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Randomized Trial of Surgery *Versus* Surgery Followed by Adjuvant Hepatic Arterial Infusion With 5-Fluorouracil and Folinic Acid for Liver Metastases of Colorectal Cancer

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Objective
To determine the impact of adjuvant hepatic arterial infusion (HAI) on survival relative to resection alone in patients with radical resection of colorectal liver metastases.

Summary Background Data
Nearly 40% to 50% of all patients with colorectal carcinoma develop liver metastases. Curative resection results in a 5-year survival rate of 25% to 30%. Intrahepatic recurrence occurs after a median of 9 to 12 months in up to 60% of patients. The authors hypothesized that adjuvant intraarterial infusion of 5-fluorouracil (5-FU) might decrease the rate of intrahepatic recurrence and improve survival in patients with radical resection of colorectal liver metastases.

Methods
Between April 5, 1991, and December 31, 1996, patients with colorectal liver metastases from 26 hospitals were stratified by the number of metastases and the site of the primary tumor and randomized to resection of the liver metastases followed by adjuvant HAI of 5-FU (1000 mg/m^2 per day for 5 days as a continuous 24-hour infusion) plus folinic acid (200 mg/m^2 per day for 5 days as a short infusion), or liver resection only.

Results
The first planned intention-to-treat interim analysis after inclusion of 226 patients and 91 events (deaths) showed a median survival of 34.5 months for patients with adjuvant therapy *versus* 40.8 months for control patients. The median time to progression was 14.2 months for the chemotherapy group *versus* 13.7 months for the control group. Grade 3 and 4 toxicities (World Health Organization), mainly stomatitis (57.6%) and nausea (55.4%), occurred in 25.6% of cycles and 62.9% of patients.

Conclusion
According to this planned interim analysis, adjuvant HAI, when used in this dose and schedule in patients with resection of colorectal liver metastases, reduced the risk of death at best by 15%, but at worst the risk of death was doubled. Thus, the chance of detecting an expected 50% improvement in survival by the use of HAI was only 5%. Patient accrual was therefore terminated.

About 40% to 50% of patients with colorectal cancer have liver metastases, either at the time of first diagnosis or after radical resection of the primary tumor.[1] Currently, hepatic resection is the only curative treatment option available for patients with metastases confined to the liver.[2–4] The prognosis may depend on the number and size of the metastases, and whether a negative clearance margin can be achieved.[5–7] However, tumor relapse occurs in up to 60% of patients who underwent resection after a median of only 9 to 12 months.[3,6,8–13] In half of the patients, the first site of relapse is the remaining liver.[3,6,9,11,12,14–17] A second liver resection is seldom

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possible because of extrahepatic and often disseminated intrahepatic disease spread.

The rationale for using adjuvant hepatic arterial infusion (HAI) after liver resection was based on the observation that the liver may be the source of subclinical microscopic residual disease; even small liver tumors are supplied by the hepatic artery.[18,19] Further, 5-fluorouracil (5-FU) instead of floxuridine was chosen as the antineoplastic agent because it is not cleared by the liver completely and has additional systemic effects.[20,21] Based on vast experience from the care of patients with advanced disease, HAI is a safe and probably effective treatment approach in the adjuvant setting.

The purpose of this study was to investigate whether 5-FU and folinic acid (FA) given through the hepatic artery can improve the survival of patients after curative liver resection.

PATIENTS AND METHODS

Between April 5, 1991, and December 31, 1996, 226 patients were randomized in 26 centers in Germany and Switzerland. To be eligible, patients were required to have a maximum of six resectable liver metastases that were completely resected without extrahepatic or primary residual disease. Patients who had liver failure (defined as Quick × CHE [kU] < 200) and a Karnofsky index <70% were excluded, as were patients who had undergone palliative resection and those who had received previous chemotherapy for liver metastases. The interval between prior adjuvant chemotherapy for the primary tumor and randomization was required to be at least 6 months. Written informed consent was mandatory. The study was approved by the local ethics committee and conducted according to regulatory guidelines.

Eligible patients were stratified by the number of liver metastases (one or two and three to six) and the site of the primary tumor (colon or upper rectum and middle or lower rectum) and then randomly assigned over the telephone, in most cases during surgery, to one treatment arm.

Before randomization, all patients underwent examination by abdominal computed tomography, ultrasound, and chest x-ray. Aortoceliacomesentericography was also performed before randomization. A complete biochemical profile with a blood count, measurement of serum transaminases, cholinesterase, and tumor markers CEA and CA 19-9, and blood coagulation tests was obtained.

During surgery, the percentage of liver involvement was estimated, and the abdominal cavity was carefully evaluated for extrahepatic disease. A curative (*i.e.*, complete) resection with a minimal clearance of normal parenchyma between the cut edge of the liver and the tumor >1 cm was intended. A resection was considered curative if the surgical and histologic examination revealed no evidence of residual macroscopic or microscopic intrahepatic or extrahepatic disease.

For patients randomized to adjuvant therapy, the intraarterial catheter was implanted according to the method of Watkins et al.[26] as modified by Curley et al.[27] The tip of the catheter was tangential to the common hepatic artery. A port was placed on the right lower ribs. A prophylactic cholecystectomy was also performed. Total liver perfusion was controlled during surgery with the injection of fluorescein dye (5 ml) visualized by a Wood lamp and after surgery, before the start of the chemotherapy, with technetium-99-labeled macroaggregated albumin.

Adjuvant intraarterial chemotherapy consisted of 5-FU (1000 mg/m^2 per day for 5 days, given as a 24-hour continuous infusion) plus FA (200 mg/m^2 per day for 5 days, given as a short infusion for 10 minutes). Both were given every 28 days. The FA was given before the start of the continuous 5-FU infusion each day. Administration was started within 14 days after surgery and continued for 6 months. If grade 3 or 4 toxicity (World Health Organization) occurred, the daily 5-FU dosage was reduced by 200 mg/m^2.

For follow-up, a physical examination, biochemical profile (including tumor markers), computed tomography scan of the abdomen, and chest x-ray were obtained every 3 months for the first 2 years after surgery and every 6 months thereafter. In addition, a colonoscopy was performed every 12 months.

Statistical Analysis

Survival was chosen as the primary study endpoint. To demonstrate a 50% increase in median survival (24 to 36 months) with error levels $\alpha = 5\%$ (two-sided) and $\beta = 20\%$, we calculated a sample size of 374 patients resulting in 200 observed deaths. We used the model of Schoenfeld and Richter[22] that implemented equally distributed randomization dates and an exponential distribution of survival.

Survival was analyzed using the stratified log-rank test (two-sided p value and 95% confidence interval for hazard ratio) and Kaplan–Meier estimation. For ethical reasons, three interim analyses using a group sequential design were planned. Thus, the global $\alpha = 5\%$ was adjusted according to the α-spending procedure by Lan and DeMets.[23,24] The first planned interim analysis was performed on December 31, 1996, with a nominal level of 0.0071 (α-spending value). Using this procedure, a therapy-based difference of 2.5-fold for survival time could be detected with a sufficiently high probability of $1 - \beta = 0.8$. This interim analysis was performed according to the intention-to-treat principle.[25]

Survival was calculated from the date of randomization. Survival time was censored if the patient had definitely died of a cause other than cancer or therapy, if the patient was lost to follow-up, or if the patient was alive at the date of analysis.

Secondary endpoints were tumor recurrence in the liver, occurrence of extrahepatic metastases, result of surgery, and course of HAI chemotherapy with toxicity. The most important secondary outcome measure fixed in the protocol was the 18-month relapse rate in the liver, to

Table 1. PATIENT CHARACTERISTICS

	Adjuvant Therapy n=108 [missing]	Resection only n=111 [missing]
Sex	[0]	[0]
Male	55 (50.9%)	71 (64.0%)
Age	[0]	[0]
Median (range) in years	61 (30–76)	61 (39–76)
Karnofsky index	[1]	[3]
100%	76 (71.0%)	80 (74.1%)
90%	24 (22.4%)	17 (15.7%)
Site of primary tumor	[0]	[0]
Sigmoid alone	33 (30.6%)	36 (32.4%)
Rectum alone	40 (37.0%)	36 (32.4%)
Differentiation of the primary	[0]	[3]
Moderate	77 (71.3%)	85 (78.7%)
N-staging	[1]	[1]
Positive	53 (49.5%)	61 (55.5%)
Appearance of liver metastases	[0]	[0]
Synchronous	34 (31.5%)	50 (45.0%)
Distribution of metastases	[2]	[0]
Bilobar	26 (24.5%)	18 (16.2%)
Number of liver metastases	[2]	[0]
1	53 (50.0%)	73 (65.8%)
2	29 (27.4%)	16 (14.4%)
3–6	20 (18.9%)	21 (18.9%)
Liver involvement	[3]	[1]
< 25%	88 (83.8%)	94 (85.5%)
Symptoms of disease	[1]	[0]
No	73 (68.2%)	73 (65.8%)

219 of 226 randomized patients assessable.

be analyzed on an intention-to-treat basis by Fisher's exact test (descriptive two-sided p value) and estimation of differences. Further outcome measures were time from randomization until progression in the liver (including death) and time from randomization until tumor progression (including death). In addition to the primary intention-to-treat principle, data were analyzed by various secondary as-treated principles, at first by forming a treatment and a control group after surgery. The results of the interim analysis were submitted to the independent members of the Adjuvant Steering Committee (study protocol) in March 1997. Their recommendation to discontinue the trial was received in April 1997.

RESULTS

Patient Characteristics

A total of 113 patients were assigned to the HAI group and 113 patients were assigned to the control group. At the date of interim analysis, five patients in the HAI group and two control patients could not be assessed. The characteristics of our study population are presented in Table 1. The median age was 61 years (range 30 to 76 years); more men were registered in the control group (64% *vs.* 50.9%). Only 8.4% of the patients had a Karnofsky performance status < 90%. The primary tumor was located in the sigmoid (31.5%) or rectum (34.7%) in two thirds of the patients. Slightly more patients in the control arm (55.5% *vs.* 49.5%) had tumor invasion of regional lymph nodes. Almost 80% of the patients had one or two liver metastases; in 62.2%, the metastases were in the right lobe of the liver. Less than 25% of the liver was involved in 84.7% of all patients. Overall, patient characteristics were statistically well balanced between the two arms.

Surgical Treatment

A curative resection of the metastases was possible in 88.7% of patients, and in 146 patients an anatomically oriented resection was performed. The extent of the resection and the rate of curative resection were distributed equally between both groups (Table 2).

Surgical Mortality Rate

Within 30 days after surgery, 8 of 107 patients (7.5%) in the HAI group died of bleeding (n = 3), myocardial failure (n = 2), shock after angiography (n = 1), sepsis after treatment-related agranulocytosis (n = 1), and toxic myelosuppression (n = 1). In the control group, with liver resection alone, three of 111 patients (2.7%) died in this early period after surgery, two of hepatorenal failure and one of pulmonary embolism. In these 218 patients, the entire 30-day postsurgical period preceded the date of interim analysis. In addition, one patient from the HAI group died in 1997 within 30 days after surgery as a result of treatment-related agranulocytosis.

Adherence to Protocol

Twenty-four patients in the HAI group and 13 patients in the control group did not receive the assigned treatment.

In seven patients in the HAI group, no catheter was implanted (abnormal vessels in four patients, metastases in the root of mesentery in one patient, no reason given in two patients). In five patients, chemotherapy was not started because of hepatic malperfusion (n = 2), technical complications (n = 1), and port infection (n = 2). Two patients refused chemotherapy after randomization, and one patient with liver cirrhosis and another patient with postsurgical ileus underwent only resection. None of these 16 patients received chemotherapy; the resection of liver metastases was curative. In five patients, liver resection was impossible (n = 3) or port complications occurred (n = 2 after curative resection), and palliative HAI 5-FU/FA or systemic 5-FU/FA therapy was initiated, respectively. Three patients did not undergo resection and did not receive chemotherapy; one patient refused chemotherapy, one had no metastases in the liver, and another had

Table 2. SURGICAL TREATMENT

	Adjuvant Therapy n=108		Resection Only n=111	
	n	%	n	%
No resection	6	5.6	9	8.1
Wedge resection	31	28.7	24	21.6
Minor anatomical hepatectomies (1–3 segments)	48	44.4	43	38.7
Hemihepatectomy right	18	16.7	27	24.3
Hemihepatectomy left	3	2.8	7	6.3
Others	2	1.9	1	0.9
Curative resection	98	90.7	91	82.0
Microscopic residual tumor	2	1.9	6	5.4
Macroscopic residual tumor	0	0.0	1	0.9
Not assessable	2	1.9	4	3.6

219 of 226 randomized patients assessable.

peritoneal carcinosis. Thus, adjuvant treatment as randomized was initiated in 84 patients.

In the group of patients randomized to resection alone, 3 patients with a microscopic residual tumor received adjuvant HAI 5-FU/FA, and 10 patients received palliative systemic chemotherapy because of extrahepatic disease (n = 2 not resected) or inoperable liver metastases (n = 7 not resected, n = 1 with macroscopic residual tumor).

Thus, after resection of liver metastases, 87 patients were scheduled to receive adjuvant therapy and 114 patients formed a control group for secondary analyses. These groups were referred to as "as treated," although four patients died before the start of chemotherapy, three patients who had undergone surgery just before the date of interim analysis could not contribute to documentation of chemotherapy, and documentation of chemotherapy was not available for seven patients.

Toxicity of Chemotherapy

Chemotherapy data were available for 73 of 87 patients. Four patients died before the start of therapy, three patients had just undergone surgery, and in seven patients, documentation of chemotherapy was missing at that time. Protocol treatment was completed in 34 patients. Therapy was discontinued earlier because of technical complications (n = 19), intercurrent death (n = 8), tumor progression (n = 4), treatment-related toxicity (n = 4), and withdrawal of consent (n = 3). In one patient the adjuvant therapy was started but not completed at this time.

Toxicity data were available for 73 patients. A total of 297 cycles were documented for 70 patients, with some missing data. Severe toxicity (grade 3 or 4) was experienced by 44 patients (62.9%) and reported in 76 cycles (25.6%). The major toxicities of all grades were stomatitis (57.6%), nausea (55.4%), skin reaction (26.9%), alopecia (26.9%), pain (24.9%), and diarrhea (23.6%). The incidence of grade 3 and 4 toxicities is listed in Table 3.

Tumor Recurrence

Of the 158 patients with at least 18 months of follow-up, 129 could be assessed. For 10 patients in the HAI group and 19 patients in the control group, curative resection was not confirmed. The 18-month relapse rate in the liver was 33.3% (23/69) after adjuvant therapy and 36.7% (22/60) after resection. The difference was lower than expected (p = 0.715; 95% confidence interval for difference of relapse rate, −0.132 to 0.198).

Survival

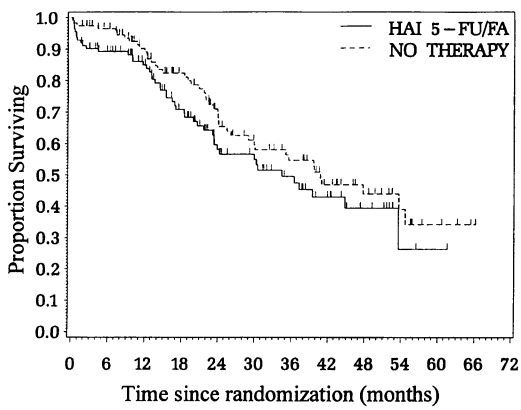
Ninety-one of the patients died before January 1997, none of them definitely from a cause other than cancer or therapy. The median survival time was 34.5 months for the HAI

Table 3. FREQUENT TOXICITIES OF ADJUVANT HAI 5-FU/FA

Toxicity	Cycles	Grades 1–4		Grades 3–4	
		n	%	n	%
Stomatitis	297	171	57.6	35	11.8
Nausea/vomiting	296	164	55.4	25	8.4
Skin reaction	297	80	26.9	4	1.3
Alopecia	297	80	26.9	2	0.7
Pain	297	74	24.9	11	3.7
Diarrhea	297	70	23.6	10	3.4
SGOT/SGPT	296	52	17.6	6	2.0
Alkaline phosphatase	296	42	14.2	0	0.0
Bilirubin	294	36	12.2	1	0.3
Constipation	297	35	11.8	0	0.0

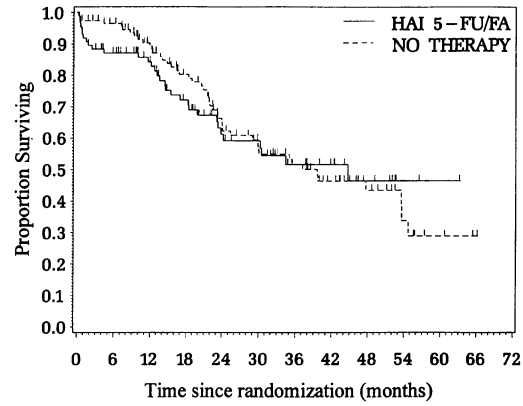
297 cycles assessable.
HAI 5-FU/FA = hepatic arterial infusion with 5-fluorouracil/folinic acid.

group *versus* 40.8 months for the control group (not statistically significant, p = 0.1519) (Fig. 1). The estimation of hazard ratio (control group/HAI group) was 0.76 (95% confidence interval 0.50 to 1.15). An increase in risk of death by intention-to-treat HAI was observed. The median survival time without relapse in the liver was 21.6 months for the HAI group and 24 months for the control group; the median survival time to progression was 14.2 months *versus* 13.7 months, respectively. When the study cohort was analyzed "as treated," the median survival with adjuvant therapy was 44.8 months *versus* 39.7 months (Fig. 2), and the median survival time to progression in the liver was nearly doubled with adjuvant therapy (44.8 *vs.* 23.3 months). The median time observed for tumor progression or death was 20 months for the HAI group and 12.6 months for the control group. However, even in selected patients the advantage of adjuvant therapy in terms of survival without relapse in the liver or progression-free survival did not influence survival.



Patients at risk (| censored)													
HAI 5-FU/FA	113	91	76	57	38	32	24	16	9	2	1	0	0
NO THERAPY	113	100	81	67	49	39	33	22	15	8	4	1	0

Figure 1. Cumulative overall survival after liver resection by treatment group ("intention to treat"): resection only *vs.* adjuvant hepatic arterial infusion with 5-fluorouracil/folinic acid (HAI 5-FU/FA) for 5 days every 28 days for 6 months (p = 0.1519).



Patients at risk (| censored)													
HAI 5-FU/FA	87	70	58	45	30	25	18	14	7	2	1	0	0
NO THERAPY	114	102	82	66	48	38	32	22	15	7	3	1	0

Figure 2. Cumulative overall survival after liver resection by treatment group ("intention to treat"); resection only *vs.* adjuvant hepatic arterial infusion with 5-fluorouracil/folinic acid (HAI 5-FU/FA) for 5 days every 28 days for 6 months.

DISCUSSION

During the last 20 years, the number of liver resections has increased rapidly based on improved knowledge of liver anatomy and experience with liver transplantation and vascular surgery as well as anesthesiology. Today, liver resection is a safe procedure and routinely performed in many centers.[3] A 5-year survival rate of 20% to 40%[8,9,11,28] is achieved with curative resection of isolated colorectal cancer liver metastases; this has not been reported with other treatment modalities. However, up to 60% of patients have relapses, either in the liver or with extrahepatic disease.[8-13] Patients with a high risk of relapse can be identified using the prognostic factors and a recently reported score.[5] The high relapse rate indicates that colorectal cancer could be a systemic disease, and resection alone may not be sufficient. This view is supported by the observation that patients with colorectal cancer who had tumor cells in the bone marrow had decreased survival compared with patients without tumor cells in the bone marrow.[29] In patients with tumor invasion of regional lymph nodes, adjuvant systemic chemotherapy after resection of the primary tumor reduces the risk of death by 30%.[30,31]

When this study was initiated, regional intraportal chemotherapy given for 7 days after resection of a primary tumor appeared promising, and palliative intraarterial chemotherapy in patients with colorectal cancer liver metastases had proven to be effective.[32,33] Adjuvant systemic therapy after liver surgery was considered to be insufficient.[34] Other treatment modalities, such as portal infusion after hepatic resection, were discontinued because of a high rate of complications.[12,35] Intraperitoneal instillation of 5-FU achieved higher peritoneal and portal vein levels than systemic application did,[14] and in one small study with 21 patients no major technical complications occurred, but only a small benefit was evidenced for patients with 4 or more metastases.[36] After adjuvant HAI, some nonrandomized reports claimed a benefit for the treated patients.[37-41] We chose HAI for our study also because of the nearly exclusive blood supply even in small colorectal liver metastases.[19,42]

Our study is the first randomized published trial to test the hypothesis that adjuvant chemotherapy may be effective after complete resection of colorectal liver metastases. However, the results of the planned interim analysis do not indicate that the natural course of the disease after liver resection may be altered by this form of adjuvant treatment. The intention-to-treat survival curves were nearly identical when interpreted starting from 1 month after randomization. Even in the as-treated analysis, no benefit at all could be discerned. Interpreting the confidence interval of hazard

ratio, the risk of death may be reduced by 15% at best but doubled at worst in patients receiving adjuvant HAI relative to liver resection only. Therefore, the study coordinators decided to end recruitment after the recommendation of the independent steering committee because the chance of detecting an improvement of survival in this trial was low and because there was no confidence in achieving a relevant improvement of survival from the administration of adjuvant HAI 5-FU/FA.

Several reasons can be postulated for the failure of this postsurgical adjuvant treatment. Six months of adjuvant HAI treatment may be too short. However, in systemic adjuvant treatment of primary tumors, this period of time proved to be sufficient.[43] The comparison of 6 months of treatment with 12 months of treatment revealed that patients receiving 5-FU, levamisole, and FA had the same survival chance.[44] The reported change of the assigned treatment in our trial demonstrated the difficulty in managing HAI treatment. In some patients catheter implantation was impossible; some had complications, other refused treatment, and for some others HAI treatment was not performed because of their poor general condition. This resulted in a reduced number of patients in whom treatment was actually initiated.

We decided to use ports instead of implantable continuous infusion pumps because of significantly lower costs. Unlike the experience of Wagman et al,[41] technical complications led to early cessation of treatment in 19 patients. This rate is higher than reported by others and may result from different levels of experience in the participating hospitals.[41,45,46] Treatment termination before the anticipated end occurred frequently. This resulted in an average number of four instead of the planned six cycles. However, a cessation rate of 30% was also reported in the study of Moertel et al.[30]

We decided to use 5-FU because of its proven high local efficacy, at least comparable to that of floxuridine, and because its local toxicities were less than those of floxuridine (*e.g.*, sometimes fatal biliary sclerosis). Although tolerance to this regimen was good in a palliative pilot study, grade 3 and 4 toxicities were observed in 25.6% of all cycles and 62.9% of the treated patients. Overall, six deaths were the result of treatment. This may be explained by the reduced hepatic extraction of 5-FU after liver resection.

A low surgical mortality rate and a high rate of curative resection with negative margins attested overall to a good quality of surgery in >90% of the patients. Overall, the 30-day death rate was comparable to that of retrospective monocenter reports (0% to 10%).[3,11,16,47,48] The implantation of the intraarterial catheter was associated with a slightly higher mortality risk for that procedure. However, the increase in the 30-day death rate in the HAI group was mainly attributable to two chemotherapy-related deaths and three catheter-induced postsurgical hemorrhages, two myocardial failures that may have been induced by 5-FU, and one case of postangiography shock after successful surgery.

As a result of this first trial with an adjuvant therapy, resection seems to be the treatment of choice in resectable colorectal liver metastases. Further adjuvant intraarterial therapy should be performed only in controlled studies. New modalities such as neoadjuvant therapy or immunotherapy will soon be prospectively evaluated in patients with resectable liver metastases.

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