Quality assurance in the surgical treatment of gastric cancer

Claassen, Y.H.M.

CHAPTER 6

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

Y.H.M. Claassen, R. 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,
and C.J.H. van de Velde

Ann of Surg. 2018; epub ahead of print.

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.

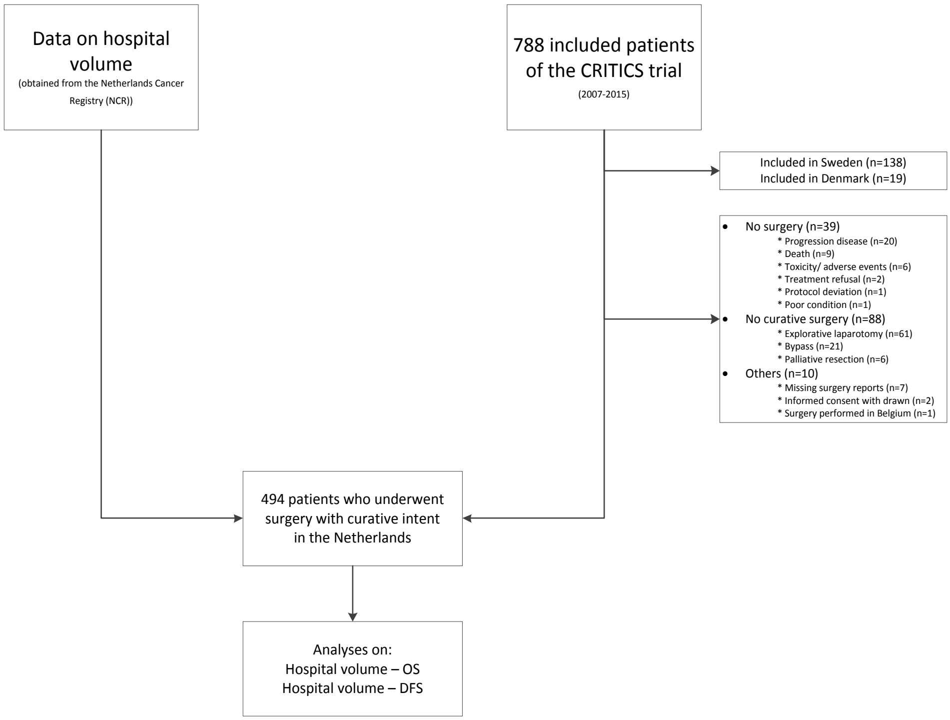


Figure 1. Study flow chart depicting the inclusion and exclusion of patients in the current analysis

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)	

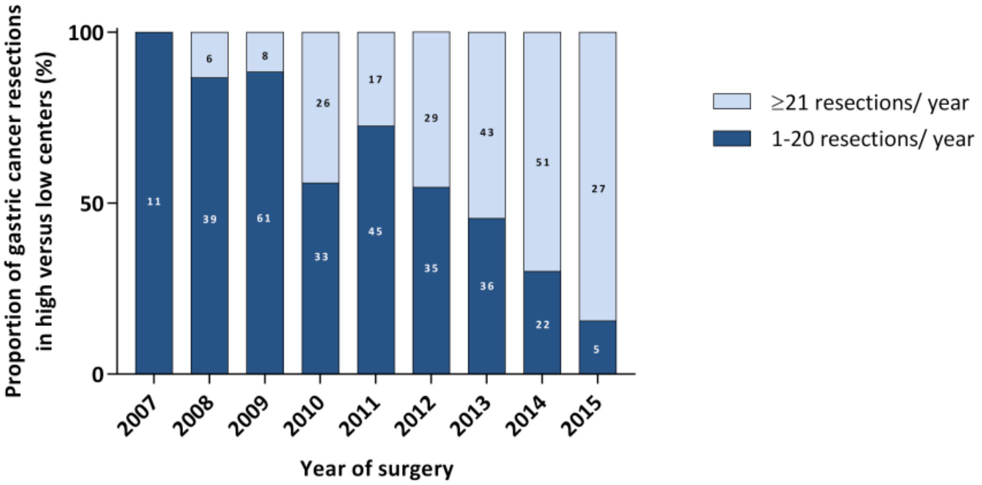
Table 1 continues

6

	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.



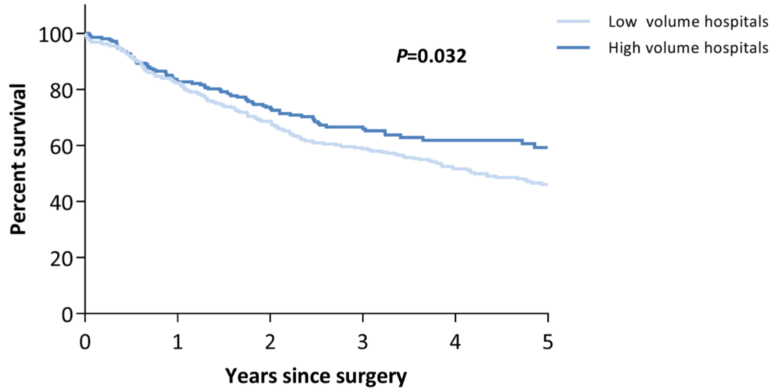
Numbers in the boxes represent number of gastric resections

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)

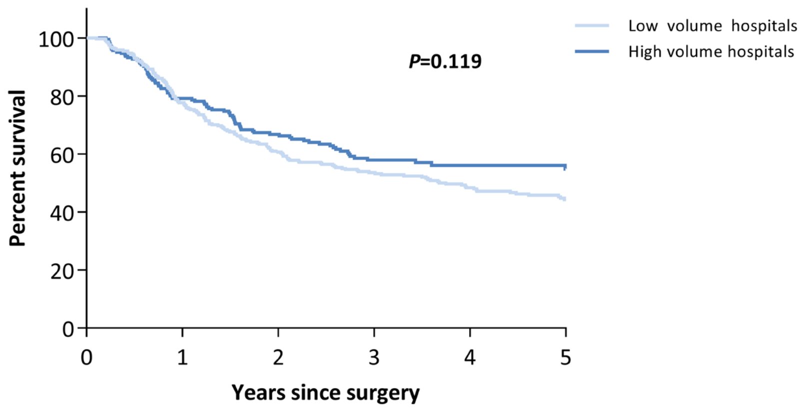
	Overall survival since surgery			**Disease free survival since surgery**		
	HR	*p-value*	CI	HR	*p-value*	CI
Hospital volume						
Low (1-20)	1			1		
High (21+)	0.69	*0.020*	0.50-0.94	0.73	*0.040*	0.54-0.99
Year of surgery	0.96	0.241	0.89-1.03	0.99	0.788	0.93-1.06
Age	1.02	*0.005*	1.01-1.03	1.02	*0.015*	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*).



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

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.