Oxaliplatin added to fluorouracil-based preoperative chemoradiotherapy and postoperative chemotherapy of locally advanced rectal cancer (the German CAO/ARO/AIO-04 study): final results of the multicentre, open-label, randomised, phase 3 trial

Claus Rödel, Ullrich Graeven*, Rainer Fietkau, Werner Hohenberger, Torsten Hothorn, Dirk Arnold, Ralf-Dieter Hofheinz, Michael Ghadimi, Hendrik A Wolff, Marga Lang-Welzenbach, Hans-Rudolf Raab, Christian Wittekind, Philipp Ströbel, Ludger Staib, Martin Wilhelm, Gerhard G Grabenbauer, Hans Hoffmanns, Fritz Lindemann, Anke Schlenska-Lange, Gunnar Folprecht, Rolf Sauer*, Torsten Liersch*, on behalf of the German Rectal Cancer Study Group†*

Summary

Background Preoperative chemoradiotherapy with infusional fluorouracil, total mesorectal excision surgery, and postoperative chemotherapy with fluorouracil was established by the German CAO/ARO/AIO-94 trial as a standard combined modality treatment for locally advanced rectal cancer. Here we compare the previously established regimen with an investigational regimen in which oxaliplatin was added to both preoperative chemoradiotherapy and postoperative chemotherapy.

Methods In this multicentre, open-label, randomised, phase 3 study we randomly assigned patients with rectal adenocarcinoma, clinically staged as cT3–4 or any node-positive disease, to two groups: a control group receiving standard fluorouracil-based combined modality treatment, consisting of preoperative radiotherapy of 50·4 Gy in 28 fractions plus infusional fluorouracil (1000 mg/m² on days 1–5 and 29–33), followed by surgery and four cycles of bolus fluorouracil (500 mg/m² on days 1–5 and 29); or to an investigational group receiving preoperative radiotherapy of 50·4 Gy in 28 fractions plus infusional fluorouracil (250 mg/m² on days 1–14 and 22–35) and oxaliplatin (50 mg/m² on days 1, 8, 22, and 29), followed by surgery and eight cycles of oxaliplatin (100 mg/m² on days 1 and 15), leucovorin (400 mg/m² on days 1 and 15), and infusional fluorouracil (2400 mg/m² on days 1–2 and 15–16). Randomisation was done with computer-generated block-randomisation codes stratified by centre, clinical T category (cT1–3 *vs* cT4), and clinical N category (cN0 *vs* cN1–2) without masking. The primary endpoint was disease-free survival, defined as the time between randomisation and non-radical surgery of the primary tumour (R2 resection), locoregional recurrence after R0/1 resection, metastatic disease or progression, or death from any cause, whichever occurred first. Survival and cumulative incidence of recurrence analyses followed the intention-to-treat principle; toxicity analyses included all patients treated. Enrolment of patients in this trial is completed and follow-up is ongoing. This study is registered with ClinicalTrials.gov, number NCT00349076.

Findings Of the 1265 patients initially enrolled, 1236 were assessable (613 in the investigational group and 623 in the control group). With a median follow-up of 50 months (IQR 38–61), disease-free survival at 3 years was 75·9% (95% CI 72·4–79·5) in the investigational group and 71·2% (95% CI 67·6–74·9) in the control group (hazard ratio [HR] 0·79, 95% CI 0·64–0·98; p=0·03). Preoperative grade 3–4 toxic effects occurred in 144 (24%) of 607 patients who actually received fluorouracil and oxaliplatin during chemoradiotherapy and in 128 (20%) of 625 patients who actually received fluorouracil chemoradiotherapy. Of 445 patients who actually received adjuvant fluorouracil and leucovorin and oxaliplatin, 158 (36%) had grade 3–4 toxic effects, as did 170 (36%) of 470 patients who actually received adjuvant fluorouracil. Late grade 3–4 adverse events in patients who received protocol-specified preoperative and postoperative treatment occurred in 112 (25%) of 445 patients in the investigational group, and in 100 (21%) of 470 patients in the control group.

Interpretation Adding oxaliplatin to fluorouracil-based neoadjuvant chemoradiotherapy and adjuvant chemotherapy (at the doses and intensities used in this trial) significantly improved disease-free survival of patients with clinically staged cT3–4 or cN1–2 rectal cancer compared with our former fluorouracil-based combined modality regimen (based on CAO/ARO/AIO-94). The regimen established by CAO/ARO/AIO-04 can be deemed a new treatment option for patients with locally advanced rectal cancer.

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See Comment page 883

*Contributed equally

†Investigators listed in the appendix

Department of Radiotherapy and Oncology, University of Frankfurt and German Cancer Consortium (DKTK) partner site, Frankfurt, Germany (Prof C Rödel MD); **German Cancer Research Center (DKFZ), Heidelberg, Germany** (Prof C Rödel); **Department of Hematology/Oncology and Gastroenterology, Kliniken Maria Hilf GmbH Mönchengladbach, Germany** (U Graeven MD); **Department of Radiation Therapy** (Prof R Fietkau MD, M Lang-Welzenbach MSc, Prof R Sauer MD), **Department of Surgery** (Prof W Hohenberger MD), **Department of Medical Informatics, Biometry and Epidemiology, University of Erlangen-Nürnberg, Germany** (Prof T Hothorn); **Epidemiology, Biostatistics and Prevention Institute, University of Zurich, Switzerland** (Prof T Hothorn PhD); **Tumor Biology Center Freiburg, Freiburg, Germany** (Prof D Arnold MD); **Interdisciplinary Tumor Center, University Hospital Mannheim, University of Heidelberg, Germany** (Prof R-D Hofheinz MD); **Department of General, Visceral and Pediatric Surgery** (Prof M Ghadimi MD,

Prof T Liersch MD), **Department of Radiotherapy** (H A Wolff MD), **Institute of Pathology, University Medical Center Göttingen, Göttingen, Germany** (Prof P Ströbel MD); **Department of General and Visceral Surgery, University of Oldenburg, Germany** (Prof H-R Raab MD); **Institute of Pathology, University of Leipzig, Germany** (Prof C Wittekind MD); **Department of Surgery, Klinikum Esslingen, Germany** (Prof L Staib MD); **Department of Hematology/Oncology, Klinikum Nürnberg, Nürnberg, Germany** (Prof M Wilhelm MD); **Department of Radiation Oncology and Radiotherapy, DiaCura & Klinikum Coburg, Germany** (Prof G G Grabenbauer MD); **Department of Radiation Oncology, Kliniken Maria Hilf GmbH Mönchengladbach, Germany** (H Hoffmanns MD); **Department of General and Visceral Surgery, Friedberg, Germany** (F Lindemann MD); **Department of Internal Medicine, Oncology, Hematology, Krankenhaus Barmherzige Brüder, Regensburg, Germany** (A Schlenska-Lange MD); **and Medical Department I, University Hospital Carl Gustav Carus, University Cancer Center, Dresden, Germany** (Prof G Folprecht MD)

Correspondence to:
Prof Claus Rödel, Department of Radiotherapy and Oncology, University of Frankfurt, Theodor-Stern-Kai 7, 60590 Frankfurt, Germany
claus.roedel@kgu.de

See Online for appendix

Research in context

Evidence before this study

The design of this randomised phase 3 study (CAO/ARO/AIO-04) was based on the results of our earlier phase 3 study (CAO/ARO/AIO-94) and the results of two other phase 3 studies that established chemoradiotherapy with fluorouracil before total mesorectal excision surgery as standard treatment for locally advanced rectal cancer. With this treatment, local recurrence rates have been markedly reduced; however, no randomised trials so far have shown a disease-free survival benefit using total mesorectal excision-based surgical techniques and preoperative radiotherapy alone or chemoradiotherapy with fluorouracil. The addition of oxaliplatin to fluoropyrimidine-based adjuvant chemotherapy of colon cancer has been shown to improve disease-free survival; however, no clear evidence exists for the efficacy of adding oxaliplatin to the multimodal treatment of patients with locally advanced rectal cancer. Computerised bibliographic searches of PubMed and abstracts of American Society of Clinical Oncology, American Society of Radiation Oncology, and European Society for Radiotherapy and Oncology meetings, conducted between Jan 1, 2010, and March 1, 2015, using the search terms "rectal cancer", "randomised", and "oxaliplatin", identified four other randomised phase 3 trials that added oxaliplatin to preoperative fluorouracil-based chemoradiotherapy (one of which also included adjuvant chemotherapy with or without oxaliplatin into the randomisation). Two further randomised trials investigated adjuvant fluorouracil-based chemotherapy with oxaliplatin after standard preoperative fluorouracil-based preoperative chemoradiotherapy for stage II and III rectal cancer.

Added value of this study

The addition of oxaliplatin to both preoperative fluorouracil-based chemoradiotherapy and postoperative chemotherapy—at the doses and intensities used in this trial—was associated with acceptable toxicity and good compliance of all treatment components. To our knowledge, this is the first large, randomised phase 3 trial with long-term follow-up (median 50 months) to show a disease-free survival benefit of adding oxaliplatin to fluorouracil-based combined modality treatment when compared with standard treatment with fluorouracil alone for patients with stage II and III rectal cancer.

Implications of all the available evidence

Three of the above-mentioned other randomised trials adding oxaliplatin to combined modality treatment also had disease-free survival as their primary endpoint. One trial (CHRONICLE) closed prematurely because of poor patient accrual. One smaller randomised phase 2 study (ADORE) showed improved disease-free survival when oxaliplatin was added to adjuvant chemotherapy after preoperative fluorouracil-based chemoradiotherapy and curative surgery (R0) for patients with pathological TNM stage II or III. The larger randomised phase 3 (PETACC-6) could, with shorter follow-up, did not confirm a disease-free survival benefit for the addition of oxaliplatin to both preoperative chemoradiotherapy and adjuvant chemotherapy with capecitabine. Standard combined modality treatment of locally advanced rectal cancer will thus remain controversial. However, the regimen established by CAO/ARO/AIO-04 can now be deemed a new treatment option for patients with locally advanced rectal cancer.

Introduction

Substantial improvements have been made in the management of rectal cancer over the past 20 years. The adoption of total mesorectal excision surgery has dramatically reduced local recurrences and improved survival.[1] Randomised clinical trials have shown that short-course radiotherapy[2,3] or the addition of fluorouracil to conventionally fractionated radiotherapy[4,5] before surgery further improves local control. In patients with locally advanced rectal cancer judged to be nonresectable at initial presentation, one randomised trial showed that the addition of fluorouracil and leucovorin to preoperative radiotherapy, and as adjuvant chemotherapy, improved local control and cancer-specific survival compared with preoperative radiotherapy alone.[6] Following publication of the German phase 3 trial (CAO/ARO/AIO-94) in 2004,[7] preoperative radiotherapy with infusional fluorouracil, total mesorectal excision, and adjuvant chemotherapy with fluorouracil became a standard multimodal treatment for locally advanced rectal cancer. However, even with long-term follow-up, none of these trials reported a survival benefit.[8,9] Thus, to increase disease-free survival and overall survival, we need to achieve better control of systemic disease.

Although the addition of oxaliplatin to fluoropyrimidine-based adjuvant chemotherapy of colon cancer has been shown to improve disease-free survival and overall survival,[10,11] no clear evidence exists for the efficacy of adding oxaliplatin to the multimodal treatment of patients with locally advanced rectal cancer. Therefore, the German Rectal Cancer Study Group tested the addition of oxaliplatin to oral fluoropyrimidines, both together with preoperative radiotherapy and as an adjuvant treatment, in phase 1–2 trials to establish an active and feasible regimen for a phase 3 trial.[12,13] These early trials showed that this investigational regimen was tolerable and associated with excellent compliance when a chemotherapy treatment gap was introduced into the third week of preoperative radiotherapy.

In the CAO/ARO/AIO-04 trial presented here, the previously established regimen of fluorouracil-based preoperative chemoradiotherapy, total mesorectal excision, and 4 months of postoperative fluorouracil adjuvant chemotherapy[7] was compared with an investigational regimen in which oxaliplatin was added to both

preoperative chemoradiotherapy and postoperative chemotherapy. We previously published the interim data;[14] here we present the final results of the primary outcome of disease-free survival.

Methods

Study design and participants

The study was a multicentre, open-label, randomised, phase 3 trial. Details of the study design and methods were published previously.[14] Eligible patients were aged 18 years or older with histopathologically confirmed rectal adenocarcinoma located no more than 12 cm above the anal verge as assessed by rigid proctoscopy. The tumour had to show evidence of perirectal fat infiltration (any cT3) or infiltration of adjacent tissues or organs (cT4), or lymph-node metastases (cN1–2) as assessed by endorectal ultrasound, multi-slice pelvic CT, or MRI. MRI was recommended for local staging but was not mandatory. Pretreatment assessment included an abdominal CT, and chest radiography, supplemented by a lung CT in case of any suspicious findings on chest radiography. Further inclusion criteria were an Eastern Cooperative Oncology Group performance status of 2 or less, and adequate bone marrow function (defined as haemoglobin >10 g/dL, neutrophils >1500 cells per µL, platelets >100 000 cells per µL), liver function (total bilirubin <2 mg/dL; aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, and γ-glutamyltransferase <3×the upper limit of normal), and kidney function (creatinine <1·5 mg/dL, calculated creatinine clearance <50 mL/min). We excluded patients with metastatic disease, patients who had previously received chemotherapy or radiotherapy to the pelvis and patients who had previous or concurrent malignancies, with the exception of adequately treated basal cell carcinoma of the skin or in-situ carcinoma of the uterine cervix. Pregnant or breastfeeding women, patients with unstable cardiac angina or myocardial infarction within the past 6 months, patients with peripheral neuropathy more than grade 2 according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE; version 3·0), or chronic diarrhoea more than grade 1, were also excluded.

The study was 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.

Randomisation and masking

Patients were enrolled by study investigators, and eligible patients were randomly assigned centrally using computer-generated randomisation codes (sequential permuted blocks of four and eight for a-priori small and large centres, respectively) stratified for centre, clinical T category (cT1–3 *vs* cT4), and clinical N category (cN0 *vs* cN1–2). Patient assignment was done centrally and implemented through a fax 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. Neither patients nor physicians were masked to treatment allocation.

Procedures

Preoperative radiotherapy consisted of 50·4 Gy in 28 fractions, delivered with a minimum energy of 6 MV photons to the primary tumour and to mesorectal, presacral, and internal iliac lymph nodes. In the control group, preoperative concurrent chemotherapy was given as a continuous infusion of fluorouracil (1000 mg/m² on days 1–5 and 29–33 of radiotherapy). Adjuvant chemotherapy in the control group comprised four cycles of fluorouracil intravenous bolus (500 mg/m²) on days 1–5 and 29, for a total of 4 months. Patients in the investigational 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 given on days 1 and 15 in each of 4 months consisted of eight cycles of oxaliplatin (100 mg/m²) 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). In both groups, total mesorectal excision surgery was scheduled 5–6 weeks after completion of chemoradiotherapy, and adjuvant chemotherapy was scheduled 4 weeks after surgery. All resection specimens were examined using a standardised protocol that included TNM classification, number of examined and involved lymph nodes, and status of resection margins.[15] According to this classification, R0 defines negative resection margins, R1 defines microscopic involvement of margins, and R2 gross residual tumour. The quality of the mesorectal resection was classified using the system proposed by Quirke and colleagues.[16]

Patients were monitored weekly during chemoradiotherapy and before each adjuvant treatment cycle, with regard to vital signs and haematological and biochemical blood tests (haemoglobin, neutrophils, platelets, liver function [total bilirubin, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, γ-glutamyltransferase], and kidney function [creatinine, electrolytes]). Acute adverse effects during or within 30 days after chemoradiotherapy or adjuvant chemotherapy were graded according to the CTCAE (version 3.0). Specific dose adjustments of fluorouracil and oxaliplatin during preoperative chemoradiotherapy, adjuvant chemotherapy, and interruptions of radiotherapy, in response to toxic effects were done according to predefined guidelines. Patients who required treatment interruptions of more than 2 weeks discontinued protocol-specified treatment.

Follow-up visits were at intervals of 6 months after surgery for 2 years, and then once yearly for 3 years.

For more on **predefined guidelines, analysis set, computer codes, and the trial protocol** see http://caoaroaio04.org

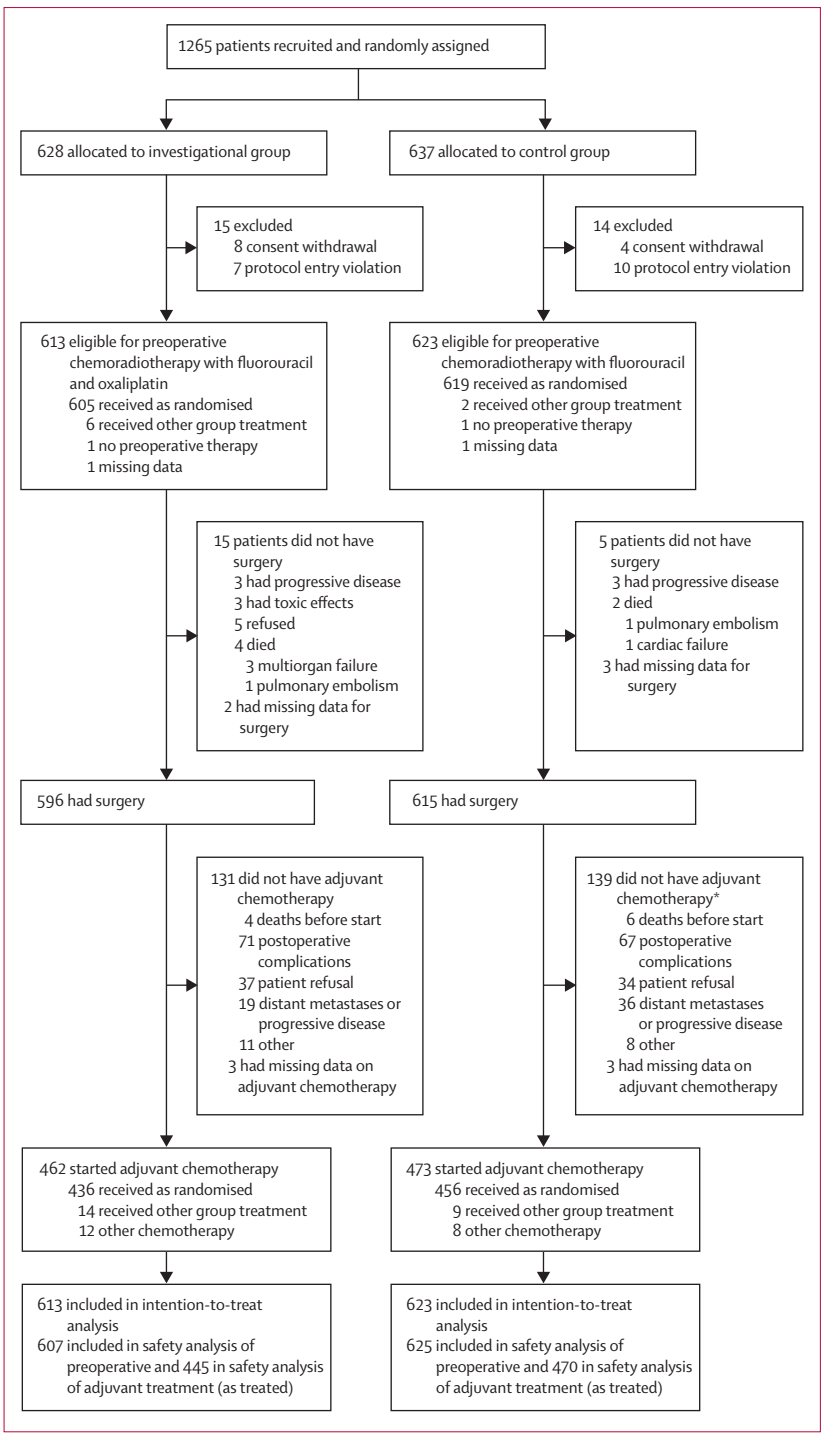

Figure 1: **Trial profile**
Numbers differ from the previous report[14] because data have now become available for several patients with missing data for preoperative treatment, surgery, and postoperative treatment at the time of the first report. *Multiple reasons possible.

Assessments consisted of patient history, physical examination, abdominal ultrasonography, and serum carcinoembryonic antigen at every visit. Following guidelines of the German Cancer Society,[17] abdominal pelvic CT was repeated 3 months after completion of tumour-specific treatment, and coloscopy was done at 6 months, if not done preoperatively, otherwise at 1 year and 5 years after surgery. Chest radiography was recommended once yearly for 5 years. Histological confirmation of locoregional recurrence, defined as a colorectal cancer within the true pelvis or perineal scar, and distant recurrence was encouraged. Late adverse events were recorded at 1, 3, and 5 years after surgery and graded according to CTCAE (version 3.0) criteria. We did not do a central review for disease status during follow-up.

Outcomes

The primary endpoint, disease-free survival, was defined as the time between randomisation and one of the following events: non-radical surgery of the primary tumour (R2 resection), locoregional recurrence after R0/1 resection of the primary tumour, metastatic disease or progression, or death from any cause, whichever occurred first. Second non-colorectal malignancies were disregarded in the analyses of disease-free survival. Overall survival, a secondary endpoint, was defined as time from randomisation to death from any cause. Additional secondary endpoints included the proportion of patients who achieved a pathological complete response (defined as ypT0N0), the proportion of patients having R0 resection, the number of patients having sphincter-sparing surgery, and acute and late toxicity. The cumulative incidence of locoregional and distant recurrence was defined as the time between randomisation and occurrence of any loco-regional and distant recurrence, respectively, irrespective of whether this was a first event or not.

Statistical analysis

We hypothesised that the 3-year disease-free survival would improve from 75% in the control group to 82% in the investigational group (hazard ratio [HR] 0·81). With a power of 80% and a type I error of 5%, the sample size needed to show this improvement was 1200 patients (ie, a reduction from 170 events in the control group to 123 events in the investigational group). The null hypothesis of equal disease-free survival times in both treatment groups was tested by a log-rank test stratified by centre and clinical cN category. The HR and the corresponding 95% CI were estimated with a mixed-effects Cox model with centre or clinical cN category-specific random intercepts. The same procedures were used to compare disease-free survival in subgroups, and overall survival between the two treatment groups. Kaplan-Meier curves were parallel on the log-log scale, which indicated proportional hazards and thus validity of the Cox model. The cumulative incidence of local recurrence after R0/1 resection, and distant recurrence, was calculated with death as a competing risk.

Patient eligibility was assessed in pre-analysis meetings. Patients who did not meet the inclusion criteria, according

to findings derived from source data verification, were identified and excluded. All randomly assigned patients who fulfilled the inclusion criteria were included in the efficacy analysis. All eligible patients who had received at least one application of study treatment were included in safety assessments. All analyses concerning survival and cumulative incidence of recurrence followed the intention-to-treat principle. Results on toxicity and treatment compliance were analysed as treated. According to the study protocol, the difference in disease-free survival was the only hypothesis to be tested formally, and no formal equivalence margins were specified for secondary endpoints. All data for other endpoints were descriptive. The Cochran-Mantel-Haenszel χ^2 test for independence of number of pathological complete responses and treatment group (conditional on strata and without continuity correction) is reported as an unplanned exploratory analysis. All results were computed in the R system for statistical computing, version 3.1-2,[18] with add-on packages coxme (version 2.2-3),[19] prodlim (version 1.4.3),[20] coin (1.0-23),[21] and cmprsk (2.2-7).[22] This study is registered with ClinicalTrials.gov, number NCT00349076.

	Investigational group (n=613)	Control group (n=623)
Age (years)		
Mean (SD)	62 (10)	62 (10)
Median (IQR)	64 (55–70)	63 (55–70)
Sex		
Male	434 (71%)	440 (71%)
Female	179 (29%)	183 (29%)
ECOG performance status		
0	483 (79%)	475 (76%)
1–2	123 (20%)	141 (23%)
Missing	7 (1%)	7 (1%)
Clinical T category		
cT2	22 (4%)	32 (5%)
cT3	549 (90%)	537 (86%)
cT4	41 (7%)	50 (8%)
Missing	1 (<1%)	4 (<1%)
Clinical N category		
cN0	146 (24%)	159 (26%)
cN1–2	452 (74%)	451 (72%)
Missing	15 (2%)	13 (2%)
Clinical disease stage		
Stage II	146 (24%)	159 (26%)
Stage III		
cT1–2 N1–2	22 (4%)	32 (5%)
cT3–4 N1–2	430 (70%)	419 (67%)
Missing	15 (2%)	13 (2%)
Location from anal verge		
0–5 cm	249 (41%)	216 (35%)
>5–10 cm	302 (49%)	336 (54%)
>10 cm	55 (9%)	64 (10%)
Missing	7 (1%)	7 (1%)
Histology		
Adenocarcinoma	599 (98%)	597 (96%)
Mucinous adenocarcinoma	5 (<1%)	11 (2%)
Signet-ring cell carcinoma	3 (<1%)	4 (<1%)
Other or missing	6 (1%)	11 (2%)
Tumour differentiation		
Well differentiated (G1)	33 (5%)	31 (5%)
Moderately differentiated (G2)	496 (81%)	502 (81%)
Poorly differentiated (G3)	49 (8%)	50 (8%)
Missing data	35 (6%)	40 (6%)

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

Table 1: **Baseline characteristics**

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, data analysis, data interpretation, writing the report, or the decision to submit for publication. CR, UG, TH, RS, and TL had access to the raw data. The corresponding author (CR) had full access to all study data and final responsibility for the decision to submit for publication.

Results

From July 25, 2006, to Feb 26, 2010, 1265 patients were recruited. After randomisation in 88 centres in Germany, 29 patients were excluded as they did not meet the inclusion criteria or withdrew consent, leaving 613 eligible patients in the investigational group and 623 eligible patients in the control group (figure 1). Baseline characteristics were well balanced between groups (table 1). Early results on safety, compliance, surgery, and pathology were published previously,[14] and are updated with data from missing patients and briefly summarised here (see appendix for comprehensive data).

	Investigational group (n=613)	Control group (n=623)
Macroscopically incomplete local resection (R2)	4 (<1 %)	9 (1%)
Locoregional recurrence (after R0/R1 resection)		
As first event	12 (2%)	23 (4%)
Cumulative*	18 (3%)	38 (6%)
Distant metastasis or progression		
As first event	107 (17%)	140 (22%)
Cumulative†	118 (19%)	151 (24%)
Death as first event‡	36 (6%)	26 (4%)
First event for disease-free survival (total)	159 (26%)	198 (32%)

*Includes locoregional recurrence as first event and those occurring together with or after occurrence of distant metastases. †Includes distant metastases as first event and those occurring together with or after occurrence of locoregional recurrences. ‡Includes death due to intercurrent disease, unknown cause, treatment-related death, and death from secondary malignancy.

Table 2: **Intention-to-treat analysis of first events for primary endpoint disease-free survival**

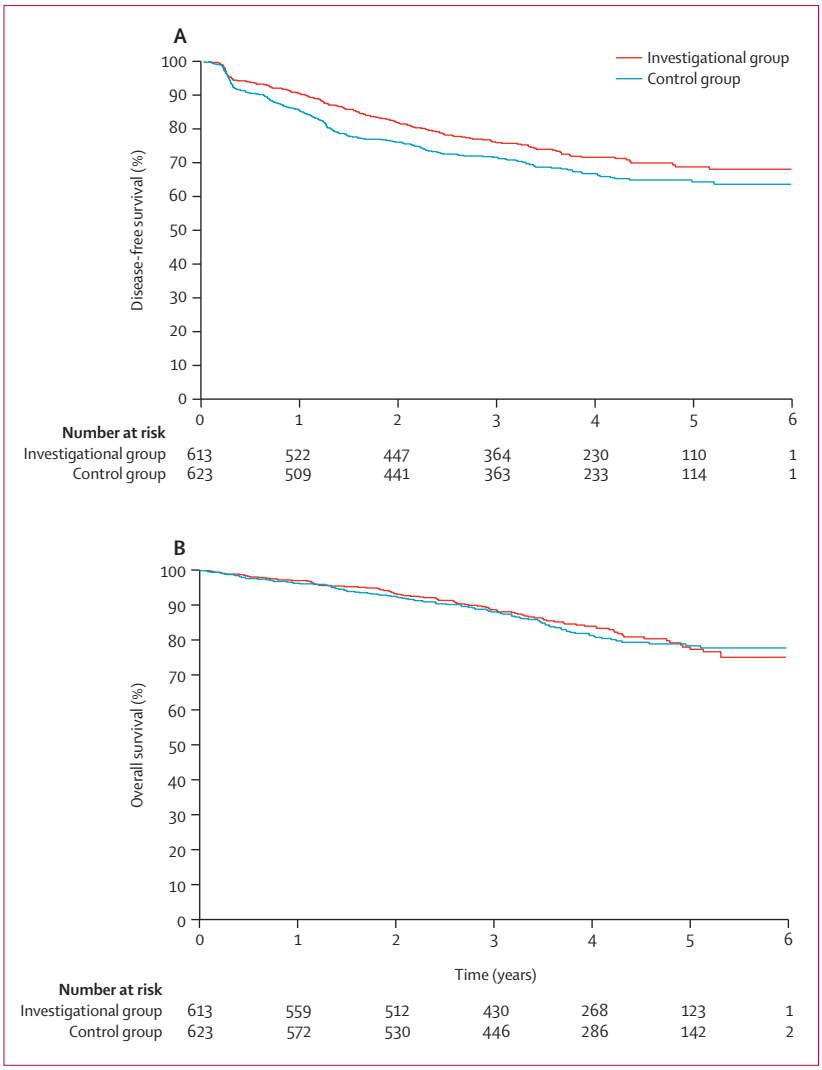

Figure 2: **Disease-free survival (A) and overall survival (B) in the intention-to-treat population**

607 patients received fluorouracil and oxaliplatin during neoadjuvant chemoradiotherapy: 605 were randomly assigned to receive this treatment, and two patients randomly assigned to the control group received this other treatment. 625 patients received the control treatment of fluorouracil alone during neoadjuvant chemoradiotherapy: 619 were randomly assigned to fluorouracil alone treatment, and six patients randomised to the other treatment received the control. Preoperative grade 3 or higher acute toxicity occurred in 144 (24%) of 607 patients who actually received fluorouracil and oxaliplatin during chemoradiotherapy and in 128 (20%) of 625 who actually received fluorouracil alone (see appendix for specific grade 1–2, 3, 4, and 5 adverse events). Grade 3 or higher gastrointestinal side-effects were more common in those who received fluorouracil and oxaliplatin-based chemoradiotherapy (125 [21%] of 607 *vs* 94 [15%] of 625 for all gastrointestinal grade 3–4 side-effects; 74 [12%] *vs* 52 [8%] for grade 3–4 diarrhoea). Treatment-related deaths occurred in four (<1%) patients in the fluorouracil and oxaliplatin group (three infection-related multiorgan failures, one pulmonary embolism) and in two (<1%) patients in the fluorouracil group (one cardiac failure, one pulmonary embolism). Of 607 patients treated with fluorouracil and oxaliplatin chemoradiotherapy, treatment-related adverse events led to radiotherapy interruptions in 59 (10%) patients, radiotherapy dose reduction in 19 (3%) patients, and concurrent chemotherapy dose reduction in 92 (15%) patients. Of the 625 patients who received fluorouracil chemoradiotherapy, 42 (7%) patients had radiotherapy interruption, 16 (3%) patients had radiotherapy dose reduction, and 131 (21%) patients had concurrent chemotherapy dose reduction (appendix).

A complete locoregional resection (R0) was achieved in 567 (95%) of 596 operated patients in the investigational group and in 584 (95%) of 615 operated patients in the control group (appendix). The median interval between completion of chemoradiotherapy and surgery was 42 days (IQR 37–48) in the investigational group and 42 days (36–47) in the control group. Pathological complete response (ypT0N0) was reported in 104 (17%) of 596 operated patients in the investigational group and 81 (13%) of 615 operated patients in the control group (odds ratio [OR] 1·41, 95% CI 1·03–1·94; p=0·031), and distant metastases were detected at surgery in 20 (3%) of the investigational group and 35 (6%) of the control group. Pathologically confirmed good quality of surgery was noted in 455 (76%) of 596 operated patients in the investigational group and 475 (77%) of 615 operated patients in the control group. Incidence of sphincter-sparing resections and postoperative grade 3 or worse complications did not differ between groups (appendix). Four (<1%) of 596 operated patients in the investigational group had died 60 days after surgery (two patients from pulmonary embolism, one from cardiac failure, and one unknown), and six (1%) of 615 operated patients in the control group (two pulmonary embolism, one sepsis, one cardiac failure, one aspiration, one unknown).

Among 613 patients in the investigational group, 131 (21%) did not start postoperative systemic treatment. The corresponding number for the control group was 139 (22%) of 623 patients. The main reasons for this were postoperative complications, patient refusal, or progressive disease (figure 1). The median interval between surgery and adjuvant chemotherapy was 39 days (IQR 33–47) in the investigational group and 38 days (IQR 32–46) in the control group. Of 445 patients who actually received adjuvant fluorouracil and leucovorin and oxaliplatin, 158 (36%) had grade 3–4 acute adverse events, as did 170 (36%) of 470 patients who actually received adjuvant fluorouracil (appendix). As expected, more patients treated with adjuvant fluorouracil and leucovorin and oxaliplatin had grade 3 or worse sensory neuropathy than patients in the control group (41 [10%] *vs* five [1%]), whereas grade 3 or worse leucopenia mainly

occurred in patients who received fluorouracil alone (38 [9%] *vs* 116 [25%]). Chemotherapy-related deaths occurred in four (1%) patients who received adjuvant fluorouracil and leucovorin and oxaliplatin (two infection-related multiorgan failures, two cardiac failures) and in one (<1%) patient who received fluorouracil alone (cardiac failure). 363 (82%) of 445 patients who began adjuvant chemotherapy with fluorouracil and leucovorin and oxaliplatin completed all cycles (135 [30%] patients with dose reduction), as did 393 (84%) of 470 patients who received fluorouracil alone (55 [12%] patients with dose reductions, appendix).

The median follow-up was 50 months (IQR 38–61) overall. In the investigational group, 159 (26%) of 613 patients either underwent incomplete resection (R2), relapsed locally after R0/1 resection, developed distant metastases, or died, as compared with 198 (32%) of 623 patients in the control group (table 2). Disease-free survival was different in the two treatment groups (p=0·03, exact stratified log-rank test; figure 2). The HR for disease-free survival was 0·79 (95% CI 0·64–0·98, p=0·03, mixed effects Cox model). The probability of disease-free survival at 3 years was 75·9% (95% CI 72·4–79·5) in the investigational group and 71·2% (95% CI 67·6–74·9) in the control group (figure 2).

Overall, 96 patients died in the investigational group and 106 in the control group (HR 0·96, 95% CI 0·72–1·26), and 3-year overall survival was 88·7% (95% CI 86·0–91·3) in the investigational group and 88·0% (95% CI 85·3–90·7) in the control group (figure 2). In the investigational group, 54 patients died of rectal cancer, eight deaths were related to (neo)adjuvant treatment, and four died within 60 days after surgery. In the control group, 69 deaths were related to rectal cancer, three to (neo)adjuvant treatment, and six occurred within 60 days after surgery. Numbers and proportions of deaths from secondary cancers, intercurrent disease, or unknown deaths are listed in table 3.

At 3 years, the cumulative incidence of local recurrences after R0/1 resection was 2·9% (95% CI 1·5–4·3) in the investigational group and 4·6% (95% CI 2·9–6·4) in the control group (figure 3). The cumulative incidence of distant recurrences at 3 years was 18·5% (95% CI 15·2–21·7) in the investigational group and 22·4% (95% CI 19·1–25·8) in the control group (figure 3).

Exploratory subset analysis of primary endpoint disease-free survival in the intention-to-treat population according to pretreatment factors and for surgical or pathological factors after preoperative chemoradiotherapy (figure 4) showed a significant benefit for the investigational group for younger patients (below 61 years), male patients, and patients with clinically node-negative disease (cN0), low-lying tumours (<5 cm from anal verge), and abdominoperineal resection surgery. When analysed according to pathological ypTNM subgroups, we detected no significant differences between the investigational and control groups.

Overall grade 3 or worse adverse events occurring at any time during follow-up after completion of protocol-specified treatment were reported for 112 (25%) of

	Investigational group (n=613)	Control group (n=623)
All-cause deaths	96 (16%)	106 (17%)
Rectal cancer	54 (9%)	69 (11%)
Toxicity from neoadjuvant or adjuvant chemotherapy	8 (1%)	3 (<1%)
Postoperative death within 60 days after surgery	4 (<1%)	6 (1%)
Secondary malignancy	3 (<1%)	1 (<1%)
Intercurrent disease	20 (3%)	17 (3%)
Unknown or missing	7 (1%)	10 (2%)

Table 3: **Intention-to-treat analysis of all-cause deaths**

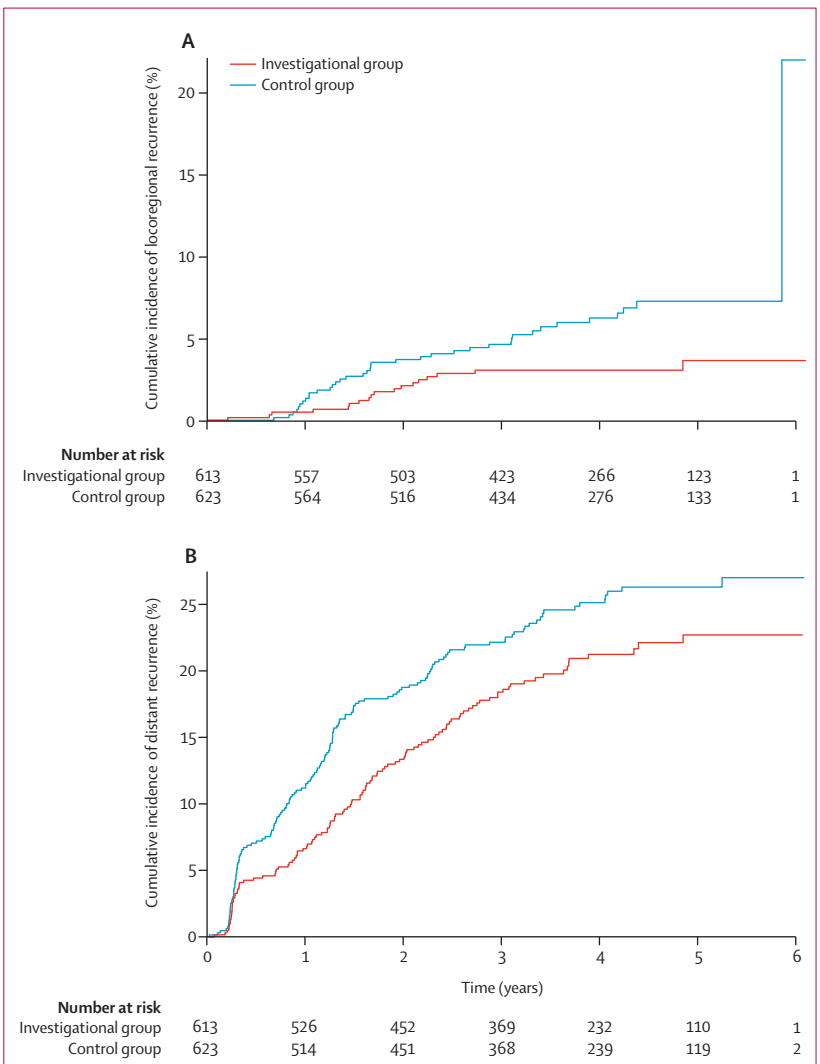

Figure 3: **Cumulative incidence of locoregional recurrences (A) and cumulative incidence of distant recurrences (B) in the intention-to-treat population**

445 patients who actually received adjuvant fluorouracil and leucovorin and oxaliplatin, as compared with 100 (21%) of 470 patients who actually received adjuvant fluorouracil alone. Grade 3 or worse diarrhoea was the most frequent chronic adverse effect in both groups (31 [7%] in the investigational group *vs* 42 [9%] in the control group). The incidence of grade 3–4 sensory neuropathy in the fluorouracil and leucovorin and oxaliplatin group decreased from 41 (10%) patients during treatment to 13 patients (3%) at 1 year follow-up. Among the 326 patients in the fluorouracil and leucovorin and oxaliplatin group having sphincter-sparing surgery,

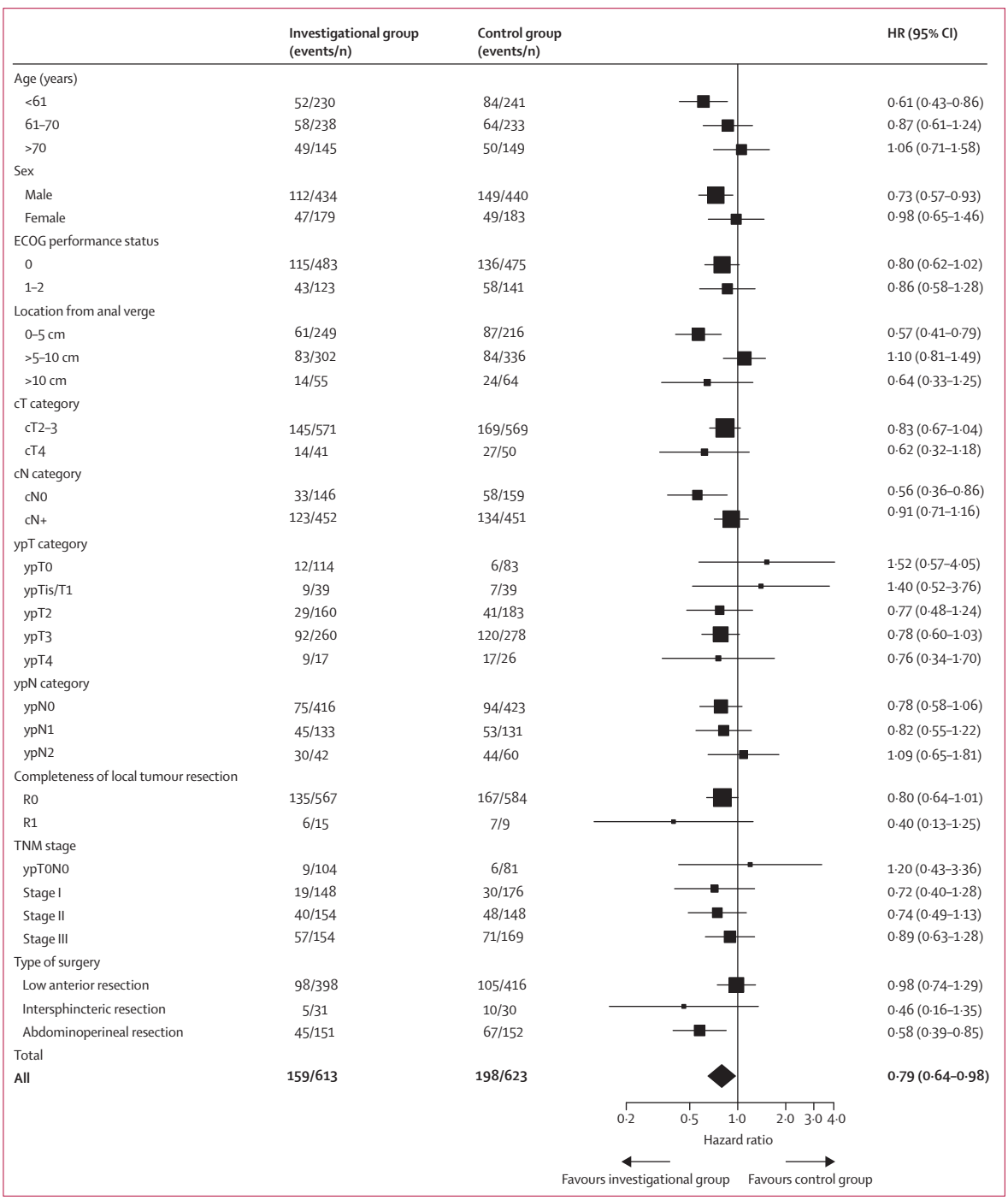

Figure 4: **Disease-free survival in the intention-to-treat population by patient subgroups according to pretreatment and surgical or pathological factors after preoperative chemoradiotherapy**

The size of the quadrats represents the proportion of patients. HR=hazard ratio. ECOG=Eastern Cooperative Oncology Group.

18 (6%) patients reported some form of faecal incontinence and four (1%) patients had grade 3–4 anastomotic strictures. Of 357 patients in the fluorouracil-alone group, 20 (6%) reported some form of faecal incontinence and 11 (3%) had grade 3–4 anastomotic strictures.

Discussion

The final results of the CAO/ARO/AIO-04 trial show that addition of oxaliplatin to both fluorouracil-based preoperative chemoradiotherapy and postoperative chemotherapy after total mesorectal excision surgery is feasible, with good compliance, acceptable toxicity, and low surgical morbidity, and, with a median follow-up of 50 months, the primary endpoint of disease-free survival was significantly better for patients in the investigational group than for those in the control group. Good total mesorectal excision quality was pathologically confirmed in 930 (77%) of 1211 patients as a result of optimised surgery. Fewer patients died from rectal cancer in the investigational group compared with the control group; however, we observed a slight increase in neoadjuvant or adjuvant treatment-related causes of death, death from secondary malignancies, and intercurrent disease in the investigational group. With the current follow-up, no significant difference for overall survival was observed between the two groups.

Our previous CAO/ARO/AIO-94 trial[7] had used the same fluorouracil schedule during preoperative chemoradiotherapy, and as adjuvant chemotherapy, as the control group of our CAO/ARO/AIO-04 trial. In the previous CAO/ARO/AIO-94 trial,[7] 8% patients achieved a pathological complete response, the cumulative incidence of local recurrence was 6%, and disease-free survival was 68% at 5 years.[7] The corresponding results in the control group of CAO/ARO/AIO-04 were 13%, 4·6%, and 71·2% at 3 years, respectively. 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.

We examined the results of our trial in the context of other randomised trials of preoperative fluorouracil-based chemoradiotherapy with or without oxaliplatin for rectal cancer: STAR-01, ACCORD 12/0405-Prodige 2, NSAPB R-04, and PETACC-6.[23–26] Only the latter trial also included adjuvant chemotherapy with or without oxaliplatin into the randomisation, and the primary endpoint (disease-free survival) was similar to that of our trial. These studies showed that adding oxaliplatin to various regimens of preoperative fluoropyrimidine-based chemoradiotherapy increases acute toxicity, but fails to increase the proportion of patients achieving a pathological complete response. The reasons for this are not completely understood, but might include poorer compliance as a consequence of increased toxic effects, resulting in more dose reduction and treatment interruptions. By contrast, the addition of oxaliplatin to preoperative chemoradiotherapy within the schedule used in our trial was well tolerated, associated with high compliance, and resulted in an increased proportion of those achieving a pathological complete response.

The aim of adding oxaliplatin to fluorouracil-based combined modality treatment in our trial was not primarily to improve radiosensitisation, pathological complete response, or even local control. Preoperative fluorouracil-based chemoradiotherapy (or short-course radiotherapy alone) and optimised total mesorectal excision surgery have markedly reduced local recurrence rates in locally advanced rectal cancer to well below 10% at 5 years in recent trials.[3,8,9] Indeed, we could confirm very low cumulative incidences of local recurrences in both groups (at 3 years, 2·9% in the investigational group and 4·6% in the control group). Although these rates might increase slightly with longer follow-up,[9] it is clear that the main cause for failure in rectal cancer is now distant metastases. Based on the hypothesis that oxaliplatin might reduce the risk of systemic metastases, we added oxaliplatin to both the preoperative and postoperative treatment component. Most of the gain seen in the risk of distant metastasis occurred early in the course of treatment (figure 3), suggesting that the addition of oxaliplatin to pre-operative fluorouracil-based chemoradiotherapy might have contributed to this effect. A more detailed analysis on the dynamics of local and distant recurrences will be published separately.

With a (shorter) median follow-up of 31 months, the PETACC-6 trial[26] did not show a benefit of adding oxaliplatin to preoperative and postoperative treatment with capecitabine (disease-free survival at 3 years: 73·9% with oxaliplatin *vs* 74·5% without, p=0·78). The ACCORD 12/0405-Prodige 2 trial[27] also reported disease-free survival at 3 years as a secondary endpoint and showed no significant difference (72·7% with preoperative oxaliplatin *vs* 67·9% without, p=0·39). However, it must be noted that compliance to adjuvant chemotherapy with capecitabine and oxaliplatin was restricted in the PETACC-6 trial (66% of patients started with oxaliplatin, 57% completed all cycles), and that the ACCORD12/0405-Prodige 2 trial only included oxaliplatin during preoperative treatment.

A phase 2 randomised trial from South Korea (ADORE)[28] randomly assigned 321 patients with pathological TNM stage II or III after preoperative fluorouracil-based chemoradiotherapy and curative surgery (R0) to two different adjuvant chemotherapy regimens with either four cycles of fluorouracil plus leucovorin alone or eight cycles of fluorouracil plus leucovorin plus oxaliplatin. Disease-free survival as the primary endpoint was significantly improved when oxaliplatin was added to adjuvant chemotherapy (71·6% *vs* 62·9% at 3 years, p=0·047). A British phase 3 trial (CHRONICLE[29]) also randomly assigned patients after preoperative fluorouracil-based chemoradiotherapy and surgery to groups with and without adjuvant capecitabine plus oxaliplatin. However,

this trial closed prematurely because of poor patient accrual.[29]

Although adjuvant treatment of patients with rectal cancer remains controversial[30] and standards differ substantially across Europe and the USA, the American NCCN guidelines recommend fluoropyrimidine-based chemotherapy with oxaliplatin as the preferred adjuvant treatment for all patients with rectal cancer who received preoperative fluorouracil-based chemoradiotherapy, regardless of surgical pathology results.[31] This recommendation was solely based on extrapolation from colon cancer trials, but can now be supported in part by the ADORE study (for patients with pathological TNM stage II or III). Our trial differed from the ADORE study (and the NCCN guidelines) because oxaliplatin was integrated into both the neoadjuvant and adjuvant treatment. Counterintuitively, subgroup analyses of our trial suggested that the benefit of adding oxaliplatin was observed in patients with clinical cN0 rather than cN1–2 status. However, it should be noted that any clinical staging of the cN category is inaccurate and poorly distinguishes between uninvolved and involved lymph nodes. We also noted that patients with pathological stage I and II, rather than ypT0N0 or stage III disease, after preoperative chemoradiotherapy seemed to benefit from the addition of oxaliplatin. This finding is consistent with observations that patients with complete response after chemoradiotherapy have an excellent prognosis with little risk of developing distant metastases.[32] Conversely, residual lymph-node metastases after preoperative chemoradiotherapy (especially ypN2) suggest a more aggressive tumour biology that is probably poorly responsive to any kind of conventional chemotherapy.[33] However, these subgroup analyses are only exploratory and might not be applicable for patients treated exclusively with preoperative fluorouracil-based chemoradiotherapy alone.

Our trial does have limitations. First, the fluorouracil schedules during neoadjuvant chemoradiotherapy and postoperative chemotherapy in the two groups differed. This difference might have contributed to the differences in outcome, irrespective of the addition of oxaliplatin in the investigational group. The fluorouracil regimen in the control group was derived from our previous CAO/ARO/AIO-94 trial. This regimen was recommended as a standard schedule of applying fluorouracil during combined modality treatment in our national guidelines,[17] but might today be considered a suboptimum use of fluorouracil, both with respect to toxic effects and efficacy. Continuous administration of fluoropyrimidines during the entire course of preoperative radiotherapy and as adjuvant chemotherapy might be superior.[34] Second, the trial design does not allow us to determine whether preoperative or postoperative inclusion of oxaliplatin or both is more important for the observed gain in disease-free survival. This was likely a composite effect because we recorded both better local control (less R2 resection, fewer local recurrences) and fewer distant metastases. Third, MRI was not mandatory for local staging. Important prognostic MRI features, such as the subclassifications of the cT3 category (cT3a–d), the radial distance of the tumour with respect to the mesorectal fascia, and extramural venous invasion[35] were not taken into account in this trial. Patients most likely to benefit from intensified chemotherapy might be better selected by using these MRI features of advanced disease.

In summary, this is to our knowledge the first large, randomised phase 3 trial with long-term follow-up to show a disease-free survival benefit by adding oxaliplatin to both preoperative fluorouracil-based chemoradiotherapy and adjuvant chemotherapy for patients with locally advanced rectal cancer. The multimodal treatment of this disease might be further refined by giving combination chemotherapy as an induction therapy before preoperative chemoradiotherapy and surgery rather than as an adjuvant treatment. This concept of total neoadjuvant treatment is currently being addressed in our CAO/ARO/AIO-12 randomised phase 2 study (ClinicalTrials.gov, number NCT02363374).

Contributors

CR, UG, RF, WH, TH, DA, CW, RS, and TL contributed to the study design, data collection, data analysis, and interpretation. R-DH, MG, HAW, ML-W, H-RR, PS, LS, MW, GGG, HH, FL, AS-L, and GF contributed to data collection, data analysis, and interpretation. All authors contributed to writing or review of the manuscript, and approved the final manuscript.

Declaration of interests

CR reports grants from Deutsche Krebshilfe, during the conduct of the study; personal fees from Roche, grants and personal fees from Sanofi-Aventis, grants from Merck-KGaA, outside the submitted work. UG reports grants and personal fees from Roche Pharma AG, personal fees from Merck Serono GmbH, grants and personal fees from Bayer Pharma GmbH, grants and personal fees from Amgen GmbH, grants and personal fees from Lilly Deutschland GmbH, personal fees from Hexal AG, personal fees from GlaxoSmithKline GmbH, personal fees from Sanofi-Aventis Deutschland GmbH, personal fees from MSD Sharp Dohme GmbH, personal fees from Falk Foundation, grants from Celgene, grants from Mologen, outside the submitted work. RF reports personal fees from Sanofi-Aventis, outside the submitted work. DA reports grants and personal fess from Roche, grants and personal fees from Sanofi-Aventis, grants and personal fees from Merck KGaA, personal fees from Amgen, outside the submitted work. GGG reports grants from Fresenius-AG, outside the submitted work. GF reports grants and personal fees from Merck KGaA, personal fees from Roche, personal fees from Sanofi-Aventis, personal fees from Amgen, personal fees from Lilly, outside the submitted work. RS reports grants from Deutsche Krebshilfe, during the conduct of the study. All other authors declare no competing interests.

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References

1 Heald RJ, Ryall RD. Recurrence and survival after total mesorectal excision for rectal cancer. *Lancet* 1986; **1:** 1479–82.

2 Kapiteijn E, Marijnen CA, Nagtegaal ID, et al. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer. *N Engl J Med* 2001; **345:** 638–46.

3 Sebag-Montefiore D, Stephens RJ, Steele R, et al. Preoperative radiotherapy versus selective postoperative chemoradiotherapy in patients with rectal cancer (MRC CR07 and NCIC-CTG C016): a multicentre, randomised trial. *Lancet* 2009; **373:** 811–20.

4 Bosset JF, Collette L, Calais G, et al. Chemotherapy with preoperative radiotherapy in rectal cancer. *N Engl J Med* 2006; **355:** 1114–23.

5 Gérard JP, Conroy T, Bonnetain F, et al. Preoperative radiotherapy with or without concurrent fluorouracil and leucovorin in T3-4 rectal cancers: results of FFCD 9203. *J Clin Oncol* 2006; **24:** 4620–25.

6 Braendengen M, Tveit KM, Berglund A, et al. Randomized phase III study comparing preoperative radiotherapy with chemoradiotherapy in nonresectable rectal cancer. *J Clin Oncol* 2008; **26:** 3687–94.

7 Sauer R, Becker H, Hohenberger W, et al. Preoperative versus postoperative chemoradiotherapy for rectal cancer. *N Engl J Med* 2004; **351:** 1731–40.

8 van Gijn W, Marijnen CA, Nagtegaal ID, et al. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer: 12-year follow-up of the multicentre, randomised controlled TME trial. *Lancet Oncol* 2011; **12:** 575–82.

9 Sauer R, Liersch T, Merkel S, et al. Preoperative versus postoperative chemoradiotherapy for locally advanced rectal cancer: results of the German CAO/ARO/AIO-94 randomized phase III trial after a median follow up of 11 years. *J Clin Oncol* 2012; **30:** 1926–33.

10 Andre T, Boni C, Navarro M, et al. Improved overall survival with oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment in stage II and III colon cancer in the MOSAIC trial. *J Clin Oncol* 2009; **27:** 3109–16.

11 Yothers G, O'Connell MJ, Allegra CJ, et al. Oxaliplatin as adjuvant therapy for colon cancer: updated results of NSABP C-07 trial, including survival and subset analyses. *J Clin Oncol* 2011; **29:** 3768–74.

12 Rödel C, Grabenbauer GG, Papadopoulos T, et al. Phase I/II trial of capecitabine, oxaliplatin, and radiation for rectal cancer. *J Clin Oncol* 2003; **21:** 3098–104.

13 Rödel C, Liersch T, Hermann RM, et al. Multicenter phase II trial of chemoradiation with oxaliplatin for rectal cancer. *J Clin Oncol* 2007; **25:** 110–17.

14 Rödel C, Liersch T, Becker H, et al. 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. *Lancet Oncol* 2012; **13:** 679–87.

15 Sobin LH, Wittekind C, eds. International Union Against Cancer TNM classification of malignant tumours, 6th edn. Hoboken, NJ: John Wiley & Sons, 2002.

16 Quirke P, Steele R, Monson J, et al. Effect of the plane of surgery achieved on local recurrence in patients with operable rectal cancer: a prospective study using data from the MRC CR07 and NCIC-CTG CO16 randomised clinical trial. *Lancet* 2009; **373:** 821–28.

17 Schmiegel W, Pox C, Adler G, et al. S3-guidelines conference "colorectal carcinoma" 2004. *Z Gastroenterol* 2004; **42:** 1129–77 (in German).

18 R Development Core Team. R: a language and environment for statistical computing, version 3.1-2. http://CRAN.R-project.org (accessed Oct 11, 2014).

19 Therneau T. coxme: mixed effects Cox models, R package version 2.2-3. http://CRAN.R-project.org/package=coxme (accessed July 16, 2014).

20 Gerds TA. prodlim: product-limit estimation, R package version 1.4.5. http://CRAN.R-project.org/package=prodlim (accessed Sept 3, 2014).

21 Hothorn T, Hornik K, van de Wiel MA, et al. A Lego system for conditional inference. *Am Stat* 2006; **60:** 257–63.

22 Gray B. cmprsk: subdistribution analysis of competing risks. R package version 2.2-7 http://CRAN.R-project.org/package=cmprsk (accessed July 16, 2014).

23 Aschele C, Cionini L, Lonardi S, et al. Primary tumor response to preoperative chemoradiation with or without oxaliplatin in locally advanced rectal cancer: pathologic results of the STAR-01 randomized phase III trial. *J Clin Oncol* 2011; **29:** 2773–80.

24 Gérard JP, Azria D, Gourgou-Bourgade S, et al. Comparison of two neoadjuvant chemoradiotherapy regimens for locally advanced rectal cancer: results of the phase III trial ACCORD 12/0405-Prodige 2. *J Clin Oncol* 2010; **28:** 1638–44.

25 O'Connell MJ, Colangelo LH, Beart RW, et al. Capecitabine and oxaliplatin in the preoperative multimodality treatment of rectal cancer: surgical end points from National Surgical Adjuvant Breast and Bowel Project trial R-04. *J Clin Oncol* 2014; **32:** 1927–34.

26 Schmoll HJ, Haustermans K, Rice TJ, et al. Preoperative chemoradiotherapy and postoperative chemotherapy with capecitabine and oxaliplatin versus capecitabine alone in locally advanced rectal cancer: disease-free survival at interim analysis. *Proc Am Soc Clin Oncol* 2014; **32:** abstract 3501.

27 Gérard JP, Azria D, Gourgou-Bourgade S, et al. Clinical outcome of the ACCORD 12/0405 PRODIGE 2 randomized trial in rectal cancer. *J Clin Oncol* 2012; **30:** 4558–65.

28 Hong YS, Nam BH, Kim KP, et al. Oxaliplatin, fluorouracil, and leucovorin versus fluorouracil and leucovorin as adjuvant chemotherapy for locally advanced rectal cancer after preoperative chemoradiotherapy (ADORE): an open-label, multicentre, phase 2, randomised controlled trial. *Lancet Oncol* 2014; **15:** 1245–53.

29 Glynne-Jones R, Counsell N, Quirke P, et al. Chronicle: results of a randomised phase III trial in locally advanced rectal cancer after neoadjuvant chemoradiation randomising postoperative adjuvant capecitabine plus oxaliplatin (XELOX) versus control. *Ann Oncol* 2014; **25:** 1356–62.

30 Breugom AJ, Swets M, Bosset JF, et al. Adjuvant chemotherapy after preoperative (chemo)radiotherapy and surgery for patients with rectal cancer: a systematic review and meta-analysis of individual patient data. *Lancet Oncol* 2015; **16:** 200–07.

31 NCCN clinical practice guidelines in oncology, rectal cancer, version I. 2015. http://www.nccn.org/professionals/physician_gls/pdf/rectal.pdf (accessed Sept 12, 2014).

32 Maas M, Nelemans PJ, Valentini V, et al. Long-term outcome in patients with a pathological complete response after chemoradiation for rectal cancer: a pooled analysis of individual patient data. *Lancet Oncol* 2010; **11:** 835–44.

33 Fokas E, Liersch T, Fietkau R, et al. Tumor regression grading after preoperative chemoradiotherapy for locally advanced rectal carcinoma revisited: updated results of the CAO/ARO/AIO-94 trial. *J Clin Oncol* 2014; **32:** 1554–62.

34 Hofheinz RD, Wenz F, Post S, et al. Chemoradiotherapy with capecitabine versus fluorouracil for locally advanced rectal cancer: a randomised, multicentre, non-inferiority, phase 3 trial. *Lancet Oncol* 2012; **13:** 579–88.

35 Chand M, Swift RI, Tekkis PP, Chau I, Brown G. Extramural venous invasion is a potential imaging predictive biomarker of neoadjuvant treatment in rectal cancer. *Br J Cancer* 2014; **110:** 19–25.