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ORIGINAL REPORT

Modulation of Fluorouracil by Leucovorin in Patients With Advanced Colorectal Cancer: An Updated Meta-Analysis

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

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ABSTRACT

Purpose

The modulation of fluorouracil (FU) by folinic acid (leucovorin [LV]) has been shown to be effective in terms of tumor response rate in patients with advanced colorectal cancer, but a meta-analysis of nine trials previously published by our group failed to demonstrate a statistically significant survival difference between FU and FU-LV. We present an update of the meta-analysis, with a longer follow-up and the inclusion of 10 newer trials.

Patients and Methods

Analyses are based on individual data from 3,300 patients randomized in 19 trials on an intent-to-treat basis. Two trials had multiple comparisons, leading to a total of 21 pair-wise comparisons. FU doses were similar in both arms in 10 pair-wise comparisons, 15% to 33% higher in the FU-alone arm in six comparisons, and more than 66% higher in five comparisons.

Results

Overall analysis showed a two-fold increase in tumor response rates (11% for FU-LV *v* 21% for FU alone; odds ratio, 0.53; 95% CI, 0.44 to 0.63; $P < .0001$) and a small but statistically significant overall survival benefit for FU-LV over FU alone (median survival, 11.7 *v* 10.5 months, respectively; hazards ratio, 0.90; 95% CI, 0.87 to 0.94; $P = .004$), which were primarily seen in the first year. We observed a significant interaction between treatment benefit and dose of FU, with tumor response and overall survival advantages of FU-LV over FU-alone being restricted to trials in which a similar dose of FU was prescribed in both arms.

Conclusion

This updated analysis demonstrates, on a large data set, that FU-LV improves both response rate and overall survival compared with FU alone and that this benefit is consistent across various prognostic factors.

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INTRODUCTION

Approximately 50% of patients diagnosed with colorectal carcinoma have metastatic or nonresectable disease at time of diagnosis or will develop metastases and/or a local recurrence after their initial diagnosis. Despite the recent development of new chemotherapy compounds, the outcome of patients with advanced colorectal carcinoma (ACC) remains grim. Introduced in clinical practice in the late 1950s, fluorouracil (FU) remains an essential component of chemotherapy regimens in ACC. Substantial progress has been made over the past 20 years in the use of FU. In a series of meta-analyses published in the 1990s, our group, the Meta-Analysis Group in Cancer (MAGIC), showed that FU alone delivered as a bolus infusion has a limited efficacy in

patients with ACC, providing a tumor response rate of 10% to 15%, whereas the modulation of FU either by leucovorin (LV)[1] or methotrexate[2] led to a doubling of tumor response rates. A similar increase in tumor response rate was also observed with the use of FU as an intravenous continuous infusion,[3] and an even greater efficacy was reported in patients with metastases confined to the liver treated by locoregional administration of fluoropyrimidines, using hepatic artery infusion.[4] Even though the impact on overall survival of these FU administration modalities remains modest,[5] a small but statistically significant survival benefit was reported in each of these meta-analyses, with the exception of the FU versus FU-LV meta-analysis.[1] Meanwhile, FU-LV has proven to be an efficient regimen in the adjuvant setting for patients with resected stage II or III colon cancer.[6-8] Therefore, we hypothesized that the lack of survival benefit reported in the initial FU-LV meta-analysis published in 1992 may have been because of a lack of statistical power and because heterogeneity across the trials was not sufficiently taken into account. We decided to reassess the comparison of FU with FU-LV through an update of the initial FU-LV meta-analysis, including new trials and longer follow-up.

PATIENTS AND METHODS

The search for eligible trials and the data collection were performed by MAGIC (Creteil, France). Data were checked in the Department of Biostatistics of Gustave Roussy Institute (Villejuif, France), where analyses were also performed in collaboration with MAGIC.

Eligible Trials

All strictly randomized trials comparing FU-LV to FU alone in front-line treatment for ACC were considered as eligible for the meta-analysis. Trials using a protracted continuous-infusion FU-based regimen for more than 24 hours were not eligible for this meta-analysis because the biochemical mechanism of FU modulation by LV may differ when FU is administered as a continuous infusion over several days.[9] In regard to the FU-LV–based regimens, trials using either low- (< 100 mg/m^2/d) or high-dose LV (200 to 500 mg/m^2/d) were eligible. Trials using oral LV were not included because of the potential variation in the bioequivalence compared with intravenous administration schemes. Trials incorporating interferon were eligible only if interferon was delivered in a similar fashion in both treatment arms.

On the basis of the findings of our previous analyses,[2,3] trials were stratified according to the difference in prescribed FU dose between treatment arms. This stratification by FU dose was not performed in the initial FU-LV meta-analysis.

Search for Relevant Trials

The present meta-analysis was based on the trials previously included in the initial meta-analysis,[1] which were updated if needed, and on the trials conducted thereafter. The search for new relevant randomized trials was initiated in November 1998 by consulting all major medical journals, references of the selected trials, Medline, CancerLit, Physician Data Query, and the proceedings of major congresses held since 1990, and through personal contacts with principal investigators of individual trials.

The previous meta-analysis included the following nine trials: City of Hope,[10] Toronto,[11] Genova,[12] Bologna,[13] Gruppo Italiano Studio Carcinomi Apparato Digerente,[14] Roswell Park Cancer Institute,[15] Gruppo Oncologico Italiano di Ricerca Clinica,[16] Gastrointestinal Tumor Study Group (GITSG),[17] and Northern California Oncology Group (NCOG).[18] Updated patient data were obtained for the Toronto trial[11]; update of patient follow-up was not necessary in the remaining trials.

The following 13 additional trials were identified: North Central Cancer Treatment Group (NCCTG)-Mayo Clinic,[19] Siena,[20] Crema,[21] Schweizerische Arbeitsgruppe fur Klinische Krebsforschung (SAKK),[22] European Organization for Research and Treatment of Cancer (EORTC),[23] Southwest Oncology Group (SWOG),[24] Arbeitsgemeinschaft Internische Onkologie (AIO),[25] Hellenic Cooperative Oncology Group,[26] Spain,[27] Hungary,[28] Bern,[29] Arbeitsgemeinschaft Gastroenterologische Onkologie Nordheim-Westfalen,[30] and Tubingen.[31] Three of the additional trials,[29-31] representing a total of 331 patients, were not made available for the meta-analysis.

Thus, the present meta-analysis was based on 19 trials, including 3,338 patients (Table 1). The SWOG trial[24] and the EORTC trial[23] had two different FU-LV arms. Thus, control arms of these two trials were considered twice in analysis, bringing the total number of pair-wise comparisons to 21 and the total number of patients for the calculations to 3,597.

The FU predictive cumulative dose was calculated for each study arm at the end of the 17th week of treatment. The pair-wise comparisons were stratified in three groups according to the difference in predictive cumulative FU dose between treatment arms (Table 1). Group 1 consisted of 10 comparisons (1,791 patients) in which no difference in FU dose was found between the two arms (City of Hope,[10] Toronto,[11] NCCTG-Mayo Clinic,[19] Genova,[12] Crema,[21] Bologna,[13] Gruppo Italiano Studio Carcinomi Apparato Digerente,[14] SAKK,[22] and EORTC 1[23]) and one comparison in which FU was administered at a slightly lower dose in the FU alone arm (Siena[20]). Group 2 consisted of six comparisons (834 patients) in which FU was given at a 15% to 33% higher dose in the FU alone arm (Roswell Park Cancer Institute,[15] Gruppo Oncologico Italiano di Ricerca Clinica,[16] SWOG 1 and 2[24], AIO,[25] and Hellenic Cooperative Oncology Group[26]). Group 3 consisted of five comparisons (972 patients) in which FU dose was at least 66% higher in the FU alone arm (GITSG,[17] NCOG,[18] Spain,[27] Hungary,[28] and EORTC 2[23]).

Protocol for the Meta-Analysis

In 1999, all principal investigators received a protocol for the meta-analyses and were asked to provide individual patient data. Information requested for every randomized patient included date of randomization, tumor measurability (ie, measurable or nonmeasurable tumors), treatment assigned by randomization, age, sex, performance status according to the Eastern Cooperative Oncology Group scale, primary tumor site (colon or rectum), site of metastases, overall response status with the first assigned treatment, date of response or progression with the first allocated treatment, date of death or last visit, survival status, and cause of death if applicable. Data on toxicity were not collected.

Data Collection

All individual patient data were received by October 2003, checked, reanalyzed, and discussed with the principal investigators

Table 1. Randomized Clinical Trials Comparing FU (± IFN-α) to FU-LV (± IFN-α) in Advanced Colorectal Cancer

Trial	Treatment Arms	No. of Patients
Same dose FU or < 15% increase in the FU alone arm		
City of Hope[10]	FU 370 bolus,* days 1-5, every 28 days	40
	FU 370 bolus* + LV 500 24-hour infusion, days 1-5, every 28 days	39
Toronto[11]	FU 425†, days 1-5, every 28 days	64
	FU 370 + LV 200, days 1-5, every 28 days	66
NCCTG-Mayo Clinic[19]	FU 500 bolus, days 1-5, every 35 days	70
	FU 370-425 bolus‡ + LV 20 bolus, days 1-5, every 28-35 days	73
	FU 370 bolus + LV 200 bolus, days 1-5, every 28-35 days	69
Genova[12]	FU 600 bolus, every 7 days	73
	FU 600 bolus + LV 500 2-hour infusion, every 7 days	75
Siena[20]	FU 400, days 1-5, every 28 days	91
	FU 400 + LV 200, days 1-5, every 21 days	94
Crema[21]	FU 370 30-minute infusion, days 1-5, every 28 days	50
	FU 370 30-minute infusion + LV 200 bolus, days 1-5, every 28 days	100
Bologna[13]	FU 600 bolus, once weekly, for 6 weeks, followed by a 2-week rest period	30
	FU 600 bolus + LV 200 1-hour infusion, once weekly, for 6 weeks, followed by a 2-week rest period	34
GISCAD[14]	FU 400 bolus, days 1-5, every 28 days	90
	FU 400 bolus + LV 200 bolus, days 1-5, every 28 days	92
SAKK[22]	FU 400 bolus, days 1-5, every 28 days	158
	FU bolus 400 + LV 20 bolus, days 1-5, every 28 days	152
EORTC 1[23]	FU 2,600 24-hour infusion, once weekly, for 6 weeks, followed by a 2-week rest period	166
	FU 2,600 24-hour infusion + LV 500 2-hour infusion, once weekly, for 6 weeks, followed by a 2-week rest	165
15% to 33% FU increase in the FU alone arm		
RPCI[15]	FU 450 bolus, days 1-5 + FU 200 days 7, 9, 11, 13, 15, and 17 every 45 days	23
	FU 600 bolus + LV 500 2-hour infusion, once weekly, for 6 weeks, followed by a 2-week rest period	30
GOIRC[16]	FU 13.5 mg/kg/d§ bolus, days 1-5, every 28 days	90
	FU 400 bolus + LV 200 bolus, days 1-5, every 28 days	91
SWOG 1[24]	FU 500 bolus, days 1-5, every 35 days	93
	FU 425 bolus + LV 20 bolus, days 1-5, every 28-35 days	89
SWOG 2[24]	FU 500 bolus, days 1-5, every 35 days	93
	FU 600 bolus + LV 500 3-hour infusion, once weekly, for 6 weeks, followed by a 2-week rest period	89
AIO[25]	FU 2,600 24-hour infusion, once weekly, for 6 weeks, followed by a 2-week rest, + IFN 3 MUI/d, 3 days a week, before FU	49
	FU 2,000 24-hour infusion + LV 500 2-hour infusion, once weekly, for 6 weeks, followed by a 2-week rest, + IFN 3 MUI/d, 3 days a week, before FU	49
HeCOG[26]	FU 600 2-hour infusion, once weekly, for 6 weeks, followed by a 2-week rest	68
	FU 500 1-hour infusion + LV 200 2-hour infusion, once weekly, for 6 weeks, followed by a 2-week rest	70
> 66% increase in the FU alone arm		
GITSG[17]	FU 500 bolus,‖ days 1-5, every 28 days	113
	FU 600 bolus + LV 25 2-hour infusion for 6 weeks, followed by a 2-week rest	115
	FU 600 bolus + LV 500 2-hour infusion day 1, for 6 weeks, followed by a 2-week rest	115
NCOG[18]	FU 12 mg/kg/d§ bolus, days 1-5, then 15 mg/kg/d§ bolus, every 7 days (from day 12)	55
	FU 400 bolus + LV 200 bolus, days 1-5, every 28 days	107
Spain[27]	FU 1200 bolus, every 14 days	33
	FU 600 bolus + LV 200 1-hour infusion, every 14 days	29
Hungary[28]	FU 750 4-hour infusion, days 1-5, + IFN 3 MUI/d, 3 days a week, every 28 days	34
	FU 425 24-hour infusion + LV 20 bolus, days 1-5, + IFN 3 MUI/d, 3 days a week, every 28 days	38
EORTC 2[23]	FU 2,600 24-hour infusion, once weekly, for 6 weeks, followed by a 2-week rest	166
	FU 425 bolus + LV 20 bolus, days 1-5, every 28-35 days	167
Total	FU	1,390¶
	FU-LV	1,948

NOTE. Doses in mg/m^2/d unless otherwise stated.

Abbreviations: FU, fluorouracil; IFN-α, interferon alfa; LV, leucovorin; NCCTG, North Central Cancer Treatment Group; GISCAD, Gruppo Italiano Studio Carcinomi Apparato Digerente; SAKK, Schweizerische Arbeitsgruppe für Klinische Krebsforschung; EORTC, European Organization for Research and Treatment of Cancer; RPCI, Roswell Park Cancer Institute; GOIRC, Gruppo Oncologico Italiano di Ricerca Clinica; SWOG, Southwest Oncology Group; AIO, Arbeitsgemeinschaft Internische Onkologie; MUI/d, millions of units per day; HeCOG, Hellenic Cooperative Oncology Group; GITSG, Gastrointestinal Tumor Study Group; NCOG, Northern California Oncology Group.

*FU 250 with dose escalation to 370 if previous radiotherapy.

†FU 370 with dose escalation, 30 per step (mean dose administered to patients, 425).

‡FU dose increase after an interim toxicity analysis.

§1 mg/kg = 37 mg/m^2.

‖FU 500 with dose escalation by 25 mg by cycles.

¶For analyses, two control arms are counted twice (SWOG and EORTC), leading to a total of 1,649 patients rather than 1,390 patients.

of each trial. An investigator meeting was held in Chicago, IL, in May 2003.

Patient Characteristics

A total of 3,338 patients were considered in the meta-analysis; 1,390 patients had been allocated to FU alone, and 1,948 patients had been allocated to FU-LV. The median age was 62 years (range, 20 to 99 years). The male to female ratio was 60:40. Sixty-seven percent of the patients had primary colon cancer. The performance status was less than 2 in 82% of the patients. Thirty-six percent of the patients had metastases confined to the liver, and 8% had metastases confined to the lung. At the time of analysis, 90% of the patients had died. There were no major differences in patient characteristics between treatment arms. The main patient characteristics are listed in Table 2.

Tumor Response and Survival

Complete response and partial response criteria adopted in all individual trials followed the WHO recommendations.[32] For the purpose of the meta-analyses, patients experiencing minimal response, stable disease, or progressive disease were considered to have no response. In all trials, treatment was maintained until disease progression or severe toxicity. Duration of survival was calculated from the date of randomization to the date of death, whatever its cause.

Statistical Analysis

The statistical methods for meta-analyses based on individual patient data were described in detail in previous publications.[1-4,33,34] All analyses were based on an intent-to-treat basis, without any patient exclusion. Tumor responses were displayed as odds ratio (OR) in individual trials and overall and analyzed using a Mantel-Haenszel test.[35] Prognostic factors for response were identified through a logistic regression model.[36] Survival times were compared through hazard ratios (HR) in individual trials and overall by a fixed-effect model.[37] χ^2 heterogeneity tests were used to test for statistical heterogeneity across trials. An indirect comparison was performed between trials according to the difference in predicted cumulative FU dose between treatment arms through a test for trend and for interaction. Residual heterogeneity after accounting for predicted cumulative FU dose was tested using the difference between the χ^2 value for global heterogeneity and the χ^2 value for interaction.[38]

Subgroup analyses were performed to check the effects of the treatment on predefined patient characteristics. Median follow-up was computed by the potential follow-up method.[39] Prognostic factors for survival were identified through a proportional hazards regression model.[40] CIs for the proportion of responders are based on normal approximations. All P values were two-sided.

RESULTS

Tumor Response Analysis

Overall tumor response rate for the entire population was 17% (95% CI, 16% to 18%). Six individual trials (City of Hope,[10] Toronto,[11] NCCTG,[19] Crema,[21] SAKK,[22] and GITSG[17]) showed a benefit of FU-LV over FU alone in terms of tumor response. In the combined analysis, the tumor response rate was 11% (95% CI, 9% to 12%) for patients allocated to FU alone and 21% (95% CI, 19% to 23%) for patients allocated to FU-LV. This result was statistically significant ($P < .0001$), with an OR for response of 0.53 (95% CI, 0.44 to 0.63). The ORs for tumor response for individual trials and overall are presented in Figure 1. There was a significant heterogeneity between trials, with a significant interaction between treatment benefit in terms of tumor response and the predictive cumulative FU dose (Fig 1). No statistically significant difference in tumor response rate was demonstrated for trials in which the FU dose was increased (> 15%) in the FU alone arm, although there was a trend toward improved response rates with FU-LV in all three strata. There was no significant residual heterogeneity ($P = .38$) beyond this one.

In three comparisons (EORTC 1,[23] AIO,[25] and Hungary[28]), FU was administered as a continuous infusion in both

Table 2. Patient Characteristics

Accrual Period and Treatment	No. of Patients	Male (%)	Median Age (years)	PS < 2 (%)	Primary Colon (%)	Metastasis	
						Liver Only (%)	Lung Only (%)
Same dose FU or < 15% increase in FU alone arm, 1983-1998							
FU	832	57	61	72	70	41	11
FU-LV	959	62	62	72	67	38	11
15% to 33% FU increase in the FU alone arm, 1984-1998							
FU	416	67	63	90	65	21	4
FU-LV	418	59	62	89	65	23	4
> 66% FU increase in the FU alone arm, 1984-1998							
FU	401	61	63	85	76	35	9
FU-LV	571	59	62	86	81	31	6
Total, 1983-1998							
FU	1649	59	62	81	68	37	9
FU-LV	1948	61	62	82	67	34	7

Abbreviations: PS, performance status; FU, fluorouracil; LV, leucovorin.

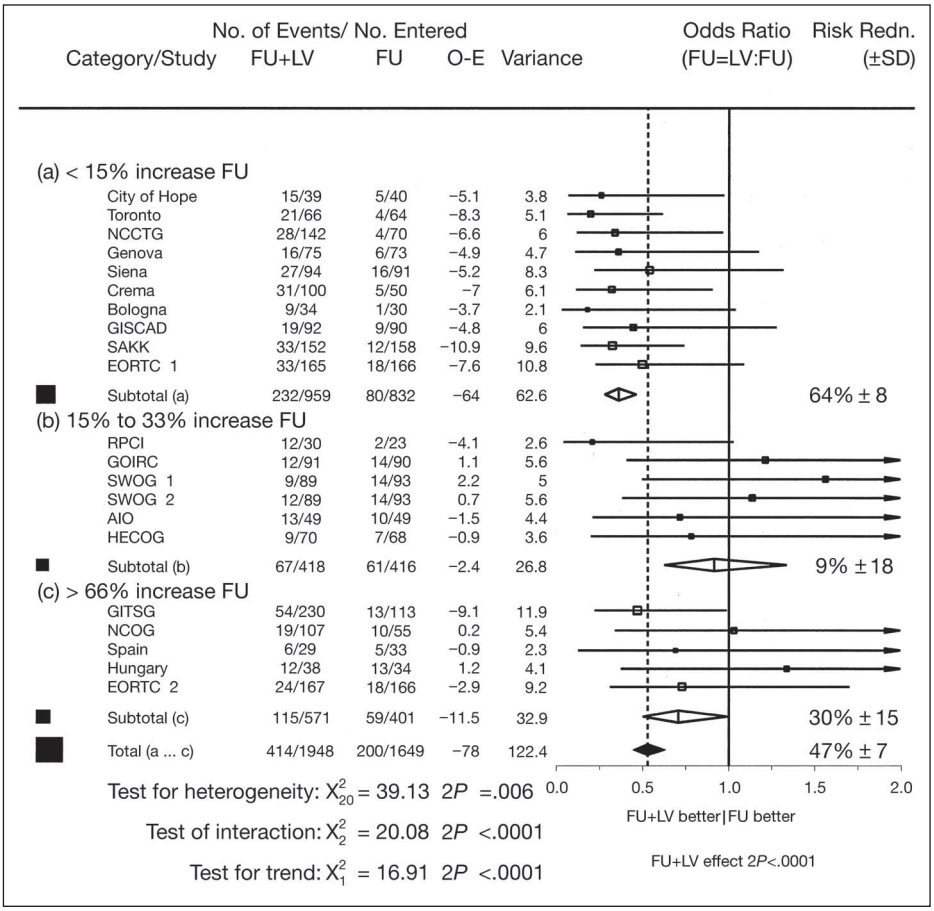


Fig 1. Forest plot for odds ratios of tumor response. Trials are ranked chronologically by start date (oldest trial first). FU, fluorouracil; LV, leucovorin; SD, standard deviation; O-E, observed minus expected; Redn, reduction; NCCTG, North Central Cancer Treatment Group; GISCAD, Gruppo Italiano Studio Carcinomi Apparato Digerente; SAKK, Schweizerische Arbeitsgruppe fur Klinische Krebsforschung; EORTC, European Organization for Research and Treatment of Cancer; RPCI, Roswell Park Cancer Institute; GOIRC, Gruppo Oncologico Italiano di Ricerca Clinica; SWOG, Southwest Oncology Group; AIO, Arbeitsgemeinschaft Internische Onkologie; HeCOG, Hellenic Cooperative Oncology Group; GITSG, Gastrointestinal Tumor Study Group; NCOG, Northern California Oncology Group.

arms. A sensitivity analysis showed that after exclusion of these three trials, the advantage of FU-LV over FU in terms of tumor response remained highly significant (OR, 0.49; 95% CI, 0.40 to 0.59).

In a logistic regression model, good performance status ($P < .0001$), metastases confined to the liver ($P = .002$), and FU-LV arm allocation ($P < .0001$) were found to be independent favorable prognostic factors for tumor response. The tumor response rate was 19%, 18%, and 11% for patients with a performance status of 0, 1, and 2 or more, respectively. The tumor response rate was 20% for patients with metastases confined to the liver compared with 16% for patients with other metastatic sites.

Subgroup analyses for the predefined patient characteristics showed no significant interactions between the treatment effect and patient characteristics. However, the interaction for performance status showed a strong trend at $P > .05$, with patients who had a performance status of 2 receiving the maximal benefit (Fig 2).

Survival Analysis

For the entire patient population, the median follow-up was 45 months. The median overall survival duration was 11.1 months. Only one individual trial (Crema[21]) showed a statistically significant survival benefit in favor of the FU-LV regimen. The combined analysis found a statistically significant survival benefit in favor of FU-LV (HR, 0.90; 95% CI, 0.87 to 0.94; $P = .004$). The survival HRs for individual trials and overall are presented in Figure 3. The median survival time was 10.5 months for patients allocated to FU alone and 11.7 months for patients allocated to the FU-LV. A test for proportionality of the HRs calculated over 6-month periods of time is presented in Table 3 and indicates that the survival differences between FU alone and FU-LV do not evolve constantly over time (test for interaction, $P = .03$).

Significant heterogeneity between trials was found (test for heterogeneity, $P = .03$), with a significant interaction between treatment survival benefit and differences in predictive FU cumulative dose between treatment arms (test for interaction, $P = .02$; and test for trend, $P = .005$). The survival benefit of biochemical modulation was restricted to trials using the same FU dose in the two treatment arms. No statistically significant difference was found in trials in which the dose of FU was increased (> 15%) in the FU alone arm. The difference of the size of treatment effect between the three trial groups explains most of the

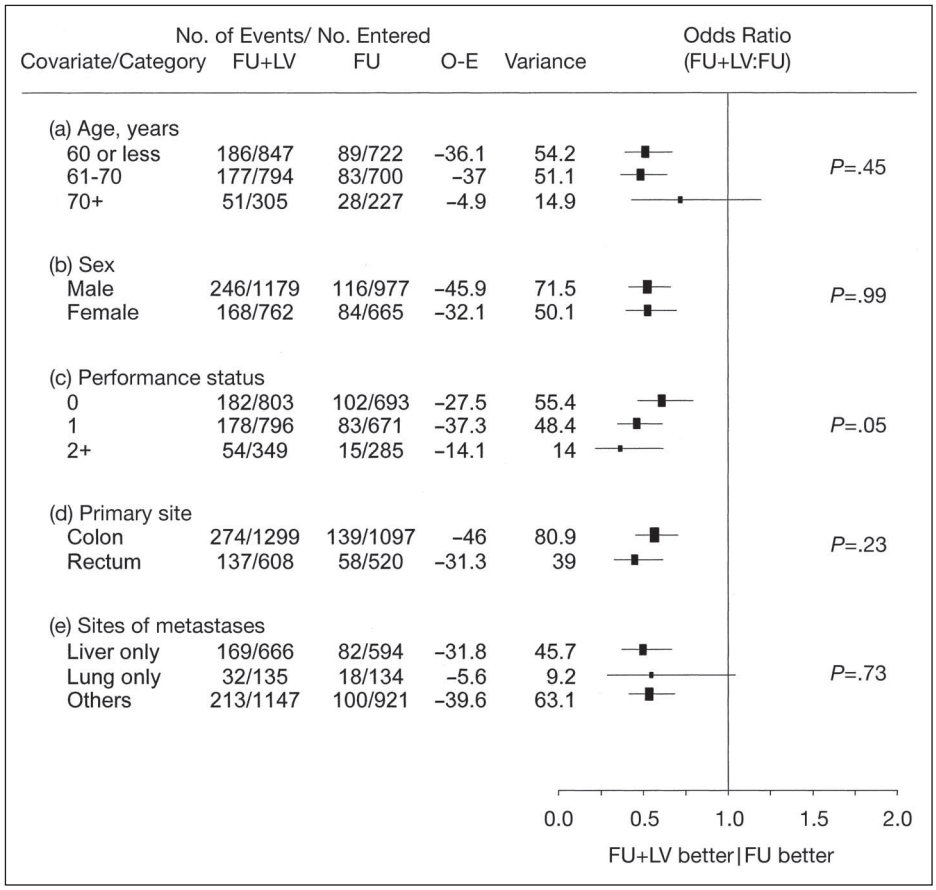


Fig 2. Subgroup analysis for treatment effect on tumor response according to patient characteristics (test for trend for age and performance status; otherwise, test for interaction). FU, fluorouracil; LV, leucovorin; O-E, observed minus expected.

heterogeneity. There is no significant residual heterogeneity ($P = .11$) beyond this one. A sensitivity analysis showed that the heterogeneity was no longer significant after removing the only positive trial[13] (test for heterogeneity, $P = .46$), whereas the benefit in survival in favor of FU-LV persisted (HR, 0.92; 95% CI, 0.86 to 0.99; $P = .03$).

One-year survival rates were 47% for patients allocated to FU-LV versus 37% for patients allocated to FU alone in the same dose of FU group, 55% versus 55% in the 15% to 33% increase in FU group, and 46% versus 46% in the more than 66% increase in FU group. A sensitivity analysis showed that the benefit of FU-LV over FU alone persists after exclusion of the three comparisons in which FU was administered as a continuous infusion in both arms (HR, 0.89; 95% CI, 0.82 to 0.96).

Using a Cox regression model, good performance status ($P < .0001$, when used as categorical variable), metastases confined to the liver ($P = .0002$) and to the lung ($P < .0001$), and FU-LV chemotherapy ($P = .0001$) were independent good prognosis factors for overall survival. One-year survival rates were 63% for patients with a performance status of 0, 45% for patients with a performance status of 1, and 20% for patients with a performance status of 2 or more. The 1-year survival rates were 50% for patients with liver metastases only, 57% for patients with lung metastases only, and 44% for patients with other metastatic sites.

Subgroup analyses for treatment effect showed no significant interactions between patient characteristics and treatment benefit (Fig 4). Again, there was the suggestion of an interaction between treatment benefit and performance status, with patients who had a performance status of 2 showing the greatest benefit. Overall survival curves by performance status and treatment are illustrated in Figure 5.

DISCUSSION

This updated meta-analysis has demonstrated that, in patients with ACC, the advantage of FU-LV over FU alone is not limited to tumor response. The present study found that, in addition to a two-fold increase in tumor response rate (OR, 0.53; $P < .0001$), there is a small but statistically significant improvement in overall survival (HR, 0.90; $P = .004$) in favor of FU-LV. Compared with the initial meta-analysis, the inclusion of more recent trials did not significantly increase the median survival duration, despite the recent availability of second-line

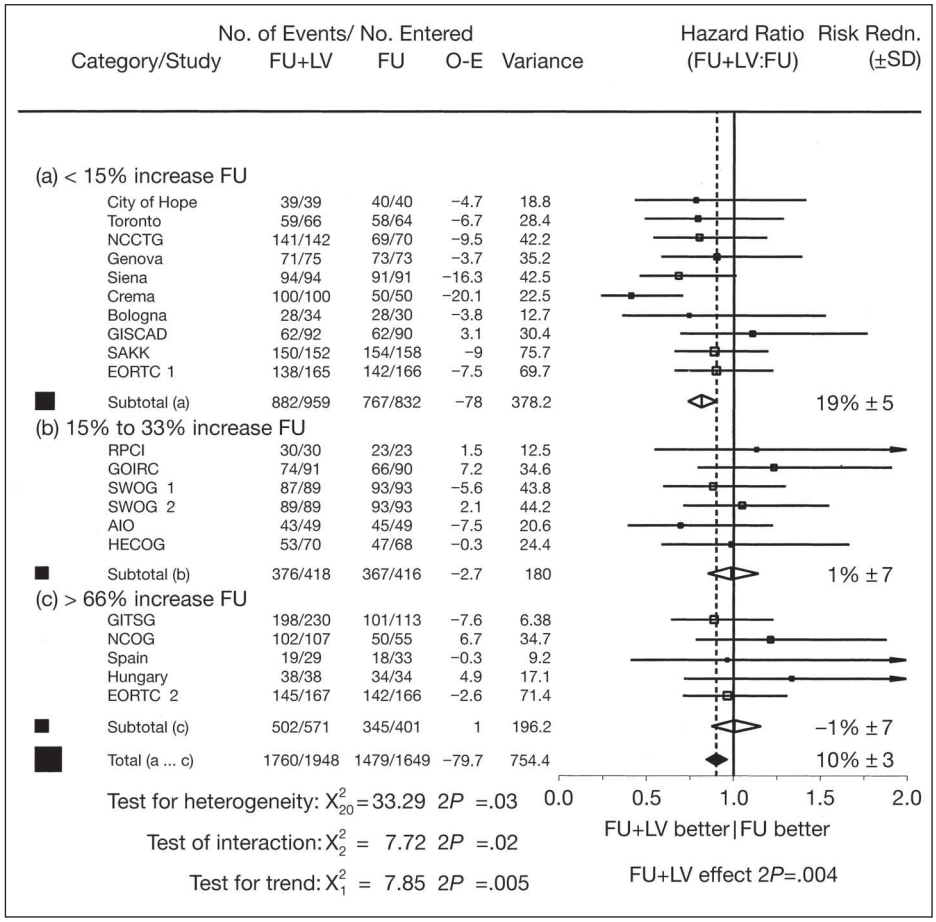


Fig 3. Forest plot for overall survival (hazard ratios). FU, fluorouracil; LV, leucovorin; SD, standard deviation; O-E, observed minus expected; Redn, reduction; NCCTG, North Central Cancer Treatment Group; GISCAD, Gruppo Italiano Studio Carcinomi Apparato Digerente; SAKK, Schweizerische Arbeitsgruppe fur Klinische Krebsforschung; EORTC, European Organization for Research and Treatment of Cancer; RPCI, Roswell Park Cancer Institute; GOIRC, Gruppo Oncologico Italiano di Ricerca Clinica; SWOG, Southwest Oncology Group; AIO, Arbeitsgemeinschaft Internische Onkologie; HeCOG, Hellenic Cooperative Oncology Group; GITSG, Gastrointestinal Tumor Study Group; NCOG, Northern California Oncology Group.

chemotherapy regimens. In fact, the treatment benefit was primarily observed in the first year (HR, 0.84; 95% CI, 0.76 to 0.94, for time period of 6 to 12 months) but not for the time period of 12 to 18 months (HR, 0.94; 95% CI, 0.83 to 1.06). The 1- and 2-year survival rates were 43% and 17%, respectively, for the patients allocated to FU alone and 49% and 17%, respectively, for the patients allocated to FU-LV. These findings provide indirect evidence that the chemotherapy regimen chosen as first-line therapy has a definitive impact, albeit small, on survival.

Table 3. HR Over Time*

Time Period	HR	95% CI
0-6 months	0.90	0.81 to 1.01
6-12 months	0.84	0.76 to 0.94
12-18 months	0.94	0.83 to 1.06
18-24 months	0.95	0.83 to 1.09
24+ months	0.97	0.85 to 1.11

NOTE. Test for interaction, $P = .027$.
Abbreviation: HR, hazard ratio.
*Overall HR, 0.90; 95% CI, 0.87 to 0.94; $P = .004$.

A possible FU dose effect was hypothesized after the results of two previous meta-analyses.[1,2] The initial FU versus FU-LV meta-analysis[1] and the FU versus FU plus methotrexate meta-analysis[2] generated the hypothesis that the benefit of FU modulation could be compensated by an increase of the FU dose in the FU alone arm. Therefore, a stratification of trials according to FU doses was prospectively planned in the statistical design of the present study to further address this issue. The updated meta-analysis confirmed a clear interaction between treatment benefit and FU dose, both for tumor response ($P < .0001$) and survival ($P = .02$). For both end points, the advantage of the modulation was restricted to trials using similar FU dosage in both arms. In this group of trials, 1-year survival rates were 37% for patients allocated to FU alone versus 47% for patients allocated to FU-LV, and 2-year survival rates were 12% versus 14%, respectively. Thus, the data presented here could suggest that high-dose FU can be substituted with FU modulation by LV. This statement would not take into consideration the increase of toxicity that is observed with high-dose FU. Although no data were recorded on toxicity in the meta-analysis, individual trials have clearly

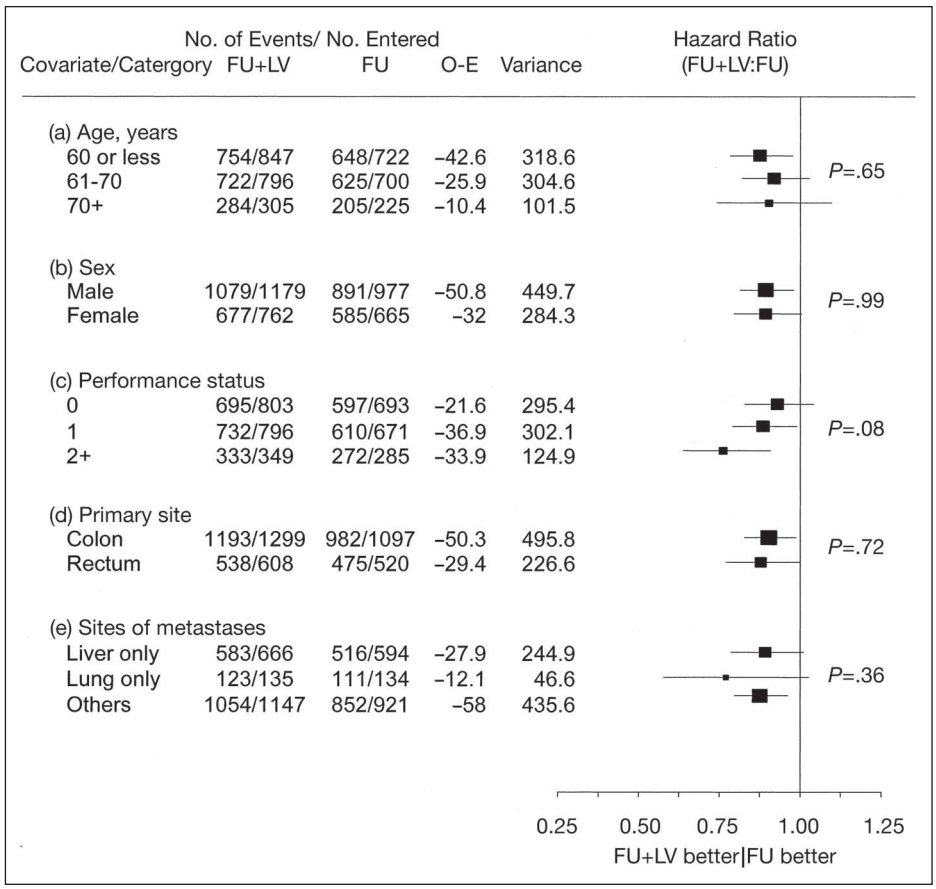


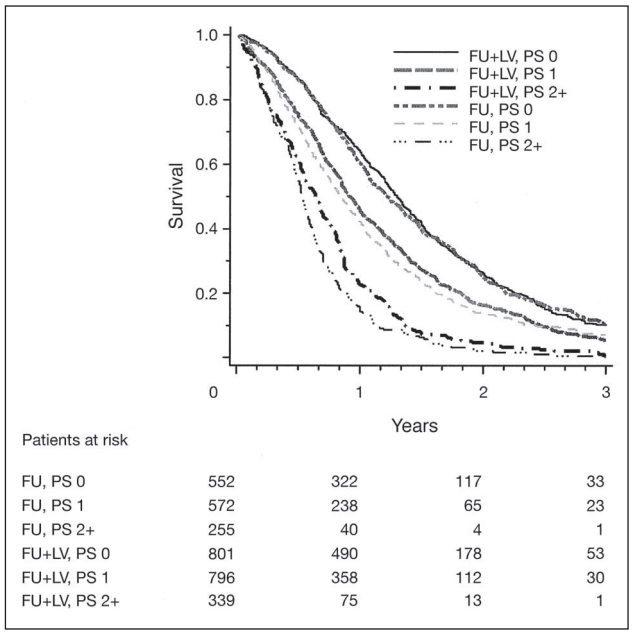
Fig 4. Subgroup analyses for treatment effect on survival according to patient characteristics (test for trend for age and performance status; otherwise, test for interaction). FU, fluorouracil; LV, leucovorin; O-E, observed minus expected.

shown that the toxicity induced by high-dose FU is not acceptable. In the NCOG trial[18] for instance, treatment efficacy was similar in the high-dose FU alone and the FU-LV arms, but toxicity was much higher in the FU alone arm. This greater toxicity of high-dose FU alone compared with FU-LV was not only observed for grades 3 and 4 hematologic toxicity (21% *v* 12%, respectively) but also for nonhematologic toxicity (42% *v* 24%, respectively). The authors concluded that "experimental regimens had superior therapeutic ratios of benefits versus toxicity."[18]

Analyses based on the actual administered dose would have needed the collection of chemotherapy doses delivered at every course of treatment. Because a retrospective collection of this information on 3,300 patients was not feasible, we used projected doses instead of actually administered doses. The potential limitations of this approach, especially when individual patient toxicity data were not available, must be underlined. However, the interaction between treatment benefit and FU dose is so clear that our findings concerning the importance of FU dose seem reliable.

The assessment of prognostic factors is one of the advantages of meta-analyses based on individual patient data; however, such analyses are limited to those parameters prospectively recorded. Because of the time period during which the trials included in the meta-analyses were conducted, only main clinical characteristics were available for prognostic factors analyses. Performance status was already reported in our meta-analyses as the most relevant prognostic factors for tumor response[2,3] and overall survival.[1-4,34] Metastases confined to the liver or to the lung were also reported as favorable independent prognostic factors for overall survival in a meta-analysis.[34] Rectum as the primary tumor site was associated with higher tumor response rate[34] and better survival.[3,34] The present meta-analysis confirms the relevance of simple clinical factors, such as performance status and site of metastases, for the outcome of patients with ACC treated with fluoropyrimidines. Should new biologic markers be prospectively collected in large-scale individual clinical trials, future meta-analyses will be able to better establish the prognosis of patients with ACC.

The meta-analysis did not identify clear subgroups of patients who benefit more from FU-LV regimen. The interaction test between treatment effect and performance status had a borderline significant effect both for tumor response ($P = .05$) and survival ($P = .08$). Because most of the



Patients at risk

FU, PS 0	552	322	117	33
FU, PS 1	572	238	65	23
FU, PS 2+	255	40	4	1
FU+LV, PS 0	801	490	178	53
FU+LV, PS 1	796	358	112	30
FU+LV, PS 2+	339	75	13	1

Fig 5. Overall survival curves according to treatment and performance status. FU, fluorouracil; LV, leucovorin; PS, performance status.

patients with a performance status of 2 belong to the group of trials with the same FU dose (68%) and 23% belong to the Siena trial, this result should be interpreted with caution. The updated meta-analysis confirms the value of FU-LV in the management of patients with ACC.

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The acknowledgment is included in the full-text version of this article, available online at www.jco.org. It is not included in the PDF (via Adobe® Acrobat Reader®) version.

Appendix

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An additional appendix is included in the full-text version of this article, available online at www.jco.org. It is not included in the PDF (via Adobe® Acrobat Reader®) version.

Authors' Disclosures of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.

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