Predicting Tumor Response in Patients with Colorectal Hepatic Metastases

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Until now, there has been no reliable means of predicting tumor response to chemotherapy in patients with metastatic colorectal cancer. Using arterial nuclide flow scans as a determinant of tumor response, the degree of tumor perfusion was evaluated in a blinded prospective study. Seventy-three patients with colorectal hepatic metastases received continuous hepatic arterial (N = 52) or systemic intravenous (N = 21) chemotherapy using an implantable pump. All patients had pretreatment hepatic arteriography and arterial flow scans using ^{99m}Tc macroaggregated albumin (^{99m}Tc-MAA). An arteriogram was characterized as positive if it showed tumor hypervascularity; the ^{99m}Tc-MAA flow scan was considered positive if it showed increased tumor uptake relative to the liver. Of 47 patients with an evaluable ^{99m}Tc-MAA flow scan who were treated with arterial infusion, 31 had a positive scan; in this group 16 responded to chemotherapy. The ^{99m}Tc-MAA scan was negative in 16 patients, of whom one responded to chemotherapy ($p < 0.006$). The ^{99m}Tc-MAA scan had the greatest predictive value in previously untreated patients (sensitivity = 91%; specificity = 77%). The arteriogram was positive in 25 of 46 evaluable patients, but this finding had little predictive value for tumor response (sensitivity = 56%; specificity = 46%). Of 21 patients receiving systemic intravenous infusion, the scan was positive in nine patients, of whom seven responded to chemotherapy. The ^{99m}Tc-MAA scan was negative in 12 patients, of whom one responded to chemotherapy (sensitivity = 88%; specificity = 85%). When ^{99m}Tc-MAA-positive and -negative groups were compared, there were no differences in mean patient age, per cent liver involvement, tumor size, or plasma liver function tests. Hepatic tumor perfusion as determined by MAA arterial flow scan is a reliable predictor of tumor response in patients with metastases from large bowel cancer. The test provides a valuable criterion for selecting individuals for treatment of metastases from large bowel cancer by infusion chemotherapy.

MORE THAN 120,000 NEW CASES of large bowel cancer occur each year in the United States. Large bowel cancer accounted for 53,000 deaths in 1981.[1] The most common site of distant metastases from these tumors is the liver; among patients whose colorectal cancer progresses to an advanced state, 40 to 70% have hepatic involvement.[2-3] In 30% of patients who have undergone operative resection of the primary tumor, the liver is the sole site of initial tumor recurrence. Thus, effective therapy for hepatic metastases could benefit up to 35,000 patients annually.

Results of systemic chemotherapy for metastatic colorectal cancer have been disappointing, with average tumor response rates of 15 to 20%.[4] Use of regional intrahepatic arterial chemotherapy has increased tumor response rates in comparison with previous standard therapy, but increased treatment morbidity has also been noted.[5-8] Dissatisfaction with these findings has prompted efforts to define more clearly which patient population will benefit from chemotherapy. Studies have shown a correlation of several factors—pretreatment performance, serum bilirubin, albumin and hepatic enzyme levels, presence of hepatomegaly, and weight loss—with the duration of survival.[4,9] These measurements all reflect in some degree the extent to which metastatic disease has involved the liver. Tumor response to treatment is generally correlated with prolongation of survival. The purpose of our prospective trial was to evaluate those pretreatment determinants which predict tumor response to hepatic arterial or systemic intravenous chemotherapy infusion, and which should thus represent an important guide to patient selection.

Materials and Methods

Patients evaluated in this report were studied during two consecutive prospective clinical studies. The first study was a Phase II protocol evaluating the efficacy of hepatic arterial infusion for colorectal hepatic metastases. The

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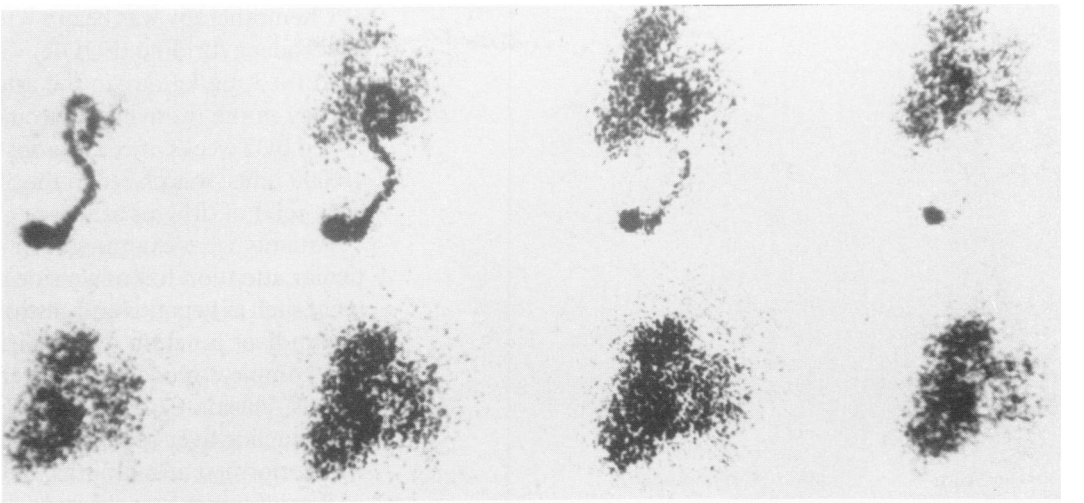

FIG. 1. A hepatic arterial flow scan after injection of 3 mCi ^{99m}Tc-macroaggregated human serum albumin shows bilateral liver uptake.

second trial was a randomized study comparing continuous hepatic arterial infusion with continuous systemic intravenous infusion. All patients had biopsy-proven metastatic colorectal carcinoma. In all cases the liver was determined by operative staging to be the sole site of metastatic disease. The volume of hepatic involvement was assessed by manual and visual examination during exploration.

All patients had a preoperative chest roentgenogram, complete blood cell count, blood chemistry studies using an automated multiple analysis system, plasma carcinoembryonic antigen (CEA) assay, radionuclide liver-spleen scan, abdominal computed tomographic (CT) scan, and celiac and superior mesenteric angiograms. Depending on the hepatic arterial anatomy, patients undergoing hepatic arterial cannulation had catheters placed into the gastroduodenal, splenic, left gastric, and/or replaced right hepatic arteries.[8] In patients randomized to receive systemic intravenous chemotherapy, the catheter from the Infusaid® pump (Infusaid Corp., Norwood, MA) was tunnelled subcutaneously and placed into the superior vena cava *via* the external jugular or cephalic vein. However, an Infus-a-Port® (Infusaid Corporation) was also placed subcutaneously with its catheter tip in the hepatic arterial system.

Within 5 days after the operation, a radionuclide hepatic arterial flow scan was done to evaluate distribution in the tumor and liver (Fig. 1). ^{99m}Tc-macroaggregated human serum albumin (MAA) (3 mCi in a total volume < 1 ml) was injected into the hepatic arterial catheter (the pump side-port or the Infus-a-port) over 30 seconds immediately followed by a 2-minute flush with 10 ml of saline containing heparin. Dynamic images of the liver were obtained every 2 seconds, for 64 seconds following the start of injection. Anterior, posterior, and right lateral static images were then obtained on the large field gamma camera and compared with the conventional ^{99m}Tc-sulfur colloid liver scan. The distribution of ^{99m}Tc-MAA in the tumor was designated *positive* if tumor uptake was increased relative to liver uptake (Fig. 2); *negative* if tumor uptake was decreased or similar relative to liver uptake; or as a *rim sign* if the central area was hypoperfused with a rim of increased activity relative to liver background (Fig. 3). The hepatic arteriogram was designated *positive* if the tumor area was hypervascular relative to the liver (Fig. 4); or *negative* if the tumor area was hypovascular

FIG. 2. A ^{99m}Tc sulfur colloid scan (top) shows a cold area in the right hepatic lobe. A positive ^{99m}Tc-MAA scan (bottom) in the same patient shows increased tumor uptake relative to liver in the right hepatic lobe.

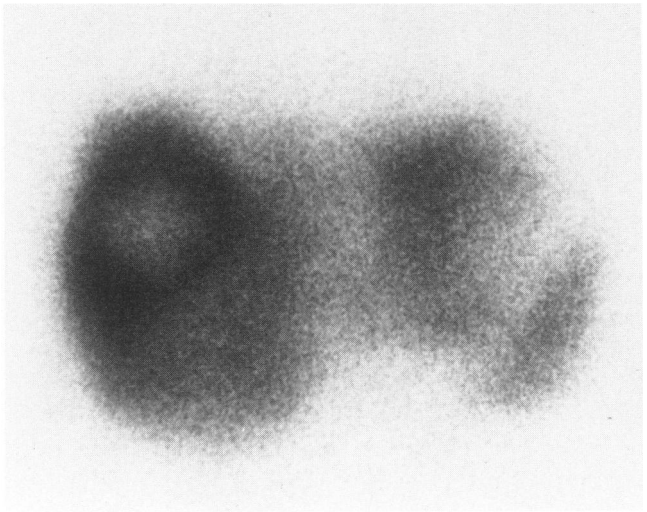

FIG. 3. This ^{99m}Tc-MAA arterial scan depicts a "rim sign" which shows a central area of tumor hypoperfusion with a rim of increased activity relative to liver background.

or normal relative to liver. These determinations were made without knowledge of the patient's clinical response to therapy.

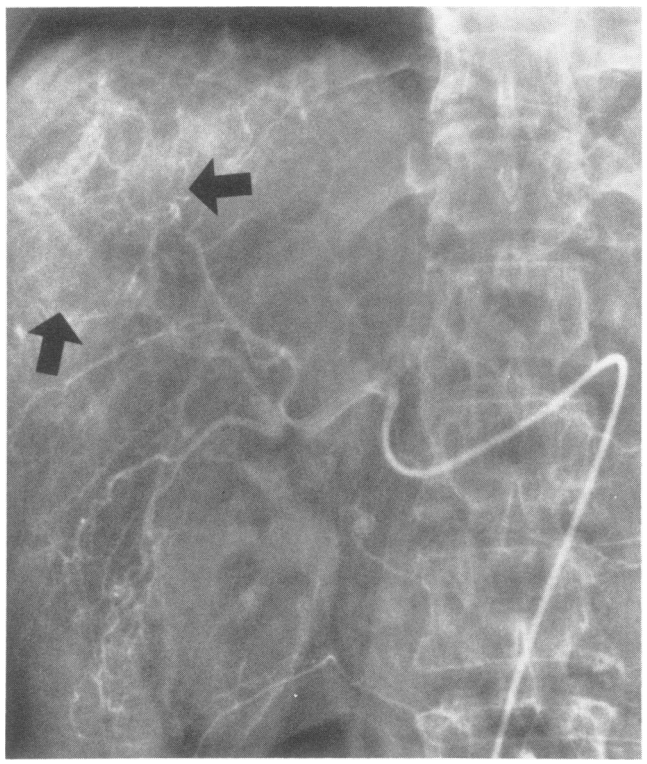

FIG. 4. A positive hepatic arteriogram demonstrates increased vascularity (arrows) relative to the liver.

Chemotherapy was begun 7 to 14 days after operation. Fluorodeoxyuridine (FUDR) was given initially at a dosage of 0.3 mg/kg/day in the arterial group and 0.15 mg/kg/day in the intravenous group for a 14-day period followed by 2 weeks of continuous saline infusion. Heparin, 10,000 units, was placed in the 50-ml pump reservoir with each refill of drug or saline.

Patients were examined at 2-week intervals with particular attention to known side effects of infusional treatment such as hepatitis and gastrointestinal tract ulceration. Serum liver function tests (bilirubin, SGOT, and SGPT) and complete blood counts were performed at these intervals. Plasma CEA levels were determined monthly. A radionuclide liver-spleen scan and/or abdominal CT scan was performed at 2 months and thereafter as indicated.

Partial tumor response was defined as: (1) a reduction by at least 50% of the sum of the products of the largest perpendicular diameters of measurable lesions as shown by the liver scan and/or CT scan; (2) no increase in any other indicator lesion; and (3) no new area of malignant disease in the liver. If hepatomegaly was used as the primary indicator, partial response was defined as a reduction of at least 50% in the sum of the measurements below the costal margin at the xiphoid process and at four intervals (5 cm) lateral to the xiphoid process. *A minor response* occurred if there was a 25 to 49% reduction in the size of measurable lesions. The tumor was considered *stable* if there was a minimal response for at least 2 months but insufficient regression to meet the above criteria. *Progression* was defined as an increase of more than 25% in the size of any measurable lesion, or the appearance of new areas of metastatic disease.

Major determinants evaluated included: prior treatment with systemic chemotherapy, patient age and sex, tumor size, per cent hepatic involvement, preoperative serum liver function studies, plasma CEA levels, and tumor vascularity as indicated by hepatic angiograms and ^{99m}Tc-MAA intraarterial flow scans.

Statistical analyses of predictive determinants were performed using the chi square test. Nonpaired Student's t-test was used to evaluate differences between groups. A positive response was defined as achieving a partial tumor response within 3 months. Survival time was defined as the period from the date of protocol entry to the date of death or the date of last follow-up for those patients still alive. Survival distributions were estimated by the method of Kaplan and Meier.[10] The survival comparisons were made using the log rank test. The chi square test was used to determine whether proportions in the two-by-two tables were similar. *Sensitivity* was defined as

$$\frac{\text{true positive tests}}{\text{(true positive tests + false negative tests)}}$$

TABLE 1. *Patient Characteristics*

	Hepatic Arterial	Systemic Intravenous
Number of patients	52	21
Median age (years)*	60 (36–79)	60 (38–75)
Sex (M/F)	36/16	12/9
Median performance status*	80 (50–90)	80 (60–90)
Mean per cent hepatic tumor replacement	47 ±20	45 ±19
Prior chemotherapy	19/52 (39%)	0

* Range ± standard deviation.

Specificity was defined as

true negative tests

÷ (true negative tests + false positive tests)

TABLE 2. *Hepatic Arterial Infusion Chemotherapy*

	MAA Positive, mean (Range)	MAA Negative, mean (Range)
Number of patients*	31	16
Mean per cent hepatic tumor replacement (%)	40% (20–80)	45% (10–80)
Mean diameter signal lesion (cm)	5.6 (3–12)	5.1 (3–9)
Mean initial plasma CEA (ng/ml)	41 (1–3100)	140 (5–3900)
Mean initial serum LDH (IU/ml)	337 (176–1266)	379 (210–2300)
Mean initial serum alk phos (IU/ml)	247 (95–1050)	216 (73–1023)
Number of patients with hypervascular lesion on arteriogram	17/25†	7/16†

* Five patients with nonevaluable MAA scan were excluded.
† Where comparison of both studies were available.

Results

A total of 73 patients were evaluated: 52 patients received hepatic arterial infusion and 21 patients received systemic intravenous infusion. The hepatic arterial group included 36 men and 16 women with a median age of 60 years (Table 1). The median Karnofsky performance status was 80%. Nineteen patients had failed prior systemic chemotherapy. The mean hepatic tumor replacement was 46%. The systemic intravenous group included 12 men and 9 women with a median age of 60 years. Median Karnofsky performance status and mean per cent hepatic tumor replacement were similar to those of the hepatic arterial group.

A total of 46 evaluable arteriograms were obtained from the 52 patients who received arterial infusion. Twenty-five of the 46 studies showed increased uptake of contrast within the tumor nodules compared with uptake by normal hepatic parenchyma (Fig. 4). However, only 10 of the 25 patients with positive arteriogram findings had a partial tumor response. Moreover, of the 21 patients whose arteriograms were negative, eight had a partial response to arterial infusion chemotherapy. The overall sensitivity of the arteriogram in predicting tumor response was 56%, and its specificity was 46%.

The ^{99m}Tc-MAA arterial flow scan was evaluated in 47 patients who underwent arterial infusion chemotherapy. In five patients, the scan was not interpreted due to inability to identify lesions smaller than 2 cm. Thirty-one patients (66%) demonstrated a positive ^{99m}Tc-MAA study or a rim sign. There was no significant difference in sex ratio, median age, or Karnofsky status score between those patients with a positive or a negative radionuclide flow scan. There also was no significant difference between groups in mean per cent hepatic tumor replacement, mean diameter of the signal lesion, or mean initial serum lactate dehydrogenase, alkaline phosphatase, or plasma CEA levels (Table 2). The number of patients with hypervascular lesions on hepatic angiogram was slightly greater (17/25 or 68%) in the ^{99m}Tc-MAA positive group than in the negative group (7/16 or 44%).

Sixteen of the 31 patients with a positive ^{99m}Tc-MAA scan had a partial tumor response to treatment (Table 3). However, only one of 16 patients with a negative study exhibited a partial tumor response ($p = 0.006$). Among

TABLE 3. *Prediction of Tumor Response by MAA Arterial Flow Scan in Patients Treated by Arterial Infusion*

N	Group	MAA	Tumor Response		Sensitivity (%)	Specificity (%)
			Partial	None		
47	All	Positive	16	15	94	50
		Negative	1	15		
39	No rim sign	Positive	14	9	93	63
		Negative	1	15		
24	No prior chemotherapy	Positive	10	3	91	77
		Negative	1	10		
15	Prior chemotherapy	Positive	4	6	100	45
		Negative	0	5		

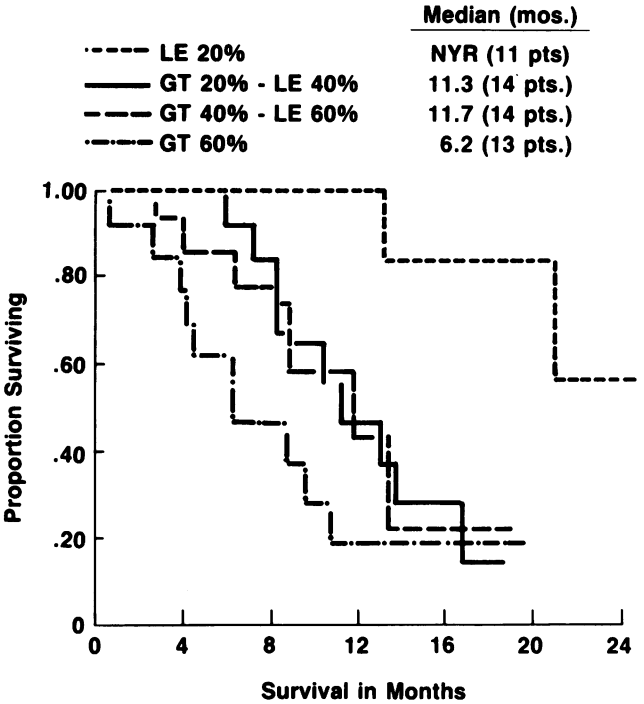

FIG. 5. Survival patterns based on operative staging of the per cent of hepatic tumor involvement demonstrate a worsening prognosis as the per cent hepatic involvement with tumor exceeds 20% and 60%.

the 30 patients who did not respond to treatment, there were 15 positive and 15 negative ^{99m}Tc-MAA scans. Thus, the ^{99m}Tc-MAA scan's sensitivity and specificity were 94% and 50%, respectively.

A *rim* sign, in which increased uptake was noted around but not within the substance of the tumor nodule, was present in eight patients (Fig. 3). This finding was of no value in predicting response: only two of these eight patients showed a partial tumor response to subsequent arterial infusion therapy. When the eight patients were deleted from analysis (Table 3), the ^{99m}Tc-MAA test was positive in 14 of 15 patients who had a partial tumor response and negative in 15 of 24 patients who had no

TABLE 4. *Systemic Intravenous Infusion Chemotherapy*

	MAA Positive, mean (Range)	MAA Negative, mean (Range)
N	9	12
Mean per cent hepatic tumor replacement (%)	49 (15–80)	42 (20–60)
Mean diameter signal lesion (cm)	6.2 (3–10)	7.6 (4–14)
Mean initial plasma CEA (ng/ml)	798 (8–3500)	243 (6–1750)
Mean initial serum LDH (IU/ml)	448 (185–801)	713 (152–2475)
Mean initial serum alk phos (IU/ml)	232 (99–605)	257 (116–560)

TABLE 5. *Prediction of Tumor Response by MAA Arterial Flow Scan in Patients Treated by Intravenous Infusion*

	Tumor Response	
MAA	Partial	None
Positive	7	2
Negative	1	11

Sensitivity, 88%; Specificity, 85%.

tumor response. Thus, the ^{99m}Tc-MAA scans provided a predictive sensitivity of 93% and a specificity of 63%.

Results of the ^{99m}Tc-MAA study were also interpreted on the basis of prior systemic treatment for hepatic metastases before insertion of the hepatic artery catheter and pump (Table 3). For 24 patients who had not received prior chemotherapy, the ^{99m}Tc-MAA arterial flow scan sensitivity was 91%, with a specificity of 77%. The sensitivity was 100% and specificity was 45% for the 15 patients who had received and failed prior chemotherapy. The ability to predict tumor response was not improved by combining the arteriogram and the nuclide flow scan.

Comparison of patient survival times revealed significant differences in length of survival which correlated inversely with the per cent hepatic tumor replacement ($p = 0.005$) as shown in Figure 5. Median survival has not yet been reached for patients with less than 20% hepatic tumor replacement, but median survival was 6.2 months in patients with greater than 60% hepatic tumor replacement. Among 21 patients with greater than 60% hepatic tumor replacement, 13 patients with positive nuclide flow scans had a median survival time of 10.7 months, compared with a median survival time of 6.2 months in eight patients with negative nuclide flow scans ($p = 0.08$). Survival time did not differ significantly between ^{99m}Tc-MAA-positive and negative groups with less than 60% hepatic tumor involvement. Similarly, there was no significant difference in survival distribution between patients with previous chemotherapy and patients who had received no prior treatment.

The ^{99m}Tc-MAA arterial flow scan was available for evaluation in 21 patients who underwent systemic intravenous infusion chemotherapy. The nuclide flow scan was positive in nine patients (43%). There was no significant difference between ^{99m}Tc-MAA positive and negative groups in terms of mean per cent hepatic tumor replacement, mean diameter of the signal lesions, or mean initial serum lactate dehydrogenase, alkaline phosphatase, and plasma CEA levels (Table 4). Seven of the nine patients with positive nuclide flow scans had a positive tumor response to treatment (Table 5), whereas only one of the 12 patients with a negative MAA study showed a partial tumor response. The number of tumor responders and nonresponders was significantly different depending on

the nuclide flow scans ($p < 0.005$). Among the 13 patients who did not respond to treatment, there were two positive and 11 negative nuclide flow scans. Thus, the ^{99m}Tc-MAA scan's sensitivity and specificity were 88% and 85%, respectively. Survival patterns based on positive nuclide scan (Group I) *versus* negative nuclide scans (Group II) showed a trend toward improved survival in Group I, with a median survival of 18 months *versus* 12 months in Group II (Fig. 6).

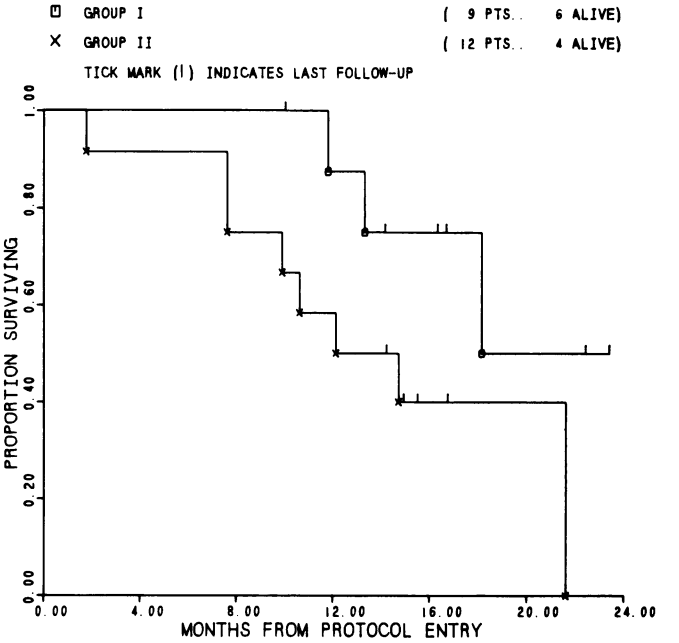

FIG. 6. Survival patterns based on positive nuclide scans (Group I) *versus* negative nuclide scans (Group II) in intravenously infused patients shows a trend ($p = 0.08$) toward improved survival in Group I compared with Group II.

Discussion

Patients with untreated colorectal metastases have a median survival time of 5 to 6 months.[11] Length of survival in both treated and untreated patients is inversely related to the degree of hepatic tumor replacement. A number of determinants, including serum hepatic enzyme levels (alkaline phosphatase and lactate dehydrogenase), serum albumin concentration, plasma CEA level, degree of weight loss, presence of hepatomegaly, jaundice, and ascites, are related indirectly to the volume of hepatic tumor replacement. Combinations of these variables have accordingly been used to estimate individual patients' survival times.[4,9] Although volume of hepatic tumor replacement correlates inversely with length of survival, no relationship between tumor volume and response to treatment has been noted.

As treatment for colorectal hepatic metastases becomes more aggressive in efforts to improve the disappointing (15 to 20%) response to systemic chemotherapy, the ability to predict tumor response to treatment is increasingly important. Hepatic arterial infusion therapy has been used since the 1960s, but widespread use of this approach has been precluded by associated technical and treatment-related morbidity.[12,13] Introduction of an implantable pump has improved patient acceptance of this form of therapy and resulted in fewer technical complications than when external catheters were used.[5–8] However, several factors, including the need for hospitalization and abdominal exploration, the cost of the pump itself, and complications related to long-term drug infusion require that we improve patient selection for this procedure. Even if we cannot predict which patients will respond to this form of treatment, the ability to identify those patients that probably will not respond would be a major contribution.

In 1954, Breedis and Young documented that the hepatic artery was the major source of blood supply to macroscopic hepatic metastases.[14] Ackerman confirmed this observation by contrast injection studies; he also noted that the thin-walled portal veins were compressed by the invading tumor cells.[15] Other investigators have tried to correlate tumor blood supply with response to subsequent therapy with or without patient survival. In 1977, Kim et al. graded tumor vascularity on preoperative hepatic angiograms from grade I (relatively hypovascular) to grade III (relatively hypervascular). In their series, 21 patients with hepatoma or metastatic colorectal cancer underwent hepatic artery ligation with or without infusion chemotherapy.[16] Patients with grade I tumors had a median survival time of 4 months after onset of treatment, whereas the median survival time was 11 months in patients with grade III tumors.

Other investigators have suggested a relationship between tumor perfusion and prognosis.[17–19] In 1980, Kaplan et al. reported 19 patients with primary or metastatic hepatic cancer who underwent radionuclide angiography using ^{99m}Tc-MAA before hepatic arterial infusion chemotherapy.[20] Tumor response, defined as more than 1 cm decrease in tumor size, occurred in 10 of 11 patients who demonstrated increased uptake of ^{99m}Tc-MAA at the site of tumor nodules or tumor-invaded hepatic lobes, as defined on prior ^{99m}Tc-sulfur colloid liver scans. No response was seen in the eight patients whose tumors did not take up the ^{99m}Tc-MAA.

However, in the study by Kaplan and colleagues, only nine of the 19 patients had metastatic colorectal cancer, and the predictive value of MAA angiography for those patients could not be ascertained. In addition, tumor response criteria in their report are not widely accepted. Finally, a major question remains: Does ^{99m}Tc-MAA uptake correlate with treatment response only in patients who receive intraarterial therapy, or does the correlation

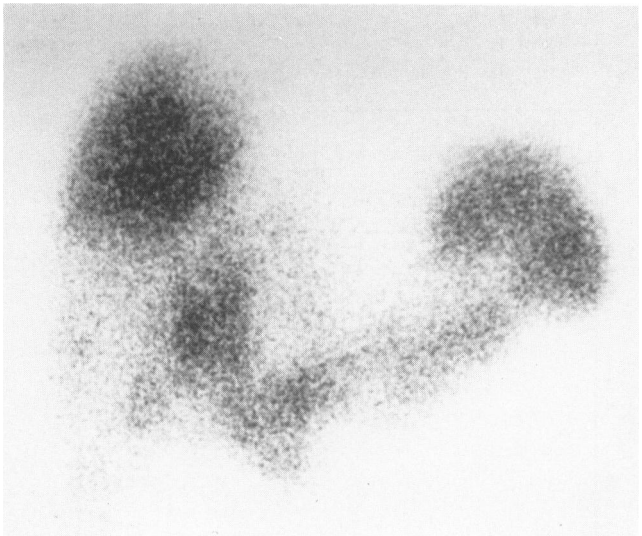

FIG. 7. A preoperative radionuclide arterial flow scan after injection of 3 mCi ^{99m}Tc-MAA into the hepatic angiogram catheter demonstrates the liver, spleen, and stomach. The tumor is noted in the right hepatic lobe.

hold also for patients receiving systemic therapy? In our study, we reviewed the course of 73 patients, all of whom had biopsy-proven colorectal hepatic metastases confined to the liver when therapy was begun. Tumor response criteria were rigidly defined. Plasma CEA levels were not employed in the definition.[21] Distribution of ^{99m}Tc-MAA in the tumor and tumor vascularity as demonstrated by angiography were ascertained by individuals unfamiliar with the patient's response to therapy.

Tumor uptake of ^{99m}Tc-MAA was a useful indicator as a determinant of tumor response. We found that the degree of tumor vascularity on hepatic angiogram was of no value in predicting response to chemotherapy. However, a statistically significant difference in tumor response rates depended on whether the patient's ^{99m}Tc-MAA study was positive or negative. This difference was not explained by the ^{99m}Tc-MAA-positive scans occurring in patients with less advanced disease, since operative staging of hepatic tumor replacement, mean size of the signal lesion, and mean initial serum liver enzyme levels were comparable in both ^{99m}Tc-MAA-positive and -negative groups.

Bledin et al. evaluated the use of ^{99m}Tc-MAA arterial perfusion studies in 39 patients with primary and metastatic hepatic neoplasms.[22] Three different patterns of tumor perfusion were observed: (1) increased central radioactivity; (2) decreased central radioactivity; and (3) mixed and/or diffuse radioactivity. Extrahepatic perfusion (stomach, pancreas, etc.) was associated with gastrointestinal complications of arterial infusion therapy; no attempt was made to correlate tumor perfusion status with tumor response. Gyves et al. used single photon emission computerized tomography (SPECT) after arterial injection of 6 mCi of ^{99m}Tc-MAA in 24 patients with primary and metastatic hepatic tumors.[23] They noted that tumor nodules greater than 9.5 cm in diameter had central regions with decreased ^{99m}Tc-MAA emissions relative to normal liver. The size of the core varied but was always surrounded by a rim of increased ^{99m}Tc-MAA activity with a median depth of 3.2 cm (range = 1.8 to 4.2 cm). Nodules less than 8 cm in diameter were always homogeneous. In all metastatic colorectal tumors studied, the ^{99m}Tc-MAA count ratios (tumor/normal liver) were greater than one (median = 2.7). In our study, the mean diameters of signal lesions were, respectively, 5.6 cm and 5.1 cm in ^{99m}Tc-MAA-positive and -negative groups undergoing arterial infusion chemotherapy.

There was no significant difference in mean nodule size between ^{99m}Tc-MAA-positive (6.2 cm) and -negative (7.6 cm) groups undergoing systemic intravenous chemotherapy. Eight patients in the arterial group had a *rim* sign; only two of these eight patients responded to chemotherapy, and the size of the nodules with *rim* signs did not vary significantly between ^{99m}Tc-MAA positive or -negative groups. Presence of a rim sign did not, therefore, predict tumor response. We cannot yet determine whether the rim of increased ^{99m}Tc-MAA activity was due to increased uptake of MAA in peripheral tumor capillaries or to compressed hepatic parenchyma around the tumor. However, a degree of central tumor necrosis is suggested by this sign.

A ^{99m}Tc-MAA flow scan can be performed during a preoperative hepatic arteriogram before a decision is made regarding treatment. We have begun evaluating this method using an injection of 3 mCI ^{99m}Tc-MAA after the contrast angiogram has defined the hepatic arterial anatomy. The patient can be moved to the Nuclear Medicine Department for static images once the arteriograms are completed. Selective angiography and placement of the catheter tip into the proper hepatic artery should be performed. Otherwise, distribution of the radioactive colloid to the spleen and stomach decreases the distribution to the liver (Fig. 7). In two cases we have obtained tumor and liver tissue within 24 hours of nuclide flow scan done at the time of contrast angiogram. One patient with a hypoperfused tumor in the liver underwent a formal right hepatic lobectomy. ^{99m}Tc-MAA uptake in the tumor and liver (counts/gm tissue) were:

$$\text{Tumor} = 1464 \pm 385 \ (n = 6) \quad \textit{versus}$$

$$\text{Liver} = 3567 \pm 681 \ (n = 13) \quad p < 0.05$$

In a second case, a hyperperfused tumor in the right hepatic lobe underwent biopsy along with adjacent normal-appearing hepatic parenchyma. ^{99m}Tc-MAA uptake (counts/gm tissue) in the tumor was 28,360 ± 3630 compared with 22,180 ± 4580 in the liver. These results suggest

good correlation of static gamma camera images with actual tissue measurements of ^{99m}Tc-MAA uptake. Some variability of colloid uptake in liver and tumor occurs depending on the site of the angiogram catheter tip, arterial flow characteristics, and perhaps the degree of tumor and liver shunting.

The ^{99m}Tc-MAA has a mean particle size of 30 to 40 μm (range = 50 to 90 μm) and localizes within the liver by capillary blockage after intraarterial injection. This distribution is independent of reticuloendothelial function, avoids the problem of recirculating tracer after ^{99m}Tc sulfur colloid injection, and provides an accurate depiction of first pass drup distribution. In subsequent experiments, 13N-labelled glutamate, glutamine, and ammonia were injected into the hepatic arterial catheter in patients prior to treatment. The uptake and distribution within the tumor and liver parenchyma were similar to that of the ^{99m}Tc-MAA.[24] Thus, nutrient blood flow documented by the 13N-labelled substrates was similar to tumor perfusion shown on the radionuclide colloid scan. These findings suggest that altering the distribution of hepatic blood flow to tumor and normal liver tissue either pharmacologically (through systemic or intraarterial vasoactive agents) or mechanically (by arterial injection of microspheres concomitant with chemotherapy) may improve tumor response to infusional therapy.[25,26]

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Discussion

DR. RICHARD E. WILSON (Boston, Massachusetts): The problem with liver metastases is obviously of very great interest to all surgeons, as demonstrated by the paper yesterday by Dr. Martin, this paper, and the paper later today on the transplantation of liver for liver cancer. Thus, it is very important to try to define the subset of patients who should be treated in which way.

We had the opportunity to look at this question a few years ago at the Brigham and the Farber Center. We approached all of our patients who had apparently "liver only" metastases by preoperative workup with three options to be decided during surgery. One, to resect unilobar disease; two, to put an infusion catheter in the hepatic artery and infuse 5-FUDR for those who had bilobar disease; and three, to give IV 5-FU for those who had extrahepatic disease. Mind you, all of these were thought to have only liver disease by work-up.

What we found was that the preoperative arteriogram, just as the authors have stated, was of very little value in both defining the extent of the disease and in serving as a predictor in terms of response.

Intraoperative fluorescein was very important to define the placement of the catheter to be sure that it diffused both lobes.

We used a postoperative macroaggregated albumin (MAA) flow, just as described here, but I think it is very important to point out that the flow rate must be identical with the flow rate given by the infusion pump.