Adjuvant regional chemotherapy and systemic chemotherapy versus systemic chemotherapy alone in patients with stage II–III colorectal cancer: a multicentre randomised controlled phase III trial

Bernard Nordlinger, Philippe Rougier, Jean-Pierre Arnaud, Muriel Debois, Jaques Wils, Jean-Claude Ollier, Olivier Grobost, Philippe Lasser, Jacob Wals, Jerome Lacourt, Jean-François Seitz, Jose Guimares dos Santos, Harry Bleiberg, Rémy Mackiewickz, Thierry Conroy, Olivier Bouché, Thierry Morin, Liliana Baila, Eric van Cutsem, Laurent Bedenne

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Hospital Ambroise Pare, Assistance Publique Hôpitaux de Paris, Boulogne-Billancourt, France (Prof B Nordlinger MD, Prof P Rougier MD); **University Centre Hospital (CHU) d'Angers, Angers, France** (Prof J-P Arnaud MD); **European Organisation for Research and Treatment of Cancer, Brussels, Belgium** (M Debois MSc, L Baila MD); **Laurentius Hospital, Roermond, Netherlands** (J Wils MD); **Anticancer Centre (CAC) Paul Strauss, Strasbourg, France** (J-C Ollier MD); **Central Hospital (CH), Montlucon, France** (O Grobost MD); **Institute Gustave Roussy, Villejuif, France** (P Lasser MD); **Atrium Medical Centre, Henri, Heerlen, Netherlands** (J Wals MD); **Saint Marie Clinic, Chalon Sur Saone, France** (J Lacourt MD); **Institute Paoli Calmettes, Marseille, France** (Prof J-F Seitz MD); **Portugese Institute of Oncology, Porto, Portugal** (Prof J Guimares dos Santos MD); **Institute Jules Bordet, Brussels, Belgium** (Prof H Bleiberg MD); **Pastmen Clinic, Valence, France** (R Mackiewickz MD); **CHU, Vandoeuvre-les-Nancy, France** (Prof T Conroy MD); **CHU, Reims, France** (O Bouché MD); **CHU, Tarbes, France** (T Morin MD); **University Hospital, Gasthuisberg, Leuven, Belgium** (Prof E van Custem MD); **and CHU, Dijon, France** (Prof L Bedenne)

Correspondence to:
Prof Bernard Nordlinger, Hospital Ambroise Pare, 9 Avenue Charles de Gaulle, Boulogne-Billancourt, Cedex 92104, France
bernard.nordlinger@apr.aphp.fr

Summary

Background **Systemic adjuvant chemotherapy can improve overall survival and reduce the incidence of distant metastases for patients with advanced colon cancer. This study aimed to investigate whether regional chemotherapy (given by intraperitoneal or intraportal methods) combined with systemic chemotherapy was more effective than was systemic chemotherapy alone in terms of survival and recurrence for patients with stage II–III colorectal cancer. The study also compared systemic chemotherapy with fluorouracil and folinic acid with that of fluorouracil and levamisole.**

Methods **During surgery, 753 patients with stage II–III colorectal cancer were randomly assigned to systemic chemotherapy alone (379 with fluorouracil and folinic acid, and 374 with fluorouracil and levamisole), and 748 to postoperative regional chemotherapy with fluorouracil followed by systemic chemotherapy with fluorouracil and folinic acid (n=368) or with fluorouracil and levamisole (n=380). Regional chemotherapy was given intraperitoneally (n=415) or intraportally (n=235) according to institution. The primary endpoint was 5-year overall survival. Secondary endpoints were 5-year disease-free survival and toxic effects. Analyses were by intention to treat.**

Findings **Median follow-up was 6·8 years (range 0·0–10·1). 5-year overall survival was 72·3% (95% CI 69·0–75·6) for patients assigned regional and systemic chemotherapy, compared with 72·0% (68·7–75·3) for those assigned systemic chemotherapy alone (hazard ratio [HR] 0·97 [0·81–1·15], p=0·69). 5-year overall survival for all patients assigned fluorouracil and levamisole was 72·0% (68·7–75·2) compared with 72·3% (69·0–75·6) for all those assigned fluorouracil and folinic acid (HR 0·98 [0·82–1·17], p=0·81). The hazard ratios for 5-year disease-free survival were 0·94 (0·80–1·10) for regional versus non-regional treatment, and 0·92 (0·79–1·08) for all fluorouracil and levamisole versus fluorouracil and folinic acid. Grade 3–4 toxic effects were low in all groups.**

Interpretation **Fluorouracil-based regional chemotherapy adds no further benefit to that obtained with systemic chemotherapy alone in patients with advanced colorectal cancer.**

Introduction

Randomised trials[1–9] have shown that systemic adjuvant chemotherapy can improve overall survival and reduce the incidence of distant metastases for patients with stage III colon cancer, and possibly for those with stage II disease. Fluorouracil combined with folinic acid or levamisole was the first standard adjuvant treatment accepted for patients with resected high-risk colon cancer.[10–16] However, new chemotherapy agents, such as capecitabine, oxaliplatin, and irinotecan, have shown encouraging results when used in adjuvant systemic-therapy regimens for patients with high-risk colorectal cancer.[17–19] Oxaliplatin combined with fluorouracil and folinic acid is more effective than fluorouracil and folinic acid alone[17] in patients with stage II–III carcinoma of the colon when given after complete resection of the primary tumour. Irinotecan was also assessed in combination with fluorouracil and folinic acid in the PETACC3 (Pan European Trials for Adjuvant Treatment of Colon Cancer) study.[19]

Adjuvant chemotherapy usually starts within weeks of surgery and is given for 6 months.[16,20] After a study by Taylor in 1985,[21] a meta-analysis of ten studies[22] of adjuvant chemotherapy delivered intraportally suggested that early regional treatment of malignant disease reduced the likelihood of liver metastases and thus increased overall survival. Regional chemotherapy delivers high concentrations of cytotoxic chemotherapy directly to the site of the tumour, allowing more effective targeting and inhibition of the development of metastases. In colorectal cancer, tumour cells spread haematogenously via the portal circulation, making the liver the first site of metastases in most patients.[23] Intraportal delivery of chemotherapy targets micrometastases that might spread to the liver via the portal system.

Intraperitoneal chemotherapy is a less well known cytotoxic treatment that is delivered into the peritoneal cavity, where up to 60% of the total dose is absorbed

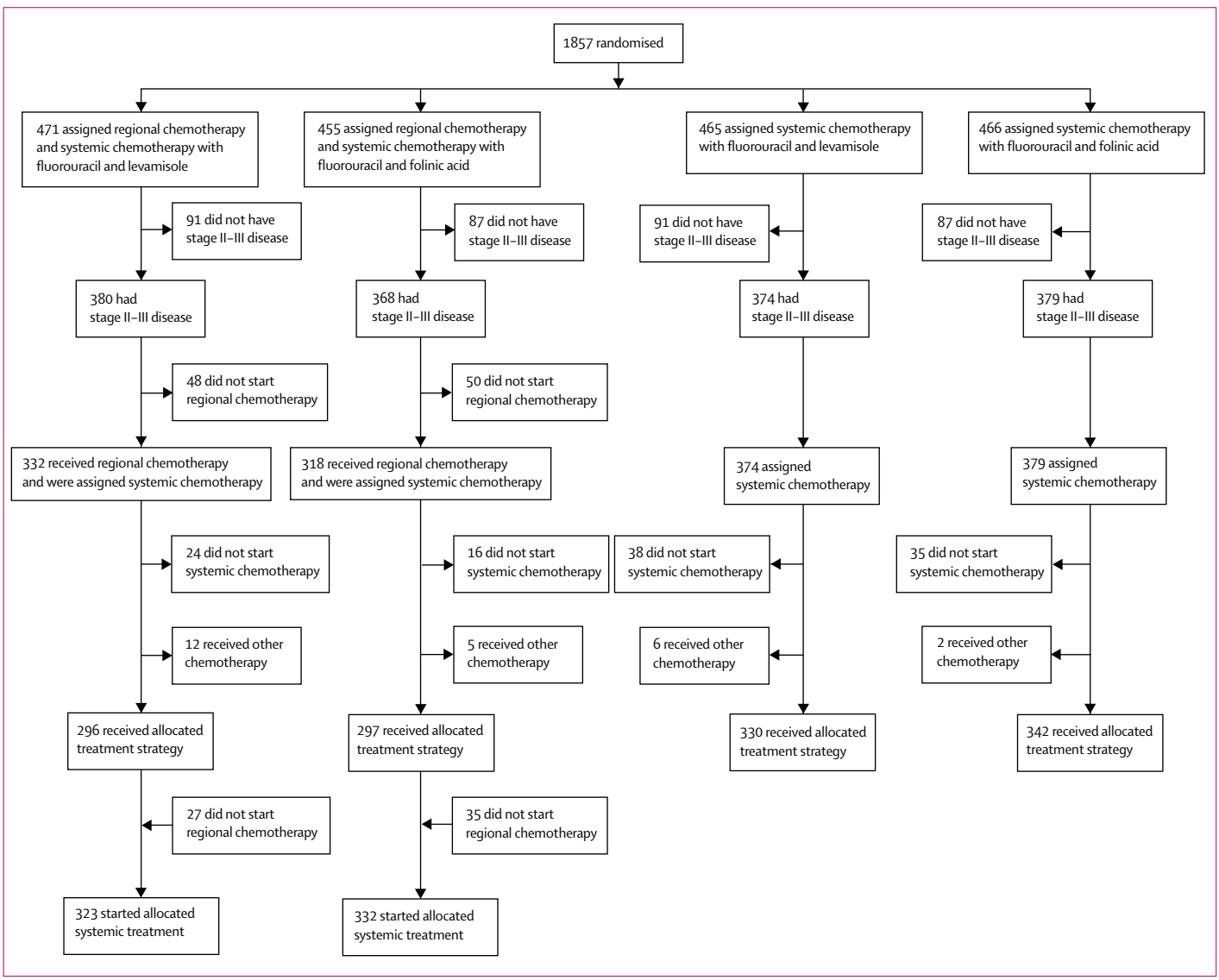

Figure 1: **Trial profile**

through the portal route to reach the liver.[24] Hepatic extraction of fluorouracil can be as high as 90%, and thus only a small amount reaches the systemic circulation, keeping systemic toxic effects to a minimum. In a randomised phase III study[25] of 267 patients, intraperitoneal chemotherapy alone did not affect survival compared with that recorded for surgery alone, but did reduce the risk of recurrence in stage II disease.[25] Theoretically, intraperitoneal chemotherapy combines the effect of intraportal chemotherapy on the liver with a direct effect on the peritoneum (a site with a high frequency of recurrence) and the resection site. Data therefore suggest that benefit can be derived by the combination of locoregional therapy, in particular by an intraperitoneal route, and systemic therapy to decrease the occurrence of local and distant metastases.

The aim of this international, multicentre phase III trial was to investigate whether addition of regional chemotherapy immediately after surgery to a standard systemic adjuvant chemotherapy regimen could improve survival and reduce recurrence compared with adjuvant systemic chemotherapy alone. Regional chemotherapy was given either intraperitoneally or intraportally in

	Regional and systemic chemotherapy		Systemic chemotherapy alone	
	Fluorouracil and levamisole (n=471)	Fluorouracil and folinic acid (n=455)	Fluorouracil and levamisole (n=465)	Fluorouracil and folinic acid (n=466)
I	91	87	91	87
II	182	197	190	197
III	198	171	184	182

Table 1: **Tumour stage of all patients assigned treatment**

accordance with the standard practice of the participating institution. Furthermore, the trial aimed to compare two established systemic regimens—fluorouracil and levamisole[10] and fluorouracil and folinic acid.[8]

Methods

Patients

Eligibility criteria for enrolment were: histologically confirmed adenocarcinoma of the colon or rectum treated with curative intent (ie, R0 resection); no evidence of metastatic disease, as assessed abdominal ultrasonography and chest radiography before surgery and by inspection and palpation during surgery (ie, stage M0); stage II–III disease; white-blood-cell count of more than 4×10^9/L; platelet count of more than 100×10^9/L; serum creatinine less than 1·25 times upper limit of normal; bilirubin within normal range; no history of substantial coronary insufficiency; absence of non-malignant systemic disease (eg, cardiovascular, renal, and hepatic); precluding chemotherapy or long-term follow-up; no psychiatric or addictive disorders; no history of other tumour except adequately treated and cured squamous-cell or basal-cell carcinoma of the skin, in-situ carcinoma of the cervix that had been treated only with surgery, well differentiated thyroid carcinoma, colorectal carcinomas, and breast cancers cured and free of relapse for more than 5 years. All patients had to be able to attend follow-up visits every 6 months and had to be well enough at randomisation to receive chemotherapy after resection. All patients provided written informed consent, and the study was done with approval of local ethics committees. The primary endpoint was 5-year overall survival; secondary endpoints were 5-year disease-free survival and toxic effects. The trial was unblinded.

Treatment

During surgery, 926 patients were randomly assigned to postoperative regional chemotherapy with fluorouracil (Fluorouracil Roche®, Roche, Neuilly sur Seine, France) followed by systemic chemotherapy with fluorouracil and folinic acid (Elvorine®, Wyeth Lederle, Rungis, France; n=455) or with fluorouracil and levamisole (Solaskil®, Sanofi-Aventis, Paris, France; n=471), and 931 patients to systemic chemotherapy alone (466 with fluorouracil and folinic acid, and 465 with fluorouracil and levamisole). At this stage, 178 patients in the first group were found not to have stage II–III disease and were excluded, as were 178 in the systemic-chemotherapy-alone group, as per protocol. These patients were, however, followed up for tumour recurrence and survival, but are not reported here. Regional chemotherapy was given intraperitoneally

	Regional and systemic chemotherapy		Systemic chemotherapy alone	
	Fluorouracil and levamisole (n=380)	Fluorouracil and folinic acid (n=368)	Fluorouracil and levamisole (n=374)	Fluorouracil and folinic acid (n=379)
Age (years)				
Median (range)	64·0 (56·0–74·0)	64·0 (57·0–69·0)	63·0 (56·0–69·0)	63·0 (54·0–70·0)
Sex				
Men	196 (52%)	214 (58%)	184 (49%)	202 (53%)
Women	184 (48%)	154 (42%)	190 (51%)	177 (47%)
Operative procedure*				
Colon resection	244 (64%)	233 (63%)	238 (64%)	235 (62%)
Anterior rectal resection	74 (19%)	72 (20%)	73 (20%)	74 (20%)
Abdomino-perineal resection	22 (6%)	22 (6%)	19 (5%)	22 (6%)
Other	40 (11%)	40 (11%)	44 (12%)	48 (13%)
Missing data	0	1 (<1%)	0	0
Lymph nodes removed				
Median (range)	11 (1–81)	10 (1–89)	10 (1–51)	12 (1–52)
Complications (number of patients)				
Associated with surgery	50 (13%)	60 (16%)	40 (11%)	37 (10%)
Tissue invasion				
Nervous	54 (14%)	39 (11%)	48 (13%)	44 (12%)
Vascular	99 (26%)	92 (25%)	85 (23%)	90 (24%)
Tumour site				
Rectum	62 (16%)	54 (15%)	57 (15%)	61 (16%)
Colon	277 (73%)	278 (76%)	281 (75%)	280 (74%)
Right	93 (34%)	94 (33%)	90 (32%)	92 (33%)
Transverse	21 (8%)	28 (10%)	23 (8%)	34 (12%)
Left	156 (56%)	154 (55%)	163 (58%)	148 (53%)
Multiple	7 (3%)	2 (<1%)	5 (2%)	6 (2%)
Colon and rectum	7 (2%)	1 (<1%)	1 (<1%)	5 (1%)
Missing data	34 (9%)	35 (10%)	35 (9%)	33 (9%)

*Percentage might not add to 100 because of rounding.

Table 2: **Baseline characteristics of patients with stage II–III disease**

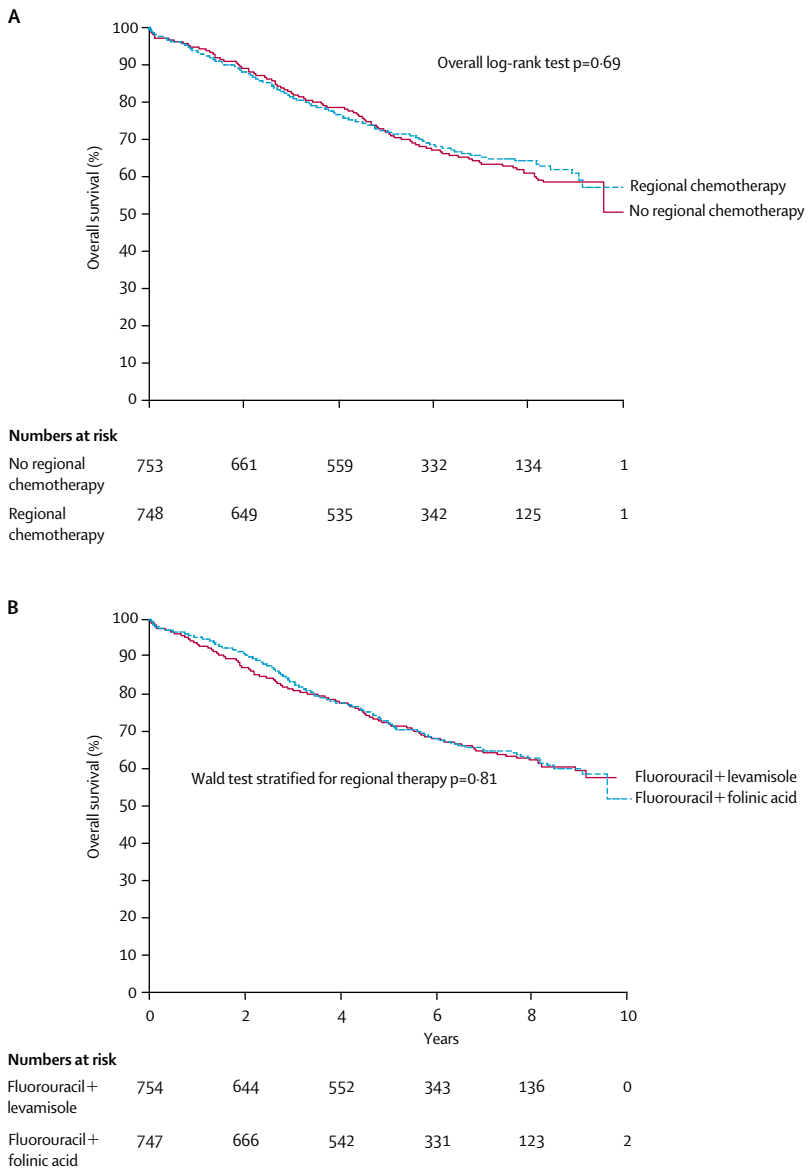

Figure 2: **Overall survival**
(A) By regional chemotherapy versus systemic chemotherapy. (B) By fluorouracil and levamisole versus fluorouracil and folinic acid.

(n=415) or intraportally (n=235) in accordance with standard practice of the participating institution. Patients were randomised centrally by use of phone or computer by the European Organisation for Research and Treatment of Cancer and Fédération Francophone de Cancérologie Digestive data centres. Patients were stratified by institution and localisation of the primary tumour (ie, colon or rectum).

Regional chemotherapy with fluorouracil was given intraperitoneally for 6 days or intraportally for 7 days. The catheter for intraportal delivery was inserted during surgery and chemotherapy started immediately after surgery with the following schedule: 500 mg/m² fluorouracil every 24 h (ie, 3500 mg/m² planned total dose) and 5000 IU heparin (Heparine Sodique®, Dakota Pharmaceutical Laboratory, Creteil, France) every 24 h for days 1–7 after surgery. The catheter for intraperitoneal delivery was a calibre 12 French silicon jejunostomy tube that was inserted during surgery through the abdominal wall; the tip was left free in the peritoneal cavity. The tube was secured to the abdominal wall and care was taken to avoid leakage of fluid during treatment. The abdominal wound was closed very carefully. Intraperitoneal chemotherapy was started as soon as the patient's condition allowed it—ie, after the patient passed gas and had no intraperitoneal complications, usually 4–10 days after surgery. 600 mg/m² fluorouracil was diluted in 1·5 L dialysis fluid and infused over 3 h with a pump on days 4–9 after surgery. The fluid was not recovered, since it was absorbed in the peritoneum. The amount of dialysis fluid infused in the peritoneum was calculated from the total amount of intravenous infusion, with the aim of delivering a planned total dose of 3600 mg/m² fluorouracil. Wide-spectrum prophylactic antibiotic therapy was given in accordance with practice at the participating institutions.

Systemic chemotherapy was planned to be started no later than 35 days after surgery (after histological staging of the tumour). Patients allocated fluorouracil and levamisole were scheduled to receive 450 mg/m² fluorouracil a day given by intravenous bolus on days 1–5 followed by this dose once a week from day 28, and to 50 mg levamisole given orally three times a day on days 1–3 and then for 3 days every 2 weeks. Treatment was continued for a maximum of 24 weeks, or until disease progression (as assessed clinically, radiologically, or both), occurrence of severe toxic effects, or patient refusal. Patients allocated fluorouracil and folinic acid were scheduled to receive 375 mg/m² fluorouracil given as an intravenous infusion for 30 min a day followed immediately by 100 mg/m² folinic acid given as an intravenous bolus injection for 5 days every 4 weeks and repeated from day 28 for a maximum of six cycles (ie, 24 weeks' treatment). The levogyre (L) form of folinic acid was used in this regimen. Patients were examined every 4 weeks during treatment, and blood counts were done every 2 weeks.

If, on the first day of any treatment, the neutrophil count was less than 2000×10^6/L or platelets were less than 100×10^9/L, systemic treatment was delayed for a maximum of 1 week, and blood counts were taken twice a week. The doses of treatment were modified if counts did not return to within the normal range. The dose of fluorouracil was reduced to 75% of the initial dose for WHO grade 1 neutrophils or platelets or for WHO grade 3 mucositis and diarrhoea, and to 50% for WHO grade 2 neutrophils or platelets. Treatment was discontinued if the patient developed grade 2 or higher neutrophils or platelets, or grade 4 diarrhoea or mucositis.

Follow-up after completion of treatment was done every 3 months during the first year, every 6 months during the second year, and every year thereafter. Patients who had recurrence of disease received any appropriate treatment. At every follow-up visit clinical investigations, blood counts, liver ultrasonography or CT scans, and chest radiography were scheduled. Other investigations were done at the discretion of the participating centres. In accordance with the protocol, all patients with rectal cancer had radiotherapy by use of the declared policy of the institution.

Statistical analysis

Overall survival was defined as the time from randomisation to death from any cause. Patients who are alive were censored at the date of last documented visit. Disease-free survival was defined as the time from randomisation to disease recurrence or death from any cause, whichever occurred first. Patients alive and free of disease at last follow-up were censored at the date of last visit. A total of 532 events were needed to detect a 30% difference in the median duration of survival for each of the two treatment comparisons, from 6·78 years to 8·81 years (hazard ratio [HR] for calculation of sample size 0·769), by use of a two-sided log-rank test with α=0·05 and β=0·15 (ie, power=0·85).

The effect of systemic chemotherapy was analysed after stratification for regional chemotherapy. Overall survival and disease-free survival were estimated by use of the Kaplan-Meier technique. Differences in survival were compared with the log-rank test on the basis of intention-to-treat analysis.

Role of the funding source

The sponsor of the trial had no role in the study design; collection, analysis, or interpretation of data; or the writing of the report. The corresponding author had full access to all data in the study and had final responsibility to submit the paper for publication.

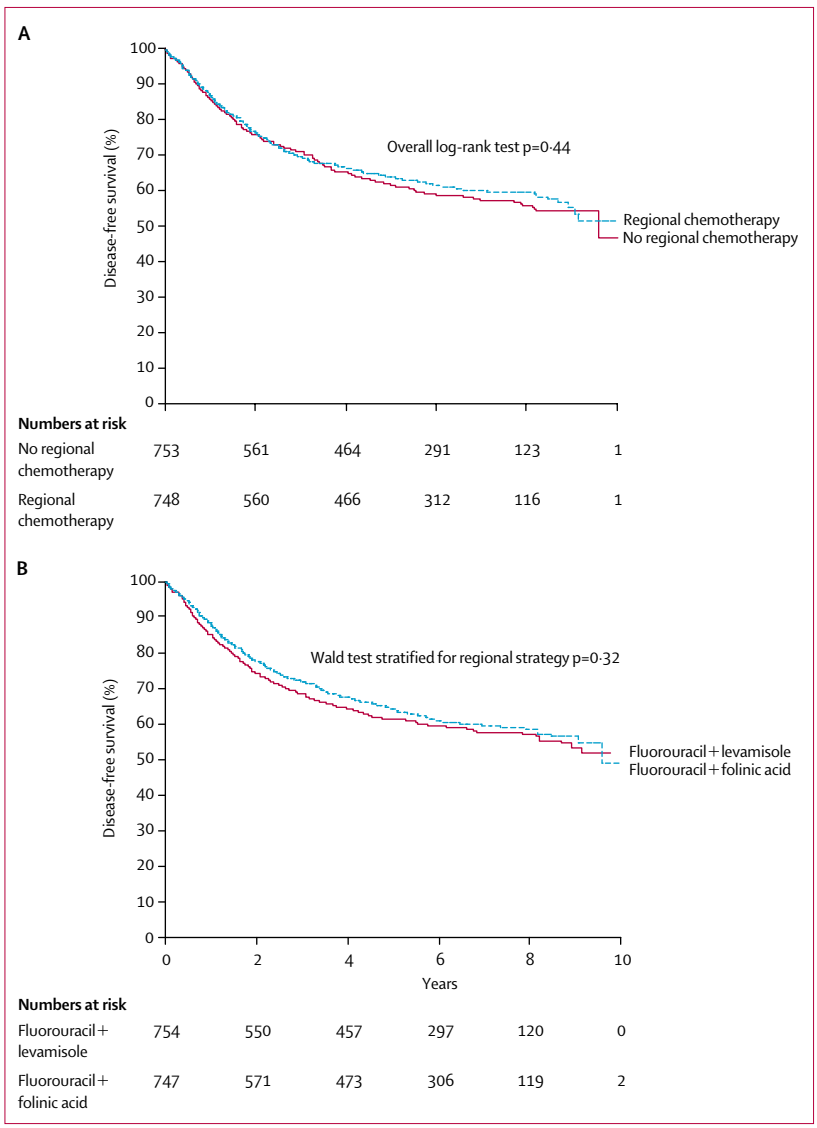

Figure 3: **Disease-free survival**
(A) By regional and systemic chemotherapy alone. (B) By fluorouracil and levamisole versus fluorouracil and folinic acid.

Results

Between Feb 1, 1993, and June 30, 1998, 1857 patients were enrolled into this multicentre study (figure 1). 634 patients were from institutions affiliated to the European Organisation for the Research and Treatment of Cancer, and 1223 from institutions from the Fédération Francophone de Cancérologie Digestive. 1501 patients had pathologically confirmed stage II or III colorectal carcinoma (table 1), 748 of whom were assigned regional and systemic chemotherapy and 753 of whom were assigned systemic chemotherapy alone (figure 1). Table 2 shows baseline characteristics of randomised groups.

5-year overall survival was 72·3% (95% CI 69·0–75·6) for patients assigned regional and systemic chemotherapy, compared with 72·0% (68·7–75·3) in those assigned systemic chemotherapy alone (HR 0·97 [0·81–1·15], p=0·69). 5-year overall survival for all patients assigned fluorouracil and levamisole was 72·0% (68·7–75·2) compared with 72·3% (69·0–75·6) for all those assigned fluorouracil and folinic acid (HR 0·98 [0·82–1·17], p=0·81; figure 2). Disease-free survival at 5 years was 63·9% (60·4–67·4) for patients allocated regional treatment compared with 61·4% (57·9–64·9) for those who were not allocated regional treatment (HR 0·94 [0·80–1·10], p=0·44). 5-year disease-free survival for all patients assigned fluorouracil and levamisole was 61·3% (57·8–64·8) compared with 64·0% (60·5–67·5) for all those assigned fluorouracil and folinic acid (HR 0·92 [0·79–1·08], p=0·32; figure 3). Comparison of patients with stage II disease with those who had stage

	Intraportal chemotherapy (n=235)	Intraperitoneal chemotherapy (n=415)
Full dose	201 (86%)	317 (76%)
Median relative dose intensity (range)	99·0% (24·9–137·5)	98·3% (13·2–125·1)
Abdominal complications	22 (9%)	41 (10%)
WHO grade 3–4 toxic effects	17 (7%)	24 (6%)

Data are for patients who started regional chemotherapy.

Table 3: **Regional chemotherapy: relative dose intensity and complications**

III disease, and of patients with colon cancer with those who had rectal cancer, showed that overall survival and disease-free survival were much the same for both groups (data not shown). Moreover, for all patients with stage II or III disease and for patients only with stage II disease, overall survival and disease-free survival did not differ with the route of regional treatment (data not shown). Of the 499 patients who died, 338 (68%) died from malignant disease. Disease progression was noted for 479 (32%) patients.

120 (48%) of 248 patients with stage II or III adenocarcinoma of the rectum, or colon and rectum, received radiotherapy before surgery, and 21 (8%) of 248 after surgery. 650 (87%) of 748 patients with stage II or III disease who were allocated regional chemotherapy received it. The most common reason for not starting regional treatment was that the surgeon thought that the postoperative status of the patient was not yet clear, and that it was not safe to start chemotherapy shortly after surgery as required by the protocol. 1327 (88%) of 1501 patients with stage II or III disease started the systemic chemotherapy that had been assigned at randomisation, and 1265 (84%) started the treatment they were assigned at randomisation (figure 1). The median follow-up was 6·8 years (range 0·0–10·1). 270 (18%) of 1501 patients were followed for more than 8 years, and 117 (8%) for more than 9 years.

Of the 650 patients who started regional chemotherapy, 415 (64%) received intraperitoneal treatment and 235 (36%) intraportal treatment. 518 patients (80%) received the full dose of regional chemotherapy (table 3). The median time to starting intraportal treatment was 1 day (range 0–8). 135 patients (57%) delayed starting intraportal treatment for 1–8 days, but only 43 (18%) had a delay exceeding 1 day. The median time to start intraperitoneal treatment was 7 days (0–38). In 33 (8%) patients the start of intraperitoneal chemotherapy was delayed by more than 10 days. Both intraperitoneal and intraportal regional chemotherapy had about the same proportion of patients with complications.

Four of the 17 adverse events in the intraportal group and five of the 24 in the intraperitoneal group were judged as unrelated to chemotherapy (table 3). The following toxic effects were recorded in the intraportal group: haematological (n=1); intra-abdominal abscess or peritonitis (n=2); hepatitis (n=1); diarrhoea or vomiting (n=2); intra-abdominal bleeding (n=1); anastomotic fistula (n=1); evisceration (n=2); intestinal obstruction (n=2); portal-vein thrombosis (n=2); cardiovascular event (n=1); precordialgia (n=1); and cholecystitis (n=1). Three patients, respectively, with abdominal infection, anastomotic fistula, and parietal haemorrhage died. In the intraperitoneal group, the following were noted: haematological (n=2); intra-abdominal abscess or peritonitis (n=3); fever of unknown origin (n=1); diarrhoea or vomiting (n=3); anastomotic fistula (n=3); intestinal obstruction (n=3); gastrointestinal bleeding (n=1); abdominal pain (n=6); cholecystitis (n=1); and cardiac arrhythmia (n=1).

The median total dose of fluorouracil was 6090 mg (range 412–8400) in the intraportal group and 6000 mg (400–9100) in the intraperitoneal group. The dose intensity defines the dose delivered per time unit, expressed as mg/m^2 per week. The relative dose intensity is a ratio of the dose intensity received to the

	Fluorouracil and levamisole		Fluorouracil and folinic acid	
	Regional and systemic chemotherapy (n=323)	Systemic chemotherapy only (n=330)	Regional and systemic chemotherapy (n=332)	Systemic chemotherapy only (n=342)
Number of cycles				
Median (range)	6 (1–6)	6 (1–6)	6 (1–6)	6 (1–6)
Treatment*				
Full dose, no delay	181 (56%)	185 (56%)	185 (56%)	207 (61%)
Full dose, delay	52 (16%)	52 (16%)	53 (16%)	51 (15%)
Dose reduced, no delay	39 (12%)	43 (13%)	31 (9%)	39 (11%)
Dose reduced, delayed	17 (5%)	11 (3%)	14 (4%)	13 (4%)
Dose not given	33 (10%)	39 (12%)	49 (15%)	32 (9%)
Missing data	1 (<1%)	0	0	0
Relative dose intensity, median (range)				
Fluorouracil	99·5% (19·0–79·2)	98·8% (36·4–129·4)	98·0% (47·0–127·3)	98·7% (19·9–248·2)
Levamisole	100·0% (14·3–200·0)	100·0% (7·1–200·0)	NA	NA
Folinic acid	NA	NA	97·8% (22·3–189·1)	98·8% (19·3–238·8)

NA=not applicable. *Might not add to 100% because of rounding.

Table 4: **Systemic chemotherapy in patients with stage II–III disease who started allocated treatment: relative dose intensity**

	Fluorouracil and levamisole		Fluorouracil and folinic acid	
	Regional and systemic chemotherapy (n=323)	Systemic chemotherapy only (n=330)	Regional and systemic chemotherapy (n=332)	Systemic chemotherapy only (n=342)
Haemological				
Leucocytes	8 (2%)	7 (2%)	2 (<1%)	10 (3%)
Platelets	2* (<1%)	0	2 (<1%)	0
Gastrointestinal				
Oral	1* (<1%)	2 (<1%)	12 (4%)	14 (4%)
Nausea and vomiting	3 (<1%)	5 (2%)	8* (2%)	14 (4%)
Diarrhoea	6 (2%)	8 (2%)	26 (8%)	28 (8%)
Other				
Cutaneous	1 (<1%)	0	3 (<1%)	1 (<1%)
Hair loss (grade 3)†	1 (<1%)	0	2 (<1%)	2 (<1%)
Infection (grade 3)†	1 (<1%)	0	2 (<1%)	3 (<1%)
Cardiac	2 (<1%)	1 (<1%)	3 (<1%)	0
Neurological (grade 4)‡	0	1 (<1%)	0	0
Constipation	0	1 (<1%)	1 (<1%)	1 (<1%)
Other	16 (5%)	13* (4%)	7 (2%)	7 (2%)

*One patient died from these effects. †No grade 4 toxic effects. ‡No grade 3 toxic effects.

Table 5: **Systemic chemotherapy in patients with stage II–III disease who started allocated treatment: grade 3–4 toxic effects**

theoretical dose intensity specified in the protocol (table 3). Three (1%) patients in the intraportal group and four (1%) patients in the intraperitoneal group had a relative dose intensity of more than 115% (this intensity might be more than 100% becuase of overestimation of body surface area between investigators and data-centre recalculations).

Of the 1327 patients who started systemic chemotherapy allocated at randomisation, 1126 (85%) received six cycles of treatment as per protocol: 544 (83%) who were assigned fluorouracil and levamisole, and 582 (86%) who were assigned fluorouracil and folinic acid. The median time to starting systemic chemotherapy was 27 days (range 3–391) in the 672 patients who did not receive regional chemotherapy and 31 days (0–118) in the 655 patients who received regional chemotherapy (one patient started systemic chemotherapy before randomisation). 175 patients (13%) started systemic treatment more than 35 days after surgery, although 101 (58%) of these patients started before day 45 after surgery. Most patients with stage II or III disease who started the systemic chemotherapy assigned at randomisation had a relative dose intensity of higher than 98% (table 4). Of the 1327 patients who started systemic chemotherapy, 214 (33%) patients assigned fluorouracil and levamisole and 201 (30%) patients assigned fluorouracil and folinic acid had at least one cycle delayed, received a reduced dose, or both.

The most commonly recorded adverse events after systemic treatment were haematological or gastrointestinal (table 5). Two deaths from toxic effects were reported: one patient assigned regional chemotherapy and systemic chemotherapy with fluorouracil and levamisole died from oral toxic effects and neutropenia, and one patient allocated systemic chemotherapy only with fluorouracil and levamisole had hypokalaemia and severe diarrhoea, and died from cardiac arrest. Although oral toxic effects, nausea, and diarrhoea were more frequent in patients assigned fluorouracil and folinic acid, groups did not differ substantially in the frequency of toxic effects. The main reasons for stopping systemic treatment were patient refusal (61 [5%] patients), major toxic effects (41 [3%] patients), and disease progression (39 [3%] patients).

10 years after the start of the study, 499 (33%) patients with stage II or III disease had died. The final analysis was done despite the required 532 deaths not being obtained. This decision was made because deaths were occurring slower than expected, the trial was running beyond the planned deadlines, and because under the conditions initially defined by the protocol, 83% power could be achieved with 499 deaths.

Discussion

This trial has shown that postoperative adjuvant regional chemotherapy before systemic chemotherapy does not increase overall survival or disease-free survival compared with systemic chemotherapy alone in patients with stage II or III colorectal carcinoma. Moreover, folinic acid was not more effective than was levamisole when both agents were combined with fluorouracil.

Previous comparisons of the use of regional adjuvant chemotherapy with systemic therapy with that of systemic chemotherapy alone for advanced colorectal cancer have shown conflicting results.[22] This trial has assessed issues of sample size and timing of treatment. Although some delays were reported, regional chemotherapy was generally delivered per protocol—ie, on the day of surgery for intraportal treatment and between 4 days and 10 days after surgery for intraperitoneal treatment.

Homogeneous distribution of the drug within the peritoneal cavity is a key factor for intraperitoneal chemotherapy,[26] for which 1–2 L of fluid are needed. Furthermore, intraperitoneal adhesions resulting from surgery or from peritoneal carcinomatosis might limit diffusion of the chemotherapeutic agent. In this trial, intraperitoneal chemotherapy was given within a few days after surgery, before adhesions could develop fully. Distribution of the chemotherapeutic agents in the peritoneal cavity was verified to be homogeneous by ultrasonography or CT scanning.

Comparison of intraperitoneal fluorouracil after surgery with resection alone in patients with stage II or III colorectal cancer by Vaillant and colleagues[25] showed that adjuvant fluorouracil increased 5-year disease-free survival in patients with stage II cancer but not in those with stage III cancer. The researchers concluded that regional chemotherapy is effective in patients with disease still confined to the abdomen, whereas it might not be sufficient in patients with metastatic lymph nodes. Thus combination of intraperitoneal and intraportal treatment might ensure better control of cancer spread.

The lack of survival benefit for regional chemotherapy combined with systemic chemotherapy in this trial suggests that no cumulative effects were obtained. Patients given chemotherapy with either fluorouracil and levamisole or with fluorouracil and folinic acid might respond irrespective of how it is given. By contrast with the benefit of regional chemotherapy noted in the study by Vaillant and colleagues,[25] the lack of benefit recorded in the trial reported here could have been because systemic chemotherapy was given to all treatment groups. Sugarbaker and co-workers[27] did a randomised comparison of adjuvant systemic chemotherapy and intraperitoneal regional chemotherapy, and noted no survival benefit but a reduced frequency of peritoneal carcinomatosis in patients assigned intraperitoneal chemotherapy. Scheithauer and colleagues[28] compared adjuvant systemic chemotherapy with fluorouracil and levamisole with systemic chemotherapy with the same agents and intraperitoneal regional chemotherapy given to 236 patients during the perioperative period and on days 1 and 3 of every treatment cycle every 4 weeks for 6 months. The researchers concluded that survival did not differ between groups. Labianca and colleagues[29] randomly assigned 1084 patients with stage II or III colon cancer to systemic infusion of fluorouracil and folinic acid for 6 months, portal-vein infusion of fluorouracil for 7 days, or to a combination of the two regimens, and reported that the combined regimen had no benefit over either of the single regimens. These data suggest that regional chemotherapy combined with systemic chemotherapy confers no additional survival advantages over that obtained with systemic chemotherapy alone.

Although regional chemotherapy has not fulfilled its initial promise in the adjuvant setting it has become a very useful aid in the treatment of patients with colorectal cancer who have isolated liver metastases. In this setting hepatic arterial infusion is the treatment of choice and can decrease tumour size before surgery or adjuvant chemotherapy.[30]

The trial reported here shows no difference in overall or disease-free survival between fluorouracil and levamisole, and fluorouracil and folinic acid. These findings are consistent with those of the INT-0089 trial,[4] in which patients with high-risk stage II and stage III colorectal carcinoma were randomly assigned to postoperative fluorouracil and levamisole (standard treatment), fluorouracil and low-dose folinic acid, fluorouracil and high-dose folinic acid, or to fluorouracil, folinic acid, and levamisole. The researchers reported no differences between groups, except that overall survival was significantly increased for patients with stage III disease who were assigned fluorouracil, folinic acid, and levamisole compared with those assigned fluorouracil and levamisole (65% *vs* 60%, p=0·0054).

Several studies have reported in favour of either levamisole or folinic acid combined with fluorouracil for the adjuvant treatment of colorectal carcinoma.[4,5,16] However, this trial shows that these two regimens do not differ in effectiveness. The dose of L-folinic acid used in our study (100 mg/m^2 per day) theoretically has the same activity as the 200 mg/m^2 per day DL-folinic acid used in other studies.

Fluorouracil combined with folinic acid is a basic regimen for adjuvant treatment of colorectal carcinoma after resection. Modified doses and method of use (ie, bolus *vs* infusion) have improved its effectiveness. More commonly, fluorouracil and folinic acid are combined with cytotoxic drugs such as irinotecan and oxaliplatin.

An alternative to the standard regimens of fluorouracil and folinic acid for adjuvant treatment is oral therapy with fluoropyrimidines such as capecitabine,[31,32] and is being assessed in several trials.

After results from a randomised phase III study showed that bevacizumab (a monoclonal antibody that targets vascular endothelial growth factor) combined with fluorouracil, folinic acid, and irinotecan was efficacious in patients with metastatic colorectal carcinoma,[31,33] the drug is now being assessed with other cytotoxic agents in the adjuvant setting.

Cetuximab (a monoclonal antibody against epidermal growth factor receptor) might be useful in the adjuvant setting because it has been approved for patients with advanced colorectal carcinoma who become refractory to agents such as fluorouracil and irinotecan.[34,35] Further trials are needed to investigate fully the potential of cetuximab and other new agents in the adjuvant setting.

In conclusion, this trial showed no additional benefit of fluorouracil-based regional chemotherapy with systemic chemotherapy for patients with advanced colorectal carcinoma. Whether the synergism between systemic chemotherapy and regional chemotherapy will remain absent with new agents such as irinotecan, oxaliplatin, or biological agents is unknown.

Author contributions

B Nordlinger and P Rougier were the study coordinators, and had a role in organisation, analysis, and publication; M Debois did statistical analysis, organisation, reporting, and publication; L Baila was the coordinating physician and did organisation, reporting, and pubication; J Wils, J-P Arnaud, J-C Ollier, O Grobost, P Lasser, J Wals, J Lacourt, J-F Seitz, J Guimares dos Santos, H Bleiberg, R Mackiewickz, T Conroy, O Bouché, T Morin, E van Cutsem, and L Bedenne did recruitment of patients and publication review.

Conflict of interest

We declare no conflicts of interest.

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Trial contributors

Fédération Francophone de Cancerologie Digestive (France)—P Rougier (Hospital Ambroise Pare, Boulogne-Billancourt); J-C Ollier (Anticancer Centre [CAC] Paul Strauss, Strasbourg); O Grobost (CH, Montlucon); P Rougier, P Lasser, and M Ducreux (Institute Gustave Roussy, Villejuif); P Herr, O Ruget, and J Lacourt (Clinique Sante Marie, Chalon Sur Saone); J-F Seitz (Institute Paoli Calmettes, Marseille, and Chu La Timone, Marseille); R Mackiewickz (Clinique Pastem, Valence); O Bouché (University Centre Hospital [CHU], Reims); T Morin, G Izard, F Druard, and A Glibert (Central Hospital [CH], Tarbes); B Paillot, P Michel (CHU, Rouen); F Morvan, M Veyrieres (CHU, Pontoise); E Dorval (CHU, Tours); D Klepping (CH, Chalon Sur Saone); L Bedenne (CHU, Dijon); N Stremsdoerfer (CH, Bourgoin Jallieu); Y Lemercier (CH, Longjumeau); J-L Baroni (CH, Martigues); D Jaeck (CHU Hautepierre, Strasbourg); S Fratte (CH, Belfort); J Maurel (CHU, Caen); Y Rinaldi (Clinique Clairval, Marseille); M Ychou (CAC val d'Aurelle, Montpellier); B Tissot (CH, Agen); B Coudert (Centre François Leclerc, Dijon); D Schmitz (CH Marie Madeleine, Forbach); H Lacroix (CHU, Nantes); M Gasmi (Hopital Nord, Marseille); J Butel (CH, Abbeville); J Callens (Hopital Saint Vincent, Lille); A Gainant (CHU, Limoges); Y Courouble (CH, Beauvais); S Walter (CH, Metz); A Lacroix (CH, Auch); J-M Lantz and E Achille (Clinique Orangerie, Strasbourg); P Taurines (Clinique, Argonay); B Leduc (CH, Brive); M Boulenger (Clinique Saint Martin, Vesoul); E Echinard (Clinique, Bayonne); P Montcuquet (Clinique Saint Vincent, Besancon); J-P Ramain (CH, Blois); Y Becouarn (Institut Bergonie, Bordeaux); L Descos (CHU, Lyon Sud Oullins); P Bonnichon (Cochin, Paris); P Pienkowski (Clinique du Pont de Chaume, Montauban); Y Paratte (CH, Vesoul); D Pillon (CH, Bourg en Bresse); G Bordes (CH, Digne les Bains); J Tuaillon (Hotel Dieu, le Creusot); A Vanoli (Clinique, le Creusot); H Perrier (Hopital Saint Joseph, Marseille); M Ychou (Hopital Saint Eloi, Montpellier); R Bugat (CHU, Rangueil, Toulouse); J Laffon (CH, Aix en Provence); B Steffen (CH, Ingwiller); A Blanchi (CH, le Mans); C Paoletti (Clinique du Cedre, Rouen Bois Guillaume); H Rallier du Baty (CH, Sarlat); C Beck (Clinique, Thionville); J-Y Danielou (Clinique val d'Olonne, le Château d'Olonne); O Favre (Maison de Sante Protestante, Nimes); P Gangloff (CH, Sarreguemines); A Paupert (CH, Saint Julien en Genevois); A Bressollette (Clinique Esperance, Angers); J-P Grandjean (Clinique, Bron); J-M Ollivier and J-H Jacob (Centre Baclesse, Caen); P Piedbois (CHU, Creteil); B Watrin (Clinique, Essey les Nancy); A Moraillon (Clinique Pasteur, Granges les Valence); S Nasca (CAC, Reims); P Taurines (Clinique Generale, Annecy); A Laugros (SSM Freyming, Merlebach); J-L Legoux (Hopital de la Source, Orleans); D Vetter (CHU Hospices Civils, Strasbourg); C Platini (CH, Thionville); A Calazel (Clinique du Parc, Toulouse); C Krakowski (CH, Epinal); M Andrieu (CH, le Chesnay); B Katrangi (CH, Loches); M Rivoire (Centre Leon Berard, Lyon); M Desbannes (Hia Desgenettes, Lyon); G Guillard (CH, Nevers); G Cavaglione (Clinique Saint Laurent du Var, Nice); C-E Comte (CH, Privas); B Humeau (Clinique, Sables d'Olonne); Y Krummel (CH, Selestat); andJ-F Roche (Hospital Saint Nicolas, Verdun).
EORTC—B Nordlinger and C Penna (Hopital Saint Antoine, Paris and Hopital Ambroise Pare, Boulogne, France); D Ten Bokkel Huinink (Diakonessenhuis, Utrecht, Netherlands); H Bleiberg (Institut Jules Bordet, Brussels, Belgium); M Morret-Rauis (Hopital Universitaire Brugmann, Brussels, Belgium); A Kartheuser (Cliniques Universitaires St Luc, Brussels, Belgium); J de Greve (Akademisch Ziekenhuis Vub, Brussels, Belgium); P van Cutsem (Intercommunale de Sante Publique du Pays de Charleroi, Charleroi, Belgium); L Vanseymortier (Centre Oscar Lambret, Lille, France); T Conroy (CHU and Centre Alexis Vautrin, Vandoeuvre-les-Nancy, Frnace); J-P Arnaud (CHU d'Angers, Angers, France); R L Jansen (Academisch Ziekenhuis Maastricht, Maastricht, Netherlands); J Wils (Laurentius Ziekenhuis Roermond, Roermond, Netherlands); C Fernandez Martos (Instituto Valenciano de Oncologia, Valencia, Spain); U Vanhoefer (Universitaetsklinikum Essen, Germany); F Roelofsen (Bethesda Krankenhaus, Essen, Germany); D Civalleri (Ospedale san Martino and Cliniche Universitarie Convenzionale, Genova, Italy); D Nitti (Universita di Padova, Padova, Italy); J Guimaraes dos Santos (Instituto Portugues de Oncologia—Centro do Porto, Porto, Portugal); A Nakad (Clinique Notre-Dame, Tournai, Belgium); and J Wals (Ziekenhuis de Wever and Gregorius, Brunssum, Netherlands).

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