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ORIGINAL ARTICLE

Adjuvant chemotherapy is superior to chemoradiation after D2 surgery for gastric cancer in the per-protocol analysis of the randomized CRITICS trial

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Available online 20 November 2020

Background: The Intergroup 0116 and the MAGIC trials changed clinical practice for resectable gastric cancer in the Western world. In these trials, overall survival improved with post-operative chemoradiotherapy (CRT) and perioperative chemotherapy (CT). Intention-to-treat analysis in the CRITICS trial of post-operative CT or post-operative CRT did not show a survival difference. The current study reports on the per-protocol (PP) analysis of the CRITICS trial.

Patients and methods: The CRITICS trial was a randomized, controlled trial in which 788 patients with stage Ib—IVa resectable gastric or esophagogastric adenocarcinoma were included. Before start of preoperative CT, patients from the Netherlands, Sweden and Denmark were randomly assigned to receive post-operative CT or CRT. For the current analysis, only patients who started their allocated post-operative treatment were included. Since it is uncertain that the two treatment arms are balanced in such PP analysis, adjusted proportional hazards regression analysis and inverse probability weighted analysis were used to minimize the risk of selection bias and to estimate and compare overall and event-free survival.

Results: Of the 788 patients, 478 started post-operative treatment according to protocol, 233 (59%) patients in the CT group and 245 (62%) patients in the CRT group. Patient and tumor characteristics between the groups before start of the post-operative treatment were not different. After a median follow-up of 6.7 years since the start of post-operative treatment, the 5-year overall survival was 57.9% (95% confidence interval: 51.4% to 64.3%) in the CT group versus 45.5% (95% confidence interval: 39.2% to 51.8%) in the CRT group (adjusted hazard ratio CRT versus CT: 1.62 (1.24-2.12), $P = 0.0004$). Inverse probability weighted analysis resulted in similar hazard ratios.

Conclusion: After adjustment for all known confounding factors, the PP analysis of patients who started the allocated post-operative treatment in the CRITICS trial showed that the CT group had a significantly better 5-year overall survival than the CRT group (NCT00407186).

Key words: gastric cancer, per-protocol analysis, survival, post-operative treatment, chemoradiotherapy, chemotherapy

INTRODUCTION

Gastric cancer is one of the most frequently occurring cancers and one of the top three causes of tumor-related death worldwide.[1] Surgery is still the cornerstone of treatment. The extent of surgery, and especially the extent of lymph node dissection, contributes to a better survival over the last two decades.[2,3] The US Intergroup 0116 and the British MAGIC trial changed clinical practice for resectable gastric cancer in the USA and Europe.[4,5] Overall survival

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after surgery improved with post-operative chemoradiotherapy (CRT) and perioperative chemotherapy (CT), respectively. Building on these two regimens, the CRITICS trial was initiated in 2007. In this study, patients were randomized before start of preoperative treatment between perioperative CT or preoperative CT with post-operative CRT. Intention-to-treat (ITT) analysis in the CRITICS trial did not show a survival difference between the two treatment arms. At a median follow-up of 61.4 months, the median overall survival was 43 months [95% confidence interval (CI): 31-57] in the CT group and 37 months (95% CI: 30-48) in the CRT group.[6] The preoperative CT adherence and the percentage of patients who proceeded to surgery were similar in both groups. However, only about 60% of patients started post-operative treatment. The main reasons for not starting post-operative treatment were patient refusal, progressive or unresectable disease, toxicity during preoperative treatment, poor condition and death.[6]

As the difference in treatments between the randomized arms in the CRITICS trial started in the post-operative phase, a *post hoc* per-protocol (PP) analysis was carried out to compare overall survival, event-free survival, recurrence and patterns of recurrence in those patients who started post-operative treatment.

MATERIAL AND METHODS

CRITICS protocol

The CRITICS trial was a randomized, controlled trial in which 788 patients with stage Ib—IVa resectable gastric or esophagogastric adenocarcinoma (TNM 6th edition) were included. Patients from the Netherlands, Sweden and Denmark were randomly assigned to receive preoperative CT followed by D2 surgery and post-operative CT or CRT. CT consisted of three preoperative 21-day cycles and three post-operative cycles of intravenous epirubicin, cisplatin or oxaliplatin, and capecitabine. CRT consisted of 45 Gy in 25 fractions of 1.8 Gy, for 5 weeks, five daily fractions per week, combined with capecitabine and cisplatin. If a D1+ lymph node dissection was carried out (station 1-11 excluding station 10), we considered this a D2 lymph node dissection since the two have similar oncological outcomes.[7] The complete CRITICS treatment protocol has been reported previously by Dikken et al.[8]

Outcomes

Overall survival in the ITT analysis was defined as the time from randomization to the time of death by any cause, or to the time of last follow-up (censoring). Event-free survival was defined as the time from randomization until disease progression, unresectable disease at surgery, tumor recurrence after potentially curative surgery or death by any cause.

In the *post hoc* PP analysis, overall survival was defined as the time from the start of the post-operative treatment to the time of death from any cause, or to the time of last follow-up (censoring). Event-free survival was defined as the time from the start of the post-operative treatment to tumor recurrence or death from any cause, or last follow-up (censoring). Sites of progressive or recurrent disease were categorized as locoregional, peritoneal, distant or multiple sites (occurring within 30 days from each other). Locoregional disease was defined as tumor in the original location, adjacent organ, regional lymph nodes (stations 1-13), anastomosis, ligamentum falciforme, ingrowth into the transverse mesocolon, ingrowth into the ligamentum hepatoduodenale, portal vein or liver hilus. Distant disease was defined as tumor in the liver, colon, lung, pleura, brain, bone, lymph nodes (stations 14-16), gallbladder, adnexa or duodenum. Peritoneal disease was defined as tumor in the peritoneum, lesser/greater omentum, transverse mesocolon, diaphragm and/or presence of ascites. The patterns of recurrence were analyzed in the ITT analysis as in the PP analysis.

Procedures

Follow-up visits were every month in the first 3 months after post-operative treatment and every 3 months during the remainder of the first year. In the second year, patients had follow-up visits every 6 months until 5 years. During follow-up, computed tomography scans of the thorax/abdomen were carried out every 6 months in the first 2 years and then annually until 5 years. Positron emission tomography scans were optional. Complications were categorized in general (e.g. cardiovascular, pulmonary, renal and neurological), infectious (e.g. abdominal wound, abscess and sepsis) and surgery-related complications (bleeding, anastomotic leakage, abdominal wound dehiscence, ileus and intestinal necrosis). Toxicity was assessed before and after each CT cycle according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE; version 3.0).[9]

Statistical analysis

The objective of this paper was to describe the outcomes of patients who actually started post-operative treatment, a so-called PP analysis. Since the two treatment arms may not be balanced in such a PP analysis, adjusted proportional hazards regression analysis (adjusting for baseline, preoperative CT, surgery and pathology variables) and inverse probability weighted (IPW) analysis were used to estimate and compare overall and event-free survival.

All patients who completed preoperative treatment and subsequent surgery, and at least started post-operative treatment, were included in these analyses. Patients with progression of disease at the start of post-operative treatment and who started palliative CT were excluded. We adjusted for all known and available factors that could possibly be related to both compliance and survival. These

included country, age, sex, histological subtype at randomization, World Health Organization performance status at randomization, number of preoperative courses, pathological TNM (tumour—node—metastasis) stage (according to the sixth edition of the American Joint Committee on Cancer Staging Manual), radicality of resection (R0 vs R1, R0 defined as more than 1 mm resection margin), post-operative complications and pathological tumor response. Kaplan—Meier survival curves were used to estimate the (unadjusted) survival curves, and the log-rank test was used to test for differences between the (unadjusted) survival curves. Cox proportional hazards model was used for adjusted comparisons.

The IPW analysis was carried out to account for potential differences due to differential attrition in the two treatment arms, by weighting the inverse of the probability of attrition. A time-dependent Cox regression model was used to model time to drop-out. Patients who started post-operative treatment were subsequently compared by a second Cox regression model, with overall survival (measured from the start of post-operative treatment) as the outcome, treatment as the only variable and with subjects weighted by the inverse of the probability of not having dropped out by the start of their post-operative treatment, given by the first time-dependent Cox regression model. For the time-dependent Cox model, the same variables were used as for the adjusted proportional hazards analysis.

Heterogeneity of treatment effects was assessed by including an interaction between the factor of interest and treatment in the multivariable proportional hazards model. Results of subgroup analyses (histology, age, sex, tumor location, radicality of resection, pathological T-stage and pathological N-stage) are presented in a forest plot, as hazard ratio (HR) band 95% CI for CRT compared with CT in the multivariable proportional hazards model with factor of interest excluded.

Time to first site-specific progression or recurrence accounted for competing risks and was summarized as cumulative incidence functions.

RESULTS

ITT

From January 2007 to April 2015, 788 patients were randomized, 393 patients in the CT group and 395 patients to the CRT group (Figure 1). Ninety-four percent of all patients proceeded to surgery and about 80% of all patients had a resection with potentially curative intent. Median follow-up from randomization was 7 years. Overall survival was not significantly different between the treatment arms in the updated ITT analysis [HR (CRT compared with CT) 1.05, 95% CI: 0.88-1.26, $P = 0.57$] (Figure 2). Patterns of recurrence based on the ITT analysis did not show significant differences between the two treatment arms (Table 1).

PP analysis

In the CT group, 79% of patients had a resection with potentially curative intent versus 83% in the CRT group. Post-operative treatment was started in 233 patients (59%) in the CT arm and in 245 patients (62%) in the CRT arm (Figure 1). Characteristics for patients who started post-operative therapy were not statistically different between the two treatment groups (Table 2).

Time interval between randomization and start of post-operative treatment was between 82 and 262 days in the CRT group (median 152 days) and between 88 and 284 days in the CT group (median 144 days) (supplementary Figure S1, available at https://doi.org/10.1016/j.annonc.2020.11.004).

In the CT group, 53 patients (23%) did not receive all three cycles of post-operative CT. In 39 patients (17%) this was due to toxicity. In the CRT group, 43 patients (18%) did not receive 5 weeks of CT (24 of 43 patients did receive radiation according to protocol). In 32 patients (13%), this was due to toxicity. In the CRT group, five patients (2%) did not receive 45 Gy of radiation (but all five received CT according to protocol). In two patients (1%), this was due to toxicity. Other reasons for not completing CT or CRT were

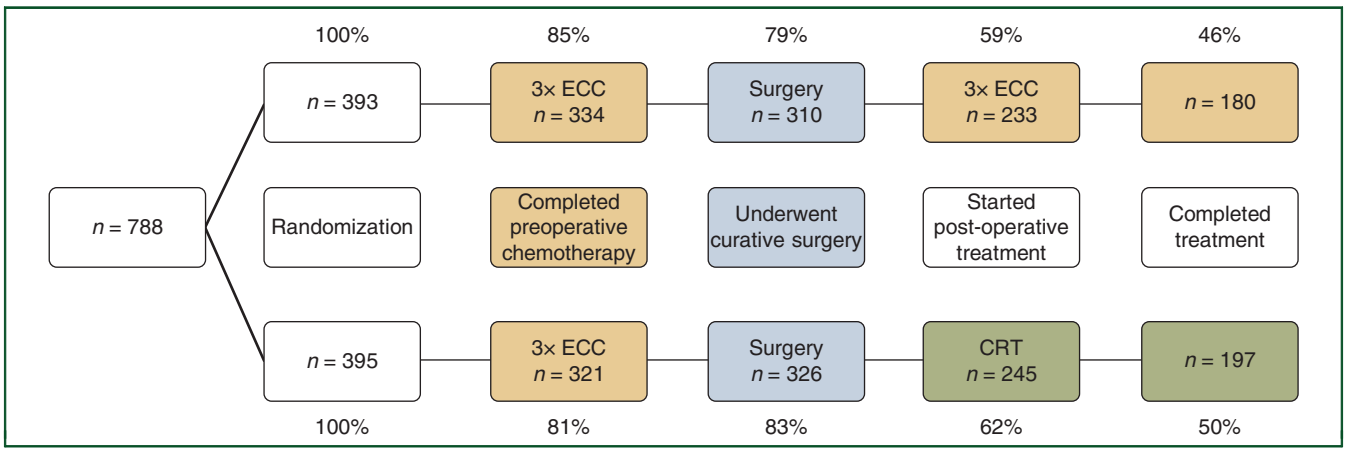

Figure 1. Study profile.
CRT, chemoradiotherapy 45 Gy/25 fractions + capecitabine + cisplatin; ECC, epirubicin, cisplatin/oxaliplatin and capecitabine (ECC/EOC).

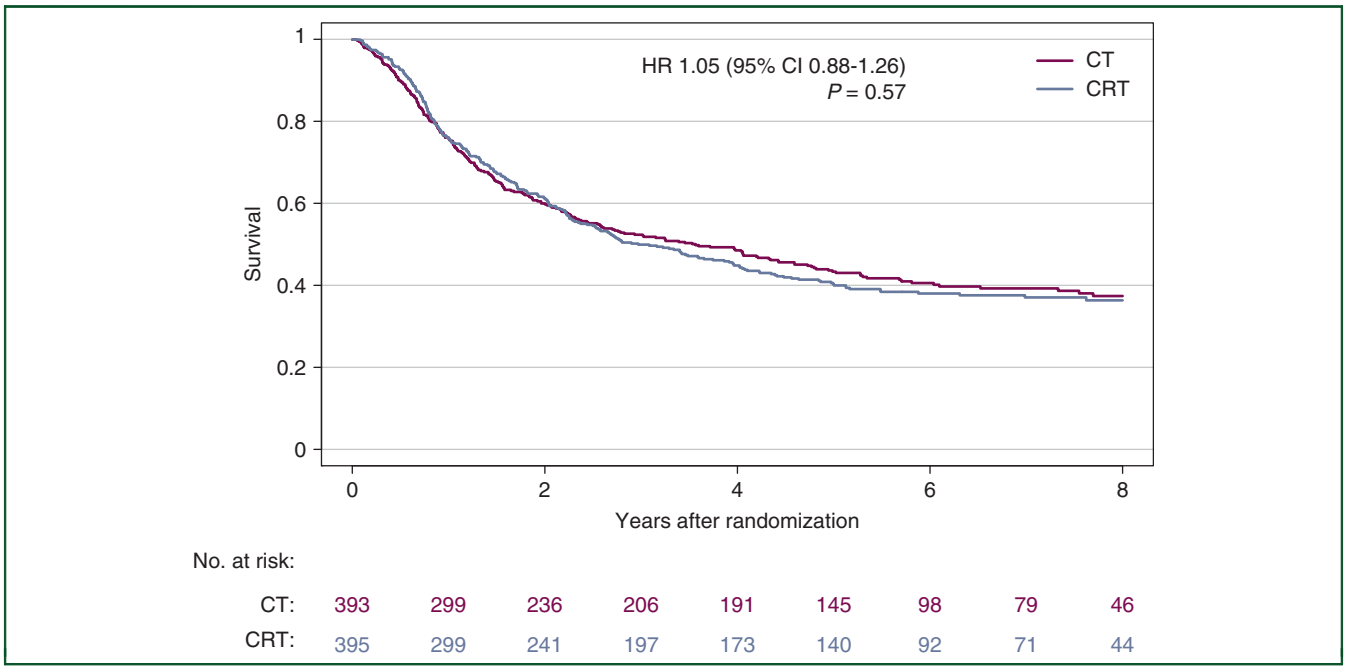

Figure 2. Kaplan–Meier curve overall survival for the chemotherapy and chemoradiotherapy group (update intention-to-treat).
CI, confidence interval; CRT, chemoradiotherapy; CT, chemotherapy; HR, hazard ratio.

progression of disease, refusal, personal event, poor condition, post-operative complications and protocol deviation.

With a median follow-up of 6.7 years from the start of post-operative randomized treatment, 104 of 233 patients (45%) in the CT group and 143 of 245 patients (58%) in the CRT group had died.

Proportional hazards regression analysis with multivariable adjustment for all confounding factors (indicated with superscript 'a' in Table 2) showed a significant difference in overall survival in favor of the CT group [adjusted HR 1.62 (95% CI: 1.24-2.12), $P = 0.0004$]. Variables that showed significant prognostic value with respect to overall survival included age, pathological TNM stage and radicality of resection (supplementary Table S1, available at https://doi.org/10.1016/j.annonc.2020.11.004).

Five-year unadjusted overall survival was 57.9% (95% CI: 51.4% to 64.3%) in the CT group versus 45.5% (95% CI: 39.2% to 51.8%) in the CRT group (Figure 3).

The IPW analysis showed an overall 5-year survival probability of 56.0% (95% CI: 50.4% to 62.2%) in the CT group versus 43.8% (95% CI: 38.4% to 50.0%) in the CRT group (HR 1.51, 95% CI: 1.14-1.99).

In the subgroup analysis for survival, there was evidence of heterogeneity of treatment for histology (*P* value for interaction 0.013) (supplementary Figure S2, available at https://doi.org/10.1016/j.annonc.2020.11.004). The subgroup analysis favors CT in intestinal type tumors, while no difference was seen between CRT and CT in diffuse type tumors. In the subgroup analysis, there was no benefit of CRT for patients with node-positive disease or patients with an R1 resection (supplementary Figure S2, available at https://doi.org/10.1016/j.annonc.2020.11.004).

For event-free survival in the PP analysis, 111 events in the CT group and 147 events in the CRT group were noted in 478 patients. Five-year unadjusted event-free survival was 55.0% (95% CI: 48.6% to 61.5%) in the CT group versus 43.6% (95% CI: 37.3% to 49.9%) in the CRT group [adjusted HR 1.53 (95% CI: 1.18-2.00), $P = 0.0014$] (Figure 4). Locoregional and distant recurrences in the PP analysis were evenly distributed over the treatment arms. Peritoneal metastases were seen less frequently in the CT group compared with the CRT group (2-year cumulative incidences, 4% versus 11%, $P = 0.005$) (Table 1 and Figure 5).

Table 1. Patterns of recurrence (intention-to-treat and per-protocol)

	CT		CRT		*P* value	CT		CRT		*P* value
	CI (%) 2-Year	CI (%) 5-Year	CI (%) 2-Year	CI (%) 5-Year		CI (%) 2-Year	CI (%) 5-Year	CI (%) 2-Year	CI (%) 5-Year	
Locoregional (only)	8	10	5	7	0.19	6	9	4	6	0.39
Peritoneal (only)	12	13	14	15	0.32	4	5	11	13	0.005
Distant (only)	10	15	10	13	0.7	12	17	11	15	0.62
Multiple sites	11	13	15	17	0.12	8	10	13	15	0.08
Total	41	51	44	52		30	41	39	49	

CI, confidence interval; CRT, chemoradiotherapy group; CT, chemotherapy group.

Table 2. Patient, surgical, and pathological characteristics of patients who started randomized treatment

	Chemotherapy group (n = 233)	Chemoradiotherapy group (n = 245)	P value
Age (years) at randomization[a]			
Age; mean (standard deviation)	59.2 (10.5)	59.9 (10.3)	0.438
<60	108 (46.4)	112 (45.7)	0.975
60-69	84 (36.1)	88 (35.9)	
≥70	41(17.6)	45 (18.4)	
Country[a]			0.524
The Netherlands	182 (78.1)	197 (80.4)	
Sweden	45 (19.3)	45 (18.4)	
Denmark	6 (2.6)	3 (1.2)	
Sex[a]			0.159
Male	168 (72.1)	161 (65.7)	
Female	65 (27.9)	84 (34.3)	
WHO at randomization[a]			0.438
0	164 (70.4)	176 (71.8)	
1	57 (24.5)	62 (25.3)	
Unknown	12 (5.2)	7 (2.9)	
Number of preoperative courses[a]			0.085
1	1 (0.4)	7 (2.9)	
2	9 (3.9)	13 (5.3)	
3	223 (95.7)	225 (91.8)	
Histological subtype at randomization/biopsy[a]			0.86
Intestinal	75 (32.2)	79 (32.2)	
Diffuse	66 (28.3)	76 (31.0)	
Mixed	13 (5.6)	15 (6.1)	
Unknown	79 (33.9)	75 (30.6)	
Tumor localization at randomization			0.663
Gastro-esophageal junction	34 (14.6)	38 (15.5)	
Proximal stomach	47 (20.2)	47 (19.2)	
Middle stomach	74 (31.8)	67 (27.3)	
Distal stomach	78 (33.5)	93 (38.0)	
Type of resection			0.899
Total gastrectomy	113 (48.5)	119 (48.6)	
Subtotal gastrectomy	95 (40.8)	101 (41.2)	
Oesophago-cardiac resection	25 (10.7)	23 (9.4)	
Unknown	0 (0.0)	2 (0.8)	
Type of lymph node dissection			0.217
<D1+	26 (11.2)	36 (14.7)	
D2	202 (86.7)	199 (81.2)	
D3	0 (0.0)	2 (0.8)	
Unknown	5 (2.1)	8 (3.3)	
Splenectomy			0.727
Yes	12 (5.2)	10 (4.1)	
No	221 (94.8)	235 (95.9)	
Unknown	0 (0.0)	0 (0.0)	
Distal pancreatectomy			0.176
Yes	1 (0.4)	6 (2.4)	
No	232 (99.6)	239 (97.6)	
Radicality of resection[a]			0.417
R0	216 (92.7)	221 (90.2)	
R1	17 (7.3)	24 (9.8)	
Post-operative surgical complication[a]			0.735
Yes	40 (17.2)	46 (18.8)	
No	193 (82.8)	199 (81.2)	
Post-op infectious complication[a]			0.306
Yes	39 (16.7)	51 (20.8)	
No	194 (83.3)	194 (79.2)	
Post-operative general complication[a]			0.733
Yes	53 (22.7)	60 (24.5)	
No	180 (77.3)	185 (75.5)	
Re-intervention due to complications			0.352
Yes	17 (7.3)	25 (10.2)	
No	213 (91.4)	219 (89.4)	
Unknown	3 (1.3)	1 (0.4)	
Pathological complete response[a]			
Yes	13 (5.6)	12 (4.9)	0.192
No	213 (91.4)	217 (88.6)	
Unknown	7 (3.0)	16 (6.5)	
pTNM stage[a]			
IA	40 (17.2)	45 (18.4)	0.063
IB	55 (23.6)	44 (18.0)	
II	49 (21.0)	69 (28.2)	
IIIA	56 (24.0)	39 (15.9)	
IIIB	11 (4.7)	17 (6.9)	
IV	22 (9.4)	31 (12.7)	

Age is presented as mean (standard deviation) and as n (%); other data are presented as n (%).

TNM, tumour—node—metastasis; WHO, World Health Organization.

[a] Variable included in both the adjusted proportional hazards regression analysis and inverse probability weighted analysis.

DISCUSSION

The ITT analysis of the CRITICS trial data did not show a survival benefit between the two treatment arms. The results of the PP analysis showed that, from those patients who started the allocated post-operative treatment, the CT group had a significant better 5-year overall survival compared with the CRT group. In the Intergroup 0116 trial, post-operative CRT significantly improved survival after surgery compared with surgery alone.[4] The 5-year overall survival rate was significantly higher in patients who underwent CRT (40% versus 28%), which was confirmed in an update with follow-up of more than 10 years.[10] This trial was, however, criticized for the fact that only 10% of all patients had an adequate (D2) lymph node dissection according to the study protocol. It has been suggested that adjuvant CRT compensated for inadequate surgery by improving loco-regional control.[4]

Evaluation of the surgical quality in the CRITICS trial showed that 88% of all operated patients had a D2 lymph node dissection or more and an average of 20 lymph nodes was evaluated per patient.[11] R0 resections were achieved in 82% of patients. Although patients with an R1 resection have a high likelihood of recurrence, we decided, in order to prevent selection bias, that these patients (7.3% in the CT group and 9.8% in the CRT group) should be included in this PP analysis. The median Maruyama index, which is considered to be the most important quality indicator of the lymph node dissection during gastric cancer surgery, was 1 (= very good) in the CRITICS-trial. This contrasts with a Maruyama index of 26 in the Dutch Gastric Cancer Trial and 70 in the Intergroup 0116 trial.[2,4] The quality in the two treatment arms in the CRITICS trial in terms of surgical performance or complications was equal and could, therefore, be an explanation for the lack of benefit of adjuvant

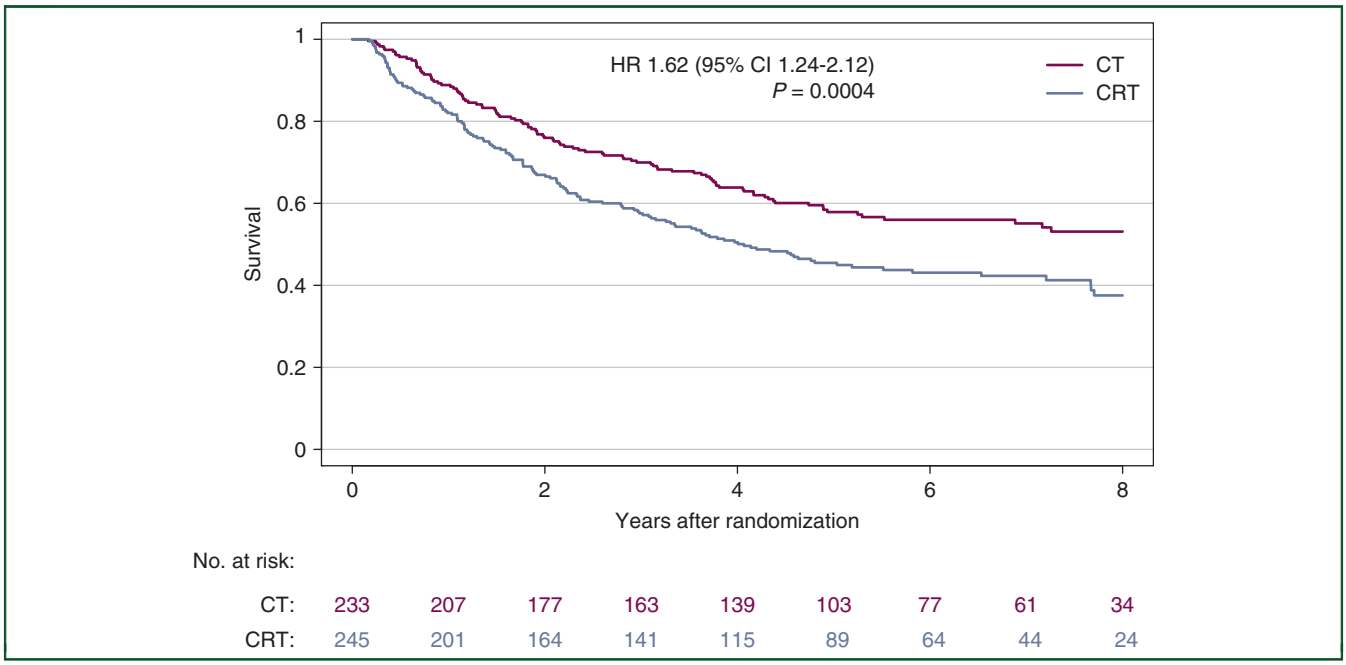

Figure 3. Kaplan–Meier curve overall survival for the chemotherapy and chemoradiotherapy group (per-protocol).
CI, confidence interval; CRT, chemoradiotherapy; CT, chemotherapy; HR, hazard ratio.

chemoradiation compared with adjuvant CT. Similarly, in the ARTIST trial, in which patients with adenocarcinoma of the stomach who had an R0 resection with a D2 lymph node dissection were randomized between CT and CRT,[12] there was no significant difference between the two treatment arms. However, in a subgroup analysis, there was a significant benefit for CRT in those patients with node-positive disease.[13] Interim results of the ARTIST-II randomized trial in stage II/III patients showed no added benefit of adjuvant chemoradiation compared with adjuvant CT (Clinical-Trials.gov identifier: NCT01761461). In our subgroup analysis, there was no benefit of CRT for patients with node-positive disease or for patients with an R1 resection.

With the combination of optimal preoperative CT (85% in the CT group and 81% in the CRT group completed preoperative treatment) and optimal surgery, maximal local control was achieved. Nevertheless, some recurrences were seen in both treatment arms. Most tumors recur within the

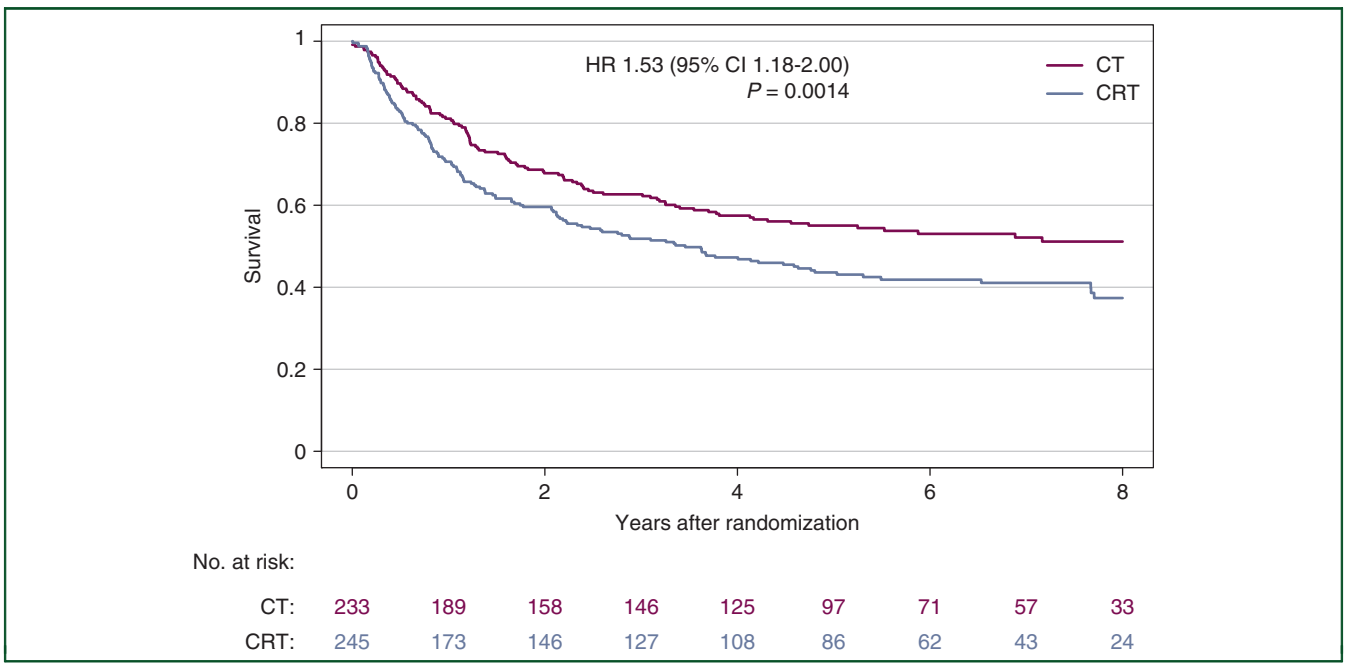

Figure 4. Kaplan–Meier curve event-free survival for the chemotherapy and chemoradiotherapy group (per-protocol).
CI, confidence interval; CRT, chemoradiotherapy; CT, chemotherapy; HR, hazard ratio.

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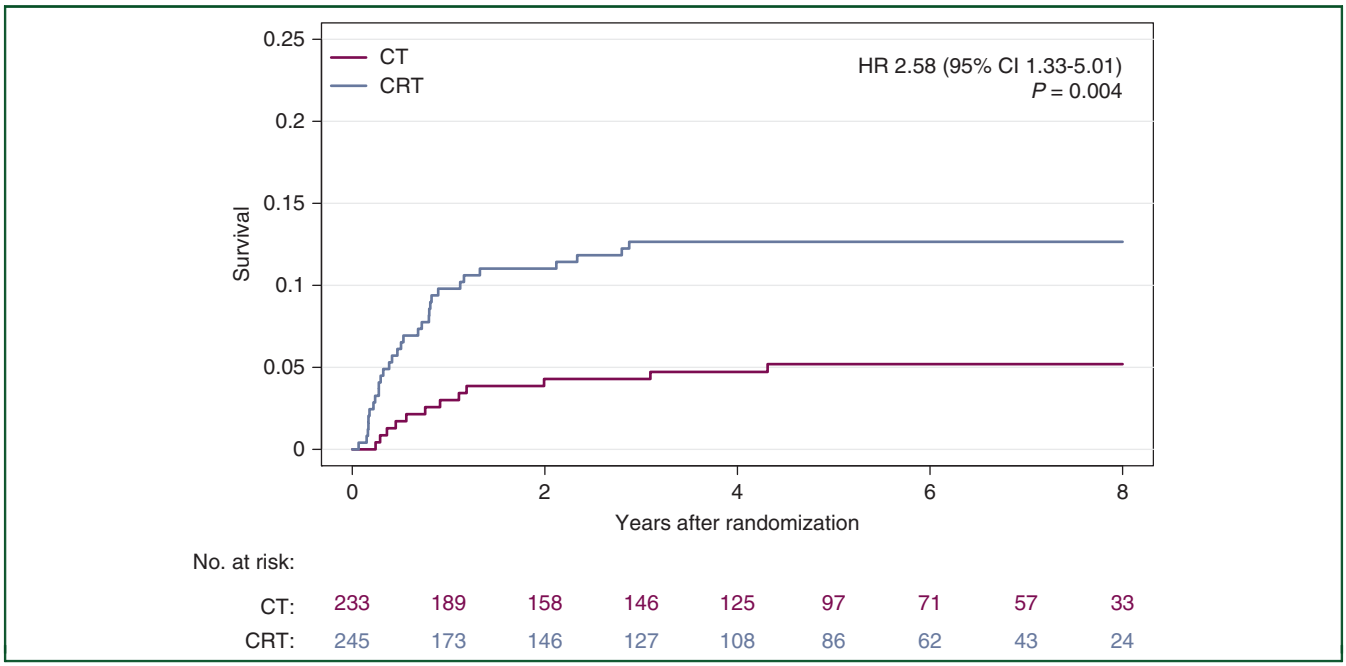

Figure 5. Survival probability peritoneal recurrence for the chemotherapy and chemoradiotherapy group (per-protocol).
CI, confidence interval; CRT, chemoradiotherapy; CT, chemotherapy; HR, hazard ratio.

first 2 years after treatment. Cumulative incidences at different sites were comparable between post-operative CT and post-operative CRT in the ITT analysis. However, the cumulative incidences in the PP analysis showed that peritoneal metastases occurred less often in the CT group. Peritoneal dissemination is associated with a very poor prognosis, which could explain the superior outcome of adjuvant CT versus adjuvant chemoradiation in the PP survival curves. Since different definitions for patterns of recurrence are used in different trials, it is difficult to compare our results with other studies.

Perioperative CT with fluorouracil plus leucovorin, oxaliplatin and docetaxel (FLOT) is the current standard of care in Europe for perioperative treatment of locally advanced resectable gastric cancer because of the improved survival compared with fluorouracil or capecitabine plus cisplatin and epirubicin (ECF/ECX).[14]

In this study patients were randomized before preoperative treatment. The disadvantage of the current analysis is that bias could have been introduced by differential attrition due to drop-out or death, so that the treatment arms may no longer be comparable at the start of post-operative randomized treatment. In our analyses, we have therefore adjusted for various known and available confounding factors that influence both survival and discontinuation of treatment (supplementary Table S1, available at https://doi.org/10.1016/j.annonc.2020.11.004). Age, radicality of resection and pathological stage were of significant influence on drop out during the study and survival and therefore possible factors for introducing bias. To minimize this bias, adjusted proportional hazards regression analysis and IPW analysis were carried out. After correction for these known factors, a survival benefit in the CT group remained. It should be noted that the validity of both analyses relies on the assumption of no unmeasured confounding, i.e. on the assumption that all possible confounders have been considered in the proportional hazards analysis and have been included in the model for drop-out in the IPW analysis. This assumption is intrinsically untestable; hence, although unlikely, we cannot exclude the possibility that, even after correction for the above factors, imbalance between the treatment arms has remained. Analysis of the patients who did not start post-operative treatment showed an opposite result. In this group, patients who were randomly allocated to the CRT group had a better survival. Unmeasured and currently unknown potential confounders may include molecular tumor characteristics or differences in the tumor (immune) microenvironment.

From studies using adjuvant treatment, it has become clear that for many patients it is difficult to complete post-operative treatment. Even in trials with post-operative randomization, like the Intergroup 0116 and the ARTIST trial, only 64% and 75%, respectively, managed to complete the adjuvant treatment.[4,15] In trials with preoperative treatment data are even worse. In the MAGIC trial only 55% of patients in the perioperative CT arm started post-operative treatment and 42% completed full treatment.[5] The same is the case for our trial, where only in about 60% of the randomized patients the allocated adjuvant treatment was started and only in about 50% the treatment was completed. We found no difference in the number of patients completing adjuvant treatment between the CT and CRT arms. With only about 50% of the patients completing the allocated treatment we must conclude that the regimen with pre- and post-operative treatment is often too demanding for patients. We therefore argue that new

regimens should focus on preoperative treatment. Several trials with this focus are currently accruing patients, including the TOPGEAR (NCT02661971) and CRITICS II trial (NCT02661971) in which CT or CRT, or a combination of those, is given preoperatively.[16,17]

Conclusion

The PP analysis of patients who started post-operative treatment in the CRITICS trial showed that after adjustment for all known confounding factors and acknowledging the limitations of a PP analysis, the CT group had a significantly better 5-year overall survival than the CRT group.

ACKNOWLEDGEMENTS

A complete list of contributors is provided in the supplementary Material, available at https://doi.org/10.1016/j.annonc.2020.11.004.

FUNDING

This work was supported by the Dutch Cancer Society [grant number NKI 2006-4167], Dutch Colorectal Cancer Group and Hoffman-La Roche. Dutch Cancer Society (CKTO 2006-02).

DISCLOSURE

MIVBH reports grants from Olympus and Stryker; personal fees from Johnson and Johnson, Medtronic, Mylan and Alesi Surgical. All fees paid to institution outside the submitted work.All remaining authors have declared no conflicts of interest.

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