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Multicentre phase II trial of capecitabine and oxaliplatin in combination with radiotherapy for unresectable colorectal cancer: The CORGI-L study

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ABSTRACT

Aims: This study assessed radiotherapy combined with capecitabine and oxaliplatin in patients with primary, inextirpable colorectal adenocarcinoma.
Patients and methods: Forty-nine patients entered the trial. Two cycles of XELOX (capecitabine 1000 mg/m^2 bid d1-14 + oxaliplatin 130 mg/m^2 d1, q3w) were followed by radiotherapy (50.4 Gy), combined with capecitabine 825 mg/m^2 bid every radiotherapy day and oxaliplatin 60 mg/m^2 once weekly. The primary end-point was objective response.
Results: Forty-seven patients were evaluable. Twenty-nine (62% [95% CI: 46–75%]) achieved complete or partial response. Thirty-eight (81%) went through surgery of whom 37 (97%) had an R0 resection and five (13%) had a pathological complete response. Seventy-eight percent were alive and estimated local progression rate was 11% at 2 years. The most common grade 3+ toxicity during chemoradiotherapy was diarrhoea (24%).
Conclusions: XELOX-RT was feasible and showed promising efficacy when treating patients with primary inextirpable colorectal cancer, establishing high local control rate.

1. Introduction

In 15–20% of colorectal cancers the tumour is locally advanced to such an extent that primary surgery is not possible or would result in a mutilating surgical procedure. In these situations, especially for rectal cancer, radiotherapy at doses in the order of 45–50 Gy leads to effective tumour shrinkage.[1] Co-administration of the chemotherapeutic drug 5-fluorouracil (5-FU) leads to better downsizing and downstaging and/or improved local control compared to radiation alone, but no survival gain.[2–4]

Capecitabine is an oral fluoropyrimidine that is converted into 5-FU preferentially in tumour cells, with equal efficacy and a favourable toxicity profile compared to 5-FU in

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metastatic colorectal cancer.[5] Given the simplicity of oral drug administration during a radiotherapy session, capecitabine is now gradually replacing intravenous 5-FU in many chemoradiotherapy protocols for locally advanced rectal cancer and has shown high efficacy and good tolerance in several phase II-studies.[6,7]

Another drug widely used in colorectal cancer is oxaliplatin. In metastatic disease oxaliplatin combined with 5-FU is more effective than 5-FU alone[8] and the combination of capecitabine and oxaliplatin (XELOX) has been shown to be equally effective as oxaliplatin together with infused 5-FU in several recent studies.[9,10] Preclinical studies indicate that oxaliplatin has radiosensitising properties in colon cancer cell lines.[11,12]

Thus, there is a strong rationale for testing XELOX in combination with radiotherapy in rectal cancer. The purpose of our study was to determine the effects of XELOX combined with radiation in the most advanced cases, with primary unresectable T4 tumours, but also allowing patients with concomitant distant metastasis to be included.

2. Patients and methods

2.1. Study outline and endpoints

CORGI-L was an open-labelled phase II trial with local radiological response at 4–6 weeks after end of chemoradiotherapy as the primary end-point. Secondary endpoints were surgical resectability, pathological complete response (pCR) rate, tolerance and safety, time to local failure and overall survival. The study was approved by the local Ethics Committees. Toxicity was assessed prospectively according to NCI-CTC version 2.[13]

2.2. Patient selection and treatment schedule

Patients with locally advanced histologically proven primary non-resectable adenocarcinoma of the colon or rectum, with or without distant metastases, T4, N0-2, M0-1 were eligible. Other inclusion criteria were age >18 years, unidimensionally measurable disease, ECOG performance status 0–1, ANC > 1.5×10^9/L, platelets > $100{,}000 \times 10^9$/L, creatinine < 1.5 × institutional upper limit of normal (IULN), bilirubin < 1.5 × IULN, ALAT < 2.5 × IULN and a signed informed consent. Patients with prior radiotherapy to the same region, prior chemotherapy for locally advanced or metastatic disease, pregnancy or breast-feeding, peripheral neuropathy > grade 1, uncontrolled diarrhoea or other serious uncontrolled concomitant illness were not eligible.

Initially, two cycles of XELOX (capecitabine 1000 mg/m^2 orally twice daily d1-14 + oxaliplatin 130 mg/m^2 i.v. 2 h infusion d1, q3w) were given. During radiotherapy, capecitabine 825 mg/m^2 was administered orally twice daily every day of radiation. Oxaliplatin 60 mg/m^2 was given i.v. once weekly.

Radiotherapy was delivered by a linear accelerator using at least 6 MV photons. The GTV (gross tumour volume) included the colorectal tumour (GTV-T) and manifest local lymph node metastases (GTV-N). A margin of 1.5 cm was added to the GTV and defined as CTV1 (Clinical Target Volume 1). CTV1 with a margin of typically 0.5–1 cm was defined as PTV1 (planning target volume 1). PTV1 received 1.8 Gy per fraction to a total dose of 50.4 Gy at the ICRU Reference point. CTV2 included regional lymph nodes and received 41.4 Gy. No CTV2 was defined for colon tumours or in case of distant metastases.

2.3. Efficacy evaluation and follow-up

Tumour response was assessed according to Response Evaluation Criteria in Solid Tumours (RECIST).[14] Surgery was recommended only if all tumour lesions seemed resectable. The surgical procedure was classified as microscopically radical (R0), macroscopically complete but microscopically non-radical (R1) or macroscopically incomplete (R2). The pathologic stage (ypTN) was recorded according to the International Union Against Cancer TNM system. Follow-up was stipulated at every 3 months for 1 year, then every 6 months until local progression, death, loss to follow-up or until 36 months after study inclusion. Subsequent oncological treatment after evaluation for surgery in the adjuvant or palliative setting was up to the treating oncologist and not monitored within this study.

2.4. Statistical analysis

Sample size considerations were based on the expected length of an approximate two-sided 95% confidence interval of the proportion of study patients in complete or partial remission at 4–6 weeks post treatment. Based on previous experience and available literature data, an objective response rate of around 30–40% was assumed. We regarded a two-sided 95% confidence interval of length less than 0.3 to be acceptable and to achieve this, approximately 40 patients were needed. The association between local response and various clinical parameters was tested by means of Fisher's exact test. Overall survival (OS) was calculated from the date of trial entry until death from any cause, or censored at last follow-up, and survival probability was determined and illustrated using the Kaplan–Meier method with a 95% Greenwood confidence band. The cumulative incidence of local failure (before or after distant failure, if any) and the cumulative incidence of the first of local and distant failure were determined with death as a competing event.[15] All tests were two-sided and p-values < 0.05 were considered statistically significant.

3. Results

3.1. Patient recruitment and characteristics

Between October 2003 and July 2005, 49 patients were recruited onto the study at six Swedish hospitals. Patient characteristics are listed in Table 1.

Two of the 49 patients were excluded from further analysis; one who withdrew the consent and the other patient was not evaluable according to RECIST criteria, thus wrongly included.

3.2. Toxicity and treatment compliance

The most common grade 3–4 toxicity was diarrhoea that occurred in 24% of the cases during the chemoradiotherapy. Other side effects are shown in Table 2.

Table 1 – Patient characteristics.

Characteristic	$n = 47$	%
Age (years)		
Median (range)	61 (43–79)	
Sex		
Male	30	64
Female	17	36
ECOG performance status		
Unknown	1	2
0	36	77
1	10	21
Diagnosis		
Rectal cancer	41	87
Colon cancer	6	13
T stage		
T3	5[a]	11
T4	42	89
M stage		
M0	41	87
M1	6	13
Median tumour size (cm)	7.1	1.5–16.7

Abbreviations: ECOG, Eastern Cooperative Oncology Group; TNM, tumour-node-metastases.
a All T3 tumours were rectal cancers.

One death occurred during treatment due to a myocardial infarction which was classified as a probably capecitabine-induced cardiotoxic event.

Fourteen patients had pain grade 1–4 at baseline, seven after two cycles of chemotherapy and six at 4 weeks after treatment cessation.

Chemotherapy dose reductions were common. The actual dose intensity decreased gradually during the treatment course and, at the last treatment cycle, 53% and 47% received full dose capecitabine and oxaliplatin, respectively. Fifteen percent of the patients obtained all chemotherapy cycles without any dose reduction.

Two of the patients evaluable for response did not receive the chemoradiotherapy according to the protocol, due to toxicity. One of those received full dose chemoradiotherapy (50.4 Gy + oxaliplatin and bolus 5-FU instead of XELOX due to cardiotoxicity), the second patient received radiotherapy alone (50.4 Gy). The radiotherapy dose given to the remaining 45 patients was 50.4 Gy to all except one (who died after 18 fractions and received 32.4 Gy). Unplanned radiation treatment interruptions of more than 2 days occurred in two cases.

3.3. *Treatment outcome*

The response rate for the 47 patients was 62% (95% CI 46–75%). The relationship between various clinical factors and the local response rate was analysed (Table 3).

Thirty-eight (81%) patients went through surgery. In 23 of the cases an abdomino-perineal resection was performed. Several of these patients had tumour growth necessitating resection of additional adjacent organs (e.g. hystero-salpingo-oophorectomy: 3, cystectomy/ureterectomy: 5,

Table 2 – Incidence of the most common toxicities experienced during the study treatment.

Toxicity	Treatment cycles 1–2 (Chemotherapy) $n = 47$		Treatment cycles 3–8 (Chemoradiotherapy) $n = 45$	
	Grade 1–2 No (%)	Grade 3–4 No (%)	Grade 1–2 No (%)	Grade 3–4 No (%)
Gastrointestinal				
Diarrhoea	18 (38)	5 (11)	20 (44)	11 (24)
Nausea	20 (43)	0 (0)	26 (58)	1 (2)
Vomiting	9 (19)	1 (2)	10 (22)	1 (2)
Anorexia	5 (11)	1 (2)	12 (27)	2 (4)
Stomatitis	6 (13)	0 (0)	7 (16)	0 (0)
Constipation	0 (0)	1 (2)	2 (4)	0 (0)
Haematological				
Leucopoenia	3 (6)	0 (0)	14 (31)	3 (7)
Thrombocytopenia	2 (4)	0 (0)	29 (64)	1 (2)
Anaemia	18 (38)	0 (0)	31 (69)	0 (0)
Skin				
Hand foot syndrome	2 (4)	0 (0)	10 (22)	1 (2)
Neurological				
Sensory neuropathy	34 (72)	1 (2)	41 (91)	1 (2)
Cardiovascular				
Cardiac ischaemia/infarction	0 (0)	1 (2)	0 (0)	1 (2)[a]
Thromboembolic event	0 (0)	0 (0)	0 (0)	2 (4)
Other				
Fatigue	14 (30)	0 (0)	23 (51)	3 (7)
Dehydration	3 (6)	0 (0)	3 (7)	0 (0)
Fever/infection	4 (9)	0 (0)	8 (18)	4 (9)

a Grade 5 cardiac toxicity.

Table 3 – Local response rate and relationship with clinical parameters.

Complete response (CR)	Partial response (PR)	Stable disease (SD)	Progressive disease (PD)	Non-evaluable
Local radiological response (n = 47), n (%) (95% CI)				
2 (4%) (0.5–15%)	27 (57%) (42–72%)	14 (30%) (17–45%)	3 (6%) (1–18%)	1 (2%)[a] (0––11%)
	(PR/CR)		(SD/PD)	*p* value
Radiological response by various clinical parameters (n = 46)				
Gender				
Male	18 (62%)		11	1.00
Female	11 (65%)		6	
Age				
>61 (median)	18 (75%)		6	0.13
⩽61 (median)	11 (50%)		11	
ECOG				
ECOG = 0	22 (63%)		13	1.00
ECOG > 0	7 (70%)		3	
Tumour type				
Rectum	24 (59%)		17	0.14
Colon	5 (100%)		0	
M stage				
M0	26 (67%)		13	0.65
M1	3 (50%)		3	
CEA				
>5	16 (59%)		11	0.56
⩽5	13 (68%)		6	

Fisher's exact test for patients evaluated for radiological response where the relevant clinical data was available.
a Patient died before response evaluation.

prostatectomy: 3, sacral excision: 1). Resection R-status for the whole study population is presented in Table 4. Downstaging was achieved for 76% (29/38) of these patients and 13% (5/38) had pCR (ypT0N0M0).

Overall survival and cumulative relapse rates are visualised in Fig. 1. The 2-year survival was 78% for the study population as a whole. The observed local progression rate in the whole population was 9% and 11% after 1 and 2 years, respec-

Table 4 – Surgery, surgical radicality and clinical T stage compared to pathological T stage.

Surgery	38 (81%)
Anterior rectal resection	9
Hartmańs resection	4
Colon resection	2
Abdomino-perineal resection	23
No surgical resection, due to:	9 (19%)
Primary tumour not resectable	1
Progressive metastatic disease	6
Patient refusal	1
Death	1
Resection margins	
R0	37
R1	0
R2	1

Baseline T stage	Pathologic staging (n = 38)				
	pT0	pT1	pT2	pT3	pT4
Preoperative T stage compared to pathological T stage					
cT3	1	2	0	1	1
cT4	4	2	2	18	7

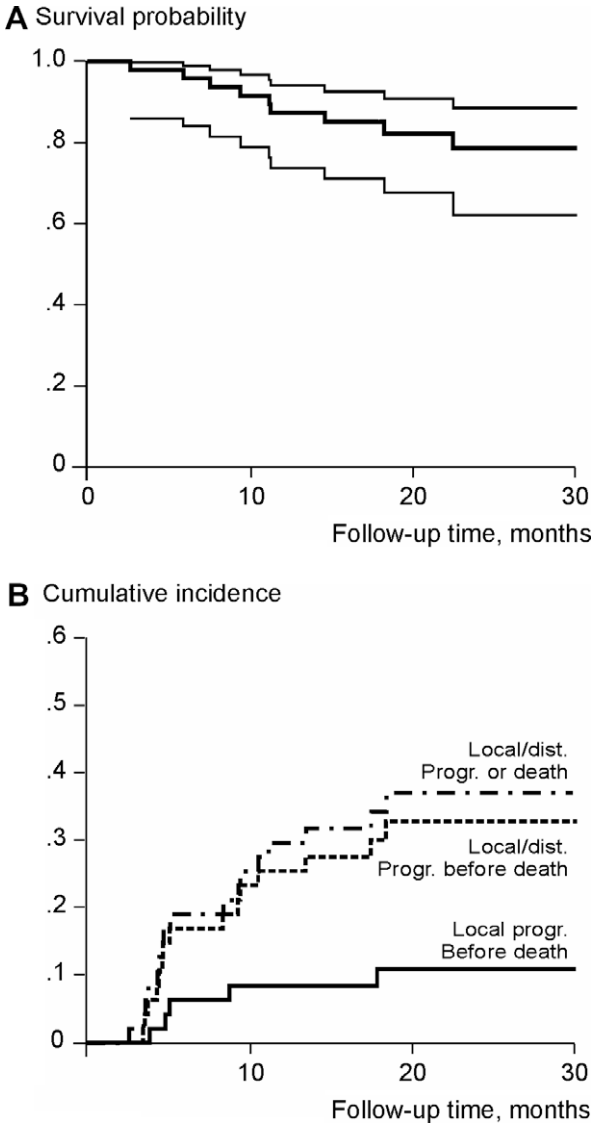

Fig. 1 – (A) Kaplan–Meier estimate of overall survival (+95% CI) in all evaluable patients (*n* = 47) with a median follow-up of 23 months. (B) Cumulative incidence of local progression as a first event, local/distant progression as first event or local/distant progression/death as a first event (*n* = 47).

tively. In patients not operated upon the estimated 1 year local progression rate was 14% and the 1 year survival was 56%.

4. Discussion

In this phase II trial, intensive chemoradiotherapy with XELOX-RT led to a 62% (95% CI 46–75%) objective response rate in a population of patients with locally advanced non-resectable, colorectal cancer. Eighty-one percent (38/47) of the patients went through secondary colorectal surgery. Thirteen percent (5/38) of these achieved a pCR compared to previously published studies using similar schedules, showing pCR rates of 10–19%.[16–19] The patient population in the present study had a very advanced disease. The median tumour size was 7 cm and forty-two (89%) of the patients had cT4 tumours, compared to previous XELOX-RT studies that included mainly primarily resectable mostly T3 tumours, (Table 5). Furthermore, 13% of the patients had synchronous distant metastases.

Our decision to also allow patients with M1 disease to be included was due to the fact that it is not obvious how patients with locally advanced colorectal tumours with synchronous distant metastases should be treated. What is clear is that uncontrolled local growth is associated with a poor prognosis, substantial morbidity and regardless of the general tumour stage, the local tumour needs to be taken care of. The results shown in Fig. 1 indicate a clearly better local than distant control of this treatment regimen, demonstrating that chemoradiotherapy gives a more durable tumour control than chemotherapy alone. Also in the subgroup that was not operated upon, the local control rate at 1 year, i.e. freedom from local progression, was as high as 86%. We find this as an argument in favour of using chemoradiotherapy not only in patients prone for later surgery, but also in the palliative setting as maintaining local control is of great importance for the patients' quality of life.

In the present study six patients with locally advanced colon cancers were included. The literature on chemoradiotherapy for these tumours is very sparse. A potential hazard with high dose radiation of a colon cancer is that large volumes of small bowel need to be included in the irradiated volume, which is a well known risk factor for radiation enteritis.[20] In order to minimise this side-effect, colon cancer patients did not receive adjuvant irradiation to their loco-regional lymph nodes. In fact none of these patients experienced grade 3–4 diarrhoea (data not shown). Based on this limited experience XELOX-RT regimen seemed safe and effective (5/5 evaluable for response had either PR or CR) to use also in locally advanced colon tumours (Table 3).

Two cycles of XELOX were administered prior to start of chemoradiotherapy. Early chemotherapy could have effects on systemic dissemination as well as local disease. Many patients with locally advanced colorectal cancer have severe symptoms. Chau and colleagues[21] found that 71% of patients had a resolution of pain during their four cycles of XELOX preceding chemoradiotherapy. This was confirmed in the present study, showing a 50% reduction of the number of patients reporting pain after two cycles of XELOX compared to baseline.

The toxicity in the present study was similar to previous XELOX-RT studies with diarrhoea as the main dose-limiting toxicity. Chemotherapy dose reductions due to toxicity were common. The oxaliplatin dose used was slightly higher than in other recent reports typically giving oxaliplatin 50 mg/m^2 weekly, whereas our capecitabine dose intensity was rather at the low end (Table 5).

In conclusion, this study confirms that XELOX-RT, followed by surgery whenever feasible, is an effective treatment for locally advanced non-resectable, colorectal cancer, with manageable toxicity. Our results suggest that intensive chemoradiotherapy is of value, not only for resectable T3 tumours included in previous studies, but also for large T4 tumours, for colon cancer and in patients with synchronous distant metastases, given the high local tumour control rate. Whether this therapeutic strategy is better than any other

Table 5 – Phase II studies of radiation combined with capecitabine and oxaliplatin in locally advanced primary rectal cancer.

Study	Study population (*n*)	% cT4 (primary tumours)	Radiotherapy (Total dose (Gy)/n. of fractions)	Oxaliplatin dose intensity, per week (mg/m^2)	Capecitabine dose intensity, per day (mg/m^2)	% Grade 3–4 diarrhoea	% pCR
Rutten and colleagues[16]	87	NA	45/25	50	1178	18	10
Rödel and colleagues[17]	104	14	50.4/28	50	1216	12	16
Machiels and colleagues[18]	40	8	45/25	50	1178	30	14
Glynne-Jones and colleagues[19]	85	NA	45/25	52	1300	9	19
CORGI-L[a]	47	89	50.4/28	60	1178	24	13

Dose intensity for capecitabine and oxaliplatin during radiotherapy is presented as the average dose per day and week, respectively.
Abbreviations: pCR, pathological complete response; NA, not available.
a Present study.

treatment for this patient population remains to be shown in randomised trials.

Conflict of interest statement

None declared.

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