Preoperative chemoradiotherapy and postoperative chemotherapy with fluorouracil and oxaliplatin versus fluorouracil alone in locally advanced rectal cancer: initial results of the German CAO/ARO/AIO-04 randomised phase 3 trial

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Summary

Background Preoperative chemoradiotherapy, total mesorectal excision surgery, and adjuvant chemotherapy with fluorouracil is the standard combined modality treatment for rectal cancer. With the aim of improving disease-free survival (DFS), this phase 3 study (CAO/ARO/AIO-04) integrated oxaliplatin into standard treatment.

Methods This was a multicentre, open-label, randomised, phase 3 study in patients with histologically proven carcinoma of the rectum with clinically staged T3–4 or any node-positive disease. Between July 25, 2006, and Feb 26, 2010, patients were randomly assigned to two groups: a control group receiving standard fluorouracil-based combined modality treatment, consisting of preoperative radiotherapy of 50·4 Gy plus infusional fluorouracil (1000 mg/m² days 1–5 and 29–33), followed by surgery and four cycles of bolus fluorouracil (500 mg/m² days 1–5 and 29; fluorouracil group); and an experimental group receiving preoperative radiotherapy of 50·4 Gy plus infusional fluorouracil (250 mg/m² days 1–14 and 22–35) and oxaliplatin (50 mg/m² days 1, 8, 22, and 29), followed by surgery and eight cycles of adjuvant chemotherapy with oxaliplatin (100 mg/m² days 1 and 15), leucovorin (400 mg/m² days 1 and 15), and infusional fluorouracil (2400 mg/m² days 1–2 and 15–16; fluorouracil plus oxaliplatin group). Randomisation was done with computer-generated block-randomisation codes stratified by centre, clinical T category (cT1–4 *vs* cT4), and clinical N category (cN0 *vs* cN1–2) without masking. DFS is the primary endpoint. Secondary endpoints, including toxicity, compliance, and histopathological response are reported here. Safety and compliance analyses included patients as treated, efficacy endpoints were analysed according to the intention-to-treat principle. This study is registered with ClinicalTrials.gov, number NCT00349076.

Findings Of the 1265 patients initially enrolled, 1236 were evaluable (613 in the fluorouracil plus oxaliplatin group and 623 in the fluorouracil group). Preoperative grade 3–4 toxic effects occurred in 140 (23%) of 606 patients who actually received fluorouracil and oxaliplatin during chemoradiotherapy and in 127 (20%) of 624 patients who actually received fluorouracil chemoradiotherapy. Grade 3–4 diarrhoea was more common in those who received fluorouracil and oxaliplatin during chemoradiotherapy than in those who received fluorouracil during chemoradiotherapy (73 patients [12%] *vs* 52 patients [8%]), as was grade 3–4 nausea or vomiting (23 [4%] *vs* nine [1%]). 516 (85%) of the 606 patients who received fluorouracil and oxaliplatin-based chemoradiotherapy had the full dose of chemotherapy, and 571 (94%) had the full dose of radiotherapy; as did 495 (79%) and 601 (96%) of 624 patients who received fluorouracil-based chemoradiotherapy, respectively. A pathological complete response was achieved in 103 (17%) of 591 patients who underwent surgery in the fluorouracil and oxaliplatin group and in 81 (13%) of 606 patients who underwent surgery in the fluorouracil group (odds ratio 1·40, 95% CI 1·02–1·92; p=0·038). In the fluorouracil and oxaliplatin group, 352 (81%) of 435 patients who began adjuvant chemotherapy completed all cycles (with or without dose reduction), as did 386 (83%) of 463 patients in the fluorouracil group.

Interpretation Inclusion of oxaliplatin into modified fluorouracil-based combined modality treatment was feasible and led to more patients achieving a pathological complete response than did standard treatment. Longer follow-up is needed to assess DFS.

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Introduction

Radiotherapy, chemotherapy, and surgery are important elements of multimodal treatment for patients with rectal cancer. The optimum sequence and combination of these elements has been investigated in several randomised trials, and preoperative fluorouracil-based chemoradiotherapy is the preferred treatment for a range of endpoints, including treatment compliance, toxic

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For the **study protocol** see http://www.kgu.de/uploads/media/Protocol_Synopsis_CAO-ARO-AIO-04.pdf

effects, and local control.[1–4] After publication of the CAO/ARO/AIO-94 phase 3 trial in 2004,[1] preoperative radiotherapy combined with infusional fluorouracil, total mesorectal excision (TME) surgery, and adjuvant chemotherapy with fluorouracil became the standard of care for patients with stage II–III rectal cancer in Germany.

With optimised local treatment, achieved with preoperative radiotherapy or chemoradiotherapy and TME surgery, local recurrence rates have been markedly reduced. The main cause for failure in rectal cancer is now distant metastases. No randomised trials so far have shown a survival benefit for combined modality treatment of rectal cancer using modern TME-based surgical techniques and preoperative radiotherapy alone or chemoradiotherapy with fluorouracil.[1–3,5,6] Any improvement in overall survival will require better control of systemic disease while keeping the rate of local recurrences below 5–10%.

Along these lines, the German Rectal Cancer Study Group investigated new chemotherapy regimens in phase 1–2 trials to establish an active and feasible regimen for a phase 3 trial.[7,8] These regimens included oral fluoropyrimidines and oxaliplatin, with preoperative radiotherapy and as adjuvant treatment. We learned from these early trials that the maximum tolerable dose of weekly oxaliplatin during preoperative chemoradiotherapy was 50 mg/m², and that the tolerability of this experimental schedule was excellent when a chemotherapy treatment gap was introduced in week 3 of preoperative radiotherapy.[7,8]

In the CAO/ARO/AIO-04 trial presented here, we used the better treatment regimen of our former CAO/ARO/AIO-94 trial as a control: fluorouracil-based chemoradiotherapy, TME surgery, and 4 months of postoperative fluorouracil.[1] The experimental group for the present study incorporated oxaliplatin into preoperative and postoperative treatments, based on our phase 1–2 results. Disease-free survival (DFS) is the primary endpoint. Here, we present the results for secondary endpoints, including toxicity, surgical quality and morbidity, treatment compliance, and early efficacy data.

Methods

Study design and patients

CAO/ARO/AIO-04 is a multicentre, open-label, randomised, phase 3 study, approved by the central ethics committee of the University of Erlangen (Erlangen, Germany), and the institutional review boards of all participating institutions. Each patient provided written informed consent before participating in the study.

Eligible patients were aged 18 years or older with histopathologically confirmed rectal carcinoma with an inferior margin no more than 12 cm above the anal verge, as assessed by rigid proctoscopy. According to German national guidelines for diagnosis and treatment of rectal cancer,[9] patients were eligible for preoperative chemoradiotherapy if their tumours showed evidence of perirectal fat infiltration (cT3–4) or lymph-node involvement (cN+), as assessed by endorectal ultrasound, multislice CT, or MRI. MRI was recommended for local staging but was not mandatory. Further inclusion criteria were Eastern Cooperative Oncology Group (ECOG) performance status 2 or lower, and adequate haematological, liver, and renal function. Exclusion criteria included metastatic disease, prior radiotherapy or chemotherapy, other cancers, pregnancy, lactation, clinically significant cardiac disease, and known peripheral neuropathy.

Randomisation and masking

Participants were enrolled by study investigators, and eligible patients were randomly assigned to one of the two groups (figure 1) using computer-generated randomisation codes (sequential permuted blocks) based on centre, clinical T category (cT1–3 *vs* cT4), and clinical N category (cN0 *vs* cN1–2) as strata. Randomisation was done centrally and patient assignment was implemented through a fax interface and web interface hosted by the Department of Medical Informatics, Biometry, and Epidemiology, University of Erlangen (Erlangen, Germany), ensuring that the next assignment in the sequence was masked. Treatment groups were not masked throughout the trial, because the treatments involved different administration and schedules.

Procedures

Patients randomly assigned to the standard fluorouracil-based treatment group received preoperative chemoradiotherapy, TME surgery, and adjuvant chemotherapy with fluorouracil as in the preoperative group of our previous CAO/ARO/AIO-94 study (figure 1).[1] In brief, radiotherapy consisted of 50·4 Gy total in 28 fractions (1·8 Gy daily, Monday–Friday), delivered with a minimum energy of 6 MV photons via a three-field or four-field box technique to the primary tumour and to mesorectal, presacral, and internal iliac lymph nodes. Concurrent chemotherapy was administered as a continuous infusion of fluorouracil (1000 mg/m²) on days 1–5 and 29–33 of radiotherapy. Adjuvant chemotherapy comprised four cycles of intravenous fluorouracil bolus (500 mg/m²) on days 1–5 and 29, for a total of 4 months.

Patients randomly assigned to the experimental group received the same preoperative radiotherapy, combined with continuous infusion of fluorouracil (250 mg/m²) on days 1–14 and 22–35, and a 2-h infusion of oxaliplatin (50 mg/m²) on days 1, 8, 22, and 29. Adjuvant chemotherapy consisted of eight cycles of oxaliplatin (100 mg/m²) administered on day 1 as a 2-h infusion, followed by a 2-h infusion of leucovorin (400 mg/m²), followed by a continuous 46-h infusion of fluorouracil (2400 mg/m²), repeated on day 15, for a total of 4 months.

Patients were monitored weekly during chemoradiotherapy and before each adjuvant treatment cycle, with regard to vital signs and haematological and biochemical analyses. Doses were modified in response to toxicities according to predefined guidelines. Acute adverse events during or within 30 days after chemoradiotherapy or adjuvant chemotherapy were graded according to the Common Terminology Criteria for Adverse Events, version 3.0.

All resection specimens were examined using a standardised protocol that included TNM classification according to the American Joint Committee on Cancer and International Union Against Cancer (sixth edition),[10] the number of examined and involved lymph nodes, and the status of proximal, distal, and circumferential resection margins. The quality of mesorectal resection (good, moderate, or poor plane of the mesorectal compartment) was monitored and graded by local histopathologists using classification proposed by Quirke and co-workers.[11] Residual tumour mass after preoperative treatment was semi-quantitatively evaluated according to Dworak and colleagues'[12] five-point grading system for rectal cancer regression. We used predefined pathology case report forms with dedicated definitions for TME quality and rectal cancer regression grading, including for image material. Pathological complete response (pCR) was defined as absence of viable tumour cells in the primary tumour and lymph nodes (ypT0 pN0).

A quality assurance programme, headed by reference institutions for surgery, radiotherapy, and chemotherapy, reviewed the information submitted on case report forms. Training classes for participating surgeons, pathologists, radiation oncologists, and medical oncologists were held at study meetings twice a year, and a central review was done of arbitrarily selected patients (two from each participating centre) regarding compliance with protocol-defined standard operating procedures. We did not do a central review for all patients, or a systematic assessment of interobserver and intraobserver variability in TME quality and tumour regression grading.

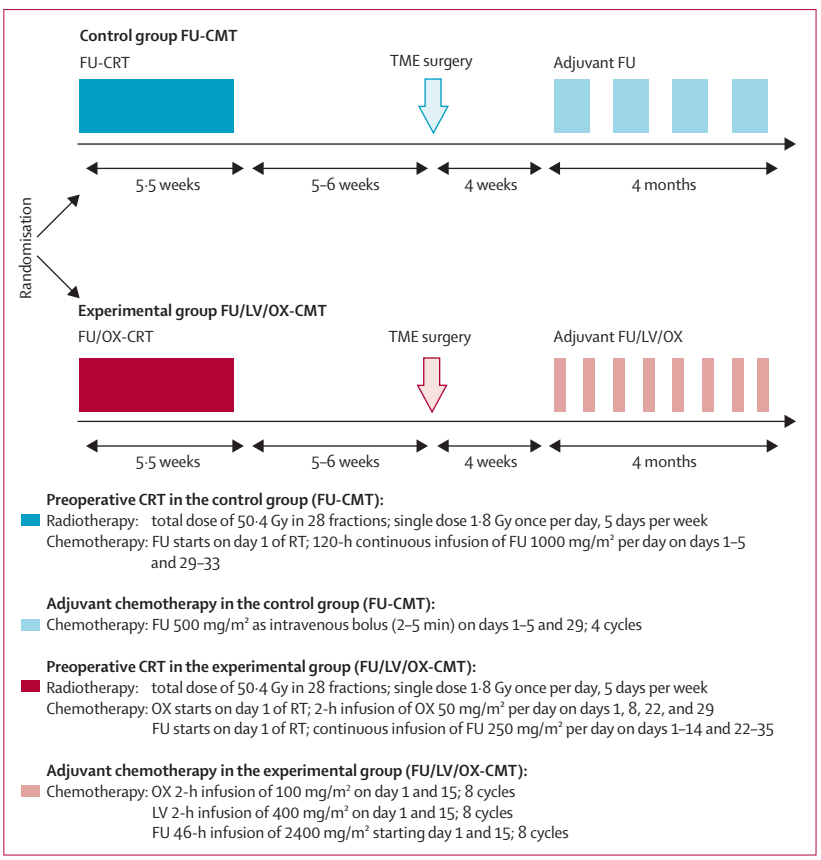

Figure 1: **Treatment schedules**
FU=fluorouracil. CMT=combined modality treatment. CRT=chemoradiotherapy. TME=total mesorectal excision. LV=leucovorin. OX=oxaliplatin. RT=radiotherapy.

Statistical analysis

The primary endpoint, DFS, was defined as the time between randomisation and the first of the following events: macroscopically non-radical surgery, loco-regional or metastatic recurrence, or death from any cause. We postulated that 3-year DFS would improve from 75% in the fluorouracil group to 82% in the fluorouracil plus oxaliplatin group. A sample size of 1200 patients was required to show this improvement with a power of 80% and type I error of 5%. Secondary endpoints included toxic effects, compliance, and early efficacy endpoints (pCR, ypN0, and R0 resection rate). According to the study protocol, the difference in DFS was the only hypothesis to be tested formally, and no formal equivalence margins were specified for secondary endpoints. Thus, the initial results for secondary endpoints reported here are merely descriptive and should not be interpreted as statistically significant. The Cochran-Mantel-Haenszel χ^2 test for independence of number of pCRs and treatment group (conditional on strata and without continuity correction) is reported as an unplanned exploratory analysis. All analyses were done according to the intention-to-treat principle, except for safety and compliance endpoints, where patients were included as treated. The R system for statistical computing, version 2.14.2, was used for all analyses.[13]

This study is registered with ClinicalTrials.gov, number NCT00349076.

Role of the funding source

The funding source provided a research grant for the trial, but had no role in the study design, data collection, analysis, or interpretation, writing of the report, or the decision to submit for publication. CR, TL, TH, HS, SP, and RS had access to the raw data. The corresponding author had full access to all study data and final responsibility for the decision to submit for publication.

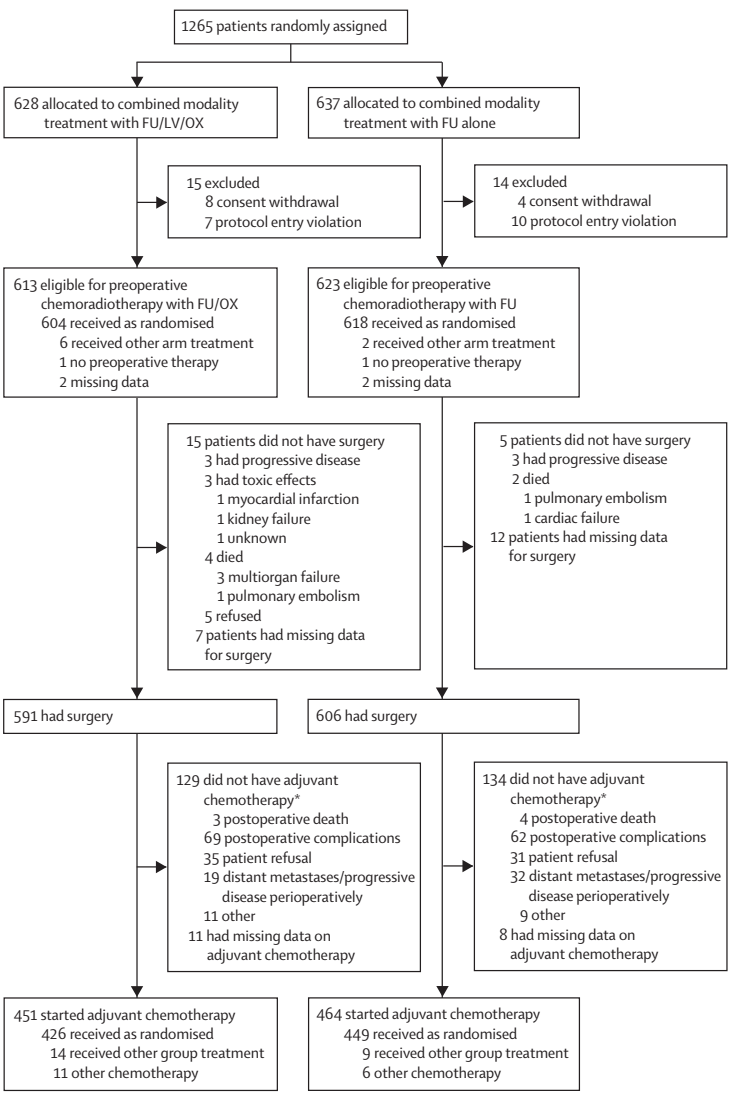

Figure 2: **CONSORT diagram**
FU=fluorouracil. LV=leucovorin. OX=oxaliplatin. *Multiple assignments possible.

	Fluorouracil and oxaliplatin group (n=613)	Fluorouracil group (n=623)
Age (years)		
Mean (SD)	62 (10)	62 (10)
Median (range)	64 (24–84)	63 (24–83)
Sex		
Male	435 (71%)	441 (71%)
Female	178 (29%)	182 (29%)
ECOG performance status		
0	479 (78%)	473 (76%)
1–2	124 (20%)	141 (23%)
Missing	10 (2%)	9 (1%)
Clinical T category		
cT1–2	25 (4%)	37 (6%)
cT3	545 (89%)	526 (84%)
cT4	40 (7%)	50 (8%)
Unknown or missing	3 (<1%)	10 (2%)
Clinical N category		
cN0	145 (24%)	157 (25%)
cN1–2	448 (73%)	444 (71%)
Unknown or missing	20 (3%)	22 (4%)
Clinical disease stage		
Stage II	145 (24%)	156 (25%)
Stage III		
cT1–2 N1–2	25 (4%)	35 (6%)
cT3–4 N1–2	423 (69%)	409 (66%)
Unknown or missing	20 (3%)	23 (4%)
Location from anal verge		
0–5 cm	247 (40%)	215 (35%)
>5–10 cm	299 (49%)	331 (53%)
>10 cm	53 (9%)	64 (10%)
Missing	14 (2%)	13 (2%)
Histology		
Adenocarcinoma	599 (97%)	596 (96%)
Mucinous adenocarcinoma	5 (<1%)	10 (2%)
Signet-ring cell carcinoma	2 (<1%)	4 (<1%)
Other or missing	7 (1%)	13 (2%)
Tumour differentiation		
Well differentiated (G1)	33 (5%)	30 (5%)
Moderately differentiated (G2)	493 (80%)	500 (80%)
Poorly differentiated (G3)	49 (8%)	49 (8%)
Missing	38 (6%)	44 (7%)

Data are number of patients (%) unless otherwise stated. ECOG=Eastern Cooperative Oncology Group.

Table 1: **Baseline characteristics**

Results

From July 25, 2006, to Feb 26, 2010, 1265 patients were recruited in 88 centres in Germany. 29 patients proved ineligible after enrolment. Of the remaining 1236 eligible patients, 613 patients were randomised to the fluorouracil and oxaliplatin group and 623 to the fluorouracil group (figure 2). Local staging was done with MRI for 593 (48%) of the 1236 eligible patients (298 in the fluorouracil and oxaliplatin group and 295 in the fluorouracil group), and with endorectal ultrasound plus pelvic CT scan for the other 643 (52%) of patients (315 in the fluorouracil and oxaliplatin group and 328 in the fluorouracil group). Baseline characteristics were well balanced between groups (table 1).

Preoperative grade 3–4 toxic effects occurred in 140 (23%) of 606 patients who actually received fluorouracil plus oxaliplatin during chemoradiotherapy, and in 127 (20%) of 624 patients who actually received fluorouracil during chemoradiotherapy (table 2). More patients who received fluorouracil and oxaliplatin based chemoradiotherapy had grade 3–4 gastrointestinal toxic effects, versus those who

	Fluorouracil and oxaliplatin group (n=606)*	Fluorouracil group (n=624)*
Toxicity (NCI-CTC version 3.0)		
All grade 3–4	140 (23%)	127 (20%)
Grade 3–4 haematological	32 (5%)	36 (6%)
Leucopenia	3 (<1%)	12 (2%)
Anaemia	2 (<1%)	4 (<1%)
Thrombocytopenia	2 (<1%)	2 (<1%)
Infection or fever	25 (4%)	11 (2%)
Grade 3–4 gastrointestinal	122 (20%)	93 (15%)
Diarrhoea	73 (12%)	52 (8%)
Nausea or vomiting	23 (4%)	9 (1%)
Proctitis	7 (1%)	7 (1%)
Fatigue	11 (2%)	5 (<1%)
Grade 3–4 genitourinary	10 (2%)	8 (1%)
Grade 3–4 metabolic or laboratory	9 (1%)	5 (<1%)
Grade 3–4 radiation dermatitis	10 (2%)	15 (2%)
Grade 3–4 hand-foot syndrome	2 (<1%)	1 (<1%)
Grade 2–3 neuropathy	11 (2%)	3 (<1%)
Treatment compliance		
Received total dose of radiotherapy	571 (94%)	601 (96%)
With radiotherapy interruptions	59 (10%)	42 (7%)
Radiotherapy discontinuation (total dose <50·4 Gy)	19 (3%)	16 (3%)
Missing data on radiotherapy	16 (3%)	7 (1%)
Received full dose of chemotherapy during radiotherapy	516 (85%)	495 (79%)
Chemotherapy dose reduction	89 (15%)	128 (21%)
Missing data on chemotherapy	1 (<1%)	1 (<1%)

Data are number of patients (%). NCI-CTC=National Cancer Institute Common Terminology Criteria for Adverse Events. *Six patients randomly assigned to preoperative fluorouracil-plus-oxaliplatin chemoradiotherapy and two assigned to fluorouracil alone received the chemoradiotherapy regimen of the other group. As shown here, for safety analysis, they were considered in the group of the treatment actually received.

Table 2: **Acute adverse effects and treatment compliance in patients who received preoperative chemoradiotherapy**

	Fluorouracil and oxaliplatin group (n=591)	Fluorouracil group (n=606)
Type of surgery		
Low anterior resection	391 (66%)	416 (69%)
Intersphincteric resection	32 (5%)	29 (5%)
Abdominoperineal resection	149 (25%)	146 (24%)
Other	17 (3%)	14 (2%)
Missing	2 (<1%)	1 (<1%)
Postoperative morbidity		
Overall complications (any grade)	278 (47%)	265 (44%)
Overall complications grade 3–4*	76 (13%)	63 (10%)
Anastomotic leakage	40 (7%)	29 (5%)
Wound-healing problems	16 (3%)	23 (4%)
Ileus	15 (3%)	5 (<1%)
Fistula	4 (<1%)	1 (<1%)
Second surgery for complications	14 (2%)	13 (2%)
Postoperative mortality	3 (<1%)	4 (<1%)
Grading of operative specimen		
Mesorectal plane (good)	450 (76%)	464 (77%)
Intramesorectal plane (moderate)	82 (14%)	82 (14%)
Muscularis propria plane (poor)	24 (4%)	29 (5%)
Missing	35 (6%)	31 (5%)

Data are number of patients (%). TME=total mesorectal excision. *Multiple assignments possible.

Table 3: **Surgical procedures, related toxicities, and grading of TME in patients who underwent surgery**

received fluorouracil-based chemoradiotherapy (122 [20%] of 606 *vs* 93 [15%] of 624). This was mainly due to diarrhoea (73 [12%] of 606 *vs* 52 [8%] of 624) and nausea or vomiting (23 [4%] *vs* nine [1%]). Six patients died in the interval after starting neoadjuvant treatment and before planned surgery: four patients who received fluorouracil and oxaliplatin chemoradiotherapy (three from multiorgan failure, one from pulmonary embolism) and two who received fluorouracil chemoradiotherapy (one from cardiac failure, one from pulmonary embolism; figure 2). With a cumulative oxaliplatin dose of 200 mg/m² during preoperative chemoradiotherapy, grade 2 or higher neuropathy was reported in only 11 (2%) of the 606 patients who received fluorouracil and oxaliplatin-based chemoradiotherapy. 571 (94%) of 606 patients who received fluorouracil and oxaliplatin-based chemoradiotherapy had the full dose of radiotherapy, and 516 (85%) had the full dose of chemotherapy; 601 (96%) of 624 who received fluorouracil-based chemoradiotherapy had the full dose of radiotherapy, and 495 (79%) had the full dose of chemotherapy (table 2).

After neoadjuvant chemoradiotherapy, 591 (96%) of 613 patients in the fluorouracil and oxaliplatin group and 606 (97%) of 623 in the fluorouracil group underwent surgery; in the fluorouracil and oxaliplatin group, seven patients had missing data for surgery and 15 patients did not have surgery for various reasons, in the fluorouracil group, these numbers were 12 and five (figure 2). The median interval between completion of chemoradiotherapy and surgery was 42 days in both groups (range 19–134 and 11–115). Abdominoperineal resection was restricted to 149 (25%) of 591 patients in the fluorouracil and oxaliplatin group and 146 (24%) of 606 patients in the fluorouracil group (table 3). The proportion of patients with postoperative complications of any grade was similar between groups (table 3). Three patients in the fluorouracil and oxaliplatin group and four patients in the fluorouracilgroup died within 60 days of surgery. Good-quality TME with a pathologically confirmed mesorectal plane of surgery was noted in 450 (76%) of 591 resected patients in the fluorouracil and oxaliplatin group and in 464 (77%) of 606 in the fluorouracil group; moderate TME was documented for 14% of patients in both groups, and poor-quality TME for 4% and 5%, respectively (table 3).

	Fluorouracil and oxaliplatin group (n=591)	Fluorouracil group (n=606)
Completeness of local tumour resection		
R0	557 (94%)	576 (95%)
R1	15 (3%)	8 (1%)
R2	5 (<1%)	7 (1%)
RX	7 (1%)	9 (1%)
Missing data	7 (1%)	6 (<1%)
Circumferential resection margin		
≤1 mm	32 (5%)	35 (6%)
>1 mm	384 (65%)	426 (70%)
Not applicable due to ypT0 pN0	103 (17%)	81 (13%)
Missing data	72 (12%)	64 (11%)
Pathological T category		
ypT0	113 (19%)	83 (14%)
ypTis	3 (<1%)	5 (<1%)
ypT1	38 (6%)	38 (6%)
ypT02	155 (26%)	181 (30%)
ypT03	259 (44%)	270 (45%)
ypT04	16 (3%)	26 (4%)
Missing data	7 (1%)	3 (<1%)
Number of lymph nodes examined	14 (0–79)	15 (0–81)
Pathological N category		
ypN0	412 (70%)	416 (69%)
ypN1	129 (22%)	129 (21%)
ypN2	41 (7%)	58 (10%)
Unknown or missing data	9 (1%)	3 (<1%)
Pathological stage		
ypT0N0	103 (17%)	81 (13%)
ypTisN0	3 (<1%)	5 (<1%)
I	145 (25%)	165 (27%)
IIA	139 (24%)	133 (22%)
IIB	12 (2%)	10 (2%)
IIIA	43 (7%)	48 (8%)
IIIB	81 (14%)	74 (12%)
IIIC	24 (4%)	46 (8%)
IV	21 (4%)	34 (6%)
Missing data	20 (3%)	10 (2%)
Tumour regression grading (primary tumour)		
Total regression (grade 4)	113 (19%)	83 (14%)
Major regression (grade 3)	149 (25%)	151 (25%)
Moderate regression (grade 2)	223 (38%)	235 (39%)
Minimal regression (grade 1)	66 (11%)	97 (16%)
No regression (grade 0)	18 (3%)	22 (4%)
No regression	22 (4%)	18 (3%)

Data are number of patients (%) or median (range).

Table 4: **Pathological characteristics in patients who underwent surgery**

	Fluorouracil and oxaliplatin group (n=435)*	Fluorouracil group (n=463)*
Toxicity (NCI-CTC version 3.0)		
All grade 3–4	153 (35%)	168 (36%)
Grade 3–4 haematological†	78 (18%)	165 (36%)
Leucopenia	37 (9%)	115 (25%)
Anaemia	4 (<1%)	12 (3%)
Thrombocytopenia	11 (3%)	6 (1%)
Infection or fever	25 (6%)	32 (7%)
Grade 3–4 gastrointestinal†	58 (13%)	61 (13%)
Diarrhoea	25 (6%)	19 (4%)
Nausea	8 (2%)	9 (2%)
Vomiting	7 (2%)	1 (<1%)
Stomatitis	1 (<1%)	12 (3%)
Fatigue	10 (2%)	17 (4%)
Grade 2 sensory neuropathy	89 (20%)	7 (2%)
Grade 3–4 sensory neuropathy	37 (9%)	5 (1%)
Grade 2 motor neuropathy	16 (4%)	5 (1%)
Grade 3–4 motor neuropathy	8 (2%)	3 (<1%)
Grade 3–4 metabolic or laboratory	5 (1%)	5 (1%)
Grade 3–4 cardiac	5 (1%)	2 (<1%)
Grade 3–4 genitourinary	8 (2%)	6 (1%)
Treatment compliance		
Maximum number of cycles received per patient (FU/LV/OX or FU alone)		
1–2 or 1	31 (7%)	35 (8%)
3–4 or 2	24 (6%)	26 (6%)
5–6 or 3	28 (6%)	16 (3%)
7–8 or 4	352 (81%)	386 (83%)
Completed all cycles with full dose	190 (44%)	301 (65%)
Completed all cycles with protocol-specified dose reduction	123 (28%)	57 (12%)
Missing data on dose received	39 (9%)	28 (6%)
Did not receive all cycles	83 (19%)	77 (17%)
Toxicity	38 (9%)	32 (7%)
Disease progression	2 (<1%)	5 (1%)
Patient preference	24 (6%)	23 (5%)
Other	18 (4%)	15 (3%)
Unknown	1 (<1%)	2 (<1%)

Data are number of patients (%). FU=fluorouracil. LV=leucovorin. OX=oxaliplatin. NCI-CTC=National Cancer Institute Common Terminology Criteria for Adverse Events. *14 patients randomly assigned to adjuvant FU/LV/OX and nine assigned to FU alone received the chemotherapy regimen of the other group. As shown here, for safety analysis, these patients were considered in the group of treatment actually received. †Multiple assignments possible.

Table 5: **Acute adverse effects and treatment compliance in patients who began protocol-specified adjuvant treatment**

Local complete R0 resections were recorded in 557 (94%) of 591 patients in the fluorouracil and oxaliplatin group and 576 (95%) of 606 in the fluorouracil group, and circumferential resection margins of 1 mm or less in 32 (5%) and 35 (6%), respectively (table 4). Complete remission of the primary tumour (ypT0, tumour regression grade 4) was achieved in 113 (19%) of the patients in the fluorouracil and oxaliplatin group and 83 (14%) in the fluorouracil group. The median number of lymph nodes examined was 14 (range 0–79) in the fluorouracil and oxaliplatin group and 15 (0–81) in the

	ACCORD 12/0405-Prodige 2	STAR-01	NSAPB R-04	CAO/ARO/AIO-04
Number of patients	598	747	1608	1236
Main inclusion criteria	cT3–4 adenocarcinoma, accessible to digital rectal examination, ≤80 years	cT3–4 or cN+adenocarcinoma, within 12 cm from anal verge, ≤75 years	cT3–4 or cN+adenocarcinoma, within 12 cm from anal verge, no upper age limit	cT3–4 or cN+adenocarcinoma, within 12 cm from anal verge, no upper age limit
Primary endpoint	pCR	Overall survival, pCR as protocol-planned comparative analysis	Locoregional relapse pCR, sphincter-saving surgery	Disease-free survival
Preoperative chemoradiotherapy regimen	50 Gy+capecitabine 1600 mg/m² daily 5 days a week+oxaliplatin 50 mg/m² once a week during radiotherapy *vs* 45 Gy+capecitabine 1600 mg/m² daily 5 days a week during radiotherapy	50·4 Gy+fluorouracil 225 mg/m² daily+oxaliplatin 60 mg/m² once a week during radiotherapy *vs* 50·4 Gy+fluorouracil 225 mg/m² daily during radiotherapy	50·4 Gy+capecitabine 1600 mg/m² daily 5 days a week with or without oxaliplatin 50 mg/m² once a week during radiotherapy *vs* 50·4 Gy+fluorouracil 225 mg/m² daily with or without oxaliplatin 50 mg/m² once a week during radiotherapy	50·4 Gy+fluorouracil 250 mg/m² daily plus oxaliplatin 50 mg/m² once in weeks 1, 2, 4, 5 of radiotherapy *vs* 50·4 Gy+fluorouracil 1000 mg/m² weeks 1 and 5 of radiotherapy
Cumulative dose of preoperative concurrent chemotherapy (planned)	Capecitabine 40 000 mg/m² with or without oxaliplatin 250 mg/m²	Fluorouracil 8550 mg/m² with or without oxaliplatin 360 mg/m²	Fluorouracil 8550 mg/m², capecitabine 40 000 mg/m², with or without oxaliplatin 250 mg/m²	Fluorouracil 7000 mg/m² plus oxaliplatin 200 mg/m² *vs* fluorouracil 10 000 mg/m²
Compliance with preoperative chemoradiotherapy in oxaliplatin groups	Radiotherapy: 87% received full dose Oxaliplatin: 41% received full dose	Radiotherapy: 84% received full dose Oxaliplatin: 66% received all six infusions (with or without dose reduction)	Not reported	Radiotherapy: 94% received full dose Oxaliplatin: 85% received full dose
Grade 3–4 toxicity: preoperative chemoradiotherapy with oxaliplatin *vs* without	25% *vs* 11% (p<0·001)	24% *vs* 8% (p<0·001)	15% *vs* 7% (p<0·001) (only grade 3–4 diarrhoea)	23% *vs* 20%
pCR rate: with oxaliplatin *vs* without	19% *vs* 14% (p=0·09)	16% both groups (p=0·90)	21% *vs* 19% (p=0·46)	17% *vs* 13% (p=0·04)
Distant metastasis at surgery: with oxaliplatin *vs* without	2·8% *vs* 4·2% (abdominal)	0·5% *vs* 2·9% (abdominal)	Not reported	4% *vs* 6% (all sites)
Adjuvant chemotherapy	No specific recommendation	Fluorouracil-based	No specific recommendation	Fluorouracil, leucovorin, and oxaliplatin *vs* fluorouracil

ACCORD=Actions Concertées dans les Cancers Colorectaux et Digestifs. Prodige=Partenariat de Recherche en Oncologie Digestive. STAR=Studio Terapia Adiuvante Retto. NSAPB=National Surgical Adjuvant Breast and Bowel Project. CAO/ARO/AIO=Chirurgische Arbeitsgemeinschaft für Onkologie/Arbeitsgemeinschaft Radiologische Onkologie/Arbeitsgemeinschaft Internistische Onkologie. pCR=pathological complete response.

Table 6: **Phase 3 trials adding oxaliplatin to preoperative fluorouracil-based chemoradiotherapy in stage 2–3 rectal cancer**

fluorouracil group; upon histopathological examination, negative nodes were reported in 412 (70%) of 591 patients in the fluorouracil and oxaliplatin group and 416 (69%) of 606 patients in the fluorouracil group. Overall, a pCR (ypT0 pN0) was achieved in 103 (17%) of 591 patients in the fluorouracil and oxaliplatin group and 81 (13%) of 606 in the fluorouracil group (odds ratio 1·40; 95% CI 1·02–1·92, p=0·038). Distant metastases were detected perioperatively in 21 (4%) patients who underwent surgery in the fluorouracil and oxaliplatin group and in 34 (6%) in the fluorouracil group.

129 (22%) of 591 resected patients in the fluorouracil and oxaliplatin group and 134 (22%) of 606 in the fluorouracil group did not receive any postoperative chemotherapy, with no apparent difference between the groups with regard to reasons for not receiving treatment (figure 2). 153 (35%) of 435 patients who actually received adjuvant fluorouracil, leucovorin, and oxaliplatin according to protocol had grade 3–4 acute toxic effects, as did 168 (36%) of 463 patients who actually received adjuvant fluorouracil alone (table 5). More patients who received fluorouracil alone had grade 3–4 haematological toxic effects (165 [36%] of 463 *vs* 78 [18%] of 435), whereas grade 3–4 sensory neuropathy mainly occurred in patients who received adjuvant fluorouracil, leucovorin, and oxaliplatin (37 [9%] *vs* five [1%]). Overall, 352 (81%) of 435 patients who began adjuvant chemotherapy with fluorouracil, leucovorin, and oxaliplatin and 386 (83%) of 463 who began adjuvant chemotherapy with fluorouracil completed all planned treatment cycles. The full dose of adjuvant chemotherapy was administered in 190 (44%) of 435 patients receiving the three-drug regimen and in 301 (65%) of 463 receiving fluorouracil alone (table 5).

Discussion

This large randomised trial showed that, compared with our standard protocol of fluorouracil given as a 120-h continuous infusion in weeks 1 and 5 of preoperative radiotherapy for rectal cancer, addition of weekly oxaliplatin, with a chemotherapy gap in the third week of radiotherapy, was feasible and resulted in a greater proportion of patients achieving a pCR and no increased acute toxicity. In our previous CAO/ARO/AIO-94 trial[1] the proportion of patients who achieved a pCR after preoperative treatment was only 8%, compared with 13% among those who received fluorouracil-only chemoradiotherapy in the present trial, even though the same fluorouracil schedule was used in both trials. A major difference was that patients with upper rectal cancer (ie, 12–16 cm from the anal verge) were included in the previous trial but not in the present trial, which might affect cross-trial comparisons.

Panel: **Research in context**

Systematic review

The design of this randomised phase 3 study, in which oxaliplatin was added to standard fluorouracil-based combined modality treatment for locally advanced rectal cancer, is based on the results of our earlier phase 3 study[1] and on two other phase 3 studies[2,3] that established preoperative fluorouracil-based combined modality treatment as standard therapy for stage II–III rectal cancer. These studies showed improved local control with preoperative fluorouracil-based combined modality treatment versus postoperative chemoradiotherapy[1] or versus preoperative radiotherapy alone without concurrent fluorouracil-based chemotherapy,[2,3] but no survival benefit. Several subsequent phase 1 and 2 studies, including two from our group,[7,8] integrated more effective systemic treatment into fluorouracil-based treatment for patients with rectal cancer. Searches of PubMed and abstracts of oncology society meetings using the terms "rectal cancer", "randomised", and "oxaliplatin" confirmed three other randomised phase 3 trials that added oxaliplatin to preoperative fluorouracil-based treatment.[14–16]

Interpretation

Addition of oxaliplatin to preoperative fluorouracil-based combined modality treatment—at the doses and intensities used in this trial, which differ from those of the three other phase 3 trials—was well tolerated and associated with an increased proportion of patients achieving a pathological complete response compared with such treatment incorporating fluorouracil only. Surgery was quality controlled in this trial, and the rate of pathologically confirmed, good total mesorectal excision specimens exceeded 75%. Also, by contrast with the three other trials, oxaliplatin was a component of preoperative and postoperative chemotherapy, and 80% of patients who began adjuvant chemotherapy completed all cycles. These analyses of early endpoints suggest that addition of oxaliplatin to fluorouracil-based combined modality treatment might be an attractive option for patients with locally advanced rectal cancer. However, longer follow-up is needed to assess the primary endpoint, disease-free survival.

These initial results of the CAO/ARO/AIO-04 trial should be interpreted in the context of other recently completed phase 3 trials of preoperative fluorouracil-based chemoradiotherapy, with or without oxaliplatin, for rectal cancer: STAR-01, ACCORD 12/0405-Prodige 2, and NSAPB R-04 (table 6). By contrast with the results of our study, these trials showed that adding weekly oxaliplatin to various fluoropyrimidine chemoradiotherapy regimens increased acute toxicity without substantially improving rates of pCR (table 6).[14–16] Since the main inclusion criteria of these four randomised trials largely overlap, different treatment-related factors are probably responsible for the differences in outcomes. First, in our trial, the fluorouracil schedules in the two groups differed, whereas the other trials used the same fluoropyrimidine schedules for both treatment groups (although ACCORD 12/0405-Prodige 2 used different radiotherapy doses in the two groups). In these three other trials, fluoropyrimidines were continuously administered during the entire course of radiotherapy, a strategy that might have maximised tumour response with little room for further improvement in local efficacy by oxaliplatin. Although there is no clear evidence from randomised trials that any fluoropyrimidine schedules during radiotherapy are superior,[17,18] the fluorouracil schedule used in the control group of our study (and recommended in our national guidelines)[9] might be a suboptimum use of fluorouracil. Thus, we cannot exclude that the different fluorouracil schedules applied in the two groups of our study might have contributed to the differences in outcome.

Second, the planned cumulative doses and application modes of fluoropyrimidines and oxaliplatin during preoperative radiotherapy were different in the four trials. In the STAR-01 and ACCORD trials, compliance with all components of preoperative chemoradiotherapy, including radiotherapy, was markedly lower in the groups that received oxaliplatin, probably because of increased acute toxic effects (table 6). In our trial, 94% of patients receiving preoperative fluorouracil plus oxaliplatin received a full dose of radiotherapy, and 85% received a full dose of concurrent chemotherapy, whereas only 79% in the fluorouracil group received a full dose of preoperative chemotherapy. Thus, the addition of oxaliplatin to fluorouracil-based chemoradiotherapy, with the doses and intensities as used in this trial, resulted in excellent compliance rates. Administering a preoperative chemoradiotherapy regimen that can be completed by most patients, without dose compromises, has better potential for full efficacy. An exploratory subgroup analysis of patients who completed all radiotherapy and chemotherapy in the STAR-01 trial (although mentioned only in the discussion, with no numbers given) did not show an increased pCR rate.[14]

Third, apart from the proportion of patients who achieved a pCR, none of the other early indicators of local treatment efficacy (ie, rates of R0 resections, circumferential resection margins >1 mm, or lymph-node negativity) differed between the two groups in our trial. Thus, overall, the initial results of our trial should be interpreted with caution and do not unequivocally support the hypothesis that adding oxaliplatin to preoperative fluorouracil-based chemoradiotherapy substantially improves local efficacy.

To focus on the potential systemic benefit of adding oxaliplatin, the only formally tested endpoint in this trial will be DFS. Indeed, the rationale to incorporate oxaliplatin into combined modality treatment for rectal cancer was not necessarily to improve radiosensitisation, pCR rates, or even local control. Preoperative chemoradiotherapy with fluorouracil (or short-course radiotherapy alone) and TME surgery for rectal cancer yield local control rates of around 95%, provided surgical quality is adequate.[19] Optimum surgery with an intact mesorectal excision plane was confirmed by pathologists for more than 75% of the patients in our trial (a percentage of quality controlled, good TME surgery that far exceeds any other published data from phase 3 trials),[11,20] so it is possible that the final study data might show even lower rates of local recurrences than the present data, leaving very little room for improvement by the addition of further agents. Clearly, the most important clinical objective is to prevent distant metastases.

Based on the hypothesis that oxaliplatin might reduce the risk of systemic metastases, we added oxaliplatin

to preoperative chemoradiotherapy and postoperative chemotherapy. An encouraging finding from STAR-01, ACCORD 12/0405, and our trial was that a lower proportion of patients had distant metastases detected perioperatively after preoperative chemoradiotherapy with oxaliplatin compared with fluorouracil alone (table 6). It remains to be seen whether the addition of oxaliplatin to postoperative chemotherapy in our trial will further reduce the risk of systemic relapse. As an early result, compliance with 4 months of postoperative fluorouracil, leucovorin, and oxaliplatin was encouraging; more than 80% of patients who began adjuvant chemotherapy completed all cycles (with or without dose reduction). A full dose of adjuvant chemotherapy was administered in 44% of patients receiving fluorouracil, leucovorin, and oxaliplatin and 65% receiving fluorouracil alone. Data from a randomised phase 2 trial suggest that delivery of systemic agents might be further optimised by the application of induction chemotherapy before chemoradiotherapy and surgery, rather than by adjuvant chemotherapy.[21] Several phase 2 and 3 trials are investigating an induction chemotherapy approach.[22]

In summary, the addition of oxaliplatin to modified fluorouracil-based combined modality treatment was well-tolerated and was associated with high compliance and increased pCR rates compared with standard fluorouracil-based combined modality treatment (panel). TME surgery was quality controlled, and the rates of pathologically confirmed, good TME specimens exceeded 75%. A median number of 14–15 lymph nodes was examined after preoperative chemoradiotherapy in both groups, which is a measure of high quality pathology in the context of a multicentre trial. Mature data regarding the primary endpoint, DFS, will be available near the end of 2013.

Contributors

CR, TL, HB, RF, WH, TH, UG, DA, CW, and RS contributed to the study design. All authors contributed to data collection, analysis, and interpretation, writing or review of the manuscript, and approved the final manuscript.

Conflicts of interest

CR has received honoraria from Roche and Sanofi-Aventis, and research funding from Roche, Sanofi-Aventis, and Merck-KGaA. RF has received honoraria from Sanofi-Aventis. UG has served as a consultant and advisory board member for, and received honoraria from, Sanofi-Aventis. DA has served as a consultant and advisory board member for, and has received honoraria from, Roche, Sanofi-Aventis, Merck-Serono, and Amgen, and has received research funding from Merck-KGaA, Roche, and Sanofi-Aventis. GGG has received research funding from Fresenius AG. GF has served as a consultant and advisory board member for Merck KGaA, Roche, and Bristol-Myers Squibb, has received honoraria from Merck KGaA, Roche, and Novartis, and has received research funding from Merck KGaA. All other authors declared no conflicts of interest.

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