Multivariate Analysis of a Personal Series of 247 Patients with Liver Metastases from Colorectal Cancer

II. Treatment by Intrahepatic Chemotherapy

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One hundred and seventeen patients with colorectal hepatic metastases had insertion of catheters for infusional chemotherapy. The two-year survival estimate of patients with less than 50% hepatic replacement and no other adverse factors was 37%. Nine of 39 patients in this group are alive at 24 months. The catheters were placed into the hepatic artery (HA), 23; into the portal venous system (PV), 18; into both HA and PV, 64; or into an accessory HA following ligation, 12. Fifty-nine patients had ligation of the common HA also. The 30-day postoperative mortality rate was 1.7% (2/117) and morbidity was 37.6%. The majority of complications were related to fever (61%, 27/44). Over the past 2 years, 87% of patients have been discharged within 10 days following surgery. Preoperative CEA ranged from 0.5–12,150 ng/ml (median 165 ng/ml); 93% (78/84) had plasma CEA levels exceeding 5 ng/ml. All patients had careful intraoperative staging: per cent hepatic replacement (PHR) ranged from 5–95% (median 60%); portal, celiac, or periaortic lymph node metastases were observed in 31% (36/117). Initial intrahepatic chemotherapy programs consisted of either CAMF (9 patients), MAFL (60 patients), BFS (22 patients), continuous infusion FUDR (14 patients), or miscellaneous drugs (4 patients). Median survival time of 109 evaluable patients was 11.5 months. The effect of 20 variables on the observed survival time was analyzed using a multivariate proportional hazard model. Three variables were found to have influenced survival: PHR emerged as the most significant, p = 0.000001. Increased PHR was associated with decreased survival time. Lymph node metastases and prior chemotherapy were prognostic factors also, p = 0.0006 and p = 0.03, respectively. No patient with PHR greater than 80% lived more than 8 months. Utilization of these variables would appear to be necessary for accurate stratification and evaluation of future chemotherapy trials in patients with colorectal hepatic metastases.

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HEPATIC METASTASES from colorectal cancer have been treated most commonly with systemic chemotherapy. Fluorouracil (5FU) does not appreciably improve survival but does have an objective response rate of about 20%.[1] Polychemotherapy appears to improve the response rate, although survival of patients with hepatic metastases may be only slightly improved.[2] Median survival of untreated hepatic metastases has been reported to range from 3.4 to 24 months depending upon the extent of liver replacement.[3–7]

Infusion of 5FU or 5-fluoro-2-deoxyuridine (FUDR) via the hepatic artery results in a 5- to 10-fold increase in tumor drug concentration compared with systemic administration.[8] A number of studies have demonstrated a response rate of 50–70% using regional intrahepatic administration of 5 FU or FUDR even in patients previously treated with systemic 5 FU.[9–11] More recently, Ensminger et al.[12] reported an 83% overall response rate with intra-arterial FUDR using an implantable pump drug delivery system. Median survival of highly selected patients with metastases only in the liver was approximately 21 months.

In none of the reports using either systemic or infusional chemotherapy does there appear to have been a systematic attempt to identify patients with surgically resectable disease. Great reliance has been placed on indirect assessment of the extent and location of metastatic disease using liver scans, computerized axial tomography, and physical examination. Although indirect measurements including angiography are quite accurate in detecting recurrent disease, they are highly inaccurate in assessing the location and extent of liver involvement by cancer.[13] It would appear that patients with potentially surgically curable

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TABLE 1. *Site of Catheter Placement*

Catheter Site	Common Hepatic Artery		Total
	Ligation	No Ligation	
Hepatic artery (HA) only	19	4	23
Portal vein (PV) only	16	2	18
HA and PV	14	50	64
Accessory hepatic artery (AHA)*	6	—	6
AHA* and PV	4	2	6
Total	59	58	117

* In all cases the accessory hepatic arteries (12 patients) were ligated proximal to the catheter insertion site.

metastatic coloretal cancer in the liver may have been included in some series of patients treated only by chemotherapy.

Factors affecting survival of treated patients with colorectal metastases have been investigated by few authors. Almersjo[14] found that survival time varied inversely with per cent hepatic replacement. Cady[15] found the per cent of liver replacement to be the most significant determinant of survival. Others[6,16] have used clinical findings with or without laboratory data to stage patients. However, none of these studies have evaluated the interdependence of clinical, intraoperative, or biochemical variables. In the present study, 117 consecutive patients, staged at surgery by the senior author and shown to have nonresectable disease, have had catheters placed in their hepatic artery and/or portal vein for regional chemotherapy. In an attempt to define independent prognostic factors, a multivariate proportional hazard model was used to evaluate the effects of 20 variables on the patients' survival. They are a subset of 582 patients with primary or secondary liver disease treated by the senior author at Memorial Sloan-Kettering Cancer Center during the past 11 years.

TABLE 2. *Thirty-day Postoperative Morbidity Following Intrahepatic Catheters*

Complication	Number*
Fever	27
Atelectasis	8
Bleeding	5
Pneumonia	2
Pleural effusion	1
Hepatorenal syndrome	1
Total	44

* Excludes complications in two 30-day postoperative deaths and one death at 42 days.

TABLE 3. *Sites of Extrahepatic Metastatic Disease*

Lymph Node Metastases	Intraperitoneal Metastases			
	None	Peritoneal Surface	Pelvic	Omental
None	67	7	5	—
Portal (P)	3	—	—	—
P and Celiac (C)	17	3	2	1
P and C and Aortic	3	3	3	1
Total*	90	13	10	2

* Excludes two patients in whom nodal and peritoneal status could not be determined.

Materials and Methods

Patient Population

The charts of 247 patients with a histologic diagnosis of colorectal cancer metastatic to the liver were reviewed. The 117 patients (47%) who had insertion of hepatic and/or portal vein catheters for intrahepatic chemotherapy are the basis of this report.[17–20] Seventy-five patients (30%) who had surgical removal of their metastatic liver disease are the subject of a companion report[21] and are not considered here. Three patients who had hepatic artery ligation without catheter insertion, two who had isolation chemotherapy perfusion,[22] and 50 who had a biopsy only are not included in this analysis.

Preoperative evaluation of the patients included liver function tests and, since 1974, plasma levels of CEA. Computerized tomography scans, as well as selected celiac and superior mesenteric angiography were done before surgery.[23] At laparotomy, the extent of liver replacement by tumor was estimated by inspection and palpation and a search made for extrahepatic metastatic disease. Following biopsy of hepatic metastases and other suspected intraabdominal disease or lymph node metastases, a catheter (since 1976, a Raimondi (American Heyer-Schulte, Goleta, California) anti-reflux catheter) has been placed in the hepatic artery via the gastroduodenal artery and/or into the portal venous system via the inferior mesenteric vein.[24]

Surgical Procedure

The site of catheter insertion and operative procedure are shown in Table 1. Twenty-three patients had insertion of a catheter into the hepatic artery only; 18 patients had a catheter placed in the portal venous system only; and 64 patients had catheters inserted into both the hepatic artery and portal vein. Fifty-nine of the 117 patients had ligation of their common hepatic artery also. Twelve other patients had hepatic arterial anatomy necessitating catheter placement into an aberrant vessel with concomitant

proximal ligation. Seven patients had small accessory hepatic arteries which were ligated in addition to the above procedures. Ninety per cent (79/88) of portal vein catheters were placed via the inferior mesenteric vein (25 catheters) or a branch of the middle colic vein (54 catheters).

The 30-day postoperative mortality rate was a gratifying 1.7% (2/117). Both deaths occurred in patients with more than 75% liver replacement. One additional patient died of hepatic failure on the forty second day after hepatic artery ligation and cannulation. The postoperative morbidity was 37.6% (Table 2). The majority of complications (61%) were related to unexplained fever (temperature > 38.5 C) which usually occurred on the second through fourth postoperative day without elevation of neutrophil count or chest x-ray changes. This was considered likely due to tumor or tumor necrosis. The median postoperative hospital stay was 11 days. In the past 2 years, 87% of patients have been discharged within 10 days following surgery.

The results of intraoperative staging are shown in Table 3. Sixty-seven patients (58%) had liver involvement only. In addition to liver metastases, 23 patients had regional or periaortic lymph node metastases and 12 had minimal peritoneal metastases. An additional 13 patients had both lymph node and peritoneal metastases. Eighteen patients had a small amount of ascites. Per cent hepatic replacement (PHR) in 114 patients ranged from 5–95% with a median of 60% (Figure 1). PHR was not recorded in three patients.

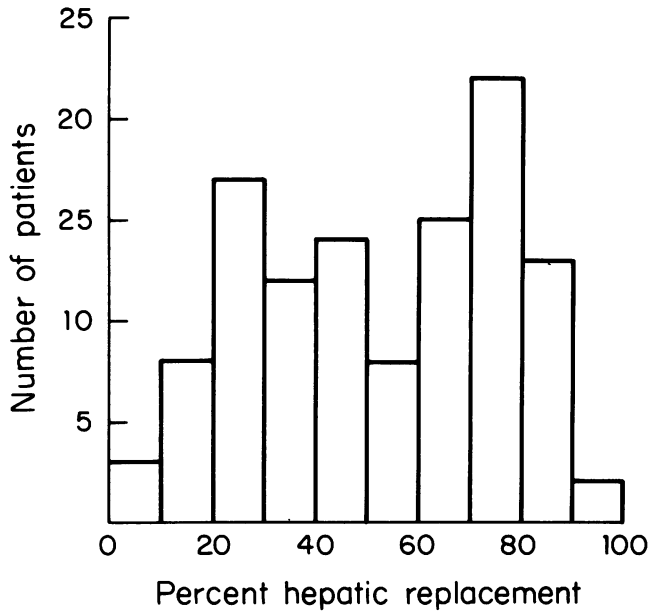

FIG. 1. Per cent hepatic replacement in patients with colorectal hepatic metastases determined at laparotomy.

Chemotherapy

One of the 4 intrahepatic drug combinations, CAMF, MAFL, BFS, or FUDR, was used in the majority of patients (Table 4). CAMF was used from 1973 to 1975 and consisted of Cytoxan (1 mg/kg) orally each day. Actinomycin D (1 mg), Methotrexate (10 mg) and 5FU (10 mg/kg) were given together once weekly via intrahepatic catheter. MAFL was used from 1976 to 1979. It consisted of a 3-week cycle of bolus intrahepatic chemotherapy: Actinomycin D (1 mg) + 5FU (10 mg/kg) week 1, Actinomycin D (1 mg) week 2, and Methotrexate (20 mg) + Levamisole (150 mg/day p.o. for 3 days) week 3. Beginning in 1979, a modification of the MOF regimen originally described by Moertel[25] was used. BFS consisted of a 70-day cycle of bolus intrahepatic injections of BCNU (30 mg/m^2, daily × 5 days week 1); 5FU (300 mg/m^2, daily × 5 days week 1 and 6) and Streptozotocin (500 mg/m^2, once weekly for 11 weeks). Continuous intrahepatic infusion of FUDR (0.3 mg/kg/day for 14 days followed by 14 days saline infusion) was used in the most recent patients. When patients had evidence of local failure (liver progression) a second regimen of intrahepatic chemotherapy was usually given. All patients in this series received at least 2 weeks of intrahepatic chemotherapy. When patients had distant metastases or catheter failure, systemic chemotherapy was instituted.

Statistical Analyses

All data were stored in CLINFO (a data analysis system, Bolt, Beranek and Newman, Boston, MA). Data were analyzed for significance using statistical programs resident in CLINFO and included descriptive statistics, two-tailed t-test, the product-limit life table analysis, and generalized Wilcoxon test for life tables. Evaluation of the

TABLE 4. *Initial Intrahepatic Chemotherapy*

Chemotherapy Regimen*	Number of Patients
MAFL	60
BFS	22
FUDR	14
CAMF	9
Miscellaneous	4
Total	109†

† Excludes eight patients: two 30-day postoperative deaths, one 42-day death, and five patients receiving less than 2 weeks of intrahepatic chemotherapy.

* See Chemotherapy section in Materials and Methods for explanation of the chemotherapy regimens MAFL, BFS, FUDR, and CAMF.

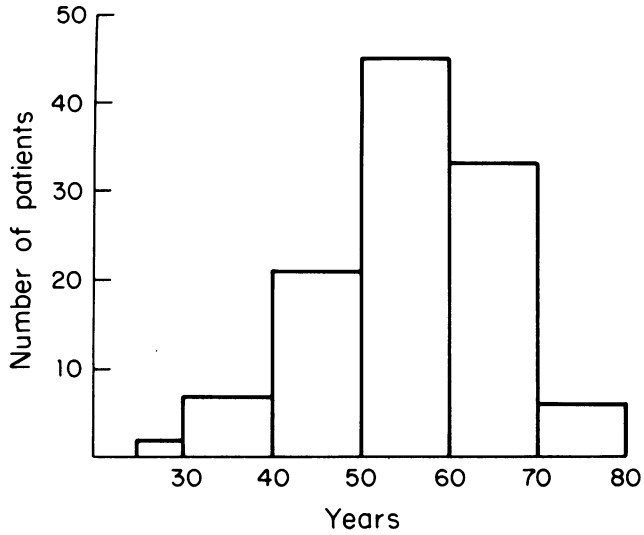

FIG. 2. Age distribution of patients with colorectal hepatic metastases treated with intrahepatic chemotherapy.

effect of multiple variables on the survival of patients was carried out using a step-wise proportional hazard analysis. The association of putative prognostic factors with survival duration were estimated using Cox's proportional hazard survival regression model.[26] In this model:

$$\lambda_i(t) = \lambda_o(t) \exp\left(\sum_j \beta_j \chi_{ij}\right),$$

where λ_i and λ_o are the hazard functions for the individual and overall group; β_j is the regression coefficient for the jth covariate, and χ_{ij} is the value of the jth covariate in the ith patient. The β_j are estimated using the maximum likelihood techniques. The criterion for inclusion of a variable in the model was significance level less than 0.1 for its step-wise inclusion. Significant regression coefficients are interpreted as having an adverse prognostic implication when the coefficient is positive and a favorable implication when negative.

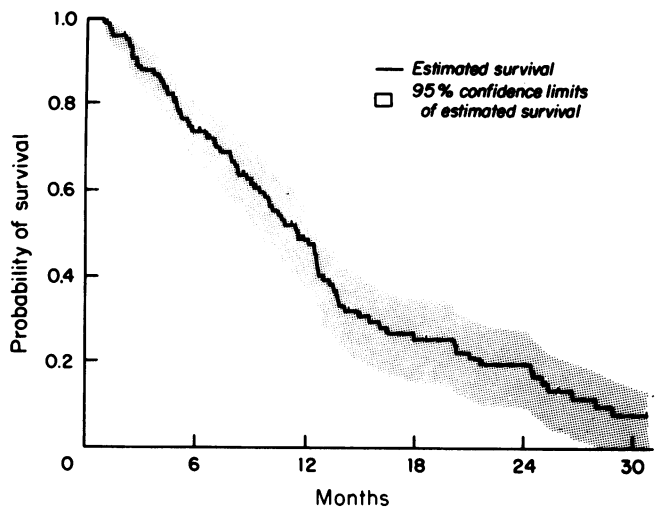

FIG. 3. Survival of 109 patients with colorectal hepatic metastases treated with intrahepatic chemotherapy. Vertical marks: patients alive at last examination.

Results

Patient Population

There were 68 men and 49 women with a median age of 56 years (range 26–79 years, Fig. 2). The age distribution of male patients did not differ from female patients. Karnofsky performance status ranged from 50% to 90% with a median of 80%. The sigmoid colon (41/117) or right colon (27/117) represented the most common sites of primary disease. Most patients (83/117) had Dukes' C primary lesions, 28 had Dukes' B, and 6 were unclassified. Fifty-five per cent (64/117) of the population had liver metastases at the time of colon resection. Since 1977, 71% of patients with metachronous liver metastases have had the diagnosis of liver metastasis first suspected on the basis of an elevated post-colon resection CEA level. Preoperative CEA levels ranged from 0.5–12,150 ng/ml, with a median value of 165 ng/ml. Ninety-three per cent (78/84) of patients had values above 5 ng/ml; 63% (53/84) had CEA levels above 100 ng/ml, and 24% (20/84) had CEA levels exceeding 1,000 ng/ml.

Survival Analysis

Median survival of 109 evaluable patients was 11.5 months from time of catheter placement (Fig. 3). Eight patients were excluded for the following reasons: three patients died postoperatively and five patients received less than 2 weeks of intrahepatic chemotherapy. The initial intrahepatic chemotherapy regimens administered during the period of this study are shown in Table 4.

The effect of 20 variables on patient survival was analyzed using a step-wise proportional hazard model (Table 5). Per cent hepatic replacement emerged as the most significant determinant of survival, $p = 10^{-6}$. Increasing PHR was associated with shorter survival times (positive correlation coefficient). The extent of lymph node metastases was also a significant variable, $p = 0.006$. More extensive nodal involvement was associated with decreased survival. Prior chemotherapy was a significant prognostic factor, $p = 0.03$; previously treated patients had decreased survival time compared with untreated patients. Among the remaining 17 variables, only SGOT had borderline prognostic significance, $p = 0.08$. Site of catheter placement (hepatic artery, portal vein, or both), ligation of common hepatic artery, or intrahepatic chemotherapy regimen were not predictors of survival in this

model. Dukes' classification, site of colon primary, disease-free interval, interval from colon resection to catheter insertion, preoperative laboratory tests (bilirubin, alkaline phosphatase, lactic dehydrogenase, 5′ nucleotidase, and CEA) did not add further information to the multivariate survival model (Table 5).

The three significant variables were combined in an attempt to delineate prognostic groups. Evaluable patients were stratified into three groups based on per cent hepatic replacement: group I, PHR ≤ 50%; group II, PHR from 55% to 80%; and group III, PHR > 80%. Each group was divided into two subgroups based on the presence or absence of other prognostic variables. Subgroup A patients consisted of untreated patients with liver only involvement, while B patients were positive for one or both adverse prognostic factors; *i.e.*, they had either lymph node metastases or prior chemotherapy or both. Increased per cent hepatic replacement was associated with a greater proportion of B patients; 26% (14/53) group I patients had lymph node metastases and/or prior chemotherapy compared with 61% (25/41) group II and 69% (9/13) group III patients (Table 6).

Group IA patients enjoyed increased survival with a median survival time of 17.8 months (Fig. 4). The 2-year survival estimate was 37%. Nine of these 39 patients were alive at 24 months. In contrast, Group IB and IIA had similar survival times with a median survival of 12.5 and 11.6 months (Fig. 4 and Table 6). Group IIB patients had significantly shorter survival time than IIA patients, p = 0.03. Patients with >80% PHR had a uniformly dismal prognosis regardless of other factors. No patient in either IIIA or IIIB lived for more than 8 months.

Treatment Failure

In the group of 109 evaluable patients, 44 patients (40%) had no evidence of progression of intrahepatic disease prior to death or at most recent follow-up. Nineteen patients (17%), without evidence of progression of intrahepatic disease, were placed on systemic chemotherapy as a result of failure of their intrahepatic catheter. Fourteen patients (13%) were placed on systemic chemotherapy as they had appearance of extrahepatic metastatic disease without progression of hepatic disease (12 patients had lung metastases, one each bone and retroperitoneal metastasis). Thirty patients (28%) had intrahepatic progression of disease and had a second course of intrahepatic or systemic chemotherapy. The status of two patients could not be determined.

Discussion

There was a gratifying 37% 2-year survival estimate for patients with less than 50% hepatic replacement and no other adverse factors. Nine of the 39 patients in this group are alive at 24 months. The infusional chemotherapy programs reported here appear to have been effective for about 30% of people whose colorectal metastases replaced no more than 50% of their liver.

All patients in this program had advanced disease as determined by direct inspection and palpation of the liver and other abdominal contents. Forty-two per cent of the patients were found to have metastatic disease in addition to liver metastases at the time of surgery. Combination of systemic with infusional chemotherapy might produce better results in these and other patients with only occult metastatic disease.

Hepatic artery ligation and infusion or hepatic artery infusion alone were abandoned in this study for patients

TABLE 5. *Multivariate Proportional Hazard Analysis in Patients with Colorectal Hepatic Metastases*

Variable	Regression Coefficient	Chi square	p
Percent hepatic replacement	1.72	37.2	$<10^{-6}$
Lymph node metastases	0.74	7.4	0.006
Prior chemotherapy	1.00	4.7	0.03
SGOT	1.28	3.0	0.08

Variables with p > 0.1 included site of catheter (hepatic artery, portal vein, or both), ligation of common hepatic artery, chemotherapy regimen, Dukes' classification, site of colon primary, disease-free interval, interval from colon resection to catheter insertion, presence of peritoneal metastases,* preoperative bilirubin, alkaline phosphatase, lactic dehydrogenase, 5′NT, carcinoembryonic antigen, age sex, and performance status.

* Only patients with *minimal* peritoneal metastases evaluated as those with more advanced extrahepatic disease would not have been candidates for intrahepatic catheter placement.

TABLE 6. *Estimated Survival (Kaplan-Meier) for Patients with Colorectal Hepatic Metastases Treated with Intrahepatic Chemotherapy*

Percent Hepatic Replacement*	n	Estimated Survival (mos) 6	12	18	24
I					
A	39	95%	83%	48%	37% (9)
B	14	85%	50%	20%	10% (2)
II					
A	16	75%	41%	20%	— (1)
B	25	60%	20%	4%	4% (1)
III					
A	4	0%	—	—	—
B	9	12%	—	—	—
Totals	107†	74%	49%	25%	20% (13)

* I—PHR ≤ 50%; II—PHR 55 to 80%; III—PHR > 80%; A—No extrahepatic involvement or prior chemotherapy; B—Either nodal metastases and/or prior chemotherapy.

† Excludes 10 patients: two in whom nodal and peritoneal status were not recorded; two 30-day postoperative deaths; one 42-day death; and five patients receiving less than 2 weeks of intrahepatic chemotherapy.

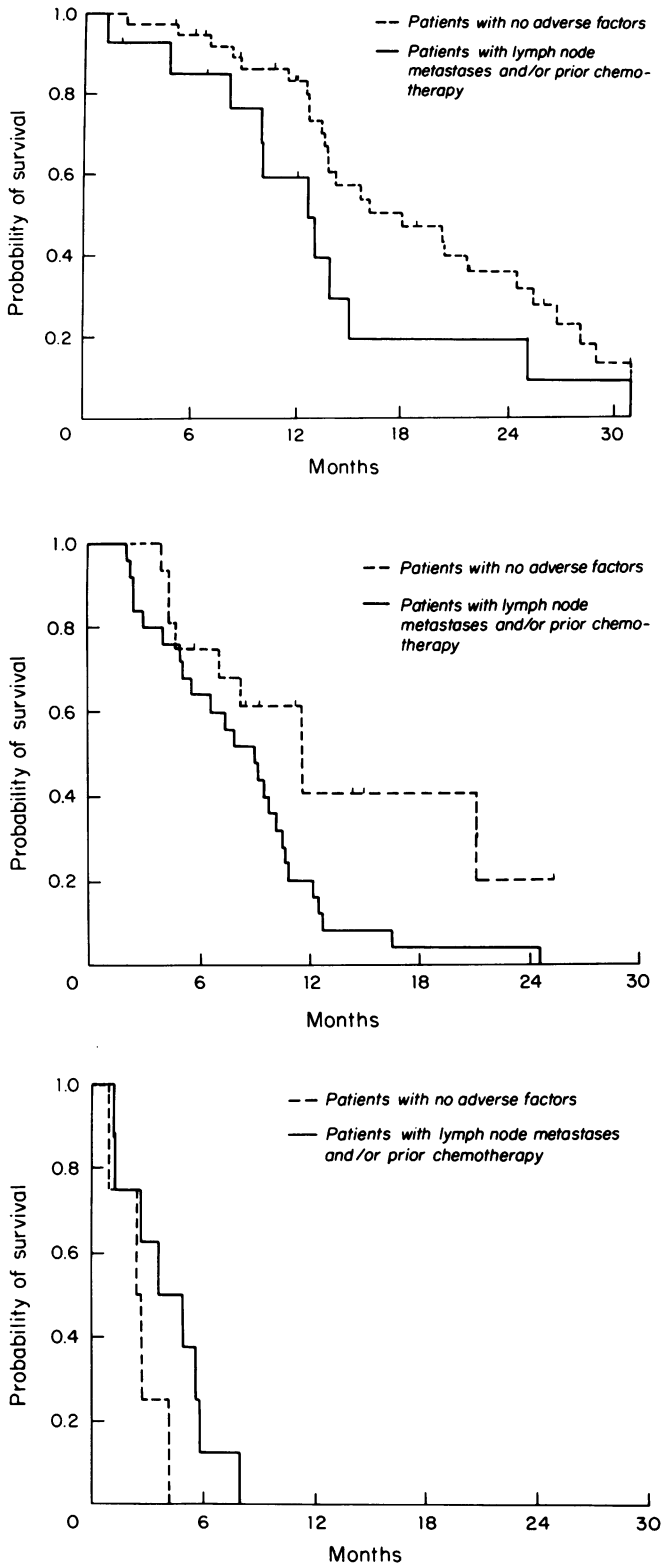

FIG. 4. Survival of 107 patients with colorectal hepatic metastases treated with intrahepatic chemotherapy grouped by prognostic variables. (*Top*) Survival of patients with less than 55% PHR; (*Middle*) Survival of patients with PHR 55 to 80%; and (*Bottom*) Survival of patients with PHR greater than 80%. Vertical tic marks: patients alive at last examination.

with avascular metastases on angiography. Only about 10%[27] of patients with metastatic colon cancer in the liver have increased vascularity on hepatic arterial injection. Their route to the liver had been portal venous so that it appears that the predominant blood supply for 90% of these patients was also the portal venous route. Subsequent experiences proved that there was no difference in patient survival as related to hepatic artery or portal vein routes of drug administration. The portal venous route was chosen since it has been free of the gastrointestinal complications seen with the arterial route; the catheter is easier to place, and free of troublesome complications. Problems posed by hepatic arterial anomalies are avoided.

Comparison of these results with those of others is difficult.[28,29] The patients may not be comparable since it seems likely that our patients with limited disease were surgically resected[21] but such patients are likely to have been included in other reports dealing with the results of systemic or infusional chemotherapy. Accurate intraoperative staging of the patient's disease is essential to evaluating resectability and this has seldom been done. Response rates rather than survival times are most commonly used. Response of liver metastases to chemotherapy is particularly difficult to assess. The healing surgical wound can make accurate liver measurements impossible; often, different observers will obtain quite different liver sizes at a given examination. This is further compounded when a different person sees the patient at sequential examinations. Technetium scans are unreliable in determining the extent of disease. Comparison of sequential CAT scans of the liver gives only a rough estimate unless very dramatic changes have occurred. Accurate assessment otherwise would require the same tomographic cut on each scan and this is not done ordinarily.

Despite these difficulties, certain comparisons can be made tentatively. Patients with untreated colorectal hepatic metastases have a median survival time which ranges from 3.4 to 24 months.[6,7,30] Systemic chemotherapy with 5FU does not improve the survival appreciably. Various polychemotherapy programs appear to improve response rate, although survival of patients with hepatic metastases may be only slightly improved.

Kemeny et al.[31] initiated a pilot study of MOF-Strep in 1976 in patients with advanced measurable colorectal cancer. Seventy-four patients received an adequate trial of therapy with a complete or partial response rate of 32% (24/74). Forty-five per cent (26/58) of liver metastases responded to therapy compared with a 17% response rate reported in previous protocols using MOF alone. A subsequent prospective randomized study was carried out using somewhat higher doses of mCCNU and 5FU.[32] The complete or partial response rates were 34% (12/35) for MOF-Strep and 6% (2/34) for MOF alone.

The best reported results to date for infusional chemotherapy appear to be those of Ensminger et al., who reported an 83% overall response rate with intra-arterial FUDR using an implantable pump drug delivery system.[12] Median survival of patients with presumed hepatic only metastases was about 21 months. More time must elapse before these results can be fully evaluated. The study has the limitations described above, including the likely presence of localized, surgically resectable disease in the most favorable group where the metastases were confined to the liver. In the most favorable group of the present report (IA) the median survival was 17.8 months. This is unlikely to be significantly different from that reported by Ensminger.

The effectiveness of infusional chemotherapy *vs.* systemic chemotherapy can only be shown by a randomized study of carefully staged patients. This has not been carried out to date and was not done in this study due to limitations in available clinical material. The present analysis has identified three prognostic variables which should be considered in the conduct of future studies.

It would appear desirable to use survival time as the end-point in evaluating results. One possibility is to use survival time until activity of the patient declines to less than 60% on the Karnofsky performance scale. Sixty per cent is defined as when patients are unable to work but are able to live at home and care for most of their needs but require occasional assistance.[33]

Staging of liver metastases as in this series has been used previously only to a limited extent. Almserjo et al.[14] attempted this in a small series of patients in whom the median survival was only 4 months. Cady and Oberfield observed among patients receiving intra-arterial FUDR infusion that median survival time decreased as percentage liver involvement by tumor increased: median survival time was 16 months for those with less than 25% liver replacement, 13 months for those with 25–50% involvement, and 8 months for those with more extensive hepatic disease.[5]

The data of this report indicated little benefit from any therapy after more than 50% of the liver was replaced by tumor. In this multivariate analysis, per cent hepatic replacement proved to be the most important of the 20 factors examined. Other significant variables related to the amount of metastatic disease in and outside the liver, *i.e.,* extent of lymph node involvement. Prior chemotherapy was important, possibly since there would appear to be a natural selection of patients with resistant cancers to this program. Other factors were not influential: the disease-free interval, Dukes' classification and site of colon primary, age, sex, and liver function tests other than SGOT. The preoperative CEA level was not a determinant factor.

The low morbidity and mortality rates with relatively short hospitalization periods are gratifying. This is especially so when it is realized that the median amount of liver replacement in this series was 60%. These rates are distinctly better than those experienced earlier, primarily due to better patient selection. Patients with a massive liver replaced by cancer, with jaundice, ascites, portal venous thrombosis, or a Karnofsky performance status <60% are at excessive risk and will not benefit. Infusional chemotherapy with presently available agents is best reserved for those who have nonresectable disease but with 50% or less of the liver involved.

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