



# Perioperative FOLFOX4 chemotherapy and surgery versus surgery alone for resectable liver metastases from colorectal cancer (EORTC 40983): long-term results of a randomised, controlled, phase 3 trial

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## Summary

**Background** Previous results of the EORTC intergroup trial 40983 showed that perioperative chemotherapy with FOLFOX4 (folinic acid, fluorouracil, and oxaliplatin) increases progression-free survival (PFS) compared with surgery alone for patients with initially resectable liver metastases from colorectal cancer. Here we present overall survival data after long-term follow-up.

**Methods** This randomised, controlled, parallel-group, phase 3 study recruited patients from 78 hospitals across Europe, Australia, and Hong Kong. Eligible patients aged 18–80 years who had histologically proven colorectal cancer and up to four liver metastases were randomly assigned (1:1) to either perioperative FOLFOX4 or surgery alone. Perioperative FOLFOX4 consisted of six 14-day cycles of oxaliplatin 85mg/m<sup>2</sup>, folinic acid 200 mg/m<sup>2</sup> (DL form) or 100 mg/m<sup>2</sup> (L form) on days 1–2 plus bolus, and fluorouracil 400 mg/m<sup>2</sup> (bolus) and 600 mg/m<sup>2</sup> (continuous 22 h infusion), before and after surgery. Patients were centrally randomised by minimisation, adjusting for centre and risk score and previous adjuvant chemotherapy to primary surgery for colorectal cancer, and the trial was open label. Analysis of overall survival was by intention to treat in all randomly assigned patients. This trial is registered with ClinicalTrials.gov, number NCT00006479.

**Findings** Between Oct 10, 2000, and July 5, 2004, 364 patients were randomly assigned to a treatment group (182 patients in each group, of which 171 per group were eligible and 152 per group underwent resection). At a median follow-up of 8.5 years (IQR 7.6–9.5), 107 (59%) patients in the perioperative chemotherapy group had died versus 114 (63%) in the surgery-only group (HR 0.88, 95% CI 0.68–1.14; p=0.34). In all randomly assigned patients, median overall survival was 61.3 months (95% CI 51.0–83.4) in the perioperative chemotherapy group and 54.3 months (41.9–79.4) in the surgery alone group. 5-year overall survival was 51.2% (95% CI 43.6–58.3) in the perioperative chemotherapy group versus 47.8% (40.3–55.0) in the surgery-only group. Two patients in the perioperative chemotherapy group and three in the surgery-only group died from complications of protocol surgery, and one patient in the perioperative chemotherapy group died possibly as a result of toxicity of protocol treatment.

**Interpretation** We found no difference in overall survival with the addition of perioperative chemotherapy with FOLFOX4 compared with surgery alone for patients with resectable liver metastases from colorectal cancer. However, the previously observed benefit in PFS means that perioperative chemotherapy with FOLFOX4 should remain the reference treatment for this population of patients.

**Funding** Norwegian and Swedish Cancer Societies, Cancer Research UK, Ligue Nationale Contre Cancer, US National Cancer Institute, Sanofi-Aventis.

## Introduction

Surgery is the only potentially curative treatment for resectable liver metastases; however, only 15–20% of patients with hepatic metastases are initially eligible for a radical surgical approach. The proportion of patients who achieve 5-year survival after resection ranges from 20% to 50%.<sup>1,2</sup> After liver resection with curative intent, recurrences are reported in two-thirds of patients, half occurring in the residual liver.<sup>3–5</sup> The most likely

explanation for recurrence is the persistence of microscopic residual disease after surgery. Therefore, combining chemotherapy with resection of colorectal cancer liver metastases is of major interest. So far, the results of randomised trials of adjuvant chemotherapy given after liver resection either intravenously or through the hepatic artery have provided some indication that prognosis has improved, but the benefit of adjuvant chemotherapy has not yet been formally proven.<sup>6–9</sup>

Lancet Oncol 2013; 14: 1208–15

Published Online

October 11, 2013

[http://dx.doi.org/10.1016/S1470-2045\(13\)70447-9](http://dx.doi.org/10.1016/S1470-2045(13)70447-9)

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For that reason, our study group proposed to assess the use of perioperative chemotherapy (ie, before and after surgery) in a randomised phase 3 trial, even in patients with resectable disease—the rationale being that this method would treat micrometastatic disease. In patients without (readily) resectable disease, further aims were to increase the proportion of patients who have a complete resection and to reduce the size of liver metastases, therefore helping to improve results of hepatectomies.

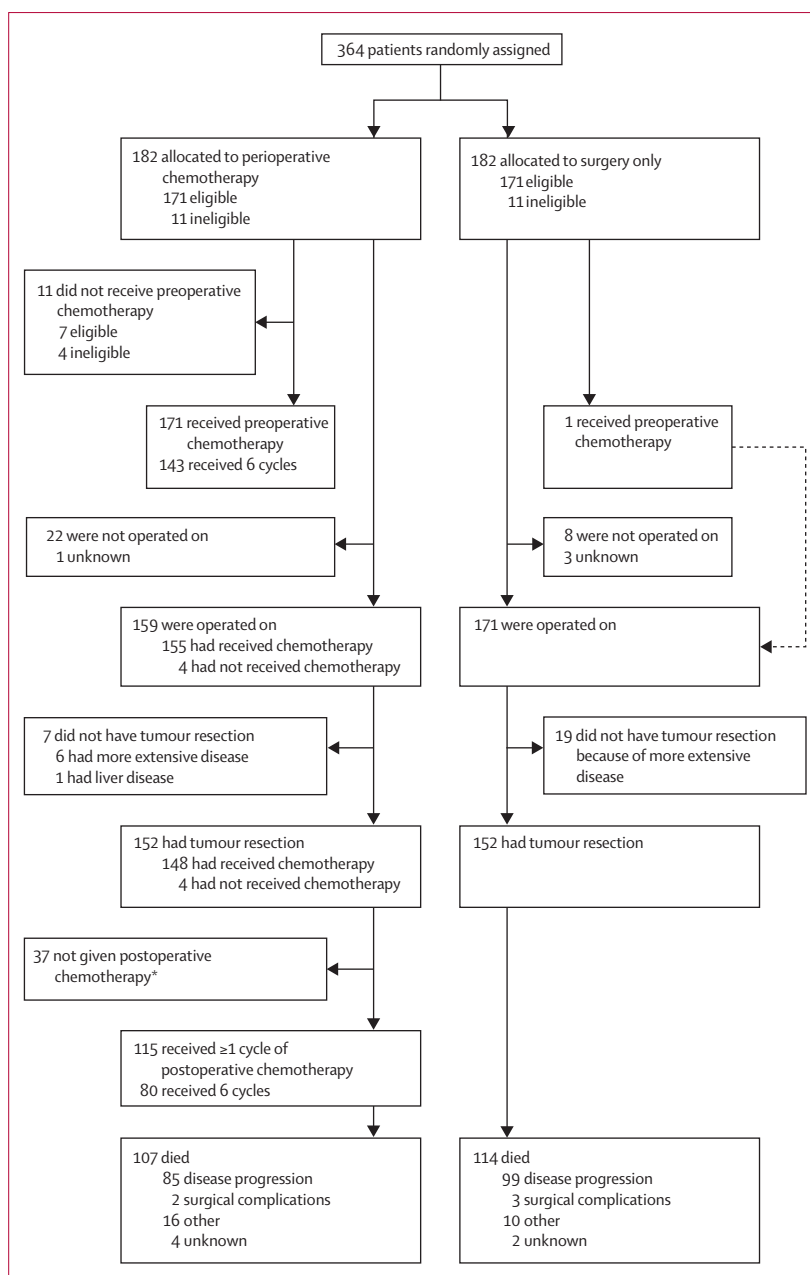
Previously published results of the European Organisation for Research and Treatment of Cancer (EORTC) intergroup trial 40983<sup>10</sup> (EPOC) showed that the combination of perioperative chemotherapy with FOLFOX4 (folinic acid, fluorouracil, and oxaliplatin) and surgery increases progression-free survival (PFS) compared with surgery alone for patients with liver-only metastases from colorectal cancer deemed resectable on preoperative imaging. The absolute difference in the proportion of patients alive and progression free at 3 years was 7·3% (3-year PFS was 28·1% [95·66% CI 21·3–35·3] in the surgery-only group compared with 35·4% [28·1–42·7] in the perioperative chemotherapy group; hazard ratio [HR] 0·79 [0·62–1·02];  $p=0·058$ ) in all randomised patients. For all patients eligible for analysis —ie, those who were assessed by the study coordinator to fulfil eligibility criteria as defined in the protocol—the absolute difference in 3-year PFS was 8·1% (28·1% [95·66% CI 21·2–36·6] in the surgery-only group vs 36·2% [28·7–43·8] in the perioperative chemotherapy group; HR 0·77 [0·60–1·00];  $p=0·041$ ). A higher proportion of patients had reversible postoperative complications after chemotherapy with surgery than after surgery alone (40 [25%] of 159 vs 27 [16%] of 171;  $p=0·0401$ ). However, the proportion of patients who were operated on who had a non-therapeutic laparotomy was lower in the perioperative chemotherapy group than in the surgery-only group (eight [5%] of 159 patients vs 18 [11%] of 171 patients;  $p=0·069$ ).

After extended follow-up, we aimed to compare the secondary outcome of overall survival in patients who received perioperative chemotherapy with those who received surgery alone.

## Methods

### Study design and patients

The EORTC intergroup trial 40983 was a randomised, controlled, phase 3 trial. Details of the trial design and study procedures have been reported previously.<sup>10</sup> Patients were recruited from 78 hospitals in Australia, Austria, Belgium, France, Germany, Hong Kong, Italy, Norway, Sweden, the Netherlands, and the UK. Eligible patients were aged 18–80 years, with a WHO performance status of 2 or less, histologically proven colorectal cancer, one to four liver metastases that were resectable, and no detectable extrahepatic tumours. The primary tumour had to be either previously resected (R0 resection) or judged to be resectable (in case of synchronous metastases) by a multidisciplinary



**Figure 1: Trial profile**

\*37 patients who had a tumour resection were not given postoperative chemotherapy; 68 of all patients assigned to perioperative chemotherapy were not given postoperative chemotherapy.

team at the treating hospital. Full inclusion and exclusion criteria have been previously reported.<sup>10</sup> The trial was approved by the medical ethics committees of all participating centres. Written informed consent was obtained from all patients before randomisation.

### Randomisation

Patients were randomly assigned (1:1) to perioperative FOLFOX4 or surgery alone by the minimisation method

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|   | Perioperative<br>chemotherapy<br>(n=182) | Surgery only<br>(n=182) |
|---|--|-------------------------|
| Age, years  | 62 (29–79)                               | 64 (25–78)              |
| Sex   |  |                         |
| Men   | 127 (70%)                                | 114 (63%)               |
| Women   | 54 (30%)                                 | 65 (36%)                |
| No data documentation<br>(ineligible)                                     | 1 (1%)                                   | 3 (2%)                  |
| WHO performance status  |  |                         |
| 0   | 136 (75%)                                | 150 (82%)               |
| 1   | 44 (24%)                                 | 31 (17%)                |
| 2   | 2 (1%)                                   | 1 (1%)                  |
| Number of liver metastases  |  |                         |
| 1   | 92* (51%)                                | 96 (53%)                |
| 2   | 49 (27%)                                 | 45 (25%)                |
| 3   | 27 (15%)                                 | 23 (13%)                |
| 1–3 (exact number unknown)  | 2 (1%)                                   | 2 (1%)                  |
| 4   | 12 (7%)                                  | 14 (8%)                 |
| >4 (ineligible)   | 0  | 2 (1%)                  |
| Synchronicity of liver metastases   |  |                         |
| Metachronous  | 121 (66%)                                | 115 (63%)               |
| Synchronous   | 61 (34%)                                 | 67 (37%)                |
| Time from diagnosis of primary cancer to diagnosis of liver<br>metastases |  |                         |
| <2 years  | 133 (73%)                                | 139 (76%)               |
| ≥2 years  | 49 (27%)                                 | 43 (24%)                |
| Tumour category of primary cancer   |  |                         |
| T1  | 3 (2%)                                   | 2 (1%)                  |
| T2  | 28 (15%)                                 | 26 (14%)                |
| T3  | 124 (68%)                                | 129 (71%)               |
| T4  | 27 (15%)                                 | 21 (12%)                |
| TX  | 0  | 4 (2%)                  |
| Lymphatic spread of primary cancer  |  |                         |
| N0  | 81 (45%)                                 | 72 (40%)                |
| N1  | 69 (38%)                                 | 67 (37%)                |
| N2  | 31 (17%)                                 | 37 (20%)                |
| NX  | 1 (1%)                                   | 6 (3%)                  |
| Location of primary cancer  |  |                         |
| Colon   | 95 (52%)                                 | 107 (59%)               |
| Rectum  | 84 (46%)                                 | 68 (37%)                |
| Multiple sites  | 1 (1%)                                   | 3 (2%)                  |
| Unknown   | 2 (1%)                                   | 4 (2%)                  |
| Previous adjuvant chemotherapy for primary cancer                         |  |                         |
| No  | 104 (57%)                                | 106 (58%)               |
| Yes, without oxaliplatin  | 78 (43%)                                 | 76 (42%)                |
| Plasma CEA at diagnosis of liver metastases                               |  |                         |
| ≤5.0 ng/mL  | 66 (36%)                                 | 68 (37%)                |
| 5.1–30.0 ng/mL  | 55 (30%)                                 | 60 (33%)                |
| >30 ng/mL   | 61 (34%)                                 | 54 (30%)                |

Data are median (range) and number (%). CEA=carcinoembryonic antigen. \*One patient was randomly assigned to a treatment group too early and was found to have seven metastases on a later CT scan, and thus was ineligible.

**Table 1: Baseline characteristics**

via the online randomisation system of the EORTC headquarters (the coordinating data centre), accessed by authorised local investigators. Randomisation was stratified according to centre, previous adjuvant chemotherapy to primary surgery for colorectal cancer, and a risk score developed previously by Nordlinger and colleagues.<sup>11</sup> The trial was open label.

### Procedures

Patients assigned to perioperative FOLFOX4 received six cycles of oxaliplatin 85mg/m<sup>2</sup>, folinic acid 200 mg/m<sup>2</sup> (DL form) or 100 mg/m<sup>2</sup> (L form) on days 1–2 plus bolus, and fluorouracil 400 mg/m<sup>2</sup> (bolus) and 600 mg/m<sup>2</sup> (continuous 22 h infusion) before and after surgery. Each cycle of chemotherapy lasted 14 days, with the subsequent cycle starting on day 15. Details of this regimen have been previously reported.<sup>12</sup>

Patients were assessed for PFS and overall survival every 3 months for 2 years after the end of treatment and every 6 months thereafter. Recurrence was diagnosed by imaging and confirmed by cytology, or histology if clinically needed. After recurrence, patients were given further treatment at the physician's discretion.

We recorded the type of treatment given at first progression for all patients. Data on long-term adverse events (eg, late side-effects) were not systematically obtained for this follow-up study.

The primary trial endpoint was PFS, and tumour resectability and tumour response were other secondary endpoints, the results of which have been published previously.<sup>10</sup> The objective of this present study was to assess the secondary endpoint of overall survival. Overall survival was defined as the time interval between the date of randomisation and the date of death.

### Statistical analysis

The trial was planned to detect a 40% increase in median PFS or, equivalently, an increase in 3-year PFS from 21.0% to 32.8%, in all patients randomly assigned to perioperative chemotherapy (HR 0.714) with 80% power at a two-sided 5% significance level, requiring 278 progression events or deaths. The trial was expected to provide this number of events after 6.5 years; however, 6.5 years after the trial's start (Sept 20, 2006) the events had not accumulated at the pace expected, but the pressure from the medical community to disclose the trial results was very strong. Therefore, a stopping boundary for efficacy was implemented and an interim analysis was then done 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, because the stopping boundary had been reached. The results were 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. The trial's final data for PFS were published while overall survival was still being monitored.<sup>10</sup>

The trial was not powered upfront to detect an increase in overall survival. A-posteriori calculations computed that at least 194 deaths would be needed to reach 80% power to detect an increase of 10 percentage points in the proportion of patients alive at 3 years in the preoperative chemotherapy group compared with the surgery alone group, from 65% to 75% (HR 0.668), with a two-sided log-rank test at a level of significance of 5%.

After a median follow-up of 8.5 years and 221 reported deaths, we compared overall survival between groups with a two-sided non-stratified log-rank test at the 0.05 level of significance. This length of time was not prespecified in the protocol; rather, it was a compromise based on the number of deaths we could reach given the number of patients accrued. The primary analysis for this trial (ie, the analysis of overall survival) was done in all randomly assigned patients according to the intention-to-treat principle. We estimated overall survival rates using the Kaplan-Meier method<sup>13</sup> and summarised effects with HRs and 95% CIs. We did sensitivity analyses using data from eligible patients (some randomly assigned patients were subsequently found to be ineligible) and patients whose cancer was resected, and with adjustment for stratification factors. Patients who were still alive when last traced were censored at the date of last follow-up.

We did a competing-risk analysis to investigate the effect of deaths from other causes on overall survival. We estimated the cumulative incidences of deaths due to cancer progression, protocol treatment, or unknown causes (referred to as cancer-specific deaths), which we compared using a Gray test.<sup>14</sup> We estimated cancer-specific survival, defined as the time interval between randomisation and death due to cancer progression, protocol treatment, or unknown cause using the Kaplan-Meier method and compared the results between groups. We did all statistical analyses with SAS software (version 9.3).

This 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 MM had full access to all the data in the study. BN and MM had final responsibility for the decision to submit for publication.

### Results

As previously reported, between Oct 10, 2000, and July 5, 2004, 364 patients were randomly assigned to a treatment group (182 patients in each group; figure 1). Baseline tumour and patient characteristics were similar between

|  | Perioperative chemotherapy (n=182) | Surgery only (n=182) |
|--|------------------------------------|----------------------|
| Survival status                              |                                    |                      |
| Alive  | 75 (41%)                           | 68 (37%)             |
| Dead   | 107 (59%)                          | 114 (63%)            |
| Main cause of death                          |                                    |                      |
| Progression of disease                       | 85 (47%)                           | 99 (54%)             |
| Toxicity of protocol treatment               | 1 (1%)*                            | 0                    |
| Complication of protocol surgery             | 2 (1%)                             | 3 (2%)               |
| Other  | 15 (8%)                            | 10 (5%)              |
| Toxicity of further cancer treatment         | 3 (2%)                             | 3 (2%)               |
| Cardiac death                                | 4 (2%)                             | 2 (1%)               |
| Cerebrovascular accident                     | 4 (2%)                             | 0                    |
| Cerebral haemorrhage                         | 1 (1%)                             | 0                    |
| Pulmonary embolism (new primary lung cancer) | 1 (1%)                             | 0                    |
| Bronchopneumonia                             | 0                                  | 1 (1%)               |
| Thoracic aneurysm                            | 0                                  | 1 (1%)               |
| Decrease of health status (not progression)  | 1 (1%)                             | 0                    |
| Suicide                                      | 1 (1%)                             | 2 (1%)               |
| Euthanasia                                   | 0                                  | 1 (1%)               |
| Unknown                                      | 4 (2%)                             | 2 (1%)               |

\*One patient died suddenly (intercurrent death from unknown origin) while on protocol treatment before planned surgery, the investigator reported the serious adverse event as possibly related to protocol treatment.

**Table 2: Survival status and main causes of death**

the two groups, and 188 (52%) of all 364 patients had only one metastatic liver lesion (table 1). Of the 182 patients in each group, 171 were considered to be part of the eligible population for analysis and 152 underwent resection.

After a median follow-up of 8.5 years (IQR 7.6–9.5), 107 (59%) patients in the perioperative chemotherapy group had died compared with 114 (63%) in the surgery-only group (table 2). Only 29 patients were lost to follow-up at the time of the analysis (13 in the perioperative chemotherapy group and 16 in the surgery-only group). 15 patients in the perioperative chemotherapy group and 10 in the surgery-only group died from causes other than progressive disease, toxicity of the protocol treatment, and complications of protocol surgery (table 2). More details were provided by the investigators on other causes of death (appendix). Six patients per group were judged to have died from toxicity of protocol treatment, complications of protocol surgery, or toxicity of further cancer treatments (table 2). Of the three patients who died from further cancer treatments in the perioperative chemotherapy group, one died from liver failure after further surgery for progression, one died from septicaemia and urinary tract infection after second-line treatment for progression, one did not start protocol treatment, needed immediate surgery for colostomy prolapse, and died from sepsis due to change of biliary

See Online for appendix

|  | Patients (N) | Deaths (n [%]) | HR (95% CI)      | Median overall survival (months [95% CI]) | Estimated 5 year overall survival (% [95% CI]) | p value (log-rank)* |
|--|--------------|----------------|------------------|---|--|---------------------|
| Primary analysis in randomly assigned patients |              |                |                  |   |  |                     |
| Perioperative chemotherapy                     | 182          | 107 (59%)      | 0.88 (0.68–1.14) | 61.3 (51.0–83.4)                          | 51.2% (43.6–58.3)                              | 0.34                |
| Surgery only                                   | 182          | 114 (63%)      | 1.00             | 54.3 (41.9–79.4)                          | 47.8% (40.3–55.0)                              |                     |
| Sensitivity analyses                           |              |                |                  |   |  |                     |
| Eligible patients                              |              |                |                  |   |  |                     |
| Perioperative chemotherapy                     | 171          | 101 (59%)      | 0.87 (0.66–1.14) | 63.7 (52.7–87.3)                          | 52.4% (44.6–59.7)                              | 0.30                |
| Surgery only                                   | 171          | 109 (64%)      | 1.00             | 55.0 (41.9–79.4)                          | 48.3% (40.6–55.6)                              |                     |
| Resected patients                              |              |                |                  |   |  |                     |
| Perioperative chemotherapy                     | 152          | 84 (55%)       | 0.87 (0.64–1.17) | 77.5 (59.4–94.6)                          | 57.3% (49.0–64.8)                              | 0.35                |
| Surgery only                                   | 152          | 90 (59%)       | 1.00             | 73.3 (53.7–95.5)                          | 54.4% (46.1–62.0)                              |                     |

HR=hazard ratio. \*p value comparing overall survival between groups over the whole period of the study.

Table 3: Overall survival

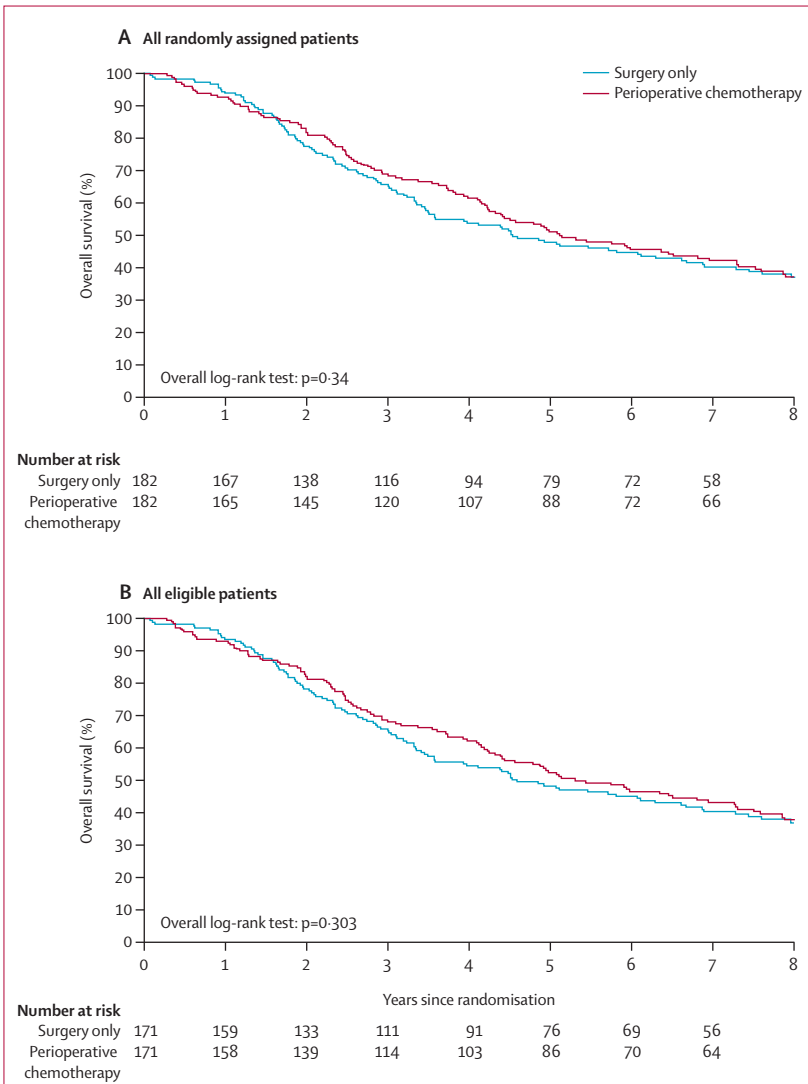


Figure 2: Overall survival  
Kaplan-Meier curves of overall survival in all randomly assigned patients (A) and all eligible patients (B) per treatment group.

stent. One patient in the perioperative chemotherapy group died suddenly (intercurrent death from unknown origin) while on protocol treatment before planned surgery, and the investigator reported the serious adverse event as possibly related to protocol treatment. In the surgery-only group, of the three patients who died from further cancer treatments, one died from septic shock while receiving FOLFIRI (folinic acid, fluorouracil, and irinotecan) after progression, one died from port-catheter-related sepsis after starting second-line chemotherapy for progression, and one died from complications of further surgery for progression. Causes of deaths were reviewed by the study coordinator to assess their possible relation to protocol treatment and further cancer treatments.

Overall survival in all randomly assigned patients did not differ significantly between groups (HR 0.88, 95% CI 0.68–1.14; p=0.34) nor did overall survival in eligible patients (HR 0.87, 95% CI 0.66–1.14; p=0.30; table 3). Kaplan-Meier curves for overall survival in all randomly assigned patients and all eligible patients are shown in figure 2. In all randomised patients, median overall survival was 61.3 months (95% CI 51.0–83.4) in the perioperative chemotherapy group and 54.3 months (41.9–79.4) in the surgery-only group. In the eligible population median overall survival was 63.7 months (52.7–87.3) and 55.0 months (41.9–79.4) in the perioperative chemotherapy and surgery-only groups, respectively. In all randomised patients, the absolute difference between groups in the proportion of patients with 5-year overall survival was 3.4% (95% CI –7.1 to 13.8); in all eligible patients it was 4.1% (–6.6 to 14.8).

The results of sensitivity analyses for overall survival are presented in the appendix. Updated results on PFS are displayed in table 4 and figure 3.

Of patients who had cancer progression (130 [71%] in the surgery-only group vs 124 [68%] in the perioperative chemotherapy group), 100 (77%) in the surgery-only group received chemotherapy as part of first treatment for progression compared with 73 (59%) patients in the



|                            | Patients (N) | Patients with progression events (n [%]) | HR (95% CI)      | Median PFS (months [95% CI]) | Estimated 3 year PFS (% [95% CI]) | p value (log-rank) |
|----------------------------|--------------|--|------------------|------------------------------|-----------------------------------|--------------------|
| Randomly assigned patients |              |  |                  |                              |                                   | 0.068              |
| Perioperative chemotherapy | 182          | 136 (75%)                                | 0.81 (0.64–1.02) | 20.0 (15.9–27.6)             | 38.2% (31.1–45.2)                 |                    |
| Surgery only               | 182          | 139 (76%)                                | 1.00             | 12.5 (9.7–17.7)              | 30.3% (23.7–37.1)                 |                    |
| Eligible patients          |              |  |                  |                              |                                   | 0.035              |
| Perioperative chemotherapy | 171          | 129 (75%)                                | 0.78 (0.61–0.99) | 20.9 (17.1–28.9)             | 39.0% (31.7–46.3)                 |                    |
| Surgery only               | 171          | 134 (78%)                                | 1.00             | 12.5 (9.7–18.2)              | 29.9% (23.2–36.9)                 |                    |

PFS was measured according to the protocol definition of the primary endpoint. HR=hazard ratio. PFS=progression-free survival.

**Table 4: Progression-free survival (long-term update)**

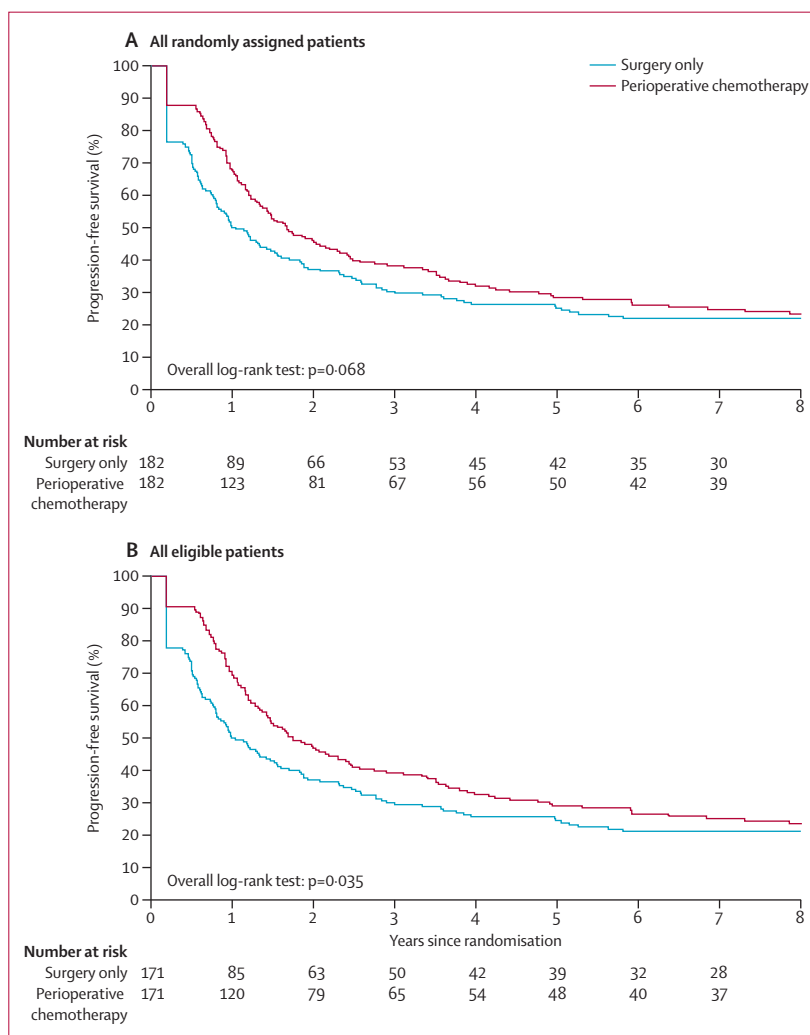
perioperative chemotherapy group ( $p=0.0029$ ), 52 (40%) in the surgery-only group versus 57 (46%) in the perioperative group had repeat surgery, three (2%) versus 11 (9%) had radiotherapy, and eight (6%) versus 14 (11%) received symptomatic treatment (appendix). Only data for first therapy for progression can be reported because data for further successive treatments were not obtained systematically.

The results of the competing-risk analysis and the analysis of cancer-specific survival showed a trend towards an increased difference in favour of the perioperative chemotherapy group, especially with respect to the long-term results, but this difference was not statistically significant (appendix).

## Discussion

Our long-term overall survival analysis showed that there was no significant difference in overall survival between perioperative chemotherapy and surgery alone; however, median overall survival was longer in the perioperative group, and a greater proportion of patients were alive at 5 years than in the surgery alone group (panel).

The failure to show a significant difference in overall survival might be explained by several reasons. First, this trial was designed to detect a PFS benefit and was not powered for overall survival, which was a secondary endpoint. The 4.1% absolute survival benefit at 5 years in the eligible population is similar to other positive adjuvant trials in primary colorectal cancer. The MOSAIC trial<sup>15</sup> reported a 4.2% overall survival benefit at 6 years of follow-up. Of patients with stage III colon cancer (672 patients in the FOLFOX4 group and 675 in the LV5FU2 [bolus plus continuous-infusion fluorouracil plus folinic acid] group), the probabilities of surviving at 6 years were 72.9% in the FOLFOX4 group and 68.7% in the LV5FU2 group (HR 0.80, 95% CI 0.65–0.97;  $p=0.023$ ). Because a relatively large sample size was used (1347 patients with stage III cancer), generating significant results, these findings led to the establishment of oxaliplatin as standard of care for adjuvant treatment of stage III colon cancer. The National Surgical Adjuvant Breast and Bowel Project (NSABP) C-07 trial<sup>16</sup> (FULV [fluorouracil plus



**Figure 3: Progression-free survival (long-term update)**

Kaplan-Meier curves of progression-free survival in all randomly assigned patients (A) and all eligible patients (B) per treatment group.

folinic acid] vs FLOX [FULV plus oxaliplatin]) and a multicentre colorectal cancer trial<sup>17</sup> comparing XELOX (capecitabine plus oxaliplatin) with bolus fluorouracil plus folinic acid as adjuvant therapy showed significant

**Panel: Research in context****Systematic review**

We did a systematic review to identify randomised studies on preoperative or postoperative chemotherapy for resectable liver metastases from colorectal cancer by searching electronic databases, scanning reference lists of articles, conference abstracts, and trial databases, and consulting experts in the field. We applied no language restrictions. We searched PubMed (January, 1966–December, 1999), Embase (January, 1991–December, 1999), and conference abstracts from the American Society of Clinical Oncology, European Cancer Organisation, and European Society For Medical Oncology with the search terms “colon or rect\* or colorectal”, “cancer or adenocarcinoma”, “liver metastasis”, “chemotherapy”, “randomized trial or random allocation or double-blind method”, and “humans”. We only selected prospectively randomised trials. We identified three studies,<sup>8–9,18</sup> one of which assessed intravenous chemotherapy.<sup>18</sup>

**Interpretation**

Neoadjuvant chemotherapy combined with surgery is evolving as the standard of care in many gastrointestinal malignancies. Our study is the largest ever trial to assess perioperative chemotherapy for resectable liver metastases. The difference in survival shown in this study is similar to that reported in other colorectal cancer studies into adjuvant treatment for stage II and III cancer. Therefore, although our results were not statistically significant, we believe that perioperative chemotherapy with FOLFOX4 (folinic acid, fluorouracil, and oxaliplatin) should be the reference treatment for resectable liver metastases. More studies into its effectiveness would be useful and clinicians should, if possible, participate in new trials for resectable liver metastasis from colorectal cancer, such as the BOS-2 trial (bevacizumab or panitumumab vs perioperative FOLFOX4 chemotherapy; NCT01508000).

increases in disease-free survival with the regimens containing oxaliplatin, but not in overall survival, as in our trial, despite more than 1800 patients included in both trials. Such numbers of patients are most likely impossible to accrue in trials on resectable colorectal cancer liver metastases. Future progress in this specialty will probably have to rely on surrogate endpoints for overall survival such as PFS or pathological response.

Next, the good long-term outcome in the surgery-only group meant that demonstration of a treatment benefit for perioperative chemotherapy was more difficult. 3-year PFS in the surgery-only group was 28·1% and higher than expected (21%) for all randomly assigned patients when the trial was originally designed.<sup>10</sup> Mitry and colleagues<sup>8</sup> reported a median overall survival of 62·2 months in patients randomly assigned to adjuvant chemotherapy after successful complete resection of colorectal liver or lung metastases compared with 47·3 months in the surgery-alone group.<sup>18</sup> In our trial, median overall survival was 73·3 months in the surgery-only group for resected patients (a comparable group to that in Mitry and colleagues' study<sup>18</sup>), which is even higher than the median overall survival reported by Mitry and colleagues in the adjuvant chemotherapy group. The high proportion of surviving patients reported in this trial might be due to high surgical quality or better preoperative imaging excluding smaller

metastases in the remaining liver or at other sites. Both studies included mainly patients with only one metastatic liver lesion (67% in the pooled analyses of Mitry and colleagues and 52% in our study).

Finally, overall survival is subject to competing risks in a long-term follow-up, as is PFS. The higher number of deaths that were not cancer related in the perioperative chemotherapy group than in the surgery group could have also contributed to the lack of difference between the two groups. Also, overall survival is a composite endpoint that is heavily affected by the treatment, either surgical or medical, of the recurrences. The fact that chemotherapy was administered more frequently at first progression to patients in the surgery-only group might have affected the overall survival results. The reason for this imbalance is unclear and we are restricted in our conclusion by the fact that data for treatments administered for second and further progressions were not obtained systematically.

So far, the evidence is unclear as to whether adjuvant (postoperative) chemotherapy only would be an alternative to the perioperative chemotherapy approach. The pooled analysis<sup>18</sup> done by Mitry and colleagues on 278 patients enrolled in two different randomised clinical trials showed a marginal statistical significance in favour of adjuvant chemotherapy with a fluorouracil bolus regimen after complete resection of colorectal cancer metastases. However, these results are difficult to compare with ours because in trials of postoperative chemotherapy, patients are randomly assigned after a successful surgical procedure, so the patient population is selected upfront. By comparison, the perioperative chemotherapy approach has been assessed in all patients initially judged to be resectable by imaging, including those with unsuccessful radical surgery. Furthermore, as already mentioned, median overall survival of resected patients in our surgery-only group was better than the median overall survival in the adjuvant chemotherapy group reported by Mitry and colleagues. Finally, we believe the chances for patients to receive chemotherapy as part of the treatment strategy for their resectable liver metastases are higher if chemotherapy is administered before surgery than after surgery.

Perioperative chemotherapy with FOLFOX4 improves PFS in the treatment of resectable colorectal cancer liver metastases. However, our trial was not powered a priori to detect a survival difference and in combination with the remarkably long survival of patients who received only surgery, we cannot report a statistically significant survival difference. Nonetheless, we believe that our findings do not modify the conclusion of the previous publication—ie, that perioperative chemotherapy with FOLFOX4 is compatible with major liver surgery and reduces the risk of events of progression-free survival in eligible patients.

**Contributors**

BN and PR were responsible for the design of the trial. BN, HS, BG, GJP, PMS, PR, JNP, WOB, ETW, MF-J, DJ, DM, RWP, EVC, WS, and TG enrolled patients and reviewed and approved the manuscript. MM and ET analysed the trial data, contributed to the writing of the manuscript, and approved the final version.

**Conflicts of interest**

HS has received honoraria from Roche and Pfizer and has consulted for Sanofi-Aventis, Amgen and Bayer. GJP has received grants from Sanofi-Aventis, Pfizer, Merck-Serono, Novartis, and Ipsen and has consulted for Sanofi-Aventis. PR has served on the advisory board, has consulted for Sanofi-Aventis and Pfizer and has received honoraria from Sanofi-Aventis. WOB has received research grants and honoraria from Sanofi-Aventis. ETW has received research grants from and has served on the advisory boards for Sanofi-Aventis, Merck, and Novartis. TG has consulted for Roche and Merck-Serono. All other authors declare that they have no conflict of interest.

**Acknowledgments**

The sponsor of this trial was the European Organisation for Research and Treatment of Cancer (EORTC). This clinical trial was supported by an educational grant from Sanofi-Aventis, by grants from the Norwegian and Swedish Cancer Societies, Cancer Research UK, and the Ligue Nationale Contre le Cancer (France) through the EORTC Charitable Trust and the US National Cancer Institute (grants 5U10-CA11488-28 to 5U10-CA11488-40). Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the National Cancer Institute. Sanofi-Aventis also offered free oxaliplatin supplies.

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