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ORIGINAL ARTICLE

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Sequential intrahepatic and systemic fluoropyrimidine-based chemotherapy for metastatic colorectal cancer confined to the liver. A phase II study

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Abstract *Purpose:* Several trials have suggested that intrahepatic chemotherapy increases the likelihood of response in advanced colon cancer patients, but has no significant impact on survival due to the development of extrahepatic metastases. We report our experience of combined hepatic intraarterial and systemic chemotherapy in advanced colorectal cancer patients. *Methods:* A group of 35 patients received intrahepatic FUDR (0.3 mg/kg per day for 14 days by continuous infusion), followed, after 1 week's rest, by systemic 5-FU and L-leucovorin (370 and 100 mg/m^2 per day, respectively, both for 5 consecutive days). After another week off therapy, the combined intrahepatic and systemic regimen was repeated and cycles continued until disease progression. *Results:* Of 32 assessable patients, 17 (53.1%) had an objective response, while 8 (25%) had disease stabilization. Median time to progression (TTP) was 32 weeks (range 8–104 weeks), while the median overall survival was only 39 weeks (range 9–109 weeks). Incomplete liver perfusion was the only variable that showed a significant correlation with a poorer survival ($P = 0.046$, log-rank test). *Conclusions:* Our results are in agreement with previous data suggesting a relative efficacy of such a treatment approach for advanced colon cancer patients. More thorough investigations are warranted, especially as an adjuvant treatment for selected high-risk patients.

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Introduction

The liver is the primary site of metastasization of malignant neoplasms arising from the colon. Indeed, metastases confined to the liver account for about 20% of deaths in metastatic colorectal cancer patients [20]. This fact, together with the observation that most liver metastases are supplied by arterial blood [4], has justified in recent years the development of locoregional strategies – particularly hepatic intraarterial treatments – for the palliative treatment of these patients.

Several randomized trials have been performed to study the effectiveness of intrahepatic arterial infusion of fluoropyrimidines, especially 5-fluorouracil (5-FU) and fluorodeoxyuridine (FUDR) in the treatment of these patients. The results, which have recently been the subject of two authoritative meta-analyses, suggest that this treatment option increases the likelihood of response, but has no significant impact on resulting survival as compared with systemic fluoropyrimidines [7, 15]. The failure to improve survival is largely due to the development of extrahepatic metastases which are left untreated by locoregional therapy and ultimately lead to the patient's death. The combination of hepatic intraarterial and systemic chemotherapy is therefore an attractive treatment option. However, a recent trial by the North Central Cancer Treatment Group and Mayo Clinic, has yielded controversial results. Indeed, the sequential regimen had encouraging short-term results, but no impact on long-term progression-free survival [16].

We report our experience with a similar combined regimen in advanced colorectal cancer patients with liver metastases. We administered FUDR intrahepatically by continuous infusion for 2 weeks and, after 1 week's rest, systemic fluorofolates according to schedule of Mac-

hover et al. [13] for 5 consecutive days. After another week off therapy, the combined locoregional and systemic treatment was repeated until disease progression.

Patients and methods

Patients

Patients were enrolled if they had a histologically proven colorectal cancer with a measurable metastatic disease confined to the liver. CT of chest and abdomen and a bone scan were required to exclude the presence of extrahepatic metastases. The hepatic lesions had to be unresectable because of their number, size or site within the liver. Other inclusion criteria were: an ECOG performance status [17] of 2 or lower, age ≤ 75 years, no previous therapy (including both adjuvant chemotherapy or combined radiochemotherapy, and treatment for metastases), and normal renal, hepatic and bone marrow functions (serum creatinine <2 mg/dl, serum bilirubin <1.5 mg/dl, alkaline phosphatase, sGOT and sGPT levels less than three times the normal values, WBC count $\geq 3000/mm^3$ and platelets $\geq 100{,}000/mm^3$). Patients were excluded if pregnant or lactating, or if they had ascites, major underlying liver disease (especially hepatitis-related liver cirrhosis), medical contraindications to laparotomy, or evidence of portal vein occlusion or of major hepatic artery anomalies at preoperative liver angiography. Finally, all patients gave their informed consent to enrollment, according to institutional requirements.

Treatment

All patients underwent abdominal laparotomy (together with cholecystectomy to avoid the risk of chemical cholecystitis) to position the hepatic artery catheter, which was connected to a subcutaneous port fixed to the abdominal muscular wall. Postoperatively, a perfusion study was carried out to confirm the correct placement and function of the infusion device.

FUDR was administered through a portable infusion pump connected to the port, at a dose of 3 mg/kg per day (combined with 10,000 U heparin) for 14 consecutive days by continuous infusion. After 1 week's rest, 5-FU was administered at a dose of 370 mg/m^2 per day as a 30-min i.v. infusion immediately after bolus injection of L-leucovorin (L-LV) at a dose of 100 mg/m^2 per day. The L-LV preparation contained 0.5% or less of the inactive stereoisomer D-LV. The systemic treatment was administered for 5 consecutive days. After another week off therapy, the combined intrahepatic and systemic regimen was repeated and cycles continued until disease progression. The treatment schedule is summarized in Fig. 1. No dose reduction was considered for grade III toxicity, while treatment was discontinued for grade IV (life-threatening) toxicity.

Follow-up procedures and response criteria

The patients underwent a physical examination before each treatment cycle. WBC count, hemoglobin and platelets were evaluated before each administration of both intrahepatic FUDR and systemic 5-FU/L-LV. Liver function tests were performed before the start of each intrahepatic treatment cycle. Complete serum biochemistry was finally performed every other complete treatment cycle.

Response was evaluated with abdominal CT every third treatment cycle, but only if the patient had completed at least two cycles. Abdominal CT was preferred to ultrasonography because the latter technique is unreliable for monitoring response of liver metastases to treatment [6]. Chest radiography (two projections) was also performed to exclude the development of thoracic metastases and chest CT followed, if necessary.

Complete response (CR) required the disappearance of all assessable tumor. Partial response (PR) was defined as a 50% reduction in the product of the largest perpendicular diameters of the most clearly measurable known malignant disease, with no increase in the size of other measurable lesions and no new lesions. Duration of response was calculated from the time the response began until progression. Stable disease (SD) required no change in size of the measurable lesions, a decrease in tumor size of $<50\%$ or

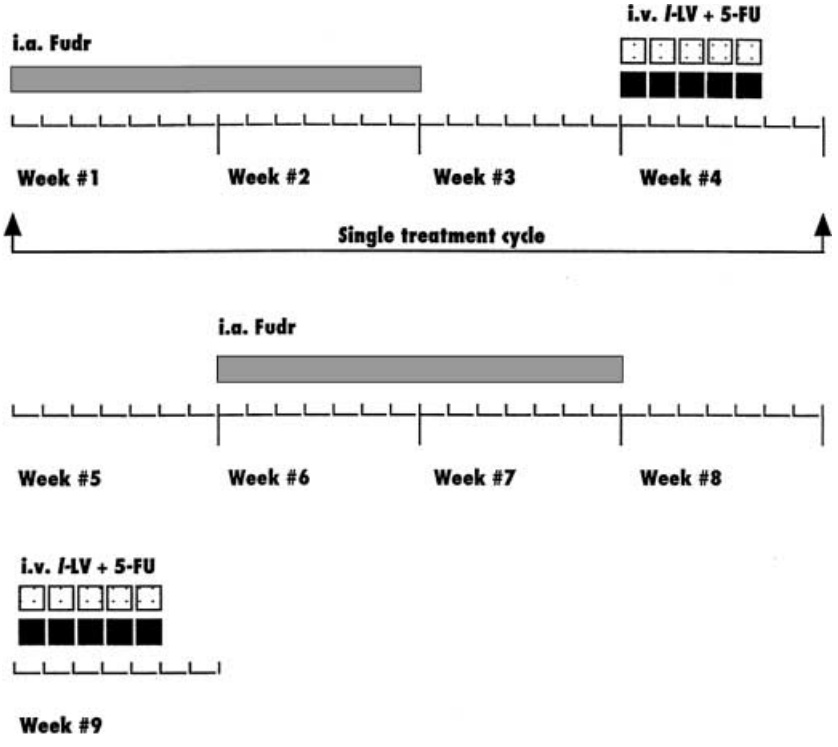

Fig. 1 Summary of treatment schedule

an increase of < 25%, with no new lesions; SD was also required to be of at least 8 weeks' duration. Progression (P) was defined as the appearance of any new lesion and/or growth of any existing lesions by ≥25% since the start of treatment. Toxicity was recorded using commonly accepted WHO grading criteria [21].

Statistical analysis

Overall survival was estimated by the Kaplan-Meier method [8], while the influence on resulting survival of some clinical parameters, i.e. sex, age (< 65 or ≥65 years), presence of complete or partial hepatic perfusion following intrahepatic catheter placement, and extent of hepatic involvement by the tumor (< 50% or ≥50%), was evaluated comparing the different groups using the log-rank test. A *P*-value of less than 0.05 was considered as statistically significant and all tests were two-sided. Statistical analysis was performed using the Statistica software package (1997, StatSoft, Tulsa, Okla.).

Results

Patients characteristics

Of 35 patients who underwent surgical laparotomy to position the intrahepatic catheter and the subcutaneous port, 32 were enrolled in this study. The other 3 were excluded because previously unknown extrahepatic metastases were found at laparotomy. Thus our study group consisted of 20 men and 12 women whose median age on surgical admission was 59 years (mean 58.8 years, range 36–74 years). Abnormal hepatic arterial circulation was observed in three patients (9.3%), and partial hepatic perfusion was seen in five patients (15.6%) postoperatively. The patients' characteristics are summarized in Table 1.

Table 1 Patient characteristics

		%
Age		
Median (years)	59	
Mean (years)	58.8	
Range (years)	36–74	
Patients older than 64 years	12	37.5
Sex		
Male	20	62.5
Female	12	37.5
Primary tumor site		
Sigmoid colon	13	40.6
Hepatic flexure	6	18.7
Rectum	5	15.6
Splenic flexure	3	9.4
Cecum	2	6.2
Descending colon	1	3.1
Ascending colon	1	3.1
Transverse colon	1	3.1
Amount of liver replaced by tumor (%)		
Median	25	
Mean	30.9	
Range	5–70	
Patients with ≥50% of liver involvement	9	28.1
Anomalous hepatic arterial perfusion at preoperative angiography		
Yes	3	9.37
No	29	90.62
Extent of hepatic perfusion postoperatively		
Complete	27	84.37
Partial	5	15.62

Treatment

A total of 234 complete treatment cycles were administered with an average of 7.31 cycles per patient. Seven patients received a minimum of two cycles due to documented tumor progression at first disease evaluation. The largest number of complete treatment cycles received by one patient was 18. Subsequently, due to port rupture, this male patient was treated only with systemic chemotherapy until disease progression which was recorded 8 weeks later.

Toxicity

Complications following the surgical positioning of the intrahepatic catheter were observed in four patients (12.5%) and they were: hematoma in one patient, port system infection in two patients and inadequate liver perfusion due to catheter displacement and/or malpositioning requiring reintervention in two patients.

Intrahepatic FUDR administration was complicated by severe biliary sclerosis in three patients (9.3%), while a less-severe FUDR-related elevation in liver transaminases and/or cholestasis indices was seen in five other patients (15.6%). Elevated liver enzymes in documented disease progression (evidenced at scheduled times) was not considered a treatment-related toxicity. During treatment, other events were considered treatment-related toxicities or complications. These included one port rupture and one displacement leading to intrahepatic treatment discontinuation (3.1% each), two port infections (6.2%) and a cutaneous hematoma (3.1%) after catheter heparinization.

The spectrum of systemic chemotherapy toxicity was as expected: 14 patients (43.7%) experienced mucositis, 12 (37.5%) diarrhea, 7 (21.8%) nausea and/or vomiting, 6 (18.7%) cutaneous toxicity (hyperpigmentation or skin rash), 4 (12.5%) leukocytopenia (never exceeding grade II) and 2 (6.25%) grade II anemia. No signs of cardiac toxicity were recorded during either systemic or intrahepatic treatment.

Tumor response and survival

Of the 32 patients, 17 (53.1%) had an objective response in liver metastases, but only 1 patient (3.1%) experienced a complete response. Response was seen at the first restaging in all but three patients, who were considered to have responded at the second assessment. Disease stabilization was the best treatment result in eight patients (25%).

Median time to progression (TTP) was 32 weeks (range 8–104 weeks), i.e. 7.4 months. Even though one

patient experienced a particularly long TTP (104 weeks, 24.2 months), seven patients (21.8%) were judged as progressing at the first assessment after the first two treatment cycles. Despite locoregional treatment, the liver remained the main site of disease progression in 19 of the 32 patients (59.3%), while the other 13 (40.7%) progressed at extrahepatic sites – mostly peritoneum (seven patients), lung (five patients), the central nervous system, and skin (one patient each). All patients eventually died as a result of tumor progression. The median overall survival was 39 weeks (range 9–109 weeks), i.e. 9.1 months. TTP and overall survival curves are shown in Fig. 2 (TTP, Fig. 2 inset).

We also investigated the degree of correlation between some clinical characteristics and overall survival. However, of sex, age, complete/partial liver perfusion after intrahepatic catheter positioning, and extent of hepatic involvement by the tumor, only incomplete liver perfusion showed a significant correlation with poorer survival ($P = 0.460$, log-rank test; Fig. 3a–d).

Discussion

Colorectal cancer is one of the main cancer killers in the world. In 1998 alone as many as 131,0020 new cases were expected to occur in the US, with 56,000 patients estimated to succumb to this disease in the same year [11]. The vast majority of such patients eventually develop liver metastases. To target the cancer within the organ it most commonly affects, and at the same time limit chemotherapy-related systemic toxicity, is therefore a reasonable treatment strategy. However, the role of intrahepatic chemotherapy in the treatment of advanced colorectal cancer is a most controversial topic in gastrointestinal oncology. Indeed, even though objective responses can be achieved with such an approach, in a great number of patients, controlled trials have failed to document a substantial increase in survival, mainly because of concurrent disease progression at extrahepatic sites [7, 15].

This led to the rationale of combining locoregional and systemic treatments. Unfortunately, the sequential regimen had no impact on long-term progression-free survival in a recent trial combining intrahepatic and systemic chemotherapy [16]. This was true despite better short-term results than the same authors had observed with intrahepatic FUDR alone [14]. Another recently published comparative phase II study aimed at exploring the potential of chronomodulated infusion yielded inconclusive results [5]. Finally, in two other trials, one of which has not yet been fully published, systemic chemotherapy was combined with another, far more inva-

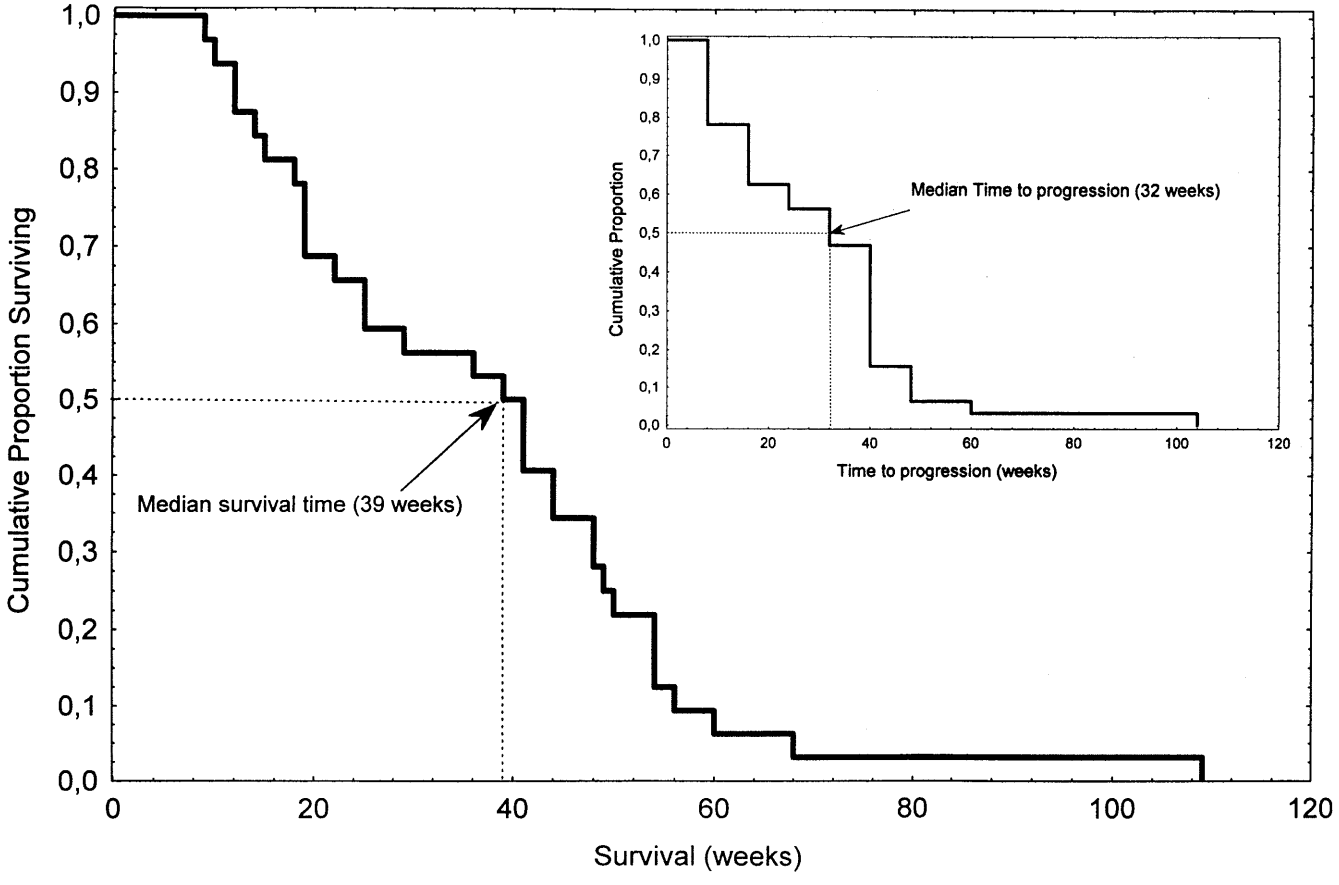

Fig. 2 Kaplan-Meier estimates of overall survival and time to progression (inset)

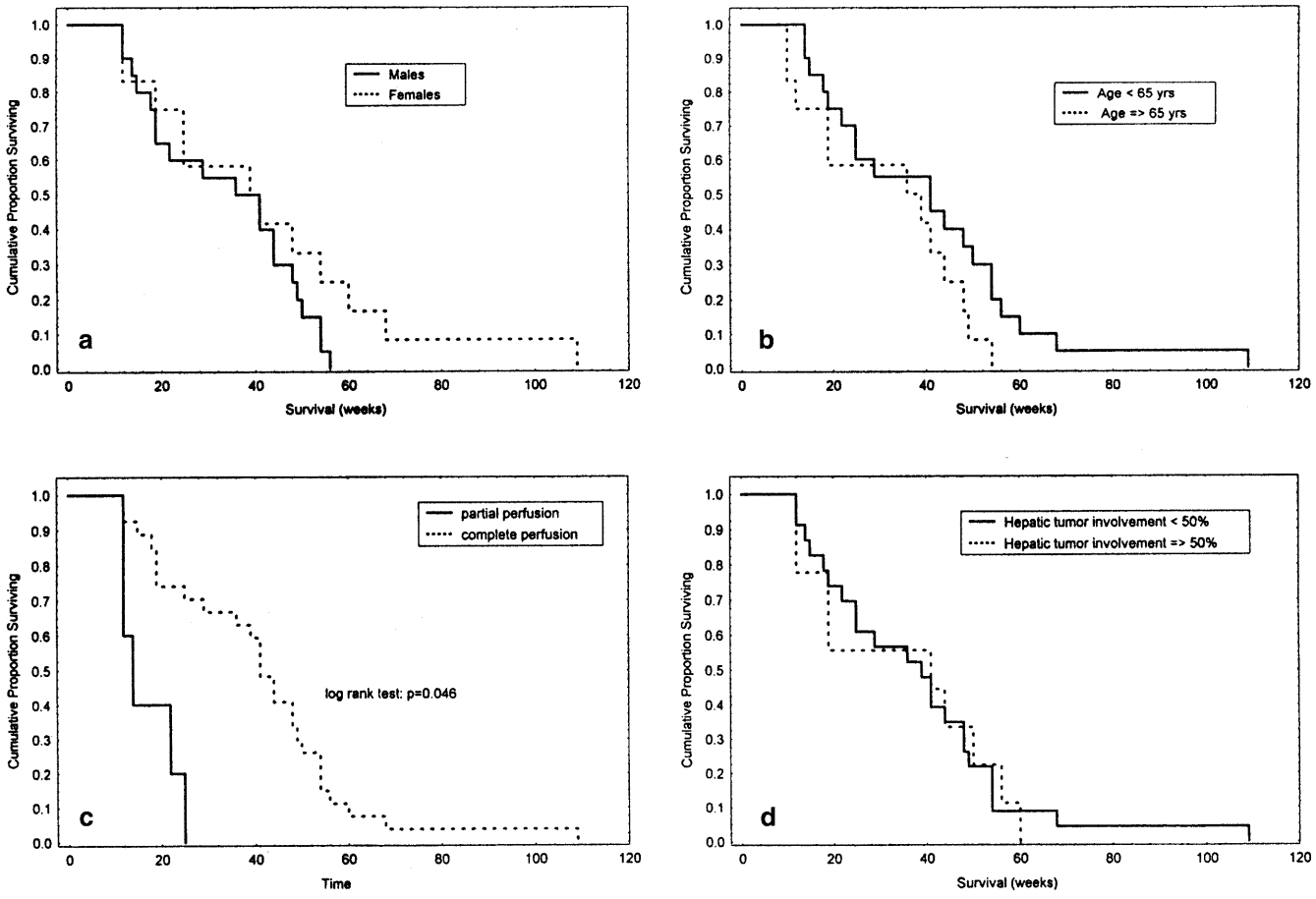

Fig. 3a–d Effect of sex (**a**), age (**b**), type of postoperative liver perfusion (**c**) and extent of hepatic involvement by the tumor (**d**) on overall survival (Kaplan-Meier plots). Only the presence of incomplete liver perfusion had prognostic importance, being significantly correlated ($P=0.046$, log-rank test) with a poorer survival

sive, locoregional treatment – hepatic artery chemoembolization [1, 18]. One of the trials yielded interesting results, but the other provided inconclusive findings, which leaves open the question of the effectiveness of such a combined approach.

Thus, we designed our phase II study combining the established intrahepatic FUDR infusion with the regimen of Machover et al. [13], one of the most widely used systemic schedules in Europe. The choice of FUDR as the drug to be administered by the intrahepatic route may now be criticized since Lorenz and Müller, on behalf of the German Cooperative Group on Liver Metastases, have recently demonstrated that intrahepatic 5-FU/LV is superior to intrahepatic FUDR in terms of time to progression, median survival and decreased progression at hextrahepatic sites [12]. However, at the time our study was designed, FUDR represented the most attractive and widely used drug for intrahepatic administration.

Our results have much in common with those of O'Connel et al. [16], especially in relation to efficacy. On the one hand we confirmed the anticancer activity of this combined approach in terms of objective responses, but on the other hand the resulting survival seemed not to be improved. Thus, we found a median TTP of 7.4 months and a median overall survival time of only 9.1 months, the latter figure being clearly nearly identical to the median survival time of 9 months observed in patients randomized to the systemic 5-FU/L-LV arm of a previous trial in which we participated [3].

Toxicity rates with our combined protocol were higher than those reported by O'Connel et al., but strategies to optimize surgical procedures and the tolerability of intrahepatic FUDR such as those developed by the Memorial Sloan Kettering Cancer Center [9] may clearly improve the rates. Also our search for clinical characteristics significantly correlated with clinical outcome confirmed the results of the North Central Cancer Treatment Group and Mayo Clinic. Thus, incomplete liver perfusion causing insufficient exposure of liver metastases to FUDR proved to be an unfavorable prognostic factor which was significantly correlated with shorter overall survival. In contrast, no such correlation was found for sex, age and, surprisingly, even the extent of liver involvement by the tumor.

On the whole, our results and those of O'Connel et al. [16] suggest that the combined approach, even though still improvable, should not be considered the ultimate answer to the treatment of advanced colorec-

tal cancer, since the results with this approach are still generally unsatisfactory. Even the recent results of Lorenz and Müller [12], despite suggesting a way of improving the results of intrahepatic chemotherapy, suggest the need for extreme caution. Indeed, both intrahepatic and combined systemic and intrahepatic chemotherapy cannot be recommended as routine therapy for patients with metastatic colorectal cancer confined to the liver.

However, such an aggressive combined approach might be more thoroughly investigated as an adjuvant treatment for selected high-risk patients, or in the presence of minimal residual disease after metastasectomy of liver metastases. Indeed, a large randomized trial recently reported by the Memorial Sloan Kettering group indicates that a combination of hepatic arterial infusion of floxuridine and intravenous fluorouracil given to patients who had undergone resection of liver metastases from colorectal cancer improves the outcome at 2 years. In the combined-therapy group 90% of the patients were alive without hepatic recurrences (vs 42% in the monotherapy group, $P < 0.001$), while the respective rates of progression-free survival were 57% in the combined-therapy group and 42% in the monotherapy group ($P = 0.07$) [10].

Finally, the recent development of other drugs which have proved to be active against colorectal cancer in vivo, e.g. CPT-11 [19] and oxaliplatin [2], suggests that combining other systemic schedules with intrahepatic infusion of fluoropyrimidines may have potential in the treatment of these patients in the near future.

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