VOLUME 24 · NUMBER 31 · NOVEMBER 1 2006

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Multicenter Randomized Trial of Adjuvant Fluorouracil and Folinic Acid Compared With Surgery Alone After Resection of Colorectal Liver Metastases: FFCD ACHBTH AURC 9002 Trial

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Submitted April 6, 2006; accepted July 24, 2006.

Supported in part by grants from the Association pour la Recherche Contre le Cancer and from the Ligue Nationale Contre le Cancer.

Presented in part at the 38th Annual Meeting of the American Society of Clinical Oncology, Orlando, FL, May 18-21, 2002, and at the Annual Meeting of the Société Nationale Française de Gastro-Entérologie, Paris, France, March 22, 2006.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

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0732-183X/06/2431-4976/$20.00

DOI: 10.1200/JCO.2006.06.8353

ABSTRACT

Purpose
Complete resection of liver metastases of colorectal origin is the only potentially curative treatment. In order to decrease recurrences, the use of adjuvant systemic chemotherapy after liver resection is controversial because no randomized study demonstrated its benefit.

Patients and Methods
In a multicenter trial, we randomly assigned 173 patients with completely resected (R0) hepatic metastases from colorectal cancer to surgery alone and observation (87 patients) or to surgery followed by 6 months of systemic adjuvant chemotherapy with a fluorouracil and folinic acid monthly regimen (86 patients). The main outcome criterion was disease-free survival. Secondary outcome measures were overall survival and treatment-related toxicity.

Results
The intention-to-treat analysis was based on 171 patients, after a median follow-up of 87 months (SE = 5.8). The 5-year disease-free survival rate, after adjustment for major prognostic factors, was 33.5% for patients in the chemotherapy group and 26.7% for patients in the control group (Cox multivariate analysis: odds ratio for recurrence or death = 0.66; 95% CI, 0.46 to 0.96; P = .028). With regard to secondary outcome measures, a trend towards increased overall survival was observed but did not reach statistical significance (5-year overall survival: chemotherapy group, 51.1% *v* control group, 41.1%; odds ratio for death, 0.73; 95% CI, 0.48 to 1.10; P = .13).

Conclusion
Despite a suboptimal regimen, which was the standard at the beginning of the study, adjuvant intravenous systemic chemotherapy provided a significant disease-free survival benefit for patients with resected liver metastases from colorectal cancer.

J Clin Oncol 24:4976-4982. © 2006 by American Society of Clinical Oncology

INTRODUCTION

Liver metastases from colorectal cancer, with a spontaneous overall 5-year survival rate ranging from 0.4% to 4%,[1] have a poor prognosis, if no active treatment is administered. Palliative chemotherapy with fluorouracil results in a 3-year survival of 5% to 10%.[2] Complete surgical resection, when feasible, results in a 5-year survival rate of approximately 25% (from 4% to 60%, depending on prognostic factors).[3-5] Most treatment failures are due to local hepatic recurrences, lung metastases or both, and most recurrences occur within the first 2 years after surgery. Adjuvant (postoperative) chemotherapy may improve long-term survival, but its routine use is not universal due to the lack of supporting evidence. Local hepatic arterial infusion (HAI) chemotherapy has proved to reduce hepatic recurrences and increase survival, but is impaired by technical difficulties and case specific complications.[6-8] No randomized trials have been published yet comparing systemic chemotherapy to observation for this indication.

We report the results of a multicenter randomized trial comparing systemic intravenous adjuvant chemotherapy with observation alone after curative resection of liver metastases from colorectal cancer.

PATIENTS AND METHODS

Inclusion Criteria

Eligible patients underwent a complete macroscopic and microscopic (R0) resection of histologically proven liver metastases from colorectal cancer. No specific surgical technique was suggested. Oncologic data (time between resection of primary tumor, location of primary tumor, maximum size of liver metastases, number of liver segments involved, preoperative carcinoembryonic antigen [CEA]); operative and postoperative details (number of liver segments resected, number of peroperative decrease in blood pressure, postoperative complications); and surgical margin were recorded in a specific data sheet.

Exclusion Criteria

Exclusion criteria consisted of the following: patients older than 75 years of age, altered WHO performance status (≥ 2), cardiac dysfunction or coronary disease, bone marrow dysfunction (neutrophil count $\leq 2 \times 10^9$/L, platelet count $\leq$ 100,000), renal dysfunction (creatinine concentration $\geq$150 μmol/L), liver dysfunction (bilirubin concentration ≥ 35 μmol/L), extrahepatic metastases (including portal lymph node metastasis), local relapse of primary tumor, incomplete resection of liver metastases, previous history of non-colorectal malignant tumor, chemotherapy in the year preceding liver surgery, radiotherapy within 1 month before liver surgery, or more than 35 days between liver surgery and beginning of chemotherapy.

The study was conducted according to the principles of the Helsinki Declaration and Good Clinical Practice Guidelines. All the patients provided written informed consent before inclusion in the trial approved by Toulouse University Ethics Committee.

After surgical resection of liver metastases, each patient was randomly assigned to receive chemotherapy or observation. Randomization was achieved using the minimization technique in a centralized institution.

Before random assignment, patients were stratified according to the size of the largest metastases ($<$ 5 cm or not), the number of metastases (single or not), and time between resection of the primary tumor and detection of liver metastases (less or more than 12 months).

Adjuvant Therapy

Monthly adjuvant treatment was started between day 10 and day 35 after liver surgery. Chemotherapy consisted of an intravenous bolus injection of folinic acid (200 mg per square meter) followed by an intravenous bolus injection of fluorouracil (400 mg per square meter) each day for 5 consecutive days every 28 days for six cycles.

Clinicians were asked to record the more severe episodes (grade 3 to 4) of myelotoxic effects, stomatitis, diarrhea, and other adverse events. Adverse effects were assessed according to the WHO toxicity criteria and a clearly defined protocol was used for doses modifications and delays in the treatment.

Patient follow-up was performed every 3 months for 2 years, then once per year until death or until the end of the study. Follow-up included clinical examination, abdominal ultrasonography, chest x-rays, and CEA and thoracoabdominal computed tomography when pathologic findings were found in previous tests. The decision to treat recurrences, including administration of second line chemotherapy, was left to the physicians.

Statistical Analysis

The primary outcome measure was disease-free survival; secondary outcome measures included overall survival and the incidence of adverse effects.

The aim of the study was to detect a 20% absolute difference in the 2-year disease-free survival between the control group and the treated group (20% to 40%). With a two-sided α risk of 5% and a power of 90%, 200 patients were required, 134 events were expected.

Disease-free survival was calculated from the date of liver resection until the date of proven recurrence or death from any cause. For patients lost to follow-up, data collection was stopped on the date the patient was last seen alive without recurrence. Survival estimates were achieved using the Kaplan-Meier method, and the log-rank test was used to assess differences in survival estimates among the groups. The Cox proportional hazards model was used to investigate and adjust for major prognostic and stratification factors. Factors with less than .10 significance in univariate analysis were included in the Cox multivariate model. Hazard ratios indicating the effects of treatment on the risk of recurrence or death were calculated. All analyses were carried out according to the intention-to-treat principle, and all reported P values are two sided.

RESULTS

Between December 1991 and December 2001, a total of 173 patients from 47 hospitals in France and Switzerland underwent random assignment. Inclusions were then stopped because of a too low accrual rhythm.

Two patients lost to follow-up with incomplete data, assigned to surgery alone, were excluded from the analysis.

Clinical features and characteristics of metastases were similar according to the groups (Table 1), except for the extent of liver resection. The proportion of extended hepatic resections was slightly higher in the chemotherapy arm than in the surgery alone arm ($P = .19$). The median time from resection to randomization was 19.5 days (SE = 1.7).

Survival Analyses

The median duration of follow-up was 87.4 months (SE = 5.8) and was similar for both groups (chemotherapy group, 84.5; SE = 9.0; observation group, 90.5; SE = 7.2; $P = .64$).

Disease-Free Survival

A total of 118 events (recurrence or death from any cause) were recorded. The total number of recurrences was 107 (chemotherapy group, n = 52; observation group, n = 55). In case of recurrence, second-line treatments were administered to 44 of 52 patients in the chemotherapy group and 47 of 55 patients in the observation group. The median disease-free survival was 24.4 months (SE = 3.6) for the 86 treated patients and 17.6 months (SE = 2.7) for the 85 control patients. Two-year and 5-year disease-free survival were 50.4% (SE = 5.5) and 33.5% (SE = 5.4), respectively, for treated patients and 38.1% (SE = 5.3) and 26.7% (SE = 5.1), respectively, for control patients (Fig 1). Univariate analysis revealed that negative prognostic factors for disease-free survival were synchronous metastases, multiple metastases, stage III primary tumor, peroperative hypotension, postoperative complications, and elevated preoperative CEA. Cox multivariate analysis confirmed a statistically significant positive effect of chemotherapy on disease-free survival (odds ratio for recurrence or death, 0.66; 95% CI, 0.46 to 0.96; $P = .028$; Table 2).

Overall Survival

During follow-up, 42 patients died in the chemotherapy group (38 cancer related deaths, two from other causes, and two unknown), and 54 patients died in the control group (48 cancer related, four from other causes, and two unknown). The median survival was 62.1 months (SE = 10.7) for the 86 treated patients group and 46.4 months (SE = 4.6) for the 85 patients in the control group. Two-year and 5-year overall survival estimates were 81.1% (SE = 4.3) and 51.1% (SE = 5.7), respectively, in the chemotherapy group, and 82.0% (SE = 4.2) and 41.9% (SE = 5.7), respectively, for control group (Fig 2). After Cox multivariate analysis, odds ratio for death in the chemotherapy group was 0.73 (95% CI, 0.48 to 1.10) but the difference did not reach statistical significance ($P = .13$; Table 3).

Table 1. Patient Characteristics

Characteristic	Chemotherapy No.	Chemotherapy %	Surgery Alone No.	Surgery Alone %	Total No.	P
Total	86	100	85	100	171	
Period						.94
1991-1994	40	46.5	40	47.1	80	
1995-2001	46	53.5	45	52.9	91	
Sex						.24
Male	46	53.5	53	62.4	99	
Female	40	46.5	32	37.6	72	
Age, years						.87
< 55	16	18.6	15	17.6	31	
55-64	34	39.5	37	43.5	71	
65 and older	36	41.9	33	38.9	69	
No. of metastases						.95
1	59	68.6	59	69.4	118	
2	16	18.6	17	20	33	
3	7	8.1	5	5.9	12	
4 and more	4	4.7	4	4.7	8	
Maximum tumor size, cm						.47
≤ 5	64	74.4	59	69.4	123	
> 5	22	25.6	26	30.6	48	
Localization of primary tumor						.60
Rectum	35	40.7	34	40.0	69	
Left colon	31	36.0	36	42.4	67	
Ascending colon	19	22.1	15	17.6	34	
Rectum + ascending	1	1.2	0	0	1	
Stage of primary tumor						.79
I/II	36	41.9	30	35.3	66	
III	25	29.1	28	32.9	53	
IV	24	27.9	25	29.4	49	
Unknown	1	1.2	2	2.4	3	
Delay, months						.83
< 12	24	27.9	25	29.4	49	
> 12	62	72.1	60	70.6	122	
Distribution						.85
Unilobar	74	86.0	74	87.1	148	
Bilobar	12	14.0	11	12.9	23	
Extent of liver resection						.19
Two segments or less	45	52.3	53	62.3	98	
More than two segments	41	47.7	32	37.7	73	
Peroperative hypotensions						.47
No	77	89.5	73	85.9	140	
Yes	9	10.5	12	14.1	21	
Postoperative complications						.79
No	79	91.9	79	92.9	158	
Yes	7	8.1	6	7.1	13	
CEA						.65
Normal (< 5 U)	20	23.3	25	29.4	45	
Raised	49	56.9	44	51.8	93	
Unknown	17	19.8	16	18.8	33	

Abbreviation: CEA, carcinoembryonic antigen.

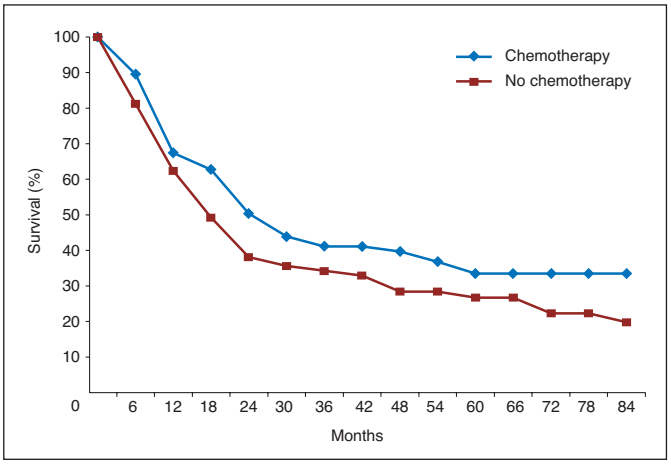

Fig 1. Disease-free survival after liver resection according to whether patients received chemotherapy.

Compliance and Adverse Effects

A total of 86 patients were assigned to receive chemotherapy. Most protocol violations were due to the patient's decision not to receive the randomly assigned treatment. Treatment details were available for 84 of 86 patients assigned to chemotherapy, of whom three were not treated (two refused and one transmission error). For the 85 patients assigned not to receive chemotherapy, three received treatment (two from patient choice and one transmission error).

Adverse events of grade 3 or 4, according to the WHO classification, were reported in 20 patients (24.7%). Most frequent grade 3 to 4 toxicities were hematologic (n = 6), stomatitis (n = 6), nausea (n = 6), diarrhea (n = 7), and neuropathy (n = 2). Twelve patients experienced more than one grade 3 to 4 toxicity.

In the chemotherapy group, 54 (66.7%) of 81 treated patients had a complete treatment (more than 85% of the planned dose).

Among the 27 other patients, 14 had less than 6 months of treatment because of toxicity (n = 9), progressive disease (n = 2), patient refusal (n =1), and unknown reason (n = 1). Twelve other patients had dose reductions of more than 15%.

Table 2. Cox Regression Model of the Effect of Adjuvant Chemotherapy on Disease-Free Survival Rate After Liver Resection

Characteristic	OR	95% CI	P
Treatment arm			
Observation	1		
Chemotherapy	0.66	0.46 to 0.96	.028
Maximum tumor size, cm			
≤ 5	1		
> 5	1.36	0.91 to 2.04	.14
No. of metastases			
1	1		
≥ 2	1.47	0.98 to 2.20	.07
Delay, months			
> 12	1		
< 12	2.08	1.37 to 3.14	.0008
Postoperative complications			
No	1		
Yes	2.26	1.22 to 4.16	.02
Preoperative CEA			
Normal	1		
Raised (> 5 U)	1.52	1.01 to 2.28	.04

NOTE. OR are adjusted to the No. of patients in each center.
Abbreviations: OR, odds ratio; CEA, carcinoembryonic antigen.

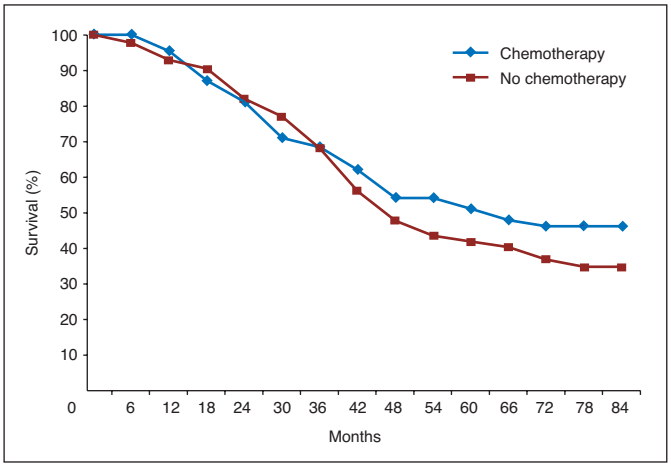

Fig 2. Overall survival after liver resection for liver metastases from colorectal cancer, according to treatment arm: chemotherapy versus observation.

DISCUSSION

The rationale for using systemic adjuvant treatment after curative surgery for liver metastases of colorectal origin is based on studies showing efficacy in stage III patients, as well as the effective response and survival benefit of fluorouracil and folinic acid-based chemotherapy in stage IV patients with measurable disease. Therefore, the French practice guidelines published in 2002 proposed adjuvant chemotherapy using a fluorouracil and folinic acid combination or a more effective regimen (like the oxaliplatin, fluorouracil, and folinic acid [FOLFOX4] regimen) after liver resection as a therapeutic option, with a low level of evidence.[9]

Table 3. Cox Regression Model of the Effect of Adjuvant Chemotherapy on Overall Survival Rate After Liver Resection

Characteristic	OR	95% CI	*P*
Treatment arm			
Observation	1		
Chemotherapy	0.73	0.48 to 1.10	.13
Delay, months			
< 12	1		
> 12	1.28	0.82 to 2.01	.28
Maximum tumor size, cm			
≤ 5	1		
> 5	1.60	1.00 to 2.53	.05
No. of metastases			
1-2	1		
≥ 3	1.97	1.11 to 3.51	.03
Primary tumor			
Descending colon	1		
Rectum or ascending colon	1.52	0.98 to 2.36	.055
Peroperative hypotension			
No	1		
Yes	1.95	1.07 to 3.55	.04
Preoperative CEA			
Normal	1		
Raised (> 5 U)	1.53	1.00 to 2.36	.056

NOTE. OR are adjusted to the No. of patients in each center.
Abbreviations: OR, odds ratio; CEA, carcinoembryonic antigen.

Randomized controlled trials of adjuvant treatment after liver resection are summarized in Table 4.

Five studies compared adjuvant HAI chemotherapy with surgery alone.[8,10-13] Disease-free survival was significantly increased in the treated group in three studies.[7,10,11] Overall survival was increased in two studies, including 40 and 38 patients, respectively.[10,11] Three studies failed to demonstrate an overall survival benefit. The largest study by Lorenz et al[14] (226 patients) stopped after a planned intermediate analysis that showed HAI-related toxicity and intention-to-treat negative results for disease-free survival and overall survival. The study by Kemeny et al[7] (75 patients), using HAI and systemic fluorouracil chemotherapy versus surgery alone, showed a trend toward better overall survival for actually treated patients, but intention-to-treat overall survival, although not significant, was decreased in the treated group (37% *v* 49%).

Three studies of combined HAI chemotherapy and intravenous systemic chemotherapy versus intravenous chemotherapy alone showed an increase of disease-free survival.[7,15,16] Overall survival was significantly increased in the treated group in the study by Lygidakis et al (122 patients).[16] In the first report of the study by Kemeny et al[6] including 156 patients, overall survival was increased after 2 years in the combined treatment group, but not in their updated results after 5 years.[8] Median overall survival was 68.4 months (combined treatment group) versus 58.8 months (systemic only group) compared with the present study's 62.2 months (systemic group) versus 46.4 months (surgery alone group).

HAI chemotherapy requires surgical implantation of a hepatic arterial catheter and requires the use of an implantable pump, which is not used in Europe for three reasons: the lack of authorization for the floxuridine use, the cost and the technicity of pump implantation, and the existence of a high rate of induced specific complications thus reducing compliance. The use of intra-arterial fluorouracil is not an alternative in this situation because of the negative results reported by Lorenz et al.[14] In their study, only 34 of 113 patients could have the total planned dose of HAI. Pump-related complications and HAI-related toxicity were encountered in the randomized study reported by Kerr et al[17] for unresectable liver metastases, in which 37% of 290 patients could not begin HAI after catheter insertion, and 29% more did not receive the total planned dose. In the combined treatment group of the study by Kemeny et al, [8] only 26% of patients could have more than 50% of the HAI planned dose.

Two randomized studies of systemic intravenous adjuvant chemotherapy were reported as abstracts. In 2003, Lopez-Ladron et al[18] reported a trend toward increased overall survival without statistical significance but with a small sample size (N = 38). In 2002, Langer et al[19] reported the results of a Canadian and European intergroup randomized trial comparing adjuvant systemic chemotherapy with fluorouracil and folinic acid to observation alone. This study showed no survival difference between the groups most probably due to the insufficient sample size (107 patients) and the fact that lung metastases were also included. Their study was prematurely closed because of slow accrual. A pooled analysis of this trial and ours is currently ongoing in order to increase statistical power.

Our study is the first published multicenter randomized trial to compare adjuvant systemic chemotherapy with observation alone for this indication. The chosen end point was disease-free survival. One could argue that disease-free survival may not be a reliable indicator

Table 4. Randomized Studies of Adjuvant Chemotherapy After Curative Resection of Liver Metastases From Colorectal Origin

Study	Treatment Arm	Sample Size	Follow-Up	DFS	OS
Lygidakis et al[10]	Surgery + HAI/immunotherapy *v* surgery alone	40 (20/20)	2 years	100% *v* 58%	Mean: 20 *v* 11 months; $P < .05$
Lygidakis et al[16]	Surgery + HAI/immunotherapy *v* surgery + IV FU/immunotherapy	122 (62/60)	2 years	58% *v* 34%; $P = .002$	5 years: 73% *v* 60%; $P = .05$
Asahara et al [11]	Surgery + HAI *v* surgery alone	38 (10/28)	NA	NA	4 years: 100% *v* 47%; $P < .05$
Rudroff et al[12]	Surgery + HAI FU/MMC *v* surgery alone	30 (14/16)	5 years	5 years: 15% *v* 23%; $P > .05$	5 years: 25% *v* 31%; $P > .05$
Lorenz et al[13]	Surgery + HAI FU/LV *v* surgery alone	226 (113/113)	18 months	Median ITT: 14.2 *v* 13.7 months; $P > .05$)	Median: 34.5 *v* 40.8 months; $P > .05$
Kemeny et al[7]	Surgery + HAI FUDR + IV FU *v* surgery alone	75 (45/30)	51 months	4 years: 46% *v* 25%; $P = .04$	4 years: 61.5% *v* 52.7%; $P = .19$
Kemeny et al[6]	Surgery + HAI FUDR/DEXA + IV FU/LV *v* surgery + IV FU/LV	156 (74/82)	2 years	2 years: 57% *v* 42%; $P = .07$	2 years: 86% *v* 72%; $P = .03$
Kemeny et al[8]	Surgery + HAI FUDR/DEXA + IV FU/LV *v* surgery + IV FU/LV	156 (74/82)	6 years	Median: 31 *v* 17 months; $P = .02$	10 years: 41.1 *v* 27.2%; $P = .10$
Tono et al[15]	Surgery + HAI FU + oral FU *v* surgery + oral FU	19 (9/10)	62.2 months (mean)	3 years: 66.7% *v* 20.0%; $P = .045$	3 years: 77.8% *v* 50%; $P = .2686$
Langer et al[19]	Surgery + FU/LV *v* surgery alone	107 (52/55)	NA	4 years 45%*v* 35%; $P = .35$	4 years: 57% *v* 47%; $P = .39$
Lopez-Ladron et al[18]	Surgery + CT *v* surgery alone	38 (28/10)	15 months (median)	15 *v* 9 months; $P = .352$	30 *v* 15 months; $P = .066$
Present study	Surgery + FU/LV *v* surgery alone	171 (86/85)	5 years	5 years: 50% *v* 33%; $P = .028$	5 years: 51% *v* 42%; $P = .13$

Abbreviations: DFS, disease-free survival; OS, overall survival; HAI, hepatic arterial infusion; IV, intravenous; FU, fluorouracil; MMC, mitomycin C; LV, leucovorin; ITT, intention-to-treat; FUDR, floxuridine; DEXA, dexamethasone; NA, not available; CT, chemotherapy.

for overall survival. This choice was based on statistical sample estimations, assuming that in a study with a non-treated arm, inclusions of a larger number of patients would be difficult. Indeed, as in Langer et al study,[19] we experienced difficulties in obtaining a sufficient number of patients in both groups as many refused to be part of the untreated group. In addition, after the publication of the results obtained by Moertel et al[20] showing the benefit of adjuvant chemotherapy after resection of stage III colorectal cancers, many patients had received chemotherapy in an adjuvant setting after resection of the primitive tumor, and thus were not eligible for the study. The chosen end point for the Kemeny et al[7] study of HAI versus surgery alone was disease-free survival for the same reasons, and enrolled only 109 patients over a 9-year period.

We agree with Di Leo et al, [21] that increase in overall survival remains the ultimate goal of many clinical trials, but that the choice of overall survival benefit as a mandatory requirement to register new compounds could lead to underestimation of a drug's real efficacy. The meta-analysis by Sargent et al[22] suggested that disease-free survival after 3 years of median follow-up is an appropriate end point for adjuvant colon cancer clinical trials of fluorouracil-based regimens because of a very closed correlation between 3-year disease-free survival and 5-year overall survival; although, marginally significant disease-free survival improvements may not translate into significant overall survival benefits. It is not proven that these conclusions could be applied to resected liver metastases studies.

The chosen chemotherapy schedule was the standard chemotherapy regimen at the time when the study began. Its efficacy in adjuvant setting was confirmed by large randomized trials and meta-analyses.[23] Despite the fact that it is now known to have a modest efficacy and high toxicity, this intent-to-treat study demonstrated a significant disease-free survival benefit for patients in the chemotherapy group.

Since the study began in 1990, most of the included patients were thought to be of good enough prognosis after liver resection to justify surgery, meaning moderate liver involvement (50% had < two liver segments resected), with less than three metastases (69% had only one tumor), small lesions (74% < 5 cm), and metachronous metastases (72%). It explains why the 5-year survivals in our study are high (computed tomograhy, 51% *v* control, 41.9%) compared with other published studies of liver resection for metastases. Considering the clinical risk score described by Fong et al,[3] most of the patients in this study had 0 to 2 pejorative factors, which should translate in an expected 5-year survival between 60% and 40%. In fact, patients in current trials have more pejorative prognostic factors according to the Fong classification.[3] However, these stratification criteria were well balanced between the two groups after randomization. When comparing the patients' characteristics of this study with other trials (Table 4), prognostic factors were similar, with 20% to 31% synchronous metastases, 50% of minor liver resections, and more than 60% of single lesions except for the Kemeny trial (36%).[6] The worse patients' prognosis in this latter trial could explain why survival decreased after 4 years, which was not the case in this study.

This study failed to detect a statistically significant overall survival benefit. However, we observed a trend towards improved overall survival after adjuvant chemotherapy, as shown by the increased survival percentage in this group of patients after 4 years ($P = .13$). These findings are consistent with the Kemeny trial[6] results that showed an increase in overall survival in the combined treatment group (median, 68 *v* 58 months) although not significant ($P = .10$). Several factors could be discussed: the effect of the used chemotherapy regimen on global survival was probably modest. As stated herein, and similarly to the Kemeny trial,[7] the sample size was not calculated for global survival as an end point. Moreover, recurrences in both arms were treated by second-line chemotherapy, or by repeat liver resections, which influenced the natural history of the disease. For this reason, it was difficult to identify the single effect of adjuvant chemotherapy on overall survival.

In future trials, a longer follow-up and larger sample size could be necessary to reach statistical significance for overall survival. New chemotherapy regimens using oxaliplatin or camptothecin-11 (CPT-11), have proved to be more effective in palliative situations and are now the standard treatments for metastatic colorectal cancer[24-26] or in an adjuvant setting.[27] Large studies of adjuvant chemotherapy after liver resection for metastases using these new regimens are needed.[28] The benefit of adding hepatic arterial infusion to modern systemic chemotherapy is still under investigation.[29-31] Adjuvant floxuridine HAI combined with intravenous CPT-11 after potentially curative liver resection seemed feasible with a 2-year survival rate of 89% in a phase II study by Kemeny et al.[32] New targeted biotherapies (cetuximab and bevacizumab), which are effective in a palliative setting will probably be added to the therapeutic panel.[24,33-35]

In conclusion, this adds to the currently available data, which strongly supports the fact that curative surgery for patients with resectable liver metastases from colorectal cancer should be followed by adjuvant treatment. The best regimen has now to be determined among the numerous therapeutic agents and infusion modalities (systemic and/or intra-arterial) that are nowadays available. Control arms in future randomized trials should include at least systemic chemotherapy.

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Acknowledgment

We thank the following physicians for their participation to the study: Milan Chantal (MD; statistical analysis FFCD; Dijon), Choine C. Guiliani, F. Moreau (data managers FFCD), and coinvestigators: M. Gillet, MD, M. Pelletier, MD, R.J. Salmon, MD, P. Segol, MD, P. Bachelier, MD, M. Scotte, MD, T. Conroy, MD, B. Coudert, MD, J.P. Sales, MD, D. Couturier, MD, M. Chazal, MD, G. Lorimier, MD, P. Etienne, MD, P. Bernades, MD, G. Dabouis, MD, B. Millat, MD, PhD, P. Marre, MD, P. Montcuquet, MD, A. Joyeux, MD, H. Cosme, MD, P. Thevenet, MD, S. Beorchia, MD, G. Becouarn, MD, PhD, J.P. Arnaud, MD, PhD, A. Nabet, MD, J. Baulieux, MD, PhD, P. Cartalat, MD, N. Farabos, MD, N. Al Aukla, MD, J.B. Cazals, MD, A. Soupison, MD, B. Denis, MD, D. Auby, MD, and P. Geoffroy, MD.

Authors' Disclosures of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.

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