Perioperative chemotherapy with FOLFOX4 and surgery versus surgery alone for resectable liver metastases from colorectal cancer (EORTC Intergroup trial 40983): a randomised controlled trial

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Summary

Background Surgical resection alone is regarded as the standard of care for patients with liver metastases from colorectal cancer, but relapse is common. We assessed the combination of perioperative chemotherapy and surgery compared with surgery alone for patients with initially resectable liver metastases from colorectal cancer.

Methods This parallel-group study reports the trial's final data for progression-free survival for a protocol unspecified interim time-point, while overall survival is still being monitored. 364 patients with histologically proven colorectal cancer and up to four liver metastases were randomly assigned to either six cycles of FOLFOX4 before and six cycles after surgery or to surgery alone (182 in perioperative chemotherapy group *vs* 182 in surgery group). Patients were centrally randomised by minimisation, adjusting for centre and risk score. The primary objective was to detect a hazard ratio (HR) of 0·71 or less for progression-free survival. Primary analysis was by intention to treat. Analyses were repeated for all eligible (171 *vs* 171) and resected patients (151 *vs* 152). This trial is registered with ClinicalTrials.gov, number NCT00006479.

Findings In the perioperative chemotherapy group, 151 (83%) patients were resected after a median of six (range 1–6) preoperative cycles and 115 (63%) patients received a median six (1–8) postoperative cycles. 152 (84%) patients were resected in the surgery group. The absolute increase in rate of progression-free survival at 3 years was 7·3% (from 28·1% [95·66% CI 21·3–35·5] to 35·4% [28·1–42·7]; HR 0·79 [0·62–1·02]; p=0·058) in randomised patients; 8·1% (from 28·1% [21·2–36·6] to 36·2% [28·7–43·8]; HR 0·77 [0·60–1·00]; p=0·041) in eligible patients; and 9·2% (from 33·2% [25·3–41·2] to 42·4% [34·0–50·5]; HR 0·73 [0·55–0·97]; p=0·025) in patients undergoing resection. 139 patients died (64 in perioperative chemotherapy group *vs* 75 in surgery group). Reversible postoperative complications occurred more often after chemotherapy than after surgery (40/159 [25%] *vs* 27/170 [16%]; p=0·04). After surgery we recorded two deaths in the surgery alone group and one in the perioperative chemotherapy group.

Interpretation Perioperative chemotherapy with FOLFOX4 is compatible with major liver surgery and reduces the risk of events of progression-free survival in eligible and resected patients.

Introduction

Liver metastases are detected in 40–50% of the nearly one million patients who are diagnosed with colorectal cancer worldwide every year. When surgical resection of these metastases is possible, 5-year survival approaches 35%.[1] However, relapse is common and occurs in 75% of patients.[2]

Chemotherapy and surgery combined can reduce the risk of relapse. Preoperative chemotherapy potentially allows surgery on small tumours that have become smaller after preoperative chemotherapy (or in response to chemotherapy).[3] This method also allows the responsiveness of these liver metastases to chemotherapy

to be assessed, and thus provides guidance about whether chemotherapy should be given after the resection of metastases. Postoperative chemotherapy should theoretically be effective in dormant cancer cells in the remnant liver. It improves the outcome of patients with stage III colon cancers[4] and therefore might also be effective in stage IV disease after surgery.

Previous phase III trials comparing combined treatment to surgery alone did not recruit the targeted number of patients and thus did not have sufficient statistical power.[5–9] However, these trials showed some benefit of postoperative chemotherapy based on fluorouracil combined with surgery. Some trials used

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intrahepatic arterial infusion and others intravenous chemotherapy. Consequently, a varied pattern of practice has evolved.

Although surgical resection alone is still regarded as the standard of care, many patients are given combined treatment. Others receive chemotherapy alone and are not referred to liver surgeons, even though their hepatic metastases are resectable. Thus, there remains a need for clear evidence for whether combined treatment with chemotherapy is better than surgery alone in patients with resectable liver metastases from colorectal cancer.

The present European Intergroup trial aimed to compare perioperative chemotherapy—ie, before and after surgery—with surgery alone in patients with one to four hepatic colorectal cancer metastases that are considered to be resectable on imaging. The trial design did not attempt to assess preoperative versus postoperative chemotherapy.

Methods
Patients
We recruited 364 patients from 78 hospitals (in Australia, Austria, Belgium, France, Germany, Hong Kong, Italy, Norway, Sweden, Netherlands, UK) between Oct 10, 2000, and July 5, 2004. To be eligible for enrolment, patients had to be aged between 18 and 80 years with a WHO performance status of 2 or less, histologically proven colorectal cancer, one to four liver metastases that were potentially resectable, and no detectable extrahepatic tumour. The primary tumour had to be either already resected (R0 resection) or judged to be resectable (in case of synchronous metastases) by the multidisciplinary team at the treating hospital. Patients with previous chemotherapy with oxaliplatin were excluded. We excluded those with any history of cancer in the past 10 years (except non-melanoma skin carcinoma or in-situ cervix cancer), major hepatic insufficiency, an absolute neutrophil count less than $1·5×10^9$/L, platelet counts less than $100×10^9$/L, serum creatinine more than twice the upper limit of normal, grade of common toxicity criteria[10] more than 1 for peripheral neuropathy, uncontrolled congestive heart failure, angina pectoris, hypertension, arrhythmia, history of significant neurological or psychiatric disorders, or active infection. Pregnant or breastfeeding women were also excluded.

Clinical examination, chest radiography, abdomino-pelvic CT scan with contrast medium (spiral CT was recommended) or MRI, electrocardiogram, and standard laboratory work-up were undertaken within 14 days of study entry. The trial was approved by the medical ethics committees of all participating centres. Written informed consent was obtained from all patients before randomisation.

Procedures
Randomisation was done at the European Organisation for Research and Treatment of Cancer (EORTC) Headquarters in Brussels with the minimisation technique,[11] and was stratified for centre, previous adjuvant chemotherapy to primary surgery for colorectal cancer, and a risk score derived from Nordlinger and colleagues.[2]

We chose the FOLFOX4 regimen for the study, since patients with metastatic colorectal cancer assigned to this treatment have previously shown a response rate above 50% and an increase in progression-free survival.[12] Details of this regimen have been previously reported.[13] Patients were randomly assigned to either six cycles of FOLFOX4 before and six cycles after surgery (perioperative chemotherapy group), which were given unless the tumour progressed during preoperative chemotherapy, or to surgery alone. Each cycle of chemotherapy lasted 14 days, with the subsequent cycle to start on day 15.[12]

In both groups, the study treatment had to start within 3 weeks of randomisation. In the perioperative chemotherapy group, liver resection was done 2–5 weeks after the last administration of preoperative chemotherapy, and whenever patients had completely recovered from side-effects of chemotherapy with a WHO performance status of 0 or 1, and adequate liver function.

Surgical exploration consisted of inspection of the peritoneal cavity to exclude extrahepatic involvement, and histological examination of frozen sections of any suspicious lesion. We used intraoperative ultrasonography to detect and localise all hepatic metastases. The type and extent of curative liver resection (wedge resection, or mono-segmentectomy or plurisegmentectomy) was decided by the surgeon with the multidisciplinary team at the treating hospital at the time of randomisation, but was modified if previously undetected deposits were discovered, or if the tumour was larger than was expected.

Clinical and neurological examination and assessment of haematology, biochemistry, and toxic effects[12] were undertaken before each chemotherapy cycle, and up to 30 days after treatment. An abdomino-pelvic CT scan (or MRI) was done after the first three chemotherapy cycles, and before and after liver surgery. The tumour response in the liver was assessed by contrast CT scan after three and six cycles of preoperative chemotherapy and was scored according to response criteria in solid tumour (RECIST)[14] by the local radiologist; no confirmation of response was needed. Chest radiography, abdominal ultrasound or CT scan, and carcinoembryonic antigen concentrations were assessed every 3 months for 2 years after the end of treatment and every 6 months thereafter. Recurrence was diagnosed by imaging, cytology, or histology. When deemed unresectable or after recurrence, patients were treated at the physician's discretion.

The primary trial endpoint was progression-free survival, counted from randomisation to the date of either progressive or recurrent disease, surgery if metastases were deemed not resectable, or death of any cause. To address the lead-time bias that was inherent to the design, the event time to have occurred at 10 weeks was assigned in both

treatment groups in the following circumstances: any patient who was operated upon but in whom the tumour was not actually resectable, any patient whose tumour was resected but recurred within week 1 and 20, or those who died between week 1 and 20 of follow-up. Week 10 was chosen as being in the middle of these 20 weeks.

The study was planned to detect a 40% increase in median progression-free survival, or equivalently an increase of the 3-year progression-free survival from 21·0% to 32·8%, in all patients randomly assigned to perioperative chemotherapy (hazard ratio [HR]=0·714) with 80% power at a two-sided 5% significance level, requiring 278 events. The trial was expected to provide this number of events after 6·5 years. However, at 6·5 years after trial start (Sept 20, 2006) the events had not accumulated at the pace anticipated, but the pressure from the medical community to have the trial results disclosed was very strong. Therefore, a stopping boundary for efficacy was implemented (on a gamma family alpha spending function with parameter γ=–4).[15] An interim analysis was then undertaken in November, 2006, (at 235 events) and shown only to the EORTC independent data monitoring committee, who recommended to release updated results for the American Society of Clinical Oncology (ASCO) meeting in June, 2007, since the stopping boundary had been reached. The results were thus updated in March, 2007, for the ASCO late-breaking abstracts deadline (254 events, 4-year median follow-up) and presented at the two-sided 0·0434 significance level because of the interim analysis.

Statistical analysis

Rates of progression-free survival were estimated by the Kaplan-Meier method[16] and compared by the logrank test.[17] Effects are summarised by the HR and 95·66% CI. We used adjusted CIs for all analyses (adjusting for the interim analysis), which were set as 95·66% CIs, since the type I error rate was α=0·0434. Toxic effects and compliance rates were compared by the χ^2 test. In all analyses, patients stayed assigned to the group that they had been randomly allocated to. The primary analysis was done in all randomised patients. Sensitivity analyses (not protocol-specified but decided before data analysis) were undertaken both in all eligible patients and all those with resectable liver metastases. Inference about overall survival is deferred until longer follow-up becomes available.

The trial is registered with ClinicalTrials.gov, number NCT00006479.

Role of the funding source

The study design, management, data analysis, and data interpretation were done at the EORTC headquarters (Brussels, Belgium) independently of any commercial interest and from all funding bodies. BN and LC had full access to all the data in the study. The corresponding author had final responsibility for the decision to submit for publication.
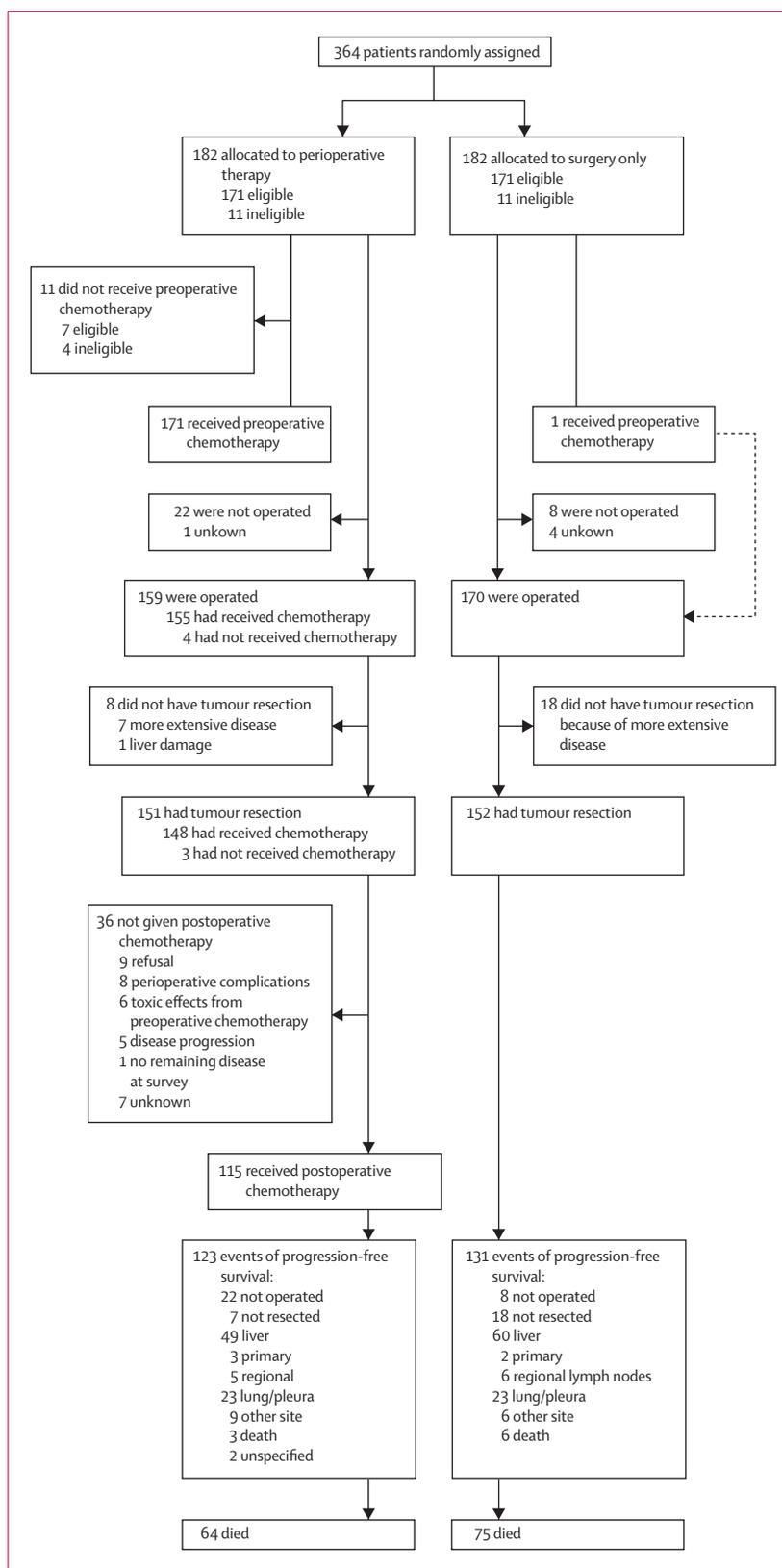

Figure 1: Trial profile

	PeriOpCT group (N=182)	Surgery group (N=182)	Total (N=364)
Age (years)			
Median (IQR)	62 (29–79)	64 (25–78)	63 (25–79)
Mean (SD)	60·7 (9·35)	62·4 (9·63)	61·6 (9·5)
Sex			
Men	127 (70%)	114 (63%)	241 (66%)
Women	54 (30%)	65 (36%)	119 (33%)
No data documentation (ineligible)	1 (1%)	3 (2%)	4 (1%)
WHO performance status			
0	136 (75%)	150 (82%)	286 (79%)
1	44 (24%)	31 (17%)	75 (21%)
2	2 (1%)	1 (1%)	3 (1%)
Number of liver metastases			
1	92* (51%)	95 (52%)	188 (52%)
2	49 (27%)	49 (27%)	94 (26%)
3	27 (15%)	27 (15%)	50 (14%)
1–3 (exact number unknown)	2 (1%)	2 (1%)	4 (1%)
4	12 (7%)	14 (8%)	26 (7%)
>4 (ineligible)	0	2 (1)	2 (1%)
Synchronicity of liver metastases			
Metachronous metastases	121 (66%)	115 (63%)	236 (65%)
Synchronous metastases	61 (34%)	67 (37%)	128 (35%)
Time from diagnosis of primary to diagnosis of liver metastases (years)			
<2	133 (73%)	139 (76%)	272 (75%)
≥2	49 (27%)	43 (24%)	92 (25%)
T category of the primary cancer			
T1	3 (2%)	2 (1%)	5 (1%)
T2	28 (15%)	26 (14%)	54 (15%)
T3	124 (68%)	129 (71%)	253 (70%)
T4	27 (15%)	21 (12%)	48 (13%)
TX	0	4 (2%)	4 (1%)
Lymphatic spread of the primary cancer			
N0	81 (45%)	72 (40%)	153 (42%)
N1	69 (38%)	67 (37%)	136 (37%)
N2	31 (17%)	37 (20%)	68 (19%)
NX	1 (1%)	6 (3%)	7 (2%)
Location of primary cancer			
Colon	95 (52%)	107 (59%)	202 (56%)
Rectum	84 (46%)	68 (37%)	152 (42%)
Multiple	1 (1%)	3 (2%)	4 (1%)
Unknown	2 (1%)	4 (2%)	6 (2%)
Previous adjuvant chemotherapy for primary cancer			
No	104 (57%)	106 (58%)	210 (58%)
Yes (without oxaliplatin)	78 (43%)	76 (42%)	154 (42%)
Plasma CEA at diagnosis, if liver metastases (ng/mL)			
≤5·0	66 (36%)	68 (37%)	134 (37%)
5·1–30·0	55 (30%)	60 (33%)	115 (32%)
>30	61 (34%)	54 (30%)	115 (312%)

Data are number (%) unless otherwise indicated. PeriOpCT=perioperative chemotherapy with 5-fluorouracil/leucovorin and oxaliplatin. CEA=carcinoembryonic antigen. *One patient was randomised too early and was found to have seven metastases on a later CT scan, and thus was ineligible.

Table 1: Baseline characteristics

Results

Figure 1 shows the trial profile. 364 patients were enrolled, 182 in each group. No log was kept of the number of patients who were screened for eligibility. Patient and tumour characteristics were much the same between the two groups at baseline (table 1). 11 patients in each group were ineligible. The reasons for ineligibility were more advanced disease than was allowed by the protocol (five in perioperative chemotherapy group and six in surgery group), primary liver cancer (one in both groups), no data (two in perioperative chemotherapy group and three in surgery group), second cancer (one in surgery group with colon cancer), late informed consent (one in perioperative chemotherapy group), high serum creatinine (one in perioperative chemotherapy group), and resection of primary less than 14 days of randomisation (one in perioperative chemotherapy group).

In the chemotherapy group, 143 (79%) patients completed the planned six cycles of preoperative chemotherapy, and 11 (6%) of 182 did not start treatment (four ineligible patients and seven eligible patients: four who refused, one with colostomy requiring immediate surgery, one with alcohol abuse, and one with previous raltitrexed treatment).

Table 2 shows compliance, treatment tolerance, and treatment response in the perioperative chemotherapy group, and table 3 the toxic effects. We recorded no deaths due to toxic effects. Partial or complete response (according to RECIST) was recorded in more than two-fifths of patients and the total lesion diameter was reduced by about a quarter after chemotherapy (table 2). 12 (7%) patients progressed during chemotherapy: eight after 3–4 cycles (three of whom underwent subsequent resection) and four after six cycles (one resected). Of the eight patients who could not undergo resection, unresectability was due to appearance of new lesions in four. None of these patients started the postoperative protocol chemotherapy. Apart from one patient randomly assigned to surgery alone who received the whole perioperative chemotherapy at his request, none of the patients in the surgery group received chemotherapy before recurrence.

Surgery according to the protocol was undertaken at a median of 16·6 (range 0·1–30) weeks in the perioperative chemotherapy group and 2 (0·1–16) weeks in the surgery alone group. Surgery was done in a median of 4·1 (2·0–16·4) weeks after the last administration of preoperative chemotherapy. More patients received the operation in the surgery group than in the perioperative chemotherapy group (table 4). In both groups, a similar number of patients received potentially curative resection (table 4). The most frequent reason for non-resectability was disease that was more advanced than was expected (table 4). In one patient, resection was not done because of macroscopic liver damage, which was most probably related to chemotherapy. Reversible postoperative complications occurred more often after chemotherapy

	Preoperative chemotherapy (N=171)	Postoperative chemotherapy (N=115)
Administration of chemotherapy		
Number of cycles		
1	6 (4%)	7 (6%)
2	1 (1%)	10 (9%)
3	8 (5%)	5 (4%)
4	7 (4%)	5 (4%)
5	6 (4%)	8 (7%)
6	143 (84%)	80 (70%)*
Median (range)	6 (1–6)	6 (1–8)
Relative dose intensity		
5-fluorouracil (%)	92·3% (50·0 to 111·3)	82·0% (36·9 to 112·2)
Oxaliplatin (%)	92·1% (54·6 to 106·0)	79·1% (0·0 to 106·5)
Dose reduction(s)	58 (34%)	69 (60%)
Delayed cycle(s)	75 (44%)	73 (64%)
Response to preoperative chemotherapy (RECIST)†		
Complete response	4 (3%)	..
Partial response	63 (40%)	..
Stable disease	60 (38%)	..
Progressive disease	11 (7%)	..
After 3–4 cycles	7‡ (64%)	..
After 6 cycles	4§ (36%)	..
Not assessable	21 (13%)	..
Ineligible	5 (24%)	..
Benign lesion	2 (10%)	..
<3 cycles	10 (48%)	..
No follow-up measurements	4 (19%)	..
Sum of the largest diameters of lesions on imaging		
At entry (mm)	50 (20 to 255)	..
After preoperative chemotherapy (mm)	33 (0 to 230)	..
Relative reduction (%)	−25·6% (−100 to 228·6)	..

Data are number (%) or median (range). RECIST=response criteria in solid tumours.[13] *Including one patient who received seven cycles and one who received eight cycles. †Assessed in patients with at least one baseline lesion 20 mm or more (N=159). ‡Three of seven patients underwent resection, one further patient who is not eligible for RECIST response assessment progressed after three cycles and did not undergo resection. §One of four patients underwent resection.

Table 2: Compliance, treatment tolerance, and treatment response to perioperative chemotherapy

	PeriOpCT group	Surgery group
Tolerance to preoperative chemotherapy (N=171)		
Allergy grade 3*	1 (1%)	..
Diarrhoea grade 3*	14 (8%)	..
Nausea grade 3*	6 (4%)	..
Vomiting		
Grade 3	4 (3%)	..
Grade 4	1 (1%)	..
Stomatitis/pharyngitis grade 3*	11 (7%)	..
Hand-foot skin syndrome grade 3*	0	..
Sensory neuropathy grade 3*	4 (2%)	..
Cholinergic syndrome grade 3*	1 (1%)	..
Dysaesthesia grade 3*	4 (2%)	..
Other neurological toxicity grade 3*	10 (6%)	..
Hepatic grade 3*	5 (3%)	..
Cardiovascular grade 3*	4 (2%)	..
Febrile neutropenia		
Grade 3	1 (1%)	..
Grade 4	1 (1%)	..
Infection grade 3*	5 (3%)	..
Catheter-related infection grade 3*	0	..
Leucopenia		
Grade 3	9 (5%)	..
Grade 4	1 (1%)	..
Neutropenia		
Grade 3	19 (11%)	..
Grade 4	12 (7%)	..
Thrombocytopenia grade 3*	2 (1%)	
Haemoglobin grade 3*	1 (1%)	..
Postoperative complications		
Number in group	159	170
Reversible postoperative complications†	40 (25%)	27 (16%)
Cardio-pulmonary failure	3 (2%)	2 (1%)
Bleeding	3 (2%)	3 (2%)
Biliary fistula	13 (8%)	7 (4%)
Output >100 mL/day for >10 days	9 (6%)	2 (1%)
Hepatic failure	11 (7%)	8 (5%)
Bilirubin >100 mg/day for >3 days	10 (6%)	5 (3%)
Wound infection	5 (3%)	4 (2%)
Intra-abdominal infection	11 (7%)	4 (2%)
Need for reoperation	5 (3%)	3 (2%)
Urinary infection	4 (3%)	0
Pleural effusion	3 (2%)	1 (1%)
Pulmonary embolism/deep-venous thrombosis	2 (1%)	1 (1%)
Pneumopathy	2 (1%)	0
Neutropenia	2 (1%)	0
Ascites	1 (1%)	1 (1%)
Ileus	2 (1%)	1 (1%)
Cardiac arrhythmia	0	1 (1%)
Renal failure	0	1 (1%)
Other	4 (3%)	4 (2%)
Postoperative death	1 (1%)	2 (1%)

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than after surgery alone (p=0·04; table 3). After surgery we recorded two deaths in the surgery alone group and one in the perioperative chemotherapy group. Further results regarding the translational research and pathology will be presented elsewhere.

115 (63%) patients started postoperative protocol chemotherapy, of whom 80 (70%) received six cycles. Table 3 shows the tolerance to postoperative chemotherapy. Figure 1 shows the reasons why postoperative protocol chemotherapy was not started in the remaining patients.

As of March 2007, the median follow-up was 3·9 years. We recorded 254 events of progression-free survival (the

	PeriOpCT group	Surgery group
(Continued from previous page)		
Tolerance to postoperative chemotherapy (N=115)		
Allergy		
Grade 3	4 (4%)	..
Grade 4	1 (1%)	..
Diarrhoea grade 3*	6 (5%)	..
Nausea grade 3*	5 (4%)	..
Vomiting grade 3*	3 (3%)	..
Stomatitis/pharyngitis grade 3*	0	..
Hand-foot skin syndrom grade 3*	1 (1%)	..
Sensory neuropathy grade 3*	11 (10%)	..
Cholinergic syndrome grade 3*	1 (1%)	..
Dysaesthesia grade 3*	5 (4%)	..
Other neurological toxicity grade 3*	14 (12%)	..
Hepatic grade 3*	6 (5%)	..
Cardiovascular grade 3*	1 (1%)	..
Febrile neutropenia grade 3*	4 (4%)	..
Infection grade 3*	2 (2%)	..
Catheter-related infection grade 3*	5 (4%)	..
Leucopenia grade 3*	14 (12%)	..
Neutropenia		
Grade 3	32 (28%)	..
Grade 4	8 (7%)	..
Thrombocytopenia grade 3*	8 (7%)	..
Haemoglobin grade 3*	1 (1%)	

Data are n (%) unless otherwise stated. Patients may have several complications, therefore number of complications does not add up to the total number of patients. Common toxicity criteria[20] version 2.0 was used. PeriOpCT=perioperative chemotherapy with fluorouracil or leucovorin and oxaliplatin *No grade 4 reported. †p=0·04.

Table 3: **Adverse events during chemotherapy and postoperative complications**

	PeriOpCT group (N=182)	Surgery group (N=182)
Operated	159 (87%)	170 (93%)
Resected	151 (83%)	152 (84%)
Monosegmentectomy or wedge resection	31 (20%)	33 (22%)
Plurisegmentectomy*	86 (57%)	81 (53%)
Multiple resections	33 (22%)	36 (24%)
Unknown	1 (1%)	2 (1%)
Not resected	8 (4%)	18 (10%)
More extensive disease	7 (88%)	18 (100%)
Liver damage	1 (13%)	0
Not operated	22 (12%)	8 (4%)
More advanced disease	10 (45%)	7 (88%)
Refusal	4 (18%)	0
Poor condition/death	3 (14%)	0
Other reason	5 (23%)	1 (13%)
Unknown	1 (1%)	4 (2%)
Time to surgery (weeks)	16·6 (0·1–30)	2 (0·1–16)

Data are number (%) or median (range). *Major resection, two or more segments. PeriOpCT=perioperative chemotherapy with fluorouracil or leucovorin and oxaliplatin.

Table 4: **Patients who received surgery and resection**

primary endpoint) in all randomised patients (figure 1), including 240 events in eligible patients. 22 patients assigned to chemotherapy and 19 to surgery were alive without disease and had been followed up for less than 3 years. A total of 139 patients have died (figure 1).

The HR for progression-free survival was 0·79 (95·66% CI 0·62–1·02; p=0·058) in all randomly assigned patients corresponding to a 7·3% increase in the rate of progression-free survival at 3 years from 28·1% (21·3–35·3) to 35·4% (28·1–42·7) with chemotherapy and to an increase of the median progression-free survival from 11·7 months to 18·7 months (figure 2). An analysis of only patients who were eligible to enter the trial showed an HR of 0·77 (0·60–1·00, p=0·041), corresponding to an 8·1% increase in the rate of progression-free survival at 3 years from 28·1% (21·2–36·6) to 36·2% (28·7–43·8) with chemotherapy (figure 2). In the 303 patients in whom resection was actually achieved after study entry, the analysis showed that the HR was 0·73 (0·55–0·97, p=0·025) and the rate of progression-free survival at 3 years was increased by 9·2% from 33·2% (25·3–41·2) to 42·4% (34·0–50·5) (figure 2).

When the usual definition of progression-free survival was used to compare treatments in all 364 randomised patients (ie, those not operated or not resected were not penalised as events until further disease progression or death), the HR was 0·76 (0·59–0·98, p=0·023) corresponding to a 7·3% increase in the rate of progression-free survival at 3 years from 28·6% (21·7–35·8) to 37·9% (30·5–45·3) with chemotherapy. Adjustment of the primary analysis for the stratification factors (risk grouping and previous adjuvant chemotherapy) did not change the results (data not shown).

Discussion

We have shown that perioperative chemotherapy with FOLFOX4 reduced the risk of progression-free survival events at 3 years by a quarter in patients with resectable liver metastases. In all patients randomly assigned to study treatments, the study showed a trend favouring administration of chemotherapy, which was not significant when a correction was used for the different timings of surgery in the two treatment groups. In all eligible and all resected patients the benefit was statistically significant. Our results have shown that perioperative chemotherapy was compatible with major liver surgery. Operative mortality was less than 1% in both treatment groups, which is very low after this type of liver surgery in a multicentre study. Reversible complications of surgery

were more frequent in patients who had received preoperative chemotherapy than in those who had received surgery alone, but remained within the range commonly noted after resection of liver metastases.[1,3,18]

In patients with advanced colorectal cancer, several studies have compared various chemotherapy regimens. However, very few prospective studies have investigated the combination of chemotherapy with surgery, and none has assessed perioperative chemotherapy. Most trials did not achieve the planned recruitment for multifactorial reasons (table 5).[5–9] Although no level I evidence for a benefit of combining chemotherapy and surgery was reported, individual opinions in favour of one or the other treatment option prevented some oncologists and surgeons from including patients in trials. This trial met its target accrual, thanks to an intercontinental collaboration involving Europe, Australia, and Hong Kong. Any future trial of this type is unlikely to have a surgery-only group.[19]

The primary objective of this trial was to assess perioperative chemotherapy in patients qualifying for resection of their metastatic disease. Had we assessed postoperative chemotherapy only, randomisation could have been done after successful resection of the metastases, and no patient would have been excluded because of ineligibility or unresectability. Because of the specific objective in our trial, patients had to be randomly assigned imperatively before surgery—ie, without any certainty that metastases assessed by imaging were actually resectable. This uncertainty represents a fundamental difficulty for all studies assessing preoperative treatment and makes such studies difficult to undertake and analyse. For example, in the MAGIC (Medical Research Council Adjuvant Gastric Infusional Chemotherapy) trial[13] that assessed perioperative chemotherapy in gastric cancer, many randomised patients did not undergo complete resection of the cancer. In our trial, some metastases that were initially considered to be resectable at randomisation were actually more advanced and not resectable at surgical examination. Therefore we examined not only all randomised and eligible patients, but also those who received resection. All analyses were done according to the allocated treatment group (ie, including the patients who did not receive the allocated treatment). The number of patients who finally underwent resection was much the same in both treatment groups.

The principal reason for non-resectability was more advanced disease than was expected, which was probably mostly due to a discrepancy between imaging and surgical examination. However, we noted a trend towards fewer failures to resect in the perioperative chemotherapy group than in the surgery group because of extensive disease, and a higher rate of failures to resect because of refusal or poor condition of the patient, which could introduce a selection bias. Results of progression-free survival in resected patients might be of interest in view
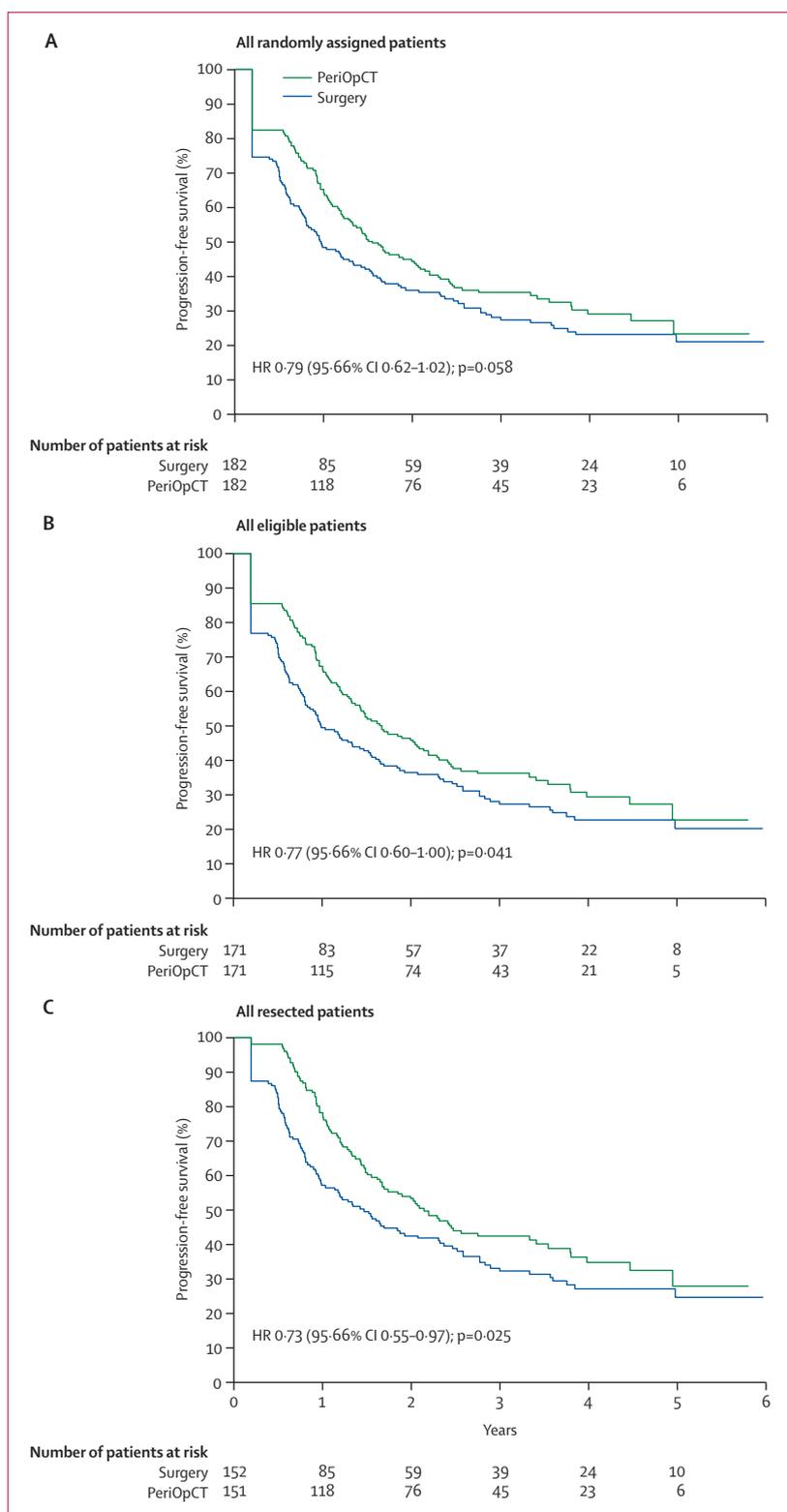
Figure 2: Progression-free survival by treatment group
(A) All randomly assigned patients. (B) All eligible patients. (C) All resected patients. For all patients randomly assigned and those who were eligible, no surgery or no resection were regarded as events for the primary endpoint of progression-free survival. PeriOpCT=perioperative chemotherapy with fluorouracil or leucovorin, and oxaliplatin.

	Number of resected metastases	Median follow-up (months)	Number of patients	Randomised postoperative treatments	Median TTP/PFS (months)	Median overall survival (months)
Lorenz M (1998)[5]	≤6 liver metastases	≥18	108 vs 111	HAI FU/FA vs surgery alone	14·2 vs 13·7 (NS)	34·5 vs 40·8 (p=0·15)
Kemeny N (1999)[6]	Any number of liver metastases	62·7	74 vs 82	Systemic FU/FA+HAI FUDR vs systemic FU/FA	37·4 vs 17·2 (p=0·06)	72·2 vs 59·3 (p=0·21)
Kemeny M (2002)[7]	1–3 liver metastases	51	30 vs 45	HAI FUDR+systemic FU vs surgery alone	45·7%* vs 25·2%* (p=0·04)	63·7 vs 49·0 (p=0·60)
Mitry E (2006)[8]	≤4 liver or lung metastases	NR	138 vs 140	Systemic FU/FA vs surgery alone	26·4 vs 18·6 (p=0·059)	61·1 vs 46·9 (p=0·125)
Portier G (2006)[9]	Any number of liver metastases	87	86 vs 87	Systemic FU/FA vs surgery alone	24·4 vs 17·6 (p=0·028)	62·1 vs 46·4 (p=0·13)

TTP=time to progression. PFS=progression-free survival. HAI=hepatic arterial infusion. FUDR=floxuridine. FU=fluorouracil. FA=folinic acid. NS=not significant. NR=not reported. *4-year progression-free survival rates.

Table 5: Previous studies of adjuvant chemotherapy in patients with resected liver metastases from colorectal cancer

of all other trials in this specialty, which assess postoperative chemotherapy only in patients with resected liver metastases since randomisation is done after surgery.[5–9] Progress in imaging techniques (with spiral CT scan, MRI, PET scan, and contrast ultrasound) has further reduced the gap between imaging and surgery exploration when the resectability of liver metastases is assessed.[20]

In accordance with the statistical design in the protocol, unresected patients in both groups were counted as events for the primary endpoint of progression-free survival, which inevitably results in a dilution of the observed treatment difference in all analyses including the unresected patients. The protocol considered all events of non-resection to have occurred at week 10 to not bias results because of the different timing of surgery in the two groups.

In this study, metastases progressed during preoperative chemotherapy in 12 patients (7%), four of whom were subsequently non-resectable because of the appearance of new lesions and four because of progression of already known metastases. In the four patients with new lesions, immediate surgery would not have been beneficial since new metastases would have appeared anyway. In the four patients with progression of the known metastases, resection would also probably have been followed by progression.[21] Progression during preoperative chemotherapy should rather be regarded as a biological marker for poor prognosis and an indication for administration of second-line chemotherapy before surgery is considered.

Chemotherapy does induce liver damage which varies according to the drugs given. Vascular lesions, but no steatohepatitis, have been noted after administration of oxaliplatin.[22–24] Whether these liver lesions might affect the safety of subsequent surgery and thus counterbalance the potential benefits of treatment is unknown. Karoui and colleagues[25] showed that the risk of surgical complications after preoperative chemotherapy is related to the number of chemotherapy cycles, and that this risk remains low if not more than six cycles are given preoperatively. We administered only six cycles preoperatively. The mortality rate was very low. The complication rate was higher in the chemotherapy group than in the surgery group but was similar to other series

of patients undergoing hepatectomy.[1,3,18] These complications were reversible. We believe that this moderate increase in the risks of liver surgery after chemotherapy does not compromise the potential benefits of the treatment.

In this study, chemotherapy was given before and after surgery. Previous trials[5–9] showed a trend towards a benefit of postoperative-only chemotherapy; however, our trial was not designed to compare preoperative and postoperative chemotherapy. The improvement in progression-free survival with chemotherapy was recorded during the first 2 years but afterwards the curves seemed to remain parallel. Similarly, the MAGIC trial showed that perioperative chemotherapy increases overall survival, whereas most trials of postoperative chemotherapy alone did not show a benefit.[13,26]

This trial was restricted to patients with four or fewer metastases to reduce the proportion of patients that would be entered and later found to have more metastases than were detected on imaging, some of which would be unresectable. This restriction was not intended to serve as a definition of unresectability, but to serve as a selection criterion for the trial. These patients with a few metastases are those with best prognosis after surgical resection. We believe that the conclusions from this trial would probably also be valid for patients at higher risk. Future trials could thus investigate the potential benefit of intensified perioperative chemotherapy in resectable liver metastases from colorectal cancer. The combination of targeted agents with cytotoxic therapy has shown high response rates[27–29] and thus warrants assessment in the perioperative setting. At present the EORTC 40051 BOS (Biologics, Oxaliplatin and Surgery) trial[30] is assessing perioperative chemotherapy with FOLFOX6 and cetuximab with or without bevacizumab in patients with resectable hepatic metastases from colorectal cancer.

We conclude that perioperative FOLFOX4 chemotherapy reduced the risk of events of progression-free survival by a quarter and was compatible with major surgery. In all randomised patients the study showed a trend favouring administration of chemotherapy. In all eligible and in all resected patients, the benefit of administering chemotherapy was significant.

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