



Phase I/II trial

Preoperative chemoradiotherapy in locally advanced gastric cancer, a phase I/II feasibility and efficacy study



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ABSTRACT

Objectives: This study was initiated to investigate the feasibility and efficacy of preoperative radiotherapy with weekly paclitaxel and carboplatin in locally advanced gastric cancer.

Methods: In a prospective study, patients with locally advanced gastric cancer stage IB–IV(M0) were treated with chemoradiotherapy followed by surgery 4–6 weeks after the last irradiation. Chemoradiotherapy consisted of radiation to a total dose of 45 Gy given in 25 fractions of 1.8 Gy, combined with concurrent weekly carboplatin and paclitaxel.

Results: Between December 2007 and January 2012, 25 patients with cT3 (64%) or cT4 (36%) gastric cancer were included. One patient discontinued concurrent chemotherapy in the 4th week due to toxicity, but completed radiotherapy. Another patient discontinued chemoradiotherapy after the 3rd week due to progressive disease. Grade III adverse events of chemoradiotherapy were: gastrointestinal 12%, haematological 12% and other 8%. All patients, except one who developed progressive disease, were operated. Surgical complications were: general/infectious 48%, anastomotic leakage 12%, and bowel perforation 8%. Postoperative mortality was 4%. Microscopically radical resection rate was 72%. Pathological complete response rate was 16% and near complete response rate 24%.

Conclusions: In this study, preoperative chemoradiotherapy for patients with locally advanced gastric cancer was associated with manageable toxicity and encouraging pathological response rates.

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Surgery is the only curative option for gastric cancer patients. Despite many efforts to optimise surgery [1], the prognosis after gastric cancer resection remains poor [2]. This is mainly due to a high local recurrence rate, up to 88%, even after radical surgery [3]. This indicates a need for more effective local treatments.

The INT 0116 trial showed that postoperative chemoradiotherapy (CRT) improves local control and overall survival compared to surgery alone [4]. Despite optimisation [5–8], compliance with postoperative CRT is unfortunately frequently compromised due to surgical complications and toxicity. In the INT 0116 trial, only 64% of the patients assigned to postoperative CRT completed

treatment as planned. The main reason for discontinuation was toxicity (17%).

Higher compliance rates can be achieved with a neoadjuvant approach. For example, in the MAGIC trial, gastric cancer patients showed good compliance with preoperative chemotherapy (86% completed three cycles), while compliance with postoperative chemotherapy (CT) was poor (55% started postoperative CT, and 41% completed three cycles) [9]. Moreover, compliance of oesophageal cancer patients with preoperative CRT was good in the CROSS trial [10], as 91% of the patients completed this regimen as planned.

In addition, in both the MAGIC [9] and the CROSS [10] trials, preoperative treatment improved resectability and overall survival without increasing surgical complications. These favourable results can be attributed to downstaging. In the trial by Stahl et al., patients with adenocarcinoma of the oesophagogastric junction (OGJ) were randomised for either preoperative CT or CRT. The trial was prematurely closed, but analysis showed a trend towards

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higher pathological complete response (pCR) and improved survival in the CRT arm [11]. Preoperative treatment also allows the avoidance of surgery and associated morbidity and mortality in patients with early progressive (metastatic) disease [9,10].

Postoperative CRT and perioperative CT are welcome additions to the therapeutic arsenal of gastric cancer. Postoperative treatment, however, has several drawbacks that can seriously limit its efficacy. Most importantly, patients can be impaired for an extended period of time after gastrectomy. These patients will not start with adjuvant treatment or will not tolerate complete delivery of the planned adjuvant treatment. Therefore, treatment strategies in which the entire regimen can be given before surgery should be explored. Since 2002, several phase I and II studies have been performed to investigate the feasibility and efficacy of preoperative CRT in resectable gastric and OGJ cancer (Supplement 1) [11–19]. Preoperative CRT has been documented as a feasible treatment strategy in all of these studies, because toxicity of CRT was not the predominant reason of withdrawal from surgery. However, in these trials CRT regimens varied considerably in radiation dose and type of CT.

The reported feasibility and improved surgical results of the CROSS regimen (radiotherapy with concurrent weekly paclitaxel and carboplatin) in oesophageal cancer patients prompted us to investigate the feasibility and efficacy of this regimen in patients with locally advanced gastric cancer.

Patients and methods

The data of two separately conducted prospective phase I/II clinical trials investigating preoperative CRT in gastric cancer were combined for analysis, because the study protocols were identical. Both trials were approved by the medical ethical committees of the participating centres (METC2007.162 and 2007-004818-14).

Patients

TNM-classification was done according to the sixth edition of the Union Internationale Contre le Cancer. Patients older than 18 years with stage IB–IV(M0) histologically proven (adeno)carcinoma of the stomach were eligible if >50% of the bulk of the tumour was located in the stomach. The Z-line was considered the upper border of the stomach. Staging procedures included Endoscopic Ultra Sound, Computed Tomography and ¹⁸F-FDG Positron Emission Tomography (PET) scans. Laparoscopy was mandatory in case of suspected peritoneal carcinomatosis and to assess irresectability. Gastric cancer was considered as initially irresectable in case of cT4, and/or ≥ 7 suspected lymph nodes on EUS or CT-scan, and/or one large lymph node (mass or conglomerate), and/or >3 suspected lymph nodes near coeliac trunk, para-aortal or at the hilus of the spleen.

Patients had to be in adequate general condition (WHO performance status 0–2) and had to have sufficient caloric intake (>1500 kcal/day). Haematological (white blood cell count $\geq 4.0 \times 10^9/L$, platelet count $\geq 100 \times 10^9/L$), renal (creatinine clearance ≥ 50 ml/min), and hepatic (serum bilirubin $\leq 1.5 \times$ ULN) function had to be adequate. Written informed consent was mandatory.

Study treatment

Within 10 days after registration, patients started treatment with preoperative CRT followed by standardised gastric cancer surgery within 4–6 weeks after the last irradiation. Patients were re-staged by CT-scan 2 weeks after CRT.

Preoperative chemoradiotherapy

External beam radiotherapy was given to a total dose of 45 Gy in 25 fractions of 1.8 Gy, 5 times a week. Concurrent chemotherapy consisted of weekly carboplatin (AUC 2) and paclitaxel (50 mg/m²) intravenously on days 1, 8, 15, 22 and 29 of irradiation.

Clinical target volume (CTV) encompassed the entire stomach and at least draining lymph node stations 1–13 according to the Japanese Classification [20]. Planning target volume was constructed by extending the CTV with 1 cm. No dietary instructions were used due to the high frequency of tube feeding. Position verification was performed by cone-beam CT-scan or EPID according to strict department protocol. Conformal 3D and IMRT planning techniques were used and dose distributions were planned according to the International Commission on Radiation Units and Measurements recommendations. Established dose constraints were applied to kidneys (<18 Gy to at least two-thirds of one kidney), liver (mean dose <30 Gy), spinal cord (maximum dose <45 Gy) and heart (30% of the silhouette <40 Gy).

Surgery

The type of gastric cancer surgery was left to the expertise of the surgeon. The protocol allowed partial or total gastrectomy via midline laparotomy and oesophageal-cardia resection via thoracalaparotomy or transhiatal resection. A D1+ lymph node dissection (LND), i.e. an extended D2 LND with the removal of at least 15 nodes without resection of the pancreas and spleen, was preferred [1,21]. Adjacent organs could be resected in case of tumour involvement.

Pathology

In the absence of macroscopic tumour, any abnormality was embedded in total to adequately assess tumour response. The margin was considered microscopically radical if no vital tumour cells were found at 1 mm or less.

Pathological response was scored using the criteria of Becker et al. [22]; Grade 1a complete response (0% vital residual tumour cells), grade 1b near complete response (<10% vital residual tumour cells), grade 2 partial response (10–50% vital residual tumour cells), and grade 3 no response (>50% vital residual tumour cells).

Follow-up

Patients had follow-up visits at 4, 8 and 12 weeks after surgery followed by 3 monthly visits in the first year of follow-up. Thereafter, visits were every 6 months. Follow-up consisted of physical examination, laboratory assessments, and CT-scan.

Endpoints

The primary endpoint was feasibility. The study treatment was considered feasible if the withdrawal rate from surgery due to toxicity of CRT was less than 10%. The secondary endpoint was efficacy measured by surgical resectability rate and pathological response rate.

Statistical analysis

Follow-up data were collected until December 2012. Survival time was calculated from registration to death or last follow-up visit. Overall survival (OS) was estimated using the Kaplan–Meier method. Statistical analysis was performed with SPSS, version 20.0 (SPSS).

Results

Between December 2007 and January 2012, 25 patients with stage II–IV(M0) gastric cancer from three hospitals were enrolled in the study (Table 1). We included patients with locally advanced (cT3 64% and cT4 36%) gastric cancer, of whom 12 were deemed initially irresectable (assessed with diagnostic laparoscopy). Seven (out of 12) patients were deemed initially irresectable due to tumour growth into adjacent organs, mainly pancreas, the other five due to extensive pathologic lymph nodes. All, except two patients underwent a PET-scan at baseline. All patients signed informed consent.

All patients started preoperative CRT, of whom 23 (92%) completed preoperative treatment without delay or dose reduction of chemotherapy or radiotherapy (Fig. 1). One patient discontinued CT in the fourth week due to toxicity, but completed radiotherapy, and another patient discontinued CRT after the third week due to peritoneal carcinomatosis confirmed on CT-scan. The remaining 24 patients including the patient that discontinued concurrent CT but completed radiotherapy, had no progressive disease on the response evaluation CT-scan. As none of these patients withdrew from surgery due to toxicity, 24 patients (96%) were operated to assess resectability.

Twenty-one (84%) patients underwent a macroscopically radical resection. In the other 3 patients unexpected widespread peritoneal carcinomatosis (histologically proven by frozen sections) was present during surgery. One of these patients underwent palliative resection and 2 did not undergo resection. On average surgery was performed 43 days after the end of CRT (median 40.5, range 30–73). Eleven patients were not operated within 6 weeks after CRT due to hospital logistics.

All but one patient experienced grade I/II adverse events during preoperative CRT until surgery. Three (12%) patients experienced grade III gastro-intestinal adverse events (Table 2), and had to start tube feeding during CRT. However, the majority of patients started

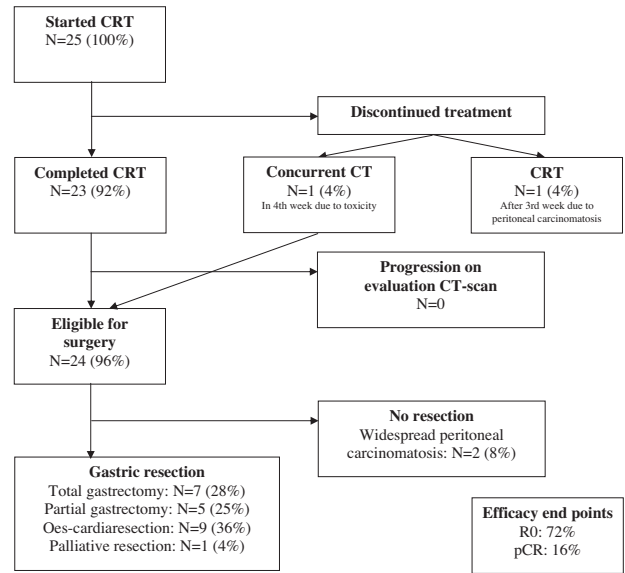


Fig. 1. Flow chart of received treatment. All patients were analysed for end points. Abbreviations: CRT = chemoradiotherapy, CT = chemotherapy, R0 = microscopically radical resection, pCR = pathological complete response grade 1a.

tube feeding prior to the start of CRT due to insufficient caloric intake, and continued with tube feeding throughout the treatment. The average weight loss before start of nutritional support or inclusion was 14% of body weight, and during chemoradiotherapy 3.6% (range +2% to –10%). Grade III leucopenia was present in 3 (12%) patients and febrile neutropenia in 1. No grade IV or V adverse events occurred.

Surgery-related complications (Table 2) consisted of anastomotic leakage in 3 patients and bowel perforation in 2. Postoperative mortality was 4%.

Table 1
Patient and treatment characteristics.

Patients Characteristic	N = 25 N (%)	Pathological evaluation of the gastric resection specimen Characteristic	N = 22 N (%)
Age (years)		Resection margins	
Mean	61	R0	18 (72)
Range	42–76	R1	3 (12)
Sex		R2	1 (4)
Male	17 (68)	Number of examined lymph nodes	
Female	8 (32)	<15 lnn	13 (52)
WHO		≥ 15 lnn	9 (36)
0	15 (60)	Tumour response	
1	9 (36)	pCR – grade 1a	4 (16)
2	1 (4)	pPR – grade 1b	6 (24)
Clinical T stage		pPR – grade 2	7 (28)
T3	16 (64)	no response – grade 3	5 (20)
T4	9 (36)	Pathologic T stage	
Clinical N stage		T0	5 (20)
N0	2 (8)	T1	0
N1	17 (68)	T2	12 (48)
N2	6 (24)	T3	5 (20)
Lauren classification		T4	0
Intestinal	12 (48)	Pathologic N stage	
Diffuse	5 (20)	N0	8 (32)
Unknown	7 (28)	N1	11 (44)
Squamous cell	1 (4)	N2	3 (12)
		Lauren classification	
		Intestinal	9 (36)
		Diffuse	3 (12)
		Unknown	5 (20)
		Not assessable	8 (32)

Abbreviations: R0 = microscopically radical resection, R1 = microscopically irradical resection, R2 = macroscopically irradical resection, WHO = World Health Organization, pCR = pathological complete response, pPR = pathological partial response, TNM staging according to the sixth edition of the Union Internationale Contre le Cancer.

Table 2
Toxicity of chemoradiotherapy until surgery, and postoperative complications.

Toxicity of chemoradiotherapy N = 25	
Grade III adverse event	N (%)
Gastro-intestinal	
Oesophagitis	1 (4)
Anorexia	1 (4)
Nausea	1 (4)
Haematological/vascular	
Leucopenia	3 (12)
Febrile neutropenia	1 (4)
Thrombosis	1 (4)
Constitutional	
Fatigue	1 (4)
Postoperative complications N = 22	
Postoperative complications	
General complications	
Cardiac	5 (20)
Infectious complications	
Urinary tract infection	1 (4)
Pneumonia	3 (12)
Sepsis	3 (12)
Surgery related complications	
Anastomotic leakage	3 (12)
Bowel perforation	2 (8)
Death	
In-hospital and 30-day	1 (4)

All tumours were adenocarcinomas except for one squamous cell carcinoma (Table 1). A microscopically radical (R0) resection was achieved in 18 patients (72% of 25 patients treated, 86% of 21 patients who underwent surgery with curative intent), a microscopically irradical (R1) in 3 and a macroscopically irradical (R2) in 1. The pCR (grade 1a) rate was 16%, including the one patient with squamous cell carcinoma. Grade 1b response rate was 24%, grade 2 28% and grade 3 20%.

The 21 patients who were macroscopically disease-free after surgery (R0 or R1) were evaluated for first recurrences. Site of recurrence was local in 5 patients: gastric bed/remnant in 3 (in-RT field), oesophageal-jejunal anastomoses in 1 (in- or out-RT field not reliably assessable), and lymph node station 8 (along the common hepatic artery, in-RT field) in 1 patient. Peritoneal carcinomatosis occurred in 2 patients and distant metastasis in 6: liver metastases in 3, brain metastases in 2, and supraclavicular lymph nodes in 1.

At the date of evaluation 18 patients (72%) had died, of whom 13 (52%) were of the disease. The estimated median OS was 15 months (Fig. 2). Three out of 4 patients with a pCR were disease free and alive at time of analyses. Survival was 9 months for the patient that died, and at time of analysis 56, 35 and 33 months for the three other patients.

Discussion

This study showed that preoperative radiotherapy with concurrent paclitaxel and carboplatin (CROSS regimen-based) is a feasible treatment strategy in gastric cancer patients, because toxicity was manageable and did not lead to delay or withdrawal of surgery. Importantly, the CRT regimen was given in the outpatient clinic which is both patient-friendly and logistically attractive. The treatment compliance observed in this study is comparable to that observed in the CROSS [10] and the MAGIC trial [9].

Both haematologic and gastro-intestinal toxicity were mostly limited to grade 1 and 2. This is also comparable with the results in the aforementioned studies. In our patients, toxicity was managed mainly by tube feeding, emphasising the importance of this measure. Also, postoperative complication rates (i.e. anastomotic

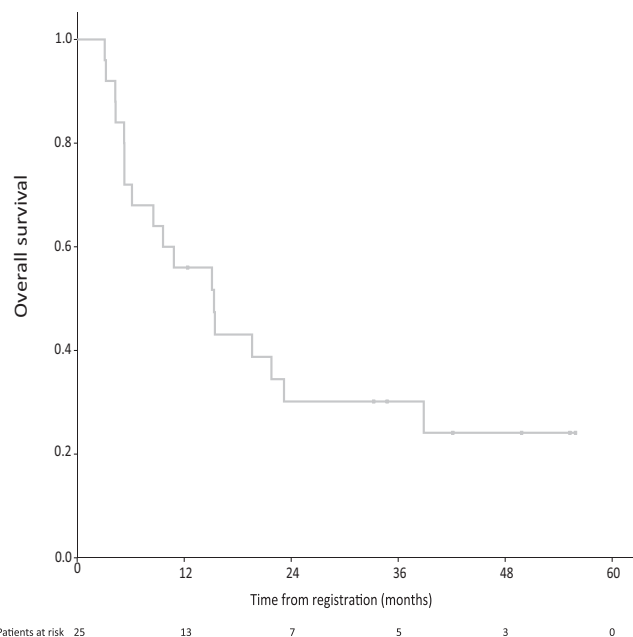


Fig. 2. Overall survival after preoperative chemoradiotherapy followed by surgery for locally advanced gastric cancer.

leakage 12%) and postoperative mortality (4%) were comparable to other studies investigating preoperative treatment [9–19] and surgical only studies [23]. Therefore, preoperative CRT seems to have no to minimal impact on postoperative morbidity and mortality, but this should be further investigated in a randomised trial.

In addition to the standard diagnostic work-up, all except two patients in this study underwent a PET-scan. All patients with initially irresectable gastric cancer (48%) also underwent diagnostic laparoscopy before start of treatment. Despite these additional diagnostic procedures, the single reason for not undergoing macroscopically radical surgery was peritoneal carcinomatosis (four patients). Three out of four patients with peritoneal carcinomatosis had diffuse type gastric cancer, which is known to spread more easily to the peritoneal cavity [24]. Accurate staging of peritoneal carcinomatosis in gastric cancer and especially in diffuse type remains a problem even with the incorporation of diagnostic laparoscopy. Nonetheless, diagnostic laparoscopy is advised in locally advanced gastric cancer [25,26].

This study also showed that preoperative radiotherapy with concurrent paclitaxel and carboplatin is an effective regimen for locally advanced gastric cancer. The R0 and pCR rate were similar to those in the CROSS trial [10] and other phase I-II studies [11–19]. Considering that half of the patients in our study had initially irresectable gastric cancer, and 9 patients had a cT4 tumour (36%), the R0 rate (72%) was high [27,28]. Eight out of 12 patients (67%) with initially irresectable gastric cancer had undergone R0 surgery, which may not have been achieved without preoperative CRT [10,11]. Moreover, considering that all patients had a clinical T3 (64%) or T4 (36%) tumour, the pathological complete response rate of 16% was also high.

In our study population, especially the patients with a pCR had a good survival. After preoperative CT alone, pCR rates were significantly lower in the MAGIC trial and in the trial by Stahl et al. [9,11]. Also, pCR rates after preoperative CT and CRT were independently prognostic for OS in several studies [12,22,29].

Currently, several treatment strategies can be applied in gastric cancer, as both treatment with postoperative CRT and perioperative CT improved overall survival to an equal extent. In the CRITICS trial, which is still actively recruiting, postoperative CRT is investigated for its additional advantage when combined with

preoperative CT versus perioperative CT for resectable gastric cancer (registered with ClinicalTrials.gov number NCT00407186) [30]. As mentioned before, due to the poor compliance of postoperative treatment, further research should focus on treatment regimens that can be entirely given preoperatively. The current study supports the motivation to investigate the possible superiority of preoperative CRT according the CROSS regimen in a randomised clinical trial. Depending on the results of the CRITICS trial, the arm with the best outcome could subsequently be compared to a study arm incorporating preoperative CRT.

A point of discussion remains the incorporation of an optimal systemic dose of CT, and timing of this treatment, in future trials for gastric cancer. In our study, patients only received CT as radiosensitizer and did not receive an optimal systemic dose. As investigated in many other studies [11–19], induction or adjuvant CT could be incorporated. On the other hand, local treatment with preoperative CRT for patients with oesophageal and oesophagogastric-junction cancer in the CROSS trial improved overall survival without the addition of induction or adjuvant CT.

In conclusion, preoperative radiotherapy with carboplatin/paclitaxel (CROSS regimen) for patients with locally advanced gastric cancer was associated with manageable toxicity and resulted in an encouraging pathological response rate.

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Disclosure

The authors have declared no conflicts of interest.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.radonc.2014.05.003>.

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