Quality assurance in the surgical treatment of gastric cancer

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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.

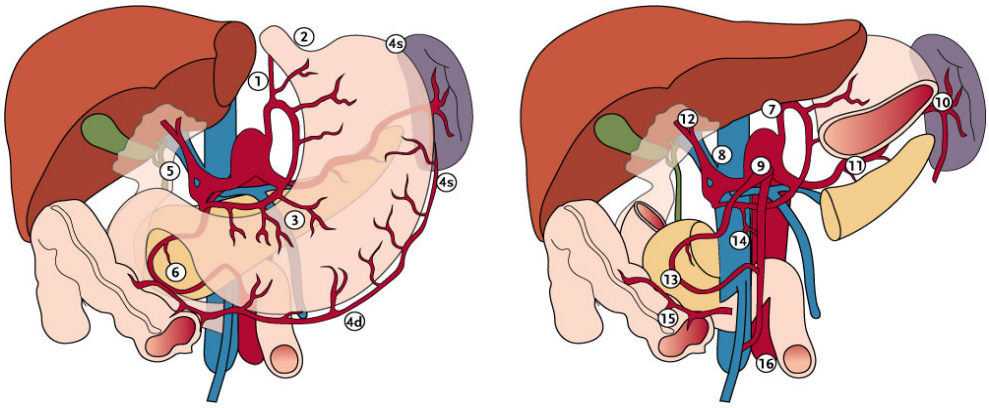
METHODS

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.



N1 Lymph nodes (perigastric)
1 Right cardiac nodes
2 Left cardiac nodes
3 Nodes along the lesser curvature
4 Nodes along the greater curvature
5 Suprapyloric nodes
6 Infrapyloric Nodes

N2 Lymph nodes (branches coeliac axis)
7 Nodes along root left gastric artery
8 Nodes along common hepatic artery
9 Nodes around celiac axis
10 Nodes at splenic hilum
11 Nodes along splenic artery

N3 Lymph nodes
12 Nodes at the hepatoduodenal ligament
13 Retropancreatic (perioduodenal) nodes
14 Nodes at the root of the mesentery

N4 Lymph nodes
15 Nodes along the middle colic vein
16 Para-aortic nodes

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.

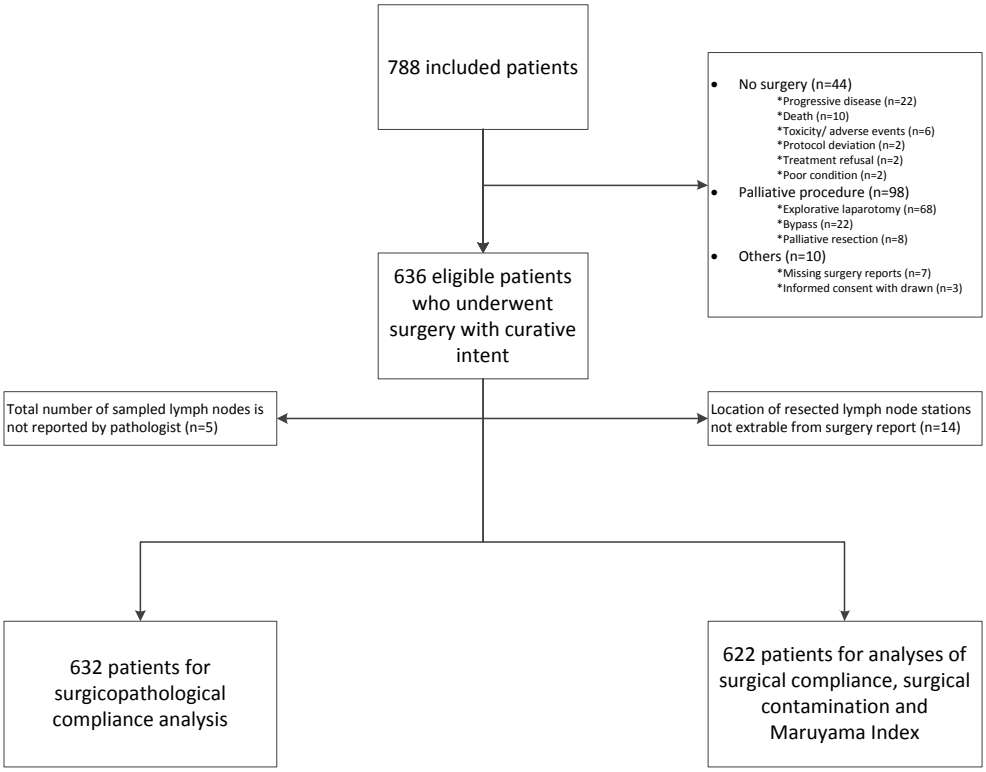


Figure 2. Study flow chart

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*

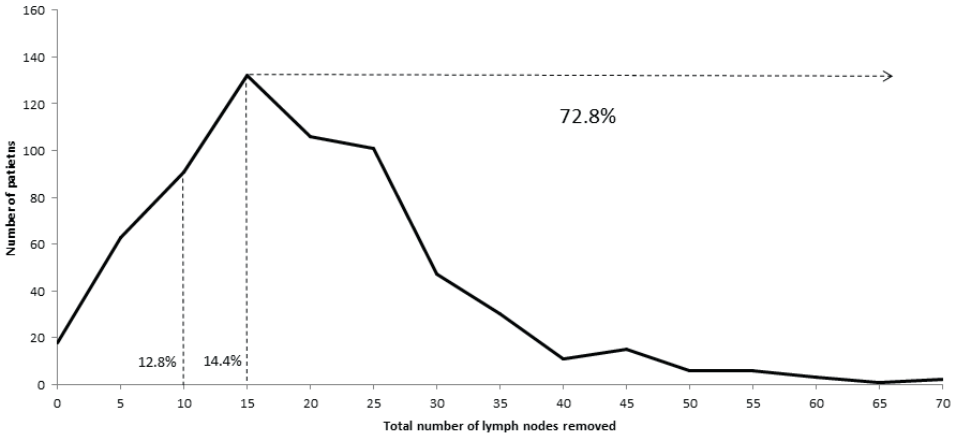


Figure 3. Surgicopathological compliance

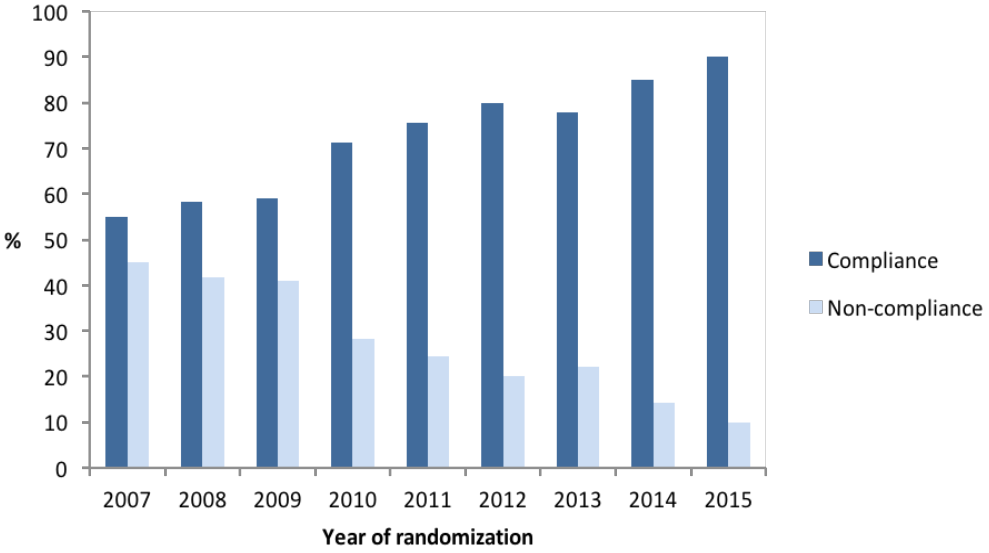


Figure 4. Surgicopathological compliance over time

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.

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