Chemotherapy versus chemoradiotherapy after surgery and preoperative chemotherapy for resectable gastric cancer (CRITICS): an international, open-label, randomised phase 3 trial

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Summary

Background Both perioperative chemotherapy and postoperative chemoradiotherapy improve survival in patients with resectable gastric cancer from Europe and North America. To our knowledge, these treatment strategies have not been investigated in a head to head comparison. We aimed to compare perioperative chemotherapy with preoperative chemotherapy and postoperative chemoradiotherapy in patients with resectable gastric adenocarcinoma.

Methods In this investigator-initiated, open-label, randomised phase 3 trial, we enrolled patients aged 18 years or older who had stage IB– IVA resectable gastric or gastro-oesophageal adenocarcinoma (as defined by the American Joint Committee on Cancer, sixth edition), with a WHO performance status of 0 or 1, and adequate cardiac, bone marrow, liver, and kidney function. Patients were enrolled from 56 hospitals in the Netherlands, Sweden, and Denmark, and were randomly assigned (1:1) with a computerised minimisation programme with a random element to either perioperative chemotherapy (chemotherapy group) or preoperative chemotherapy with postoperative chemoradiotherapy (chemoradiotherapy group). Randomisation was done before patients were given any preoperative chemotherapy treatment and was stratified by histological subtype, tumour localisation, and hospital. Patients and investigators were not masked to treatment allocation. Surgery consisted of a radical resection of the primary tumour and at least a D1+ lymph node dissection. Postoperative treatment started within 4–12 weeks after surgery. Chemotherapy consisted of three preoperative 21-day cycles and three postoperative cycles of intravenous epirubicin (50 mg/m² on day 1), cisplatin (60 mg/m² on day 1) or oxaliplatin (130 mg/m² on day 1), and capecitabine (1000 mg/m² orally as tablets twice daily for 14 days in combination with epirubicin and cisplatin, or 625 mg/m² orally as tablets twice daily for 21 days in combination with epirubicin and oxaliplatin), received once every three weeks. Chemoradiotherapy consisted of 45 Gy in 25 fractions of 1·8 Gy, for 5 weeks, five daily fractions per week, combined with capecitabine (575 mg/m² orally twice daily on radiotherapy days) and cisplatin (20 mg/m² intravenously on day 1 of each 5 weeks of radiation treatment). The primary endpoint was overall survival, analysed by intention-to-treat. The CRITICS trial is registered at ClinicalTrials.gov, number NCT00407186; EudraCT, number 2006-004130-32; and CKTO, 2006-02.

Findings Between Jan 11, 2007, and April 17, 2015, 788 patients were enrolled and randomly assigned to chemotherapy (n=393) or chemoradiotherapy (n=395). After preoperative chemotherapy, 372 (95%) of 393 patients in the chemotherapy group and 369 (93%) of 395 patients in the chemoradiotherapy group proceeded to surgery, with a potentially curative resection done in 310 (79%) of 393 patients in the chemotherapy group and 326 (83%) of 395 in the chemoradiotherapy group. Postoperatively, 233 (59%) of 393 patients started chemotherapy and 245 (62%) of 395 started chemoradiotherapy. At a median follow-up of 61·4 months (IQR 43·3–82·8), median overall survival was 43 months (95% CI 31–57) in the chemotherapy group and 37 months (30–48) in the chemoradiotherapy group (hazard ratio from stratified analysis 1·01 (95% CI 0·84–1·22; p=0·90). After preoperative chemotherapy, in the total safety population of 781 patients (assessed together), there were 368 (47%) grade 3 adverse events; 130 (17%) grade 4 adverse events, and 13 (2%) deaths. Causes of death during preoperative treatment were diarrhoea (n=2), dihydropyrimidine deficiency (n=1), sudden death (n=1), cardiovascular events (n=8), and functional bowel obstruction (n=1). During postoperative treatment, grade 3 and 4 adverse events occurred in 113 (48%) and 22 (9%) of 233 patients in the chemotherapy group, respectively, and in 101 (41%) and ten (4%) of 245 patients in the chemoradiotherapy group, respectively. Non-febrile neutropenia occurred more frequently during postoperative chemotherapy (79 [34%] of 233) than during postoperative chemoradiotherapy (11 [4%] of 245). No deaths were observed during postoperative treatment.

Interpretation Postoperative chemoradiotherapy did not improve overall survival compared with postoperative chemotherapy in patients with resectable gastric cancer treated with adequate preoperative chemotherapy and surgery. In view of the poor postoperative patient compliance in both treatment groups, future studies should focus on optimising preoperative treatment strategies.

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See Online for appendix

Introduction

Gastric cancer ranks fifth in cancer mortality globally.[1] In patients from Europe and North America with localised or locally advanced disease, prognosis remains dismal after surgery alone, with most patients relapsing within 2 years after treatment. Extended lymph node dissections improve cancer-specific survival, but also increase surgical morbidity and mortality.[2,3]

In 2001, the US Intergroup 0116 trial[4] reported that postoperative fluorouracil monotherapy in combination with fluorouracil-based chemoradiotherapy improved both locoregional control and overall survival compared with surgery alone in medically fit patients who had a microscopically radical resection.[4] This beneficial effect persisted after more than 10 years of follow-up.[5] Meanwhile, results from the British Medical Research Council Adjuvant Gastric Infusional Chemotherapy (MAGIC) study showed that perioperative combination chemotherapy with epirubicin, cisplatin, and fluorouracil was associated with tumour downsizing and downstaging, and a significant overall survival benefit compared with surgery alone.[6]

We designed the ChemoRadiotherapy after Induction chemoTherapy In Cancer of the Stomach (CRITICS) study to incorporate both treatment strategies. The study addresses the question of whether postoperative chemoradiotherapy improves survival as compared with postoperative chemotherapy in patients who are treated with preoperative chemotherapy followed by surgery. Because oxaliplatin and capecitabine have equal efficacy and better tolerability than cisplatin and fluorouracil in advanced gastric cancer,[7] we substituted fluorouracil with capecitabine and used either cisplatin or oxaliplatin in the combination chemotherapy regimens.

Methods

Study design and participants

The CRITICS study is an investigator-initiated, open-label, randomised phase 3 trial, with patients recruited from the Netherlands (44 hospitals), Sweden (11 hospitals), and Denmark (one hospital; appendix pp 1–2). A detailed description of the study has been published previously.[8] The study protocol is provided in the appendix (pp 3–65).

Research in context

Evidence before this study

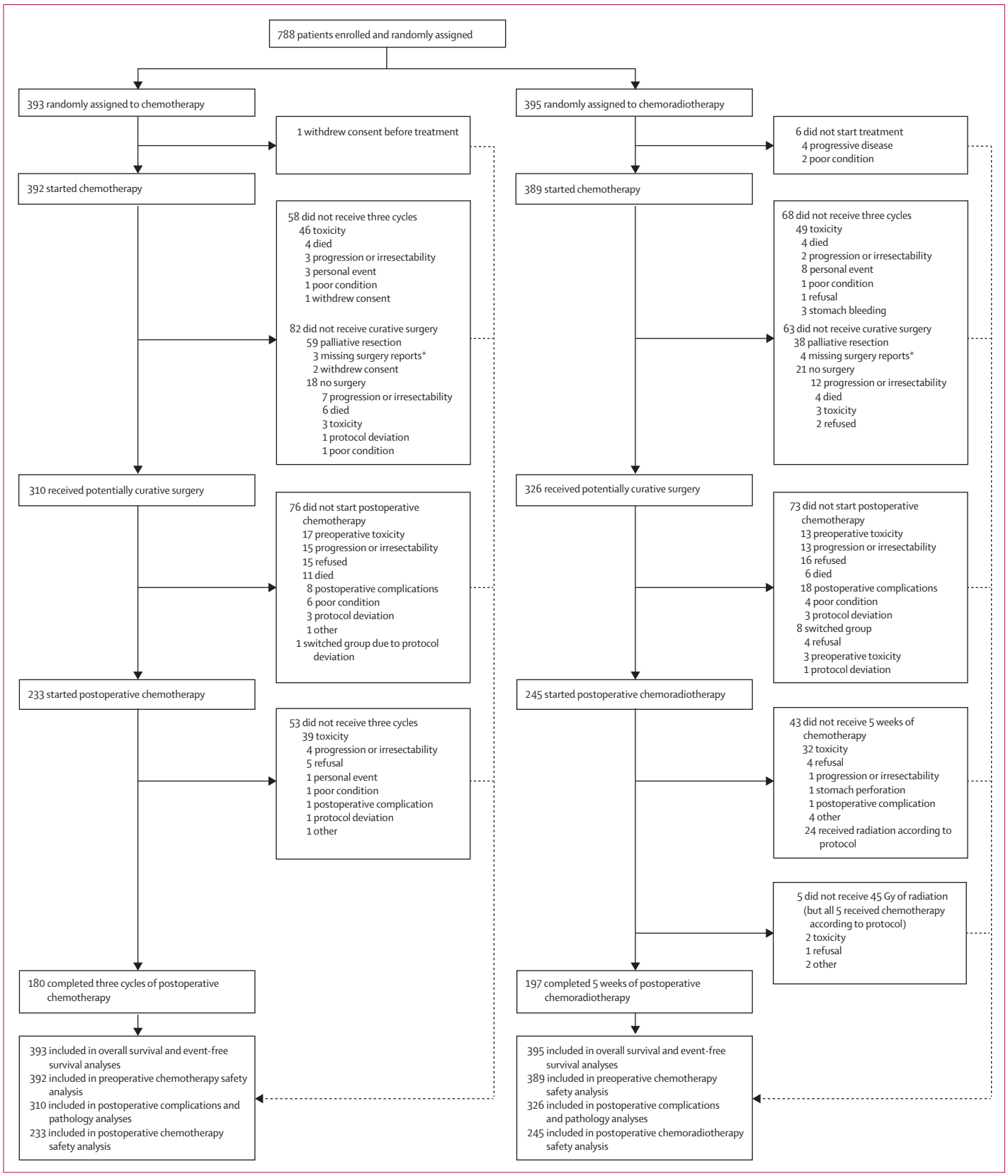
In March 15, 2006, when writing the study protocol, we searched PubMed and abstracts of the main annual oncology meetings for publications relating to adjuvant and neoadjuvant chemotherapy and chemoradiotherapy in patients with resectable gastric cancer. We limited this search to articles published in English since Jan 1, 2000. We used the search terms "gastric cancer", "stomach cancer", "adenocarcinoma", "neoadjuvant", "adjuvant", "preoperative", "postoperative", "chemotherapy", "chemoradiotherapy", "combined modality", "gastrectomy", "randomised", and "phase 3". Because of the substantial difference in treatment outcome and survival between patients from Europe and North America versus those from Asia, we focused on patients from Europe and North America. In 2001, the US Intergroup 0116 trial reported that postoperative chemoradiotherapy improved both locoregional control and overall survival compared with surgery alone, and consequently became the standard treatment in the USA. In 2006, the UK MAGIC trial showed tumour downsizing and downstaging and improvement in survival in patients receiving perioperative chemotherapy. This was corroborated by the findings of the French FFCD trial in 2011, and thus made perioperative chemotherapy the preferred treatment method in Europe.

Added value of this study

To our knowledge, this is the first trial directly comparing two standards of care used in high-income countries for adjuvant treatment in patients with resectable gastric cancer. However, because of the previously reported tumour downsizing and downstaging potential of chemotherapy, all patients in this study were treated with preoperative chemotherapy. Results of this trial are therefore of high clinical relevance for current practice in Europe and North America. For Asian countries, the results could also provide more insight into the role of postoperative chemoradiotherapy than has previously been published. Finally, in view of the multidisciplinary nature of both treatment groups, we paid special attention to quality assurance, ensuring that state-of-the-art surgery, chemotherapy, and radiotherapy were given to all patients (in previous studies one or more components of treatment were suboptimal).

Implications of all the available evidence

The results of this trial suggest that it is unlikely that patients with resectable gastric cancer treated with preoperative chemotherapy and adequate surgery benefit more from postoperative chemoradiotherapy than postoperative chemotherapy. The implication of the results is that preoperative chemotherapy with adequate surgery can be considered the backbone of resectable gastric cancer treatment. This trial provides a rationale to focus on preoperative strategies and to explore further intensification of the preoperative phase in future studies.


788 patients enrolled and randomly assigned
393 randomly assigned to chemotherapy
1 withdrew consent before treatment
392 started chemotherapy
58 did not receive three cycles
46 toxicity
4 died
3 progression or irresectability
3 personal event
1 poor condition
1 withdrew consent
82 did not receive curative surgery
59 palliative resection
3 missing surgery reports*
2 withdrew consent
18 no surgery
7 progression or irresectability
6 died
3 toxicity
1 protocol deviation
1 poor condition
310 received potentially curative surgery
76 did not start postoperative chemotherapy
17 preoperative toxicity
15 progression or irresectability
15 refused
11 died
8 postoperative complications
6 poor condition
3 protocol deviation
1 other
1 switched group due to protocol deviation
233 started postoperative chemotherapy
53 did not receive three cycles
39 toxicity
4 progression or irresectability
5 refusal
1 personal event
1 poor condition
1 postoperative complication
1 protocol deviation
1 other
180 completed three cycles of postoperative chemotherapy
393 included in overall survival and event-free survival analyses
392 included in preoperative chemotherapy safety analysis
310 included in postoperative complications and pathology analyses
233 included in postoperative chemotherapy safety analysis
395 randomly assigned to chemoradiotherapy
6 did not start treatment
4 progressive disease
2 poor condition
389 started chemotherapy
68 did not receive three cycles
49 toxicity
4 died
2 progression or irresectability
8 personal event
1 poor condition
1 refusal
3 stomach bleeding
63 did not receive curative surgery
38 palliative resection
4 missing surgery reports*
21 no surgery
12 progression or irresectability
4 died
3 toxicity
2 refused
326 received potentially curative surgery
73 did not start postoperative chemotherapy
13 preoperative toxicity
13 progression or irresectability
16 refused
6 died
18 postoperative complications
4 poor condition
3 protocol deviation
8 switched group
4 refusal
3 preoperative toxicity
1 protocol deviation
245 started postoperative chemoradiotherapy
43 did not receive 5 weeks of chemotherapy
32 toxicity
4 refusal
1 progression or irresectability
1 stomach perforation
1 postoperative complication
4 other
24 received radiation according to protocol
5 did not receive 45 Gy of radiation (but all 5 received chemotherapy according to protocol)
2 toxicity
1 refusal
2 other
197 completed 5 weeks of postoperative chemoradiotherapy
395 included in overall survival and event-free survival analyses
389 included in preoperative chemotherapy safety analysis
326 included in postoperative complications and pathology analyses
245 included in postoperative chemoradiotherapy safety analysis

Patients were eligible if they had histologically proven stage IB–IVA gastric adenocarcinoma (as defined by the American Joint Committee on Cancer, sixth edition),[9] as assessed by oesophagogastroduodenoscopy and CT of the chest, abdomen, and pelvis. Patients with tumours of the gastro-oesophageal junction were permitted to enrol when the bulk of the tumour was predominantly located in the stomach, and could therefore consist of Siewert types II and III tumours. Because the focus of the study was on gastric cancer, patients with Siewert type I tumours were not eligible. A diagnostic laparoscopy was indicated when the preoperative CT scan suggested peritoneal carcinomatosis. PET scans were optional and were done according to local practice when clinically indicated. To be eligible, patients also had to be 18 years or older, have a WHO performance status of 0 or 1, have adequate cardiac, bone marrow, liver, and kidney function, and have had no previous radiotherapy or chemotherapy that would affect treatment for gastric cancer. Eligible participants also had a left ventricular ejection fraction of at least 50% and urinary protein excretion of less than 1 g per 24 h. In case of insufficient caloric intake or substantial weight loss, oral nutritional support or enteral tube feeding was warranted. Exclusion criteria included T1N0 tumours as assessed by endoscopic ultrasound and previous malignancy, except adequately treated non-melanoma skin cancer and in-situ cancer of the cervix uteri. Other reasons for exclusion were a solitary functioning kidney that would be located within the radiation field, major surgery within 4 weeks before start of study treatment, or lack of complete recovery from previous surgery, uncontrolled cardiac or infectious disorders, continuous use of immunosuppressive drugs, or other conditions preventing the safe use of study drugs and treatment methods. A full list of exclusion criteria is provided in the appendix (p 15). On the basis of the survival curve of the perioperative chemotherapy group in the MAGIC study,[6] which showed a median overall survival of approximately 2 years, we estimated that life expectancy of patients in this study would be about 2 years.

The study was approved by the medical ethical committee of the Netherlands Cancer Institute and by the review boards of all participating centres. All patients provided oral and written informed consent.

Randomisation and masking

Patients were randomly assigned (1:1) to either perioperative chemotherapy or preoperative chemotherapy and postoperative chemoradiotherapy. We chose to do randomisation before the start of preoperative chemotherapy because this approach most closely reflects daily practice, with treatment decisions being made after the diagnostic process, and to avoid patient selection bias after surgery. Patients were enrolled and treated by the local investigators or their delegated staff at participating centres, and registration of eligible patients could be done by telephone, fax, or online for the Central Data center of the Department of Surgery at Leiden University Medical Center. After verification of eligibility criteria, we used the ALEA Randomisation computer programme, which implements a minimisation technique described by Pocock and Simon,[10] to randomly assign patients and stratify them according to histological subtype (Lauren classification: intestinal *vs* diffuse *vs* mixed *vs* unknown), tumour location (gastro-oesophageal junction *vs* proximal stomach *vs* middle stomach *vs* distal stomach), and hospital. Patients and investigators were not masked to treatment allocation.

Procedures

Preoperative chemotherapy consisted of three 21-day cycles of epirubicin, cisplatin or oxaliplatin, and capecitabine. Epirubicin 50 mg/m², cisplatin 60 mg/m², and oxaliplatin 130 mg/m² were given intravenously on day 1 of each 21-day cycle. Capecitabine was administered

	Chemotherapy group (n=393)	Chemoradiotherapy group (n=395)
Age (years)		
Median age (IQR)	62 (54–69)	63 (56–68)
<60	164 (42%)	155 (39%)
60–69	142 (36%)	155 (39%)
≥70	87 (22%)	85 (22%)
Sex		
Male	264 (67%)	265 (67%)
Female	129 (33%)	130 (33%)
WHO performance status		
0	260 (66%)	274 (69%)
1	103 (26%)	106 (27%)
Unknown	30 (8%)	15 (4%)
Histological subtype*		
Intestinal	127 (32%)	126 (32%)
Diffuse	116 (30%)	117 (30%)
Mixed	20 (5%)	22 (6%)
Unknown	130 (33%)	130 (33%)
Tumour localisation		
Gastro-oesophageal junction	68 (17%)	67 (17%)
Proximal stomach	79 (20%)	84 (21%)
Middle stomach	120 (31%)	117 (30%)
Distal stomach	126 (32%)	127 (32%)
Diagnostic laparoscopy		
Done	36 (9%)	43 (11%)
Not done	356 (91%)	352 (89%)
Unknown	1 (<1%)	0

*Histological subtype according to the Lauren classification.

Table 1: **Baseline characteristics**

Figure 1: **Trial profile**
*Of the seven patients with missing surgery reports, six received postoperative treatment as planned and one patient had no postoperative treatment.

at doses of 1000 mg/m² orally two times per day as tablets for 14 days in the epirubicin, cisplatin, and capecitabine regimen, and 625 mg/m² orally twice daily for 21 days in the epirubicin, oxaliplatin, and capecitabine regimen. In case of difficulties with ingestion of tablets, capecitabine could be replaced by fluorouracil 200 mg/m² daily by continuous infusion for 21 days. Response assessment with CT scan was done after two chemotherapy cycles to exclude early progression. When preoperative chemotherapy was postponed for more than 2 consecutive weeks, chemotherapy was discontinued and the patient proceeded to surgery when possible.

The intent of surgery was a radical resection of the primary tumour (by means of a total gastrectomy, subtotal gastrectomy, or oesophagocardiac resection) en bloc with the N1 and N2 lymph nodes (stations 1–9 and 11) and a minimum of 15 lymph nodes (D1+ lymph node dissection),[11] and, if possible, a macroscopic proximal and distal margin of 5 cm. A potentially curative resection was defined as no evidence of macroscopic residual disease at the end of the operation, as judged by the surgeon.

Postoperative treatment had to start within 4–12 weeks after surgery. The postoperative chemotherapy regimen consisted of the same chemotherapy regimen as administered preoperatively. Postoperative chemoradiotherapy was based on previous dose-finding studies.[12–14] Capecitabine was administered at a dose of 575 mg/m² orally twice daily on radiotherapy days, for 5 weeks, with five daily fractions per week. Cisplatin was administered at a dose of 20 mg/m² intravenously on the first day of each 5 weeks of radiotherapy treatment. The radiation dose was 45 Gy, given in 25 fractions of 1·8 Gy, for 5 weeks, with five daily fractions per week. The clinical target volume included the tumour bed, surgical anastomoses, and regional lymph node stations, which were individualised according to tumour localisation. The clinical target volume had to be delineated on CT images.

	Chemotherapy group	Chemoradiotherapy group
Preoperative chemotherapy	n=392	n=389
Epirubicin	97% (82–100)	95% (76–100)
Cisplatin	95% (81–100)	96% (82–100)
Oxaliplatin	98% (87–100)	93% (85–99)
Capecitabine	91% (73–100)	90% (71–100)
Postoperative chemotherapy	n=233	n=245
Epirubicin*	83% (63–99)	..
Cisplatin	87% (66–99)	98% (80–100)
Oxaliplatin*	72% (59–97)	..
Capecitabine	76% (54–93)	90% (77–100)

Values are median percentages (IQR) of recommended dose intensities. *Patients who received postoperative chemoradiotherapy did not receive epirubicin and oxaliplatin during radiotherapy.

Table 2: **Administered doses of chemotherapeutic drugs**

Each patient was assessed for medical history, physical examination, and blood tests before each chemotherapy cycle and once per week during chemoradiotherapy. We assessed toxicity before each chemotherapy cycle, once per week during chemoradiotherapy, and once per month during follow-up until 3 months, according to National Cancer Institute Common Toxicity Criteria for Adverse Events (CTCAE; version 3.0). Dose reductions in chemotherapy were permitted according to guidance in the study protocol, with a maximum dose reduction of 50% for capecitabine in case of persisting grade 3 or 4 adverse events. Cisplatin or oxaliplatin were discontinued in patients developing significant nephrotoxicity, ototoxicity, or sensory neuro-toxicity during preoperative and postoperative treatment. We categorised postoperative complications into general (eg, cardiovascular, pulmonary, renal, and neurological complications), infectious (eg, abdominal wound, abscess, and sepsis), and surgery-related complications (bleeding, anastomotic leakage, abdominal wound dehiscence, ileus, and intestinal necrosis). After postoperative treatment patients had follow-up visits every month during the first 3 months, every 3 months during the rest of the first year, followed by every 6 months until 5 years. During these follow-up visits, history, physical examination, and blood tests were assessed. CT scans of the thorax, abdomen, and pelvis were done every 6 months during the first 2 years and then once per year until 5 years. During follow-up, renography was done once per year in the chemoradiotherapy group.

On-site data monitoring was done with source verification for informed consent, inclusion and exclusion criteria, protocol procedures, missing data, and serious adverse events for at least the first five registered patients in all participating centres. Surgical and pathological quality assurance involved central review for type and completeness of resection, including number of lymph nodes retrieved. Radiotherapy quality assurance consisted of pre-treatment assessment of treatment plans of at least the first three patients included by each radiotherapy institute, and for subsequent patients if deemed necessary by the principle investigators (EPMJ and MV), or requested by the treating radiation oncologist. Target volume delineation manuals and workshops were offered to all participating institutions.

Outcomes

The primary endpoint was overall survival, defined as the time from randomisation to death from any cause. Secondary endpoints were event-free survival, toxicity, and health-related quality of life. Other prespecified exploratory secondary endpoints were the prediction of response and recurrence risk by genomic and proteomic profiling, and determination of the value of Maruyama Index and predictive nomograms for disease recurrence. Event-free survival was defined as time from ran-domisation until disease progression, irresectable disease at surgery,

locoregional or peritoneal tumour recurrence, distant metastases, or death from any cause, whichever occurred first. Irresectable disease was assessed centrally on the basis of surgery and pathology reports, and the other events were assessed by the local investigator. Recurrences occurring at different sites within a period of 30 days were scored as multiple sites of recurrence. Because the health-related quality of life outcome, Maruyama Index, and predictive nomograms represent extensive and distinct topics, these outcomes will be reported separately. The analyses of genomic and proteomic profiles are ongoing and will be based on the biomaterial available, because this was an optional item at the patients' choice.

Statistical analysis

Based on results of the Intergroup 0116 and MAGIC trials, we expected 5-year overall survival in the chemotherapy group to be 40%. We expected the chemoradiotherapy regimen to increase 5-year overall survival to 50% in this group. To achieve 80% power to detect this effect at an α level of 5%, 405 events were needed (after protocol amendment on Jan 9, 2007). Assuming that accrual would take 4 years, the last patient would be followed up for 3 years, and 2% of patients would be lost to follow-up, an estimated sample size of 780 patients would be sufficient (after protocol amendment on Jan 9, 2007). One interim analysis was planned after half of the events had been observed. The rejection boundaries were set using the O'Brien-Flemming method. We did the interim analysis in April 8, 2014, after 254 events. The independent data monitoring committee concluded that accrual could continue as planned. The final analyses are based on data received until July 14, 2017.

Efficacy analyses were based on the intention-to-treat principle and included all randomly assigned patients. For overall survival and event-free survival, patients for whom no death or event was observed were censored on the date last seen by the physician. Safety data were analysed separately for preoperative and postoperative periods and included patients who received at least one

	Chemotherapy group (n=310)	Chemoradiotherapy group (n=326)
Type of resection		
Oesophagocardiac resection	32 (10%)	31 (10%)
Subtotal gastrectomy	119 (38%)	136 (42%)
Total gastrectomy	159 (51%)	159 (49%)
Type of lymph node dissection		
<D1+	34 (11%)	44 (13%)
D1+	244 (79%)	257 (79%)
D2	24 (8%)	16 (5%)
D3	1 (<1%)	2 (1%)
Unknown	7 (2%)	7 (2%)
Total number of examined lymph nodes		
Median (IQR)	21 (14–28)	19 (13–27)
Unknown	4 (1%)	0
Tumour diameter (cm)		
Median (IQR)	4 (2–6)	4 (2–6)
Unknown	34 (11%)	31 (10%)
Splenectomy		
No	288 (93%)	310 (95%)
Yes	22 (7%)	16 (5%)
Pancreatectomy		
No	304 (98%)	316 (97%)
Yes–partial	6 (2%)	9 (3%)
Yes–total	0	1 (<1%)
Days in hospital since surgery	11 (9–15)	11 (9–16)
In-hospital death or 30 day mortality		
No	300 (97%)	321 (98%)
Yes	10 (3%)	5 (2%)
(Continued from previous column)		
ypT stage*		
pT0	20 (6%)	20 (6%)
pTis	1 (<1%)	5 (2%)
pT1	41 (13%)	46 (14%)
pT2a	54 (17%)	58 (18%)
pT2b	54 (17%)	56 (17%)
pT3	110 (35%)	107 (33%)
pT4	30 (10%)	34 (10%)
ypN stage*		
pN0	150 (48%)	161 (49%)
pN1	109 (35%)	105 (32%)
pN2	35 (11%)	42 (13%)
pN3	16 (5%)	18 (6%)
ypM stage*		
pM0	302 (97%)	310 (95%)
pM1	6 (2%)	14 (4%)
Unknown	2 (1%)	2 (1%)
Stage*		
0	21 (7%)	22 (7%)
IA	31 (10%)	41 (13%)
IB	69 (22%)	60 (18%)
II	65 (21%)	84 (26%)
IIIA	71 (23%)	51 (16%)
IIIB	16 (5%)	22 (7%)
IV	37 (12%)	46 (14%)
Radicality of resection type		
Microscopically radical resection (R0)	248 (80%)	267 (82%)
Microscopically incomplete resection (R1)	34 (11%)	32 (10%)
Unknown	28 (9%)	27 (8%)

Data are n (%) or median (IQR). *According to the sixth edition of the American Joint Committee on Cancer Cancer Staging Manual. yp denotes the T, N, and M stages after preoperative chemotherapy and surgery.

Table 3: **Surgical and pathological outcomes in patients who had potentially curative surgery**

dose of the corresponding treatment. The survival curves were constructed using the Kaplan-Meier method and compared using the two-sided log-rank test stratified for histological subtype and tumour localisation. We calculated hazard ratios (HRs) using a stratified proportional-hazards Cox model. We assessed proportionality of hazards using the Grambsch-Therneau test.[15] We tested the homogeneity of the treatment effect across the levels of baseline factors (the stratification factors and post-hoc analyses for age and sex) using the interaction term in a Cox model, and displayed the results in a forest plot. In the subgroup analyses, we present 99% CIs for the HRs to account for additional uncertainty due to multiple testing. We summarised dose reductions and delays in chemotherapeutic drug administration in terms of relative dose intensity. We calculated the relative dose intensities were calculated for each drug according to a formula, wherein the dose planned is calculated according to the patients' square metre body surface area) at the start of the preoperative or postoperative treatment:

$$\text{Relative dose intensities} = \frac{\text{dose received (mg)}}{\text{dose planned (mg)}} \times \frac{\text{time planned (days)}}{\text{time planned + days of delay}} \times 100\%$$

We did all analyses using R (version 3.3.1).

The CRITICS trial is registered at ClinicalTrials.gov, number NCT00407186; EudraCT, number 2006-004130-32; and CKTO 2006-02.

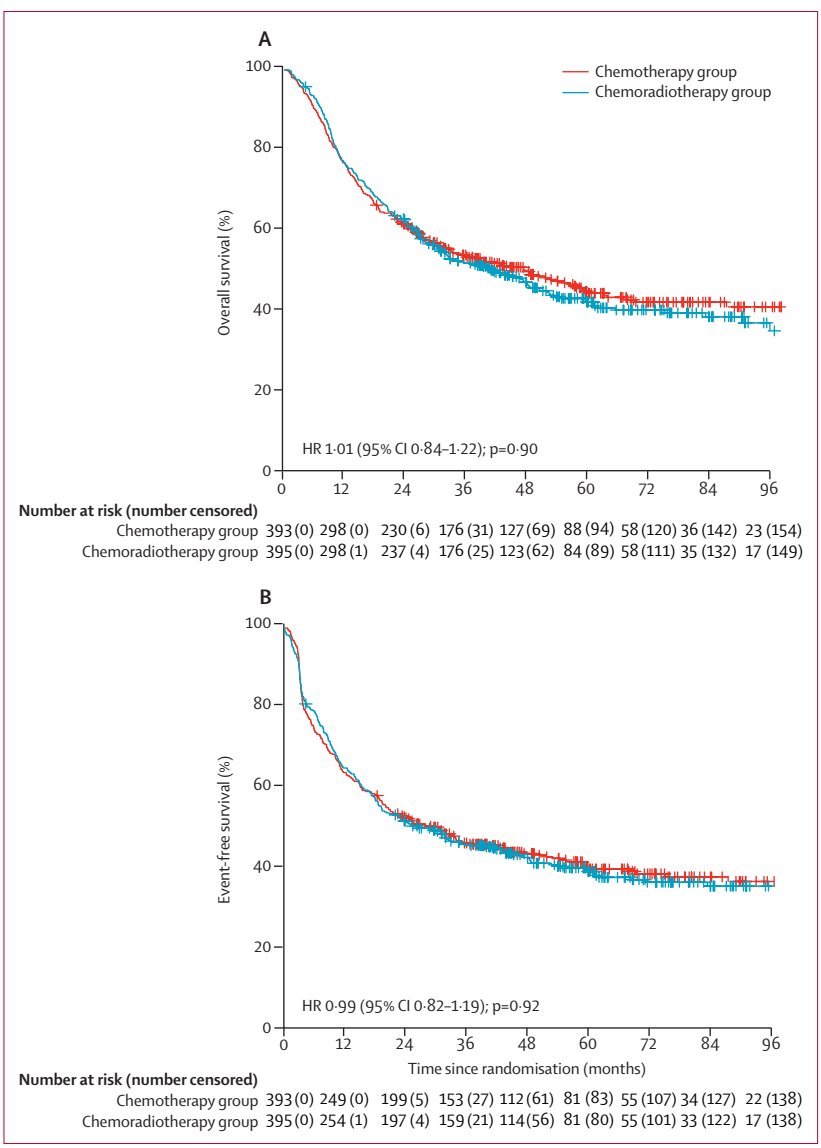


Figure 2: **Overall survival (A) and event-free survival (B)**
HR=hazard ratio.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between Jan 11, 2007, and April 17, 2015, we enrolled 788 patients and randomly assigned them to receive postoperative chemotherapy (n=393) or postoperative chemoradiotherapy (n=395; figure 1). Seven patients did not start treatment but were included in efficacy analyses (figure 1). Patient demographics and baseline disease characteristics were well balanced between the two groups (table 1).

Median time from randomisation to start of preoperative chemotherapy was 2 days (IQR 1–4) in the chemotherapy group and 2 days (1–5) in the chemo-radiotherapy group. In 15 (2%) of the 781 preoperatively treated patients (8 in the chemotherapy group and 7 in the chemoradiotherapy group), infusional fluorouracil was given because of ingestion problems, and 149 (19%) of 781 preoperatively treated patients received oxaliplatin (78 in the chemotherapy group and 71 in the chemoradiotherapy group). In the 392 patients who actually received preoperative chemotherapy in the postoperative chemotherapy group, 17 (4%) patients received one cycle of preoperative chemotherapy, 41 (10%) received two cycles, and 334 (85%) received three cycles. In the chemoradiotherapy group (n=389), 27 (7%) of 389 patients received one cycle of preoperative chemotherapy, 41 (11%) received two cycles, and 321 (83%) received three cycles. Median percentages of recommended dose intensities for all administered chemotherapeutic drugs are shown in table 2.

After preoperative chemotherapy, 372 (95%) of 393 patients in the chemotherapy group and 369 (93%) of 395 patients in the chemoradiotherapy group proceeded to surgery. Surgery was done after a median of 4 weeks

(IQR 2–5) since the last chemotherapy cycle in the chemotherapy group and 4 weeks (3–5) in the chemoradiotherapy group. A potentially curative resection, confirmed by assessment of the surgery report, was done in 310 (79%) of 393 patients in the chemotherapy group versus 326 (83%) of 395 patients in the chemoradiotherapy group (table 3). The type of resection and lymph node dissection were well balanced between both groups, as was the number of harvested lymph nodes (table 3). In 544 (86%) of these 636 patients, at least a D1+ resection was done (table 3).

A microscopically incomplete resection (R1) was documented in 66 (10%) of 636 patients who had a curative resection, as judged by the surgeon. 37 (6%) patients in this group achieved a pathological complete response. Tumour and lymph node stage were equally distributed in both groups, as were stage groups (table 3).

After potentially curative surgery, 233 patients in the chemotherapy group started postoperative treatment after a median of 7 weeks (IQR 6–9), and 245 patients in the chemoradiotherapy group started postoperative treatment after 8 weeks (7–10) weeks. One patient in the chemotherapy group and eight patients in the chemoradiotherapy group switched their treatment to that of the other group (two because of protocol deviations, four because of treatment refusals, and three because of toxicities). Reasons for not starting postoperative treatment were death in 17 (4%) of 393 patients in the chemotherapy group and 10 (3%) of 392 patients in the chemoradiotherapy group, progressive or irresectable disease in 81 (21%) and 67 (17%; including patients with progressive disease before the start of chemoradiotherapy, palliative resection, progressive disease in the no surgery group, and previous preoperative toxicity); treatment-related toxicity (ie, toxicity in patients who had no surgery, previous properative toxicity, and postoperative complications) in 28 (7%) and 34 (9%); and refusal or poor general health such that continuation of treatment was not possible in 22 (6%) and 24 patients (6%; including patients with poor condition before start of preoperative chemotherapy, those who refused in the no surgery group, those who refused after surgery, and those with poor condition after surgery; figure 1). Of the patients who started postoperative treatment, 16 (7%) of 233 patients in the chemotherapy group received one cycle, 37 (16%) received two cycles, and 180 (77%) received all three cycles of postoperative chemotherapy. In the chemoradiotherapy group, of the 245 patients who started postoperative chemo-radiotherapy, six (2%) patients received 1 week of postoperative chemotherapy, eight (3%) patients received 2 weeks, ten (4%) patients received 3 weeks, 19 (18%) patients received 4 weeks, and 202 (82%) patients received all 5 weeks (figure 1). In the intention-to-treat population, 180 (46%) of 393 patients in the chemotherapy group and 197 (50%) of 395 patients in the chemoradiotherapy group completed the allocated treatment as planned. Radiotherapy could be administered as planned in 221 (90%) of 245 patients in the chemoradiotherapy group. Of 105 patients who did not have potentially curative surgery or started the allocated treatment, 65 (62%) patients started another postoperative treatment outside the trial protocol: 31 patients in the chemotherapy group and 34 patients in the chemoradiotherapy group.

After a median follow-up of 61·4 months (IQR 43·3–82·8), 216 (55%) of 393 patients in the chemotherapy group and 230 (58%) of 395 patients in the chemoradiotherapy group had died. Overall survival was not significantly different between the groups according to the intention-to-treat analysis (figure 2A). Median overall survival was 43 months (95% CI 31–57) in the chemotherapy group and 37 months (30–48) in the chemoradiotherapy group (hazard ratio [HR] from stratified analysis 1·01 [95 CI% 0·84–1·22]; p=0·90). 5-year survival probabilities were 42% (95% CI 37–48) for chemotherapy and 40% (35–46) for chemoradiotherapy.

For the analysis of event-free survival, 474 events were recorded in 788 patients overall (233 in the chemotherapy group *vs* 241 in the chemoradiotherapy group). Median event-free survival was 28 months (95% CI 20–42) in the chemotherapy group versus 25 months (19–39) in the chemoradiotherapy group (HR from stratified analysis 0·99, 95% CI 0·82–1·19, p=0·92), and 5-year event-free survival probabilities were 39% (34–44) versus 38% (33–44; figure 2B). The event-free survival events were locoregional recurrence (35 [15%] of 233 in the chemotherapy group *vs* 27 [11%] of 241 in the chemoradiotherapy group), peritoneal recurrence (50 [21%] *vs* 61 [25%]), distant recurrence (58 [25%] *vs* 52 [22%]), and recurrence at multiple sites (50 [21%] *vs* 65 [27%]). 76 (16%) of all

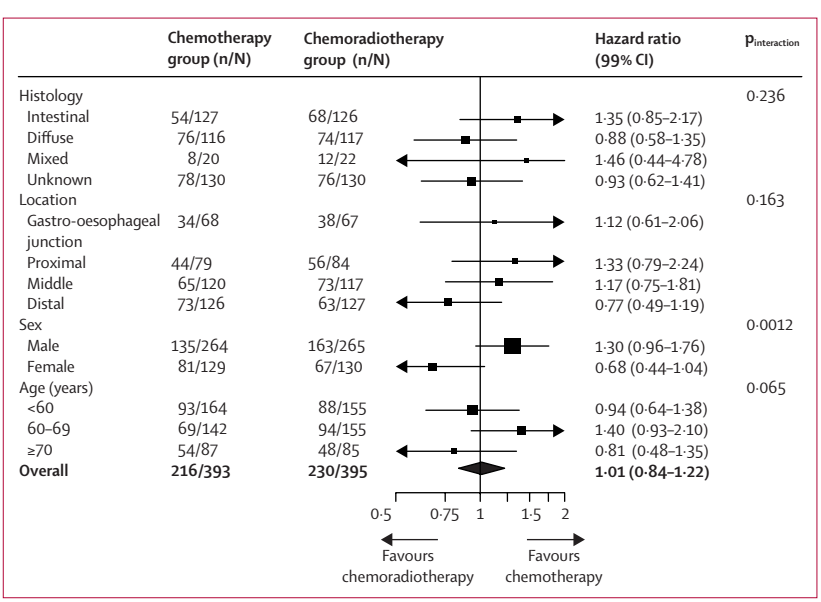


***Figure 3*: Subgroup analyses of overall survival**

The effect of trial treatment on overall survival according to baseline characteristics, including histological subtype according to Lauren classification, tumour location, sex, and age. Hazard ratios for subgroups come from Cox models corrected only for treatment group, and that for the overall result comes from a Cox model adjusted for treatment group, histology, and location. n=number of events. N=number of patients.

474 events were deaths without known progression, irresectability, or recurrence (40 [17%] of 233 in the chemotherapy group *vs* 36 [15%] of 241 in the chemoradiotherapy group). There was no evidence that the assumption of proportional hazards was violated.

In a post-hoc subgroup analysis of overall survival, there was no clear evidence for heterogeneity of treatment effect according to age, histology, and location of the tumour at the time of randomisation, but there was for sex (figure 3).

Because preoperative treatment was identical in both groups, toxicity scoring during this period was done in both groups together (all treated patients). Adverse events during preoperative treatment were reported in 767 (98%) of 781 patients who started preoperative treatment (the safety population): 52 (7%) had grade 1 events, 204 (26%) had grade 2 events, 368 (47%) had grade 3 events, 130 (17%) had grade 4 events, and 13 (2%) had grade 5 events (table 4). Causes of death were diarrhoea (n=2), dihydropyrimidine deficiency (n=1), sudden death (n=1), cardiovascular events (n=8; two cardiac arrhythmia and six ischaemic events), and gastrointestinal obstruction (n=1). All but one cardiovascular event were considered to be treatment related. Drug-related serious adverse events were reported in 227 (29%) of 781 patients: 176 (23%) had a

	Preoperative chemotherapy (n=781)				Postoperative chemotherapy (n=233)			Postoperative chemoradiotherapy (n=245)		
	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4
Haematological										
Anaemia	448 (57%)	18 (2%)	6 (1%)	0	145 (62%)	1 (<1%)	0	141 (58%)	2 (1%)	0
Leucopenia	60 (8%)	14 (2%)	7 (1%)	0	13 (6%)	1 (<1%)	0	21 (9%)	3 (1%)	0
Neutropenia	220 (28%)	174 (22%)	76 (10%)	0	66 (28%)	62 (27%)	17 (7%)	23 (9%)	10 (4%)	1 (<1%)
Lymphocytopenia	0	0	0	0	0	1 (<1%)	0	1 (<1%)	2 (1%)	0
Febrile neutropenia	0	54 (7%)	10 (1%)	0	0	4 (2%)	1 (<1%)	0	5 (2%)	0
Thrombocytopenia	39 (5%)	3 (<1%)	2 (<1%)	0	4 (2%)	0	1 (<1%)	40 (16%)	3 (1%)	1 (<1%)
Gastrointestinal										
Mucositis or stomatitis	235 (30%)	30 (4%)	2 (<1%)	0	43 (18%)	6 (3%)	0	29 (12%)	2 (1%)	0
Heartburn or dyspepsia	53 (7%)	2 (<1%)	0	0	20 (9%)	4 (2%)	0	39 (16%)	5 (2%)	0
Dysphagia	72 (9%)	19 (2%)	0	0	26 (11%)	5 (2%)	0	37 (15%)	7 (3%)	1 (<1%)
Anorexia	288 (37%)	71 (9%)	2 (<1%)	0	84 (36%)	20 (9%)	0	111 (45%)	35 (14%)	0
Nausea	459 (59%)	83 (11%)	1 (<1%)	0	130 (56%)	27 (12%)	0	171 (70%)	23 (9%)	0
Vomiting	251 (32%)	58 (7%)	3 (<1%)	0	84 (36%)	10 (4%)	0	92 (38%)	12 (5%)	0
Diarrhoea	226 (29%)	95 (12%)	5 (1%)	2 (<1%)	86 (37%)	13 (6%)	0	82 (33%)	8 (3%)	0
Constipation	265 (34%)	4 (1%)	1 (<1%)	0	40 (17%)	3 (1%)	0	59 (24%)	0	0
Bowel inflammation	2 (<1%)	6 (1%)	2 (<1%)	0	1 (<1%)	2 (1%)	0	0	1 (<1%)	0
Gastrointestinal fistula	0	0	0	0	1 (<1%)	0	0	0	1 (<1%)	0
Gastrointestinal obstruction	7 (1%)	7 (1%)	2 (<1%)	1 (<1%)	2 (1%)	2 (1%)	0	0	2 (1%)	0
Gastrointestinal perforation	1 (<1%)	4 (1%)	0	0	0	1 (<1%)	0	0	0	2 (1%)
Vascular										
Cardiac arrhythmia	21 (3%)	4 (1%)	0	2 (<1%)	3 (1%)	0	0	7 (3%)	0	0
Ischaemic event	5 (1%)	14 (2%)	7 (1%)	6 (1%)	0	2 (1%)	1 (<1%)	0	1 (<1%)	0
Thromboembolic event*	24 (3%)	44 (6%)	21 (3%)	0	0	3 (1%)	2 (1%)	0	2 (1%)	1 (<1%)
Sudden death	0	0	0	1 (<1%)	0	0	0	0	0	0
Haemorrhage	38 (5%)	8 (1%)	1 (<1%)	0	5 (2%)	1 (<1%)	0	5 (2%)	0	0
Constitutional										
Weight loss	191 (24%)	10 (1%)	0	0	77 (33%)	5 (2%)	0	99 (40%)	2 (1%)	0
Dehydration	34 (4%)	42 (5%)	2 (<1%)	0	4 (2%)	3 (1%)	0	9 (4%)	8 (3%)	0
Dizziness	63 (8%)	17 (2%)	0	0	19 (8%)	4 (2%)	0	16 (7%)	3 (1%)	0
Fatigue	483 (62%)	57 (7%)	8 (1%)	0	152 (65%)	20 (9%)	0	174 (71%)	27 (11%)	0
Hypertension	23 (3%)	12 (2%)	0	0	3 (1%)	0	0	5 (2%)	3 (1%)	0
Infection without neutropenia	115 (15%)	59 (8%)	5 (1%)	3 (<1%)	26 (11%)	8 (3%)	2 (1%)	31 (13%)	12 (5%)	2 (1%)
Insomnia	16 (2%)	1 (<1%)	1 (<1%)	0	7 (3%)	0	0	10 (4%)	1 (<1%)	0
Mood alteration	62 (8%)	5 (1%)	1 (<1%)	0	24 (10%)	1 (<1%)	0	22 (9%)	1 (<1%)	0
Pain, abdominal	109 (14%)	8 (1%)	0	0	34 (15%)	4 (2%)	0	52 (21%)	4 (2%)	0
Pain, other	150 (19%)	25 (3%)	1 (<1%)	0	30 (13%)	8 (3%)	1 (<1%)	32 (13%)	10 (4%)	0

(Table 4 continues on next page)

	Preoperative chemotherapy (n=781)				Postoperative chemotherapy (n=233)			Postoperative chemoradiotherapy (n=245)		
	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4
(Continued from previous page)										
Other										
Allergic reaction	21 (3%)	5 (1%)	0	0	0	0	0	2 (1%)	0	0
Alopecia	317 (41%)	0	0	0	64 (27%)	0	0	35 (14%)	0	0
Dermatological reaction	121 (15%)	3 (<1%)	0	0	21 (9%)	0	0	23 (9%)	2 (1%)	0
Dihydropyrimidine dehydrogenase deficiency	0	0	0	1 (<1%)	0	0	0	0	0	0
Dyspnoea	77 (10%)	2 (<1%)	0	0	25 (11%)	0	0	21 (9%)	1 (<1%)	0
Genitourinary obstruction	0	0	1 (<1%)	0	0	0	0	0	0	0
Local complication (device related)	53 (7%)	5 (1%)	0	0	13 (6%)	2 (1%)	0	2 (1%)	4 (2%)	0
Metabolic disorder†	65 (8%)	56 (7%)	16 (2%)	0	24 (10%)	5 (2%)	1 (<1%)	37 (15%)	11 (4%)	2 (1%)
Musculoskeletal disorder	31 (4%)	3 (<1%)	1 (<1%)	0	5 (2%)	0	0	9 (4%)	0	0
Neurotoxicity	230 (29%)	9 (1%)	2 (<1%)	0	83 (36%)	4 (2%)	0	43 (18%)	1 (<1%)	0
Ototoxicity	48 (6%)	1 (<1%)	0	0	22 (9%)	0	0	14 (6%)	1 (<1%)	0
Palmar-plantar erythrodysesthesia	204 (26%)	23 (3%)	1 (<1%)	0	44 (19%)	3 (1%)	0	16 (7%)	0	0
Psychosis	0	2 (<1%)	0	0	0	0	0	0	0	0
Renal toxicity	49 (6%)	11 (1%)	1 (<1%)	0	5 (2%)	3 (1%)	0	12 (5%)	2 (1%)	0
Other toxicity	92 (12%)	3 (<1%)	0	0	29 (12%)	0	0	31 (13%)	0	0
Any adverse event	256 (33%)	368 (47%)	130 (17%)	13 (2%)	94 (40%)	113 (48%)	22 (9%)	128 (52%)	101 (41%)	10 (4%)

We scored adverse events according to the National Cancer Institute Common Toxicity Criteria for Adverse Events (version 3.0). All adverse events that occurred as grade 3–5, or adverse events which occurred only as grade 1–2 in at least 10% of the population, are reported. There were no postoperative grade 5 events. We scored toxicity during the preoperative treatment period from the first preoperative chemotherapy cycle until the last preoperative chemotherapy cycle administered plus 30 days, or surgery, whatever occurred first. Toxicity during the postoperative treatment period was scored from the first postoperative treatment method (either chemotherapy or radiotherapy) until the last postoperative treatment method administered plus 30 days. *Also includes patients with superficial phlebitis. †Worsening kidney or liver functioning, or both (measured by laboratory tests).

Table 4: **Adverse events associated with preoperative and postoperative treatment**

grade 3 serious adverse event, 39 (5%) had a grade 4 event, and 12 (2%) had a grade 5 event. Of these serious adverse events, diarrhoea (64 [8%]), febrile neutropenia (54 [6%]), nausea (34 [4%]), vomiting (34 [4%]), and dehydration (28 [4%]) were the most frequently reported of these 227 serious adverse events.

General, infectious, and surgery-related complications during and after surgery occurred each in 22–28% of patients who had potentially curative surgery, and did not differ between groups (table 5). In these patients (n=636), surgical morbidity consisted of anastomotic leakage (45 [7%] overall; 18 [6%] in the chemotherapy group *vs* 27 [8%] in the chemoradiotherapy group), ileus (18 [3%]; ten [3%] *vs* eight [2%]), bleeding (18 [3%]; ten [3%] *vs* eight [2%]), abdominal wound dehiscence (ten [2%]; three [1%] *vs* seven [2%]), fistulae (six [1%]; four [1%] *vs* two [1%]), and other (73 [11%]; 37 [12%] *vs* 36 [11%]). 14 (2%) of 636 patients died in the hospital or within 30 days after surgery (ten in the chemotherapy group and four in the chemoradiotherapy group).

During postoperative treatment, 16 (7%) of 233 patients had grade 1 adverse events in the postoperative chemotherapy group versus 30 (12%) of 245 in the postoperative chemoradiotherapy group; 78 (33%) versus 98 (40%) had grade 2 adverse events; 113 (48%) versus 101 (41%) had grade 3 adverse events; and 22 (9%) versus ten (4%) had grade 4 adverse events (table 4). During postoperative treatment, no grade 5 adverse events were reported. Grade 3–4 non-febrile neutropenia occurred more frequently during postoperative chemotherapy (79 [34%] of 233) than during postoperative chemoradiotherapy (11 [4%] of 245). During postoperative chemotherapy, treatment-related serious adverse events were reported in 37 (16%) of 233 patients in the chemotherapy group versus 39 (16%) of 245 in the chemoradiotherapy group. The most frequently reported serious adverse events in the chemotherapy group were nausea (13 [6%]), diarrhoea (11 [5%]), and vomiting (six [3%]). The most frequently reported serious adverse events in the chemoradiotherapy group were fatigue (ten [4%]) and nausea (eight [3%]).

Discussion

The findings of this study do not support the hypothesis that treatment consisting of preoperative chemotherapy, surgery, and postoperative chemoradiotherapy improve survival compared with perioperative chemotherapy and surgery in patients with resectable gastric and gastro-oesophageal adenocarcinoma. This randomised study integrated two treatment strategies of perioperative chemotherapy and postoperative chemoradiotherapy that previously showed beneficial outcomes in patients from Europe and North America.

Randomisation before the start of any treatment prevented patient selection during the treatment process,

	Chemotherapy group (n=310)	Chemoradiotherapy group (n=326)
General complications*		
None	223 (72%)	231 (71%)
Yes	86 (28%)	94 (29%)
Unknown	1 (<1%)	1 (<1%)
Infectious complications†		
None	235 (76%)	251 (77%)
Yes	74 (24%)	74 (23%)
Unknown	1 (<1%)	1 (<1%)
Surgery-related complications‡		
None	239 (77%)	253 (78%)
Yes	70 (23%)	72 (22%)
Unknown	1 (<1%)	1 (<1%)
Reintervention for the management of complications		
No	269 (87%)	276 (85%)
Yes	37 (12%)	48 (15%)
Unknown	4 (1%)	2 (1%)

The complications listed in this table were recorded during hospital stay after surgery. *Including cardiovascular, pulmonary, renal, and neurological complications. †Including abdominal wound, abscess, and sepsis. ‡Including bleeding, anastomotic leakage, abdominal wound dehiscence, ileus, and intestinal necrosis.

Table 5: **Surgical complications in patients who had potentially curative surgery**

and thus most closely reflected daily practice and feasibility of the entire treatment regimen in both groups. With 94% of patients proceeding to surgery and receiving recommended dose intensities of more than 90% for all preoperatively administered chemotherapy drugs, the results of our study show that preoperative chemotherapy is feasible. Around 50% of patients completed treatment as planned, which compares slightly favourably with other studies investigating perioperative chemotherapy.[6,16–19] Nevertheless, postoperative treatment was hampered by substantial patient dropout, mainly due to irresectability of the primary tumour or early progression after surgery (approximately 18% of patients who had palliative resection plus those with progressive disease), and treatment-related toxicity, death, worsening of general health that precluded continuation of treatment (almost 20%), or patients' refusal to continue treatment (nearly 20% of patients). Additionally, the doses of administered postoperative chemotherapeutic drugs decreased to below 80–90% of the recommended dose intensities, which emphasises the limitations of the extent of treatment that can be given to this patient population.

Results from the MAGIC study[6] of perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer showed that preoperative epirubicin, cisplatin, and fluorouracil leads to tumour downsizing and downstaging, and also to enhanced overall survival versus surgery alone. However, the contribution of epirubicin to this favourable effect could be questioned. In the phase 3 UK MRC OE05 trial, four cycles of preoperative epirubicin, cisplatin, and capecitabine compared with two cycles of cisplatin and fluorouracil did not increase survival in patients with adenocarcinomas of the oesophagus or gastro-oesophageal junction.[20] In the CALGB 80101 study,[21] the addition of epirubicin and cisplatin to postoperative chemotherapy in combination with chemoradiotherapy also did not improve survival in patients with gastric or gastro-oesophageal adenocarcinomas. Results from the FLOT4 study[19] showed that perioperative chemotherapy with docetaxel, oxaliplatin, fluorouracil, and leucovorin increased both the proportion of patients who achieved a pathological complete response and overall survival compared with perioperative epirubicin, cisplatin, and fluorouracil or capecitabine in patients with gastric or gastro-oesophageal adenocarcinomas. Overall, the potential downsizing and downstaging effects of preoperative chemotherapy and the limitations of the amount of treatment that can be administered postoperatively to patients with gastric and gastro-oesophageal cancer implies that additional survival benefit is most likely to come from optimisation of preoperative treatment strategies.

Subsequently, the question arises about whether or when chemoradiotherapy adds to the efficacy of preoperative or postoperative chemotherapy. It is possible that because all patients in our study received preoperative chemotherapy, postoperative treatment did not further increase survival. Additionally, the percentage of observed events that attributed exclusively to locoregional recurrence was similar and low in both groups. Results from the Intergroup study[4] previously established the survival benefit of postoperative fluorouracil monotherapy in combination with fluorouracil-based chemoradiotherapy versus surgery only in medically fit patients who had an R0 resection. An observational study[22] from South Korea, which compared postoperative chemoradiotherapy according to the Intergroup protocol with surgery only (but including a formal D2 lymph node dissection), showed similar results—namely, that overall survival improved with postoperative chemoradiotherapy.[22] By contrast, the subsequent randomised ARTIST trial[23] compared adjuvant chemotherapy (capecitabine plus cisplatin) with or without capecitabine-based chemo-radiotherapy in patients who had D2-resected gastric cancer, but reported no difference in disease-free survival. Several factors, such as study period, ethnicity, surgical quality, and the addition of systemic chemotherapy to the control group might account for these conflicting findings. Either treatment method might contribute to improving survival for as long as it is administered, or alternatively, some patient subgroups might benefit from one of these treatments.

Surgical quality in this study was good, with a median lymph node yield of 20, an R0 resection rate of at least 81%, and a Maruyama Index (reported separately)[24] of 1. A Cochrane systematic review and meta-analysis[25] of eight randomised controlled trials consisting of 2515 patients has advocated D2 dissection over D1 and D3 dissections on the basis of a better disease-specific survival.[25] Because of the increased postoperative

mortality ascribed to the splenic and pancreatic resections,[2] the authors suggested D2 dissection without splenopancreatectomy for these patients. Findings from a 2017 randomised controlled trial[26] supported the non-inferiority of spleen preservation versus splenectomy in patients with proximal gastric cancer, in terms of overall survival. Such an approach (ie, D1+, D2, or D3 dissection) was done in more than 544 (85%) of our patients.

In our subgroup analysis in this study, the interaction between sex and treatment group was significant. The reason for this is unclear. In the Intergroup study,[4] a univariate subgroup analysis showed a difference in survival according to sex, but the multivariate analysis could not verify this observation.

In this study, postoperative toxicity was similar in the chemotherapy and chemoradiotherapy groups. Only neutropenia (including grade 3–4 neutropenia) was more frequent in the chemotherapy group, but this did not translate into more febrile neutropenia and was therefore deemed clinically irrelevant by patients' treating physicians.

A limitation of the CRITICS study is that upfront randomisation does not allow a direct comparison of postoperative chemotherapy with chemoradiotherapy. Because only 60% of all randomised patients would be included in such an analysis, all properties of randomisation are lost, precluding an unbiased investigation of a causal effect of treatment. Another limitation of our study is the low percentage of diagnostic laparoscopies (10%) done before randomisation. In the Netherlands the first national guideline for gastric cancer, in 2009,[27] advocated a diagnostic laparoscopy only in case of suspicion of peritoneal disease or poorly differentiated cT3–4 gastric tumours. The current guideline of 2016[27] demands a diagnostic laparoscopy for all cT3–4 tumours according to endoscopy and CT scan. Although the low diagnostic laparoscopy rate might implicitly have affected the dropout rate after surgery, the dropout rate in our study does not exceed that of other studies investigating perioperative chemotherapy, including those with a mandatory diagnostic laparoscopy (36% in the Intergroup study and 58% in the MAGIC study).[6,16,18,19]

In conclusion, we did not find better efficacy of postoperative chemoradiotherapy compared with postoperative chemotherapy in patients with resectable gastric cancer treated with preoperative chemotherapy and adequate surgery. Tolerability was also similar between the two adjuvant regimens. Future explorative post-hoc analyses might identify subgroups that benefit more from one of these strategies, although the findings of such exploratory analyses should be interpreted with caution. Docetaxel might be a better chemotherapy backbone than epirubicin[17,19] and might therefore be a better option in future trials. Furthermore, classification of gastric cancer on the basis of histological response, completeness of surgical resection, or nodal positivity, as well as molecular subtypes, such as *HER2* overexpression, MSI, EBV, or TCGA signature, in this and other studies, could provide the opportunity to individualise treatment in future studies. In study populations from Europe and North America, many patients are not able to have all planned postoperative treatment, and both tumour downstaging and resectability are related to overall survival. Therefore, in the successor trial (CRITICS-II; NCT02931890), all treatment, consisting of docetaxel-based chemotherapy, chemoradiotherapy, or both, will be administered before surgery.

Contributors

AC, EPMJ, NCTvG, HB, CJHvdV, and MV contributed to the study concept. AC, EPMJ, NCTvG, HB, CJHvdV, MV, JWvS, HHH, HP, and HvT contributed to study design. AKT and HAMS contributed to study coordination. AC, EPMJ, NCTvG, HB, CJHvdV, MV, KS, PL, MN, EM-KK, AKT, HAMS, JWvS, and HHH contributed to data collection. AC, EPMJ, NCTvG, HB, CJHvdV, MV, KS, PL, MN, EM-KK, JWvS, HHH, HP, HvT, HWMvL, and MIvBH contributed to data interpretation. All authors wrote the manuscript. AC, EPMJ, NCTvG, HB, CJHvdV, and MV edited the manuscript.

Declaration of interests

AC and MV received institutional financial support as investigators of this study from the Dutch Cancer Society, the Dutch Colorectal Cancer Group, and Hoffman-La Roche. AC has received support as an investigator for study conduct from Nordic Pharma and has been a consultant for Eli Lilly and Merck. MIvBH declares a consultant or advisory role for Medtronic and Olympus, and research funding from Olympus. All other authors declare no competing interests.

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