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Eur J Cancer, Vol. 27, No. 10, pp. 1226–1230, 1991.
Printed in Great Britain

0277–5379/91 $3.00 + 0.00

Prognostic Factors in Patients with Liver Metastases from Colorectal Carcinoma Treated with Discontinuous Intra-arterial Hepatic Chemotherapy

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48 patients with colorectal cancer metastatic to the liver were implanted with a subcutaneous access system allowing hepatic intra-arterial perfusion. Regional chemotherapy used 5-fluorouracil, while 17 patients also received low-dose mitomycin at the beginning of the study. Responses to the treatment occurred in 29 patients (60%) and median survival was 14.4 months. Toxicity included gastroduodenal erosions in 12.5% of the patients, leucopenia in 20.8%, catheter thrombosis in 42% and arterial thrombosis in 50%. 2 patients died of digestive haemorrhage probably related to treatment. When individually analysed, four factors were found to significantly affect survival: presence of hepatomegaly (defined as palpable liver edge exceeding the right costal margin by more than 5 cm) ($P = 0.006$), percentage of hepatic replacement superior to 50% ($P = 0.003$), more than four metastases ($P = 0.025$) and hypovascularised metastases at radionuclide liver scan with ^{99m} technetium-labelled macroaggregate albumin (MAA) ($P = 0.04$). The effect of the four variables on the observed survival time was analysed using a Cox regression model. Two variables were found to have simultaneously influenced survival. Presence of hepatomegaly emerged as the more significant ($P = 0.0001$), the other being hypovascularised metastases at ^{99m}Tc-MAA.
Eur J Cancer, Vol. 27, No. 10, pp. 1226–1230, 1991.

INTRODUCTION

HEPATIC METASTASES are the most common cause of death in patients with colorectal carcinoma [1]. For these metastases the therapeutic possibilities vary according to their extension and the context in which they occur.

When hepatic metastases are isolated, the best treatment remains surgical excision with a 20–30% 5-year survival rate [2–4]. Unfortunately, such surgery is only possible in about 10% of cases. When it is impossible, only low-efficacy intravenous chemotherapy with 5-fluorouracil (5-FU) can be envisioned [5, 6]; but for certain patients locoregional treatments may also be considered, among which intra-arterial hepatic chemotherapy (IAHC) is a first-line choice. A number of studies have demonstrated a response rate of 50–70% to intrahepatic administration of 5-FU or 5-fluorodeoxyuridine (FUDR), even in patients previously treated with systemic 5-FU [7–9].

Factors affecting survival in patients with colorectal metastases treated by locoregional therapy have been investigated by few authors. Almersjo *et al.* [10] found that survival time was inversely related to percentage of hepatic replacement (PHR). Fortner *et al.* in a multivariate study [5] found PHR, lymphnode metastases and prior chemotherapy to be the most significant determiners of survival in patients treated by IAHC. In Kemeny's multivariate prognostic study [11], the most important factor affecting survival was the assessment of liver involvement evaluated by radionuclide liver scan and computed tomography (CT). Still, the interdependence of clinical, intra-

Table 1. Description of patients treated with intra-arterial chemotherapy

	No./evaluable	%
Clinical hepatomegaly		
> 5 cm below the costal margin	28/48	58
Bilateral metastases	41/48	85
No. of metastases		
< 5	15/48	31
5–10	28/48	58
> 10	5/48	11
Percentage of hepatic replacement		
< 25	11/48	23
25–50	20/48	42
> 50	17/48	35
Quality of metastasis perfusion		
Hyper, iso or heterogeneous vascularisation	31/48	65
Hypovascularisation	17/48	35
Rise in level of alkaline phosphatase		
> 1.5 under normal value	26/48	55
Rise in level of CEA	41/48	85

operative and biochemical factors has not yet been clearly delineated. In the present study, 48 consecutive patients staged at surgery and shown to have non-resectable lesions were treated by IAHC, a catheter being placed in their hepatic artery. Univariate and multivariate analysis have been performed to determine the parameters which could predict both response to IAHC and survival.

PATIENTS AND METHODS

Between August 1983 and September 1987, 48 non-pretreated patients suffering from metastases of colorectal adenocarcinoma were operated on for placement of an arterial catheter, most often in the gastroduodenal artery [12], to deliver IAHC. For all of these patients, the extent of tumour invasion or the location of the metastases prevented resection.

Catheter implantation was always performed during surgery [12]. It was associated with a complete exploration of the abdominal cavity and a systematic cholecystectomy in order to avoid chemical cholecystitis. The implantation site was the gastroduodenal artery (91%) or the splenic artery (9%). In 31% of the patients a right and/or left hepatic artery ligature was associated with catheter implantation to redistribute liver vascularisation so that arterial circulation in the liver and the metastases originated only from one hepatic artery [12]. Quality control of liver perfusion via the catheter was performed during surgery using fluorescein dye and showed satisfactory results in 98% of the patients.

The 48 patients had an average age of 55 years (31–74 years) and the sex ratio was 1:4 (M:F); the primary cancer was located in the colon in 69% of cases and in the rectum in 31%; histologically 79% were well-differentiated adenocarcinomas. The main characteristics of the patients are listed in Table 1. Clinical hepatomegaly was defined as palpable liver edge exceeding below the right costal margin by more than 5 cm and was assessed by the same physician (P.R.). According to the estimation made by CT and ultrasound, PHR averaged 48%, and exceeded 50% in 17 patients. Quality of liver and metastasis perfusion was determined by radionuclide liver scan with ^{99m} technetium-labelled macroaggregate albumin (MAA) [13]. The hyper, iso, heterogeneous or hypovascularised quality of the liver metastases was determined by comparison of MAA uptake in the lesion and in the normal liver as delimited by standard liver scintigraphy with sulphur colloide of ^{99m}Tc. Patients with rim vascularisation around metastases were considered as having an heterogeneous vascularisation.

5-FU was administered early postoperatively during a daily 8-h perfusion at a dose of 1 g/m^2 for 7 days. This chemotherapy was started after a scintigraphic control had shown that most of the liver was perfused and there was no extrahepatic perfusion [14]. After the patients were discharged from the hospital, they received weekly 5-FU perfusions of 1 g/m^2 over an 8-h period. This dose was adapted according to tolerance: increments of 10% in event of good tolerance or decrements of 10% following intolerance. In the beginning of our study, the injections of 5-FU were given combined with an intra-arterial hepatic injection of low-dose mitomycin (1 mg/m^2). This product had in fact been administered only for an average of five times in 17 patients. These injections were later abandoned for fear of favouring arterial thrombosis, since this product is toxic to the vascular endothelium. In event of complete response, the discontinuous 5-FU perfusions were administered at an interval of every 2 weeks for 2 or 3 months and then every 4 weeks in order to maintain good tumour control for the longest possible time. Before therapy, 17% of the patients showed extrahepatic metastases which were most often identified as small metastases or lymph-node metastases in the hepatic pedicle.

Statistics

Tumoral responses were analysed according to the WHO criteria as complete response (CR), partial response (PR), stable disease (SD) or progressive disease (PD).

Univariate and multivariate analysis were performed using BMDP statistical software [15]. For the univariate and the multivariate analysis, continuous variables were analysed in a dichotomous manner. Survival was measured from the day of catheter placement until death or last follow-up. Survival curves were established using the Kaplan–Meier method [16]. These survival distributions were compared across the subgroups by the logrank test [17]. The multivariate analysis used the Cox model [18] to determine factors which had independent prognostic value on survival. The significance of the relationship between the individual prognostic factors and a response was assessed using χ^2 tests.

RESULTS

In the 48 patients, the median number of 5-FU perfusions was 28 (range 7–74); the median time the hepatic artery remained permeable was 6.5 months (range 0.5–27), and arterial thrombosis was observed in 24 patients (50%) after an average delay of 5 months. In the subgroup of the 17 patients who received mitomycin, the occurrence of arterial thrombosis was not different from the rest of the group (10/17 vs. 14/31). Catheter thrombosis occurred in 23 patients (42%) and was reversible in 13 cases with intra-arterial administration of urokinase.

48 patients were evaluable for responses. The complete and partial response rates were 12.5% and 47.9%, respectively; the

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Revised 15 April 1991; accepted 30 May 1991.

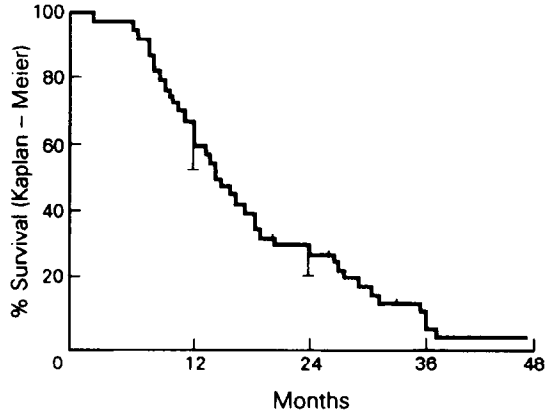

Fig. 1. Overall survival of patients treated with intra-arterial chemotherapy for liver metastases of colorectal origin (n = 48). Mean (S.D.).

objective response rate (CR + PR) was therefore 60% and the median duration of response was 7 months. 1-year mean survival was 61% (S.D. 19) and median survival was 14 months (Fig. 1). The median survival of the subgroup of 17 patients who received mitomycin was not different (13.5 months). In the 44 patients who had an initial abnormal level of carcino embryonic antigen (CEA), a drop of more than 50% was observed in 68% of the cases.

Concerning the tolerance and the toxicity of the treatment, the most frequent incident was the arterial thrombosis in 50% of the cases; in addition, mild haematological toxicity (grade II WHO) was observed in 21% of the cases due to the systemic passage of 5-FU, with only 1 patient presenting grade III leucopenia. Gastrointestinal toxicity was also noted in 31% of the cases; 5 patients developed a gastric or duodenal ulcer and 2 gastritis. 2 patients died of digestive haemorrhage, probably due to IAHC after 2 and 16 months of therapy, respectively. Hepatic toxicity proved limited; only 1 patient showed transitory hepatic insufficiency; this development was probably due to the veno-occlusive disease, for which some histological indications were later found. This patient had a good therapeutic response (CR) over 8 months following this reversible episode.

Table 2. Prognostic factors for univariate analysis

Factors	Survival 1 year	Survival 2 years	P
Percentage of hepatic replacement			
< 50%	71%	30%	0.003
> 50%	35%	0%	
Hepatomegaly			
< 5 cm below costal edge	75%	42%	0.006
> 5 cm	47%	0%	
No. of liver metastases			
< 5	72%	52%	0.025
> 5	52%	10%	
Quality of metastasis vascularisation			
Hyper, iso or heterogeneous vascularisation	71%	35%	0.04
Hypovascularisation	47%	12%	

Table 3. Final Cox regression model

Step no.	Variable	P to enter
1	No hepatomegaly	0.0001
2	No metastasis hypovascularisation	0.0001
3	Prediction of survival was not significantly improved by level of alkaline phosphatase	

Despite the treatment, an extrahepatic evolution, sometimes atypical (pulmonary, peritoneal, lymphatic, cutaneous, osseous, cerebral), was observed in 83% of the cases after an average delay of 9 months. These metastases often heralded the patient's deterioration and were partially accountable for death in 60% of cases.

Prognostic factors

Table 2 shows prognostic factors that affected survival by univariate analysis. Before beginning therapy, four variables among the 13 tested presented significance value for better prognosis: PHR inferior to 50% (P = 0.003), absence of hepatomegaly (P = 0.006), less than five metastases (P = 0.025), non-hypovascularised metastases (P = 0.04). Non-predictive factors were: performance status, sex, age, site of primitive disease, levels of serum CEA, glutamate oxalate transaminase and alkaline phosphatase.

Because of the small number of patients, three multivariate analyses were made. Hepatomegaly and PHR were highly correlated, so these two variables were never entered together in the model. In the first multivariate analysis serum alkaline phosphatase level, metastasis vascularisation and hepatomegaly were tested together. The most significant factor proved to be hepatomegaly. The inclusion of metastasis vascularisation increased the prognostic value of the model significantly (Table 3). Figures 2 and 3 show the influence of the two independent prognostic factors on survival curves. We wanted to analyse prognostic factors when hepatomegaly was not in the model: the second analysis included the number of metastases and PHR, of which the only significant factor proved to be PHR. Then, in a third multivariate analysis, serum alkaline phosphatase level and metastasis vascularisation were tested with PHR;

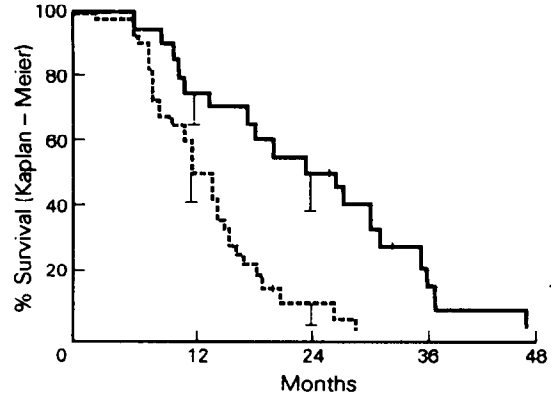

Fig. 2. Survival of patients with (n = 28,----) and without hepatomegaly (n = 20,——). Mean (S.D.).

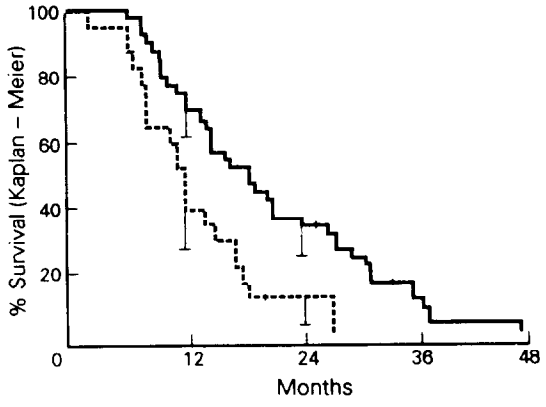

Fig. 3. Survival of patients with and without hypovascularised metastases. 17 patients had hypovascularised metastases when radionuclide liver scan with ^{99m}Tc-labelled macroaggregate albumin was performed (----) and 31 patients had metastases with heterogeneous, iso or hypervascularisation (——). Mean (S.D.).

the inclusion of metastasis vascularisation increased the prognostic value of the model significantly.

Among the five variables tested, only metastasis vascularisation as seen on the MAA radionuclide liver scan was significantly related to response. 48 patients had the MAA radionuclide liver scan before CIAH, 31 had metastases with hyper, iso or heterogeneous vascularisation, and 17 had metastases with hypovascularisation. 74% of patients with fair or good perfusion and 35% of patients with poor perfusion had a tumour response ($P = 0.001$).

DISCUSSION

With 60% objective response, the present study reports results similar to those in the literature concerning continuous infusion of FUDR with an implanted pump [7, 21]. In a previous non-randomised study, we showed similar results in 16 patients treated with continuous FUDR and 42 patients treated with discontinuous 5-FU: 52% and 53% objective response, respectively, thus showing the efficacy of discontinuous IAHC in terms of tumoral response [22].

Numerous studies have been reported concerning the usefulness of IAHC for treating hepatic metastases of colorectal origin [7]. Recently, five prospectively randomised trials clearly demonstrated that intra-arterial FUDR is superior to intravenous FUDR (both administrated with the implanted pump INFUSAID 400) in terms of response rate [8, 23, 24, 27, 28].

On the other hand, with respect to survival, IAHC efficacy is less well-defined. The retrospective studies of Balch *et al.* [25] and of Niederhuber *et al.* [26] are certainly in favour of a survival benefit when compared with a historical control group. However, most of the randomised trials have allowed crossover between intravenous and intra-arterial groups in case of failure, preventing precise analysis of survival benefit [8, 24]. Chang *et al.*'s study [23] favours survival advantage for patients without hilar lymph node involvement but the number of patients included in that study was small. Recently, the study of the North Central Cancer Treatment Group (27) comparing intravenous bolus of 5-FU with intra-arterial continuous FUDR with the Infusaid pump found a difference in median survival of 3.5 months (35%), which was not statistically significant. However, in that study the time to hepatic progression was statistically increased in the intra-arterial group [27]. The preliminary results of a French randomised study, including 163 patients, showed a 4-month survival benefit [28]. However, the frequency with which extrahepatic metastases complicate the evolution of the patients (83% in this study) makes one think that this technique is not capable by itself of healing patients, except in certain exceptional observations.

As survival advantage was not clearly demonstrated when using this expensive, sometimes toxic and technically complex therapy, we looked for prognostic factors which might help us to select patients eligible for it. Two categories of variables were correlated with patient survival: extent of hepatic metastases and events concerning IAHC.

The number and extent of hepatic metastases are correlated with survival, as has been noted by other investigators [3, 5, 11, 29, 30]. The median survival of patients with multiple metastases ranged in most series from 3–5 months. [3]. In our univariate study, three variables representing the extent of the tumoral mass had a significant value for prognosis: PHR, hepatomegaly and number of metastases. When these variables were entered into a multivariate analysis, hepatomegaly seemed to have the strongest significant prognostic value among the liver involvement parameters. Absence of hepatomegaly allowed selection of a subgroup of patients (42% in this study) whose 2-year predictive survival was 40%. However, this parameter is probably not reproducible enough between different examinators and centres to be a reliable selection criterion [31]. For this reason, and as hepatomegaly was not tested in the other prognostic studies of the literature, we tried to exclude this variable from our prognostic analysis; then PHR (more or less than 50%) had the strongest prognostic value, which is consistent with another prognostic study which showed that medical assessment with a radionuclide liver scan had a better prognostic value than surgical assessment [11].

A significant prognostic factor is directly related to use of IAHC—whether or not the metastases had hypovascularisation. Radionuclide liver scan has already been used to predict patient survival [13], but its prognostic value was not clear because its significance appeared only in the univariate analysis and disappeared when multivariate analysis was performed. In this study, adequate vascularisation of hepatic metastases was associated with a 2-year survival rate of 35%, while hypovascularisation was associated with a 2-year survival rate of 12%. Furthermore, in the multivariate analysis this factor increased prediction of survival significantly. This prognostic signification has never been previously demonstrated in a multivariate analysis.

The usefulness of clinical variables in predicting response has rarely been studied. Only one factor of the five analysed helped to predict response to chemotherapy: the absence of hypovascularisation of metastases on a MAA radionuclide liver scan. None of the liver involvement parameters significantly influenced the response rate. This result is in agreement with that of Kemeny [11] and is consistent with other studies in which radionuclide angiography has already been used to predict a patient's response to IAHC [13, 32].

To conclude, this experiment of treatment by discontinuous IAHC with 5-FU showed that the most significant factor for predicting survival was hepatomegaly (defined as palpable liver edge exceeding the right costal margin by more than 5 cm). It is a clinical, inexpensive test of neoplastic hepatic involvement. However, it could be non-reproducible in multicentre trials and in this case we have confirmed that PHR (less than 50% versus more than 50) had a good predictive value and could be used to

quantify the hepatic involvement. More accurate estimates of survival for individuals or groups of patients can be made by considering the good perfusion of hepatic metastases, as demonstrated by the MAA hepatic perfusion scan. This factor also helps to predict response to chemotherapy.

In the light of our experiment and of results reported in the literature, it may be stated that IAHC is an active treatment for hepatic metastases of colorectal cancers, regardless of the technique employed. However, the benefit to patient survival is not clearly established, but the prognostic factors revealed in this study may help us to select patients for this therapy. Patients in good general condition, with isolated but unresectable liver metastases, without clinical hepatomegaly or PHR less than 50% and with adequate perfusion of hepatic metastases probably represent a good subgroup to be treated by IAHC.

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