Quality assurance in the surgical treatment of gastric cancer

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CHAPTER 10

SUMMARY AND GENERAL DISCUSSION

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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.

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