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ORIGINAL REPORT

Adjuvant Chemotherapy After Potentially Curative Resection of Metastases From Colorectal Cancer: A Pooled Analysis of Two Randomized Trials

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ABSTRACT

Purpose

Adjuvant systemic chemotherapy administered after surgical resection of colorectal cancer metastases may reduce the risk of recurrence and improve survival, but its benefit has never been demonstrated. Two phase III trials (Fédération Francophone de Cancérologie Digestive [FFCD] Trial 9002 and the European Organisation for Research and Treatment of Cancer/National Cancer Institute of Canada Clinical Trials Group/Gruppo Italiano di Valutazione Interventi in Oncologia [ENG] trial) used a similar design and showed a trend favoring adjuvant chemotherapy, but both had to close prematurely because of slow accrual, thus lacking the statistical power to demonstrate the predefined difference in survival. We report here a pooled analysis based on individual data from these two trials.

Patients and Methods

After complete resection of colorectal liver or lung metastases, patients were randomly assigned to chemotherapy (CT arm; fluorouracil [FU] 400 mg/m^2 administered intravenously [IV] once daily plus DL-leucovorin 200 mg/m^2 [FFCD] × 5 days or FU 370 mg/m^2 plus L-leucovorin 100 mg/m^2 IV × 5 days [ENG] for six cycles at 28-day intervals) or to surgery alone (S arm).

Results

A total of 278 patients (CT, n = 138; S, n = 140) were included in the pooled analysis. Median progression-free survival was 27.9 months in the CT arm as compared with 18.8 months in the S arm (hazard ratio = 1.32; 95% CI, 1.00 to 1.76; $P = .058$). Median overall survival was 62.2 months in the CT arm compared with 47.3 months in the S arm (hazard ratio = 1.32; 95% CI, 0.95 to 1.82; $P = .095$). Adjuvant chemotherapy was independently associated with both progression-free survival and overall survival in multivariable analysis.

Conclusion

This pooled analysis shows a marginal statistical significance in favor of adjuvant chemotherapy with an FU bolus–based regimen after complete resection of colorectal cancer metastases.

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INTRODUCTION

No more than 10% to 15% of colorectal cancer (CRC) metastases are considered resectable for cure. When feasible, surgery should be performed, as the 5-year overall survival (OS) rate ranged from 28% to 38% in recent series after complete resection of liver metastases.[1-3] Relapse after resection will occur in almost 75% of the patients, with a 5-year relapse-free survival rate ranging from 15% to 35%.[1-3] Recurrences will mainly occur within the first 2 years after surgery and be located in the liver in approximately 50% of cases.[4] In this setting, adjuvant systemic chemotherapy administered after surgery may reduce the risk of recurrence and improve long-term survival.

Given the high proportion of patients with liver-only recurrence, hepatic arterial infusion chemotherapy after surgery has been evaluated. Compared with surgery alone, it was shown to reduce hepatic recurrences and increase survival, but the associated technical difficulties and complications have limited its general use.[5-7]

Two multicenter randomized phase III trials (Fédération Francophone de Cancérologie Digestive Trial 9002/Association de Chirurgie Hépato-Biliare et de Transplantation Hépatique/Association Universitaire de Recherche en Chirurgie Vasculaire trial [FFCD

trial], European Organisation for Research and Treatment of Cancer [EORTC]Trial 40923/National Cancer Institute of Canada Clinical Trials Group Trial CO.7/Gruppo Italiano di Valutazione Interventi in Oncologia CO.3 trial [ENG trial]) aimed to evaluate the efficacy of adjuvant chemotherapy with bolus fluorouracil (FU) plus leucovorin in patients with CRC who are rendered clinically free of cancer by surgical resection of metastatic disease.[8,9] Both trials had a similar design and showed a nonsignificant trend for improvement in disease-free survival (DFS; but a statistically significant positive effect of adjuvant chemotherapy on DFS on the Cox multivariable analysis in the FFCD trial) and OS for patients treated with chemotherapy. However, both trials had to close prematurely because of slow accrual, thus lacking statistical power to demonstrate the predefined difference in survival.

We report here a pooled analysis based on individual data from both trials. This combined analysis will improve the statistical power to evaluate the benefit of postoperative chemotherapy with bolus FU plus leucovorin compared with surgery alone after potentially curative resection of metastases from CRC.

PATIENTS AND METHODS

Patient Population

For the FFCD trial, 173 patients were recruited from 47 centers in France, Belgium, and Switzerland between December 1991 and December 2001. For the ENG trial, 129 patients were recruited from 67 centers in Canada and Europe between February 1994 and January 1998 (EORTC, 20 patients; National Cancer Institute of Canada Clinical Trials Group, 54 patients; Gruppo Italiano di Valutazione Interventi in Oncologia, 55 patients).

Patients in both studies were required to have histologically proven CRC. They were required to be free of clinically detectable disease by R0 surgical resection of the primary tumor and to have four or fewer metastases located in a single location (liver [FFCD trial]; liver or lung [ENG trial]). Surgical resection margins were required to be negative by histologic examination. Patients with distant lymph nodes, including metastases to the porta hepatis or mediastinal nodes, and patients with metastases to other organs were not eligible, even if metastases were completely excised.

Patients were required to have an Eastern Cooperative Oncology Group performance status of 0, 1, or 2; be younger than 76 years of age (FFCD trial); have biologic tests compatible with chemotherapy administration and no previous primary cancer of any other site; have no previous chemotherapy except adjuvant treatment of their primary tumor, provided that a minimum of 6 months had elapsed between cessation of chemotherapy and the diagnosis of metastatic disease (ENG trial) or that the adjuvant chemotherapy was finished when the metastatic disease was diagnosed (FFCD trial); and to have no uncontrolled medical condition that would be aggravated by treatment. Patients of childbearing potential were required to use adequate contraception; women could not be pregnant or lactating.

Pretreatment evaluation included patient history, physical examination, full blood cell count, biochemistry (total bilirubin, AST, ALT, alkaline phosphatase, and serum creatinine), carcinoembryonic antigen (CEA; FFCD trial only), chest x-ray (with computed tomography of chest as indicated), abdominal imaging (ultrasound, computed tomography scan, or magnetic resonance imaging [ENG trial only]).

Ethics committees at the local level approved the trial, and written consent was obtained for all participants according to national and Helsinki international guidelines.

Randomization and Treatment

In the FFCD trial, patients were stratified according to the number of metastases (one $v \geq$ two), maximum size of metastases (≤ 5 $v > 5$ cm), disease-free interval between primary tumor resection and liver progression (≤ 1 $v > 1$ year), and prior adjuvant chemotherapy (yes v no). In the ENG trial, patients were stratified according to treatment center, number of metastases (one $v \geq$ two), disease-free interval between primary tumor resection and liver progression (< 6 $v \geq 6$ months), site of resected metastatic disease (liver v lung), and prior adjuvant chemotherapy (yes v no).

The treatment schedule was similar in both trials: FU 400 mg/m^2 administered intravenously once daily for 5 days plus DL-leucovorin 200 mg/m^2 administered intravenously for 5 days (FFCD) or FU 370 mg/m^2 plus L-leucovorin 100 mg/m^2 for 5 days (ENG), both given for six cycles at 28-day intervals. Adjuvant chemotherapy started between 10 and 35 days after surgery in the FFCD trial, whereas randomization had to occur within 49 days from surgery and treatment had to begin within 7 days from randomization in the ENG trial.

Evaluation of Patients

All the patients were evaluated monthly throughout the adjuvant chemotherapy period with history and physical examination, performance status, full blood cell count, and serum biochemistry (and CEA for the FFCD trial). Thereafter, patients included in the FFCD trial were evaluated every 3 months until 2 years from randomization and then yearly with history and physical examination, chest x-ray (computed tomography of chest as indicated), abdominal ultrasound, and CEA level. Patients included in the ENG trial were evaluated at 9 and 12 months from randomization, then every 6 months until 5 years from randomization, then yearly with history and physical examination, chest x-ray (computed tomography of chest as indicated), and abdominal imaging (one of ultrasound, computed tomography, or magnetic resonance imaging).

Treatment of recurrence was left to physicians' discretion in the FFCD trial, but chemotherapy with the bolus FU plus leucovorin regimen was advised in the protocol in case of unresectable metastatic disease, whereas chemotherapy with the same regimen used in the adjuvant setting was mandatory for patients in the ENG trial with unresectable metastatic disease.

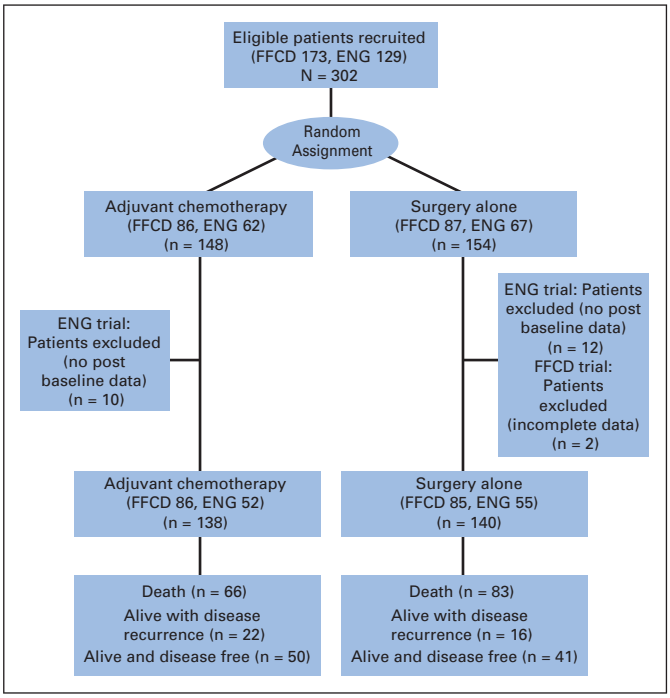

Fig 1. Study population. FFCD, Fédération Francophone de Cancérologie Digestive Trial 9002/Association de Chirugie Hépato-Biliare et de Transplantation Hépatique/Association Universitaire de Recherche en Chirugie Vasculaire trial; ENG, European Organisation for Research and Treatment of Cancer Trial 40923/National Cancer Institute of Canada Clinical Trials Group Trial CO.7/Gruppo Italiano di Valutazione Interventi in Oncologia CO.3 trial.

Statistical Analysis

The primary outcome measure in the FFCD trial was DFS at 2 years, with OS as secondary measure, whereas in the ENG trial, OS was the primary outcome measure and DFS was the secondary outcome measure. The FFCD trial was designed to demonstrate a reduction from 40% to 20% of the 2-year relapse rate in the adjuvant chemotherapy arm with a two-sided α level of 5% and a 90% power by observing 134 events from 214 patients. The ENG trial required randomization of 418 patients over 4 years to have a 90% chance of detecting an increase in 5-year survival from 30% to 45% in the adjuvant chemotherapy arm with a two-sided α level of 5% and a 90% power.

In this pooled analysis, DFS was calculated from the date of metastases resection until the date of proven recurrence or death from any cause. For patients lost to follow-up, data were censored on the date the patient was last seen alive without recurrence. OS was calculated from the date of metastases resection until the date of death from any cause. For patients lost to follow-up, data were censored on the date the patient was last seen alive. Survival estimates were derived by the method of Kaplan and Meier, and the log-rank test was used to assess differences in survival estimates among groups. Outcomes were analyzed with the Cox proportional hazards regression model with stratification by trial. The following variables were considered as potential factors for the Cox model (age, performance status, treatment group, number of metastases, maximum size of metastases, previous chemotherapy, and disease-free interval), but only factors associated with survival with a *P* value less than .1 in univariate analysis were introduced into the Cox regression model (except for the size of metastases, which was not available for the ENG trial). With a total of 149 deaths and 38 recurrences without death in the pooled database, this pooled analysis should have 80% power at a two-sided .05 level to detect a hazard ratio (HR) of 0.66 in DFS between the two arms (corresponding to a reduction from 40% to 28.6% in 2-year relapse rate with adjuvant

Table 1. Baseline Characteristics

	FFCD Trial*				ENG Trial†				Pooled Analysis‡			
	Chemotherapy (n = 86)		Surgery Alone (n = 85)		Chemotherapy (n = 52)		Surgery Alone (n = 55)		Chemotherapy (n = 138)		Surgery Alone (n = 140)	
Characteristic	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Age, years												
Median	63		63		63.5		60		63		62	
Range	35-77		36-76		35-76		20-82		35-77		20-82	
Age group, years												
< 70	68	79.1	67	78.8	42	80.8	44	80.0	110	79.7	111	79.3
≥ 70	18	20.9	18	21.2	10	19.2	11	20.0	28	20.3	29	20.7
Male sex	46	53.5	53	62.4	34	65.4	36	65.4	80	58.0	89	63.6
Primary tumor												
Rectum	35	40.7	34	40.0	14	26.9	17	30.9	49	35.5	51	36.4
Colon	50	58.1	51	60.0	32	61.5	35	60.0	82	59.4	84	60.0
Unknown	1	1.2	—		6	11.5	5	9.1	7	5.1	5	3.6
Stage of primary tumor												
T1-T3	73	84.9	79	92.9	44	84.6	43	78.2	117	84.8	122	87.1
T4	8	9.3	2	2.4	6	11.5	8	14.5	14	10.1	10	7.1
Tx	5	5.8	4	4.7	2	3.8	4	7.3	7	5.1	8	5.7
N0	46	53.5	39	45.8	24	46.1	26	47.3	70	50.7	65	46.4
N1	39	44.3	43	50.6	26	50.0	25	45.4	65	47.1	68	46.6
Nx	1	1.2	3	3.5	2	3.9	4	7.3	3	2.2	7	5.0
Prior chemotherapy												
No	64	74.4	63	74.1	34	65.4	36	65.5	98	71.0	99	70.7
Yes	22	25.6	22	25.9	17	32.7	16	29.1	39	28.3	38	27.7
Unknown	—		—		1	1.9	3	5.4	1	0.7	3	2.1
Disease-free interval, years												
≤ 1	42	48.8	39	45.9	18	34.6	21	38.2	60	43.5	60	42.9
> 1	44	51.2	46	54.1	34	65.3	34	61.8	78	56.5	80	57.1
Site of metastases												
Liver	86	100	85	100	44	84.6	46	83.6	130	94.2	131	93.6
Lung	—		—		7	13.5	6	10.9	7	5.1	6	4.3
Unknown	—		—		1	1.9	3	5.4	1	0.7	3	2.1
No. of metastases												
Median	1		1		1		1		1		1	
Range	1-7		1-4		1-4		1-4		1-7		1-4	
1	59	68.6	59	69.4	33	63.5	37	67.3	92	66.7	96	68.6
≥ 2	27	31.4	26	30.1	19	36.5	18	32.7	46	33.3	44	31.4

NOTE. Eastern Cooperative Oncology Group (ECOG) performance status was not available for the FFCD trial, all patients have an ECOG performance status ≤ 2 (inclusion criteria). Size of metastases was not available for ENG trial.

Abbreviations: FFCD, Fédération Francophone de Cancérologie Digestive Trial 9002/Association de Chirugie Hépato-Biliare et de Transplantation Hépatique/Association Universitaire de Recherche en Chirugie Vasculaire trial; ENG, European Organisation for Research and Treatment of Cancer Trial 40923/National Cancer Institute of Canada Clinical Trials Group Trial CO.7/Gruppo Italiano di Valutazione Interventi in Oncologia CO.3 trial.

*Period of inclusion, December 1991 through December 2001.

†Period of inclusion, February 1994 through January 1998.

‡No statistically significant difference between treatment groups.

chemotherapy) and an HR ratio of 0.63 in OS between the two arms (corresponding to an increase from 30% to 46.8% in 5-year OS with adjuvant chemotherapy).

All analyses were performed using STATA version 9 (STATA Corp, College Station, TX) and SAS version 8.0 (SAS Institute, Cary, NC). All *P* values are two-sided.

RESULTS

Population

A total of 302 eligible patients were recruited (FFCD, n =173; ENG, n = 129), of whom 148 patients were randomly assigned to the chemotherapy group (CT group) and 155 patients were randomly assigned to the surgery-alone group (S group). Twenty-four patients were excluded for missing data (ENG, 22 patients were excluded because there were no postbaseline data; FFCD, two patients were excluded because of incomplete data), and therefore, 278 patients were included in the present analysis (CT group, 138 patients; S group, 140 patients). At the time of analysis, 66 patients had died, 22 patients were alive with disease recurrence, and 50 patients were alive and disease-free in the CT group. The corresponding numbers for the S group were 83, 16, and 41 patients, respectively (Fig 1).

Patient and tumor characteristics are listed in Table 1 and were similar between treatment groups. There were 169 men (60.8%) and 109 women (39.2%). The median age was 62.5 years (range, 20 to 82 years), and 57 patients (20.5%) were 70 years or older. Most of the patients (71.9%) had not received previous adjuvant chemotherapy for their disease.

Overall, 261 patients (93.9%) of the pooled analysis had liver metastases and 13 patients (4.7%) had lung metastases. The interval between CRC diagnosis and metastases occurrence was greater than 1 year in 56.8% of patients (Table 1).

Adjuvant Chemotherapy

A total of 86 patients were assigned to receive chemotherapy in the FFCD trial. Among the 84 patients with available data, three patients were not treated (two patients refused and one was not treated because of a transmission error). A complete treatment, defined as more than 85% of the planned dose, was administered to 54 (66.7%) of 81 patients. Among the 27 other patients, 15 patients had less than 6 months of treatment because of toxicity (n = 9), progressive disease (n = 2), patient refusal (n = 3), and unknown reason (n = 1). Twelve other patients had dose reductions of more than 15%. Three patients assigned to surgery alone received an adjuvant chemotherapy (two from patient choice and one because of transmission error).

Among 52 patients in the ENG trial who were assigned to receive adjuvant chemotherapy and had at least one postbaseline assessment, 48 patients received treatments. Among 48 patients treated, 21 patients (44%) had at least one dose delay and 20 patients (42%) had dose reduction. Twenty-eight patients completed all six cycles of treatments.

Progression-Free Survival

The date of surgery was missing for four patients in the ENG trial (CT group, n =1; S group, n = 3) who were therefore excluded from survival analyses. The median DFS was 27.9 months (95% CI, 21.0 to 41.9 months) for the CT group compared with 18.8 months (95% CI, 14.7 to 23.8 months) for the S group. Patients from the S group had a higher risk of recurrence than patients from the CT group (HR = 1.32; 95% CI, 1.00 to 1.76; *P* = .058; Fig 2). The 2-year DFS rates were 55.3% (95% CI, 46.4% to 63.4%) in the CT group and 40.2% (95% CI, 31.8% to 48.5%) in the S group. Corresponding 5-year DFS rates were 36.7% (95% CI, 24.5% to 41.1%) and 27.7% (95% CI, 20.0% to 35.9%).

Four factors were associated with DFS in univariate analysis (with a *P* value < 0.1): treatment group, number of metastases, previous adjuvant chemotherapy, and maximum size of metastases (only available for FFCD patients; Table 2). The treatment group and the number of metastases were significantly associated with DFS in multivariable analysis. The risk of recurrence was significantly increased among patients in the S group as compared with patients in the CT group (HR = 1.39; *P* = .026) and for patients with two or more metastases compared with those with a single metastasis (HR = 1.43; *P* = .022; Table 3).

OS

The median OS was 62.2 months (95% CI, 45.2 months to not reached) for the CT group compared with 47.3 months (95% CI, 40.6 to 57.2 months) for the S group. Patients from the S group had a higher risk of death than patients from the CT group (HR = 1.32; 95% CI, 0.95 to 1.82; *P* = .095; Fig 3). The 3-year survival rates were 69.4% (95% CI, 60.5% to 76.8%) for the CT group and 71.0% (95% CI, 62.2% to 78.1%) for the S group. Corresponding 5-year survival rates were 52.8% (95% CI, 43.7% to 61.3%) and 39.6% (95% CI, 30.7% to 48.3%).

Five factors were associated with OS in univariate analysis (with a *P* value < .1): treatment group, number of metastases, disease-free interval, maximum size of metastases (only available for FFCD patients), and WHO performance status (only available for ENG patients) (Table 2). The treatment group and the number of metastases were significantly associated with survival in multivariable analysis: the risk of death was significantly increased among patients in the S group as compared with patients in the CT group (HR = 1.39; *P* = .046) and for patients with two or more metastases as compared with those with a single metastasis (HR = 1.49; *P* = .023; Table 3).

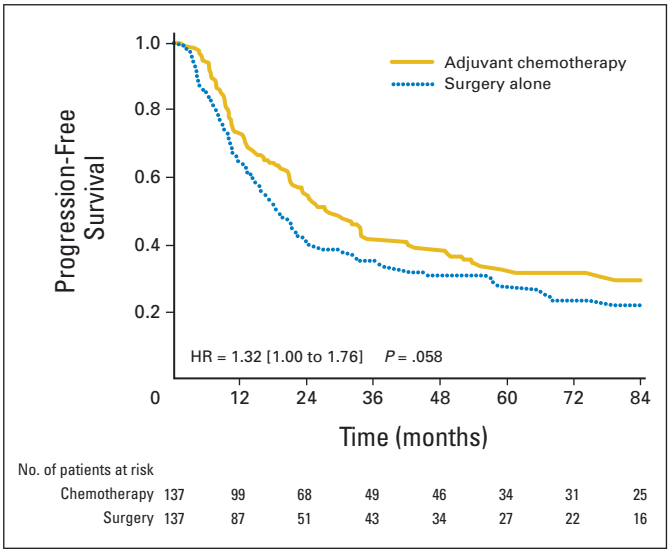

Fig 2. Progression-free survival by treatment group. HR, hazard ratio.

Table 2. Factors Associated With Survival in Univariate Analysis

Factor	Median PFS (months)	Median OS (months)	*P* (log-rank test)
Treatment group			.058
Chemotherapy	27.9		
Surgery alone	18.8		
No. of metastases			.036
1	27.2		
2+	16.8		
Previous adjuvant CT			.081
No	21.1		
Yes	33.0		
Maximum size of metastases, cm*			.052
≤ 5	23.8		
> 5	15.7		
Treatment group			.09
Chemotherapy		62.2	
Surgery alone		47.3	
No. of metastases			.02
1		64.5	
2+		40.6	
Disease-free interval, years			.07
≤ 1		46.1	
> 1		58.4	
Maximum size of metastases, cm*			.003
≤ 5		64.5	
> 5		38.5	
Performance status†			.002
0		53.4	
1		46.2	
2		20.6	

NOTE. Only factors associated with survival with a *P* value < .1 are presented.
Abbreviations: PFS, progression-free survival; OS, overall survival; CT, chemotherapy.
*Fédération Francophone de Cancérologie Digestive Trial 9002/Association de Chirugie Hépato-Biliare et de Transplantation Hépatique/Association Universitaire de Recherche en Chirugie Vasculaire trial, 171 patients.
†European Organisation for Research and Treatment of Cancer Trial 40923/National Cancer Institute of Canada Clinical Trials Group Trial CO.7/Gruppo Italiano di Valutazione Interventi in Oncologia CO.3 trial, 103 patients.

Table 3. Factors Associated With Survival in Multivariable Analysis

Factor	HR	95% CI	*P*
Progression-free survival			
Treatment group			
Chemotherapy	1		
Surgery alone	1.39	1.04 to 1.85	.026
No. of metastases			
1	1		
2+	1.43	1.05 to 1.95	.022
Prior chemotherapy			
No	1		
Yes	0.74	0.53 to 1.03	.082
Overall survival			
Treatment group			
Chemotherapy	1		
Surgery alone	1.39	1.00 to 1.93	.046
No. of metastases			
1	1		
2+	1.49	1.06 to 2.11	.023
Disease-free interval, years			
≤ 1	1		
> 1	0.74	0.54 to 1.03	.075

NOTE. Factors associated with survival with a *P* value < .1 in univariate analysis were introduced into the Cox regression model (except for the size of metastases and performance status, which were not available for all patients); regression model was stratified by trial.
Abbreviation: HR, hazard ratio.

DISCUSSION

The results of this pooled analysis of two randomized trials do support the use of systemic adjuvant chemotherapy after potentially curative resection of metastases from CRC. There was a marginal statistical significance in favor of adjuvant chemotherapy in the univariate analysis, which became significant after adjusting other factors in the multivariable analyses.

Final results of the FFCD trial have been recently published.[9] In the final report of FFCD, adjuvant chemotherapy was associated with a better progression-free survival in multivariable analysis (HR = 0.66; *P* = .028) but was not significantly associated with a better OS (HR = 0.73; *P* = .13).[9] The results from the ENG trial have not yet been published but have been reported in abstract form.[8] We believed that a combined analysis based on individual data of FFCD and ENG trials was feasible and valid because, despite different primary objectives and statistical considerations, both trials had a similar design. Inclusion criteria and period of inclusion, as well as chemotherapy regimens, were almost identical for both trials. Some biases, however, cannot be excluded because of the differences between the two trials' designs. The fact that the follow-up schedule varied from four visits during the first 24 months for the ENG study to eight visits for the FFCD trial and was also different after 2 years should be pointed out, because it could have introduced some bias into the estimation of the time to disease progression. Another important prognostic factor to consider is the interval between primary tumor resection and liver metastases progression (metachronous *v* synchronous metastases). This variable was not available and was therefore not included in the

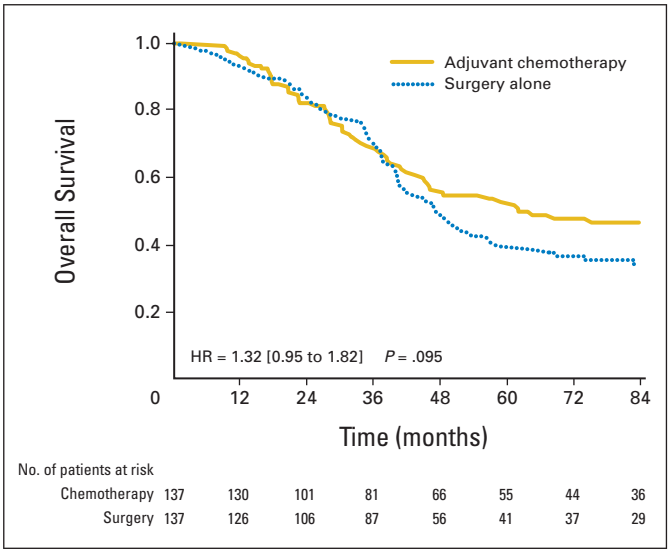

Fig 3. Overall survival by treatment group. HR, hazard ratio.

pooled analysis, but, because our multivariable analysis has taken into account disease-free interval (< 12 *v* ≥ 12 months), we don't feel that exclusion of this variable in the multivariable analysis will have an impact on the treatment comparison.

The objective of pooling data was to improve the statistical power of the survival analysis and therefore better estimate the potential benefit of postoperative chemotherapy. Indeed, trends in survival observed in the FFCD trial were confirmed by the pooled analysis. The association between adjuvant chemotherapy and improvement in median progression-free survival almost reached statistical significance ($P = .059$), and adjuvant chemotherapy was significantly associated with a better OS in the multivariable analysis ($P = .046$), although this was not observed in the FFCD trial alone ($P = .13$). Therefore, if the present results do not definitely demonstrate the advantage of adjuvant chemotherapy in this setting, they strengthen those from the FFCD trial that "provided a proof of concept of adjuvant chemotherapy"[10] after curative resection of liver or lung metastases from CRC. It is quite possible that a greater magnitude of benefit of adjuvant treatment would be achieved with currently available chemotherapy regimens that are more effective in the adjuvant stage II or III setting than bolus FU with leucovorin alone. The Multicenter International Study of Oxaliplatin/5-Fluorouracil/Leucovorin in the Adjuvant Treatment of Colon Cancer trial demonstrated that adding oxaliplatin to a regimen of FU and leucovorin improved the rate of DFS at 3 years.[11]

However, a definitive demonstration of the benefits of chemotherapy, either systemic or by hepatic artery infusion, over surgery alone for resected metastatic disease remains to be formally demonstrated. A control with surgery alone is needed to demonstrate a benefit of adjuvant chemotherapy, but this may be an obstacle for accrual. Japanese investigators recently faced the same problem of low accrual as in the FFCD and ENG trials in a phase III trial comparing surgery alone with adjuvant chemotherapy with oral leucovorin and tegafur/uracil after potentially curative liver resection.[12] With the benefit of adjuvant chemotherapy clearly established in resected stage III colon cancer, some consider that surgery alone is unethical after resection of stage IV disease and that adjuvant chemotherapy should be given, even in the absence of unquestionable proof of its benefit.

Final efficacy results of the EORTC 40983 trial were recently reported.[13] This phase III trial demonstrated that perioperative chemotherapy with infusional fluorouracil, leucovorin, and oxaliplatin regimen plus surgery improved progression-free survival as compared with surgery alone in patients with resectable liver metastases from CRC. Among eligible patients, the 3-year progression-free survival rate was significantly improved from 28.1% to 36.2% (absolute difference, +8.1%; HR = 0.77; $P = .041$). The additional benefit of the preoperative chemotherapy over effective postoperative chemotherapy remains less clear and is an important question for future study.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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