Gastric cancer : staging, treatment, and surgical quality assurance

Dikken, J.L.

PART II

Multimodality treatment

CHAPTER 7

Impact of the extent of surgery and postoperative chemoradiotherapy on recurrence patterns in gastric cancer

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ABSTRACT

BACKGROUND

The Intergroup 0116 trial demonstrated that postoperative chemoradiotherapy (CRT) improves survival in gastric cancer. We retrospectively compared survival and recurrence patterns in two phase I-II studies evaluating more intensified postoperative CRT with those from the Dutch Gastric Cancer Group Trial (DGCT) that randomized patients between D1 and D2 lymphadenectomy.

PATIENTS AND METHODS

Survival and recurrence patterns of 91 patients with adenocarcinoma of the stomach who had received surgery followed by radiotherapy combined with fluorouracil and leucovorin (N = 5), capecitabine (N = 39), or capecitabine and cisplatin (N = 47) were analyzed and compared with survival and recurrence patterns of 694 patients from the DGCT (369 D1, 325 D2). For both groups, the Maruyama Index of Unresected Disease (MI) was calculated and correlated with survival and recurrence patterns.

RESULTS

With a median follow-up of 19 months in the CRT group, local recurrence after 2 years was significantly higher in the surgery only (DGCT) group (17% versus 5%, *P* = 0.0015). Separate analysis of CRT patients who underwent a D1 dissection (N = 39) versus DGCT-D1 (N = 369) showed fewer local recurrences after chemoradiation (2% versus 18%, *P* = 0.001), while comparison of CRT-D2 (N = 25) vs DGCT-D2 (N = 325) demonstrated no significant difference. CRT significantly improved survival after a microscopically irradical (R1) resection. The MI was found to be a strong independent predictor of survival.

CONCLUSION

Following D1 surgery, the addition of postoperative CRT had a major impact on local recurrence in operable gastric cancer.

INTRODUCTION

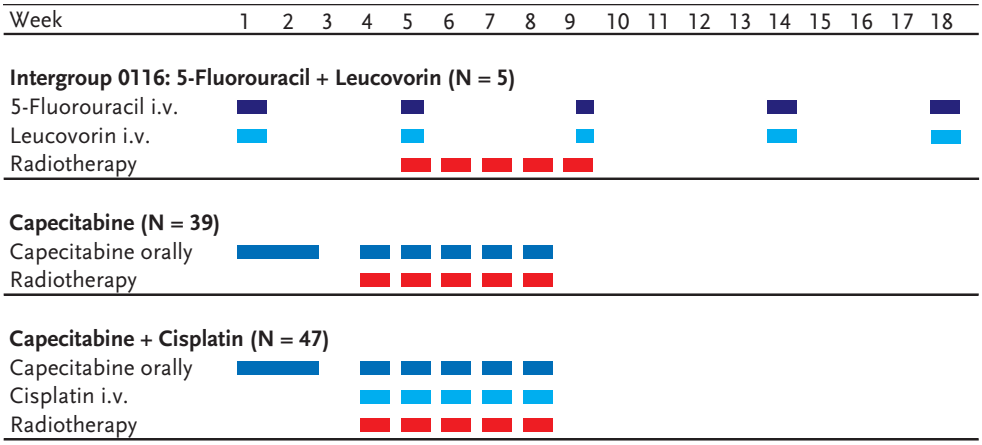
Gastric cancer is the second leading cause of cancer death worldwide,[1] and responsible for 8.1% of all cancer deaths in Europe.[2] Surgery is the only possible curative treatment, and results of gastrectomy with respect to survival, morbidity, and mortality have improved through the years.[3] Despite these improvements, up to 80% of the patients who undergo a resection with curative intent develop locoregional recurrences.[4] Although extended surgery has been associated with better staging and lower locoregional recurrence rates, randomized studies in the Western world have failed to show an improvement in survival with extended lymph node dissection.[5-7] In one of these studies, the Dutch Gastric Cancer Group Trial (DGCT), 711 patients were randomized for gastrectomy between a D1 and D2 lymphadenectomy. Long-term results of this study showed no significant benefit in survival after a D2 lymphadenectomy, which was mainly due to increased postoperative morbidity and mortality.[5] Only recently, a retrospective analysis on survival rates in the Netherlands before, during, and after the DGCT, showed that survival of patients with curatively resected non-cardia gastric cancer has improved over the last several years, which is most likely the result of standardization and surgical training.[8]

The high recurrence rate makes gastric cancer a disease difficult to cure by surgery alone, with 5-year survival rates after surgery of 34% to 70% for patients with stage I and II, and 7% to 20% for stage III and IV disease.[9] Recent data show that 5-year overall survival for all diagnosed patients in Europe is only 24.5%.[10] Considering the recent advantages in survival that have been achieved with postoperative chemoradiotherapy (CRT)[11] and perioperative chemotherapy,[12] surgery alone is no longer the standard treatment for patients with resectable (more than T2N0) gastric cancer.[13]

The Intergroup 0116 randomized study of 556 patients with resectable adenocarcinoma of the stomach or gastroesophageal junction demonstrated that postoperative CRT with fluorouracil and leucovorin improved 5-year overall survival (40% versus 22%), and local recurrence rate (19% versus 29%), compared to surgery alone.[11] A recent update on this study confirmed these results with hazard ratios (HR) for survival (HR 1.32, $P = 0.004$) and disease-free survival (HR 1.51, $P < 0.001$) favoring chemoradiation, after a median follow-up of more than ten years.[14] Based on these results, postoperative CRT has become standard treatment for gastric cancer in the United States. In a side study, the investigators calculated the Maruyama Index of Unresected Disease (MI) for each patient to predict the likelihood that the remaining lymph nodes were tumor positive. The MI was found to be a powerful independent predictor of survival.[15,16]

From 2000 to 2008, several phase I/II trials with intensified postoperative CRT (as compared to the Intergroup 0116 trial) were performed in the Netherlands, and all these trials established the feasibility of these regimens.[17-19] From these studies, a CRT regimen with daily capecitabine and weekly cisplatin has emerged, and is currently being tested in a phase III trial (CRITICS; clinicaltrials.gov NCT00407186). The objective of these

Figure 1. Treatment design phase I/II studies



Radiotherapy was administered in 5 fractions/week

adjuvant strategies is to reduce the locoregional recurrence rate and improve survival. Therefore, in the current retrospective study, the patterns of recurrence and survival of patients in the phase I/II CRT studies were compared to patterns of recurrence and survival of patients in the DGCT, in which patients were treated with surgery only. In addition to these analyses, the correlation between MI and survival and recurrence patterns in these groups was investigated.

PATIENTS AND METHODS

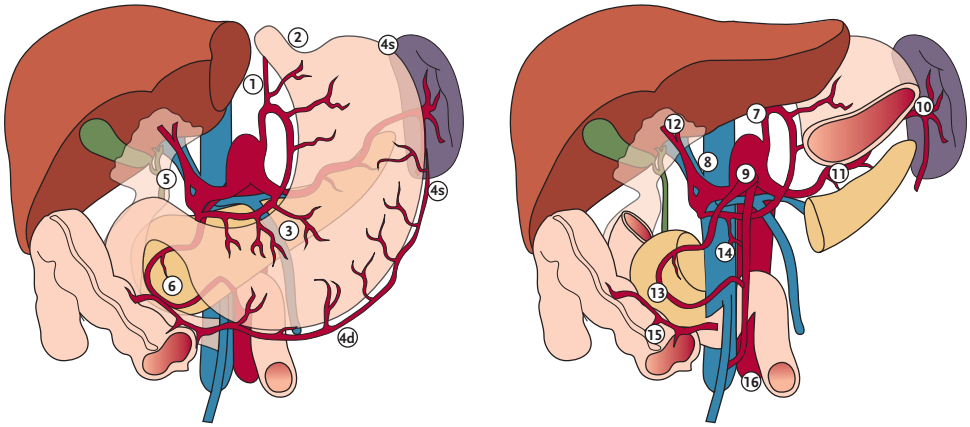
PHASE I/II CHEMORADIOTHERAPY STUDIES

From 2000 to 2008, 113 patients with histologically confirmed adenocarcinoma of the stomach or gastroesophageal junction, stage Ib-IV according to the American Joint Committee of Cancer,[20] underwent gastric resection followed by CRT at the Netherlands Cancer Institute. For a detailed description of the study design, please refer to the original publications.[17,18]

In summary, all patients underwent (partial) gastrectomy with preferably at least a D1 lymph node dissection, without routine splenectomy or pancreatic tail resection. After macroscopically radical gastric surgery, patients were asked to participate in the phase I-II studies. All patients were treated with 25 fractions of 1.8 Gy radiotherapy to a total dose of 45 Gy (5 fractions/week). The clinical target volume consisted of the gastric bed (with stomach remnant, when present), anastomoses, and draining lymph nodes. Radiotherapy was combined with escalating doses of fluorouracil and leucovorin (Intergroup 0116 scheme), capecitabine,[18] or capecitabine and cisplatin[17] (Figure 1).

Follow-up after completion of treatment consisted of physical examination, lab tests including tumor markers every 3 months and computed tomography (CT) of the abdomen every 6 months.

Figure 2. Lymph node stations as defined by the Japanese Research Society for Gastric Cancer[24]



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.

DUTCH GASTRIC CANCER GROUP TRIAL, D1 VERSUS D2

From 1989 to 1993, 1078 patients with histologically confirmed adenocarcinoma of the stomach without evidence of distant metastases were randomly assigned for D1 or D2 lymph node dissection if, at laparotomy, no signs of distant lymph node, hepatic, or peritoneal metastases were found.[5,21] D1 and D2 dissection were defined according to the guidelines of the Japanese Research Society for the Study of Gastric Cancer (JRSGC) (Figure 2).[22] In D2 dissections, resection of the spleen and pancreatic tail were only performed in proximal tumors to achieve adequate removal of D2 lymph node stations 10 and 11.

All patients were evaluated every 3 months during the first year and every 6 months thereafter. If history and physical examination were suspicious for the diagnosis of a relapse, this was considered sufficient. However, for the majority of patients, the diagnosis of recurrent disease was confirmed by radiology, endoscopy, and/or histology. For further details on study design, please refer to the original publications.[5,21]

DEFINITION OF RECURRENCE

Recurrences were categorized as local, regional or distant. Local recurrence was defined as recurrence in the gastric bed, regional gastric lymph nodes, or at the esophago/gastrojejunal anastomosis. This corresponds with the clinical target volume of radiotherapy. Peritoneal carcinomatosis was scored as regional recurrence. Distant recurrence was defined as liver or lung metastases or metastases in other organs (bone, brain, ovaries).

MARUYAMA INDEX OF UNRESECTED DISEASE

The MI was calculated using the Maruyama Computer Program,[23] which contains data of 4702 patients with gastric cancer treated at the National Cancer Center Hospital, Tokyo. The program matches a given case with the database in order to estimate the likelihood (percentage) of nodal disease for each of the 16 JRSGC-defined[24] lymph node stations (Figure 2), using 7 variables: age, sex, Borrmann type of tumor, tumor size, location, depth, and histology. The program has shown to be highly accurate in Japanese, German, and Italian series.[25-27] To quantify the likelihood of unresected nodal disease, the MI has been defined[15] as the sum of nodal disease percentages for each of the regional node stations (1-12) not removed by the surgeon. For example, a given patient undergoes a gastrectomy with removal of lymph node stations 1-10. The MI of this patient is calculated by adding up the likelihood of disease percentages of station 11 and 12, which are left *in situ*. Previous publications have shown superior survival for patients with a MI < 5.[15,16]

For the DGCT, detailed lymphadenectomy data for each patient were reported. For the CRT group, however, only the type of lymph node dissection (D0, D1, D2) was registered. Therefore, we derived the resected lymph node stations from the Japanese Classification of Gastric Carcinoma,[24] based on surgical and pathology reports.

STATISTICAL ANALYSIS

In order to account for intrinsic differences between populations, rather than matching, groups were adjusted for covariates in multivariate Cox proportional hazards models. Used covariates were: age (≥70/>70 years), sex, localization of tumor (proximal/middle/distal/diffuse), Lauren classification (intestinal/diffuse/mixed) T-stage, N-stage, gastrectomy (total/subtotal), pancreatectomy, splenectomy, type of dissection (D0/D1/D2), and radicality (R0/R1). Survival curves for the two populations are model-based curves evaluated at the mean of the covariates used in the multivariate proportional hazards models. For the pooled MI survival analysis, Kaplan-Meier survival curves were calculated and the log-rank test was used to test for differences between high and low MI groups.

Patients from the DGCT were entered in this study if they had survived surgery, while patients from the phase I/II trials were only entered into this study if they had survived surgery and completed chemoradiotherapy. To account for the fact that patients in the phase I/II trials who died before entering the trial would not be present in the CRT group, delayed entry techniques were used for all survival and recurrence analyses.[28]

For both groups, overall survival was calculated from surgery until death of any cause (event) or last follow-up contact (censored). Disease-free survival was calculated from surgery until recurrence or death (event) or the day of last follow-up without recurrence (censored). Times to recurrence (local, regional, distant) were calculated from surgery until recurrence (event) or the day of last follow-up without recurrence (censored).

All survival and recurrence analyses were performed using R software (version 2.9.1).

Table 1. Patient characteristics

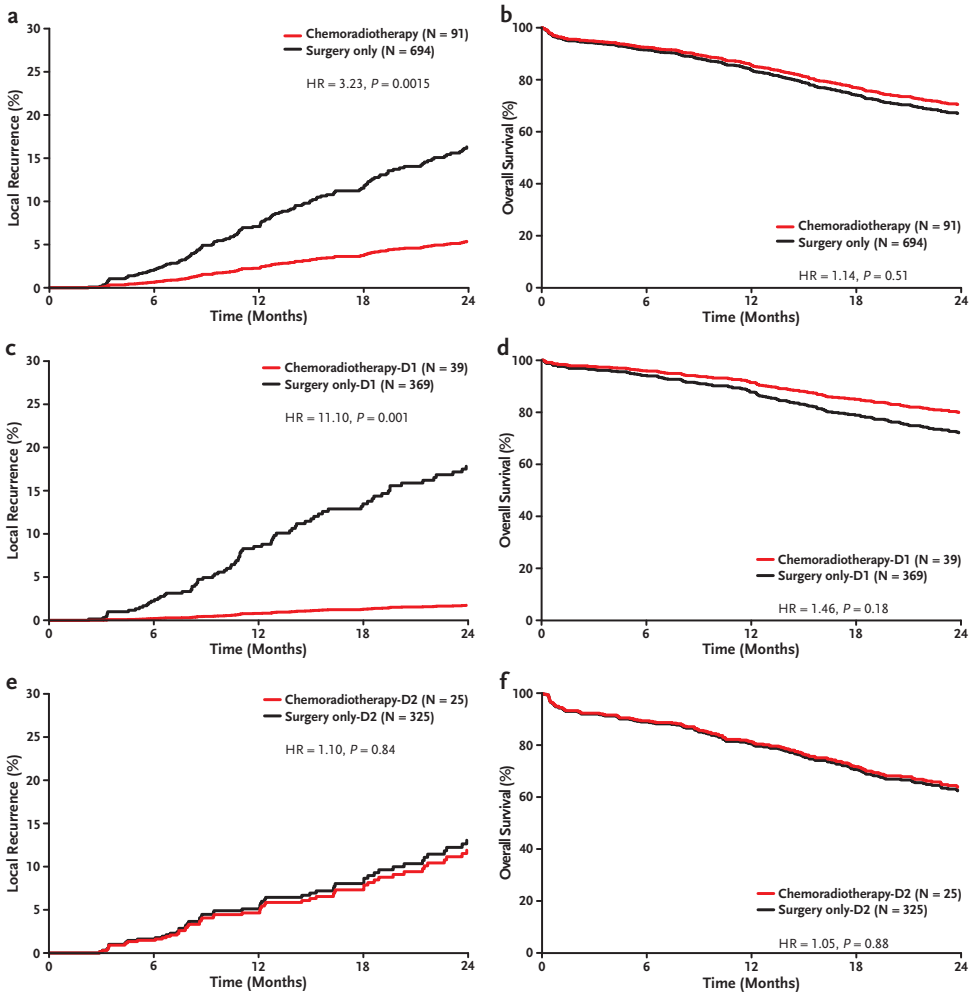
	Chemoradiotherapy		Surgery only		*P*
	N	%	N	%	
Total	91	*100*	694	*100*	
Sex					
male	63	*69.2*	392	*56.5*	0.021
female	28	*30.8*	302	*43.5*	
Age					
<70	81	*89.0*	469	*67.6*	<0.001
≥70	10	*11.0*	225	*32.4*	
Location					
proximal	11	*12.1*	91	*13.1*	0.415
middle	31	*34.1*	217	*31.3*	
distal	41	*45.1*	377	*54.3*	
diffuse	8	*8.8*	9	*1.3*	
Gastrectomy					
total	32	*35.2*	237	*34.1*	0.848
distal	59	*64.8*	457	*65.9*	
Spleen and pancreas					
not removed	74	*81.3*	529	*76.2*	0.016
spleen removed	12	*13.2*	57	*8.2*	
pancreas removed	2	*2.2*	1	*0.1*	
both removed	3	*3.3*	107	*15.4*	
Lymph node dissection					
D0	27	*29.7*			<0.001
D1	39	*42.9*	369	*53.2*	
D2	25	*27.5*	325	*46.8*	
Tumor stage					
T1	2	*2.2*	182	*26.2*	<0.001
T2	17	*18.7*	331	*47.7*	
T3	66	*72.5*	169	*24.4*	
T4	6	*6.6*	12	*1.7*	
Nodal status					
N0	6	*6.7*	309	*44.7*	<0.001
N1	45	*50.0*	248	*35.9*	
N2	27	*30.0*	93	*13.5*	
N3	12	*13.3*	41	*5.9*	
Nx	1	*0.1*	3	*0.1*	
Lauren classification					
intestinal	21	*23.1*	309	*44.5*	<0.001
diffuse	24	*26.4*	129	*18.5*	
mixed	8	*8.8*	21	*3.0*	
unknown	38	*41.8*	235	*33.9*	
Radicality					
R0	69	*75.8*	633	*91.2*	<0.001
R1	22	*24.2*	61	*8.8*	

RESULTS

PATIENT CHARACTERISTICS

Ninety-one of 113 patients from the CRT group were suitable for analysis. Patients who underwent an esophageal-cardiac resection or patients with an adenocarcinoma of the gastroesophageal junction (N = 22) were excluded. Of the 711 patients of the DGCT (surgery only) who underwent a curative resection, 17 patients were excluded because

Figure 3. Multivariate analyses of local recurrence (LR) and overall survival (OS), (a) LR all patients, (b) OS all patients, (c) LR D1 patients, (d) OS D1 patients, (e) LR D2 patients, (f) OS D2 patients, HR = Hazard Ratio



they were classified as 'T_o' or had metastatic disease, leaving 694 patients for comparative analysis.

Baseline characteristics are summarized in Table 1. D2 lymphadenectomy was performed in 46.8% of the surgery-only group compared to 27.5% in the CRT group. There were more microscopically irradical (R1) resections in the CRT group. Although Lauren classification was not available for all patients, in the CRT group there were less intestinal-type and more diffuse-type tumors. Tumor and nodal stages were more advanced in the CRT group.

Figure 4. Kaplan-Meier survival curves for MI < 5 versus MI ≥ 5, pooled data from all 716 patients in which the Maruyama Index was calculated

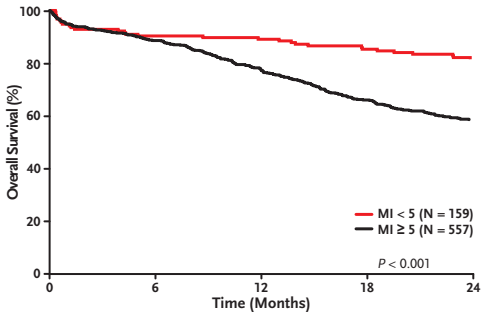
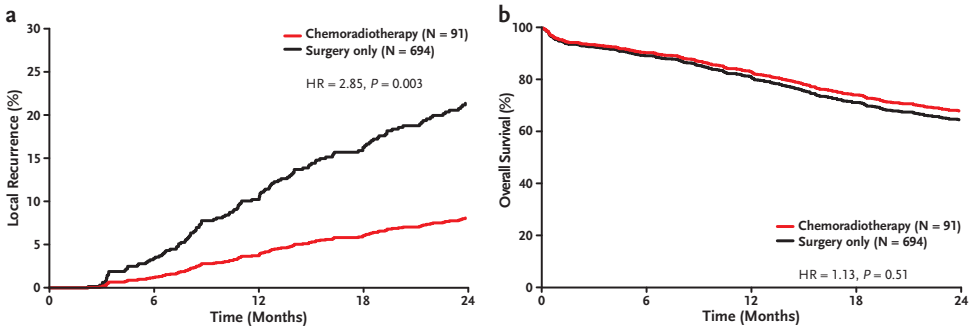


Figure 5. Multivariate analysis with adjustment for Maruyama Index, (a) local recurrence, (b) overall survival



OVERALL SURVIVAL, RECURRENCE-FREE SURVIVAL, AND RECURRENCE RATES

At time of analysis, median follow-up in the CRT group was 19 months, as compared to 51 months in the surgery only group.

Survival and recurrence analyses revealed a significant decrease in local recurrence rate in the CRT group as compared to the surgery only group (HR 3.23, $P = 0.0015$, Figure 3a). Model-based local recurrence percentages after 2 years were 5% for the CRT group, and 17% for the surgery only group. This, however, did not translate into a significant difference in 2-year overall survival (71% versus 67%, HR 1.14, $P = 0.51$, Figure 3b) or recurrence-free survival (HR 0.86, $P = 0.53$, not shown). Analysis of the regional recurrence rate (peritoneal carcinomatosis) showed an advantage for the surgery only group (6% versus 3%, HR 0.48, $P = 0.05$, not shown). There was no significant difference in distant recurrence rate (HR 0.98, $P = 0.95$, not shown).

Subgroup analysis for the extent of lymphadenectomy revealed that the decrease in local recurrence rate was largest in patients who underwent a D1 lymphadenectomy. The rate of local recurrence after 2 years was significantly lower in the CRT-D1 group compared to the surgery-only-D1 group (2% versus 18%, HR 11.10, $P = 0.001$, Figure 3c). However,

overall survival again was not different between these two groups (80% versus 72%, HR 1.46, $P = 0.18$, Figure 3d). There were no differences between patients who underwent a D2 resection followed by chemoradiation or a D2 resection alone with regards to local recurrence rate (12% versus 13%, HR 1.10, $P = 0.84$, Figure 3e) and overall survival (64% versus 63%, HR 1.05, $P = 0.88$, Figure 3f).

Subgroup analyses of radical (R0) and microscopically irradical (R1) gastrectomies demonstrated a significant improvement in 2-year overall survival in the CRT group following an R1 resection as compared to the surgery-only-R1 group (66% versus 29%, HR 2.91, $P = 0.002$). This coincided with a significant decrease in the local recurrence rate in the CRT-R1 group (6% versus 26%, HR 5.36, $P = 0.02$) and no significant differences in regional and distant recurrence rates. Although the local recurrence rate was significantly lower in the CRT-R0 group compared to the local recurrence rate for the surgery-only-R0 group (5% versus 13%, HR 2.53, $P = 0.03$), there was no significant difference in survival for patients in this subgroup.

MARUYAMA INDEX

The MI was calculated for 78 out of 91 patients in the CRT group, and for 638 out of 694 patients in the surgery-only group. Median MI in the CRT group was 74.5 compared to 25.5 in the surgery-only group. This difference is mainly explained by the low number of D2 dissections in the CRT group, in which only 6 patients had an MI < 5 (7.6%), compared to 153 (24.0%) with an MI < 5 in the surgery-only group.

Using pooled data from the CRT and the surgery-only group, comparison of patients with MI < 5 versus MI ≥ 5 shows that survival is superior for patients with an MI < 5 with 2-year survival rates of 82% versus 59% ($P < 0.001$, Figure 4). In this analysis, only the predictive power of MI is tested. The number of patients in the CRT group was too low to test the predictive value of MI within this group.

To assess the probability that patients who receive postoperative chemoradiation benefit over patients with the same MI who receive only surgery, a multivariate analysis between the two groups, with only MI as a linear covariate, was performed. This analysis revealed a significant benefit in time to local recurrence for the CRT group (8% versus 22%, HR 2.85, $P = 0.003$), and, again, no significant difference in 2-year overall survival between the groups (68% versus 65%, HR 1.13, $P = 0.51$) (Figure 5).

DISCUSSION

Extended lymph node dissection in resectable gastric cancer has never been indisputably proven to increase survival significantly in Western studies.[5-7] Several (neo)adjuvant treatment strategies have been studied in order to improve outcome for patients with gastric cancer,[29,30] but it was not until 2001, and again in 2006, that two studies revealed that patients with gastric cancer could actually benefit from such a treatment strategy.[11,12] The Intergroup 0116 trial, which now has a median follow-up of more than 10 years,

showed a significant benefit in overall survival and locoregional recurrence after postoperative CRT.[11,14] This study has received major criticism because 54% of all patients underwent a D0 gastrectomy instead of the recommended D2 gastrectomy, leading to the hypothesis that postoperative CRT might have compensated for suboptimal surgery. Notwithstanding this, no significant differences in relapse-free survival or overall survival could be detected according to the extent of the dissection.[31] Moreover, a Korean observational study did show an advantage in overall survival of 95.3 months versus 62.6 months, respectively, in 990 patients who underwent a D2 lymphadenectomy plus postoperative chemoradiation (Intergroup 0116 scheme) or D2 dissection alone.[32]

In the present retrospective study, we demonstrate that postoperative chemoradiation leads to a reduction in the local recurrence rate (5% versus 17% after 2 years), without an advantage in regional or distant recurrence rate. This difference in recurrence does not lead to a significant decrease in 2-year overall survival. This may be due to the relatively short median follow-up period of 19 months. The effect on local recurrence persists when adjusting for MI, which has shown to be a strong independent predictive parameter for relapse-free and overall survival.[15,16] The effect of CRT on local recurrence is especially strong in patients who received a D1 lymphadenectomy (2% versus 18% after 2 years), with possibly a trend towards longer overall survival.

In contrast to the benefit of chemoradiotherapy for patients receiving a D1 gastrectomy, subgroup analysis of patients who underwent a D2 lymph node dissection shows no advantage for postoperative CRT. Although the limited number of patients in the CRT-D2 group could have influenced this moderate effect of chemoradiation in the D2 group, it suggests that, in the Western population, postoperative chemoradiotherapy has a higher impact following a D1 dissection than a D2 dissection. And consequently, one questions whether a limited D1 dissection combined with CRT is equal to an extended nodal resection and/or a more extensive gastric resection.

Another subgroup that seems to particularly benefit from CRT is the subgroup of patients with an R1 resection. In this group, CRT improves both local recurrence rate and overall survival.

Despite the benefit of CRT on local recurrence, the regional recurrence rate (peritoneal carcinomatosis) is higher in the CRT group. As the multivariate analyses were adjusted for Lauren classification, the higher number of diffuse tumors in the CRT group cannot explain this observation. A possible explanation might be the more intensive follow-up with bi-annual CT scanning in the CRT group, which could have led to the earlier detection of asymptomatic ascites or peritoneal thickening. If this would be the case, this would underscore the power of local recurrence analyses as well, since the lowest local recurrence rates were found in a more intensively monitored group.[17-19] There is no significant difference in the number of distant recurrences, which might be explained by the fact that the more aggressive locoregional treatment has limited effect on systemic recurrences.

For the Intergroup 0116 study and the DGCT, MI has shown to be a strong independent predictor of survival and recurrence, whereas thus far the type of lymph node dissection has not. In the current study, MI shows to have a strong predictive value, as patients with an MI < 5 have superior 2-year overall survival rates.

We emphasize that only a prospective randomized trial can provide definite answers to the question whether postoperative CRT has a clinical benefit over surgery with extended lymphadenectomy. Currently two such studies aim to answer this question. In a Korean trial, all patients will undergo D2 lymphadenectomy, followed by postoperative chemotherapy with or without concurrent radiotherapy (clinicaltrials.gov NCT00323830). In the second study, performed in the Netherlands and Sweden, patients will receive 3 courses of ECC (epirubicin, cisplatin, capecitabine) followed by D2 lymphadenectomy without splenectomy and pancreatectomy, followed by either 3 additional courses of ECC or chemoradiation (capecitabine and cisplatin) (CRITICS, clinicaltrials.gov NCT00407186).

In conclusion, postoperative chemoradiation following surgery has a major impact on local recurrence in operable gastric cancer, while there seems to be no additional benefit on regional and distant recurrences. Especially patients with a limited D1 resection and patients with a microscopically irradical resection seem to benefit from CRT following surgery. Patients with a microscopically irradical (R1) resection also have a better overall survival following CRT.

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