

HEPATIC ARTERIAL INFUSION OF CHEMOTHERAPY AFTER RESECTION OF HEPATIC METASTASES FROM COLORECTAL CANCER

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ABSTRACT

Background Two years after undergoing resection of liver metastases from colorectal cancer, about 65 percent of patients are alive and 25 percent are free of detectable disease. We tried to improve these outcomes by treating patients with hepatic arterial infusion of floxuridine plus systemic fluorouracil after liver resection.

Methods We randomly assigned 156 patients at the time of resection of hepatic metastases from colorectal cancer to receive six cycles of hepatic arterial infusion with floxuridine and dexamethasone plus intravenous fluorouracil, with or without leucovorin, or six weeks of similar systemic therapy alone. Patients were stratified according to previous treatment and the number of liver metastases identified at operation. The study end points were overall survival, survival without recurrence of hepatic metastases, and survival without any metastases at two years.

Results The actuarial rate of overall survival at two years was 86 percent in the group treated with combined therapy and 72 percent in the group given monotherapy alone ($P=0.03$). The median survival was 72.2 months in the combined-therapy group and 59.3 months in the monotherapy group, with a median follow-up of 62.7 months. After two years, the rates of survival free of hepatic recurrence were 90 percent in the combined-therapy group and 60 percent in the monotherapy group ($P<0.001$), and the respective rates of progression-free survival were 57 percent and 42 percent ($P=0.07$). At two years, the risk ratio for death was 2.34 among patients treated with systemic therapy alone, as compared with patients who received combined therapy (95 percent confidence interval, 1.10 to 4.98; $P=0.027$), after adjustment for important variables. The rates of adverse effects of at least moderate severity were similar in the two groups, except for a higher frequency of diarrhea and hepatic effects in the combined-therapy group.

Conclusions For patients who undergo resection of liver metastases from colorectal cancer, postoperative treatment with a combination of hepatic arterial infusion of floxuridine and intravenous fluorouracil improves the outcome at two years. (N Engl J Med 1999;341:2039-48.)

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NEARLY 129,000 patients are given a diagnosis of colorectal cancer each year in the United States, and hepatic metastases develop in 60 percent of these patients.¹ Of these 77,400 patients, 15 to 25 percent have metastatic liver disease when the primary tumor is discovered.² Autopsy studies have shown that metastatic disease remains confined to the liver in a third of patients who die of colorectal carcinoma.³ Survival for five years or more is rare among patients with unresected hepatic metastases who receive conventional systemic chemotherapy or optimal supportive care. Each year, approximately 14,300 patients with colorectal cancer undergo liver resection to remove metastases. After two years, about 65 percent of these patients are alive, and 25 percent have no detectable cancer.⁴⁻⁶ Of the patients in whom the disease recurs, the liver is the site of recurrence in half of them. Approximately 75 percent of all recurrences appear within the first two years after resection of hepatic metastases.⁷ Currently, there is no standard therapeutic approach after hepatic resection of colorectal metastases. To treat suspected micrometastases in the remaining liver and prevent extrahepatic spread, a reasonable approach involves the use of a combination of regional therapy, such as hepatic arterial infusion of chemotherapy, and systemic chemotherapy.

The rationale for hepatic arterial infusion is that the liver has a dual blood supply. Established hepatic metastases derive their blood supply largely from the hepatic artery, whereas normal liver cells derive most of their blood supply from the portal vein.⁸ Since tumors that may remain after hepatic resection could have a diameter of 2 to 3 mm, they would most likely derive most of their blood supply from the arterial circulation.⁸ Infusion of chemotherapy directly into the hepatic artery thus exposes the metastases to high drug concentrations while sparing normal liver tissue.⁹ Prospective, randomized studies of patients with unresectable liver disease have reported response rates ranging from 42 to 62 percent in the groups given hepatic arterial infusion, as compared with rates of 10

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to 21 percent in the groups treated with systemic chemotherapy.¹⁰⁻¹⁵ A pilot study of hepatic arterial infusion and systemic chemotherapy (combined therapy) was conducted to establish the correct doses for concurrent treatment in patients with resected disease.¹⁶

We compared the efficacy of a regimen combining hepatic arterial infusion of floxuridine and dexamethasone and systemic administration of fluorouracil, with or without leucovorin, with a similar regimen of systemic chemotherapy alone after the resection of hepatic metastases from colorectal cancer. The study end points were overall survival, survival free of hepatic progression, and overall progression-free survival at two years.

METHODS

Eligibility Criteria, Pretreatment Evaluation, and Follow-up

All patients had histologically confirmed colorectal adenocarcinoma with completely resectable hepatic metastases. Patients were excluded from the study for any of the following reasons: extrahepatic disease, prior hepatic radiation or resection, a history of some other type of cancer (unless the patient had been free of this disease for at least five years) or a current cancer in addition to colorectal adenocarcinoma, a white-cell count of less than 3000 cells per cubic millimeter, a platelet count of less than 100,000 cells per cubic millimeter, a serum total bilirubin level of at least 2.0 mg per deciliter (34.2 μ mol per liter), or a finding of metastases to portal lymph nodes at operation. Prior treatment with chemotherapy was permitted if the last dose had been given at least one month before the date of hepatic resection (initially, patients who had received fluorouracil and leucovorin were excluded). Computed tomographic (CT) scans of the abdomen and pelvis and chest x-ray films were obtained within six weeks before surgery. All patients provided written informed consent granting permission to undergo randomization intraoperatively. Of the 514 patients who were evaluated for liver resection, resection was not performed in 128 for the following reasons: 44 had unresectable metastases, 33 had extrahepatic disease, 33 had both unresectable metastases and extrahepatic disease, 1 had no tumor, and 17 had miscellaneous reasons for not undergoing resection. Of the 386 patients who underwent resection, 156 were included in the study. The remaining 230 patients did not participate for the following reasons: 105 patients declined, 28 had previously received fluorouracil and leucovorin (an initial exclusion criterion), 13 lived too far from the treatment center, 11 had poor arterial blood supply to the liver, 16 were not considered appropriate for the protocol, 5 had had prior hepatic resection, 3 had no tumor, 35 were excluded as a result of the surgeon's decision, and 14 were excluded for miscellaneous reasons. Before resection, all patients underwent hepatic angiography, including visualization of the celiac and superior mesenteric arteries, to evaluate hepatic arterial blood supply. Only patients who were considered to have undergone complete resection by their surgeons underwent randomization. All surgical margins and nodes assessed by the examination of frozen sections at the time of operation were negative for tumor. (Subsequent pathological review revealed that 21 patients had positive surgical margins and 1 patient had positive portal lymph nodes. These patients remained in the study and were included in the analysis.)

Pretreatment evaluation included a complete history taking, physical examination, and laboratory tests within one week before chemotherapy was begun. All patients underwent CT scanning of the abdomen and pelvis and chest radiography every three months during the first two years after resection, every four months for the next two years, and every six months thereafter. All suspicious findings were reviewed with the radiologists. The resectability of

recurrences in the liver or lungs was discussed at surgical conferences. Any recurrences that were deemed resectable were resected.

Guidelines for Pump Insertion

All patients who were randomly assigned to receive combined therapy received an implantable pump (model 400, Infusaid). At the time of pump insertion, surgeons were advised to perform a biopsy of any suspicious-looking nodes or masses and to perform cholecystectomy if it had not been done previously.¹⁷ The pump's catheter was positioned at the junction of the proper and common hepatic arteries through the gastroduodenal, splenic, or celiac artery. The distal gastroduodenal artery, the right gastric artery, and small branches supplying the stomach and duodenum were ligated, as were all accessory hepatic arteries. The catheter was immobilized in the artery with two nonabsorbable ties. Postoperatively, human serum albumin macroaggregated with technetium-99m was infused through the side port of the pump to assess the adequacy of perfusion.

Chemotherapy

In the combined-therapy group, systemic chemotherapy was initiated four weeks after resection, and six cycles were scheduled. Fluorouracil was administered daily for five days as an intravenous bolus of 325 mg per square meter of body-surface area, preceded each day by a half-hour infusion of leucovorin at a dose of 200 mg per square meter. Two weeks later, the first dose of local therapy was instilled into the pump (0.25 mg of floxuridine per kilogram of body weight per day for 14 days in combination with 20 mg of dexamethasone, 50,000 U of heparin, and enough normal saline to result in a volume of 50 ml). After 14 days, the pump was emptied and the patient had a 1-week rest before the next cycle (a total of six cycles). In the monotherapy group, chemotherapy was also started four weeks after resection, and six cycles were scheduled. The same dose of leucovorin was given (200 mg per square meter), but the dose of fluorouracil was higher (370 mg per square meter intravenously for five days every four weeks).

If a patient in either group had previously received fluorouracil and leucovorin, the systemic chemotherapy (fluorouracil alone) was administered by continuous infusion. In such patients in the combined-therapy group, the daily dose of fluorouracil was 850 mg per square meter for five days every five weeks, and in patients in the monotherapy group, it was 1000 mg per square meter for five days every four weeks. In both groups the following adjustments were made in the dose of fluorouracil: 80 percent of the dose was given if the patient had a white-cell count of 1001 to 1999 per cubic millimeter and grade 3 (moderate) stomatitis or diarrhea, and 60 percent of the dose was given if the patient had a white-cell count of no more than 1000 per cubic millimeter and grade 4 (severe) stomatitis or diarrhea.

All adverse effects except for elevations in hepatic-enzyme levels that were attributable to hepatic arterial infusion were graded according to the Common Toxicity Criteria of the National Cancer Institute. On this scale a grade of 0 indicates the absence of adverse effects, a grade of 1 minimal effects, a grade of 2 mild effects, a grade of 3 moderate effects, and a grade of 4 severe effects. Modifications in the dose of floxuridine because of liver-function abnormalities have been described previously.¹⁸ Epigastric pain prompted a full workup with upper gastrointestinal endoscopy. If an ulcer or gastroduodenitis was identified, therapy was withheld for one month to allow healing. Severe abdominal pain or diarrhea during hepatic arterial infusion prompted immediate emptying of the drugs from the pump and the instillation of heparin-treated saline or 50 percent glycerol until the results of a workup (including repeated flow scanning to rule out extrahepatic perfusion) were available.

Statistical Analysis

When we designed our study, published data suggested that 75 percent of patients who undergo resection of hepatic metastases have a recurrence within two years (50 percent of these recurrences are in the liver) and that the two-year survival rate for these

patients is approximately 65 percent. In an effort to reduce the high rate of recurrence — especially in the liver — and increase the survival rate at two years, we designed this study so that it would have the ability to detect a 20 percent reduction in the rate of recurrence in the liver and elsewhere and a 20 percent increase in the two-year survival rate. Using a one-sided significance test, we calculated that to detect such differences, 156 patients were needed to give the study a power of 80 percent at an alpha level of 5 percent. Two-sided significance tests were used in the final analysis.

Patients were stratified at randomization according to the number of liver metastases and treatment history.⁷ Initially, only two groups were considered: patients who had not received prior chemotherapy and patients who had previously received fluorouracil, with or without levamisole. Within each group, patients were further stratified into three subgroups according to the number of liver metastases noted at resection: one, two to four, and more than four metastases. At surgery, these patients were randomly assigned to receive either hepatic arterial infusion plus systemic chemotherapy or systemic chemotherapy alone. The eligibility criteria were later expanded to include patients who had previously been treated with fluorouracil and leucovorin; such patients were randomly assigned to receive either hepatic arterial infusion plus fluorouracil or fluorouracil alone.

Overall survival, survival free of hepatic progression, and overall progression-free survival were analyzed from the date of liver resection to the date of death (for overall survival) or the disease recurrence or progression (for survival free of hepatic progression and overall progression-free survival). Three patients in the combined-therapy group were discovered retrospectively to have had metastases (two to the lung and one to the portal nodes) at entry; for this reason, we report disease progression as well as recurrence.

Overall survival and progression-free survival at two years were the primary end points and were estimated according to the Kaplan–Meier method¹⁹ and compared with use of the log-rank test and Wilcoxon test. Overall survival rates and progression-free survival rates at two years were derived from the corresponding Kaplan–Meier curves, and comparisons were made with use of the normal approximation test. We plotted Kaplan–Meier curves over the entire period of follow-up. All P values calculated with use of the log-rank and Wilcoxon tests were for comparisons of entire Kaplan–Meier curves in the two treatment groups.

In the analysis of prognostic factors, we confined our attention to the two-year follow-up period after resection. We examined the role of prognostic factors (univariate analysis) and their combined effect (multivariate analysis) on outcome using a Cox proportional-hazards model.²⁰ In the survival analysis, data on a patient were censored at two years if he or she had lived for a minimum of two years after resection. In the analysis of progression-free survival, data on patients were censored at two years if the patients were alive without disease progression two years after resection. Data on patients with less than two years of follow-up either were not censored on the date of death (for the analysis of overall survival) or disease progression (for the analysis of progression-free survival) or were censored on the date of the last follow-up visit or date of death if there was no evidence of progression. We used the best subgroup-selection method to choose the final multivariate Cox regression models with the help of the PROC PHREG statistical program for implementing Cox regression analysis (SAS Institute). This method identifies the model with the largest chi-square score of maximum likelihood (the one best supported by the data) for each fixed number of predictors. A model became the final model if the addition of an extra predictor to the model increased the chi-square score by less than 2. Variables considered in the univariate and the multivariate analyses had to have complete data on all 156 patients. We analyzed contingency tables by the chi-square test or Fisher's exact test, as appropriate. All tests were two-sided, and results with a P value of less than 0.05 were considered to indicate statistical significance. Statistical analyses were performed with the use of SAS software (SAS Institute) or S-Plus software (MathSoft). All analyses were performed on an intention-to-treat basis.

RESULTS

Characteristics of the Patients

The 156 patients who underwent complete resection of hepatic metastases from colorectal cancer underwent stratification and randomization intraoperatively. Seventy-four were randomly assigned to receive hepatic arterial infusion plus systemic chemotherapy, and 82 were assigned to receive systemic chemotherapy alone. The median follow-up was 62.7 months (range, 16 to 95). As of the most recent follow-up, 91 percent of our patients had been followed for at least two years and 55 percent had been followed for five years.

There were no significant differences between the two groups with respect to base-line characteristics (Table 1), including the number of liver metastases, the type of disease (metachronous vs. synchronous), Dukes' stage of disease, preoperative carcinoembryonic antigen levels, the percentage of liver involvement, the number of patients who underwent trisegmentectomy, the number whose surgical margins were positive, or the treatment history. The median time from resection of the primary tumor to the development of liver metastases was 6.8 months (range, 0.0 to 60.5) in the combined-therapy group and 9.1 months (range, 0.0 to 78.0) in the monotherapy group.

The median duration of survival was 66.7 months among patients who had not received prior chemotherapy and 67.8 months among patients who had previously received fluorouracil, levamisole, or both. As of the most recent analysis, median survival had not yet been reached in the patients who had previously been treated with fluorouracil and leucovorin. The median survival was 72.2 months in the group with one hepatic metastasis, 81.0 months in the group with two to four metastases, and 45.0 months in the group with more than four metastases.

Overall Survival

Actuarial survival rates at two years were 86 percent in the combined-therapy group and 72 percent in the monotherapy group ($P=0.03$). A univariate analysis of overall mortality at two years (Table 2) showed an unadjusted risk ratio for death of 2.13 (95 percent confidence interval, 1.01 to 4.50; $P=0.05$) in the monotherapy group as compared with the combined-therapy group. Kaplan–Meier survival curves (Fig. 1) demonstrated an estimated median survival of 72.2 months in the combined-therapy group and 59.3 months in the monotherapy group. Actuarial five-year survival rates were 61 percent in the combined-therapy group and 49 percent in the monotherapy group. If we excluded patients with extrahepatic disease at the time of enrollment or those who were never treated, the five-year survival rates were 68 percent for the combined-therapy group and 52 percent for the monotherapy group.

TABLE 1. BASE-LINE CHARACTERISTICS OF THE PATIENTS.

CHARACTERISTIC	COMBINED-THERAPY GROUP (N=74)	MONOTHERAPY GROUP (N=82)
Age — yr		
Median	59	59
Range	28–79	30–77
Sex — no. (%)		
Male	44 (59)	47 (57)
Female	30 (41)	35 (43)
Karnofsky score		
Median	90	90
Range	70–100	70–100
Liver involvement — %		
Median	20	20
Range	5–50	10–60
Serum carcinoembryonic antigen — ng/ml		
Median	11.5	13.8
Range	0.9–258.9	1.3–5600.0
Lactate dehydrogenase — U/liter		
Median	182	197
Range	105–1104	110–1398
Serum alkaline phosphatase — U/liter		
Median	84	86
Range	42–238	31–276
Serum aspartate aminotransferase — U/liter		
Median	20	21
Range	8–45	11–187
Serum total bilirubin — mg/dl*		
Median	0.5	0.6
Range	0.2–4.0	0.2–4.0
Serum albumin — g/dl		
Median	4.2	4.2
Range	2.3–5.0	1.4–5.0
White-cell count — $\times 10^{-3}/\text{mm}^3$		
Median	7.4	8.2
Range	3.5–24.0	4.4–24.0
Platelet count — $\times 10^{-3}/\text{mm}^3$		
Median	247	243
Range	131–664	109–456
No. of liver metastases — no. (%)†		
1	27 (36)	33 (40)
2–4	33 (45)	34 (41)
>4	14 (19)	15 (18)
Type of resection — no. (%)		
Trisegmentectomy	19 (26)	25 (30)
Wedge resection	2 (3)	4 (5)
Left- or right-lobe resection	36 (49)	31 (38)
Segmentectomy	11 (15)	14 (17)
Other	6 (8)	8 (10)
Type of disease — no. (%)		
Synchronous	23 (31)	27 (33)
Metachronous	51 (69)	55 (67)
Positive surgical margins — no. (%)	10 (14)	11 (13)
Prior treatment — no. (%)‡		
None	35 (47)	37 (45)
Adjuvant chemotherapy	29 (39)	33 (40)
Chemotherapy for metastatic disease	10 (14)	12 (15)
Fluorouracil and leucovorin	16 (22)	19 (23)

*To convert values for total bilirubin to micromoles per liter, multiply by 17.1.

†Eighteen patients in the combined-therapy group (24 percent) and 24 patients in the monotherapy group (29 percent) had four or more metastases.

‡Patients who had previously received treatment may have received more than one type of treatment.

To evaluate the effect of treatment while controlling for other variables, we used the best subgroup-selection method described in the Methods section to choose a multivariate regression model. After adjustment for variables selected in the final model — location of primary tumor (rectum vs. colon) and largest liver lesions (≥ 5 cm vs. < 5 cm) — the risk ratio for death in the monotherapy group as compared with the combined-therapy group was 2.34 (95 percent confidence interval, 1.10 to 4.98; $P=0.027$).

Survival Free of Hepatic Progression

During the first two years after surgery, 7 of 74 patients in the combined-therapy group and 30 of 82 patients in the monotherapy group had hepatic recurrences. The two-year actuarial rate of survival free of hepatic progression was 90 percent in the combined-therapy group and 60 percent in the monotherapy group ($P<0.001$). Kaplan–Meier estimates of survival free of hepatic progression (Fig. 2) show a clear divergence between the rates in the two groups throughout the study period ($P<0.001$ by the log-rank or Wilcoxon test). The median survival free of hepatic progression had not been reached in the combined-therapy group, but it was 42.7 months in the monotherapy group. In the univariate analysis, monotherapy and positive surgical margins were significantly associated with the risk of hepatic progression (Table 2). In a multivariate analysis, combined therapy had a strong protective effect, with a relative risk of hepatic progression in the first two years of follow-up of 5.39 in the monotherapy group as compared with the combined-therapy group (95 percent confidence interval, 2.36 to 12.31; $P<0.001$), after adjustment for the interval between the diagnosis of the primary cancer and resection (≤ 2 vs. > 2 years), the status of surgical margins (positive vs. negative), and the size of the largest liver metastases (≥ 5 cm vs. < 5 cm). Positive surgical margins were a significant risk factor for progression of hepatic metastases in both the univariate and multivariate analyses, with an adjusted risk ratio of 3.44 in the monotherapy group as compared with the combined-therapy group (95 percent confidence interval, 1.65 to 7.19; $P=0.001$). The rates of survival free of hepatic progression at five years were 74 percent (23 patients) in the combined-therapy group and 44 percent (21 patients) in the monotherapy group.

Overall Progression-free Survival

The two-year actuarial rates of overall progression-free survival were 57 percent in the combined-therapy group and 42 percent in the monotherapy group ($P=0.07$). The median duration of progression-free survival was 37.4 months in the combined-therapy group and 17.2 months in the monotherapy group (Fig. 3). In the first two years after surgery, 30 patients in the combined-therapy group and 44

TABLE 2. UNIVARIATE AND MULTIVARIATE ANALYSES OF THE RISK RATIOS FOR DEATH, HEPATIC PROGRESSION, AND OVERALL PROGRESSION DURING THE TWO YEARS AFTER COMPLETE RESECTION OF HEPATIC METASTASES.

VARIABLE	UNIVARIATE ANALYSIS		MULTIVARIATE ANALYSIS*	
	RISK RATIO (95% CI)	P VALUE	RISK RATIO (95% CI)	P VALUE
Overall†				
Treatment (monotherapy vs. combined therapy)	2.13 (1.01–4.50)	0.05	2.34 (1.10–4.98)	0.027
Location of primary tumor (rectum vs. colon)	1.91 (0.91–4.04)	0.09	2.17 (1.02–4.65)	0.05
Size of largest liver metastasis (≥5 cm vs. <5 cm)	1.48 (0.73–2.99)	0.28	1.75 (0.85–3.59)	0.13
Hepatic progression‡				
Treatment (monotherapy vs. combined therapy)	4.94 (2.17–11.25)	<0.001	5.39 (2.36–12.31)	<0.001
Primary cancer diagnosed 2 yr before liver resection (yes vs. no)	0.35 (0.11–1.15)	0.09	0.30 (0.09–0.97)	0.04
Surgical margins (positive vs. negative)	2.78 (1.35–5.76)	0.005	3.44 (1.65–7.19)	0.001
Size of largest liver metastasis (≥5 cm vs. <5 cm)	1.30 (0.67–2.53)	0.44	1.57 (0.80–3.05)	0.19
Overall progression§				
Treatment (monotherapy vs. combined therapy)	1.69 (1.06–2.70)	0.03	1.70 (1.07–2.72)	0.025
Dukes' stage (C vs. B)	1.75 (1.06–2.90)	0.03	1.68 (1.00–2.79)	0.05
Primary cancer diagnosed 2 yr before liver resection (yes vs. no)	0.50 (0.25–1.01)	0.05	0.45 (0.22–0.92)	0.03
Surgical margins (positive vs. negative)	2.05 (1.16–3.62)	0.01	2.42 (1.36–4.32)	0.003

*For each comparison, the values were adjusted for each of the other variables in the group.

†The risk ratios are for death.

‡The risk ratios are for hepatic progression.

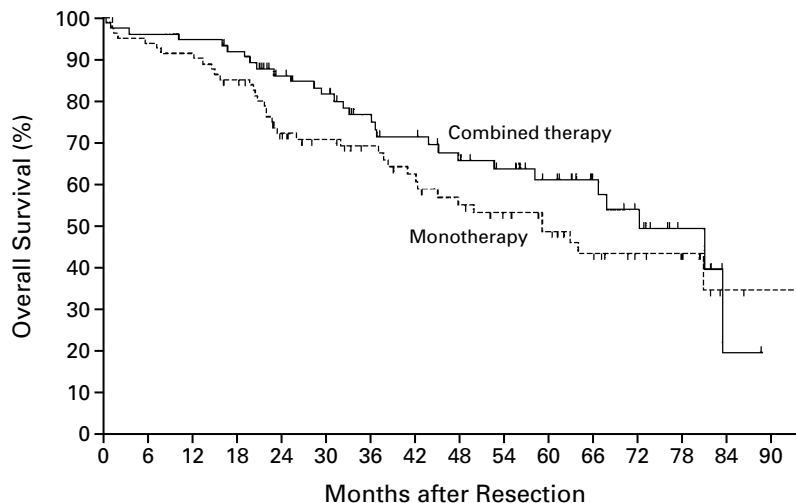


Figure 1. Kaplan–Meier Estimates of Overall Survival in the Group Assigned to Hepatic Arterial Infusion plus Systemic Chemotherapy (Combined Therapy) and the Group Assigned to Systemic Chemotherapy Alone (Monotherapy).

The estimated median survival was 72.2 months in the combined-therapy group (29 of the 74 patients died) and 59.3 months in the monotherapy group (38 of 82 patients died). Tick marks indicate the times of the last follow-up visits. Differences between groups were not significant ($P=0.11$ by the Wilcoxon test and $P=0.21$ by the log-rank test).

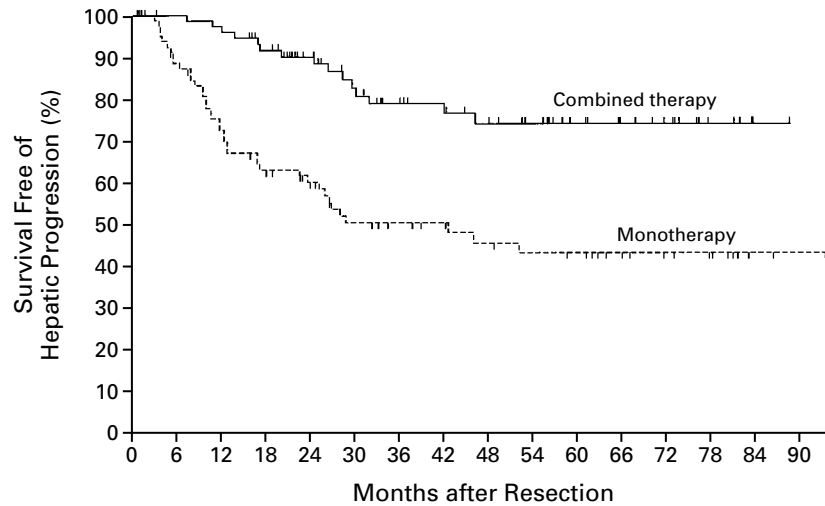


Figure 2. Kaplan–Meier Estimates of Survival Free of Hepatic Progression in the Group Assigned to Hepatic Arterial Infusion plus Systemic Chemotherapy (Combined Therapy) and the Group Assigned to Systemic Chemotherapy Alone (Monotherapy).

The estimated median survival free of hepatic progression had not been reached in the combined-therapy group (15 of 74 patients had hepatic progression) and was 42.7 months in the monotherapy group (39 of 82 patients had hepatic progression). Tick marks indicate the times of the last follow-up visits. Differences between groups were significant ($P < 0.001$ by both the Wilcoxon test and the log-rank test).

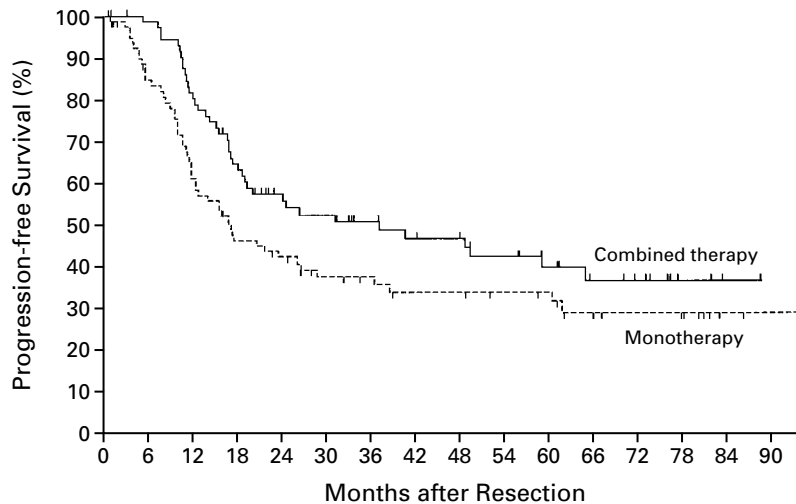


Figure 3. Kaplan–Meier Estimates of Overall Progression-free Survival in the Group Assigned to Hepatic Arterial Infusion plus Systemic Chemotherapy (Combined Therapy) and the Group Assigned to Systemic Chemotherapy Alone (Monotherapy).

The estimated median survival free of progression was 37.4 months in the combined-therapy group (40 of 74 patients had progressive disease) and 17.2 months in the monotherapy group (51 of 82 patients had progressive disease). Tick marks indicate the times of the last follow-up visits. Differences between groups were significant by the Wilcoxon test ($P = 0.01$) but not by the log-rank test ($P = 0.06$).

in the monotherapy group had disease progression, either within or outside the liver and in single or multiple sites. During this period, lung metastases were identified in 15 patients in the combined-therapy group and 17 patients in the monotherapy group. Other sites of recurrence were as follows: the liver in

7 patients in the combined-therapy group and 30 patients in the monotherapy group; the ovaries in 4 patients and 1 patient, respectively; bone in 3 patients in each group; pelvic area in 4 and 7 patients; lymph nodes in 3 and 10 patients; and other sites in 6 patients in each group. A multivariate analysis demon-

strated a risk ratio for progression of 1.70 in the monotherapy group as compared with the combined-therapy group (95 percent confidence interval, 1.07 to 2.72; $P=0.02$), after adjustment for Dukes' stage (C vs. B), interval between the diagnosis of the primary cancer and resection (≤ 2 vs. > 2 years), and status of surgical margins (positive vs. negative). Actuarial rates of progression-free survival at five years were 40 percent in the combined-therapy group and 34 percent in the monotherapy group.

In cases of recurrences, second resections were performed when possible. In the combined-therapy group, there was 1 repeated liver resection and 13 lung resections. In the monotherapy group, there were nine repeated liver resections and four lung resections. Patients in both groups were allowed to receive other types of systemic chemotherapy if they had progressive disease: 33 patients in the combined-therapy group received further chemotherapy, 18 of whom received irinotecan; 46 patients in the monotherapy group received further chemotherapy, 24 of whom received irinotecan.

Adverse Effects

A number of patients had surgical complications that required hospitalization before chemotherapy could be initiated: in the combined-therapy group, three patients had bowel obstruction, three had infection, four had pleural effusion, and three had other complications. The respective numbers in the monotherapy group were five, three, one, and six. Five patients died before receiving chemotherapy, two in the combined-therapy group (one from sepsis and the other from liver failure) and three in the monotherapy group (two from liver failure and one from pneumonia). Three patients died while receiving therapy. In the combined-therapy group, one patient died of bowel obstruction and sepsis; in the monotherapy group, one patient died of sepsis with myelosuppression and one of bowel obstruction and sepsis.

The toxic effects of chemotherapy were similar in both groups except that more patients in the combined-therapy group had diarrhea. The percentages of adverse effects of at least moderate severity were as follows: neutropenia, 18 percent in the combined-therapy group and 21 percent in the monotherapy group; diarrhea, 29 percent and 14 percent, respectively; vomiting, 10 percent and 5 percent; nausea, 13 percent and 4 percent; and stomatitis, 11 percent and 9 percent. Hospitalization for diarrhea, leukopenia, mucositis, or small-bowel obstruction was necessary in the case of 29 patients in the combined-therapy group and 18 patients in the monotherapy group ($P=0.02$). Adverse hepatic effects in the combined-therapy group included doubling of the serum alkaline phosphatase level in 29 percent of patients, tripling of serum aspartate aminotransferase levels in 65 percent, and increase in serum total bilirubin lev-

els to more than 3.0 mg per deciliter ($51.3 \mu\text{mol}$ per liter) in 18 percent. Four patients in the combined-therapy group required biliary stents, and two were alive with normal serum bilirubin levels 31 and 34 months after placement of the stents, whereas two died of progressive liver disease 10 and 23 months after stent placement. In the remaining patients, serum total bilirubin levels returned to normal when the hepatic arterial infusion was discontinued. Two patients in the monotherapy group required stents for biliary strictures.

In the combined-therapy group, six patients never received the hepatic arterial infusion: two died within two weeks after surgery; in two, clots of the hepatic artery developed; and infections of the pump pocket developed in two and required removal of the pump. Most patients in the combined-therapy group (66 percent) received more than three cycles of hepatic arterial infusion, but only 26 percent received more than 50 percent of the planned dose of floxuridine, because of reductions in the dose necessitated by elevations in serum hepatic-enzyme levels. A total of 7 patients received 25 percent or less of the total dose of floxuridine, 43 received 26 to 50 percent, 15 received 51 to 75 percent, and 3 received more than 75 percent. A total of 16 patients in the combined-therapy group received 75 percent or less of the planned dose of systemic fluorouracil, 13 received 76 to 90 percent, and 40 received more than 90 percent.

In the monotherapy group, 6 of the 82 patients did not receive chemotherapy. Three died during the postoperative period, and three others declined chemotherapy. A total of 19 patients received 75 percent or less of the planned systemic dose, 9 received 76 to 90 percent, and 48 received more than 90 percent. The doses were reduced because of myelosuppression or gastrointestinal effects.

Evaluating the effect of the dose on survival is difficult because of the small number of patients in each category. When we evaluated the effect on the basis of the amount of systemic therapy received in both groups, then patients who received more than three cycles of fluorouracil had a median survival of 81.0 months, whereas those who received three cycles or fewer had a median survival of 31.0 months. There was no significant difference in overall survival, survival free of hepatic progression, or overall progression-free survival between patients who received more than three cycles of floxuridine and those who received three cycles or fewer.

Complications of Hepatic Arterial Infusion

Of the 16 complications related to the pump or catheter used for hepatic arterial infusion, 11 occurred during the first two years of the study. In six patients, the pocket surrounding the pump became infected. Hepatic arterial thromboses developed in two patients shortly after surgery, rendering the infusion-

TABLE 3. COMPARISON OF TWO-YEAR SURVIVAL RATES AFTER LIVER RESECTION IN PATIENTS IN VARIOUS STUDIES.

STUDY	NO. OF PATIENTS	TWO-YEAR SURVIVAL				TWO-YEAR DISEASE-FREE SURVIVAL
		ALL PATIENTS	PATIENTS WITH MULTIPLE LIVER LESIONS	PATIENTS WITH DUKES' STAGE C	PATIENTS WITH POSITIVE SURGICAL MARGINS	
		percentage of patients				
Adson et al. ²³	141	58	45	40	—	—
Doci et al. ²⁴	100	50	—	—	—	25
van Ooijen et al. ²⁵	118	55	—	—	—	27
Younes et al. ⁶	116	75	—	—	—	21
Scheele et al. ²⁶	226	58	—	—	—	—
Fegiz et al. ²⁷	212	—	40	50	—	—
Cady et al. ²⁸	142	40	—	—	0	—
Hughes et al. ⁴	859	60	55	—	—	—
Foster ²⁹	192	44	—	—	—	—
Nordlinger et al. ³⁰	1568	64	—	—	—	—
Current study						
Combined therapy	74	86	83	86	90	57
Monotherapy	82	72	70	67	55	42

al device unusable. Catheters in four patients became dislodged between 9 and 46 months after implantation. In one patient this event was associated with an intra-abdominal hemorrhage, which resolved without surgery. A pseudoaneurysm of the hepatic artery appeared in one patient six months after placement of the pump.

Three pumps were discovered on scanning with human serum albumin macroaggregated with technetium-99m to be perfusing areas outside the liver. In two patients this problem was corrected with radiographic embolization; in the third patient, therapy had been completed and the pump was no longer required. In two patients, there was only partial perfusion of the remaining liver after resection.

DISCUSSION

Until recently, patients with metastases of colorectal cancer to the liver were considered to have a very poor prognosis, but this view is changing. A number of studies have demonstrated overall survival of 65 percent at two years after resection of such metastases and a two-year disease-free survival of 25 percent. Although the beneficial effect of resection of hepatic metastases on survival has been clear, the role of adjuvant chemotherapy — systemic or regional — has not. The use of hepatic arterial infusion is attractive because 50 percent of the recurrences after resection are in the liver.

In seven randomized trials that compared hepatic arterial infusion with systemic therapy, patients with

unresectable hepatic disease who received hepatic arterial infusion had higher rates of partial response.^{10-15,21} However, these randomized studies could not clearly evaluate survival, because they used a crossover design, enrolled only a small number of patients, or provided inadequate systemic chemotherapy. Since extrahepatic metastases as well as liver recurrences must be controlled after liver resection, we reasoned that a combination of hepatic arterial infusion and systemic chemotherapy might provide the most benefit.

We decided not to include an untreated control group, because systemic adjuvant therapy after colon resection has clinical benefit, and it would have been difficult to enroll sufficient patients in such a study. A multi-institutional study of hepatic arterial infusion plus systemic therapy or no further treatment after liver resection that was conducted by the Eastern Cooperative Oncology Group enrolled only 109 patients over a nine-year period.²²

Many studies of hepatic resection (Table 3) include only patients with fewer than four metastases. In our study, 27 percent of the patients had four or more metastases. In a large series of patients who underwent liver resection, six poor prognostic characteristics were identified: four or more liver metastases, liver metastases that were 5 cm or larger, a margin of resection that was less than 1 cm, an age of 60 years or older, invasion of serosa by the primary tumor, and an interval of less than two years between the primary tumor and liver metastases.³⁰ Patients with three or four of these poor prognostic charac-

teristics had an overall survival rate of 60 percent at two years, and those with five or six of these characteristics had a survival rate of 43 percent. Another large study³¹ that identified similar poor prognostic factors reported a two-year survival rate of 45 percent for patients with four or five characteristics. In our study, the two-year rates of overall survival for patients in the combined-therapy group who had three or four or five or six poor prognostic factors were 88 percent and 71 percent, respectively, as compared with respective rates of 69 percent and 64 percent in the monotherapy group.

Hepatic arterial infusion caused more adverse effects than systemic chemotherapy, the most serious being biliary toxicity. Dexamethasone was added to the floxuridine regimen to decrease hepatic toxicity.³² We assumed that the biliary effects were due to regional chemotherapy, but two patients in the monotherapy group also had biliary strictures, suggesting that such strictures may be a complication of hepatic resection. Bile leaks or fistulae are reported in approximately 4 percent of patients undergoing liver resection.³³ More patients in the combined-therapy group than in the monotherapy group were hospitalized, but the number of deaths during treatment was not significantly different between groups. The number of pump-related complications was higher in our study than in other studies of hepatic arterial infusion conducted at our center.³⁴ Combining hepatic resection with the pump-implant procedure may increase the likelihood of infection and other pump-related complications. There is a learning curve for pump placement as well as liver resection, and these procedures should be undertaken only by highly trained surgical and medical oncologists.

As a result of dose adjustments necessitated by hepatic toxicity, the total amount of floxuridine delivered by hepatic arterial infusion was less than planned in most patients. This point may indicate that a lower dose of floxuridine should be used or it may mean that a high initial dose effectively decreases the risk of recurrence, so that smaller doses are needed in subsequent cycles. The intensity of the dose might be interpreted as being greater in the combined-therapy group (since these patients received two therapies concurrently), but the dose of drug administered systemically to patients in this group was approximately 15 percent less than that administered to patients in the monotherapy group. The incidence of overall side effects (excluding hepatic toxicity) was similar in both groups, but the combined-therapy group did have a higher rate of diarrhea.

We chose to look at two-year end points because when we designed the study only 25 percent of patients with hepatic metastases from colorectal cancer were disease-free at two years. Currently, 91 percent of our patients have been monitored for at least two years. Only 55 percent of the patients have been fol-

lowed up for five years, and the actuarial five-year survival rate is 61 percent in the combined-therapy group and 49 percent in the monotherapy group. Although the survival curves appear to converge at 80 months, only six patients were included in the analysis at that time, so the death of one patient causes a deceptively large decline in the curve.

Overall progression-free survival was not increased as much as hepatic-progression-free survival in the combined-therapy group, indicating that other agents must be used in conjunction with those delivered by hepatic arterial infusion. The most common site of extrahepatic recurrence is the lung, where the level of thymidylate synthase is usually high in patients with metastatic disease.³⁵ There is evidence to suggest that fluorouracil is not effective in tumors with high levels of thymidylate synthase, whereas a drug such as irinotecan, a topoisomerase inhibitor, is effective despite the presence of high thymidylate synthase levels.³⁶ Studies of systemic irinotecan plus hepatic arterial infusion of floxuridine and dexamethasone after hepatic resection are being conducted at our center.

Our findings confirm that the use of regional hepatic chemotherapy significantly improves the control of local disease in patients who undergo resection of liver metastases from colorectal cancer. The use of hepatic arterial infusion plus systemic chemotherapy not only decreased the rate of hepatic recurrence but also improved two-year overall survival, as compared with the use of systemic therapy alone.

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CORRECTION

Hepatic Arterial Infusion of Chemotherapy for Metastatic Colorectal Cancer

To the Editor: The study of hepatic arterial infusion of chemotherapy after resection of hepatic metastases in patients with colorectal cancer, reported by Kemeny et al. (Dec. 30 issue),¹ represents a positive development in the management of colorectal cancer. However, clinicians planning to use this therapy may be confused by the dosages reported in the article. By convention, the dosage for hepatic intraarterial chemotherapy is based on the amount of drug delivered to the patient. Since infusion devices have variable flow rates and deliver only part of their contents in 14 days, the total dose of floxuridine placed in the device is much more than the dose the patient receives.

Kemeny et al. state that the infusion pump was filled with "0.25 mg of floxuridine per kilogram of body weight per day for 14 days in combination with 20 mg of dexamethasone; 50,000 U of heparin, and enough normal saline to result in a volume of 50 ml." This does not mean that the dose delivered to patients was 0.25 mg per kilogram per day for 14 days. Because the average flow rate for these devices is approximately 2.0 ml per day, the dose of floxuridine that each patient received was about 0.14 mg per kilogram per day.

Given the risk of hepatobiliary toxicity and the narrow therapeutic index for this treatment,² the dose of hepatic intraarterial floxuridine is a critical factor in the safe administration of regional chemotherapy. The dose of floxuridine should be based on the flow rate of the pump used to deliver the drug.

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To the Editor: Kemeny et al. report that among patients with resected liver metastases, the survival rate at two years was higher for the patients who received the combination of systemic chemotherapy and hepatic arterial infusion of floxuridine than for those who received systemic chemotherapy alone. However, the curves in Figure 1 of their article show that the overall survival rates for the two groups did not

differ significantly by either the Wilcoxon test or the log-rank test. Furthermore, the appearance of the curves suggests that the survival rates for the treatment groups did not differ significantly at one year or at three years. Although the rate at five years appears to be better for the combined-therapy group, this difference was probably not statistically significant, since the median follow-up was only 62.7 months.

More bothersome is the fact that although the treatment groups appear to have been well balanced with respect to the base-line characteristics enumerated by the authors, the difference in the survival rate at two years was significant only after adjustment by multivariate analysis with the use of the "best subgroup-selection method." The authors provide no reference for this method, but their description suggests a stepwise approach that may have diminished the value of the multivariate analysis.¹ Their inclusion of some variables in the models for disease progression but not in the model for survival is counter-intuitive. Certainly, the length of time since the diagnosis of primary cancer, the length of time since the last course of chemotherapy, and the lactate dehydrogenase level are all potentially important enough to be included in a multivariate model of survival. It is particularly disturbing that the location of the primary tumor, the size of the largest liver metastasis, the length of time since the diagnosis, and the length of time since the last course of chemotherapy were not reported as base-line characteristics. In addition, the authors do not mention any tests for the assumption of proportional hazards.²

Kemeny et al. suggest that hepatic arterial infusion of floxuridine improves the outcome for patients with colorectal cancer and resected liver metastases. However, the authors' data seem unconvincing. Even assuming the appropriateness of their multivariate adjustment, the difference in survival between the treatment groups appears to be small in relation to the morbidity and inconvenience associated with hepatic arterial infusion.

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To the Editor: According to the results of the single-institution study reported by Kemeny et al., hepatic arterial infusion plus intravenous chemotherapy results in a significantly lower rate of hepatic relapse and a higher rate of survival at two years than systemic chemotherapy alone in patients with resected hepatic metastases from colorectal cancer. Unfortunately, because of extrahepatic spread, differences in disease-free survival and overall survival were not significant. Thus,

the main finding of this study is that hepatic relapse is delayed with the combined treatment.

In our opinion, these results are partly biased by the heterogeneity of the patients enrolled in the study and by the difference in the duration of treatment. Since 21 patients (13 percent) had positive margins, the surgery they underwent was palliative.¹ More than half the patients had previously received chemotherapy, and the median interval from resection of the primary tumor to the development of liver metastases was short (6.8 months in the combined-therapy group and 9.1 months in the monotherapy group). These two points constituted poor prognostic factors with respect to a response to intravenous chemotherapy and survival.² On the other hand, hepatic arterial infusion has been recommended as an effective second-line therapy in patients with liver metastases that are resistant to systemic chemotherapy,³ and some of the patients enrolled in the recent study by Kemeny et al. were probably in this category.

We suggest that the improvement in survival at two years in the combined-therapy group, reported by Kemeny et al., may have been due to the advantage of hepatic arterial infusion in the subgroup of patients with positive margins. We understand that the data were analyzed on an intention-to-treat basis, but we would like to know either the rates of survival at two years for the subgroups of patients in whom surgery was palliative or curative or the results of a test of the interaction between treatment and positive or negative surgical margins in the multivariate analysis. The key point is whether there is a survival advantage with the use of adjuvant hepatic arterial infusion after curative resection. In addition, the duration of treatment was longer for the combined-therapy group than for the monotherapy group (35 weeks vs. 21 weeks), a difference that may have been particularly important for the subgroup of patients in whom surgery was palliative.

The initiation of postoperative chemotherapy was delayed in some patients, and others did not receive it because of surgical complications, refusal, or technical problems with hepatic arterial infusion. Therefore, the results of this interesting study should also prompt an investigation of the use of fluoropyrimidine-based preoperative chemotherapy, including new drugs such as irinotecan or oxaliplatin, in order to increase both the number of patients in whom subsequent surgery is curative and the overall survival rate.

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To the Editor: Kemeny et al. have previously reported on the benefit of additional hepatic arterial infusion of floxuridine and dexamethasone as compared with systemic fluorouracil and leucovorin. The authors should be credited for performing this important randomized study, and in particular for their excellent surgical results. However, the use of hepatic arterial infusion of floxuridine after liver resection, despite the fact that there is no clear overall benefit of this approach, requires some comment about the design of the study and the interpretation of its results. We had different results and are convinced that hepatic arterial infusion with fluorouracil and leucovorin is at least as effective as hepatic arterial infusion with floxuridine when one considers hepatic and extrahepatic disease.^{1,2}

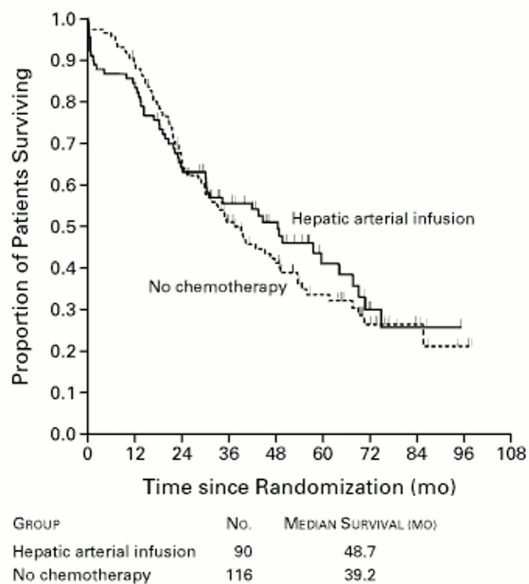
To assess internal validity, we would like more information with regard to the Consolidated Standards of Reporting Trials (CONSORT) statement³; the method of masking treatment assignments and the details of the main analyses as indicated in the study protocol are particularly important. The projected sample size was based on survival rates at two years, rates of progression, and one-sided tests without adjustment for the censoring of data and for the use of two main end points. The use of two-sided tests in the final analyses seems to be more appropriate, but the authors did not adjust the sample size in order to achieve the desired statistical power when they changed the study protocol. The interpretation of the study findings as positive is based on the improvement in the results at two years in the combined-therapy group, although for the comparison of overall survival at two years ($P=0.03$), statistical significance was not actually demonstrated because there was no outline of the multiple-testing procedure.

The authors do not explain their rationale for selecting the main end points and the statistical methods used in their analyses. The differences in the event rates at two years are particularly important, if there is the possibility of a cure. However, the data shown in Figure 1 of the article do not support the hypothesis that additional treatment with hepatic arterial infusion has a curative potential. We were also unable to demonstrate a benefit in our study, even in the final, updated analyses according to the treatment received (Figure 1), despite a reduction in the recurrence of intrahepatic disease.¹ In the analyses of end points that included the progression of disease, the data were censored for patients who died before the confirmation of progressive

disease. Thus, the estimated rates of survival free of hepatic progression and of overall progression-free survival cannot be interpreted simply as a prognosis, but must instead be interpreted as a prognosis that is conditional on the patient's being alive. Whether progression-free survival, defined in this way, can be considered clinically relevant is questionable.

Figure 1. Kaplan–Meier Estimates of Overall Survival According to the Treatment Received.

The tick marks on the curves indicate censored data. The difference in survival between the two study groups was not significant ($P=0.59$ by the log-rank test).



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The authors reply:

To the Editor: In our study, the recommended dose of floxuridine was the total dose, and it was not adjusted for the flow rate. To make an adjustment for the flow rate, the dose should be 0.14 mg per kilogram multiplied by the pump volume and divided by the pump flow rate. We chose two-year end points because they were used in many other reports. The rate of survival at two years was significantly higher in the combined-therapy group than in the monotherapy group (86 percent vs. 72 percent, $P=0.03$). A study with many more patients than the 156 in our study would be necessary to show a significant increase in overall survival. The difference in the median period of survival (72.2 months in the combined-therapy group vs. 59.3 in the monotherapy group) may have clinical importance. The best subgroup-selection method is described by Furnival and Wilson.¹ We chose the stepwise approach to pick the factors for the multivariate analysis because we believed that this approach would result in the selection of the best factors, which can differ in the models for overall and progression-free survival. With a multivariate analysis that included the potentially important variables suggested by Dr. Atkins, the risk ratio for death was 2.33 in the monotherapy group as compared with the combined-therapy group ($P=0.028$). We used Cox's proportional-hazards model for easy interpretation of the variables.

Conroy et al. suggest that we selected patients who had characteristics associated with resistance to systemic chemotherapy. If such patients can benefit from hepatic arterial infusion, then it is a useful treatment. The duration of treatment was longer for the combined-therapy group than for the monotherapy group. However, the patients in the combined-therapy group were treated every five weeks rather than every four weeks. We did not report the results of subgroup analyses of data at two years because we had too few patients to do so.

We believe hepatic arterial infusion with floxuridine is better than hepatic arterial infusion with fluorouracil plus leucovorin because of the higher hepatic extraction rate of floxuridine (minimizing toxicity elsewhere and allowing for combination with new agents such as irinotecan or oxaliplatin) and because of the poor results of the study by Lorenz et al.,² in which only 30 percent of patients completed treatment.

As outlined in the CONSORT statement, all enrolled patients were eligible and were followed. As for the method of assignment to a treatment group, sealed envelopes were picked from boxes in the operating room; the envelopes were labeled according to the number of metastases (1, 2 through 4, or more than 4) after the surgeon had confirmed how many liver metastases were present.

A one-sided statistical test was initially chosen, because we believed the combined therapy would be better than systemic therapy alone. P values for one-sided tests in the final analyses would have made our already significant results even more pronounced. The study showed improved outcome at two years. No multiple-testing procedures were used. Data on a patient were censored if death occurred before the end point, without evidence of disease. Many patients would disagree with the comments of Lorenz et al. concerning the curative potential of treatment and would choose the treatment that offered a greater chance of being alive at two years, even if it were not curative.

We would also like to note that the first sentence of the Methods paragraph in the Abstract of our article should have referred to six cycles of similar systemic therapy, not six weeks.

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