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Adjuvant Portal Liver Infusion in Colorectal Cancer With 5-Fluorouracil/Heparin Versus *Urokinase* Versus *Control*

Results of a Prospective Randomized Clinical Trial (Colorectal Adenocarcinoma Trial I)

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This prospectively randomized clinical trial was carried out in four Dutch hospitals to reduce the development of metachronous liver metastases and to get a better survival in patients with colorectal malignancies after surgically radical en bloc resection of the primary tumor and the regional lymph nodes. Three hundred seventeen patients were randomized to participate in three trial arms. One group of patients was treated by surgery alone (control group); in the other patients a catheter was placed in the dilated umbilical vein and advanced until the tip was lying in the left branch of the portal vein. Fifty percent of these patients got immediate postoperative portal infusion with 1 g 5-fluorouracil (5-FU) and 5000 U heparin daily for 7 days; the others received portal vein infusion with urokinase 10.000 U/hour for 24 hours only. Three hundred four patients were eligible. Overall hospital mortality was 3.6% (11 patients) and was not influenced by adjuvant treatment. After a median follow-up of 44 months 66 patients have died with relapse and 21 as a result of other causes. The chance of developing liver metastases and other distant metastases after portal infusion with 5-FU/heparin was one third of the chance in the control group ($P < 0.001$). Only an insignificant reduction of the average death rate in the 5-FU/heparin group was found. In the urokinase group no significant effect in reducing metastases or in survival was noted. Before recommending cytotoxic portal infusion as an adjuvant treatment in patients with colorectal cancer, detailed analysis of other ongoing portal infusion studies has to be awaited and careful calculations have to be made regarding how many patients really can be saved by this treatment.

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IN AUTOPSY STUDIES of patients who died from colorectal cancer, liver metastases were found in about 50% to 80%.[1] At time of surgery up to 25% of patients with primary colorectal cancer already have macroscopic liver metastases.[2] The number of patients with microscopic metastases is unknown.

Tumor invasion into mesenteric veins causes spread of circulating malignant cells to the portal vein.[3] These tumor cells surrounded by fibrin and platelets may form tumor clots which can adhere at the vascular endothelium of the liver capillaries. These microfoci can develop into macroscopic metastases initiated by, until now, unknown factors.

This tumor cell embolus theory sounds reasonable, the unknown factors being the induction of anesthesia, operative stress, decrease of immunologic function, hypercoagulability, and blood transfusion.[4–8] In 1975 Taylor *et al.* started a randomized controlled trial to reduce the development of macroscopic liver metastases.[9] *Via* the "obliterated" umbilical vein adjuvant cytotoxic liver infusion with 5-fluorouracil (5-FU)/heparin was given for 7 days to patients who had a curative resection for a colorectal malignancy. The initial results were encouraging.[10,11] Unfortunately it was still uncertain if the results were caused by the use of 5-FU or by the fibrinolytic effect of heparin, which was added to prevent portal vein thrombosis. Experimental studies have shown that malignant cells which are kept in circulation for 5 hours or

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longer (for instance by artificially induced fibrinolysis) are no longer viable.[12-15]

We wanted to determine if we were able to get the same good results as Taylor *et al.*[9] by doing the same investigation. Therefore, we conducted a prospective randomized trial to which we added an extra study arm: postoperative portal infusion for 24 hours with the fibrinolytic drug urokinase, to reduce the incidence of metachronous liver metastases and to get a longer survival in patients with a macroscopic curative resection for colorectal carcinomas.

Patients and Methods

From October 1981 through August 1984 a prospective randomized trial with three patient groups was done in four Dutch nonacademic teaching hospitals.

All patients had the following tests performed to exclude the presence of synchronous liver metastases and to determine the extension of rectal carcinomas in the surrounding tissue: preoperative liver function tests and carcinoembryonic antigen (CEA) determinations; and either a technetium 99m (^{99m}TC) sulphur colloid scan and/or ultrasound scan of liver and/or computed axial tomography (CT) scan of the liver and pelvic region (in case of rectal cancer). All patients had a curative resection of the primary tumor and the regional lymph nodes.

The patients were randomized during operation and allocated to one of the three groups by means of the closed envelope technique (Fig. 1). There was a stratification for the participating institutions. Access to the portal vein was achieved by dilating and cannulating the "obliterated" umbilical vein, which was found by exploring the falciform ligament.[9] A no. 72 Surgimed catheter with four side holes at the end was situated in the portal vein. A venoportogram was performed by injecting a contrast medium to ensure that infusion of the two main lobes of the liver was equal. Infusion was started in group I with 1 g 5-FU and 5000 U heparin in 5% glucose over 24 hours for 7 days. In group II infusion was started with 10000 U urokinase in normal saline solution per hour for 24 hours only. In the control group (group III) the umbilical vein was not explored.

Subcutaneous heparin and/or coumarin derivatives were given as a routine in all patients to prevent deep vein thrombosis.

Leukocyte counts and liver function tests were performed in all patients on days 2, 4, 6, 8, and 10 postoperatively; in group II the values of serum fibrinogen, fibrinogen degradation products, recalcification time, and clotting time were performed on days 0, 1, and 2 as well as the thrombocyte count on days 1 and 2.

After completion of the infusion the cannula was removed in group I after 7 days, and in group II after 24 hours by gentle traction.

Patients were followed at 3-monthly intervals for the first 2 years, 4-monthly the third year, and at 6-monthly intervals the fourth and fifth years, respectively. Physical examination and laboratory tests (erythrocyte sedimentation rate [ESR], liver function tests, CEA determination) were performed at each visit, liver investigation by ultrasound or CT scan at 6-monthly intervals, radiograph of the thorax yearly, and endoscopy after 1, 3, and 5 years.

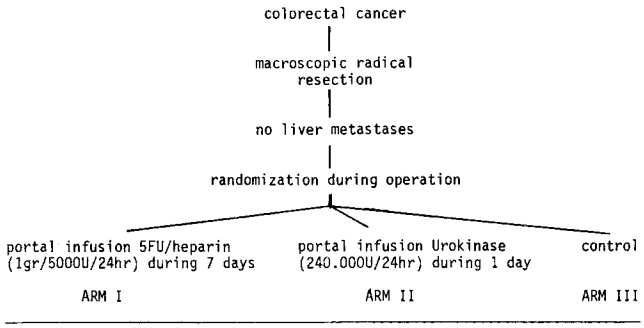

FIG. 1. Protocol for trial.

The presence of local, hepatic, peritoneal, or generalized recurrence was noted and survival time was documented.

If death occurred in a patient with known recurrence, this was assumed to be the cause of death. Postmortem examination was obtained in only a few patients.

Statistical Methods

Endpoints for the analysis were the overall survival time (failure being defined as death from any cause), the disease-free survival time (failure being relapse or death from any cause), the length of the metastasis-free period, and the length of the liver metastasis-free period. All time periods were measured from the date of operation. The survival and relapse probabilities were calculated according to the actuarial method. Unless otherwise specified survival probabilities are not corrected for death not due to carcinoma.

The expected number of deaths in this patient group was calculated from the sex-specific and age-specific death rates for the Dutch general population and the subject years at risk in the corresponding sex and age groups. This expected number was calculated to compare it with the observed number of patients who died from a cause other than colorectal carcinoma.

The log-rank test was used for univariate comparisons between the three treatment groups. For multivariate analyses the regression model of Cox was applied, with the likelihood ratio test to test for differences between the treatment groups.[16] From the regression analysis estimates of relative hazard rates could be derived together with 95% confidence limits. These relative hazard rates are measures for the ratios of the risks of dying (or relapse or development of metastasis) in two different subgroups. For instance, a relative hazard rate of 2 between group A and group B means that in group A the probability of

failure per unit of time is twice as high as in group B, averaged over the total length of follow-up.

The multivariate survival regression analysis was done to determine prognostic factors and to correct for these factors in the analysis of the differences between the three treatment groups.

Results

Three hundred seventeen patients were randomized, 13 of whom were withdrawn from the study for the following reasons: previous cholecystectomy with lesion of the umbilical vein in the falciform ligament in four patients, benign primary lesion in three patients, double malignancy in two patients, preoperative irradiation in two patients, one patient with liver metastases detected during operation, and one patient with skeletal metastases detected in the direct postoperative period.

Three hundred four patients with primary colorectal cancer were eligible. There were 158 men and 146 women (mean age, 64.8 years). One hundred two patients were randomized in the control group, 99 in the 5-FU/heparin group, and 103 in the urokinase group.

In Table 1 age, sex, Dukes' staging by site of the tumor in colon or rectum, and degree of differentiation per group are shown. There were no significant differences between the three groups concerning tumor site (overall: 19% right-sided tumors, 14% transverse, 25% left-sided colon tumors, and 42% rectosigmoid and rectum tumors) and staging (overall: 20% Dukes' A, 44% Dukes' B, and 36% Dukes' C).

Technical difficulties in cannulation of the umbilical vein occurred in 38 of 202 patients (19%), 17 patients in group I, and 21 patients in group II. Ten times the catheter was removed earlier: spontaneously (2×), leakage (5×), thrombosis of the catheter (2×), and in one patient there was a spontaneous dislodgement of the catheter tip in the free peritoneal cavity. These patients were included in the statistical analysis. The median follow-up period was 44 months (25–65 months).

TABLE 1. Age, Sex, Dukes' Stage, and Histologic Grade of Tumors Per Trial Arm

	5FU/heparin (n = 99)	Urokinase (n = 103)	Control (n = 102)	Total
Dukes				
A (20%) Colon	6	11	6	23 (8%)
Rectum	13	13	12	38 (12%)
B (44%) Colon	24	30	30	84 (28%)
Rectum	19	11	20	50 (16%)
C (36%) Colon	23	24	22	69 (23%)
Rectum	14	14	12	40 (13%)
Age (y) (mean)	64.5	65.4	64.5	
Sex				
Male	55	56	47	158 (52%)
Female	44	47	55	146 (48%)
Grade				
Well differentiated	27 (28%)	25 (24%)	33 (32%)	85 (28%)
Moderately differentiated	64 (65%)	64 (62%)	63 (62%)	191 (63%)
Poor/anaplastic	7 (7%)	14 (14%)	6 (6%)	27 (9%)
Unknown	1			1

TABLE 2. Postoperative Mortality and Morbidity Per Trial Arm

	5FU/heparin	Urokinase	Control	Total
Mortality				
Septicemia	1	—	3	4
Peritonitis	1	1	1	3
Cardial insufficiency	2	—	—	2
Pulmonary embolus	—	1	—	1
Neurologic	1	—	—	1
Morbidity				
Wound infection, perineal infection, pelvic abscess	9	7	4	20
Anastomotic dehiscence	4	2	5	11
a. Nausea	25	17	5	47
b. Vomiting	18	7	3	28
c. Diarrhea	14	7	7	28
d. Stomatitis	5	—	—	5
e. Alopecia	1	—	—	1
Total a + b + c + d + e	41 patients	20 patients	11 patients	72 patients

Postoperative Mortality

In the direct postoperative period there were 11 deaths (3.6%). The causes of deaths are shown in Table 2. No significant difference could be found between sex, groups, kind of operation, and participating institutions. There were no infusion related deaths.

Morbidity

The incidence of postoperative morbidity is given in Table 2. The morbidity related to portal infusion with 5-FU/heparin or urokinase was 30%. Most complications (nausea, vomiting, diarrhea, stomatitis) were caused by infusion with 5-FU/heparin (41%) and less by urokinase (19%). Wound infection, perineal infection, and pelvic abscess formation occurred in 20 of 304 of the operated patients (7%), and anastomotic dehiscence in 11/231 patients (4.7%).

The development of septic complications (11%) was not related to age, sex, participating institutions, or treatment groups. On the other hand there was a strong correlation between the development of surgical complications and tumor site (7% in the right-sided colon and 35% in rectosigmoid and rectal tumors, $P = < 0.001$).

No postoperative hemorrhage was noted in the urokinase group. Transient leukopenia (mean leukocyte count $< 4.1 \times 10^9$ dl) was seen in 15% to 25% of the patients in the 5-FU/heparin group, especially between the sixth and tenth day postoperatively. There were three patients

with less than 2×10^9 leukocytes/l in the peripheral blood, without signs of clinical sepsis.

All groups showed disturbed liver function tests during the first 10 postoperative days.

The rise in alkaline phosphatase and serum glutamic pyruvic transaminase (SGPT) during the first 10 postoperative days were about the same in the three groups; only the SGOT values were slightly higher in group I. All values were restored spontaneously. Determinations of blood clotting factors in the urokinase group on the day of operation and 1 day afterward were disturbed in 27/103 patients (26%). None of these patients had clinical evidence of hemorrhage.

The mean hospital stay was 19.4 days; in group I 21.1 days, in group II 18.5 days, and in the control group 18.8 days (NS).

Survival and Recurrence

After a median follow-up of 44 months 206/304 patients (68%) are still alive, of whom 184 (61%) are still disease-free whereas 22 (7%) have recurrent disease.

Ninety-eight patients have died, 11 due to postoperative mortality, 66 after relapse, and 21 without relapse and without evidence of disease. Of the 66 patients who have died after a relapse, the cause of death was the tumor for the majority (63) of them, for two patients it was cardiac, and one patient died due to uremia.

Twenty-four patients died intercurrently, three of whom with relapse (Table 3). This number is smaller than the expected number of deaths (see Statistical Methods): 29.3.

Local recurrence: In 43 patients a local recurrence developed. All local recurrences occurred within the first 40 months follow-up.

The 5-year actuarial probability of local relapse was 16% (chi-square). There was no difference between the three treatment groups in the incidence of local recurrence, but there was a strong correlation with tumor site and Dukes' classification (6% colon tumors *versus* 26% rectosigmoid/rectum tumors; 5% Dukes' A, 11% Dukes' B, and 23% Dukes' C cancers).

TABLE 3. Failures Per Trial Arm

	5-FU/ heparin (n = 99)	Urokinase (n = 103)	Control (n = 102)	Total (n = 304)
Relapse	19	31	38	88
Local	9	6	6	21
Liver	4	12	18	34
Other metastases	0	5	6	11
Local and liver	3	6	5	14
Local and other metastases	3	2	3	8
Dead	28	35	35	98
Postoperative	5	2	4	11
After relapse	13	25	28	66*
Other causes	10	8	3	21

5-FU: 5-fluorouracil.
* Three patients died intercurrently (two cardial, one uremia).

Liver metastases, other distant metastases, and survival: Objective liver metastases developed in 23/102 patients (23%) in the control group, in seven of 99 patients (7%) in the 5-FU/heparin group, and in 18/103 patients (18%) in the urokinase group ($P = 0.01$ 5-FU/heparin *versus* control; $P = 0.45$ urokinase *versus* control, log-rank test; test for difference between the three groups $P = 0.02$).

Excluding the unsuccessful cannulations the figures show only slight differences: the 5-FU/heparin group, six of 82 patients (7%); the urokinase group, 14/82 patients (17%).

Other distant metastases occurred in 19 patients (6%): lung (eight), brains (four), intraabdominal (four), and bones (two). In two patients multiple distant metastases occurred. The 5-year actuarial risk of metastases was 32%. The overall actuarial survival and disease-free survival after 3 years are, respectively, 72% and 64%; and after 5 years, 60% and 56%.

Prognostic factors: Seven factors were studied: Dukes' stage, tumor site, degree of differentiation, participating institution, preoperative CEA value, age, and sex. The most important factors were Dukes' stage and tumor site, as is also clear from the number of observed endpoints in each of the six strata defined by Dukes' stage and tumor site. The prognostic value is most pronounced for the endpoints death and relapse or death. After stratification with respect to these two factors, the influence of the others was determined with endpoints survival and metastasis. No significant difference was observed between the participating institutions. Poorly differentiated tumors showed only a slight but not statistically significantly worse prognosis than the well-differentiated tumors.

As might be expected in the patient group, older patients had a higher death rate, but there was no relationship between age and the risk of metastasis.

Male patients had a higher risk of death (relative risk [RR] = 1.7) as well as a higher risk of metastasis (RR = 1.7), than women.

Patients with an elevated preoperative CEA value also showed a higher death rate and risk of metastasis (RR = 1.6). Unfortunately the CEA was not determined in 29 patients. Therefore, CEA was not used in the following multivariate analysis.

Comparison of the Three Trial Arms

To get a proper view of the effect of portal infusion with 5-FU/heparin or urokinase on survival and the development of liver metastases, multivariate Cox regression analyses were performed with as extra covariates Dukes' stage, tumor site, sex, and age (Table 4). The chance of developing liver metastases after portal infusion with 5-

TABLE 4. Relative Hazard Rate*

Endpoint	5-FU/heparin	Urokinase
Death	0.76 (0.45, 1.3)	0.94 (0.58, 1.6)
Death or relapse	0.72 (0.46, 1.1)	0.94 (0.61, 1.5)
Metastases (all)	0.29† (0.14, 0.61)	0.77 (0.45, 1.3)
Liver metastases	0.27† (0.11, 0.65)	0.70 (0.38, 1.4)

5-FU: 5-fluorouracil.

* Relative hazard rates of both infusion-arms with regard to the control group concerning death (and relapse) and (liver) metastases with 95% confidence limits. Calculated by using the Cox regression analysis, corrected for Dukes' staging, tumor site, sex, and age.

† Two-sided significant difference ($P < 0.001$) with the control arm.

FU/heparin was one third of the chance in the control group ($P < 0.001$). Infusion with urokinase had no significant effect on the development of liver metastases.

Figure 2 shows the development of metastases in the three trial arms with relation to time. The positive effect of reduction of the incidence of liver metastases after portal infusion with 5-FU/heparin was not reflected in a significant reduction of the death rate or an improvement of the (disease-free) survival (Table 4, Fig. 3).

The average death rate in the 5-FU/heparin group was 75% of the death rate in the control group, but this difference is not significant. A probable explanation for this finding is the fact that 48 of the 98 dead patients died without distant metastases but as a result of operation mortality, local recurrence, or intercurrent death. Therefore it is to be expected that the impact of the 5-FU/heparin treatment is stronger on the incidence of liver metastases than on the overall death rate.

Discussion

Corrected 5 year survival rates of patients with curative treated colorectal cancers vary between 50 and 73%. About two thirds of all patients with colorectal malignancies can be treated by surgical resections. Synchronous liver metastases are present on initial diagnosis in about 25% of the patients with a colorectal malignancy[2]; up to 50% of the patients who die after curative resection had developed metachronous liver metastases.[17] Reducing these metachronous liver metastases will probably result in a better survival. A short survey about the development of micrometastases and macrometastases was mentioned earlier in this report. A lot of research has been done to reduce the development of liver metastases.[18–25]

Currently neither adjuvant systemic chemotherapy nor immunotherapy or combination of both results in a significantly higher rate of success than currently used surgical procedures alone. The role of the use of anticoagulant drug in colorectal cancer is in discussion since animal experiments in the 1960s showed the role of fibrin formation in tumor growth and in the development of metastatic deposits. Around tumor cells a primitive stroma of fibrin is formed by which invasion in the surrounding tissue is facilitated. Fibrin formation and platelet aggregation around circulating tumor cells is probably one of the important factors in facilitating the development of hematogenous metastases. They adhere to the vascular endothelium and become implanted. Under experimental conditions various anticoagulants have been shown both to retard primary tumor growth and to decrease or inhibit the development of distant metastases.[6]

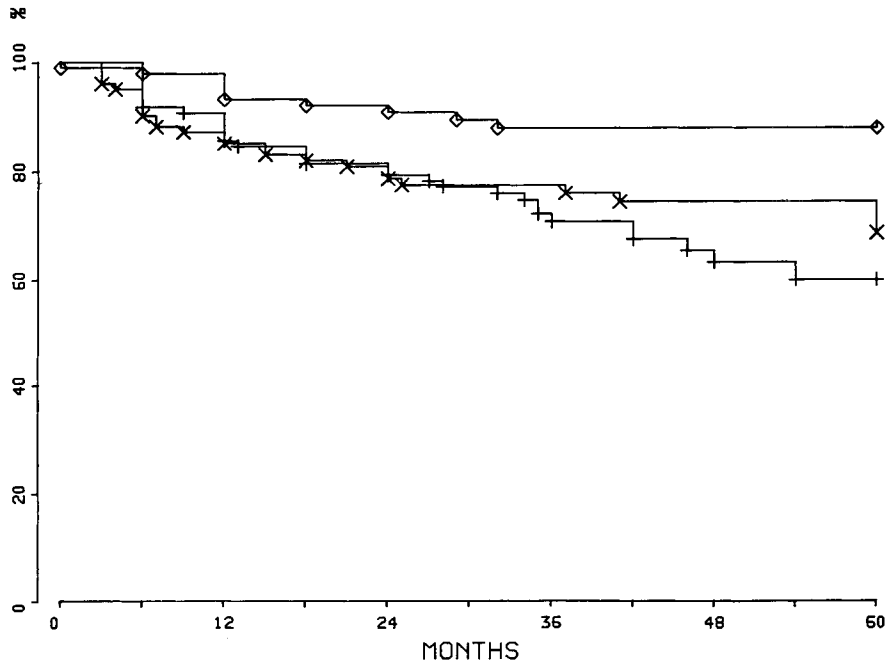

FIG. 2. Percentage of patients without metastases per trial arm in relation to the time in months (◇: 5FU/heparin; ×: urokinase; +: control).

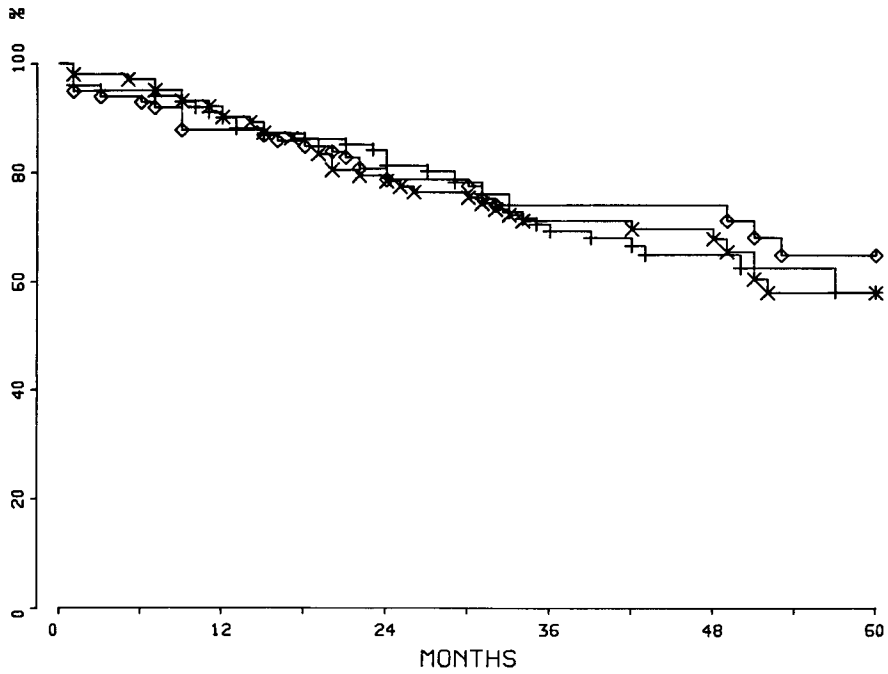

FIG. 3. Overall survival per trial arm in relation to the time in months (◇: 5FU/heparin; ×: urokinase; +: control group).

If circulating tumor cells are or can be kept in circulation for 5 hours or longer, they no longer seem to be viable.[12-15] This is probably the reason why patients with circulating malignant cells fare no worse than those without them[26,27] and even can do it better.[15] Artificial fibrinolysis can be achieved by giving urokinase, artificial hypocoagulability by heparin or coumarin derivatives. Several studies have been done with these drugs,[28-33] but the clinical value remains uncertain.

It has been suggested that one reason for disappointment in adjuvant systemic chemotherapy is that sufficiently high doses of drug cannot be given because of systemic side effects.[11] By administering relatively large doses of a cytotoxic agent directly into the liver circulation one can expect that the incidence and extent of systemic side effects would be minimal, since 5-FU is metabolized in the liver. Already in 1957 intraportal injection of cytotoxic agents at the time of surgery for colorectal carcinoma was advocated.[34] The safety of portal vein infusion in man was shown 18 years later,[35] in that same year that Taylor *et al.* started a prospective randomized adjuvant cytotoxic liver perfusion study for colorectal carcinoma.[9] The initial results were encouraging,[10] after a mean follow-up op 26 to 28 months the incidence of liver metastases in the perfusion group (two patients) was significantly lower than in the control group (13 patients).

Based on these results we started in 1981 the abovementioned prospective randomized trial according to the Taylor study with a third study-arm: infusion of the portal system with the fibrinolytic drug urokinase given for 24 hours postoperatively to keep tumor cells in circulation longer than 5 hours.

Although the effect of giving anticoagulant drugs postoperatively (to prevent deep vein thrombosis) on circulating tumor cells in the portal system is unknown, we thought it was not justifiable to omit this. In our first analysis after a median follow-up of 18 months we could not find any difference in the development of liver metastases or in survival between the three study arms.[36]

Until now at least seven prospective, controlled, adjuvant studies are in progress using portal infusion chemotherapy, from which three have an extra study arm with only anticoagulant portal infusion (heparin or urokinase) after radical surgery for colorectal cancer.

Metzger *et al.*, who initiated two portal vein infusion studies (Swiss Group for Clinical Cancer Research (SAKK) and the European Organization for Research Treatment of Cancer (EORTC) recently collected and published the data of these studies to which we add our new data (Table 5).[37]

All trials are randomized with a "no treatment" control group and all (except the study of Taylor *et al.*[9] in Liverpool) are multicentric, and some do not include rectal cancer. In all studies a radical en bloc resection of the primary tumor and regional lymph nodes was performed, and portal venous catheterization was done at laparotomy through various routes according to the protocol or the surgeon's preference. The adjuvant chemotherapy and/or anticoagulant therapy is given immediately after surgery as continuous infusion for 7 days or only 24 hours.

From three studies no data were available. The results of the other studies show that adjuvant portal infusion with 5-FU/heparin during 7 days reduces the development of liver metastases. Only in the study of Taylor *et al.*[9] did

TABLE 5. Prospectively Randomized Trials With Adjuvant Portal Infusion*

Institution	No. of patients	Entry	Primaries	Treatment (*vs.* control)	Results
Liverpool	257	1976–1980	C and R	1 g 5-FU + heparin/day × 7	Survival (4 y): 70% *versus* 50% (colon Dukes' B: 92% *versus* 60%)
St. Mary's	451	1978–1983	C and R	1 g 5-FU + heparin/day × 7 or 10.000 U heparin/day × 7	Liver metastases: 6.5% *versus* 8.8% *versus* 15.3% (control)
Rotterdam	304	1981–1984	C and R	1 g 5-FU + heparin/day × 7 or 240.000 U urokinase/24 h	Liver metastases: 7% *versus* 18% *versus* 23% (control) Survival: 74% *versus* 70% *versus* 65% (control) at 44 mo
Mayo/NCCTG	?	1980–	C	1 g 5-FU + heparin/day × 7	No data
NSABP	500	1984–	C	600 mg/m^2 5-FU + heparin/day × 7	No data
EORTC	150	1983–	C	500 mg/m^2 5-FU + heparin/day × 7 or 5.000 U heparin/day × 7 alone	No data
SAKK	460	1981–1986	C and R	500 mg/m^2 5-FU + heparin/day × 7 + 10 mg/m^2 mitomycin C day 1	Relapse: 19% *versus* 24% (control) liver metastases: 6% *versus* 10%

C: colon; R: rectum; 5-FU: 5-fluorouracil; EORTC: European Organization for Research and Treatment of Cancer; NSABP: National Surgical Adjuvant Project for Breast and Bowel Cancers; SAKK: Swiss Group for Clinical Cancer Research.

* Reproduced with permission from Metzger U, Mermillod B, Aeberhard P *et al.* Intraportal chemotherapy in colorectal carcinoma as an adjuvant modality. *World J Surg* 1987; 11:452–458.

the patients in the 5-FU/heparin group appear to have an improved survival. In that study, especially, patients with Dukes' B colon tumors had a significant improvement in overall survival; in our study this significant improvement in the whole group was seen after correction for cancer deaths only in patients who survived at least 6 months (Fig. 4), but not overall. Adjuvant postoperative portal infusion with urokinase 10000 U/hour for 24 hours postoperatively did not lower the chance of development of liver metastases, nor did it improve the survival.

Access to the portal vein in our study (as in the study of Taylor *et al.*[9]) was achieved by cannulation of the umbilical vein. Although the technique is not difficult there was a failure rate in our hands of 19%, in contrast with the results of Taylor *et al.* of 7%.[11] In the SAKK and EORTC studies a side branch of the mesenteric vein was used with a very low failure rate of 2%. In our study there were no infusion-related deaths, although until now, at least in three trials, one patient died after cytotoxic liver perfusion due to sepsis in each of the trials.[37]

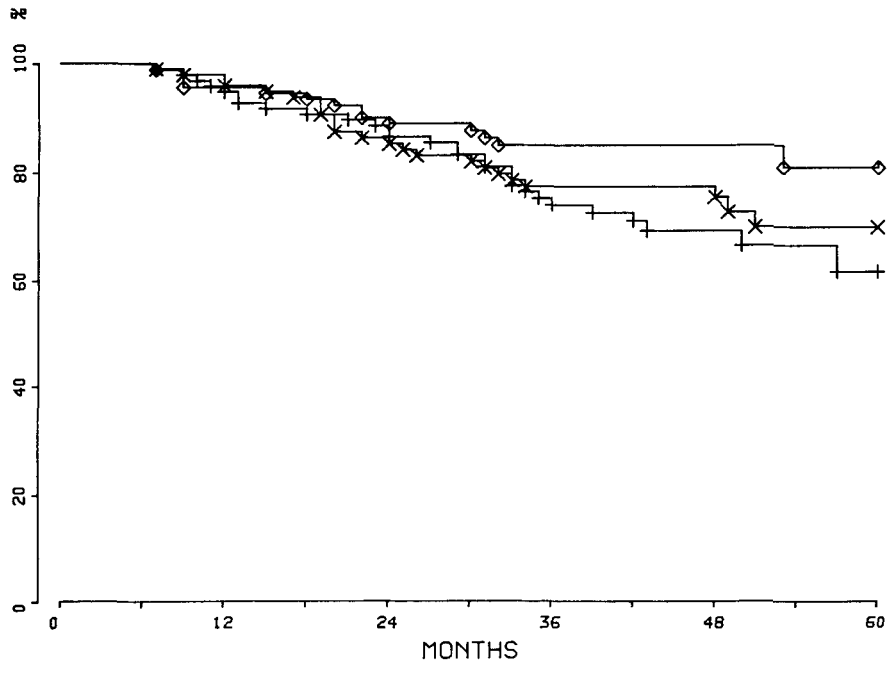

FIG. 4. Corrected survival (for patients who survived at least 6 months) per trial arm in relation to time in months (◇: 5FU/heparin; ×: urokinase; +: control group).

A recommendation for future studies of adjuvant cytotoxic portal infusion could be exclusion for patients older than 75 years of age, for insulin-dependent diabetes patients, and for patients with any evidence of intraabdominal sepsis at laparotomy or during the early postoperative period.[37]

Inconvenient morbidity was only seen in the 5-FU/heparin group: five had stomatitis and one patient experienced alopecia (7%); nausea, vomiting, and diarrhea was seen in all groups with a majority in the infusion groups, according to the other above mentioned studies. Hospital stay was not significantly delayed in the infusion groups.

Our conclusion is that adjuvant portal infusion with 5-FU (1 g over 24 hours) and heparin (5000 U in 24 hours) for 7 days postoperatively reduces, after a median follow-up of 44 months, the development of liver and other distant metastases by one third in patients with a colorectal malignancy after curative resection.

Only an insignificant reduction of the average death rate in the 5-FU/heparin group was found (75% of the death rate in the control group). Before recommending cytotoxic portal infusion as adjuvant therapy in patients after a curative resection of a colorectal malignancy, we believe that detailed analysis of the above-mentioned studies has to be awaited and we must carefully calculate how many patients we really can save by this treatment.

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