA, Macdonald JS, Benedetti J, et al. Surgical treatment variation in a prospective, randomized trial of chemoradiotherapy in gastric cancer: the effect of undertreatment. Ann Surg Oncol 2002;9(3): 278-286.
19. Hundahl SA, Peeters KC, Kranenbarg EK, et al. Improved regional control and survival with "low Maruyama Index" surgery in gastric cancer: autopsy findings from the Dutch D1-D2 Trial. Gastric Cancer 2007;10(2): 84-86.
20. Cats A, Jansen EPM, van Grieken NCT, et al. Chemotherapy versus chemoradiotherapy after surgery and preoperative chemotherapy for resectable gastric cancer (CRITICS): an international, open-label, randomised phase 3 trial. Lancet Oncol 2018; 19(5): 616-28.
21. Enzinger PC, Benedetti JK, Meyerhardt JA, et al. Impact of hospital volume on recurrence and survival after surgery for gastric cancer. Ann Surg 2007;245(3): 426-434.
22. Claassen YHM, de Steur WO, Hartgrink HH, et al. Surgicopathological Quality Control and Protocol Adherence to Lymphadenectomy in the CRITICS Gastric Cancer Trial. Ann Surg. 2017 epub ahead of print.
23. Coburn NG, Swallow CJ, Kiss A, et al. Significant regional variation in adequacy of lymph node assessment and survival in gastric cancer. Cancer 2006;107(9): 2143-2151.
24. Seevaratnam R, Bocicariu A, Cardoso R, et al. How many lymph nodes should be assessed in patients with gastric cancer? A systematic review. Gastric Cancer 2012;15 Suppl 1: S70-88.
25. Schoenleber SJ, Schnelldorfer T, Wood CM, et al. Factors influencing lymph node recovery from the operative specimen after gastrectomy for gastric adenocarcinoma. J Gastrointest Surg 2009;13(7): 1233-1237.
26. Afaneh C, Levy A, Selby L, et al. Ex Vivo Lymphadenectomy During Gastrectomy for Adenocarcinoma Optimizes Lymph Node Yield. J Gastrointest Surg 2016;20(1): 165-171.
27. Lee KG, Lee HJ, Yang JY, et al. Risk factors associated with complication following gastrectomy for gastric cancer: retrospective analysis of prospectively collected data based on the Clavien-Dindo system. J Gastrointest Surg 2014;18(7): 1269-1277.
28. Pasquer A, Renaud F, Hec F, et al. Is centralization needed for esophageal and gastric cancer patients with low operative risk?:a nationwide study. Ann Surg 2016;264(5): 823-830.
29. Mamidanna R, Ni Z, Anderson O, et al. Surgeon volume and cancer esophagectomy, gastrectomy, and pancreatectomy: a population-based study in England. Ann Surg 2016;263(4):

CHAPTER 6

EFFECT OF HOSPITAL VOLUME WITH RESPECT TO PERFORMING GASTRIC CANCER RESECTION ON RECURRENCE AND SURVIVAL: RESULTS FROM THE CRITICS TRIAL

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ABSTRACT

Objective: We examined the association between surgical hospital volume and both overall survival (OS) and disease-free survival (DFS) using data obtained from the international CRITICS (ChemoRadiotherapy after Induction chemotherapy In Cancer of the Stomach) trial.

Summary background data: In the CRITICS trial, patients with resectable gastric cancer were randomized to receive preoperative chemotherapy followed by adequate gastrectomy and either chemotherapy or chemoradiotherapy.

Methods: Patients in the CRITICS trial who underwent a gastrectomy with curative intent in a Dutch hospital were included in the analysis. The annual number of gastric cancer surgeries performed at the participating hospitals was obtained from the Netherlands Cancer Registry; the hospitals were then classified as low-volume (1-20 surgeries/year) or high-volume (≥21 surgeries/year) and matched with the CRITICS trial data. Univariate and multivariate analyses were then performed in order to evaluate the hazard ratio (HR) between hospital volume and both OS and DFS.

Results: From 2007 through 2015, 788 patients were included in the CRITICS trial. Among these 788 patients, 494 were eligible for our study; the median follow-up was 5.0 years. Five-year OS was 59.2% and 46.1% in the high-volume and low-volume hospitals, respectively. Multivariate analysis revealed that undergoing surgery in a high-volume hospital was associated with higher OS (HR=0.69, 05% CI=0.50-0.94, *P*=0.020) and DFS (HR=0.73, 95% CI:0.54-0.99, *P*=0.040).

Conclusions: In the CRITICS trial, hospitals with a high annual volume of gastric cancer surgery were associated with higher overall and disease-free survival. These findings emphasize the value of centralizing gastric cancer surgeries in the Western world.

INTRODUCTION

Gastric cancer is one of the most common types of cancer; in 2012, gastric cancer accounted for approximately 951,000 new cases and 723,000 deaths worldwide.[1] In the Western world, the survival rate of patients with gastric cancer remains dismal, as most patients develop a locoregional recurrence within two years following treatment.[2] In Europe, the 5-year survival rate among all stages of gastric cancer is approximately 25%; even after gastric cancer surgery with adequate lymph node removal, the 5-year survival rate is still only 50%.[3,4]

Recent decades have seen an increased recognition that the complex multidisciplinary care of patients with gastric cancer should occur in a high-volume hospital in order to improve surgical quality, perioperative care, and the survival rate of these patients.[5-7] Due to this increased awareness, several countries—including the UK, Denmark, and the Netherlands—established a minimum number of gastric resections performed annually at each institution.[8-10]

A previous analysis of the CRITICS (ChemoRadiotherapy after Induction chemotherapy In Cancer of the Stomach) trial revealed that surgery in a high-volume hospital is generally associated with improved surgical parameters, including removal of an adequate number of lymph nodes.[11] In the CRITICS trial, patients with resectable gastric cancer were treated with three cycles of preoperative chemotherapy, followed by surgery with extended (D1+) lymph node dissection, followed by either three cycles of either chemotherapy or chemoradiotherapy.[12] Resection of at least 15 lymph nodes during gastric resection occurred in only 50.4% of patients who were treated in a very low-volume hospital (defined as 0-10 gastric resections/year) compared to 86.7% of patients who were treated in a high-volume hospital (defined as ≥31 gastric resections/year).[13] However, whether this increase in resection rate at high-volume hospitals translates to improved oncological outcome remains unclear. In other words, does surgery performed in a high-volume hospital actually result in a lower rate of recurrence and/or increased overall survival among patients with gastric cancer?

To address this key question, we analyzed data regarding recurrence and uniform follow-up of a subset of patients included in the CRITICS trial, focusing on surgeries performed in the Netherlands. The aim of our analysis was to evaluate the association between hospital volume with respect to gastric cancer surgery and the survival and recurrence among patients who underwent gastric resection with curative intent.

METHODS

Study population

Patients who underwent gastric resection surgery with curative intent in a Dutch hospital were selected from the CRITICS database. The study protocol for the CRITICS trial

has been published previously.[12] Patients with a histologically confirmed stage Ib-IVa (based on the American Joint Committee on Cancer, 6th edition) gastric adenocarcinoma were included.[14] In order to be included in the CRITICS trial, the bulk of the tumor had to be located in the stomach, although extension into the gastro-esophageal junction was allowed. Patients who were deemed ineligible for surgery, patients with distant metastases, and patients with T1N0 disease (determined with endoscopic ultrasound) were excluded from the trial. Furthermore, patients with a previous malignancy, patients with a single functioning kidney that would be within the radiation field, and patients who underwent major surgery within four weeks prior to the start of treatment were excluded.

Surgery
In the CRITICS trial, preoperative treatment consisted of three cycles of epirubicin, cisplatin/oxaliplatin, and capecitabine (ECC or EOC) administered at three-week intervals. Surgery was scheduled for three to six weeks following the final chemotherapy cycle. Either an open or minimally invasive procedure was allowed. The principle of surgery was a potentially curative gastric resection with removal of the N1 and N2 lymph nodes in accordance with a D1+ lymph node dissection (i.e., removal of lymph node stations 1-9 and 11), with the successful removal of at least 15 lymph nodes. Splenectomy and/or resection of the pancreatic tail was performed only in cases in which there was direct ingrowth into these organs. After surgery, patients received either three cycles of ECC/EOC or concurrent chemoradiotherapy, based on the randomization protocol prior to the start of the trial.

Hospital volume
The patients in the trial were categorized by annual hospital volume, which was based on the hospital and year in which they underwent gastric resection. Annual hospital volume was defined as the number of gastric cancer resections performed in a given hospital per year and was categorized as low (1-20 resections/year) or high (≥21 resections/year). This cutoff between low-volume and high-volume hospitals was based on a minimum volume of 20 resections/year/hospital, which was established in the Netherlands in 2013. This national initiative was designed to centralize gastric cancer surgical care in high-volume hospitals and was developed by the Dutch Health Care Inspectorate. Although compliance with this initiative was strongly recommended, no sanctions were imposed on low-volume hospitals after the minimum volume was established.

Data regarding annual hospital volume was obtained from the Netherlands Cancer Registry (NCR). All Dutch hospitals that participated in the CRITICS trial agreed to share their annual number of gastric resections performed from 2007 through 2015 (the study period for the CRITICS trial). Gastric resection was defined as partial gastric resection, total gastric resection, multiorgan surgery that included gastric resection, or gastric resection not otherwise specified; surgeries that were performed for a benign

indication were excluded. Patients were included based on the date of surgery, and each patient was included only once. Because national centralization of gastric cancer surgeries occurred during the study period of the CRITICS trial, some hospitals changed from low-volume to high-volume during the trial; however, each patient was assigned to one volume category based on the date of surgery.

Overall survival, disease-free survival, and postoperative mortality
Overall survival (OS) was calculated from the date of surgery until the date of death by any cause. Disease-free survival (DFS) was calculated from the date of surgery until the date of recurrent disease (locoregional, distant, or peritoneal recurrence) or until the date of death. Locoregional recurrence was defined as a recurrence at the original location in the stomach, adjacent organs, regional lymph nodes (nodes 1-13), the site of anastomosis, falciform ligament, transverse mesocolon, hepatoduodenal ligament, or liver hilus. Distant recurrence was defined as recurrence in the liver, colon, lung, pleura/pleuritis carcinomatosa, brain, bone, distant lymph nodes (nodes 14-16), gallbladder, or ovary. Peritoneal metastasis was defined as peritoneal carcinomatosis, metastasis in the greater omentum, or the presence of tumor-positive ascites. DFS and OS were truncated at 5 years. Post-operative mortality was defined as death within 30 days of surgery.

Follow-up
The duration of follow-up was defined as the interval between the date of surgery and either the date of death or the end of follow-up (censored). In the first year, follow-up visits were performed one, two, three, six, nine, and twelve months after the end of treatment; thereafter, follow-up visits were performed once every six months until five years after the end of treatment.

Statistical analysis
Patients were analyzed irrespective of their randomly assigned adjuvant treatment. To rule out the possibility that the effect of hospital volume differed significantly between the chemotherapy group and the chemoradiotherapy group, we performed an interaction test. The Kaplan-Meier method was used to analyze OS and DFS, and differences between the volume categories were tested using the log-rank test. In addition, OS and DFS data were analyzed using Cox proportional hazard regression. Frailty models were estimated in order to account for associations and unobserved heterogeneity. The frailty variance was virtually zero; therefore, the center was not taken into account in the multivariate analyses of OS and DFS. Differences with a *P*-value <0.05 were considered statistically significant. All analyses were performed using SPSS version 21.0.

RESULTS

Patient characteristics, tumor and surgical characteristics, and postoperative treatment by hospital volume

From January 2007 through April 2015, a total of 788 patients in 56 centers in the Netherlands (n=631), Sweden (n=138), and Denmark (n=19) were randomized (*Figure 1*). For our analyses, 494 Dutch patients were included.

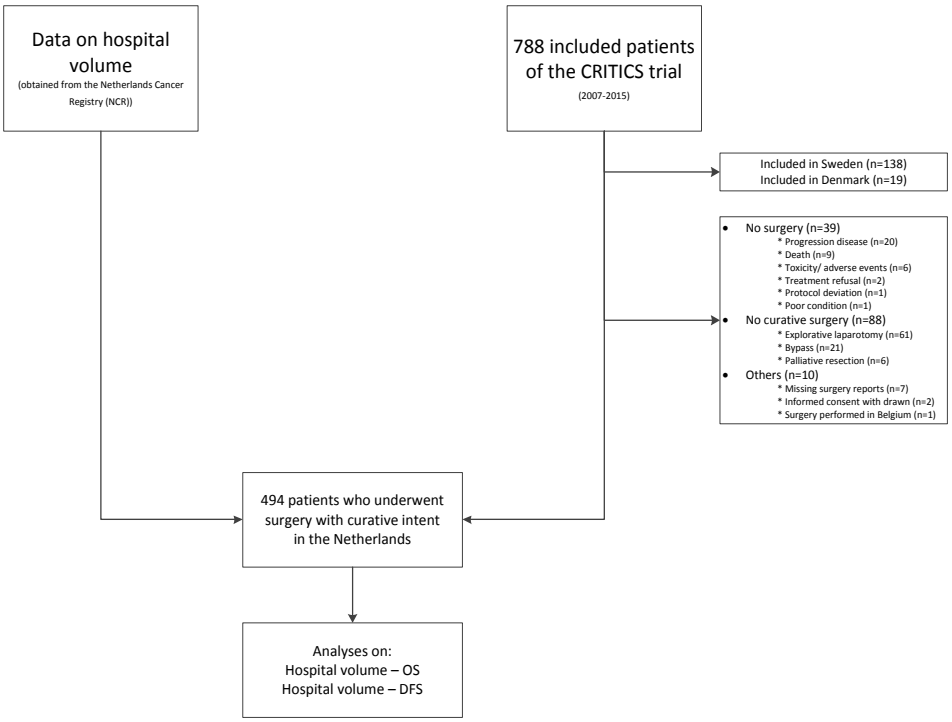


Figure 1. Study flow chart depicting the inclusion and exclusion of patients in the current analysis

A significantly higher number of high-stage tumors (*P*=0.042) and diffuse tumor types (*P*=0.023) were treated in the high-volume hospitals compared to the low-volume hospitals (*Table 1*). In contrast, the percentage of patients who completed preoperative chemotherapy was similar between the high-volume and low-volume hospitals (85.0% versus 86.1% , respectively; *P*=0.421). A microscopically radical (i.e., R0) resection was achieved more often in the high-volume hospitals than in the low-volume hospitals (87.9% versus 76.7%, respectively; *P*=0.005). The prevalence of postoperative complications was similar between high-volume and low-volume hospitals (53.6% versus 54.5%, respectively; *P*=0.961). Postoperative mortality was also similar

between high-volume and low-volume hospitals (1.0% versus 3.1%, respectively; *P*=0.093). The percentage of patients who completed either adjuvant chemotherapy or adjuvant chemoradiotherapy was approximately 50% and did not differ between high-volume and low-volume hospitals (*P*=0.300 and *P*=0.720 for chemotherapy and chemoradiotherapy, respectively).

Table 1. Patient, tumor, and treatment characteristics in low-volume and high-volume hospitals

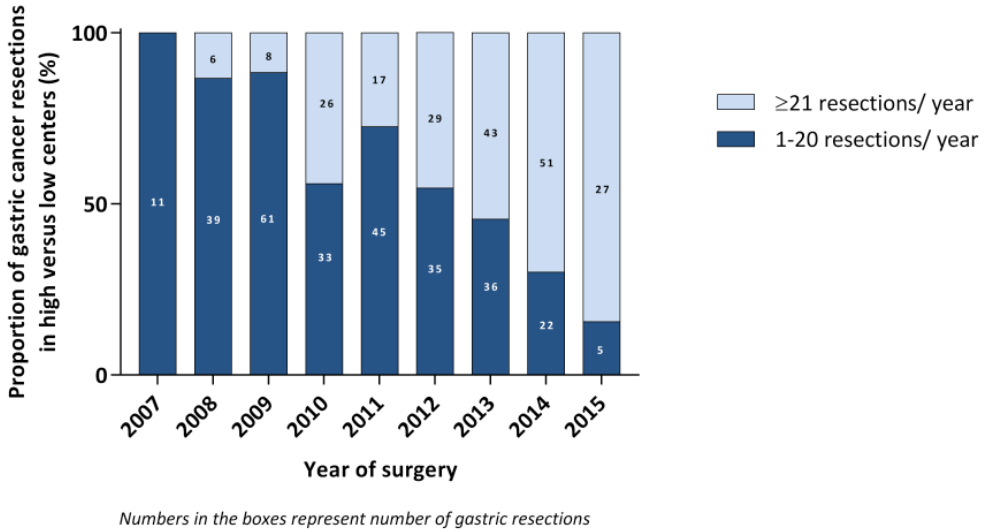
	Low volume (1-20/year)	**High volume (≥21/year)**	**p-value**
Total	287 (100)	207 (100)	
Median age (years)	62 (28-82)	63 (33-78)	
Sex			
Male	188 (65.5)	143 (69.1)	0.231
Female	99 (34.5)	64 (30.9)	
Comorbidity			
None	37 (12.9)	21 (10.1)	0.078
1-2	151 (52.6)	94 (45.4)	
≥3	99 (34.5)	92 (44.4)	
Type of gastric resection			
Total	119 (41.5)	101 (48.8)	0.270
Subtotal	138 (48.1)	87 (42.0)	
Esophago-cardiac resection	30 (10.4)	19 (9.2)	
Type of lymph node dissection			
D0	4 (1.4)	0 (0.0)	*<0.001*
D1	52 (18.1)	7 (3.4)	
D1+	209 (72.8)	191 (92.3)	
D2	9 (3.1)	8 (3.9)	
Unknown	13 (4.5)	1 (0.5)	
Radicality			
R0	119 (41.5)	101 (48.8)	*0.005*
R1	138 (48.1)	87 (42.0)	
Unknown	30 (10.4)	19 (9.2)	
Removal of ≥ 15 lymph nodes			
Yes	167 (58.2)	177 (85.5)	*<0.001*
No	118 (41.1)	30 (14.5)	
Unknown	2 (0.7)	0 (0.0)	

Table 1 continues

	Low volume (1-20/year)	High volume (≥21/year)	p-value
Tumor stage			
pT0/pTis/pT1	63 (21.9)	45 (21.7)	*0.042*
pT2	124 (43.2)	67 (32.4)	
pT3	82 (28.6)	73 (35.3)	
pT4	18 (6.3)	22 (10.6)	
Nodal stage			
pN0	140 (48.8)	105 (50.7)	0.234
pN1	108 (37.6)	64 (30.9)	
pN2	33 (11.5)	29 (14.0)	
pN3	6 (2.1)	9 (4.3)	
Histology			
Diffuse	93 (32.4)	74 (35.7)	*0.023*
Intestinal	78 (27.2)	67 (32.4)	
Mixed	15 (5.2)	14 (6.8)	
Unknown	101 (35.2)	52 (25.1)	
Splenectomy			
Yes	8 (2.8)	8 (3.9)	0.338
Distal pancreatectomy			
Yes	8 (2.8)	2 (1.0)	0.136
Allocated treatment			
CT	137 (47.7)	98 (47.3)	0.502
CRT	150 (52.3)	109 (52.7)	
Started postoperative treatment			
Yes	220 (76.7)	160 (77.3)	0.478
No	67 (23.3)	47 (22.7)	

Age is presented as median (range), other data are presented as n (%)
Abbreviations: CT = chemotherapy; CRT = chemoradiotherapy

Hospital volume over time
The number of gastrectomies performed each year is shown in *Figure 2*. In general, the relative percentage of gastrectomies performed in high-volume versus low-volume centers increased over time. Specifically, from 2007 through 2012, the majority of gastric resections were performed in low-volume hospitals; after 2012, the majority of gastric resections were performed in high-volume hospitals.



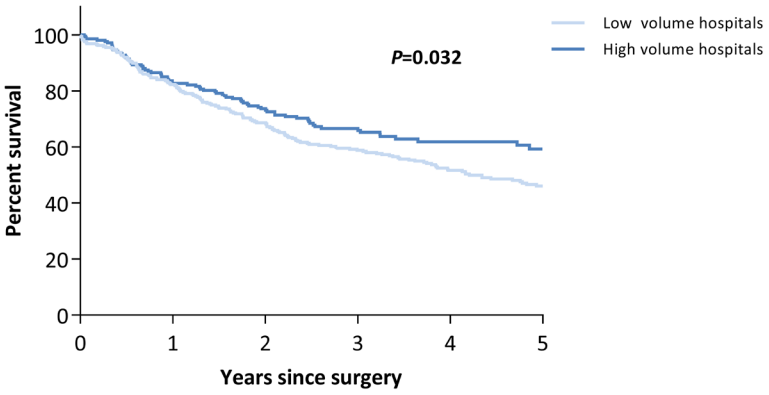
Numbers in the boxes represent number of gastric resections

Figure 2. Summary of the number of gastrectomies performed in the Netherlands in the CRITICS trial from 2007 through 2015, by hospital volume (n=494 patients)

Overall survival (OS)

At the time of our analysis, the median follow-up duration was 5.0 years. An interaction test revealed that the effect of hospital volume was similar between the two treatment group (*P*=0.828). However, as shown in *Figure 3*, OS was significantly higher in the high-volume hospitals compared to the low-volume hospitals (*P*=0.032). Specifically, 5-year survival was 59.2% for patients who underwent surgery in a high-volume hospital, compared to 46.1% for patients who underwent surgery in a low-volume hospital. Among high-volume hospitals, the 5-year survival rate ranged from 34.3% to 78.6%, compared to 0-83.3% among low-volume hospitals.

Next, we performed Cox proportional hazard regression in order to examine further the effect of hospital volume on OS (*Table 2*). A multivariate analysis revealed that undergoing surgery in a high-volume hospital was associated with a higher survival rate, with a hazard ratio (HR) for mortality of 0.69 (95% CI=0.50-0.94; *P*=0.020). The prognostic factors associated with reduced OS included a higher-stage tumor and a higher nodal stage. Furthermore, increasing age, the presence of comorbidity, a diffuse histology type, and a microscopically non-radical (R1) resection were associated with reduced OS (*Table 2*).



Volume:							
Low	N at risk	287	236	196	159	122	90
High	N at risk	207	171	134	99	56	42

Figure 3. Kaplan-Meier curve of overall survival since surgery for all 494 patients who underwent gastrectomy for gastric cancer in low-volume and high-volume hospitals in the Netherlands

Table 2. Multivariate analysis of overall survival and disease-free survival following surgery (calculated using a Cox proportional hazard model)

	Overall survival since surgery			Disease free survival since surgery		
	HR	*p-value*	CI	HR	*p-value*	CI
Hospital volume						
Low (1-20)	1			1		
High (21+)	0.69	*0.020*	0.50-0.94	0.73	*0.040*	0.54-0.99
Year of surgery	0.96	0.241	0.89-1.03	0.99	0.788	0.93-1.06
Age	1.02	*0.005*	1.01-1.03	1.02	*0.015*	1.00-1.03
Sex						
Male	1.03	0.848	0.77-1.38	1.00	0.984	0.75-1.32
Co-morbidity						
None	1			1		
1-2	1.61	*0.043*	1.02-2.56	1.50	0.070	0.97-2.31
≥3	1.64	*0.049*	1.00-2.69	1.53	0.071	0.97-2.44
Lauren classification						
Intestinal	1			1		
Diffuse	1.53	*0.017*	1.08-2.18	1.28	0.150	0.92-1.79
Mix	1.27	0.463	0.67-2.40	0.98	0.940	0.52-1.83

Table 2 continues

	Overall survival since surgery			Disease free survival since surgery		
Tumor stage						
pT0/pTis/pT1	1			1		
pT2	2.69	*0.001*	1.49-4.86	2.80	*<0.001*	1.59-5.00
pT3	5.35	*<0.001*	2.92-9.80	5.37	*<0.001*	2.98-9.54
pT4	6.10	*<0.001*	2.98-12.45	6.68	*<0.001*	3.38-13.19
Nodal stage						
pN0	1			1		
pN1	1.53	*0.014*	1.09-2.15	1.60	*0.005*	1.16-2.21
pN2	3.43	*<0.001*	2.28-5.15	3.52	*<0.001*	2.38-5.19
pN3	8.41	*<0.001*	4.47-15.83	8.60	*<0.001*	4.57-16.18
Radical resection						
R0	1			1		
R1	1.99	*<0.001*	1.38-2.89	1.93	*<0.001*	1.34-2.78

Disease-free survival (DFS)

As shown in *Figure 4*, a univariate analysis showed that DFS did not differ significantly between high-volume and low-volume hospitals (*P*=0.119). In contrast, a multivariate analysis revealed that DFS was significantly higher among patients who underwent surgery in a high-volume hospital compared to patients who underwent surgery in a low-volume hospital (HR=0.73, 95% CI=0.54-0.99; *P*=0.040); other prognostic factors for reduced DFS included a higher-stage tumor, a higher nodal stage, increasing age, and an R1 resection (*Table 2*).

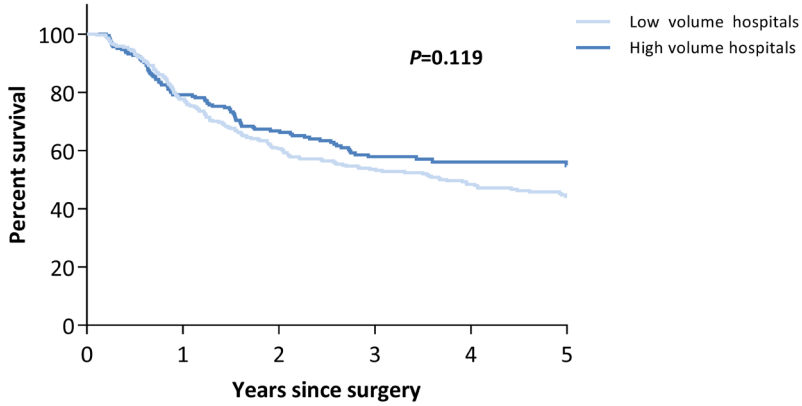


Figure 4. Kaplan - Meier curve of disease-free survival since surgery for all 494 patients who underwent gastrectomy for gastric cancer in low-volume and high-volume hospitals in the Netherlands

The most common sites of locoregional tumor recurrence were the regional lymph node basins, the stomach bed, and the site of anastomosis. The most common sites of distant tumour recurrence were the distant lymph nodes and the liver.

DISCUSSION

Here, we analyzed the relationship between hospital volume with respect to performing surgery for gastric cancer and both survival and disease recurrence, using data obtained from the prospective randomized CRITICS trial. Our multivariate analysis revealed that undergoing surgery for gastric cancer at a high-volume hospital is associated with a higher rate of overall survival, as well as increased disease-free survival.

Given that the long-term survival of patients with advanced-stage gastric cancer remains low, even in the Western world, the primary goal of the CRITICS trial was to compare outcome between two adjuvant treatment strategies consisting of adjuvant chemotherapy (the control arm) or adjuvant chemoradiotherapy (the experimental arm) and to determine whether patients in the experimental arm had improved survival. An intention-to-treat analysis revealed no significant difference between the two treatment arms, with five-year survival rates of 41.3% and 40.9% in the control and experimental arms, respectively.[15] In our study, we chose to analyze all patients who were treated in the CRITICS trial in the Netherlands, regardless of the treatment arm. In addition, the results of an interaction test allowed us to rule out any significant difference between the two study arms with respect to the effect of hospital volume. Because the majority of recurrences after gastrectomy for adenocarcinoma are identified within the first few years, we limited our follow-up period to five years in our analysis of overall survival and disease-free survival.[16]

In 2007, Enzinger et al. used data from the randomized Intergroup 0116 trial to investigate the role of hospital volume on both recurrence and survival following curative gastric cancer surgery.[17] Although they found no difference in survival between low-volume hospitals (defined in their study as 0-5 resections/year) and high-volume hospitals (defined as ≥14 resections/year), the authors reported a possible relationship with respect to improved long-term outcome in cases in which a D2 lymph node dissection was performed. In their discussion, the authors noted that their relatively small patient population may have obscured any statistically relevant differences.[17] Recently, we reported that approximately 90% of patients in the CRITICS trial underwent at least a D1+ lymph node dissection, allowing us to investigate the putative relationship seen in the Intergroup 0116 trial population with more statistical power.[13] Using a univariate analysis, we found that overall survival was significantly higher among patients who underwent surgery in a high-volume hospital compared to patients who underwent surgery in a low-volume hospital. In contrast, the difference in disease-free survival was not statistically significant based on a univariate analysis. One possible explanation

for the lack of significant with respect to DFS might be the higher prevalence of high-stage tumors and diffuse tumor types in the high-volume hospitals (see Table 1), both of which have been associated with poorer long-term outcome.[18] Our multivariate analysis revealed that both overall survival and disease-free survival were higher among patients who underwent surgery in a hospital that performed ≥21 gastric resections per year, which supports our hypothesis that undergoing surgery for gastric cancer in a high-volume hospital leads to improved outcome. Given the similarities between OS and DFS with respect to the Kaplan-Meijer survival curves, it seems that overall survival was predicated largely upon the likelihood of disease recurrence. A plausible explanation for these findings is the higher surgical quality in high-volume hospitals compared to low-volume hospitals. For example, removal of at least 15 lymph nodes—one of the most important parameters of surgical quality—is significantly more common among high-volume hospitals compared to low-volume hospitals.[19] Moreover, both adequate lymph node dissection and achieving an R0 resection were more common among high-volume hospitals than among low-volume hospitals, and these two parameters are associated with increased survival.[20,21]

Other possible explanations for the difference in survival between high-volume hospitals and low-volume hospitals can be excluded. First, we found no difference between high-volume and low-volume hospitals with respect to the percentage of patients who completed neoadjuvant chemotherapy. Second, the rate of postoperative morbidity did not differ between high-volume and low-volume hospitals, and we found no difference with respect to the percentage of patients who started with adjuvant therapy. Nevertheless, it is important to note that only the complication rate was recorded in the CRITICS trial, with no information regarding the classification and/or seriousness of the complications. Finally, the presence of a better infrastructure at high-volume hospitals—which is designed to ensure that patients receive timely, comprehensive care—might have played a role. However, the only hospital characteristic available for our analysis—the type of center—was not associated with outcome.
In addition to hospital volume, both higher tumor stage and higher nodal stage were important prognostic factors for determining poor overall survival and disease-free survival. This finding is consistent with previous studies, including a recent study in Italy that found that tumor-related factors were the strongest predictors of survival among patients with gastric cancer who underwent potentially curative resection.[22] We also found that increasing age, a diffuse histology type, the presence of comorbidity, and an R1 resection were associated with reduced survival, each of which is consistent with previous studies.[23-25]

In 2007, the Quality of Cancer Care task force, which was established by the Dutch Cancer Society, evaluated the quality of care in the Netherlands and concluded that although quality of care was generally high, it could be improved further by reducing variation among healthcare providers.[26] With respect to gastric cancer, a minimum volume of 10 resections/year/hospital was established by the Dutch Health Care Inspectorate

in 2012.[27] In 2013, this minimum volume was increased to 20 resections per hospital per year. At the time at which this minimum volume was increased, unanticipated consequences occurred related to the centralization process. For example, the delay between diagnosis and the start of treatment increased; however, this delay was reduced after an adequate structure for referring patients to the hospital was introduced.
In 2011, the Dutch Upper Gastrointestinal Cancer Audit (DUCA) was established for registering all patients in the Netherlands who undergo surgical resection for esophageal or gastric cancer. The goal of the DUCA is to improve quality of care by collecting reliable, benchmarked data regarding the surgical process and outcome parameters, as well as to provide healthcare providers access to this data. The Dutch Health Care Inspectorate ensures that all hospitals in the Netherlands participate in this program.
When the DUCA was first introduced in 2011, only 3% of all hospitals in the Netherlands performed >20 gastric resections for gastric carcinoma each year.[28] However, the annual reports presented by the DUCA showed that this percentage had increased to 60% of all hospitals in 2016.[28] These findings are consistent with our results showing a shift toward high-volume hospitals (see Figure 2). Furthermore, early data from the DUCA showed improvement over the years with respect to the outcome of patients who underwent surgery for gastric cancer; moreover, removal of ≥15 lymph nodes increased from 47.5% of patients in 2011 to 73.6% in 2014, and in-hospital mortality decreased from 9.0% in 2011 to 4.0% in 2014.[29]

Several factors regarding the centralization efforts in the Netherlands and the creation of the DUCA may have contributed to the fact that the majority of patients with gastric cancer currently receive care at a high-volume hospital, with a corresponding improvement in outcome. First, reliable registration and feedback from the DUCA given to healthcare providers regarding their own results seem to be important factors. A strength of the DUCA is its compulsory nature, which stimulates participation by dedicated hospitals, thereby preventing an underrepresentation of low-volume hospitals in the DUCA. Second, the DUCA provides weekly updates and benchmarked feedback to individual hospitals, which encourages hospitals to improve their performance. Finally, the relatively high frequency of feedback allows hospitals to act on their audit results in a timely manner. The successful centralization of gastric cancer surgeries performed in the Netherlands, combined with the above-mentioned factors, may serve as an example for developing similar centralization processes in other countries in the Western world.
Many studies have been performed to investigate the putative relationship between hospital volume and survival, yielding contradictory results.[17,30-32] In addition to small sample size, a possible cause for these contrasting results might be the design of the studies. For example, many of these studies were retrospective in nature and therefore often had limited patient information and/or incomplete follow-up data.[33] In contrast to previous studies regarding the role of hospital volume in long-term survival, our analysis used data obtained from a prospective randomized controlled trial.[30,31,34] This may be considered a disadvantage, as the patients in our analysis may not necessarily represent the general population. In addition, hospital volume was analyzed only with respect to

patients who underwent gastric resection, thereby excluding patients who were treated using non-surgical approaches. On the other hand, because we used data obtained from a randomized controlled trial, our cohort represents a population of patients for whom relatively detailed information regarding the pattern of disease recurrence is currently lacking. Thus, the high quality of uniformly documented follow-up data is a strength of our analysis. Furthermore, bias due to improving preoperative staging over time is unlikely, as preoperative staging was predetermined in the CRITICS trial protocol.

In conclusion, our analysis shows that patients who undergo surgical resection gastric cancer in a high-volume hospital have improved overall survival and disease-free survival. These findings underscore the value of centralizing gastric cancer surgeries in the Western world.

REFERENCES

1. Ferlay J, Soerjomataram I, Dikshit R, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer 2015; 136(5): E359-86.
2. Gunderson LL. Gastric cancer--patterns of relapse after surgical resection. Semin Radiat Oncol 2002; 12(2): 150-61.
3. Rosa F, Alfieri S, Tortorelli AP, et al. Trends in clinical features, postoperative outcomes, and long-term survival for gastric cancer: a Western experience with 1,278 patients over 30 years. World J Surg Oncol 2014; 12: 217.
4. De Angelis R, Sant M, Coleman MP, et al. Cancer survival in Europe 1999-2007 by country and age: results of EUROCARE--5-a population-based study. Lancet Oncol 2014; 15(1): 23-34.
5. Birkmeyer JD, Sun Y, Goldfaden A, et al. Volume and process of care in high-risk cancer surgery. Cancer 2006; 106(11): 2476-81.
6. Birkmeyer JD, Sun Y, Wong SL, et al. Hospital volume and late survival after cancer surgery. Ann Surg 2007; 245(5): 777-83.
7. Gori D, Tedesco D, Goggi R, et al. Relationship between surgical volumes and 30-day mortality in patients with oesophagus and stomach cancer: a review of the literature and metanalysis. Epidemiol Prev 2014; 38(3-4): 167-75.
8. Association of Upper Gastrointestinal Surgeons of Great Britain and Ireland (AUGIS); http://www.augis.org/wp-content/uploads/2014/05/AUGIS_recommendations_on_Minimum_Volumes.pdf ; [accessed at 22-06-2017].
9. Jensen LS, Nielsen H, Mortensen PB, et al. Enforcing centralization for gastric cancer in Denmark. Eur J Surg Oncol 2010; 36 Suppl 1: S50-4.
10. Nederlandse Vereniging voor GastroIntestinale Chirurgie; http://nvgic.nl/sites/nvgic.nl/files/Richtlijn%20maagcarcinoom.pdf;[accessed at 22-06-2017].
11. Claassen Y, Van Sandick J, Hartgrink H, et al. Association between hospital volume and quality of gastric cancer surgery in the CRITICS trial. Br J Surg 2018; 105(6):728-735.
12. Dikken JL, van Sandick JW, Swellengrebel HA, et al. Neo-adjuvant chemotherapy followed by surgery and chemotherapy or by surgery and chemoradiotherapy for patients with resectable gastric cancer (CRITICS). BMC Cancer 2011; 11: 329.
13. Claassen YHM, de Steur WO, Hartgrink HH, et al. Surgicopathological Quality Control and Protocol Adherence to Lymphadenectomy in the CRITICS Gastric Cancer Trial. Ann Surg 2017; epub ahead of print.
14. Green FL, Page DL, FLeming ID, et al. American Joint Committee on Cancer (AJCC) Staging Manual. 6th ed New York, NY: Springer 2002.
15. Cats A, Jansen EPM, Van Grieken NCT, et al. Chemotherapy versus chemoradiotherapy following surgery and preoperative chemotherapy for resectable gastric cancer (CRITICS): an international, multicentre, randomised, phase 3 trial. Lancet Oncol 2018, in press.
16. Alnoor M, Boys JA, Worrell SG, et al. Timing and Pattern of Recurrence after Gastrectomy for Adenocarcinoma. Am Surg 2015; 81(10): 1057-60.

17. Enzinger PC, Benedetti JK, Meyerhardt JA, et al. Impact of hospital volume on recurrence and survival after surgery for gastric cancer. Ann Surg 2007; 245(3): 426-34.
18. Van Cutsem E, Sagaert X, Topal B, et al. Gastric cancer. Lancet 2016; 388 (10060): 2654-2664.
19. Coburn NG, Swallow CJ, Kiss A, et al. Significant regional variation in adequacy of lymph node assessment and survival in gastric cancer. Cancer 2006; 107(9): 2143-51.
20. De Steur WO, Hartgrink HH, Dikken JL,et al. Quality control of lymph node dissection in the Dutch Gastric Cancer Trial. Br J Surg 2015; 102(11): 1388-93.
21. Bickenbach KA, Gonen M, Strong V, et al. Association of positive transection margins with gastric cancer survival and local recurrence. Ann Surg Oncol 2013; 20(8): 2663-8.
22. Posteraro B, Persiani R, Dall'Armi V, et al. Prognostic factors and outcomes in Italian patients undergoing curative gastric cancer surgery. Eur J Surg Oncol 2014; 40(3): 345-51.
23. Kang WM, Meng QB, Yu JC, et al. Factors associated with early recurrence after curative surgery for gastric cancer. World J Gastrointest Surg 2015; 21(19): 5934-40.
24. Koppert LB, Lemmens VE, Coebergh JW, et al. Impact of age and co-morbidity on surgical resection rate and survival in patients with oesophageal and gastric cancer. Br J Surg 2012; 99(12): 1693-700.
25. Raziee HR, Cardoso R, Seevaratnam R, et al. Systematic review of the predictors of positive margins in gastric cancer surgery and the effect on survival. Gastric cancer 2012; 15 Suppl 1: S116-24.
26. Wouters MW, Jansen-Landheer ML, van de Velde CJ. The Quality of Cancer Care initiative in the Netherlands. Eur J Surg Oncol 2010; 36 Suppl 1: S3-s13.
27. Dutch Upper GI Cancer Audit (DUCA); https://www.dica.nl/media/332/DICA-jaarrapportage-2015.pdf; [accessed at 22-06-2017].
28. Dutch Insitute for Clinical Auditing (DICA). 2017. https://dica.nl/nieuws/duca-juni [accessed 2 May 2018]
29. Busweiler LA, Wijnhoven BP, van Berge Henegouwen MI, et al. Early outcomes from the Dutch Upper Gastrointestinal Cancer Audit. Br J Surg 2016; 103(13): 1855-63.
30. Van de Poll-Franse LV, Lemmens VE, Roukema JA, et al. Impact of concentration of oesophageal and gastric cardia cancer surgery on long-term population-based survival. Br J Surg 2011; 98(7): 956-63.
31. Coupland VH, Lagergren J, Luchtenborg M, et al. Hospital volume, proportion resected and mortality from oesophageal and gastric cancer: a population-based study in England, 2004-2008. Gut 2013; 62(7): 961-6.
32. Thompson AM, Rapson T, Gilbert FJ, et al. Hospital volume does not influence long-term survival of patients undergoing surgery for oesophageal or gastric cancer. Br J Surg 2007; 94(5): 578-84.
33. Dikken JL, Stiekema J, van de Velde CJ, et al. Quality of care indicators for the surgical treatment of gastric cancer: a systematic review. Ann Surg Oncol 2013; 20(2): 381-98.
34. Anderson O, Ni Z, Moller H, et al. Hospital volume and survival in oesophagectomy and gastrectomy for cancer. Eur J Cancer 2011; 47(16): 2408-14.

PART III

OPTIMAL TREATMENT STRATEGY FOR SUBGROUPS OF GASTRIC CANCER PATIENTS

CHAPTER 7

NORTH EUROPEAN COMPARISON OF TREATMENT STRATEGY AND SURVIVAL IN OLDER PATIENTS WITH RESECTABLE GASTRIC CANCER: A EURECCA UPPER GASTROINTESTINAL GROUP ANALYSIS

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ABSTRACT

Background: As older gastric cancer patients are often excluded from randomized clinical trials, the most appropriate treatment strategy for these patients remains unclear. The current study aimed to gain more insight in treatment strategies and relative survival of older patients with resectable gastric cancer across Europe.

Methods: Population-based cohorts from Belgium, Denmark, The Netherlands, Norway, and Sweden were combined. Patients ≥70 years with resectable gastric cancer (cT1-4a, cN0-2, cM0), diagnosed between 2004 and 2014 were included. Resection rates, administration of chemotherapy (irrespective of surgery), and relative survival within a country according to stage were determined.

Results: Overall, 6 698 patients were included. The percentage of operated patients was highest in Belgium and lowest in Sweden for both stage II (74% versus 56%) and stage III disease (57% versus 25%). For stage III, chemotherapy administration was highest in Belgium (44%) and lowest in Sweden (2%). Three year relative survival for stage I, II, and III disease in Belgium was 67.8% (95% CI:62.8-72.6), 41.2% (95% CI:37.3-45.2), 17.8% (95% CI:12.5-24.0), compared with 56.7% (95% CI:51.5-61.7), 31.3% (95% CI:27.6-35.2), 8.2% (95% CI:4.4-13.4) in Sweden. There were no significant differences in treatment strategies of patients with stage I disease.

Conclusion: Substantial treatment differences are observed across North European countries for patients with stages II and III resectable gastric cancer aged 70 years or older. In the present comparison, treatment strategies with a higher proportion of patients undergoing surgery seemed to be associated with higher survival rates for patients with stages II or III disease.

INTRODUCTION

Gastric cancer is the fifth most common malignancy in the world, accounting for an estimated number of 723 000 deaths in 2012.[1] In the Western world, 5-year survival for gastric cancer does not exceed 50%.[2] Gastric cancer is predominantly a disease of elderly as approximately 60% of all patients is 70 years and older.[3] Surgery is the keystone in treatment for potentially curative gastric cancer.[4] Due to the high recurrence rates, multimodality approaches are standard for gastric cancer ≥stage IB disease (all M0). Since the British MAGIC trial showed a survival benefit with perioperative chemotherapy over surgery alone for advanced gastric cancer patients, this became the standard of care for most of Europe.[5]

Whereas the MAGIC trial was conducted in a study population with a median age of 62 years (range: 23-85), the median age of people diagnosed with gastric cancer in Europe is about 70.[3, 5] Older patients are underrepresented in randomized clinical trials, mainly because of age limitations and exclusion of patients with comorbidities. In older patients without comorbidities, effectivity of treatment usually equals that of younger patients with limited increase in complications. However, for the majority of older patients who do have relevant comorbidities or where frailty plays an important role, evidence for the optimal treatment strategy is limited. In the heterogeneous population of older patients with gastric cancer an increased risk of postoperative complications and an increased mortality rate has been observed.[6] Although current European guidelines do not have age-specific treatment recommendations, chemotherapy dose reduction or omitting chemotherapy or surgery is often considered in daily clinical practice for older of frail patients.[7]

Recently, an increasing survival difference was shown in The Netherlands in the last twenty years between young (<70 years) and older (≥70 years) gastric cancer patients.[8] To tailor treatment and to improve outcomes for older patients with gastric cancer, first of all more insight is needed in current treatment strategies and survival outcomes. In order to achieve this, population-based data were collected from five countries in northern Europe involved in the EURECCA (European Registration of Cancer Care) Upper Gastrointestinal initiative (Belgium, Denmark, The Netherlands, Norway, and Sweden). The purpose of the current study was to provide an overview of treatment strategies and survival in patients with potentially resectable gastric cancer aged 70 years and older across these countries.

METHODS

Data and study population

Population based datasets were collected from the Belgian Cancer Registry (BE), the Danish Clinical Registry of Carcinomas of the Esophagus, the Gastro-Esophageal

Junction and the Stomach (DECV) (DK), the Netherlands Cancer Registry (NL), the Norwegian Cancer Registry (NO), and the Swedish National Register for Oesophageal and Gastric Cancer Registry (SE). Characteristics of these registries (BE, DK, NL, and SE) are presented in *Table 1*. Accuracy and completeness (>95% of cancer patients of the population are registered) of the data were confirmed by the individual registries.[9-15]

Table 1. Characteristics of each registry according to country

		Belgium	Denmark	Netherlands	Sweden
Registry		Belgian Cancer Registry (BCR)	Danish Clinical Registry of Carcinomas of the Esophagus, the Gastro-Esophageal Junction and the Stomach (DECV)	Netherlands Comprehensive Cancer Organisation	The Swedish National Register for Oesophageal and Gastric Cancer
Organisation		Population-based cancer registry	National Quality Registry**	Population-based cancer registry	National Quality Registry
Inclusion / selection		All patients*	All patients*	All patients*	All patients*
Data collection		Per center, data managers, pathology labatories and use of medical claims data	Per center, data managers	Per center, data managers	Per center, data managers
Gastric cancer age-standardised incidence (2012#)		8.6 per 100 000	8.1 per 100 000	8.4 per 100 000	5.6 per 100 000
70+ gastric cancer standardised incidence (2012)°		59.5 per 100 000	56.8 per 100 000	58.2 per 100 000	49.8 per 100 000
Stage distribution	**I**	10.3%	7.9%	12.8%	21.1%
	II	9.4%	24.6%	10.9%	15.8%
	III	7.5%	6.7%	12.4%	26.3%
	IV	16.0%	28.7%	41.4%	15.8%
	unknown	56.8%	32.1%	22.5%	21.1%

**Accuracy and completeness (>95% of cancer patients of the population are registered) of the data were confirmed by the individual registries, ** National registry covering all patients in DK diagnosed with Carcinomas of the Esophagus and the Gastro-Esophageal Junction, # Gastric cancer incidence in Europe in 2012 from IARC (EUCAN), ° 70+ age cancer standardised incidence in 2012 using European standard population*

Patients of 70 years and older diagnosed with potentially resectable primary gastric cancer from 2004 - 2014 were included. Potentially resectable gastric cancer was

defined as cT1-4a, cN0-2, cM0 and staged using the TNM Classification of Malignant Tumours (7th edition).[16] Gastric cancer was defined as C16 according to the International Classification of Diseases (ICD-10).[17] Stage distribution was based on clinical stage. Patients with a second primary gastric cancer were excluded. As in The Netherlands before 2010 the majority of tumours were registered as cMx due to very strict conditions to register cM0 or cM1, cMx was considered cM0 during 2006-2009. Data of the Swedish Cancer Registry were available from 2006-2014. As data of clinical T, N, and M categories were not available in the Norwegian dataset, the results of all Norwegian patients are presented in the *Supplemental Tables A* and *B*, and in *Figure A*.
Localization of the tumour was divided into proximal (C16.0 and C16.1), middle (C16.2, C16.5, C16.6), distal (C16.3, C16.4), and unknown localisations (C16.8 and C16.9). Proportion of surgery (yes/no) and administration of chemotherapy (yes/no, irrespective of surgery) were analysed. Surgery was defined as a resection of the primary tumour, including endoscopic tumour resections. Construction of a gastroenterostomy without a resection and endoscopic stenting techniques were not included as gastric resection. Administration of chemotherapy was defined as proportion of patients who received chemotherapy irrespective of surgery. In the Swedish dataset, only administration of preoperative chemotherapy was registered. No data of administration of chemotherapy in Denmark was available. Follow-up time was defined as date of diagnosis until death or until end of follow-up (censored). In case follow-up data or vital status was missing, patients were excluded from survival analyses.

Statistical analyses
Relative survival (RS) and corresponding 95% Confidence Interval (CI) were estimated for each country using the Ederer II method.[18] Differences in 5-year RS between the countries were expressed as Relative Excess Risk (RER) and adjusted RER (adjusted for age, sex, and year) with corresponding 95% CI.[18] Reference category was the country with the highest proportion of surgery and administration of chemotherapy.
Treatment strategy and RS were compared between the participating countries. Analyses were stratified for stage of disease. STATA/SE version 12.0 and SPSS version 21.0 were used for all analyses. A p-value <0.05 was considered statistically significant.

RESULTS

Patient characteristics, tumour characteristics, and median follow-up
In total, 6 698 gastric cancer patients were included (*Table 2*). In all countries the majority of patients had stage II disease. Median follow-up of the pooled dataset was 471 days (interquartile range (IQR) 178-1131). Median follow-up per country was 651 days in Belgium (IQR: 221-1432), compared with 512 days in Denmark (IQR: 193-1333), 445 days in The Netherlands (IQR: 175-1070), and 319 days in Sweden (IQR: 105-700). Of the follow-up data, 0.4% was missing.

Table 2. Patient and tumour characteristics of patients with resectable gastric cancer aged ≥70 years, according to country (2004-2014)

Characteristic	Belgium (n=1 661)	Denmark (n=1 218)	The Netherlands (n=2 282)	Sweden (n=1 537)
Resectable gastric cancer				
Sex				
Male	1 066 (64.2)	886 (72.7)	14 88 (65.2)	943 (61.4)
Female	595 (35.8)	332 (27.3)	794 (34.8)	594 (38.6)
Age				
70-74	488 (29.4)	469 (38.5)	760 (33.3)	429 (27.9)
75-79	492 (29.6)	416 (34.2)	756 (33.1)	446 (29.0)
80-84	426 (25.6)	217 (17.8)	495 (21.7)	385 (25.1)
85+	255 (15.4)	116 (9.5)	271 (11.9)	277 (18.0)
Stage				
0	0 (0.0)	0 (0.0)	21 (0.9)	96 (6.2)
I	623 (37.5)	245 (20.1)	797 (34.9)	531 (34.6)
II	820 (49.4)	764 (62.7)	1141 (50.0)	852 (55.4)
III	218 (13.1)	209 (17.2)	323 (14.2)	58 (3.8)
Localisation				
Proximal	605 (36.4)	821 (67.4)	800 (35.1)	473 (30.8)
Middle	175 (10.5)	397 (32.6)ɣ	364 (15.9)	378 (24.6)
Distal	309 (18.6)	ɣ	628 (27.5)	459 (29.8)
Unknown	572 (34.4)	ɣ	490 (21.5)	227 (14.8)
Diagnosis year				
2004-2006	375 (22.6)	254 (20.9)	503 (22.0)	134 (8.7)*
2007-2009	409 (24.6)	311 (25.5)	530 (23.2)	515 (33.5)
2010-2012	497 (29.9)	380 (31.2)	698 (30.6)	510 (33.2)
2013-2014	380 (22.9)	273 (22.4)	551 (24.2)	378 (24.6)

Data is presented as n (%)

ɣ subdivision of location of gastric cancer was recorded only in proximal and middle in the Danish dataset;

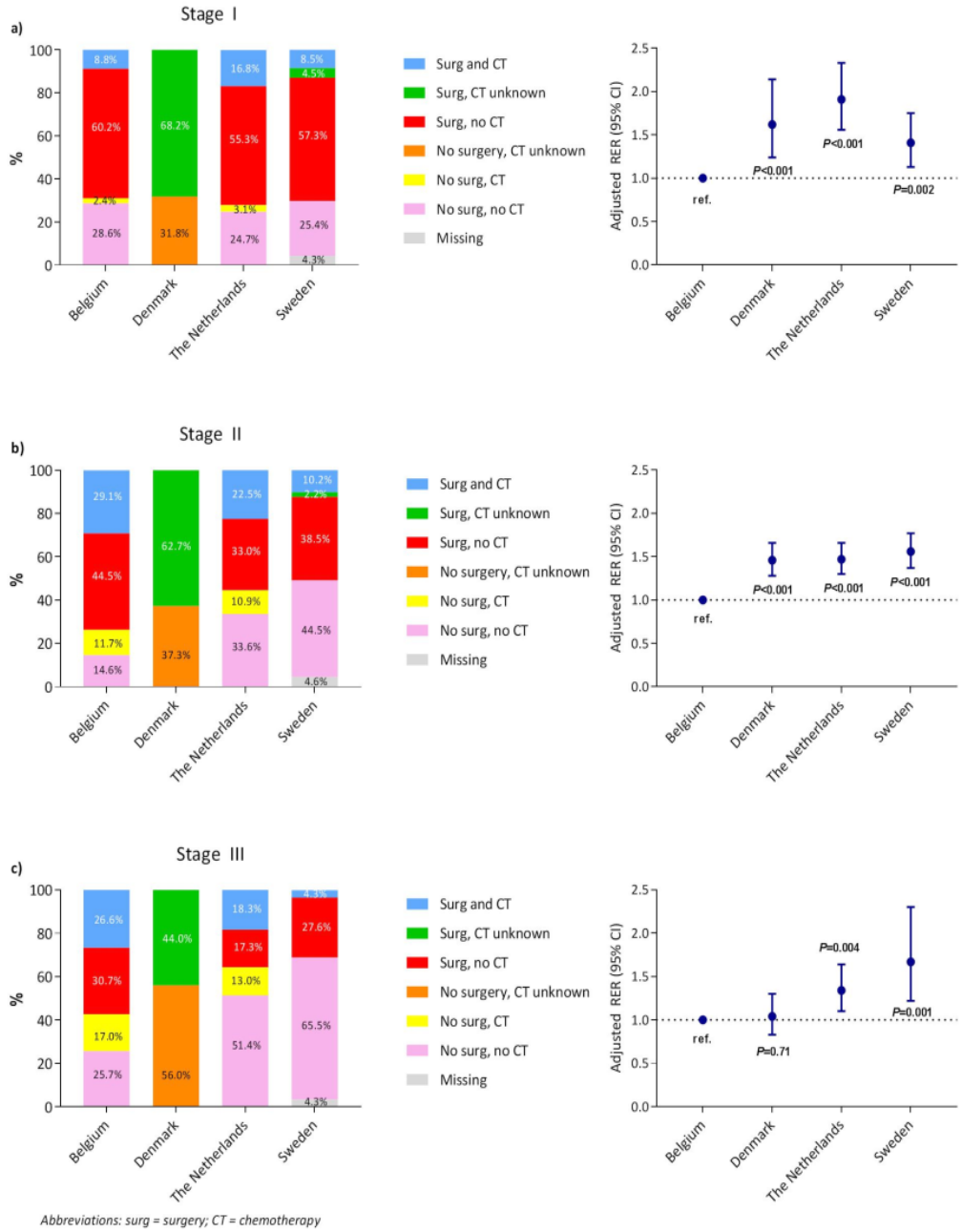
** no Swedish data available of 2004 and 2005*

Treatment strategy and relative survival

Stage I

A similar treatment strategy was observed between stage I patients in Belgium, The Netherlands, and Sweden (*Figure 1a*). The majority of patients underwent a resection but were not treated with chemotherapy (Belgium 60.2%, The Netherlands 55.3%, and Sweden 57.3%). Unfortunately the number of endoscopic resections was not registered in all countries. Almost 70% of the Danish patients underwent a resection (no data regarding administration of chemotherapy was available). The percentage of patients that did not undergo a resection nor treated with chemotherapy varied from 24.7% (The Netherlands) to 28.6% (Belgium).

Patients in Belgium had a better relative survival compared with The Netherlands (adjusted RER 1.91, 95% CI: 1.56-2.33, *P*<0.001), Denmark (adjusted RER 1.62, 95%



Abbreviations: surg = surgery; CT = chemotherapy

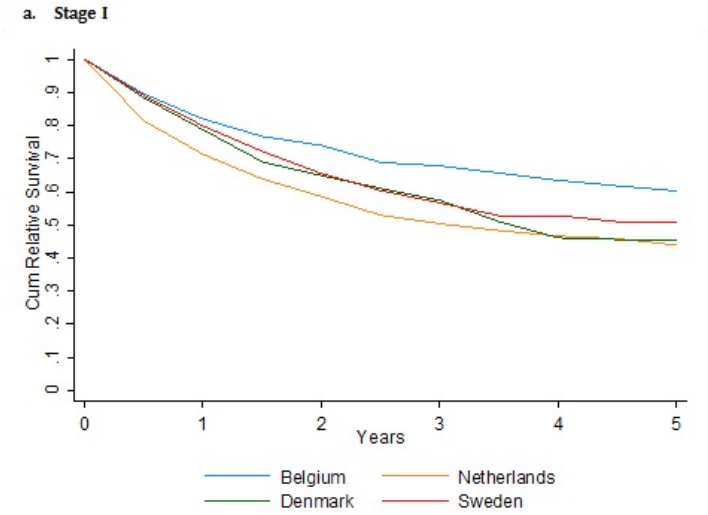
Figure 1. Treatment modality and adjusted relative excess risks (RERs, lower is better) of death for patients with resectable gastric cancer aged ≥70 years according to stage and country (2004-2014)

CI: 1.24-2.14, *P*<0.001), and Sweden (adjusted RER 1.41, 95% CI: 1.13-1.75, *P*=0.002) (*Figure 1a/ Table 3*). Three-year relative survival in Belgium was 67.8% (62.8-72.6) compared with 57.4% (49.7-64.8), 56.7% (51.5-61.7), and 50.4% (46.2-54.5) in Denmark, Sweden, and The Netherlands, respectively (*Figure 2a*).

Stage II

In Belgium, 29.1% of the patients received both surgery and chemotherapy, compared with 22.5% in The Netherlands and 10.2% in Sweden (only preoperative chemotherapy) (*Figure 1b*). The percentage of patients that received surgery without chemotherapy was 44.5% in Belgium, 38.5% in Sweden, and 33.0% in The Netherlands, respectively. Approximately 60% of the Danish patients was operated. The percentage of patients that did not undergo surgery nor received chemotherapy was 14.6% in Belgium, 33.6% in The Netherlands, and 44.5% in Sweden.

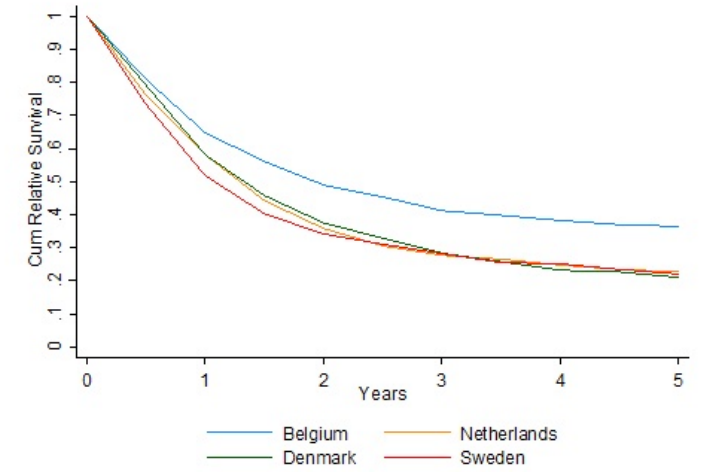
A significantly higher survival was observed in Belgium compared with The Netherlands (adjusted RER 1.47, 95% CI: 1.30-1.66, *P*<0.001), Denmark (adjusted RER 1.46, 95% CI: 1.28-1.66, *P*<0.001), and Sweden (adjusted RER 1.56, 95% CI: 1.37-1.77, *P*<0.001) (*Figure 1b/ Table 3*). Five-year survival in Belgium was 36.5% (32.1-41.0) compared with 22.7% (19.6-25.9) in The Netherlands, 22.0% (18.6-25.7) in Sweden, and 21.0% (17.6-24.8) in Denmark (*Figure 2b*).



	RS	Belgium	Netherlands	Denmark	Sweden
Stage I	*1 year*	82.1 (78.3-85.4)	71.4 (67.8-74.7)	78.8 (72.4-84.1)	80.0 (75.9-83.7)
	3 year	67.8 (62.8-72.6)	50.4 (46.2-54.5)	57.4 (49.7-64.8)	56.7 (51.5-61.7)
	5 year	60.2 (54.1-66.2)	43.9 (39.1-48.7)	45.5 (37.2-54.0)	50.6 (44.9-56.4)

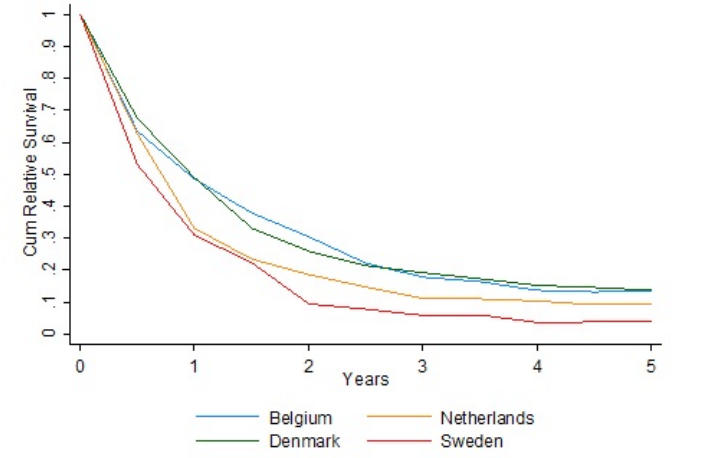
Figure 2 continues

b. Stage II



	RS	Belgium	Netherlands	Denmark	Sweden
Stage II	*1 year*	64.8 (61.1-68.2)	58.0 (55.0-61.0)	58.1 (54.3-61.7)	51.8 (48.2-55.3)
	3 year	41.2 (37.3-45.2)	27.8 (24.9-30.7)	28.3 (24.8-32.0)	28.3 (24.9-31.7)
	5 year	36.5 (32.1-41.0)	22.7 (19.6-25.9)	21.0 (17.6-24.8)	22.0 (18.6-25.7)

c. Stage III



	RS	Belgium	Netherlands	Denmark	Sweden
Stage III	*1 year*	48.6 (41.5-55.4)	33.1 (27.9-38.5)	48.9 (41.6-55.9)	30.9 (19.2-43.4)
	3 year	17.8 (12.5-24.0)	11.1 (7.7-15.2)	19.2 (13.6-25.6)	5.9 (1.5-14.8)
	5 year	13.6 (8.5-20.0)	9.5 (6.3-13.8)	13.7 (8.3-20.7)	3.9 (0.6-13.1)

Figure 2. Relative survival of patients with resectable gastric cancer patients aged ≥70 years, according to country and stage during 2004-2014

Stage III

A fourth of the Belgian patients was operated and treated with chemotherapy (26.6%), whereas this number was 18.3% and 4.3% in The Netherlands and Sweden (only preoperative chemotherapy), respectively (*Figure 1c*). The percentage of patients that was operated but not treated with chemotherapy was the highest in Belgium (30.7%), compared with 27.6% in Sweden and 17.3% and The Netherlands. About half of the Danish patients (44.0%) was operated. The percentage of patients that did not undergo a resection nor received chemotherapy was 65.5% in Sweden, 51.4% in The Netherlands and 25.7% in Belgium.

A higher survival was observed in Belgium compared with Sweden (adjusted RER 1.67, 95% CI: 1.22-2.30, *P*=0.001) and The Netherlands (adjusted RER 1.34, 95% CI: 1.10-1.64, *P*=0.004) (*Figure 1c/ Table 3*). One-year survival was 48.6% (41.5-55.4) in Belgium, 48.9% (41.6-55.9)in Denmark, 33.1% (27.9-38.5)in The Netherlands and 30.9% (19.2-43.4) in Sweden.

The majority of Norwegian patients (all stages) were operated (61.9%, *Supplemental Table B*). Three-years survival in Norway was 19.6% (17.0-22.3) (*Supplemental Figure A*).

Table 3. Relative survival according to country and stratified by stage and (adjusted) relative excess risks (RERs) of death of gastric cancer patients aged ≥70 years during 2004-2014

Resectable gastric cancer					
Stage	**Country**	**RER (95%CI)**	**p-value**	**Adjusted RER[$] (95%CI)**	**p-value**
All stages	Belgium	1.0 (reference)	<0.001*	1.0 (reference)	<0.001*
	The Netherlands	1.45 (1.32-1.59)	<0.001	1.53 (1.39-1.67)	<0.001
	Denmark	1.48 (1.34-1.65)	<0.001	1.58 (1.42-1.75)	<0.001
	Sweden	1.27 (1.15-1.41)	<0.001	1.30 (1.17-1.44)	<0.001
I	Belgium	1.0 (reference)	<0.001*	1.0 (reference)	<0.001*
	The Netherlands	1.70 (1.40-2.08)	<0.001	1.91 (1.56-2.33)	<0.001
	Denmark	1.43 (1.10-1.88)	0.01	1.62 (1.24-2.14)	<0.001
	Sweden	1.33 (1.07-1.67)	0.01	1.41 (1.13-1.75)	0.002
II	Belgium	1.0 (reference)	<0.001*	1.0 (reference)	<0.001*
	The Netherlands	1.41 (1.25-1.60)	<0.001	1.47 (1.30-1.66)	<0.001
	Denmark	1.38 (1.21-1.58)	<0.001	1.46 (1.28-1.66)	<0.001
	Sweden	1.49 (1.31-1.70)	<0.001	1.56 (1.37-1.77)	<0.001
III	Belgium	1.0 (reference)	0.0012*	1.0 (reference)	0.0007*
	The Netherlands	1.30 (1.07-1.58)	0.01	1.34 (1.10-1.64)	0.004
	Denmark	0.97 (0.78-1.21)	0.80	1.04 (0.83-1.30)	0.71
	Sweden	1.56 (1.13-2.14)	0.01	1.67 (1.22-2.30)	0.001

[$]Adjusted for age, sex, year, and stage (for all stages);

** p-value for trend using Walt test for linear trend after estimation*

DISCUSSION

The current study shows considerable variety in both treatment strategies and relative survival in a large population-based cohort of patients with resectable gastric cancer aged ≥70 years from five countries in northern Europe.

Treatment strategy

For patients with stage I disease, in all participating countries, approximately 30% of patients did not undergo surgery. However, substantial differences were observed in the proportion of patients undergoing surgery between participating countries in stage II and stage III disease. There are several possible explanations for these observed treatment differences between countries for patients with stages II and III disease. First, disparities in health status of gastric cancer patients in different countries may result in different treatment decisions. Secondly, cultural background may play a role when shared decisions are made with older patients about complex cancer treatments with relatively low chances of long term survival. Age might be a different influencing factor on treatment decisions in different countries.

Several studies investigated whether age influenced outcomes after surgery of gastric cancer revealing contradicting outcomes.[6, 19-22] Nienhueser *et al.* included 1 005 patients who underwent a resection of oesophageal or gastric cancer between 2002 and 2012.[19] A median survival of 37.4 months was observed in the patients aged younger than 70 years, compared with 30.5, 24.8, and 16.7 months in patients of 70-74, 75-79, and 80 or more, respectively. The authors concluded that advanced age as such should not be an argument to omit surgery, although this decision should be made with caution for patients aged above 80 years.[19] On the other hand, evaluation of data of gastric cancer patients of the Munich Cancer Registry during 1998-2012 showed comparable 5-year relative survival rates in age groups 50-59, 60-69, and 70-79 years (between 48 and 50%).[20] It should however be taken into account that these studies have a retrospective design and due to selection bias merely demonstrate sensible selection of older patients for successful surgery. Compared with the results of the Munich Cancer Registry, we found comparable 5-year relative survival rates for patients with stage I disease, but lower survival rates for patients with stage II or stage III disease. Furthermore it was recently shown that resection rates for patients with gastric cancer have decreased over time, especially for older patients.[23] These findings might reflect a better selection of older patients because of improvements in diagnostic accuracy and a more risk-avoiding behaviour by surgeon and/ or patient.[23]

Efficacy, safety, and feasibility of perioperative chemotherapy were proved for younger Western gastric cancer patients with resectable disease.[5] In the MAGIC trial, a five-year survival rate of 36% was seen in the patients who were operated and treated with perioperative chemotherapy compared with 23% in the patients who were operated only. Only 20% of the patients in this trial were 70 years or older.[5] Therefore it remains unclear whether this survival benefit is similar for older gastric cancer patients, as well-designed large prospective studies are absent.[24, 25] Of the participating countries

in the current study, administration of chemotherapy was registered in Belgium, The Netherlands, and Sweden. As in the latter registry only preoperative chemotherapy was registered, the administration of chemotherapy in Sweden is likely to be underrated. Unexpectedly, a lower rate of chemotherapy was recorded in the Swedish stage III patients compared with the stage II patients. This is in contrast with The Netherlands and Belgium where an evident increase of the administration of chemotherapy was observed with increasing stage of disease.
A noteworthy finding is the strong increase of the proportion of patients who did not undergo a resection nor treated with chemotherapy with increasing stage of disease. This percentage was around 25% in stage I patients, 40% in stage II patients, and 66% in stage III patients.

Treatment strategy and relative survival
In accordance with the results of the EUROCARE-5 study, Belgium belongs to the European countries with the highest survival rates of gastric cancer patients.[26] Whereas similar treatment strategies in the current study were observed among countries in patients with stage I disease, a higher proportion of patients with stage II and III disease received surgery and chemotherapy in Belgium. These findings are in line with a previous report where a tendency was shown for a more aggressive treatment approach in Belgium in both upper gastrointestinal cancers as in other cancer types such as colorectal cancer and breast cancer.[27] In the current study in all stages of disease, Belgium had a better survival compared with the other countries with exception for Danish patients with stage III disease. These findings might suggest that surgery for stage II or stage III resectable gastric cancer patients aged 70 or more is associated with a better survival. It is unclear what the exact role of the addition of administration of chemotherapy is. The population of patients who underwent surgery and received chemotherapy could reflect a selection of fit and healthy patients.

Strengths and limitations
To our knowledge, the current study for the first time provides an international overview of stage specific treatment strategy and survival in resectable gastric cancer patients aged ≥70. These results are highly important as this group of patients is being expected to increase as the population ages. As often small cohorts have been used in previous studies which investigated survival of older gastric cancer patients, the use of five large national databases in the current study enhances the results.[19, 20, 28]
Although adjustment for age, sex, and stage in the current analyses, residual confounding cannot be ruled out. Possible confounders, such as the presence and number of comorbidities could have played a significant role, especially in this older group of patients.[29] Selection criteria for surgery or chemotherapy within the countries may be driven by expected survival, which could lead to confounding by indication. Confounding by indication is bias introduced when a variable is a risk factor for disease among non-exposed persons but not in the causal pathway between exposure and disease. This kind of bias is even more likely in research with an older population as they are

known for their heterogeneity. Furthermore, there could be differences regarding the administration of chemotherapy, among them type, dose, and cycles of chemotherapy. The lack and the limited data of Denmark and Sweden regarding administration of chemotherapy was also considered a limitation.

Clinical implications

By using population based data from five North European countries, the current study showed that a treatment strategy including a high proportion of patients undergoing surgery might be associated with a better survival for gastric cancer patients aged 70 or more with stage II or stage III disease. Furthermore, the proportion of patients who did not receive treatment strongly increased with increasing stage of disease. These findings could underline that age itself is not a reason to omit a gastric resection, which offers the only chance for cure, and/ or to omit administration of chemotherapy. Shared decision making seems to be a plausible explanation for these findings, as older patients might be less motivated to be operated or to be treated with chemotherapy, with subsequently risk of postoperative complications and toxicity. In particular in high stage of disease, the median survival is quite limited. Also, the options of undergoing surgery and/ or treatment with chemotherapy might not have always been offered to the patient by the clinician.

Nevertheless, more attention is needed for certain aspects in the treatment of elderly gastric cancer patients. As described in literature, older gastric cancer patients are associated with significantly more comorbidities, poorer nutritional status, more frailty, and higher postoperative mortality rates.[6, 30] A geriatric assessment is therefore an important tool during the preoperative phase to identify the grade of frailty, as this is a strong predictor for both short- as long-term outcomes after gastrointestinal surgery.[30] Furthermore, waste of lean muscle mass, also known as sarcopenia, is associated with poor postoperative outcomes.[30] These findings emphasize the importance of preoperative risk assessment of older gastric cancer patients, not only to improve postoperative outcomes of these patients but also to determine appropriate guidelines and prediction tools for this vulnerable group of patients. Further detailed analyses of selection criteria for surgery and chemotherapy will lead to more tailored treatment in older gastric cancer patients. It would be therefore recommended to include older gastric cancer patients in randomized clinical trials as well or to design trials which focus only on older gastric cancer patients.

Conclusion

Substantial treatment differences are observed across European countries for patients with stages II and stage III resectable gastric cancer aged 70 years or older. In the present comparison, treatment strategies with a higher proportion of patients undergoing surgery seemed to be associated with higher survival rates for patients with stages II or III disease.

REFERENCES

1. Ferlay J, Soerjomataram I, Dikshit R, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer 2015; 136(5): E359-86.
2. Cats A, Jansen EPM, van Grieken NCT, et al. Chemotherapy versus chemoradiotherapy after surgery and preoperative chemotherapy for resectable gastric cancer (CRITICS): an international, open-label, randomised phase 3 trial. Lancet Oncol 2018; 19(5): 616-628.
3. Netherlands Comprehensive Cancer Organisation. The Netherlands Cancer Registry. http://www.cijfersoverkanker.nl/?language=en (2015).
4. Waddell T, Verheij M, Allum W, et al. Gastric cancer: ESMO-ESSO-ESTRO clinical practice guidelines for diagnosis, treatment and follow-up. Eur J Surg Oncol 2014; 40(5): 584-91.
5. Cunningham D, Allum WH, Stenning SP, et al. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. New Engl J Med 2006; 355(1): 11-20.
6. Pisanu A, Montisci A, Piu S, et al. Curative surgery for gastric cancer in the elderly: treatment decisions, surgical morbidity, mortality, prognosis and quality of life. Tumori 2007; 93(5): 478-84.
7. Smyth EC, Verheij M, Allum W, et al. Gastric cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2016; 27(suppl 5): v38-v49.
8. Nelen SD, Verhoeven RH, Lemmens VE, et al. Increasing survival gap between young and elderly gastric cancer patients. Gastric cancer 2017; 20 (6): 919-928.
9. Bray F, Parkin DM. Evaluation of data quality in the cancer registry: principles and methods. Part I: comparability, validity and timeliness. Eur J Cancer 2009; 45(5):747-55.
10. Parkin DM, Bray F. Evaluation of data quality in the cancer registry: principles and methods Part II. Completeness. Eur J Cancer 2009; 45(5):756-64.
11. Linder G, Lindblad M, Djerf P, et al. Validation of data quality in the Swedish National Register for Oesophageal and Gastric Cancer. Br J Surg 2016; 103(10):1326-35.
12. http://decv.gicancer.dk/Default.aspx?pID=17; accessed at 02-04-2018.
13. Henau K, Van Eycken E, Silversmit G, et al. Regional variation in incidence for smoking and alcohol related cancers in Belgium. Cancer Epidemiol 2015; 39(1):55-65.
14. http://www.kankerregister.org/media/docs/publications/BCR_publicatieCancerBurden2016_web160616.pdf; accessed at 02-04-2018.
15. Schouten LJ, Hoppener P, van den Brandt PA,et al. Completeness of cancer registration in Limburg, The Netherlands. Int J Epidemiol 1993; 22(3):369-76.
16. Greene F.L. Page D.L., Fleming, I.D., et al. AJCC Cancer Staging Manual, 6th edition. New York Springer. 2002.
17. World Health Organisation. International Statistical Classification of Disease and Related Health Problems, 10th revision. 2010.
18. Lambert PC, Dickman PW, Nelson CP, et al. Estimating the crude probability of death due to cancer and other causes using relative survival models. Stat Med 2010; 29(7-8):885-95.
19. Nienhueser H, Kunzmann R, Sisic L, et al. Surgery of gastric cancer and esophageal cancer: Does age matter? J Surg Oncol 2015; 112(4):387-95.

20. Schlesinger-Raab A, Mihaljevic AL, Egert S, et al. Outcome of gastric cancer in the elderly: a population-based evaluation of the Munich Cancer Registry. Gastric cancer 2016;19(3):713-22.
21. Kim MS, Kim S. Outcome of Gastric Cancer Surgery in Elderly Patients. J Gastric Cancer 2016;16(4):254-9.
22. Saidi RF, Bell JL, Dudrick PS. Surgical resection for gastric cancer in elderly patients: is there a difference in outcome? J Surg Res 2004;118(1):15-20.
23. Speelman AD, van Gestel YR, Rutten HJ, et al. Changes in gastrointestinal cancer resection rates. Br J Surg 2015;102(9):1114-22.
24. Bringeland EA, Wasmuth HH, Fougner R, et al. Impact of perioperative chemotherapy on oncological outcomes after gastric cancer surgery. Br J Surg 2014;101(13):1712-20.
25. Aoyama T, Yoshikawa T, Watanabe T, et al. Safety and feasibility of S-1 adjuvant chemotherapy for gastric cancer in elderly patients. Gastric cancer 2012;15(1):76-82.
26. De Angelis R, Sant M, Coleman MP, et al. Cancer survival in Europe 1999-2007 by country and age: results of EUROCARE--5-a population-based study. Lancet Oncol 2014;15(1):23-34.
27. Good Clinical Practice Brussels: Belgian Health Care Knowledge Centre (KCE) KR, 2013, https://kce.fgov.be/sites/default/files/atoms/files/KCE_200Cs_Quality_indicators_for_the_management_of_upper_gastrointestinal_cancer_synthesis_second_print_0_1.pdf, accessed at 30-04-2018.
28. Posteraro B, Persiani R, Dall'Armi V, et al. Prognostic factors and outcomes in Italian patients undergoing curative gastric cancer surgery. Eur J Surg Oncol 2014;40(3):345-51.
29. Van Gestel YR, Lemmens VE, de Hingh IH, et al. Influence of comorbidity and age on 1-, 2-, and 3-month postoperative mortality rates in gastrointestinal cancer patients. Ann Surg Oncol 2013;20(2):371-80.
30. Wagner D, DeMarco MM, Amini N, et al. Role of frailty and sarcopenia in predicting outcomes among patients undergoing gastrointestinal surgery. World J Gastrointest Surg 2016;8(1):27-40.

Supplemental Table A. Patient and tumour characteristics of patients with resectable gastric cancer aged ≥70 years from Norway during 2004-2014

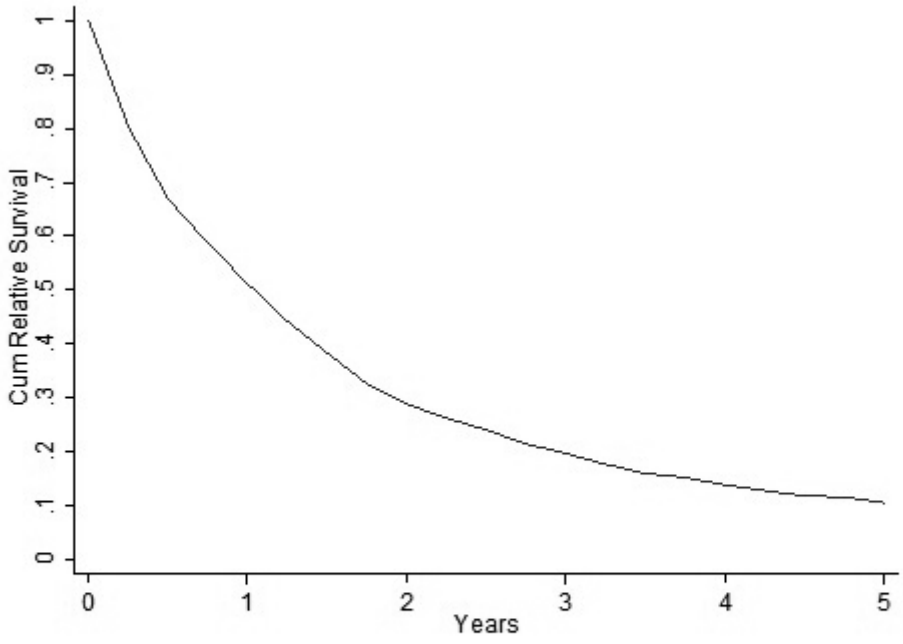
Characteristic	Norway (n=1 425)
Gastric cancer	
Sex	
Male	857 (60.1)
Female	568 (39.9)
Age	
70-74	328 (23.0)
75-79	364 (25.5)
80-84	386 (27.1)
85+	347 (24.4)
Localisation	
Proximal	316 (22.2)
Middle	252 (17.7)
Distal	429 (30.1)
Unknown	428 (30.0)
Diagnosis year	
2004-2006	464 (32.6)
2007-2009	384 (26.9)
2010-2012	365 (25.6)
2013-2014	212 (14.9)

Supplemental Table B. Proportion of patients with resectable gastric cancer aged ≥70 years from Norway who underwent a gastric resection and/or received chemotherapy during 2004-2014

Characteristic	Norway (n=1 425)
Gastric cancer	
Total	
Surgery	882 (61.9)
CT	NA

Data is presented as n (%)

Abbreviations: surgery = proportion of patients undergoing surgery; CT = proportion of administration chemotherapy; NA = not available



1year RS: 51.2 (48.1-54.3)

3years RS: 19.6 (17.0-22.3)

5years RS: 10.5 (8.4-12.9)

Supplemental Figure A. Relative survival of patients with resectable gastric cancer aged ≥70 years from Norway during 2004-2014

CHAPTER 8

INTERNATIONAL COMPARISON OF TREATMENT STRATEGY AND SURVIVAL IN METASTATIC GASTRIC CANCER

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ABSTRACT

Background: In the randomized Asian REGATTA trial, no survival benefit was shown for additional gastrectomy over chemotherapy alone in patients with advanced gastric cancer with a single incurable factor, thereby discouraging surgery for these patients. The purpose of this study was to evaluate treatment strategies for patients with metastatic gastric cancer in daily practice in five European countries, along with relative survival in each country.

Methods: Nationwide population-based data from Belgium, Denmark, the Netherlands, Norway and Sweden were combined. Patients with primary metastatic gastric cancer diagnosed between 2006 and 2014 were included. The proportion of gastric resections performed and the administration of chemotherapy (irrespective of surgery) within each country were determined. Relative survival according to country was calculated.

Results: Overall, 15 057 patients with gastric cancer were included. The proportion of gastric resections varied from 8.1 per cent in the Netherlands and Denmark to 18.3 per cent in Belgium. Administration of chemotherapy was 39.2 per cent in the Netherlands, compared with 63.2 per cent in Belgium. The 6-month relative survival rate was between 39.0 (95 per cent c.i. 37.8 to 40.2) per cent in the Netherlands and 54.1 (52.1 to 56.9) per cent in Belgium.

Conclusion: There is variation in the use of gastrectomy and chemotherapy in patients with metastatic gastric cancer, and subsequent differences in survival.

INTRODUCTION

Gastric cancer is the fifth most common malignancy in the world, responsible for an estimated 723 000 deaths in 2012.[1] In the Western world, approximately half of patients present with metastatic disease (stage IV) at time of diagnosis.[2] The prognosis for this group of patients is dismal, with a median survival of only 10 months.[3]

The value of a palliative resection in patients with metastatic gastric cancer remains controversial. According to current European clinical practice guidelines, patients with stage IV disease should be considered for palliative chemotherapy, as it improves survival, reduces disease-related symptoms and improves quality of life (QoL) compared with best supportive care alone.[3,4] Resection of the primary tumour is generally not recommended.[4] A palliative resection is indicated in some patients with bleeding, obstruction or perforation.[5] The extent to which these patients benefit from a palliative resection remains unclear.[6–8] Observational studies have considerable selection bias as only a proportion of patients undergo surgery, reflecting those who are physically more fit with better performance status.

Recently, a multicentre trial from the Far East, the REGATTA trial, investigated whether additional gastrectomy led to survival benefit compared with chemotherapy alone in patients with incurable advanced gastric cancer.[9] In this trial, 175 patients with a incurable factor, limited to either liver, peritoneum or para-aortic lymph nodes, were included from 2008 to 2013. Overall survival at 2 years in an interim analysis was 31.7 (95 per cent c.i. 21.7 to 42.2) per cent for chemotherapy alone compared with 25.1 (16.2 to 34.9) per cent for gastrectomy plus chemotherapy, leading to closure of this study due to futility. The authors stated that gastrectomy could no longer be justified for patients with incurable advanced gastric cancer.[9] The German prospective phase II AIO-FLOT3 trial recently investigated outcomes in patients with limited metastatic disease of the stomach and gastro-oesophageal junction.[10] Results of this trial showed that patients who received neoadjuvant chemotherapy followed by surgery had a favourable survival.

The purpose of the present study was to analyse treatment strategies and their relation to survival in patients with metastatic gastric cancer, using national data from five participating European countries, performed by the EURECCA (EUropean REgistration of Cancer Care) Upper GI Group.

METHODS

Patients diagnosed with primary metastatic (cardia and non-cardia) gastric cancer between 2006 and 2014 were included. Gastric cancer was defined as C16 of the ICD-1011. Localization of the tumour was divided into proximal (C160 and C161), middle (C162, C165, C166), distal (C163, C164) and unknown (C168 and C169) sites. Data were

collected from the Belgian Cancer Registry, the Danish Clinical Registry of Carcinomas of the Oesophagus, the Gastro-oesophageal Junction and the Stomach, the Netherlands Cancer Registry, the Norwegian Cancer Registry, and the Swedish National Register for Oesophageal and Gastric Cancer (*Table 1*).
Accuracy and completeness (registration of more than 95 per cent of patients with cancer patients in the population) of the data were confirmed by the individual registries.[12–18]

Table 1. Overview of registry according to country

	Belgium	Denmark	Netherlands	Norway	Sweden
Registry	Belgian Cancer Registry (BCR)	Danish Clinical Registry of Carcinomas of the Esophagus, the Gastro-Esophageal Junction and the Stomach (DECV)	Netherlands Comprehensive Cancer Organisation	The Cancer Registry of Norway	The Swedish National Register for Oesophageal and Gastric Cancer
Organisation	Population-based cancer registry	National Quality Registry	Population-based cancer registry	Population-based cancer registry	National Quality Registry
Data collection	Per center, data managers, pathology labatories and use of medical claims data	Per center, data managers	Per center, data managers	Per center, data managers	Per center, data managers

Accuracy and completeness (>95% of cancer patients of the population are registered) of the data were confirmed by the individual registries

Follow-up was from date of diagnosis to either death, end of the study period, or loss to follow-up, whichever came first. Data sets from the respective countries were merged. Patients with pM1 disease status were included. When data on pM category were missing, patients with cM1 according the sixth (2006–2009) or seventh (2010–2014) TNM classification of malignant tumours were included.[19,20]
The proportion of patients undergoing a gastric resection (yes/no) and the proportion who received chemotherapy (yes/no) were analysed. Gastric resection was defined as surgical resection of the primary tumour. Construction of a gastroenterostomy without resection and endoscopic stenting techniques were not included. Use of chemotherapy was defined as the administration of chemotherapeutic agents, irrespective of surgery. Where data on gastric resections or use of chemotherapy were missing, they were considered as being not used.

Statistical analyses

Proportions of patients undergoing gastric resection and/or chemotherapy were compared between the participating countries. Relative survival, expressed as relative excess risk (RER) and adjusted RER (adjusted for age, sex and year of diagnosis), was estimated using Ederer II method.[21] The country with the highest proportion of gastric resections and use of chemotherapy was used as reference category. STATA®/SE version 12.0 (StataCorp, College Station, Texas, USA) and SPSS® version 21.0 (IBM, Armonk, New York, USA) were used for all analyses. P <0.050 was considered statistically significant.

RESULTS

A total of 15 057 patients with metastatic gastric cancer were included. Patient characteristics according to country are shown in *Table 2*.

In Denmark, 64.2 per cent of the tumours were located proximally, compared with 37.3, 32.1, 27.7 and 4.9 per cent in Belgium, the Netherlands, Norway and Sweden respectively. Overall median follow-up was 140 (i.q.r. 51–319) days, and per country was 202 (72–421) days in Belgium, 174 (62–364) days in Denmark, 120 (46–277) days in the Netherlands, 140 (51–319) days in Norway and 112 (45–299) days in Sweden. Some 0.4 per cent of follow-up data was missing.

Table 2. Patient and tumour characteristics for primary metastatic gastric cancer, according to country

Characteristic	Belgium (n=2 742)	Denmark (n=1 994)	Netherlands (n=6 547)	Norway (n=1 288)	Sweden (n=2 486)
Primary metastatic gastric cancer patients					
Inhabitants (x10^6)*					
	11	6	17	5	10
Sex					
Male	1 820 (66.4)	1 424 (71.4)	4 250 (64.9)	775 (60.2)	1 540 (61.9)
Female	922 (33.6)	570 (28.6)	2 297 (35.1)	513 (39.8)	946 (38.1)
Age (year)					
<60	622 (22.7)	501 (25.1)	1 434 (21.9)	297 (23.1)	436 (17.5)
60-69	680 (24.8)	669 (33.6)	1 781 (27.2)	315 (24.5)	653 (26.3)
70-79	831 (30.3)	597 (29.9)	2 134 (32.6)	357 (27.7)	801 (32.2)
80+	609 (22.2)	227 (11.4)	1 198 (18.3)	319 (24.8)	596 (24.0)

Table 2 continues

Characteristic	Belgium (n=2 742)	Denmark (n=1 994)	Netherlands (n=6 547)	Norway (n=1 288)	Sweden (n=2 486)
Localisation					
Proximal	1 024 (37.3)	1 280 (64.2)	2 104 (32.1)	357 (27.7)	122 (4.9)
Middle	302 (11.0)	714 (35.8) ɣ	1 162 (17.7)	207 (16.1)	574 (23.1)
Distal	336 (12.3)	ɣ	1 227 (18.7)	203 (15.8)	400 (16.1)
Unknown	1 080 (39.4)	ɣ	2 054 (31.4)	521 (40.5)	1 390 (55.9)
Grade					
Good	171 (6.2)	3 (0.2)	58 (0.9)	24 (1.9)	4 (0.2)
Medium	614 (22.4)	25 (1.3)	762 (11.6)	183 (14.2)	22 (0.9)
Poor	1 394 (50.8)	51 (2.6)	2 638 (40.3)	653 (50.7)	66 (2.6)
No diff	85 (3.1)	6 (0.3)	33 (0.5)	4 (0.3)	9 (0.4)
Unknown	478 (17.4)	1 909 (95.7)	3 056 (46.7)	424 (32.9)	2 385 (95.9)
Diagnosis year					
2006-2008	772 (28.2)	505 (25.3)	2072 (31.6)	471 (36.6)	765 (30.8)
2009-2011	938 (34.2)	629 (31.5)	2290 (35.0)	435 (33.8)	855 (34.4)
2012-2014	1032 (37.6)	860 (43.1)	2185 (33.4)	382 (29.7)	866 (34.8)

Data are presented as n (%)

** number of inhabitants in 2014*

ɣ subdivision of location of gastric cancer not available in Danish dataset

Treatment strategy

In Belgium, approximately one in five patients (18.3 per cent) underwent a gastric resection, compared with 12.5, 9.2, 8.1 and 8.1 per cent in Norway, Sweden, the Netherlands and Denmark respectively. Information on the use of chemotherapy was available only in the Belgian and Dutch data sets. In Belgium, chemotherapy was administered in 63.2 per cent of the patients, compared with 39.2 per cent in the Netherlands. A minority (4.1 per cent) of patients in the Netherlands had both a gastric resection and received chemotherapy, compared with 11.2 per cent in Belgium. In Belgium, 6.9 per cent of patients had a gastric resection only and 46.2 per cent received chemotherapy only, compared with 4.0 and 31.5 per cent respectively in the Netherlands.

Relative survival

The 6-month relative survival rate was 54.1 (95 per cent c.i. 52.1 to 56.9) per cent in Belgium and 49.6 (47.3 to 51.9) per cent in Denmark, compared with 42.6 (39.8 to 45.4) per cent in Norway, 39.6 (37.6 to 41.5) per cent in Sweden and 39.0 (37.8 to 40.2) per cent in the Netherlands. Compared with Belgium (reference), survival was shorter in the Netherlands (adjusted RER 1.44, 95 per cent c.i. 1.38 to 1.51; P <0.001), Norway (adjusted RER 1.39, 1.29 to 1.48; P <0.001), Sweden (adjusted RER 1.33, 1.26 to 1.41; P <0.001) and Denmark (adjusted RER 1.16, 1.09 to 1.24; P <0.001).

DISCUSSION

Variations in treatment strategy and survival of patients with metastatic gastric cancer was evaluated in a large population-based cohort from five European countries. There were substantial differences in the sites of the primary tumour within the stomach across the five countries, differences in the proportions of gastric resection, and in the use of chemotherapy for the two countries with data on this treatment.

According to European guidelines, patients with metastatic gastric cancer should be considered for palliative chemotherapy and be offered appropriate targeted agents, as this strategy prolongs overall survival compared with best supportive care.[4] Not all national guidelines follow these recommendations. For instance, according to the Dutch guidelines, a partial palliative gastric resection should be considered for patients younger than 70 years and with only a single parameter of incurability.[22] These differences might have contributed to the variation found in the proportions of gastric resection between countries in the present study (range from 8.1 per cent in Denmark and the Netherlands to 18.3 per cent in Belgium). A notable finding was that in the Netherlands, the country with the highest incidence of patients with gastric cancer (*Table 1*) and therefore the largest denominator in proportion, the percentage of gastric resections was the lowest. These findings suggest that there may actually be large differences in the incidence of metastatic gastric cancer between countries or that there are significant differences in the quality of registry data or use of imaging modalities to determine the likely extent of disease.

There has been a steady increase in the use of chemotherapy for metastatic gastric cancer in the Netherlands. This was reported to have risen from 5 per cent in 1990 to 36 per cent in 2011.[23] The present findings showed that chemotherapy use in the Netherlands was 39.2 per cent between 2006 and 2014. This is still low compared with Belgium, where 63.2 per cent of patients received chemotherapy in the same time interval. This higher use of chemotherapy in Belgium has been described previously in patients with colonic cancer.[24]

Compared with the other countries, an aggressive treatment strategy was employed in Belgium involving of a high proportion of gastric resections and a high proportion of patients receiving chemotherapy. At all measured time points in the present study, the highest relative survival for all participating countries was seen in Belgium, possibly indicating that an aggressive treatment strategy might be associated with better relative survival. This assumption might be substantiated if the use of chemotherapy in all five countries were available.

QoL was not measured in the REGATTA trial, or by these national registries. QoL is just as important as survival for many of these patients. Patients may exchange a better QoL over prolonged survival, avoiding risks after surgery and toxicity from chemotherapy.

A validated QoL questionnaire for patients with gastric cancer (EORTC QLQ-OG25) should be employed in future studies.[25–27]

The present findings give an insight into the proportion of gastric resections and use of chemotherapy in daily practice. Some differences between registries are noteworthy. The distribution of tumour locations (proximal *versus* others) was quite different in Denmark than in the other countries, raising concerns over definitions. The lack of and limited data on the use of chemotherapy in the national registries of Denmark, Norway and Sweden was a further limitation and highlighted non-uniformity of registered data in these European registries. In addition, the study results are likely to be biased by residual confounding. Additional data including localization and volume of metastatic disease, co-morbidity, performance status, emergency surgery, type and number of the courses of chemotherapy could all have influenced the results. The increasing use of targeted agents may vary across countries and, as a result, systemic treatment could be quite different.[28]

The present study, using population-based data from five European countries, suggests that an aggressive treatment strategy with a gastric resection might be considered an option for patients with metastatic gastric cancer in the Western world, in contrast with the findings of the REGATTA trial.[9] There are important differences between patients in these registries and those in the REGATTA trial, where patients were excluded if they presented with acute symptoms such as bleeding or obstruction, the trial cohort was limited to 175 patients, and only those with a single incurable factor were included. Conversely, a larger cohort study using data from the Dutch Gastric Cancer Trial reported that a palliative resection was beneficial for patients younger than 70 years if metastases were restricted to one site.[6]

Despite the likelihood that patients in the present study would have a greater burden of advanced disease than those in the REGATTA trial, the more aggressive treatment strategy, including resection as practised in Belgium, seemed to be associated with better relative survival. As a result, inclusion of gastric resection in the options for patients presenting with metastatic disease should still be considered in the West. New chemotherapy regimens in combination with surgery have been shown to be beneficial in oligometastatic disease.[10]

REFERENCES

1. Ferlay J, Soerjomataram I, Dikshit R, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer 2015; 136(5): E359-86.
2. Dassen AE, Dikken JL, Bosscha K, et al. Gastric cancer: decreasing incidence but stable survival in the Netherlands. Acta Oncol 2014; 53(1): 138-42.
3. Wagner AD, Unverzagt S, Grothe W, et al. Chemotherapy for advanced gastric cancer. Cochrane Database Syst Rev 2010; (3): Cd004064.
4. Smyth EC, Verheij M, Allum W, et al. Gastric cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2016; 27(suppl 5): v38-v49.
5. Dittmar Y, Rauchfuss F, Goetz M, et al. Non-curative gastric resection for patients with stage 4 gastric cancer--a single center experience and current review of literature. Langenbecks Arch Surg 2012; 397(5): 745-53.
6. Hartgrink HH, Putter H, Klein Kranenbarg E, et al. Value of palliative resection in gastric cancer. Br J Surg 2002; 89(11): 1438-43.
7. Sun J, Song Y, Wang Z, et al. Clinical significance of palliative gastrectomy on the survival of patients with incurable advanced gastric cancer: a systematic review and meta-analysis. BMC cancer 2013; 13: 577.
8. Nelen SD, van Putten M, Lemmens V, et al. Effect of age on rates of palliative surgery and chemotherapy use in patients with locally advanced or metastatic gastric cancer. Br J Surg 2017; 104(13): 1837-46.
9. Fujitani K, Yang HK, Mizusawa J, et al. Gastrectomy plus chemotherapy versus chemotherapy alone for advanced gastric cancer with a single non-curable factor (REGATTA): a phase 3, randomised controlled trial. Lancet Oncol 2016; 17(3): 309-18.
10. Al-Batran SE, Homann N, Pauligk C, et al. Effect of Neoadjuvant Chemotherapy Followed by Surgical Resection on Survival in Patients With Limited Metastatic Gastric or Gastroesophageal Junction Cancer: The AIO-FLOT3 Trial. JAMA Oncol 2017; 3(9): 1237-44.
11. World Health Organisation. International Statistical Classification of Disease and Related Health Problems, 10th revision. 2010.
12. Bray F, Parkin DM. Evaluation of data quality in the cancer registry: principles and methods. Part I: comparability, validity and timeliness. Eur J Cancer 1990 2009; 45(5): 747-55.
13. Parkin DM, Bray F. Evaluation of data quality in the cancer registry: principles and methods Part II. Completeness. Eur J Cancer 2009; 45(5): 756-64.
14. Linder G, Lindblad M, Djerf P, et al. Validation of data quality in the Swedish National Register for Oesophageal and Gastric Cancer. Br J Surg 2016; 103(10): 1326-35.
15. http://decv.gicancer.dk/Default.aspx?pID=17; accessed at 02-04-2018.
16. Henau K, Van Eycken E, Silversmit G, et al. Regional variation in incidence for smoking and alcohol related cancers in Belgium. Cancer Epidemiol 2015; 39(1): 55-65.
17. http://www.kankerregister.org/media/docs/publications/BCR_publicatieCancer Burden2016_web160616.pdf; accessed at 02-04-2018.
18. Schouten LJ, Hoppener P, van den Brandt PA, et al. Completeness of cancer registration in Limburg, The Netherlands. Int J Epidemiol 1993; 22(3): 369-76.

19. Greene F.L. Page D.L., Fleming, I.D., et al. AJCC Cancer Staging Manual, 6th edition. New York Springer. 2002.
20. Sobin LH GM, Wittekind Ch. TNM classification of malignant tumours. UICC, 7th edition, 2009.
21. Lambert PC, Dickman PW, Nelson CP, et al. Estimating the crude probability of death due to cancer and other causes using relative survival models. Stat Med 2010; 29(7-8): 885-95.
22. https://www.oncoline.nl/maagcarcinoom; accessed at 02-04-2018.
23. Bernards N, Creemers GJ, Nieuwenhuijzen GA, et al. No improvement in median survival for patients with metastatic gastric cancer despite increased use of chemotherapy. Ann Oncol 2013; 24(12): 3056-60.
24. Breugom AJ, Bastiaannet E, Boelens PG, et al. Adjuvant chemotherapy and relative survival of patients with stage II colon cancer - A EURECCA international comparison between the Netherlands, Denmark, Sweden, England, Ireland, Belgium, and Lithuania. Eur J Cancer 2016; 63: 110-7.
25. Lagergren P, Fayers P, Conroy T, et al. Clinical and psychometric validation of a questionnaire module, the EORTC QLQ-OG25, to assess health-related quality of life in patients with cancer of the oesophagus, the oesophago-gastric junction and the stomach. Eur J Cancer 2007; 43(14): 2066-73.
26. Karpeh MS, Jr. Palliative treatment and the role of surgical resection in gastric cancer. Dig Surg 2013; 30(2): 174-80.
27. Mahar AL, Coburn NG, Karanicolas PJ, et al. Effective palliation and quality of life outcomes in studies of surgery for advanced, non-curative gastric cancer: a systematic review. Gastric cancer 2012; 15 Suppl 1: S138-45.
28. Van Cutsem E, Sagaert X, Topal B, et al. Gastric cancer. Lancet 2016; 388(10060): 2654-64.

PART IV

DIRECTIONS FOR THE FUTURE

CHAPTER 9

NEOADJUVANT TREATMENT OF GASTRIC CANCER

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Minimally invasive Surgery for Upper Abdominal Cancer 2017

INTRODUCTION

Gastric cancer remains a significant health problem. Despite the fact that the incidence of gastric cancer over the last decades decreased considerably, it is still the fifth most common malignancy in the world with approximately one million new cases each year. With over 700.000 deaths yearly it is the third leading cause of cancer deaths in both sexes worldwide, with the highest mortality rates reported in Eastern Asia (14.0 per 100,000 males and 9.8 per 100,000 females).[1]

Surgery is still the cornerstone in treatment of curable gastric cancer. Nowadays, gastrectomies are increasingly minimally invasive performed. The results of gastrectomies have improved over the last years with respect to morbidity, postoperative mortality, and survival.[2] However, whether the extended lymph node dissection contributed to this improvement is still unclear as the last decades the role of extended lymph node dissection has been controversial. In Asian countries an extended lymph node dissection (D2) has been the standard procedure for the last two decades, whereas in Western countries only a limited lymph node dissection (D1) was common practice until recently.[2] Many studies have investigated the benefit of an extended lymph node dissection (D2) over the standard limited (D1) lymphadenectomy for Western patients, including three methodologically well performed randomized clinical trials, the UK Medical Research Council (MRC) surgical trial, the Dutch Gastric Cancer Trial (DGCT), and the Italian Gastric Cancer Trial.[3-5] Initially none of these trials showed a difference in overall survival, though a D2 lymphadenectomy was associated with a significant higher morbidity- and mortality rate.[3-5] Long term follow up in the Dutch trial, however, did show a benefit for the more extended lymph node dissection, especially if morbidity and mortality could be minimalized.[4,6] Furthermore, the Italian trial showed that an extended lymph node dissection was beneficial for patients with node positive disease.[5] Nevertheless, survival after surgery alone with a D2 lymph node dissection remains poor with a 5-year survival rate around 50% in Western countries.[2]

As no further great improvements were expected in the field of surgery, new treatment strategies were urgently needed to improve survival rates of gastric cancer. In order to achieve this, numerous studies were conducted with multimodal treatment strategies, such as (neo)adjuvant chemotherapy and/or radiotherapy, in addition to surgery. First, adjuvant chemotherapy was tested in several trials with limited patients, but with promising results.[7] Later on, the role of chemotherapy in neoadjuvant setting was evaluated, starting in the Dutch FAMTX trial, and developed to an essential part of the treatment of gastric cancer.[8] Application of radiotherapy in neoadjuvant setting has also gained space over time. The last years attention has risen increasingly for chemotherapy combined with targeted agents. Consequently, in the last 15 years, major advances in the field of multimodal treatment strategies have changed clinical management of gastric cancer.

This chapter comprises the current status of neoadjuvant therapy in treatment of gastric cancer in the Western world. Future directions in the treatment of gastric cancer are addressed.

NEO-ADJUVANT/ PERIOPERATIVE CHEMOTHERAPY

The use of preoperative chemotherapy in gastric cancer was considered to achieve downstaging of the tumor, to improve resectability, and to increase the likelihood of completing multimodal treatment, because surgery is associated with substantial morbidity rates. An overview of studies investigating the impact of neo-adjuvant/ perioperative chemotherapy in gastric cancer is shown in *Table 1*. One of the first randomized clinical trials investigating the added value of neoadjuvant chemotherapy in resectable gastric cancer was the Dutch FAMTX trial (also known as the POCOM (Preoperative Chemotherapy for Operable Gastric Cancer) trial).[8] The aim of this trial was to investigate whether pre-operative chemotherapy leads to a 15% higher curative resectability rate in patients with operable gastric cancer. After adequate staging, patients were randomized to receive either four courses of FAMTX (5-fluorouracil, doxorubicin, and methotrexate), followed by surgery or surgery alone. With a two-sided significance level of 5% and a power of 90%, 225 patients were required in each arm.

Table 1. Overview of studies investigating the impact of neoadjuvant/ perioperative chemotherapy in resectable gastric cancer

Trial	Years	N	Treatment	Results	*P*
FAMTX trial[8]					
	1993 - 1996	29	FAMTX - S	Median survival : 18 months	0.17
		30	S	Median survival : 30 months	
MAGIC trial[9]					
	1994 - 2002	250	ECF - S - ECF	HR 0.75 (CI: 0.60-0.93)	0.009
		253	S		
FNLCC/ FFDC trial[10]					
	1995 - 2003	113	CF - S - CF	HR 0.69 (CI: 0.50-0.95)	0.02
		111	S		
EORTC 40954[11]					
	1999 - 2004	113	CF - S	HR 0.84 (CI: 0.52-1.35)	0.466
		111	S		

N=number, P= p-value, FAMTX=5-fluorouracil, doxorubicin, and methotrexate, S=surgery, ECF=epirubicin, cisplatin, and 5-fluorouracil, HR=hazard ratio, CI= 95% confidence interval, CF= cisplatin and 5-fluorouracil

Due to poor accrual an interim analysis was prematurely performed where no difference in resectability rates was observed between both arms. Based on these results and poor accrual, the trial was prematurely closed. Between 1993 and 1996, 59 patients were randomized of which 29 patients were allocated to the FAMTX regimen and 30 patients

to surgery alone. A beneficial effect of the pre-operative FAMTX could not be shown as the results showed equal resectability rates in both groups. The response rate (complete or partial) in the FAMTX group was only 32%, which was comparable with lower results of previous reported data. The median survival was 18 months in the FAMTX group compared to 30 months in the surgery alone group (p=0.17). At initiation of this trial in the early 90s, a FAMTX regimen was chosen because of its repeatedly demonstrated steady response rates, lower toxicity compared with EAP (etoposide, 5-fluorouracil (5-FU) and methotrexate), lower costs, and lower toxicity compared with FEMTX-P (5-FU, epidoxorubicin, methotrexate, and cisplatin). Moreover, at that time FAMTX was considered the golden standard for future randomised trials. After prematurely closing the study investigators suggested that more active regimens than FAMTX are required for future randomised trials, such as epirubicin, cisplatin, and 5-fluorouracil (ECF).

A landmark study in the field of perioperative chemotherapy for gastric cancer is the United Kingdom Medical Research Council MAGIC study in which Dutch participants contributed significantly.[9] This trial was the first randomized clinical trial showing a survival benefit for perioperative chemotherapy in gastric cancer compared to surgery alone. Patients with resectable adenocarcinoma of the stomach, esophagogastric junction (GEJ), or lower esophagus were included. Between 1994 and 2002, 250 patients were randomly assigned to perioperative chemotherapy and 253 patients to surgery alone. Chemotherapy consisted of 3 preoperative and 3 postoperative cycles of intravenous epirubicin (50 mg/m^2 body surface) and cisplatin (60 mg/m^2) on day 1, and a continuous intravenous infusion of 5-fluorouracil (200 mg/m^2/day). The primary endpoint was overall survival. Postoperative complications rates were similar in the perioperative and the surgery alone group (46% vs. 45%), as were the numbers of death within 30 days (6% vs. 6%). In the perioperative chemotherapy group more patients were able to undergo surgery (79% vs. 70%) and tumors were significantly smaller (T1/T2 52% vs. 37%) with less involved lymph nodes (N0/N1 84% vs. 71%). The perioperative chemotherapy group improved both overall survival (HR 0.75; 95% CI: 0.60-0.93, *P*=0.009; 5-year survival rate 36% vs. 23%) as disease-free survival (HR 0.66; 95% CI: 053-0.81, *P*<0.001) compared to surgery alone. Despite these promising results, this trial was criticized for the fact that only 54% of the patients completed the entire treatment, suggesting that the benefit found was largely derived from neoadjuvant ECF.

Similar outcomes as the MAGIC trial were achieved in the French FNCLCC and FFCD multicentre phase III trial.[10] A total of 224 patients with resectable adenocarcinoma of the lower esophagus, GEJ, or stomach were randomized to receive either 2-3 cycles of preoperative and 3-4 cycles of perioperative chemotherapy (5-fluorouracil 800 mg/m^2 daily for five days plus cisplatin 100 mg/m^2 on day 1 or 2, every four weeks; n=113) or surgery alone (n=111). The perioperative chemotherapy group had a better overall survival (HR 0.69; 95% CI: 0.50-0.95, *P*=0.02; 5-year survival rate 38% vs. 24%) and a better disease-free survival (HR 0.65; 95% CI: 0.48-0.89, *P*=0.003; 5-year rate 34% vs. 19%).

The European Organisation for Research and Treatment of Cancer randomized trial (EORTC 40954) was closed due to poor accrual and was not able to demonstrate a survival benefit for neoadjuvant chemotherapy compared to surgery alone (HR 0.84; 95% CI: 0.52-1.35, *P*=0.466).[11] Possible explanations according the study investigators were a low statistical power, a high rate of proximal gastric cancer, and a better outcome than expected after surgery alone. This trial, however, did show a significantly increased R0 resection rate in favour of the neoadjuvant chemotherapy group (82% vs. 67%, *P*=0.036).

A recent meta-analysis of Yang *et al*. investigated the effect of neoadjuvant chemotherapy on the survival outcomes of resectable gastric cancer.[12] Results showed that perioperative chemotherapy led to an increase in progression-free survival (HR=0.66; 95% CI: 0.55-0.78, *P*=<0.001) and reduction in distant metastases (RR=0.72, 95% CI: 0.59-0.87, *P*=0.001) compared to surgery alone. A trend toward favouring neo-adjuvant chemotherapy compared to no neo-adjuvant chemotherapy was observed in overall survival, but was not significant (HR=0.68, 95% CI: 0.44-1.05, *P*=0.08).[12]

NEOADJUVANT CHEMORADIOTHERAPY

Application of radiotherapy in the neoadjuvant setting has gained ground over the years. In theory, the gastric tumor remains intact leading to a facile treatment planning by the conserved normal anatomy and there is limited toxicity to adjacent organs. An overview of studies investigating the impact of neoadjuvant chemoradiotherapy is provided in *Table 2*. A German phase III randomized clinical trial (POET trial) aimed to address the question of whether adding chemoradiotherapy to neoadjuvant chemotherapy (cisplatin, 5-fluorouracil, and leucovorin) in tumors of the lower esophagus and gastric cardia would lead to survival benefit compared to chemotherapy alone.[13] The study was planned according a two-stage adaptive design. The alternative hypothesis was superiority of 10% in 3-year survival of the chemoradiotherapy arm compared with the chemotherapy arm. With one-sided significance level of 5% and power of 80% the required amount of 263 patients each arm was not achieved resulting in prematurely closing of the trial. From 2000 and 2006, 126 patients were randomly assigned. A significant higher probability of showing pathological complete response was found in favour of the chemoradiotherapy group (15.6% vs. 2.0%, *P*= 0.03). This study found a trend toward improved 3-year survival with the addition of chemoradiotherapy to chemotherapy alone (27.7% vs. 47.4%, *P*= 0.07). However, no statistical significance was seen, most likely due to prematurely closing of the study.

Later on, the Dutch CROSS trial was conducted to demonstrate the benefit of neoadjuvant chemoradiotherapy in esophageal or esophagogastric-junction cancer.[14] It should be notified that this study included primarily patients with esophageal cancer (76%) and a smaller part tumors of the GEJ (24%). Between 2004 and 2008, patients were

randomly assigned to carboplatin (doses titrated to achieve an area under the curve of 2mg/ml/minute) and paclitaxel (50mg/m^2/body surface) and concurrent radiotherapy (41.4 Gy in 23 fractions, 5 days per week), followed by surgery or surgery alone. Overall survival improved in the chemoradiation group (HR 0.66; 95% CI: 0.50-0.87, *P*=0.003). Complete resection (R0) was achieved in 92% of the chemoradiation group versus 69% in the surgery alone group (*P*<0.001). Acceptable adverse event rates were observed.

Since 2009, the TOPGEAR trial is accruing. Patients with resectable adenocarcinoma of the stomach or GEJ are eligible for this trial. The hypothesis of this randomized phase III trial is that adding chemoradiation to standard perioperative chemotherapy (3 cycles of ECF preoperative and postoperative) will have a positive effect on overall survival rates.[15]

Table 2. Overview of trials investigating the impact of neoadjuvant chemoradiotherapy in resectable gastric cancer

Trial	Years	N	Treatment	Results	*P*
POET trial[13]					
	2000 - 2005	60	PLF - CRT[1] - S	HR 0.67 (CI: 0.41-1.07)	0.07
		59	PLF - S		
CROSS trial[14]*					
	2004 - 2008	178	CRT[2] - S	HR 0.66 (CI: 0.50-0.87)	0.003
		188	S		
TOPGEAR trial[15]					
	2009 - 2020**		ECF - CRT[3] - S	Ongoing	
			ECF - S		

N=number, P= p-value, PLF= cisplatin, 5-fluorouracil, and leucovorin, CRT[1]= cisplatin, etoposide, and radiotherapy (30 Gy), S=surgery, HR=hazard ratio, CI= 95% confidence interval, CRT[2]=carboplatin, paclitaxel, and radiotherapy (41.4 Gy), ECF=epirubicin, cisplatin, and 5-fluorouracil, CRT[3]= 5-fluorouracil and radiotherapy (45 Gy)

**= trial including esophageal or esophagogastric-junction cancer*

***= estimation*

ADJUVANT THERAPY

Although the primary goal of this chapter is to focus on neoadjuvant treatment strategies in gastric cancer, a description of the present evidence for adjuvant therapy in gastric cancer is necessary to obtain a complete overview of the current multimodal treatment strategies of gastric cancer. Results of below mentioned studies are shown in *Table 3*.

In 2001, the SWOG/Intergroup 0116 trial showed an improvement in survival and locoregional control with the introduction of postoperative chemoradiotherapy.[16] In this trial, 556 patients were randomized to surgery and postoperative chemoradiotherapy

(45 Gy in 25 fractions in 5 weeks and 3 cycles of 5-fluorouracil and leucovorin; n=281) or surgery alone (n=275). A survival benefit was seen in the chemoradiotherapy group with a median overall survival of 36 months compared to 27 months in the surgery group (HR 1.35; 95% CI: 1.09-1.66, *P*=0.005). Relapse free survival was prolonged in the chemoradiotherapy group (19 months compared to 30 months in surgery alone group (HR 1.52; 95% CI: 1.23-1.86, *P*<0.001)). This study was criticized for its poor adherence to the surgical protocol, as only 10% of the included patients underwent the intended D2-lymphadenectomy.

Table 3. Overview of trials investigating the impact of adjuvant therapy in resectable gastric cancer

Trial	Years	N	Treatment	Results	*P*
Intergroup 0116 trial[16]					
	1991 - 1998	281	S - CRT[1]	HR 1.35 (CI: 1.09-1.66)	0.005
		275	S		
ARTIST trial[17]					
	2004 - 2008	211	S - XP - CRT[2] - XP	HR 1.130 (CI: 0.78-1.65)	0.527
		204	S - XP		
CRITICS trial[19]					
	2007 - 2015	395	ECC - S - CRT[3]	Median survival: 3.3 year	0.99
		393	ECC - S - ECC	Median survival: 3.5 year	

N=number, P= p-value, S=surgery, CRT[1]= 5-fluorouracil, leucovorin, and radiotherapy (4500 cGy), HR=hazard ratio, CI= 95% confidence interval, XP=capecitabine and cisplatin, CRT[2]=capecitabine and radiotherapy (45 Gy), ECC= Epirubicin, Cisplatin/Oxaliplatin, and Capecitabine, CRT[3]= 5-fluorouracil, cisplatin, and radiotherapy (45 Gy)

The South Korean ARTIST trial was the first study investigating the addition of radiotherapy to adjuvant chemotherapy for patients who underwent a curative gastric resection with a D2 lymph node dissection.[17] Between 2004 and 2008, 458 patients were randomized between either capecitabine plus cisplatin followed by chemoradiotherapy and two additional cycles capecitabine (n=230) or only capecitabine plus cisplatin regime (n=228). Overall, addition of chemoradiotherapy did not lead to a significant difference with regard to disease free survival (HR 0.740; 95% CI: 0.52-1.05, *P*=0.092) nor overall survival (HR 1.130; 95% CI: 0.78-1.65, *P*=0.527). Though, results showed a significant benefit in disease free survival benefit of chemoradiation in the subset of patients with node-positive disease. As a follow up of this trial the ARTIST 2 is ongoing and will evaluate the value of adjuvant chemotherapy and chemoradiation after a D2 lymph node dissection in patients with node positive gastric cancer. It should be notified that these trials are being performed in the Eastern world. Gastric cancer in the Eastern world differs compared to the Western world, regarding biology, epidemiology, stage, and prognosis. In the Eastern world gastric cancer is characterised by a higher

incidence, more distal located tumors, more often found in an early stage of the disease, more standardized surgery with a D2 lymph node dissection, and better prognosis.[18]
In order to determine the most optimal adjuvant therapy for the Western gastric cancer patient with advanced disease, the CRITICS trial was conducted and recently completed. In this randomized clinical trial patients with resectable gastric cancer were treated with three cycles of preoperative epirubicin, cisplatin/oxaliplatin, and capecitabine (ECC/EOC) and surgery with adequate lymph node dissection, followed by either three cycles of ECC/EOC (CT) or concurrent chemoradiation (CRT; 45 Gy in 25 fractions with 5- fluorouracil and cisplatin).[19] The first study results were presented during the ASCO convention in 2016 but are not published yet. The median follow up was 4.2 years. The 5-year overall survival was equal in both arms: 40.8% for CT and 40.9% for CRT, with a corresponding median survival of 3.5 years and 3.3 years. No differences were observed with regard to progression free survival across both arms (5-year 38.5% (CT) and 39.5% (CRT) with a median progression free survival of 2.3 years (CT) and 2.5 years (CRT)). Sixty-one % of the patients in the CT group and 63% in the CRT group started with postoperative treatment whereas 47% and 52% of the patients respectively were able to complete treatment. Further analyses of this trial are currently being performed. In the near future, the CRITICS-II trial aims to establish the most optimal preoperative regimen in resectable gastric cancer by comparing chemotherapy, chemotherapy and subsequent chemoradiotherapy, and chemoradiotherapy.

In 2014, Cao *et al.* aimed to assess the value of adjuvant chemotherapy in patients with gastric cancer after radical surgical resection in a meta-analysis.[20] Results showed that adjuvant chemotherapy can improve overall survival rate (RR=1.09, 95% CI: 1.06-1.23), as well as disease-free survival rate (RR=1.11, 95% CI: 1.07-1.15), and can reduce the relapse rate after curative resection (RR=0.79, 95% CI: 0.74-0.84).[20]

TARGETED THERAPY

Biomarker-targeted therapy has received increased attention in the recent years. Although high expectations, until this moment, targeted agents have no place in the standard care of curable Western gastric cancer patients after several trials obtained negative trial results. Currently, the INNOVATION trial is being conducted to investigate whether trastuzumab (a humanized monoclonal IgG antibody which inhibits the HER-2/neu receptor) or trastuzumab with pertuzumab shows more activity against standard chemotherapy after surgery in patients with HER-2 positive resectable gastric cancer and whether it can be safely administered (NCT02205047). The HER-2 positive rate in resectable gastric cancer is around 15%. Some studies suggested that HER-2 positive status is associated with a worse prognosis although the sample sizes of these studies were relatively small. Primary completion date for the INNOVATION trial is estimated for September 2020.

In contrast with the negative trial results of targeted therapy for curable gastric cancer, positive results are being achieved in trials with targeted therapy for incurable gastric cancer. The most important trials with targeted therapy in metastatic gastric cancer are discussed here and shown in *Table 4*.

In both neoadjuvant as adjuvant settings, trastuzumab has been shown to be effective regarding the treatment of HER-2 positive breast cancer. In 2010, the ToGA (Trastuzumab for Gastric Cancer) trial is conducted to evaluate the benefit of combining trastuzumab with chemotherapy versus chemotherapy alone for treatment of HER-2 positive incurable gastric or GEJ cancer.[21] Chemotherapy regimen consisted of either capecitabine plus cisplatin or 5-fluorouracil plus cisplatin every 3 weeks for six cycles or this chemotherapy regimen in combination with intravenous trastuzumab. Addition of trastuzumab significantly prolonged median overall survival compared to chemotherapy alone (HR 0.74; 95% CI: 0.60-0.91, *P*=0.005). Rates of overall grade 3 or 4 adverse events did not differ between both groups. [21] Since the results of this trial were published, trastuzumab in combination with chemotherapy could be considered as a new standard option for patients with HER-2 positive incurable gastric of GEJ cancer.

Table 4. Overview of studies investigating the impact of neoadjuvant chemotherapy combined with targeted agents in incurable gastric cancer

Trial	Years	N	Regimen	Results	*P*
ToGa trial[21]					
	2005 - 2008	298	tra - CT	HR 0.74 (CI: 0.60-0.91)	0.005
		296	CT		
AVAGAST trial[22]					
	2007 - 2008	387	bev - CT	HR 0.87 (CI 0.73-1.03)	0.100
		387	CT		
REGARD trial[23]					
	2009 - 2012	238	ram	HR 0.776 (CI: 0.60-1.00)	0.047
		117	placebo		
RAINBOW trial[24]					
	2010 - 2012	330	ram - pac	HR 0.81 (CI: 0.68-0.96)	0.017
		335	placebo - pac		

N=number, P= p-value, tra = trastuzumab, CT= chemotherapy, HR=hazard ratio, CI= 95% confidence interval, bev = bevacizumab, ram = ramucirumab, pac = paclitaxel

Additional targeted therapies for metastatic diseases have been investigated the latest years with promising results. Bevacizumab, a vascular endothelial growth factor A (VEGF-A) inhibitor, has earlier been adding to chemotherapy in colon- and rectal cancer. In 2011, the results of the AVAGAST trial (Avastin in Gastric Cancer) have been published.[22] This randomized, double-blind, placebo-controlled phase III trial evaluated the addition of an antiangiogenic agent to chemotherapy with regard to survival in patients with incurable gastric cancer. Patients received bevacizumab (vascular endothelial growth factor A, VEGF-A, inhibitor) 7.5mg/kg or placebo followed by cisplatin 80mg/m^2 on

day 1 plus capecitabine 1,000 mg/m^2 twice daily for 14 days every 3 weeks. Cisplatin was given for six cycles; capecitabine and bevacizumab were administered until disease progression of unacceptable toxicity. In total, 774 patients were enrolled, both equally assigned to each treatment group. Overall survival improved in the bevacizumab plus fluoropyrimidine-cisplatin group compared to the placebo plus fluoropyrimidine-cisplatin (HR 0.87; 95% CI 0.73-1.03; *P*=0.100). Although this trial did not reach its primary objective, it was shown that both median progression-free survival (6.7 vs. 5.3% months; HR 0.80; 95% CI: 0.68-0.93, *P*=0.004) and overall response rate (46.0% vs 37.4%; *P*=0.032) significantly improved with bevacizumab versus placebo.[22]

Furthermore, increasing attention has been given to ramucirumab, a vascular endothelial growth factor (VEGF) receptor-2 antagonist. Recently the REGARD trial aimed to assess whether ramucirumab prolonged survival in patients with incurable gastric cancer.[23] Between 2009 and 2012, 355 patients were randomly assigned to receive either ramucirumab (8mg/kg, n=238) or best supportive care (n=117). Ramucirumab improved overall survival (HR 0.78; 95% CI: 0.60-1.00, *P*=0.047) and adverse events were mostly similar between groups.[23] This international trial showed that ramucirumab, as a single drug, is the first biological treatment prolonging survival in patients with advanced gastric or GEJ adenocarcinoma after first-line chemotherapy. Between 2010 and 2012, 665 patients were randomized in the RAINBOW trial with previously treated advanced gastric cancer to receive either ramucirumab (n=330) or placebo (n=335), plus paclitaxel.[24] Overall survival was significantly higher in the ramucirumab plus paclitaxel group than in the placebo plus paclitaxel group (HR 0.81; 95% CI: 0.68-0.96, *P*=0.017).[24] From that moment, this combination of targeted therapy is regarded as a new standard second-line treatment for patients with advanced gastric cancer.

CONCLUSIONS

Gastric cancer is a common and highly lethal malignancy. The average age of patients has become higher in the past decades, leading to a higher rate of comorbidities to account for during treatment. This development gave rise to several new considerations to the approach of treatment of gastric cancer in the Western world.

Gastrectomy is considered as high-risk surgery in the Western world. Despite improved outcomes of gastric resections in centralized, high-volume centres, gastrectomies are still associated with surgical morbidity rates of 39% and mortality rates of approximately 4%.[25,26] It is well known that morbidity rates in gastrectomies are greatly influenced by age. Previous studies showed that sarcopenia and frailty of patients, which are frequently seen in older gastric cancer patients, are strong risk factors to experience severe problems once a complication occurs.[27] This emphasizes the need for careful consideration to perform a gastrectomy (and to receive adjuvant therapy) when patients are not able to complete neoadjuvant therapy.

Secondly, compliance of patients to therapy is an essential part in the multimodal treatment of gastric cancer. Several trials showed that protocol adherence to postoperative treatment is poor. For instance, treatment was completed as planned by 42% of patients in the MAGIC trial and in approximately 50% in the CRITICS trial.[9] Especially for the frail, older patient, the rate of postoperative therapy compliance is low, most likely due to the interplay between their pre-existing presence of comorbidity, diminished physical condition and postoperative morbidity. Protocol adherence to *preoperative* treatment is evidently higher because these patients did not (yet) undergo gastric resection, which is considered high-impact surgery. For instance, more than 80% of the patients in the CRITICS trial were able to complete preoperative treatment. Considering the growing population of elderly patients, neo-adjuvant treatment is therefore the future in the multimodal treatment of gastric cancer in the Western world. Ongoing and future studies will determine the most optimal neoadjuvant therapy (chemotherapy and/ or radiation) combined with optimal dose and timing.

Lastly, due to the heterogeneity of older gastric cancer patients, tailored treatment for these patients is needed. Diagnostic tools like staging/imaging, molecular/ genetic tools, and histological typing should be targeted, and should lead, together with the consideration of comorbidities, to a personalized treatment (*Figure 1*). This approach requires a multidisciplinary collaboration between medical oncologists, radiologists, nuclear oncologists, radiation oncologists, pathologists, nutritionists, and surgeons.

In conclusion, neoadjuvant therapy is a key element in the multimodal way of treatment of gastric cancer in the Western world. This is an inevitable consequence of the ageing population, since neoadjuvant treatment is associated with a better compliance. For this future personalized treatment of gastric cancer, a multidisciplinary approach remains crucial.

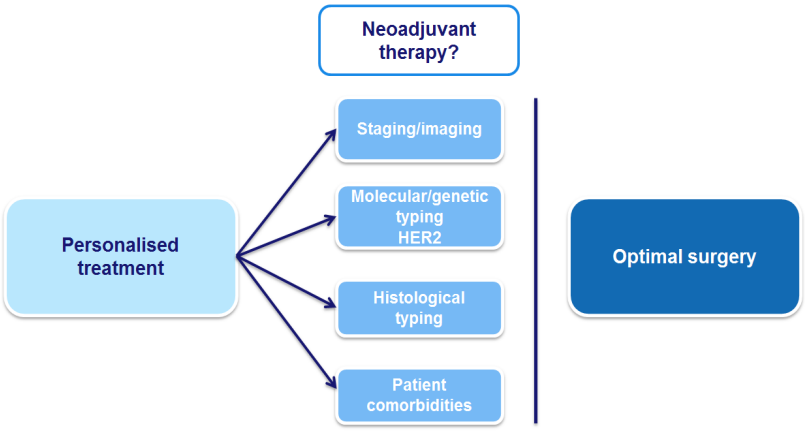

Figure 1. Tailoring treatment for gastric cancer patients in the Western world

REFERENCES

1. Ferlay J, Soerjomataram I, Dikshit R, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer 2015; 136(5): E359-86.
2. Papenfuss WA, Kukar M, Oxenberg J, et al. Morbidity and mortality associated with gastrectomy for gastric cancer. Ann Surg Oncol 2014; 21(9): 3008-14.
3. Cuschieri A, Weeden S, Fielding J, et al. Patient survival after D1 and D2 resections for gastric cancer: long-term results of the MRC randomized surgical trial. Surgical Co-operative Group. Br J Cancer 1999; 79(9-10): 1522-30.
4. Songun I, Putter H, Kranenbarg EM, et al. Surgical treatment of gastric cancer: 15-year follow-up results of the randomised nationwide Dutch D1D2 trial. Lancet Oncol 2010; 11(5): 439-49.
5. Degiuli M, Sasako M, Ponti A, et al. Randomized clinical trial comparing survival after D1 or D2 gastrectomy for gastric cancer. Br J Surg 2014; 101(2): 23-31.
6. Hartgrink HH, van de Velde CJ, Putter H, et al. Extended lymph node dissection for gastric cancer: who may benefit? Final results of the randomized Dutch gastric cancer group trial. J Clin Oncol 2004; 22(11): 2069-77.
7. Hermans J, Bonenkamp JJ, Boon MC, et al. Adjuvant therapy after curative resection for gastric cancer: meta-analysis of randomized trials. J Clin Oncol 1993; 11(8): 1441-7.
8. Hartgrink HH, van de Velde CJ, Putter H, et al. Neo-adjuvant chemotherapy for operable gastric cancer: long term results of the Dutch randomised FAMTX trial. Eur J Surg Oncol 2004; 30(6): 643-9.
9. Cunningham D, Allum WH, Stenning SP, et al. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. N Engl J Med 2006; 355(1): 11-20.
10. Ychou M, Boige V, Pignon JP, et al. Perioperative chemotherapy compared with surgery alone for resectable gastroesophageal adenocarcinoma: an FNCLCC and FFCD multicenter phase III trial. J Clin Oncol 2011; 29(13): 1715-21.
11. Schuhmacher C, Gretschel S, Lordick F, et al. Neoadjuvant chemotherapy compared with surgery alone for locally advanced cancer of the stomach and cardia: European Organisation for Research and Treatment of Cancer randomized trial 40954. J Clin Oncol 2010; 28(35): 5210-8.
12. Yang Y, Yin X, Sheng L, et al. Perioperative chemotherapy more of a benefit for overall survival than adjuvant chemotherapy for operable gastric cancer: an updated Meta-analysis. Scientific reports 2015; 5: 12850.
13. Stahl M, Walz MK, Stuschke M, et al. Phase III comparison of preoperative chemotherapy compared with chemoradiotherapy in patients with locally advanced adenocarcinoma of the esophagogastric junction. J Clin Oncol 2009; 27(6): 851-6.
14. van Hagen P, Hulshof MC, van Lanschot JJ, et al. Preoperative chemoradiotherapy for esophageal or junctional cancer. N Engl J Med 2012; 366(22): 2074-84.

15. Leong T, Smithers BM, Michael M, et al. TOPGEAR: a randomised phase III trial of perioperative ECF chemotherapy versus preoperative chemoradiation plus perioperative ECF chemotherapy for resectable gastric cancer (an international, intergroup trial of the AGITG/TROG/EORTC/NCIC CTG). BMC Cancer 2015; 15: 532.
16. Macdonald JS, Smalley SR, Benedetti J, et al. Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction. N Engl J Med 2001; 345(10): 725-30.
17. Park SH, Sohn TS, Lee J, et al. Phase III Trial to Compare Adjuvant Chemotherapy With Capecitabine and Cisplatin Versus Concurrent Chemoradiotherapy in Gastric Cancer: Final Report of the Adjuvant Chemoradiotherapy in Stomach Tumors Trial, Including Survival and Subset Analyses. J Clin Oncol 2015; 33(28): 3130-6.
18. Bickenbach K, Strong VE. Comparisons of Gastric Cancer Treatments: East vs. West. J Gastric Cancer 2012; 12(2): 55-62.
19. Dikken JL, van Sandick JW, Swellengrebel HA, et al. Neo-adjuvant chemotherapy followed by surgery and chemotherapy or by surgery and chemoradiotherapy for patients with resectable gastric cancer (CRITICS). BMC Cancer 2011; 11: 329.
20. Cao J, Qi F, Liu T. Adjuvant chemotherapy after curative resection for gastric cancer: a meta-analysis. Scan J Gastroenterol 2014; 49(6): 690-704.
21. Bang YJ, Van Cutsem E, Feyereislova A, et al. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. Lancet 2010; 376(9742): 687-97.
22. Ohtsu A, Shah MA, Van Cutsem E, et al. Bevacizumab in combination with chemotherapy as first-line therapy in advanced gastric cancer: a randomized, double-blind, placebo-controlled phase III study. J Clin Oncol 2011; 29(30): 3968-76.
23. Fuchs CS, Tomasek J, Yong CJ, et al. Ramucirumab monotherapy for previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (REGARD): an international, randomised, multicentre, placebo-controlled, phase 3 trial. Lancet 2014; 383(9911): 31-9.
24. Wilke H, Muro K, Van Cutsem E, et al. Ramucirumab plus paclitaxel versus placebo plus paclitaxel in patients with previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (RAINBOW): a double-blind, randomised phase 3 trial. Lancet Oncol 2014; 15(11): 1224-35.
25. Bartlett EK, Roses RE, Kelz RR, et al. Morbidity and mortality after total gastrectomy for gastric malignancy using the American College of Surgeons National Surgical Quality Improvement Program database. Surgery 2014; 156(2): 298-304.
26. Pasquer A, Renaud F, Hec F, et al. Is Centralization Needed for Esophageal and Gastric Cancer Patients With Low Operative Risk?: A Nationwide Study. Ann Surg 2016; 264(5):823-830.
27. Wagner D, DeMarco MM, Amini N, et al. Role of frailty and sarcopenia in predicting outcomes among patients undergoing gastrointestinal surgery. World J Gastrointest Surg 2016; 8(1): 27-40.

CHAPTER 10

SUMMARY AND GENERAL DISCUSSION

SUMMARY AND GENERAL DISCUSSION

Since Theodor Billroth performed the first successful gastric resection in 1881, surgery became the mainstay for the treatment of gastric cancer up to the present day. Whereas limited lymph node dissection, also known as D1 dissection, used to be standard of care in the Western world, an extensive lymph node dissection (D2) became standard of care after the long-term results of the Dutch Gastric Cancer Trial showed a survival benefit for this type of dissection.[1] Nevertheless, in the Western world, outcomes for gastric cancer patients remain dismal with 5-year survival rates of 25%.[2]

To improve survival addition of (neo)adjuvant chemotherapy and/or radiotherapy has been studied. Eventually, two randomized clinical trials changed current practice with multimodality treatment for advanced gastric cancer: the US Intergroup 0116 trial and the British MAGIC trial.[3,4] The first trial showed a survival benefit, with overall survival increasing from 27 months to 36 months when surgery was followed by adjuvant chemoradiotherapy, whereas the MAGIC trial showed a 5-year survival benefit of 10% with the addition of perioperative chemotherapy. As these trials had different study designs and inclusion criteria study results could not be compared directly. To this means, the *'ChemoRadiotherapy after Induction chemotherapy In Cancer of the Stomach'* trial was initiated, abbreviated as the CRITICS trial.[5] In this trial, patients from The Netherlands, Denmark, and Sweden were upfront randomized to undergo three cycles of chemotherapy, followed by surgery with an adequate D1+ lymph node dissection, followed by either chemotherapy (*control arm*) or chemoradiotherapy (*experimental arm*).

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

High surgical quality in multimodality gastric cancer trials has shown to be a crucial but demanding part. Although adjuvant chemoradiotherapy became standard of care in the US after publishing the results of the Intergroup 0116 trial, this trial had a major shortcoming. Because of the quality of surgery – only 10% of the patients underwent the intended D2 lymph node dissection – the reliability of the primary outcomes of this trial can be questioned as chemoradiothearpy may have been more effective because of the poor surgical quality.[3] To prevent this kind of issue, surgical quality assurance in the CRITICS trial was strictly monitored. In the CRITICS trial, a D1+ lymph node dissection was mandatory, consisting of removal of lymph node stations of 1-9 and 11. All participating surgeons received an instruction book and DVD. Furthermore, feedback on the number of retrieved lymph nodes to the participating surgeons was given by the study coordinator. This was performed in order to encourage to harvest a minimum of 15 lymph nodes. This parameter is one of the most important surgical quality indicators and is associated with improved survival.[6] Although the number of retrieved lymph nodes is currently under debate, as an increasing number of harvested

lymph nodes seems to be associated with improved outcomes, the number of 15 lymph nodes is still widely used.[7] In 73% of the patients in the CRITICS trial (**Chapter 1**) at least 15 lymph nodes were removed (surgicopathological compliance). This number was 55% at the beginning of the trial in 2007 and rose to 90% in 2015. This improvement over time is most probably a consequence of the quality assurance within the trial and centralisation of the gastric cancer surgery in the Netherlands. In 2012, a minimum volume of 10 gastric resections per year per institution was incorporated by the Dutch Healthcare Organisation in order to improve the outcomes after gastric cancer surgery.[8] Since 2013, this norm was increased to 20 resections. Furthermore, the Maruyama Index, one of the most important proven parameters in gastric cancer surgery, was calculated for each patient.[9,10] The lower the Maruyama Index, the better the surgical quality. In the Intergroup 0116 trial and in the Dutch Gastric Cancer Trial a median Maruyama Index of 70 and 26 were calculated, whereas a median Maruyama Index of 1 was calculated in the CRITICS trial. These results showed the success of the strategy aimed to optimize high surgical quality in the CRITICS trial. A great part of this success is due to the performance of the surgeon, who is found in the centre of a multidisciplinary team consisting of radiation oncologists, medical oncologists, gastroenterologists, pathologists, and anaesthesiologists. However, the awareness and the dedication of the pathologist may also play a role. Recently it was shown that the pathology technician is an important factor influencing the total number of lymph nodes reported and that ex vivo dissection of lymph nodes during a gastric resection optimizes lymph node yield.[11,12] All the more these results should be considered as a team effort.

Although there is consensus nowadays that an extensive lymph node dissection is favoured over a limited lymph node dissection, the increased risk of postoperative morbidity and mortality accompanied with an extended lymph node dissection should be taken into account. Gastric cancer surgery is considered high-risk surgery. The risk on postoperative complications is around 40% and postoperative mortality around 5%.[13,14] In the CRITICS trial, postoperative morbidity was moderate with 47%, without resulting in a high postoperative mortality, as this rate was low with only 1.6% (**Chapter 2**). This postoperative morbidity percentage is slightly higher than previous randomised gastric cancer trials, among them the Medical Research Council (46%) and the Dutch Gastric Cancer Trial (43%).[15,16] An explanation for the slightly increased morbidity rate in the CRITICS trial might be the growing awareness to register complications and the more vulnerable status of patients due to preoperative chemotherapy. Postoperative mortality in this study was most often caused by complications due to anastomotic leakage (5 of the 14 patients). In the literature, anastomotic leakage after gastrectomy has been reported in 1.2%-5.0% of the cases, with a related mortality of 21.1%.[17,18]

Patients that did not complete preoperative chemotherapy, mainly due to toxicity, were more than twice as likely to develop postoperative complications (OR=2.15, *P*=0.003) and had a higher postoperative mortality rate (**Chapter 2**). Furthermore, undergoing a splenectomy (OR=2.82, *P*=0.012) was associated with increased risk for postoperative

complications. Recently the randomised JCOG-0110 trial showed that performing a splenectomy was associated with an increased risk of complications without improving survival.[19] In accordance with these results our findings emphasize to not perform a splenectomy unless there is direct tumour ingrowth or the radicalism of the resection is questioned.[19] Additionally a total gastrectomy was associated with a greater risk for morbidity compared to subtotal gastrectomy (OR=1.88, *P*=0.001), which has been described earlier in literature.[20]

The CRITICS trial was criticized for the moment of upfront randomization. Opponents stated that the quality of surgery might be influenced by the timing of randomization, as the surgeon was aware of the adjuvant treatment strategy that would follow. We therefore studied the quality of surgery in relation to randomization in **Chapter 3**. Surgicopathological compliance, the Maruyama Index, surgical compliance to protocol (aiming for extended lymph dissection), and surgical contamination (removal of one or more lymph node stations outside the intended extent of resection) did not differ between study arms. These findings show that upfront randomization was not associated with differences in surgical quality between the study arms and emphasize the reliability of the primary outcomes of the CRITICS trial. Furthermore, a great advantage of this design of the CRITICS trial is the insight in the whole chain of multimodality treatment. As a consequence, the low compliance of completing treatment according to the study protocol was observed, a highly important issue, which will be further pursued in part IV of this thesis. On the contrary, a disadvantage of this design is that a per-protocol analysis is needed to investigate whether there are survival differences between both study arms for the patients who underwent the *actual* intended adjuvant treatment (around the 50% of all patients). By definition, this analysis is limited since the two treatment arms are not inherently balanced as randomization did not took place at that moment.

PART II – INFLUENCE OF HOSPITAL VOLUME OF GASTRIC CANCER SURGERY

Since Luft et al first published about the possible association between outcomes and hospital volume, surgical hospital volume has become a point of discussion up to the present day.[21] Thereafter, several publications by Birkmeyer followed around 1990 regarding improved outcomes in high volume centres for complex surgical procedures. This resulted in an increasing consensus that gastric cancer surgery should be centralized.[22,23] In several countries, a minimum volume standard has been incorporated. Gastric cancer surgery has been centralized in Great-Britain since 2001 and gastric cancer surgery was restricted to five hospitals in Denmark since 2003.[24,25] After the centralisation in Denmark in 2003, improved outcomes were observed in 2008 as the proportion of removal of 15 lymph nodes increased from 19% to 86% and postoperative mortality decreased from 8% to 2%, respectively.[24] Since 2013, a minimum volume of 20 gastric resections per year per institution was established in

The Netherlands to improve the outcomes after gastric cancer surgery.[8] The number of 20 resections is based on clinical consensus, as literature is not unanimous regarding this threshold. Theoretically, centralisation of gastric cancer surgery should lead to improved quality of surgery and eventually a lower recurrence rate and better survival rates. Many studies investigated the relationship of hospital volume and postoperative mortality, as data of quality of surgery and data of recurrences often were lacking. We linked data of the Dutch patients in the CRITICS trial, based on the date of surgery, with data of annual hospital volume of the Netherlands Cancer Registry. In that way, the detailed data regarding quality of surgery and recurrences from the CRITICS trial could be combined with annual hospital volume from the Netherlands Cancer Registry. First, in **Chapter 4**, we investigated the influence of hospital volume on surgical quality and postoperative morbidity. It was shown that increasing hospital volume was associated with a higher surgicopathological compliance, higher surgical compliance to protocol, and a lower Maruyama Index. Subsequently, we investigated whether this short-term benefit also resulted in improved long-term outcomes (**Chapter 5**). In other words; does surgery performed in high volume hospitals result in a decreased recurrence rate and an improved overall survival for gastric cancer patients? We demonstrated in the CRITICS trial, that patients who had surgery performed in hospitals with more than 20 gastric resections per year had better overall survival and better disease-free survival.

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

Elderly patients are scarcely represented in randomised clinical trials and therefore population-based observational studies may be a suitable way to gain new insights in treatment strategies and survival outcomes for this group. In **Chapter 6**, treatment strategies and relative survival of patients with gastric cancer aged 70+ were compared across five different European countries, performed by the European Registration of Cancer Care (EURECCA) Upper Gastrointestinal (UGI) group. No significant differences in treatment strategy were observed in patients with stage I disease. On the contrary, clear differences in treatment strategy were observed in stage II and stage III disease. Possible explanations for these findings might be disparities in health status of the gastric cancer patients in different countries with as a consequence different treatment decisions. Secondly, differences in cultural background may be an important factor when shared decisions are made. In this study, countries with higher proportions of patients undergoing surgery and chemotherapy had better survival for patients with stages II or III disease. The usual flaws accompanied with population-based studies, such as residual confounding and confounding by indication, should be taken into account when interpreting these results.

Another subgroup of patients for whom the optimal treatment strategy is unclear, is the group of gastric cancer patients with metastatic disease (stage IV). According to the

current European clinical practice guidelines, stage IV patients should be considered for palliative chemotherapy.[26] It improves survival, reduces disease-related symptoms, and improves quality of life compared to best supportive care alone.[26] The role of a palliative resection for stage IV disease has been, however, under debate for a long time. Recently, the results of the REGATTA trial were presented. This is the first randomized clinical trial investigating the addition of a gastric resection to chemotherapy in gastric cancer patients with one non-curable factor with regard to survival.[27] No overall survival benefit was shown for the surgery and chemotherapy group over chemotherapy alone group. Therefore the authors concluded that a palliative resection could not be justified anymore in this group of patients. The German prospective phase II AIO-FLOT3 trial indicated a favourable survival for patients with limited metastatic disease having surgery after neoadjuvant chemotherapy, and this is further being evaluated in the ongoing randomized RENAISSANCE trial.[28,29] Due to the uncertainty regarding the optimal treatment strategy for metastatic gastric cancer patients, in particular the role of palliative resection, applied treatment strategy in daily practice and its relation to survival is unknown. Therefore, an EURECCA UGI study was performed to investigate this using national datasets of Belgium, Denmark, The Netherlands, Norway, and Sweden (**Chapter 7**). Variation was observed in the use of a gastrectomy for patients across these countries and wide variation was seen for the two countries with data on chemotherapy. The proportion of palliative gastric resections varied from 8% in the Netherlands to 18% in Belgium, whereas the use of chemotherapy was 39% in the Netherlands and 63% in Belgium. The lack of data on administration of chemotherapy in Denmark, Norway, and Sweden highlights the non-uniformity of national data registries across Europe.

Quality of life was not recorded in the REGATTA trial nor in the national registries. Although this is an essential outcomes for this group of patients with sober survival outcomes. It might be that these patients chose for a better quality of life instead of prolonged survival. Nevertheless, no validated quality of life tools of patients with gastric cancer in a palliative setting are currently available.[30] This underlines that a well conducted prospective study for metastatic gastric cancer patients with special attention to quality of life is needed in the future. Similar to the previous study, this study was also limited by (hidden) confounders such as timing of surgery (emergency/elective), extent of metastases, comorbidity, performance status, type and chemotherapy regimen. Unfortunately this information was not collected in national registries.

PART IV – DIRECTIONS FOR THE FUTURE

Although the intention-to-treat analysis of the CRITICS trial was not able to show a survival benefit for the chemoradiotherapy study arm compared to the chemotherapy arm, important lessons can be learned from this trial.[31] Compliance of patients to complete study protocol has shown to be low in the CRITICS trial, as only 47% and

52% of the patients of the chemoradiotherapy and the chemotherapy study arm respectively, completed treatment according to the study protocol. For future treatment, a neoadjuvant treatment strategy should therefore be considered. An overview of the current evidence of neoadjuvant treatment in gastric cancer is given in **Chapter 8**. The Dutch FAMTX trial (also known as the POCOM (Preoperative Chemotherapy for Operable Gastric Cancer) trial was one of the first trials investigating the added value of neoadjuvant chemotherapy and surgery in resectable gastric cancer over surgery alone.[32] Due to poor accrual and no found difference between the arms during an interim analysis the trial was prematurely closed without showing a beneficial effect of the preoperative FAMTX regimen. A landmark study in the field of perioperative chemotherapy is the earlier mentioned British MAGIC trial. This trial showed a survival benefit with perioperative chemotherapy and surgery over surgery alone.[4] Similar results as in the MAGIC trial were achieved in the French FNLCLCC and FFCD trial with perioperative chemotherapy.[33] On the other hand, the EORTC 40954 was not able to show a survival benefit, possible due to prematurely closing.[34] Application of radiotherapy in the neoadjuvant setting is growing. The German POET trial investigated whether the addition of chemoradiotherapy in the neoadjuvant setting compared to chemotherapy alone would lead to survival benefit.[35] A trend was observed but did not reach statistical significance in favour of the chemoradiotherapy arm. In addition to the Intergroup 0116 trial, which has been described extensively earlier, the South Korean ARTIST trial was an important trial investigating the addition of radiotherapy to adjuvant chemotherapy for patients who underwent a curative gastric resection with a D2 lymph node dissection (removal of station 1,3, 5-9 during partial gastrectomy and station 1-11 during total gastrectomy).[3,36] Although no difference in overall survival and disease free survival was observed in the entire study population, positive results were found for a subset of patients with node positive gastric cancer. Furthermore, increased attention has arisen for the biomarker-targeted therapy for gastric cancer. Although at this moment, targeted agents do not have a place in standard care of curable Western gastric cancer patients due to several negative trial results. On the contrary, positive results are obtained with targeted agents for incurable gastric cancer patients. The ToGa trial and the AVAGAST trial investigated the efficacy of trastuzumab and bevacizumab, respectively, with standard regime of chemotherapy compared to chemotherapy alone.[37,38] Furthermore, increasing attention has been given to ramucirumab, a vascular endothelial growth factor (VEGF) receptor-2 antagonist. The REGARD trial showed that ramucirumab, as a single drug, is the first biological treatment prolonging survival in patients with advanced gastric or GEJ adenocarcinoma after first-line chemotherapy.[39] In the RAINBOW trial, an overall survival benefit was shown for patients in the ramucirumab plus paclitaxel group compared to the placebo plus paclitaxel group. As a consequence, this became the new standard second-line treatment for patients with advanced gastric cancer.[40]

For the future, it will be important to investigate whether efficacy of standard treatment forms apply for certain subgroups of patients as well. As earlier described, perioperative chemotherapy and surgery became standard of care in most countries of Europe since the results of the MAGIC trial.[4] No subgroup analysis were performed for signet ring cell adenocarcinomas, although the survival of this group of patients is significantly worse compared to the survival of non-signet ring cell adenocarcinomas.[41] Whether the optimal treatment for this type of tumour with such an aggressive behaviour consisted of neoadjuvant chemotherapy with delayed surgery was therefore questioned by many clinicians. A French retrospective multicentre study was performed to investigate this further.[42] Multivariate analysis showed that pre-operative chemotherapy was an independent predictor of poor survival (HR=1.4, 95% CI 1.1-1.9, p-value=0.042).[42] Following these results, the PRODIGE-19-FFCD1103-ADCI002 phase II/III trial currently aims to evaluate the appropriate perioperative therapeutic strategy for resectable signet ring cell adenocarcinomas in a prospective randomized study.[43] Patients will be randomized between standard perioperative (ECF) chemotherapy and primary surgery followed by adjuvant chemotherapy (ECF). This is only one example which illustrates the importance of subgroup analysis and emphasizes that optimal treatment strategy in several subgroups of patients can differ compared to the standard treatment.

FUTURE PERSPECTIVES

Obtaining the optimal treatment strategy for locally advanced gastric cancer in the Western world is a challenging task. After the Intergroup 0116 trial and the MAGIC trial changed current practice by showing a survival benefit with adjuvant chemoradiotherapy and perioperative chemotherapy, respectively, the results of the CRITICS trial were long awaited to determine the best adjuvant treatment approach. In the intention-to-treat analysis, no survival differences between both study arms were observed.[31] Although future subgroup analyses of the CRITICS trial can still bear survival benefit for one of treatment strategies, there was hope to determine one superior adjuvant treatment strategy. Nevertheless, highly important lessons can be learned from this trial for the future of treatment of gastric cancer. First, despite promising results in other types of cancer, the addition of chemotherapy and/or radiotherapy to surgery in gastric cancer so far has limited survival benefits. Surgery remains the cornerstone of treatment for advanced gastric cancer in the Western world up to the present day. Therefore surgery in gastric cancer trials should get the subsequent attention it deserves. Although this statement sounds straightforward, there are still randomized clinical trials, which are still considered the highest level of evidence, without strict surgical quality assurance programmes or even without a surgical part in the study protocol. As a consequence, reliability of primary outcomes of the trial might be questioned. To prevent this, a strict surgical quality assurance program should be an obligated part of the study protocol. The succeeding of the strict surgical quality assurance program within the CRITICS trial was presented in this thesis and can serve as an example for future randomized clinical gastric cancer trials.

In addition to the importance of surgical quality assurance in the CRITICS trial, this trial showed us the importance of *timing* of treatment. As adjuvant treatment strategies are compared in the CRITICS trial (which resulted in low compliance), efficacy of the multimodality treatment regimens might have been underestimated. Therefore *neo*-adjuvant multimodality treatment might be the future, taking into account the higher compliance accompanied with neo-adjuvant treatment compared to adjuvant treatment. Other ongoing randomized clinical trials, such as the TOPGEAR trial and the CRITICS-II trial, are focussing on comparing different neoadjuvant treatment strategies in gastric cancer. Obtaining the optimal treatment strategy together with optimal timing will be the key to improve outcomes for patients with locally advanced gastric cancer in the Western world.

Looking with a glance on aspects in the field of gastric cancer to improve outcomes further, centralization of gastric cancer surgery is one of them. The studies in part III of this thesis showed, as one of the first studies, that surgery in high volume hospitals was associated with both improved quality of surgery and better overall survival. These results emphasise the value of centralisation of gastric cancer surgery in the Western world. Furthermore, it underlines the importance of clinical pathways in

hospitals for gastric cancer patients. In that way, the most optimal care can be given by a multidisciplinary team with a central role for the surgeon. With increasing centralisation of gastric cancer surgery in the Netherlands it is expected that outcomes will improve further. However, some reservations should be made as, after all, tumour and nodal stage remain the most important prognostic factors for overall survival.

Randomized clinical gastric cancer trials are often performed within a small framework of inclusion criteria and exclusion of elderly patients. Nowadays population based cohort studies are highly valuable as these results can be directly translated to daily practice. Especially for certain subgroups, among them elderly, this is a suitable alternative in order to determine appropriate guidelines. Collaboration of European countries is needed to reduce variation in treatment strategies and to improve eventually the outcomes of gastric cancer patients. These goals are aimed by the EURECCA UGI Audit.

In conclusion, by combining the optimal treatment strategy, the appropriate timing of it, further centralization of gastric cancer surgery, and collaboration between European audits, the future will give us possibilities to enhance the outcomes of gastric cancer patients in the Western world.

REFERENCES

1. Songun I, Putter H, Kranenbarg EM, et al. Surgical treatment of gastric cancer: 15-year follow-up results of the randomised nationwide Dutch D1D2 trial. Lancet Oncol 2010; 11(5): 439-49.
2. Rosa F, Alfieri S, Tortorelli AP, et al. Trends in clinical features, postoperative outcomes, and long-term survival for gastric cancer: a Western experience with 1,278 patients over 30 years. World J Surg Oncol 2014; 12: 217.
3. Macdonald JS, Smalley SR, Benedetti J, et al. Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction. New Engl J Med 2001; 345(10): 725-30.
4. Cunningham D, Allum WH, Stenning SP, et al. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. New Engl J Med 2006; 355(1): 11-20.
5. Dikken JL, van Sandick JW, Swellengrebel HA, et al. Neo-adjuvant chemotherapy followed by surgery and chemotherapy or by surgery and chemoradiotherapy for patients with resectable gastric cancer (CRITICS). BMC cancer 2011; 11: 329.
6. Coburn NG, Swallow CJ, Kiss A, et al. Significant regional variation in adequacy of lymph node assessment and survival in gastric cancer. Cancer 2006; 107(9): 2143-51.
7. Seevaratnam R, Bocicariu A, Cardoso R, et al. How many lymph nodes should be assessed in patients with gastric cancer? A systematic review. Gastric Cancer 2012; 15 Suppl 1: S70-88.
8. Nederlandse Vereniging voor GastroIntestinale Chirurgie; http://nvgic.nl/sites/nvgic.nl/files/Richtlijn%20maagcarcinoom.pdf;[accessed at 22-06-2017]
9. Peeters KC, Hundahl SA, Kranenbarg EK, et al. Low Maruyama index surgery for gastric cancer: blinded reanalysis of the Dutch D1-D2 trial. World J Surg 2005; 29(12): 1576-84.
10. Hundahl SA, Peeters KC, Kranenbarg EK, et al. Improved regional control and survival with "low Maruyama Index" surgery in gastric cancer: autopsy findings from the Dutch D1-D2 Trial. Gastric Cancer 2007; 10(2): 84-6.
11. Schoenleber SJ, Schnelldorfer T, Wood CM, et al. Factors influencing lymph node recovery from the operative specimen after gastrectomy for gastric adenocarcinoma. Journal Gastrointest Surg 2009; 13(7): 1233-7.
12. Afaneh C, Levy A, Selby L, et al. Ex Vivo Lymphadenectomy During Gastrectomy for Adenocarcinoma Optimizes Lymph Node Yield. J Gastrointest Surg 2016; 20(1): 165-71; discussion 71.
13. Bosing NM, Goretzki PE, Roher HD. Gastric cancer: which patients benefit from systematic lymphadenectomy? Eur J Surg Oncol 2000; 26(5): 498-505.
14. Bartlett EK, Roses RE, Kelz RR, et al. Morbidity and mortality after total gastrectomy for gastric malignancy using the American College of Surgeons National Surgical Quality Improvement Program database. Surgery 2014; 156(2): 298-304.
15. Cuschieri A, Fayers P, Fielding J, et al. Postoperative morbidity and mortality after D1 and D2 resections for gastric cancer: preliminary results of the MRC randomised controlled surgical trial. The Surgical Cooperative Group. Lancet 1996; 347(9007): 995-9.
16. Bonenkamp JJ, Songun I, Hermans J, et al. Randomised comparison of morbidity after D1 and

D2 dissection for gastric cancer in 996 Dutch patients. Lancet 1995; 345(8952): 745-8.
17. Tsou CC, Lo SS, Fang WL, et al. Risk factors and management of anastomotic leakage after radical gastrectomy for gastric cancer. Hepato-gastroenterology 2011; 58(105): 218-23.
18. Kawamura Y, Satoh S, Suda K, et al. Critical factors that influence the early outcome of laparoscopic total gastrectomy. Gastric Cancer : 2015; 18(3): 662-8.
19. Sano T, Sasako M, Mizusawa J, et al. Randomized Controlled Trial to Evaluate Splenectomy in Total Gastrectomy for Proximal Gastric Carcinoma. Ann Surg 2017; 265(2): 277-83.
20. Bozzetti F, Marubini E, Bonfanti G, et al. Subtotal versus total gastrectomy for gastric cancer: five-year survival rates in a multicenter randomized Italian trial. Italian Gastrointestinal Tumor Study Group. Ann Surg 1999; 230(2): 170-8.
21. Luft HS, Bunker JP, Enthoven AC. Should operations be regionalized? The empirical relation between surgical volume and mortality. New Engl J Med 1979; 301(25): 1364-9.
22. Birkmeyer JD, Sun Y, Goldfaden A, et al. Volume and process of care in high-risk cancer surgery. Cancer 2006; 106(11): 2476-81.
23. Birkmeyer JD, Sun Y, Wong SL, et al. Hospital volume and late survival after cancer surgery. Ann Surg 2007; 245(5): 777-83.
24. Jensen LS, Nielsen H, Mortensen PB et al. Enforcing centralization for gastric cancer in Denmark. Eur J Surg Oncol 2010; 36 Suppl 1: S50-4.
25. Association of Upper Gastrointestinal Surgeons of Great Britain and Ireland (AUGIS), Guidance on minimum surgeon volumes [Available from: http://www.augis.org/wp-content/uploads/2014/05/AUGIS_recommendations_on_Minimum_Volumes.pdf , accessed at 05-06-2017]
26. Waddell T, Verheij M, Allum W, et al. Gastric cancer: ESMO-ESSO-ESTRO clinical practice guidelines for diagnosis, treatment and follow-up. Eur J Surg Oncol 2014; 40(5): 584-91.
27. Fujitani K, Yang HK, Mizusawa J, et al. Gastrectomy plus chemotherapy versus chemotherapy alone for advanced gastric cancer with a single non-curable factor (REGATTA): a phase 3, randomised controlled trial. Lancet Oncol 2016; 17(3): 309-18.
28. Al-Batran SE, Homann N, Pauligk C, et al. Effect of Neoadjuvant Chemotherapy Followed by Surgical Resection on Survival in Patients With Limited Metastatic Gastric or Gastroesophageal Junction Cancer: The AIO-FLOT3 Trial. JAMA oncology 2017; 3(9): 1237-44.
29. Al-Batran SE, Goetze TO, Mueller DW, et al. The RENAISSANCE (AIO-FLOT5) trial: effect of chemotherapy alone vs. chemotherapy followed by surgical resection on survival and quality of life in patients with limited-metastatic adenocarcinoma of the stomach or esophagogastric junction - a phase III trial of the German AIO/CAO-V/CAOGI. BMC cancer 2017; 17(1): 893.
30. Karpeh MS, Jr. Palliative treatment and the role of surgical resection in gastric cancer. Dig Surg 2013; 30(2): 174-80.
31. Cats A, Jansen EPM, van Grieken NCT, et al. Chemotherapy versus chemoradiotherapy after surgery and preoperative chemotherapy for resectable gastric cancer (CRITICS): an international, open-label, randomised phase 3 trial. Lancet Oncol 2018; 19 (5):616-628.
32. Hartgrink HH, van de Velde CJ, Putter H, et al. Neo-adjuvant chemotherapy for operable gastric cancer: long term results of the Dutch randomised FAMTX trial. Eur J Surg Oncol

2004; 30(6): 643-9.
33. Ychou M, Boige V, Pignon JP, et al. Perioperative chemotherapy compared with surgery alone for resectable gastroesophageal adenocarcinoma: an FNCLCC and FFCD multicenter phase III trial. J Clin Oncol 2011; 29(13): 1715-21.
34. Schuhmacher C, Gretschel S, Lordick F, et al. Neoadjuvant chemotherapy compared with surgery alone for locally advanced cancer of the stomach and cardia: European Organisation for Research and Treatment of Cancer randomized trial 40954. J Clin Oncol 2010; 28(35): 5210-8.
35. Stahl M, Walz MK, Stuschke M, et al. Phase III comparison of preoperative chemotherapy compared with chemoradiotherapy in patients with locally advanced adenocarcinoma of the esophagogastric junction. J Clin Oncol 2009; 27(6): 851-6.
36. Park SH, Sohn TS, Lee J, et al. Phase III Trial to Compare Adjuvant Chemotherapy With Capecitabine and Cisplatin Versus Concurrent Chemoradiotherapy in Gastric Cancer: Final Report of the Adjuvant Chemoradiotherapy in Stomach Tumors Trial, Including Survival and Subset Analyses. J Clin Oncol 2015; 33(28): 3130-6.
37. Bang YJ, Kim YW, Yang HK, et al. Adjuvant capecitabine and oxaliplatin for gastric cancer after D2 gastrectomy (CLASSIC): a phase 3 open-label, randomised controlled trial. Lancet 2012; 379(9813): 315-21.
38. Ohtsu A, Shah MA, Van Cutsem E, et al. Bevacizumab in combination with chemotherapy as first-line therapy in advanced gastric cancer: a randomized, double-blind, placebo-controlled phase III study. J Clin Oncol 2011; 29(30): 3968-76.
39. Fuchs CS, Tomasek J, Yong CJ, et al. Ramucirumab monotherapy for previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (REGARD): an international, randomised, multicentre, placebo-controlled, phase 3 trial. Lancet 2014; 383(9911): 31-9.
40. Wilke H, Muro K, Van Cutsem E, et al. Ramucirumab plus paclitaxel versus placebo plus paclitaxel in patients with previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (RAINBOW): a double-blind, randomised phase 3 trial. Lancet Oncol 2014; 15(11): 1224-35.
41. Piessen G, Messager M, Leteurtre E, et al. Signet ring cell histology is an independent predictor of poor prognosis in gastric adenocarcinoma regardless of tumoral clinical presentation. Ann Surg 2009; 250(6): 878-87.
42. Messager M, Lefevre JH, Pichot-Delahaye V, et al. The impact of perioperative chemotherapy on survival in patients with gastric signet ring cell adenocarcinoma: a multicenter comparative study. Ann Surg 2011; 254(5): 684-93.
43. Piessen G, Messager M, Le Malicot K, et al. Phase II/III multicentre randomised controlled trial evaluating a strategy of primary surgery and adjuvant chemotherapy versus peri-operative chemotherapy for resectable gastric signet ring cell adenocarcinomas - PRODIGE 19 - FFCD1103 - ADCI002. BMC cancer 2013; 13: 281.

NEDERLANDSE SAMENVATTING

Het onderzoek in dit proefschrift richt zich op de verschillende aspecten van de kwaliteit van maagkankerchirurgie, dé hoeksteen van de behandeling van maagkanker.

Epidemiologie
Maagkanker is wereldwijd de vierde meest voorkomende maligniteit en verantwoordelijk voor een miljoen nieuwe patiënten per jaar. Maagkanker is nummer drie in doodsoorzaken wereldwijd. Grote geografische verschillen zijn zichtbaar in de incidentie van maagkanker tussen de Westerse en de Oosterse wereld met een piek in Zuid Korea (incidentie van 33,000 per jaar). In Europa is maagkanker de zesde meest voorkomende type kanker met een slechte overleving. De meerderheid van de patiënten met maagkanker ontwikkelt een lokaal recidief binnen twee jaar en slechts 25% van alle maagkankerpatiënten is nog in leven na 5 jaar.

Chirurgie
Sinds Theodor Billroth de eerste succesvolle maagresectie uitvoerde in 1881 hebben grote veranderingen plaatsgevonden in de behandeling van maagkanker in de Westerse wereld. Zo is veelvuldig onderzocht of de toevoeging van chemotherapie en/of radiotherapie aan chirurgie een overlevingsvoordeel gaf. Desalniettemin, tot op de dag van vandaag, blijft chirurgie nog altijd de basis van de behandeling voor maagkanker. Het is gebleken dat de uitgebreidheid van de lymfeklierdissectie tijdens de maagresectie sterk samenhangt met de overleving. Echter, diverse regimes hiervan zijn gebruikelijk in de wereld voor patiënten met lokaal gevorderde maagkanker. In de Oosterse wereld is minstens een uitgebreide lymfeklierdissectie (D2-dissectie; verwijdering van lymfeklierstations 1-11) gebruikelijk, terwijl in de Westerse wereld een gelimiteerde lymfeklierdissectie (D1-dissectie; verwijdering van lymfeklierstations 1-6) standaard was tot zeer recent. De lange termijn resultaten van de Dutch Gastric Cancer Trial hebben namelijk een overlevingsvoordeel getoond voor de uitgebreide lymfeklierdissectie, met name als morbiditeit en mortaliteit zo laag mogelijk gehouden konden worden.

Multimodale behandeling
Meerdere maagkankertrials hebben getracht de overleving te verbeteren voor patiënten met lokaal gevorderde maagkanker, door (neo)adjuvante chemotherapie en/of radiotherapie toe te voegen aan de chirurgie. De Amerikaanse Intergroup 0116 trial en de Britse MAGIC trial hebben veel invloed gehad op de huidige behandelingsstrategie voor resectabel maagkanker in de Westerse wereld. In de Intergroup 0116 trial werd een overlevingsvoordeel aangetoond voor chirurgie met adjuvante chemoradiotherapie (45 Gy gecombineerd met 5-fluoroucil) ten opzichte van chirurgie alleen. Daarentegen werd in de MAGIC trial een betere overleving gezien met peri-operatieve chemotherapie (epirubicine, cisplatin, en 5-fluoroucil) ten opzichte van chirurgie alleen. Sinds de resultaten van deze trials bekend zijn is adjuvante chemoradiotherapie de standaard

behandeling in de Verenigde Staten terwijl peri-operatieve chemotherapie de behandeling van keuze is in Europa – en dus ook in Nederland – voor lokaal gevorderde maagkanker. Door verschillende inclusie criteria en een verschillend studie ontwerp waren de resultaten van de Intergroup 0116 trial en de MAGIC trial niet direct vergelijkbaar. Om beide behandelingsstrategieën toch te vergelijken en om de meest optimale strategie te bepalen voor patiënten met resectabel maagkanker is de CRITICS (ChemoRadiotherapy after Induction chemotherapy In Cancer of the Stomach) trial geïnitieerd. In deze prospectieve, internationale, multicenter trial werden patiënten behandeld met drie kuren preoperatieve chemotherapie (epirubicine, cisplatin/ oxaliplatin, en capecitabine (ECC/EOC)), gevolgd door chirurgie met een adequate lymfeklierdissectie (D1+ dissectie: verwijdering van lymfeklierstation van 1-9 en 11), gevolgd door ofwel drie kuren van chemotherapie (ECC/ EOC, *standaard arm*) ofwel chemoradiotherapie (45 Gy met capecitabine en cisplatin, *experimentele arm*).

DEEL 1 – CHIRURGISCHE KWALITEITSBEWAKING IN DE CRITICS MAAGKANKERTRIAL

Hoge chirurgische kwaliteit is essentieel in maagkanker trials met multimodale behandelingen. Echter, het naleven van het protocol van de lymfeklierdissectie is vaak een probleem. In de Dutch Gastric Cancer Trial was de chirurgische kwaliteit strikt gemonitord. Een significant hogere postoperatieve mortaliteit werd gezien bij de patiënten die een D2-lymfeklierdissectie ondergingen ten opzichte van de patiënten die een D1-lymfeklierdissectie hadden ondergaan. Dit heeft er mogelijk voor gezorgd dat pas na lange follow-up tijd een overlevingsvoordeel werd gezien voor een D2-dissectie. Ook in de CRITICS trial werd de chirurgische kwaliteit strikt gemonitord. In **Hoofdstuk 1** wordt de kwaliteit van de chirurgie en het navolgen van het lymfeklierdissectie in de CRITICS trial beschreven. Resultaten lieten zien dat zeer hoge kwaliteit van de chirurgie was bedreven, ook vergeleken met eerdere maagkankertrials zoals de Dutch Gastric Cancer Trial en de Intergroup 0116 trial.

Maagkankerchirurgie wordt beschouwd als hoog risico chirurgie. Huidige chirurgische morbiditeit en mortaliteit cijfers liggen rond de 39% en 5%, respectievelijk. **Hoofdstuk 2** laat zien dat deze cijfers in de CRITICS trial 47% en 2% zijn. De enigszins wat verhoogde morbiditeit cijfers zouden enerzijds verklaard kunnen worden, doordat er meer bewustwording is van het registreren van complicaties in een trial, als anderzijds door de meer kwetsbare status van patiënten na het ondergaan van de preoperatieve chemotherapie.

Het moment van randomiseren in maagkankertrials met multimodale behandelingen is vaak een punt van discussie, mede geïllustreerd door de kritiek op de CRITICS trial. In de CRITICS trial vond randomisatie plaats vóór de start van de behandeling. Critici zagen dit moment als een limitatie, aangezien de kwaliteit van de chirurgie beïnvloed zou kunnen worden doordat de chirurg op de hoogte was welke adjuvante behandeling de patiënt zou krijgen. Om de mogelijke invloed van het randomiseren

van postoperatieve behandeling op de kwaliteit van de chirurgie in de CRITICS trial te onderzoeken, worden chirurgische parameters in beide studie armen vergeleken, beschreven, en geëvalueerd in **Hoofdstuk 3**. Geen significant verschil werd gevonden in alle onderzochte chirurgische kwaliteitsparameters tussen beide studiearmen. Hiermee wordt niet alleen bovengenoemde kritiek ontkracht maar ook de betrouwbaarheid van de primaire uitkomsten van de CRITICS trial benadrukt.

DEEL II – INVLOED VAN ZIEKENHUISVOLUME OP UITKOMSTEN VAN MAAGKANKERCHIRURGIE

In de laatste decennia is ziekenhuisvolume een hot topic geworden in de maagkankerchirurgie. Er is toenemende consensus dat de complexe zorg van maagkankerchirurgie zou moeten plaatsvinden in hoog volume ziekenhuizen. In vele Europese landen – waaronder Nederland – is een minimum grens van het aantal maagresecties per instituut vastgesteld. Sinds 2013 dienen er in Nederland minimaal 20 resecties per jaar per instituut te worden uitgevoerd, dit met als doel de kwaliteit van de chirurgie te verbeteren. Echter, deze grens van 20 is gebaseerd op klinische consensus. Daarbij is gedetailleerde informatie over de chirurgische kwaliteit schaars. Door data van de CRITICS trial te koppelen aan data van de Nederlandse Kanker Registatie is getracht dit gat in de literatuur te dichten. Resultaten in **Hoofdstuk 4** laten zien dat chirurgie in hoog volume ziekenhuizen geassocieerd is met verbeterde chirurgische kwaliteitsparameters. Om te onderzoeken of chirurgie uitgevoerd in hoog ziekenhuisvolume ook resulteert in verbeterde lange termijn uitkomsten is in **Hoofdstuk 5** het effect van ziekenhuisvolume van maagkankerchirurgie onderzocht op recidieven en overleving. Een verbeterde overleving en ziektevrije overleving werd geobserveerd in de hoog volume ziekenhuizen. Kortom, zowel de resultaten van **Hoofdstuk 4** en **Hoofdstuk 5** benadrukken de waarde van de centralisatie van de maagkankerchirurgie in de Westerse wereld. Daarbij moet in acht worden genomen dat deze resultaten altijd beschouwd moet worden als een teamprestatie van vele medische zorgprofessionals samen waarbij de chirurg een belangrijke en centrale rol in heeft.

DEEL III – OPTIMALE BEHANDELINGSSTRATEGIE VOOR SUBGROEPEN VAN MAAGKANKERPATIËNTEN

Het verbeteren van de kwaliteit van zorg van maagkankerpatiënten in de Westerse wereld is een grote uitdaging. Dit geldt nog meer voor bepaalde subgroepen zoals bijvoorbeeld de oudere maagkankerpatiënt. Door een bovengrens te stellen aan de leeftijd in gerandomiseerde klinische trials worden oudere maagkankerpatiënten vaak geëxcludeerd. Daarbij zijn ouderen een diverse groep van patiënten die bekend staan om (meer) co-morbiditeit, een verhoogd risico op postoperatieve complicaties, en een verhoogde postoperatieve mortaliteit. Om inzicht te krijgen in de behandelingsstrategie

en overleving van de oudere maagkankerpatiënt zijn nationale data van vijf Europese landen (België, Denemarken, Nederland, Noorwegen, en Zweden) verzameld van patiënten van 70 jaar of ouder met resectabel maagkanker, uitgevoerd door de UGI EUropean REgistration of Cancer CAre (EURECCA) groep (**Hoofdstuk 6**). Substantiële verschillen tussen de participerende landen werden gezien in het percentage patiënten die werden geopereerd en het percentage patiënten dat werd behandeld met chemotherapie, met name in stadium II en III patiënten. In de landen waar een hoog percentage patiënten geopereerd werden en chemotherapie ondergingen werd een betere overleving gezien voor de stadium II en III patiënten.
Een andere subgroep van maagkankerpatiënten waarbij de optimale behandelingsstrategie onbekend is, zijn de patiënten met gemetastaseerde ziekte op afstand (stadium IV). Meer dan twee derde van de maagkankerpatiënten heeft gemetastaseerde ziekte op het moment van diagnose. De behandeling van keuze voor deze groep patiënten is chemotherapie, al blijft de rol van een palliatieve maagresectie een punt van discussie. Recentelijk zijn de resultaten van de REGATTA trial gepubliceerd die als eerste gerandomiseerde klinische trial de rol van een palliatieve resectie heeft onderzocht in patiënten met een niet-curabele factor zonder dat er aanwijzingen waren voor obstructie of bloedingen. Geen overlevingsvoordeel werd gezien voor patiënten die een palliatieve resectie ondergingen met chemotherapie vergeleken met chemotherapie alleen; hiermee werd volgens de auteurs een palliatieve resectie afgeraden. Een overzicht van de behandelingsstrategieën in de dagelijkse praktijk, en met in het bijzonder de rol van de palliatieve maagresectie, in vijf Europese landen (België, Denemarken, Nederland, Noorwegen, en Zweden) is uitgevoerd door de UGI EURECCA groep en wordt gepresenteerd in **Hoofdstuk 7**. Tussen de vijf landen werd een grote variatie geobserveerd in de mate waarin een tumorresectie werd uitgevoerd, als ook de mate van het gebruik van chemotherapie voor de twee landen die chemotherapie gebruik geregistreerd hadden. Naast overleving is kwaliteit van leven een zeer belangrijke uitkomst voor deze groep van patiënten, maar deze was helaas niet geregistreerd in de nationale datasets. Een goed uitgevoerde prospectief opgezette studie voor patiënten met op afstand gemetastaseerde maagkanker met focus op kwaliteit van leven is dan ook zeker noodzaak voor in de toekomst.

DEEL IV – AANWIJZINGEN VOOR DE TOEKOMST VAN MAAGKANKER

Hoewel verbeteringen op het gebied van chirurgische technieken, perioperatieve zorg, en uitbreiding van multimodale regimes hebben plaatsgevonden, blijft de overleving voor de maagkankerpatiënt in de Westerse wereld matig. Ondanks dat de CRITICS trial vooralsnog geen overlevingsvoordeel heeft kunnen aantonen tussen de chemotherapie arm en de chemoradiotherapie arm heeft deze trial wel degelijk nieuwe inzichten gegeven. De compliance van patiënten om de gehele behandeling te voltooien in de CRITICS trial was laag. Slechts 47% en 52% van de patiënten die in de chemotherapie arm en de chemoradiotherapie arm, respectievelijk zaten, waren in staat de gehele behandeling te

voltooien. Deze resultaten indiceren dat de huidige multimodale behandelingsstrategie (te) veeleisend is voor de Westerse maagkankerpatiënt. Voor de toekomst zal de focus dan ook liggen op een verschuiving van adjuvante behandelstrategie naar neo-adjuvante behandelstrategie. Momenteel zijn onder andere de CRITICS-II gaande om neo-adjuvante behandelingsstrategieën voor maagkanker met elkaar te vergelijken. In **Hoofdstuk 8** is een overzicht gegeven van de huidige literatuur over neo-adjuvante behandelstrategieën van maagkanker in de Westerse wereld. Nieuwe ontwikkelingen zoals de opkomst van targeted therapie komen daarbij ook aan bod.

LIST OF PUBLICATIONS

Y.H.M. Claassen, J.L. Dikken, H.H. Hartgrink, W.O. de Steur, M. Slingerland, R. Verhoeven, E. van Eycken, J. Verbeeck, J. Johansson, I. Rouvelas, E. Johnson, G.O. Hjortland, L.S. Jensen, H.J. Larsson, W.H. Allum, E. Bastiaannet, C.J.H. van de Velde.
European comparison of treatment strategy and survival in older (≥70 years) patients with resectable gastric cancer, *EJSO,* 2018, accepted for publication.

Y.H.M. Claassen, M.J.M. van der Valk, A.J. Breugom, M.A. Frouws, E. Bastiaannet, G.J. Liefers, C.J.H. Van de Velde, E. Kapiteijn.
Survival differences with immediate versus delayed chemotherapy for asymptomatic incurable metastatic colorectal cancer, *Cochrane Database of Systematic Reviews,* 2018, in press.

Y.H.M. Claassen, H.H. Hartgrink, W.O. de Steur, J.L. Dikken, J.W. van Sandick, N.C.T. van Grieken, A. Cats, A.K. Trip, E.P.M. Jansen, W.M. Meershoek-Klein Kranenbarg, J.P.B.M. Braak, H. Putter, M.I. van Berge Henegouwen, M. Verheij, C.J.H. van de Velde.
Impact of upfront randomization for postoperative treatment on quality of surgery in the CRITICS gastric cancer trial, *Gastric Cancer*, 2018, epub ahead for print.

Y.H.M. Claassen, E. Bastiaannet, H.H. Hartgrink, J.L. Dikken, W.O. de Steur, M. Slingerland, R. Verhoeven, J. Verbeeck, M. Lindblad, J. Hedberg, E. Johnson, G.O. Hjortland, L.S. Jensen, H.J. Larsson, T. Koessler, M. Chevallay, W.H. Allum, C.J.H. van de Velde.
International comparison of treatment strategy and survival in metastatic gastric cancer: a survey from the EURECCA Upper GI group (European Registration of Cancer CAre), *BJS Open*, 2018, in press.

Y.H.M. Claassen, N.C.A. Vermeer, L.H. Iversen, E. van Eycken, M.G. Guren, P. Mrockowski, A. Martling, A. Codina Cazador, R. Johansson, T. Vandendael, A. Wibe, B. Moller, H. Lippert, H.J. Rutten, J.E.A. Portielje, G.J. Liefers, F.A. Holman, C.J.H. van de Velde, E. Bastiaannet.
Treatment and survival of rectal cancer patients over the age of 80 years; a EURECCA international comparison, *Br J Cancer,* 2018: 199(4): 517-522.

Y.H.M. Claassen, R.M. van Amelsfoort, H.H. Hartgrink, J.L. Dikken, W.O. de Steur, J.W. van Sandick, N.C.T. van Grieken, A. Cats, H. Boot, A.K. Trip, E.P.M. Jansen, W.M. Meershoek-Klein Kranenbarg, J.P.B.M. Braak, H. Putter, M.I. van Berge Henegouwen, M. Verheij, C.J.H. van de Velde.
Effect of hospital volume of gastric cancer surgery on recurrence and survival: results from the CRITICS trial, *Ann Surg*, 2018, epub ahead of print.

N.C.A. Vermeer, **Y.H.M. Claassen**, M.G.M. Derks, L.H. Iversen, E. van Eycken, M.G. Guren, P. Mrockowski, A. Martling, R. Johansson, T. Vandendael, A. Wibe, B. Moller, H. Lippert, J.E.A. Portielje, G.J. Liefers, K.C.M.J. Peeters, C.J.H. van de Velde, E. Bastiaannet.
Treatment and survival of patients with colon cancer aged 80 years and older; an EURECCA international comparison, *The Oncologist*, 2018; 23(8): 982-990.

Y.H.M. Claassen*, W.O. de Steur*, H.H. Hartgrink, J.L. Dikken, J.W. van Sandick, N.C.T. van Grieken, A. Cats, A.K. Trip, E.P.M. Jansen, W.M. Meershoek-Klein Kranenbarg, J.P.B.M. Braak, H. Putter, M.I. van Berge Henegouwen, M. Verheij, C.J.H. van de Velde.
Surgicopathological Quality Control and Protocol Adherence to Lymphadenectomy in the CRITICS Gastric Cancer Trial, *Ann Surg*, 2017, ahead of print.

Y.H.M. Claassen, H.H. Hartgrink, J.L. Dikken, W.O. de Steur, J.W. van Sandick, N.C.T. van Grieken, A. Cats, A.K. Trip, E.P.M. Jansen, W.M. Meershoek-Klein Kranenbarg, J.P.B.M. Braak, H. Putter, M.I. van Berge Henegouwen, M. Verheij, C.J.H. van de Velde.
Surgical morbidity and mortality after neoadjuvant chemotherapy in the CRITICS gastric cancer trial, *EJSO*, 2018; 44(5):613-619.

Y.H.M. Claassen, J.W. van Sandick, H.H. Hartgrink, J.L. Dikken, W.O. de Steur, N.C.T. van Grieken, H. Boot, A. Cats, A.K. Trip, E.P.M. Jansen, W.M. Meershoek-Klein Kranenbarg, J.P.B.M. Braak, H. Putter, M.I. van Berge Henegouwen, M. Verheij, C.J.H. van de Velde.
Association between hospital volume and quality of gastric cancer surgery in the CRITICS trial, *BJS*, 2018; 105(6):728-735.

Y.H.M. Claassen, H.H. Hartgrink, W.O. De Steur, M. Slingerland, C.J.H. Van de Velde.
Chapter "Neoadjuvant treatment of Gastric Cancer" in the book *Minimally Invasive Upper Abdominal Surgery*, 2017.

Y.H.M. Claassen, A.J. Breugom, M.A. Frouws, E. Bastiaannet, C.R. Sabajo, G.J. Liefers, C.J.H. Van de Velde, E. Kapiteijn.
Cochrane meta-analysis: Survival differences with immediate versus delayed chemotherapy for asymptomatic incurable metastatic colorectal cancer (Protocol), *Cochrane Database of Systematic Reviews* 2016, Issue 10. Art no.:CD012326

M.A. Frouws, **Y.H.M. Claassen**, A.J. Breugom, E. Bastiaannet, S. Mocellin, C.J.H. Van de Velde, G.J. Liefers, E. Kapiteijn.
Cochrane meta-analysis: Intermittent versus continuous systemic therapy as treatment for unresectable metastatic colorectal cancer (Protocol), *Cochrane Database of Systematic Reviews* 2016, Issue 12. Art no.:CD012440.

Y.H.M. Claassen, E. Bastiaannet, E. van Eycken, N. Van Damme, A. Martling, R. Johansson, L.H. Iversen, P. Ingeholm, V.E.P.P. Lemmens, G.J. Liefers, F.A. Holman, J.W.T. Dekker, J.E.A. Portielje, H.J. Rutten, C.J.H. van de Velde.
Time trends of short-term mortality for octogenarians undergoing a colorectal resection in North Europe, *Ann Surg Oncol*, submitted.

F. Mazzotti, A. Cucchetti, **Y.H.M. Claassen**, A.C.R.K. Bos, E. Bastiaannet, G. Ercolani, J.W.T. Dekker.
Years of life-lost for elderly patients after colorectal cancer diagnosis, *EJSO*, *submitted*.

M.J.M. van der Valk, **Y.H.M. Claassen**, M.A. Frouws, A.J. Breugom, E. Bastiaannet, S. Mocellin, C.J.H. Van de Velde, G.J. Liefers, E. Kapiteijn.
Cochrane meta-analysis: Intermittent versus continuous systemic therapy as treatment for unresectable metastatic colorectal cancer, *Cochrane Database of Systematic Reviews,* submitted.

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CURRICULUM VITAE

Yvette Hélène Madeleine Claassen was born in Breda on August 31th of 1989. She grew up in Breda with her father (Rudolf), mother (Hélène), two brothers (Rogier and Marc) and sister (Nathalie). In 2007, she graduated from the Mencia de Mendoza (gymnasium) in Breda. Thereafter, she started her study medicine at the University of Leiden. During her internship Surgery she became interested in the surgical oncology, resulting in several surgical internships abroad (Barcelona, Cape Town) as well as a senior internship at Haaglanden Medisch Centrum in The Hague. In 2013, she successfully achieved her medical degree and directly started working as a surgical resident not in training in the Haaglanden Medisch Centrum. After approximately a year work experience, in August 2015 she started with her PhD traject with research on gastric and colorectal cancer under supervision of dr. H.H. Hartgrink (co-promotor) and prof. C.J.H. van de Velde (promotor) at the department of Surgical Oncology at the Leids University Medical Center. Here, she performed several studies on surgery performed in the CRITICS (ChemoRadiotherapy after Induction chemotherapy In Cancer of the Stomach) gastric cancer trial, an international randomized clinical trial collaborated between the Leids University Medical Center and Antoni van Leeuwenhoek. Furthermore, she performed several European Registration of Cancer Care (EURECCA) studies for both gastric and colorectal cancer. The results of her studies were presented on different national and international congresses such as European Society of Surgical Oncology (ESSO) and European Cancer Organisation (ECCO).

Currently, Yvette lives in Amsterdam and starts her surgical residency in January 2019.

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