Randomized Trial of Intraportal and/or Systemic Adjuvant Chemotherapy in Patients With Colon Carcinoma

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For The ACOI/GIVIO/GISCAD Investigators

Background: **5-Fluorouracil–based adjuvant chemotherapy after surgical resection of colon cancer is standard treatment. However, the choice of best delivery route—that is, systemic (i.e., intravenous or oral) or regional (i.e., intraportal, intraperitoneal, or hepatic arterial infusion)—has been controversial. In a randomized clinical trial of patients with colon cancer, we compared the benefits of chemotherapy delivered by these routes individually or in combination.** ***Methods:*** **From April 2, 1992, through April 30, 1998, 1084 eligible patients with Dukes' stage B or C colon carcinoma were randomly assigned: 369 patients to the IP regimen (continuous portal vein infusion of 5-fluorouracil at 500 mg/m^2 of body surface daily and heparin at 5000 IU daily for 7 consecutive days, beginning on the day of surgery), 358 patients to the SY regimen (six 28-day courses of systemic leucovorin at 100 mg/m^2 daily on days 1 through 5 followed by systemic bolus 5-fluorouracil at 370 mg/m^2 daily on days 1 through 5, with treatment initiated 15–35 days after surgery), and 357 patients to the IP+SY regimen (the IP regimen followed by the SY regimen, with the same scheduling). Survival rates were analyzed with the log-rank statistic and a Cox multivariable regression model. All statistical tests were two sided.** ***Results:*** **At a median follow-up time of 99 months, 389 events (recurrences, second malignancies, or deaths) had occurred, and 361 patients died. Sites of first recurrences were similar among the three arms. At 5 years, overall and event-free survival rates were similar among those on the IP (74% and 68%, respectively), SY (78% and 71%), and IP+SY (73% and 67%) regimens. When compared with the group on the SY regimen, the risk for death associated with the IP regimen (hazard ratio [HR] = 1.05, 95% confidence interval [CI] = 0.82 to 1.36) was similar to that associated with the IP+SY regimen (HR = 1.12, 95% CI = 0.78 to 1.45) (*P* = .69), as were the risks for first event (HR = 1.07, 95% CI = 0.84 to 1.37 and HR = 1.10, 95% CI = 0.86 to 1.41, respectively) (*P* = .74).** ***Conclusion:*** **Overall and event-free survival rates were similar in all three arms. The combined regimen was no better than either single regimen alone. [J Natl Cancer Inst 2004;96:750–8]**

Colorectal cancer is one of the most frequently diagnosed cancers worldwide, ranking third in men and second in women. Every year, about 1 million new cases are diagnosed, and about 500 000 patients die from the disease *(1)*. Overall survival has improved only marginally in the last few decades, despite advances in surgery and early detection. A potentially curative resection can be performed in only 70%–80% of patients, and even in these patients, the overall survival rate at 5 years does not exceed 60%, thus indicating the need for effective adjuvant treatment.

The use of systemic chemotherapy for colorectal cancer is well established. Patients with stage III (Dukes' stage C) colon cancer *(2–6)* and about 30% of patients with stage II (Dukes' stage B) colon cancer *(7)* receive systemic adjuvant treatment in common clinical practice, and high-risk patients are included in most ongoing trials. Adjuvant intraportal vein infusion is another delivery strategy. The liver is the most common site for the metastasis of colorectal cancer, being involved at diagnosis in 25%–30% of patients; such patients have an overall survival time of only 5–6 months. Regional chemotherapy, if administered early enough, could inhibit tumor cell proliferation. Tumor cells reach the portal vein system through the mesenteric vessels and then invade the liver. Liver metastases originate from microscopic tumor cell deposits that are too small to be detected during surgery for the primary cancer. Therefore, the development of regional chemotherapy capable of eliminating these deposits is warranted *(8–10)*. The liver receives higher levels of active 5-fluorouracil metabolites when 5-fluorouracil is given regionally rather than systemically *(11)*, and previous investigations have shown that intraportal infusion of 5-fluorouracil, even when not effective in reducing the incidence of liver metastasis among patients at risk, appears to decrease the risk of extrahepatic disease recurrence

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See "Appendix" for information regarding data management and statistical analysis and for a list of institutions and consultants contributing patients to the SMAC protocol.

See "Notes" following "References."

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(12). However, the choice of the best delivery route, systemic (i.e., intravenous or oral) or regional (i.e., intraportal, intraperitoneal, or hepatic arterial infusion), remains controversial. Moreover, the combination of systemic and intraportal therapies appears rational (because they have different times of administration and nonoverlapping side effects), and the benefit from combination therapy may be greater than the benefits of the individual treatment regimens without increasing toxicity.

To evaluate whether the combined systemic and intraportal (SY+IP) regimen was superior to the standard SY regimen (5-fluorouracil plus leucovorin, i.e., l-folinic acid) or to the well-established IP regimen (a short course of 5-fluorouracil), a collaboration of scientists began a large phase III clinical trial in Italy in 1992. This collaborative effort included ACOI (Italian Association of Hospital Surgeons), GIVIO (Italian Group for the Evaluation of Interventions in Oncology), and GISCAD (Italian Group for the Study of Digestive Tract Cancer). In this article, we report the results of the final analysis.

PATIENTS AND METHODS

Patients

Before surgery, each patient had routine hematologic and blood chemistry analyses, chest radiograms, and an abdominal ultrasound examination. To enter the trial, patients were required to have histologically proven Dukes' stage B (T3 or T4, N0, M0) or C (T1, -2, -3, or -4; N1, -2, or -3; M0) colon adenocarcinoma without evidence of distant metastases, which was confirmed after laparotomy (an intraoperative liver ultrasound examination was strongly encouraged and was mandatory if a preoperative ultrasound examination was missing), and no contraindications to IP or SY regimens of 5-fluorouracil chemotherapy (i.e., $\geq 3.9 \times 10^9$ white blood cells per liter, $\geq 100 \times 10^9$ platelets per liter, and adequate liver and kidney function). Colon cancer was defined as a cancer that did not require opening the pelvic peritoneum to define the distal extent of the tumor. Patients were excluded if they showed one of the following characteristics: a World Health Organization (WHO) performance status greater than 2; inadequate liver function, defined by serum bilirubin and aspartate aminotransferase values of more than twice the upper level of the normal range for the individual institution; inadequate renal function, defined as a serum creatinine level of more than 134 μmol/L; a history of medically significant atrial or ventricular arrhythmias, congestive heart failure, or documented myocardial infarction within the 6 months preceding surgery; or a positive history of cancer (with the exception of adequately treated *in situ* cervical carcinoma or nonmelanomatous skin tumor). The trial inclusion criteria had no strict age limit and allowed entry of patients with intestinal obstruction for which radical surgery would be needed. The study was approved by the ethics committees with jurisdiction for the 67 participating institutions throughout Italy. From April 2, 1992, through April 30, 1998, 1084 eligible patients with Dukes' stage B or C carcinoma of the colon were enrolled. Written informed consent was obtained from each patient before study entry.

Randomization

Randomization was performed centrally by telephone at the Mario Negri Institute (Milan, Italy) and was stratified according to each institution. The regimens were randomly selected by computer with equal frequency in blocks of six patients. All patients were randomly assigned to treatment during surgery. We randomly assigned 369 patients to the IP regimen, 358 patients to the SY regimen, and 357 patients to the IP+SY regimen.

Chemotherapy

Patients assigned to the IP regimen received continuous portal vein infusion of 5-fluorouracil (500 mg/m^2 of body surface daily) and heparin (5000 IU/day); the infusion was started on the day of surgery and was administered for 7 consecutive days. A radio-opaque catheter was inserted in the portal vein at the end of laparotomy. Access to the portal vein was achieved by dilatation and cannulation of the umbilical vein or by insertion of the catheter into portal vein tributaries (the right gastroepiploic [the preferred vein] or the ileocolic, colic, or inferior mesenteric vein). The position of the catheter tip was checked by Patent Bleu infusion (one 2-mL vial diluted in 20 mL of saline) to ensure perfusion of the hepatic segments. We used a peristaltic or a continuous infusion pump rather than a gravity drip. 5-Fluorouracil and heparin (doses for each patient were calculated based on their body surface area) were diluted in 1000 mL of 5% dextrose (and infused at a rate of 40 mL/h with the peristaltic pump) or in 50 mL of 5% dextrose (and infused at a rate of 2 mL/h with the continuous pump). In the SY regimen, between 2 and 5 weeks from surgery, patients received leucovorin (100 mg/m^2 daily on days 1 through 5) administered intravenously as a 2-hour infusion, followed by an intravenous bolus of 5-fluorouracil (370 mg/m^2 daily on days 1 through 5); this course of treatment was repeated every 28 days for a total of six courses. In the combined treatment (IP+SY) regimen, patients received the IP regimen followed by the SY regimen, with the same scheduling as that described for a single regimen.

In the event of relapse, the choice of the further treatment (surgery, chemotherapy, or other therapy) was left to the clinical investigator and was not strictly mandated by the protocol because of the large-scale and pragmatic characteristics of this trial. Until 1996 or 1997, the most common salvage treatment was modulated 5-fluorouracil (bolus or continuous infusion)–based chemotherapy. A wider variety of treatments (including irinotecan or oxaliplatin) was probably used thereafter. The use of chemotherapy (or whenever appropriate, surgery) at relapse was not tracked in this study.

Dose Modifications and Follow-up

Intraportal 5-fluorouracil infusion was permanently discontinued if one of the following events occurred: gastrointestinal toxicity of grade 2 or more, dermatitis, a white blood cell count of less than 3.0×10^9 cells per liter, a platelet count of less than 75×10^9 cells per liter, alanine aminotransferase and/or aspartate aminotransferase measurements of more than 2.5 times the upper limit of the normal range, any sign of catheter infection, or any severe complication after surgery (i.e., serious wound infection, febrile or thromboembolic episodes, intestinal obstruction, or cardiovascular events).

During the SY regimen, patients were assessed by physicians monthly before each treatment cycle. Full blood cell counts and blood biochemistry evaluations were also performed monthly; toxicity was scored according to criteria of the WHO scoring

system *(13)*. If side effects developed, strict criteria for 5-fluorouracil dose reduction were adopted. The dose was modified according to the white blood cell count and the thrombocyte count on the first day of the course of treatment and on the basis of any previous toxicity. Patients were required to have a white blood cell count of at least 3.9×10^9 cells per liter and a platelet count of at least 100×10^9 platelets per liter on the first day of each course. If the white blood cell count was less than 3.9×10^9 cells per liter but more than 2.0×10^9 cells per liter or the thrombocyte count was less than 100×10^9 thrombocytes per liter but more than 50×10^9 cells per liter, the 5-fluorouracil treatment was postponed week by week until recovery, but the dose was not reduced. If the white blood cell count was between 1.0×10^9 and 2.0×10^9 cells per liter or the thrombocyte count was between 25×10^9 and 49×10^9 thrombocytes per liter, 5-fluorouracil treatment was postponed, and the dose was reduced to 200 mg/m^2 instead of 370 mg/m^2. If the white blood cell count was less than 10^9 cells per liter, the platelet count was less than 25×10^9 platelets per liter, or the nonhematologic toxicity was grade 3 or higher, treatment was stopped. A reduction in the 5-fluorouracil dose, to 280 mg/m^2, was also required if grade 2 gastrointestinal toxicity occurred between cycles.

Because we did not have standard recommendations for follow-up, formal protocol requirements for the first 5 years were as follows: a history; physical examination, blood tests, and carcinoembryonic antigen determination at 3, 6, 12, 18, 24, 36, 48, and 60 months; liver ultrasound examination or computed tomography scan on a semiannual basis for the first 2 years and then yearly thereafter; and colonoscopy or barium enema at 6 and 12 months and then yearly from the second year. A yearly chest x-ray was recommended. Follow-up continued beyond 5 years but without protocol requirements. Information about compliance with the monitoring schedule was not collected. Stratification of patients by institution kept the influence of follow-up procedures on outcome to a minimum. The diagnosis of local relapse and/or distant metastases had to satisfy the requirement in the protocol that recurrences be histologically or cytologically proven. If a recurrence was not histologically verified, then an increased tumor size had to be demonstrated in two separate radiologic/echographic assessments. Deaths were identified by use of the National Death Registry.

Statistical Methods

The primary end points for this trial were overall survival, defined as the time from randomization to death from any cause, and event-free survival, defined as the time to the first event (i.e., the first occurrence of a tumor relapse, a second primary cancer, or death). The number of events required for this analysis was estimated by assuming an exponential lifetime (i.e., a hazard that does not change with time) for patients and a 5-year survival rate of 65% for those receiving a less active treatment. To have an 80% chance of detecting a 10% improvement in overall survival at 5 years (which translates into a 50% reduction in the annual death rate) using the 5% level of a conventional two-sided test, we determined that approximately 400 events were required. Although it was difficult to estimate *a priori* the proportions of patients at each stage, we originally planned to accrue 1200 patients. The number of events for the overall survival comparison was achieved on October 31, 2002. All patients deemed eligible were analyzed on an intention-to-treat basis.

Overall survival and event-free survival curves were constructed with standard Kaplan–Meier methods. The duration of follow-up was calculated by using the Kaplan–Meier estimate of the median duration by reversing status of censoring and death in the dataset. The log-rank test and Cox proportional hazards models were used to compare survival distributions among the treatment groups in univariate and multivariable analyses. Proportional hazard assumptions were checked and satisfied. The global hypothesis of equal failure rates among the three treatment arms was assessed with the Wald test. Pairwise tests were performed when the global test indicated rejection of the null hypothesis. The 95% confidence intervals (CIs) for the hazard ratios (HRs) of treatment effect and other prognostic factors were provided to indicate the range of values consistent with the observed data and were determined from the asymptotic standard errors in the Cox regression model. All statistical tests were two sided. Statistical analyses were performed with SAS (Cary, NC) procedures.

Results

Administrative Data

The trial was opened on April 2, 1992, and enrollment was stopped on April 30, 1998. By the end of enrollment, 1199 patients had been randomly assigned to treatment at 67 institutions throughout Italy. One hundred fifteen (9.6%) of these patients were subsequently found to be ineligible (Fig. 1) and were excluded from the analyses. Most of these patients (104 patients or 90.4%) were deemed ineligible because they had Dukes' stage A or D disease; this problem was expected because randomization occurred during surgery, and intraoperative pathology reports were not always available. However, an analysis comparing the whole group of 1199 patients with the 1084 eligible patients showed no statistically significant differences in overall survival and event-free survival. By May 2, 2003, the median time of follow-up for the 1084 eligible patients was 99 months (25th–75th percentiles = 84–112 months).

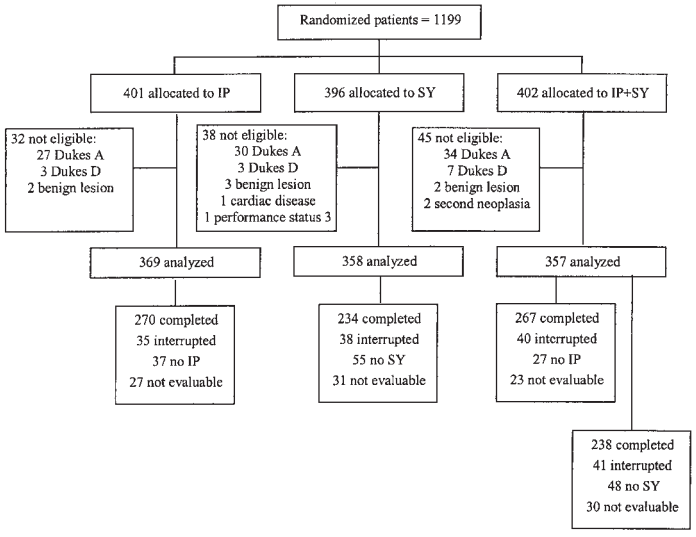

Fig. 1. Progress of patients through the trial (CONSORT diagram). IP = intraportal regimen; SY = systemic regimen; IP+SY = intraportal and systemic combination regimen.

Patient Characteristics and Compliance With Treatment

Table 1 lists the distribution by treatment group of patients according to age, sex, WHO performance status, Dukes' stage, and site of primary tumor. Groups were similar across all categories. Thirty-seven patients assigned to the IP regimen and 27 patients assigned to the IP+SY regimen did not start portal vein infusion (39 because of difficulty in inserting the catheter, 10 because of surgical complications, and 15 because of reasons not specified). Fifty-five patients assigned to the SY regimen and 48 patients assigned to the SY regimen or to the IP+SY regimen did not start systemic chemotherapy (two declined the treatment, 23 developed other diseases, 10 died early, 53 moved to other nonparticipating centers, and 15 underwent other treatments). Figure 1 shows that intraportal infusion could not be evaluated in 27 patients assigned to the IP regimen and in 23 patients assigned to the IP+SY regimen and that systemic therapy could not be evaluated in 31 patients assigned to the SY regimen and in 30 patients assigned to the IP+SY regimen because of early losses to follow-up and because hospitals stopped following the study protocol within a few months after randomization. These patients were tracked for information on vital status.

Eighty-eight percent (537 patients) of the 612 patients who began the IP regimen and 86% (472 patients) of the 551 patients who began the SY regimen received full treatment. The most common reasons for not completing the planned portal vein infusion were surgical complications (25 patients), excessive toxicity (17 patients), technical problems with the catheter of the infusion pump (15 patients), refusal to comply (one patient), and other or unreported causes (17 patients). The most frequent reasons for not completing the assigned systemic chemotherapy were toxicity (33 patients), other diseases (14 patients), relapsing cancer (four patients), early death (two patients), and other or unreported causes (25 patients). Only one patient refused to complete systemic chemotherapy. The relative dose intensity for patients who received systemic chemotherapy was 92% for the SY regimen and 91% for the IP+SY regimen.

Toxicity

Table 2 shows the side effects observed in the three groups. At least 47% of patients on the SY regimen experienced one adverse reaction, but severe grade 3–4 toxicity was rare (overall, 7%). Patients appeared to tolerate the IP regimen better than they tolerated the SY regimen, the incidence of a toxic effect (any grade) being only 9% in patients assigned to the IP regimen compared with 47% in patients assigned to the SY regimen. As expected with these chemotherapy regimens, almost all toxic effects reported were gastrointestinal. No death occurred during chemotherapy.

Event-Free and Overall Survival

Overall, 232 relapses were recorded. Table 3 shows the initial sites of recurrence across the treatment groups: this pattern was not statistically significantly different in the three arms. The occurrences of second primary cancers and of tumor-unrelated deaths were also equally distributed in treatment arms. As of the median follow-up time of 99 months, which occurred on May 2, 2003, 389 events (recurrences, second malignancies, or deaths, whichever came first) had occurred among the 1084 patients, and 361 of these had died: 120 (33%) of the 369 patients on the IP regimen, 121 (34%) of the 358 on patients the SY regimen, and 121 (34%) of the 357 patients on the IP+SY regimen. Death was caused by colon cancer in 223 patients (69 on the IP regimen, 77 on the SY regimen, and 77 on the IP+SY regimen; $P = .75$).

Figures 2 and 3 show the event-free and overall survival curves, respectively, for all eligible patients entered in the trial. At 5 years, overall survival and event-free survival were similar among patients assigned to the IP (74% and 68%, respectively),

Table 1. Characteristics of patients at baseline

Characteristic	Regimen*		
	IP (n = 369)	SY (n = 358)	IP+SY (n = 357)
Age			
Median, y	65	65.5	65
25th–75th percentiles, y	58–72	58–72	57–71
Range, y	27–89	24–86	25–86
No. > 70 y (%)	111 (30)	105 (29)	100 (28)
Sex, No. (%)			
Male	180 (49)	194 (54)	177 (50)
WHO performance status, No. (%)			
0	275 (75)	252 (70)	273 (76)
1	92 (25)	102 (28)	80 (22)
2	2 (<1)	4 (1)	4 (1)
Dukes' stage, No. (% of evaluable)			
B	214 (61)	191 (56)	206 (62)
C	136 (39)	149 (44)	128 (38)
Not known	19 (5)	18 (5)	23 (6)
Site of primary tumor, No. (% of evaluable)†			
Right colon	120 (34)	114 (34)	114 (34)
Left colon	221 (63)	210 (62)	212 (64)
Multiple	9 (3)	15 (4)	7 (2)
Not known	19 (5)	19 (5)	24 (7)

*IP = intraportal regimen; SY = systemic regimen; IP+SY = intraportal and systemic combination regimen.

†Right colon = caecum, ascending, hepatic flexure, and transverse; left colon = splenic flexure, descending, sigmoid, and rectosigmoid junction.

Table 2. Toxic effects of chemotherapy in different treatment arms*

Highest toxicity per patient	Regimen			
			IP+SY	
	IP (n = 305)	SY (n = 272)	IP (n = 307)	SY (n = 279)
No. with hematologic toxicity				
All grades	3	25	2	28
Grade 3–4	—	3	1	1
No. with hepatic toxicity				
All grades	7	3	5	1
Grade 3–4	2	—	—	—
No. with diarrhea				
All grades	12	70	12	83
Grade 3–4	4	11	—	9
No. with mucositis				
All grades	1	62	2	80
Grade 3–4	—	7	—	15
No. with nausea and vomiting				
All grades	4	65	7	63
Grade 3–4	2	4	2	5
No. with other toxic effects				
All grades	2	4	1	10
Grade 3–4	—	—	1	1
No. with any toxic effect (%)				
All grades	27 (8.9)	125 (46.0)	28 (9.1)	137 (49.0)
Grade 3–4	8 (2.6)	18 (6.6)	4 (1.3)	23 (8.2)

*Analysis of toxicity was carried out in 612 patients who had at least 1 day of IP treatment and in 551 patients who had at least one course of SY treatment. IP = intraportal regimen; SY = systemic regimen; IP+SY = intraportal and systemic combination regimen. — = none.

SY (78% and 71%), and IP+SY (73% and 67%) regimens. Survival rates and unadjusted HRs are reported in Table 4: no statistically significant difference in event-free or overall survival was detected among the three arms and, in particular, the combined treatment was not superior to either single treatment alone. In the multivariable proportional hazard model, only sex, stage, and age were statistically significantly associated with an increased risk of event or death (Table 5). When compared with the SY group, the risks of death associated with IP (HR = 1.05, 95% CI = 0.82 to 1.36) and IP+SY (HR = 1.12, 95% CI = 0.78 to 1.45) regimens were similar to each other (P = .69), as were the risks for first event (HR = 1.07, 95% CI = 0.84 to 1.37 and HR = 1.10, 95% CI = 0.86 to 1.41, respectively) (P = .74).

Table 3. Events in different treatment arms*

Event	Regimen		
	IP (n = 369)	SY (n = 358)	IP+SY (n = 357)
Total relapse, No.	76	77	79
Local	15	13	16
Liver only	24	29	20
Lung only	12	8	6
Other site only	5	8	10
Multiple	15	15	23
Unknown	5	3	4
Relapse as first event, No.	75	76	77
Second tumor as first event, No.	13	14	13
Death as first event, No.			
Surgical treatment–related	4	2	5
Not related to treatment	39	38	33
Total events, No. (%)	131 (35.5)	130 (36.3)	128 (35.9)

*IP = intraportal regimen; SY = systemic regimen; IP+SY = intraportal and systemic combination regimen.

DISCUSSION

To our knowledge, this is the largest study of patients with colon cancer that has compared the efficacy of adjuvant 5-fluorouracil–based chemotherapy delivered directly into the portal vein (IP regimen), intravenously (SY regimen), and by using a combination of both routes (IP+SY regimen). The main result of this study is that the combination IP+SY regimen did not provide an additive benefit and, in fact, was similar to that of the chemotherapy delivered by either the IP regimen or the SY regimen alone. Overall survival and event-free survival rates were similar among all three groups.

Controversy Surrounding Intraportal Therapy

As early as 1957, Morales et al. *(8)* advocated the use of portal vein infusion of antitumor drugs at the time of resection of colorectal cancer to prevent the development of hepatic metastases. When our trial was designed in 1991, the regional chemotherapy delivery system was still of interest because of the pioneer investigations of Taylor et al. *(9,10)*, who found that intraportal chemotherapy had a considerable effect on survival.

In 1997, the Liver Infusion Meta-analysis Group, coordinated by Piedbois and Buyse *(14)*, conducted a large systematic review of about 4000 patients who were enrolled in 10 studies (some of which had not been published before the meta-analysis was conducted). Data were retrieved for patients included in phase III trials that started before 1987 in which results of a 5- to 7-day continuous postoperative portal vein infusion were compared

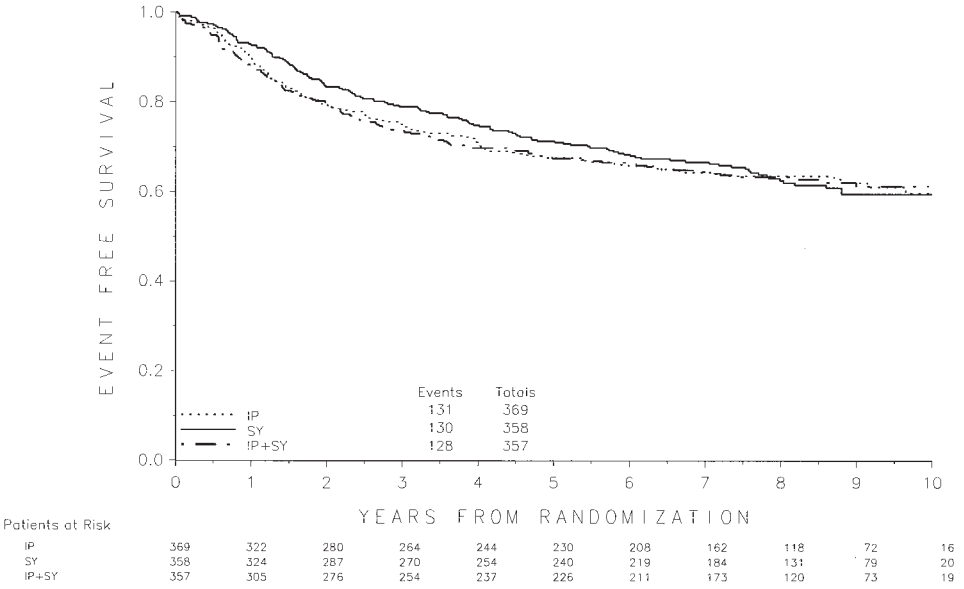

Fig. 2. Event-free survival for eligible patients with Dukes' stage B or C colon carcinoma treated with intraportal (IP) versus systemic (SY) versus intraportal and systemic (IP+SY) 5-fluorouracil drug regimens. The 5-year event-free survival rates were as follows: IP = 68% (95% confidence interval [CI] = 63% to 72%), SY = 71% (95% CI = 67% to 76%), IP+SY = 67% (95% CI = 62% to 72%). χ^2 (log-rank) = 0.1176; P = .943.

with those of no further treatment after primary tumor resection. They found that survival with and without intraportal chemotherapy was the same for the first 24 months but then diverged, with an absolute survival improvement of 4.7% (P = .006) at 6 years or longer, for the intraportal chemotherapy. When the analysis was restricted to patients with Dukes' stage A, B, or C disease (about 90% of the total), the absolute effect of intraportal chemotherapy on 5-year survival increased to 6.0%. Despite this survival benefit, the meta-analysis confirmed that, in contrast to the statistically significant reduction in liver metastases reported by Taylor et al. *(10)*, the decreased incidence observed in the subsequent nine hypothesis testing trials was not statistically significant (P = .2). In the studies with control groups other than patients treated with surgery alone, there was a survival advantage for patients treated with cytotoxic portal vein infusion chemotherapy compared with those receiving a nonantiproliferative intraportal drug or systemic chemotherapy. Therefore, the authors concluded that "intraportal infusion of 5-fluorouracil, with or without other cytotoxic drugs, for about 1 week after surgery in patients with colorectal cancer may produce an absolute improvement in 5-year survival of a few percent and that this finding, although encouraging, is not statistically secure" *(14)*. (It should be emphasized that, if a widely used adjuvant treatment achieved a 5% increase in long-term overall survival, its widespread use would avoid many thousands of deaths worldwide each year.) However, two large randomized trials recently found no survival advantage for adjuvant portal vein infusion of 5-fluorouracil compared with no further treatment *(15,16)*.

A large-scale European Organisation for Research and Treatment of Cancer (EORTC) trial of patients with histologically confirmed resectable cancer of the colon or rectum without distant metastases *(15)* found no survival advantage for patients treated with intraportal adjuvant chemotherapy compared with patients treated with surgery alone. However, if these data were added to data from the trials included in the meta-analysis, the decrease in the risk of mortality would no longer be statistically significant, and the odds ratio for mortality would increase from

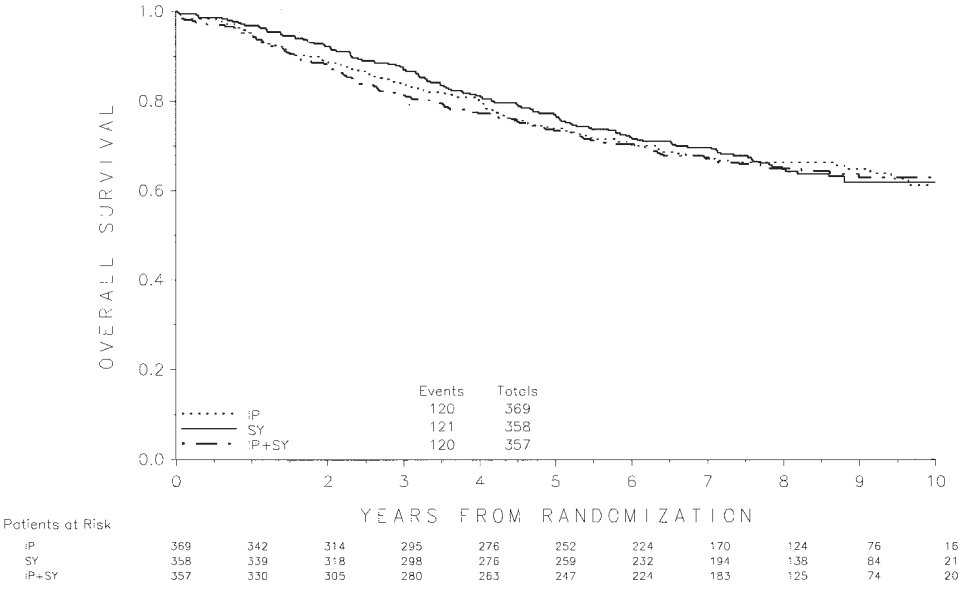

Fig. 3. Overall survival for eligible patients with Dukes' stage B and C colon carcinoma treated with intraportal (IP) versus systemic (SY) versus intraportal and systemic (IP+SY) 5-fluorouracil drug regimens. The 5-year overall survival rates were as follows: IP = 74% (95% confidence interval [CI] = 69% to 79%), SY = 78% (95% CI = 73% to 81%), IP+SY = 73% (95% CI = 69% to 78%). χ^2 (log-rank) = 0.0913; P = .955.

Table 4. Event-free and overall survival data from univariate analysis*

Survival category	Stage B	Stage C	Total
5-year event-free survival (95% CI)			
IP	0.74 (0.68 to 0.80)	0.57 (0.49 to 0.65)	0.68 (0.63 to 0.72)
SY	0.79 (0.73 to 0.85)	0.61 (0.53 to 0.69)	0.71 (0.67 to 0.76)
IP+SY	0.77 (0.70 to 0.82)	0.54 (0.45 to 0.62)	0.67 (0.62 to 0.72)
Hazard ratio for event-free survival (95% CI)			
SY	1.00 (referent)	1.00 (referent)	1.00 (referent)
IP	1.12 (0.79 to 1.59)	1.00 (0.71 to 1.42)	1.04 (0.81 to 1.32)
IP+SY	0.98 (0.68 to 1.41)	1.14 (0.81 to 1.60)	1.04 (0.81 to 1.33)
5-year overall survival (95% CI)			
IP	0.81 (0.76 to 0.87)	0.62 (0.54 to 0.70)	0.74 (0.69 to 0.79)
SY	0.84 (0.79 to 0.89)	0.68 (0.61 to 0.76)	0.78 (0.73 to 0.81)
IP+SY	0.82 (0.77 to 0.88)	0.59 (0.50 to 0.68)	0.73 (0.69 to 0.78)
Hazard ratio for overall survival (95% CI)			
SY	1.00 (referent)	1.00 (referent)	1.00 (referent)
IP	1.10 (0.76 to 1.61)	0.99 (0.70 to 1.40)	1.01 (0.79 to 1.30)
IP+SY	0.97 (0.66 to 1.43)	1.17 (0.84 to 1.66)	1.04 (0.81 to 1.34)

*IP = intraportal regimen; SY = systemic regimen; IP+SY = intraportal and systemic combination regimen.

0.89 to 0.92. The authors concluded that the intraportal infusion of 5-fluorouracil at 500 mg/m^2 daily for 7 days "cannot be recommended as the sole adjuvant treatment for high-risk colorectal cancer after complete surgical excision" *(15)*.

In the large-scale AXIS trial *(16)*, 3681 patients with colorectal cancer were randomly assigned to intraportal infusion of 5-fluorouracil (1 g/24 h for 7 days) plus heparin (5000 U daily for 7 days) or to surgery alone. With 1426 patients having died and an adequate median follow-up of 4 years, an estimated survival benefit for intraportal infusion at 5 years of 2.5% (95% CI = –3% to 7%) was observed. The benefit appeared to be greater, 4% (95% CI= –1% to 9%), in colonic tumors. Consequently, the possible increase in survival from the addition of intraportal chemotherapy appeared to be lower than that observed in the meta-analysis.

Systemic Chemotherapy

Unlike the controversy associated with the role of regional adjuvant chemotherapy, the value of systemic chemotherapy, at least in lymph node–positive patients with colon cancer, has been established. Since 1990, systemic chemotherapy regimens involving 5-fluorouracil for 6–8 months have been the standard of care for patients with Dukes' stage C (lymph node positive) colon cancer *(2)*. Recently, two reports *(17,18)* have shown that 5-fluorouracil–based adjuvant chemotherapy confers similar survival benefits to elderly patients and to younger patients. This result further confirms the feasibility and effectiveness of the adjuvant chemotherapy strategy.

Limited data on the combination of regional plus systemic drug administration are available. In 1998, Scheithauer et al. *(19)* reported results of a trial of patients with stage II and III (both high risk) colon cancer who were randomly assigned to conventional adjuvant chemotherapy (5-fluorouracil plus levamisole) or to the combination of systemic with intraperitoneal chemotherapy (5-fluorouracil and leucovorin). Although intraperitoneal drug delivery was used specifically to target microscopic residual tumor deposits on intraperitoneal surfaces, pharmacokinetic studies have demonstrated that this route also achieves high intraportal/intrahepatic drug concentrations *(20)*. Intraperitoneal chemotherapy was given during the perioperative period and on days 1 and 3 of each treatment cycle, which was scheduled every 4 weeks for a total of six cycles *(19)*. This study *(19)* enrolled 236 eligible patients and found that overall survival was statistically significantly better ($P<.001$) in the group

Table 5. Multivariable analysis of prognostic factors*

	Event-free survival		Overall survival	
Data category	Hazard ratio for first event (95% CI)	*P*	Hazard ratio for death (95% CI)	*P*
Treatment group				
SY	1.00 (referent)		1.00 (referent)	
IP	1.07 (0.84 to 1.37)	.74	1.05 (0.82 to 1.36)	.69
IP+SY	1.10 (0.86 to 1.41)		1.12 (0.87 to 1.45)	
Sex				
Female	1.00 (referent)		1.00 (referent)	
Male	1.34 (1.09 to 1.64)	.005	1.3 (1.07 to 1.63)	.001
Age, y				
≤70	1.00 (referent)		1.00 (referent)	
>70	1.93 (1.57 to 2.37)	<.001	2.01 (1.69 to 2.60)	<.001
Dukes' stage				
B	1.00 (referent)		1.00 (referent)	
C	1.94 (1.58 to 2.37)	<.001	2.22 (1.80 to 2.74)	<.001

*CI = confidence interval; IP = intraportal regimen; SY = systemic regimen; IP+SY = intraportal and systemic combination regimen.

receiving systemic with intraperitoneal chemotherapy (4-year survival rates were 65% and 83% in the systemic and the combined systemic with intraperitoneal chemotherapy arms, respectively). Although these findings suggest an additive positive effect of the systemic and regional combination route, the different chemotherapy regimens tested in the two arms and the burden of intraperitoneal drug delivery over 6 months make the comparison between that trial and our trial difficult. Moreover, recently published results from an Arbeitsgemeinschaft Gastrointestinale Onkologie trial showed that intraperitoneal chemotherapy was indeed less effective than combination chemotherapy *(20)*. In 1992, the EORTC–Gastrointestinal Tract Cancer Cooperative Group initiated an adjuvant trial in which a double randomization was planned. Patients were first randomly assigned to surgery only or to the addition of perioperative chemotherapy (intraportal or intraperitoneal, according to the choice of the individual investigator) and then randomly assigned to receive 6-month postoperative chemotherapy with 5-fluorouracil plus leucovorin or 5-fluorouracil plus levamisole *(21)*. This trial was closed to accrual in 1998, with about 2500 patients enrolled, but data are not yet available.

We provide what is to our knowledge the first evidence that a delivery combination of systemic and regional chemotherapy (IP+SY regimen) is feasible, even in a pragmatic multicenter trial. However, the event-free survival and overall survival rates achieved by this combination were similar to those achieved by either of the two single delivery modalities alone (i.e., IP regimen or SY regimen). This result was apparent regardless of whether the patients had Dukes' stage B or C cancer, but this subgroup analysis should be viewed with caution because the trial did not have the statistical power to compare the chemotherapy regimens in these subsets of patients. The combination therapy also did not alter the subsequent incidence or even the pattern of local and distant recurrences. This result was surprising because we had expected that the regional–systemic combination—which achieves higher intrahepatic drug concentrations than the SY regimen and larger cumulative doses of 5-fluorouracil than the IP regimen—would reduce the number of liver metastases. One explanation for our result, that the inclusion of heparin in the intraportal therapy might negatively interfere with the activity of 5-fluorouracil, is not consistent with the fact that the benefits from the IP regimen and the SY regimen were similar to each other or with the results of the trial reported by Fielding et al. *(22)*. In fact, their three-arm trial of adjuvant portal vein infusion showed that the survival was longer and the incidence of liver metastases was lower in the group that received the infusion of 5-fluorouracil plus heparin than in the group that received intraportal heparin alone or than in the control group.

The EORTC–Gastrointestinal Tract Cancer Cooperative Group *(21)* and our trials had an intraportal plus systemic arm and a systemic-alone arm. Consequently, a meta-analysis of these trials would provide more precise estimates of the relative effectiveness of the therapeutic approaches. Intraportal therapy is simple and inexpensive. Catheterization of a tributary of the portal venous system requires only 10–15 minutes during colorectal cancer surgery. 5-Fluorouracil is one of the most inexpensive cytotoxic drugs, major side effects are rare, and no extra days of hospitalization are usually required. It can undoubtedly be argued that, had a longer treatment and/or higher dose of 5-fluorouracil been used, possibly in combination with other drugs or biomodulators, some improvement with the IP regimen would have been apparent. Notwithstanding this argument, our conclusions that the IP regimen is not better than the SY regimen and that the IP+SY combination regimen does not produce better results than single regimens decrease the initial enthusiasm for intraportal chemotherapy (at least with the low doses and the short course of treatment used in the reported trials). Moreover, recently published data suggest that new systemic chemotherapeutic regimens such as 5-fluorouracil plus oxaliplatin or irinotecan have a good toxicity profile and can even provide better results than the standard 5-fluorouracil regimen *(23)*. Indeed, at present, most medical oncologists may prefer to use a systemic adjuvant treatment.

APPENDIX

Data management and statistical analysis were performed at the SMAC office of the Mario Negri Institute (Milan, Italy) by M. Flann, A. Cattaneo, R. Fossati, A. Tinazzi, and V. Torri.

Following is a list of institutions and consultants contributing five or more patients to the SMAC protocol (the number in parentheses indicates the number of patients enrolled). *Florence, Careggi Hospital:* M. Scatizzi, G. Bacci, R. Moretti, B. Arcangeli (99); *Merate (CO) Hospital:* S. Banducci, C. Magni, U. Bonaldi (69); *Pontedera (PI), F. Lotti Hospital:* G. Consani, G. Di Grazia, G. Biondi (60); *S. Giovanni Rotondo (FG) Hospital:* N. Mastrodonato, F. Bucci, B. Tardio (50); *Cosenza Hospital:* A. Petrassi, S. Palazzo, A. Scarpelli, V. Liguori, C. Mastroianni (46); *Massa, SS Giacomo e Cristoforo Hospital:* C. Sillano, G. Uggeri (42); *Catanzaro, A. Pugliese Hospital:* R. Aidala, E. Rocca, D. Bava (34); *Verona, Borgotrento Hospital:* F. Turturo, F. Caprioli (33); *Bazzano (BO) Hospital:* M. D'Astuto (30); *Belluno Hospital:* M. Giusto, F. Favretti, C. Puccetti, A. Da Rold (29); *Copparo (FE), S. Giuseppe Hospital:* G. Ervi, M. Felloni (29); *Padova, Clinica Chirurgica II:* D. Nitti, M. Lise, A. Marchet, S. Alessio (29); *Gallarate (VA) S. Antonio Abate Hospital:* E. Caronno, G. Reggiori (28); *Milan, S. Carlo Borromeo Hospital:* A. Pessi, G. Samori, G. Mortara, G. Martignoni (28); *Genoa, Chirurgia I, S. Martino Hospital:* E. Ciferri, S. Fazio, G. Gazzaniga (25); *Mantua, Chirurgia I:* P. Tenchini (24); *Mantua, Oncologia–Chirurgia II:* E. Aitini, F. Smerieri, C. Rabbi (24); *Genoa, Policlinico Universitario:* D. Civalleri, F. De Cian, U. Bonalumi (23); *Rome, FBF Hospital:* R. Lupattelli Gencarelli, G. Cucchiara (22); *Cuorgnè (TO) Hospital:* F. Peradotto (20); *Brescia, Spedali Civili:* G. Marini, A. Zaniboni, P. Marpicati, E. Damiani (19); *Cinisello Balsamo (MI) Bassini Hospital:* B. Monzio Compagnoni, G. D. Beretta, F. Ferrante, G. Sansonetti (17); *Bentivoglio (BO) Hospital:* S. Sacco, M. Bedosti, L. Geminiani (16); *Genoa, Chirurgia II, S. Martino Hospital:* P. Torelli, S. Dallera, E. Spagliardi (16); *Tradate (VA), L. A. Galmarini Hospital:* C. Crespi, M. Zanaboni, C. Balaban (16); *Legnano (MI) Hospital:* E. Gassi, M. Luoni, A. Tosi (15); *Modena, S. Agostino Hospital:* I. Selmi, A. Lanzani (15); *Naples, S. Gennaro Hospital:* C. Calì, A. Santoro, L. Maiorino (13); *Padua, Chirurgia II, Civile Hospital:* G. Fabris, B. Epifani, A. Fornasiero (13); *Piombino (LI), Villamarina Hospital:* A. Andreini, A. Salvietti (13); *Pescara Hospital:* A. Caracino, E. Liberatore, M. Lombardo (12); *Venice, Al Mare–Civile Hospital:* W. Visconti, A. Buricelli, S. Ramoscello (12); *Bergamo, Chirurgia II, Riuniti Hospital:* P. Fantoni, B. Stivala, M. Pina, S. Signorelli, M. Monelli (11); *Imperia Hospital:* E. Ramò, P. Mossi (11); *Iseo (BS) Hospital:* S. Mutti (11); *Magenta (MI) Hospital:* G. Bragherio, G. Sarro, L. Ceccarelli, S. Negretti, V. Lanzetti (11); *Brescia, Clinica Chirurgica III:* S. Giulini (10); *Vittorio Veneto (TV) Hospital:* S. Pintaldi, G. Tonietto (10); *Sanremo (IM) Hospital:* M. Mauro, A. Amato (9); *Milan, Niguarda Hospital:* M. Mariani, A. Moretti Montefusco, S. Noto (8); *Perugia, Silvestrini Hospital:* R. Ciaccarini, U. Mercati, V. Trancarelli (8); *Cuneo, S. Croce Hospital:* G. Mariani, G. Grecchi, T. Marzano (7); *S. Giovanni Bianco*

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