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Intra-Abdominal Extrahepatic Disease in Patients with Colorectal Hepatic Metastases

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The resection of hepatic metastases in patients with extrahepatic disease is of no proven benefit. Preoperative identification of extrahepatic disease may prevent unnecessary laparotomy. Preoperative evaluation including physical examination, computed tomography of the abdomen, full lung tomography or chest-computed tomography, and radionuclide bone scanning identified extrahepatic metastases, most commonly in the lung, in 25 of 132 patients with purported isolated liver metastases. Of 107 patients with negative staging evaluations, intra-abdominal extrahepatic metastases were found in 26 percent (28 of 107) at laparotomy, most commonly in portal and celiac lymph nodes. The presence of extrahepatic disease correlated with greater than 25 percent hepatic replacement by tumor, presence of symptoms, and Dukes' C primary lesions; however, none was predictive. We were unable to develop a model to preoperatively predict the presence of intra-abdominal extrahepatic disease. The authors recommend a preoperative evaluation including physical examination, and computed tomographic scans of the abdomen and chest. A bone scan is required only in patients with symptoms referable to bone. Despite a negative preoperative evaluation, however, a considerable proportion of patients with colorectal hepatic metastases will have extrahepatic disease at the time of abdominal exploration. [Key words: Extrahepatic metastases; Liver metastases]

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COLORECTAL CARCINOMA remains a major cause of morbidity and mortality in the United States, with over 140,000 new cases each year. Approximately 35 percent of these people will develop hepatic metastases during the course of their disease.[1] It is estimated that 10 to 20 percent of these patients would benefit potentially from hepatic resection. It has been shown that resection of isolated liver metastases, when single or in small numbers, can result in improved long-term survival. In the presence of extrahepatic disease, however, resection may offer little benefit. Therefore, preoperative identification of extrahepatic disease may prevent unnecessary laparotomy.

This report is concerned with 161 patients referred to the Surgery Branch of the National Cancer Institute from 1978 through 1986, 66 of whom underwent hepatic resection. The authors have emphasized the preoperative evaluation of the 107 patients who underwent exploratory laparotomy to correlate the results with findings at laparotomy. In particular, the authors were interested in any parameters useful in predicting the presence of extrahepatic disease.

Patients and Methods

From 1978 to 1986, a total of 161 patients were referred to the Surgery Branch of the National Cancer Institute for treatment of purportedly isolated hepatic metastases. There were ongoing clinical studies during this time to evaluate hepatic resection, and infusional chemotherapy given regionally or systemically by an implantable

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pump. Patient suitability for a given protocol was determined after complete workup.

Evaluation included physical examination, carcinoembryonic antigen (CEA) determination, routine blood chemistries, full lung tomography, chest X-ray, computerized tomography of the abdomen, liver-spleen scan, barium enema, bone scan, intravenous pyelogram, ultrasound examination of the liver, and hepatic angiogram. After all or part of this evaluation was completed, 16 patients were rejected from further treatment at the National Cancer Institute for reasons including patient refusal, medical contraindications, and absence of demonstrable liver metastases. Thirteen patients with unresectable disease were randomized to receive a systemic infusion pump, and did not undergo laparotomy. The remaining 132 patients were considered for exploratory laparotomy and possible resection or possible insertion of a regional perfusion pump. At the time of laparotomy those patients who were believed to have technically resectable disease underwent resection, those unresectable but with disease confined to the liver had placement of a perfusion pump, and those with extrahepatic disease were closed without further operative intervention.

The charts of all 132 patients were retrospectively reviewed. The presence of extrahepatic disease discovered on preoperative evaluation precluded laparotomy in 25 patients. Associations between the presence of extrahepatic disease and the following parameters were calculated for the remaining 107 patients: age, sex, CEA, LDH, Dukes' stage of the primary lesion, percent hepatic replacement by tumor, disease-free interval, and presence of symptoms. A logistic regression model[2] was then developed using those parameters which were most highly associated with extrahepatic disease to try to predict the presence of extrahepatic disease on the basis of those factors. The model was developed using a randomly selected half of the data and tested on the other half.

Results

Preoperative evaluation identified extrahepatic metastatic disease in 25 of the 132 patients (19 percent) studied. Laparotomy was therefore avoided in these patients. Extrahepatic sites of metastatic disease were detected by full lung tomography (N = 14), chest x-ray (N = 3), computed tomographic (CT) scan of the abdomen (N = 3), and physical exam (N = 5). No patient had a bone scan consistent with metastatic disease. Four patients with negative chest roentgenograms had disease identified on full lung tomograms. The remaining 107 patients underwent exploratory laparotomy, and form the basis for the remainder of this report.

These 107 patients included 67 males and 40 females with an average age of 56.6 years (range, 26 to 77). Sixty-six patients had resection of their hepatic metastases, including five patients who had simultaneous resection of extrahepatic sites of disease. The remaining 41 patients underwent placement of an intra-arterial infusion pump (N = 23) or exploration only (N = 18). At operation, intra-abdominal extrahepatic metastases were identified in 28 (26 percent) patients. Sites of intra-abdominal extrahepatic disease are shown in Table 1. The most common sites of extrahepatic disease were the hepatic lymph nodes (portal and celiac), which were found to be involved in 15 of the 28 patients.

TABLE 1. *Sites of Extrahepatic Disease Found at Laparotomy Despite a Negative Preoperative Evaluation in 107 Patients*

Site	No. of Patients
Lymph nodes	
Celiac	9
Portal	6
Retroperitoneal	1
Peritoneum	7
Omentum	2
Adrenal	1
Local recurrence	1
Abdominal wall	1
TOTAL	28

Preoperative CEA measurements were available for 105 patients, and elevated in 89 (85 percent). Preoperative LDH level was elevated in 69 (67 percent) of the 103 patients for whom those data were available. Percent hepatic replacement, estimated from preoperative CT scans, showed less than 25 percent replacement in 55 patients, 25 to 75 percent replacement in 34, and greater than 75 percent replacement in eight patients. Disease-free interval was less than six months in 65 patients (61 percent) and greater than six months in 42 (39 percent). Only 21 (20 percent) patients reported abdominal symptoms preoperatively. Only one patient in this series had a Dukes' A primary lesion, while 34 were classified as Dukes' B, and 63 were Dukes' C lesions. Since Dukes' stage of the primary lesion only was classified, no patient had a Dukes' D lesion.

Simple two by two tables were constructed to relate each of the above preoperative parameters and the presence or absence of extrahepatic disease and showed that the factors with greatest association included: Dukes' stage C primary lesions ($P = .04$), greater than 25 percent hepatic replacement ($P = .03$), and the presence of symptoms ($P = .03$). The distribution of patients with and without extrahepatic disease is shown for each of these factors in Table 2.

Although these three factors were associated with the presence of extrahepatic disease, none was predictive. The authors attempted to use logistic regression to formulate a

TABLE 2. *Association of Preoperative Parameters with the Presence of Intra-abdominal Extrahepatic Disease*

Parameter	Extrahepatic Disease (Number of Patients)		*P*-Value*
	Present	Absent	
Age			
Mean	56.4	56.6	> .25†
Range	31–70	26–77	
Sex			
Male	17	50	.81
Female	11	29	
CEA			
≤ 3	5	13	.80
> 3	23	66	
LDH			
≤ 200	9	25	1.00
> 200	19	50	
Dukes' stage of primary lesion			
A,B	4	31	.04
C	20	43	
Percent hepatic replacement by tumor			
< 25%	9	46	.03
> 25%	16	26	
Disease-free interval			
0–6 months	18	47	.83
> 6 months	10	32	
Abdominal symptoms			
Yes	10	11	.03
No	18	68	

*Two-sided *P*-values are reported.
†By Wilcoxon two-sample test.

model which would be useful as a predictive tool. The best model included Dukes' stage of the primary lesion as the only predictive factor. While 12 of 15 patients in the data set used to develop the model with Dukes' A or B lesions were without extrahepatic disease, 18 of 26 patients with Dukes' C lesions also were without extrahepatic disease. Thus, this model was not suitable for prediction.

A subgroup of patients with a Dukes' A or B primary lesion, less than 25 percent hepatic replacement, and no symptom was identified as being more favorable. However, while 15 of 16 patients who met these criteria did not have extrahepatic disease, 48 of 73 patients who did not meet these criteria also did not have extrahepatic disease. Thus, among patients who had the desirable set of traits, extrahepatic disease was rare; however, for those without all three desirable traits, the authors were unable to predict who would or would not have extrahepatic disease.

Discussion

The treatment of liver metastases from colorectal carcinoma remains a challenge, with surgery offering the only hope for improved long-term survival. A lack of knowledge of the true extent of metastatic disease contributes to disappointing results in these patients. The presence of extrahepatic disease is a negative prognostic factor in patients undergoing hepatic resection.[5] Furthermore, preoperative detection of metastatic disease outside the liver will prevent unnecessary laparotomy, since liver resection in the face of extrahepatic metastases is of little value.[4,5]

A routine staging evaluation should be performed for all patients being considered for hepatic resection. In this series, the most common site of metastatic disease identified preoperatively was the lung. Patients were evaluated by full lung tomography or chest CT, and chest x-ray. Four patients with negative chest x-rays had positive findings on tomography, indicating the importance of tomographic studies. CT of the chest is more sensitive in detecting pulmonary nodules compared with conventional linear tomography in patients with metastatic disease.[6] Pass *et al.*[7] demonstrated the superiority of CT over linear tomography in detecting metastatic sarcoma nodules when using dynamic analysis. The authors suspect that this will also be true for pulmonary metastases from colorectal tumors. In addition to routine physical examination, preoperative staging should also include CT scan of the abdomen.

While a bone scan was included as part of the staging, no patient had a positive bone scan. Bonnheim and coworkers[8] reported a 4 percent incidence of osseous metastases in a study of 1406 patients over ten years. In patients with colorectal cancer and pelvic or back pain, however, Antoniades *et al.*[9] found that 75 percent of these patients had positive bone scans for metastases, despite a negative bone x-ray. In the absence of symptoms referable to bone, bone scanning is not required as part of the routine staging evaluation.

In this series, 26 percent of patients had intra-abdominal, extrahepatic metastases despite a negative preoperative evaluation. Most commonly, metastatic disease was located in intra-abdominal lymph nodes, as shown in Table 1. The involvement of portal and celiac lymph nodes probably represents "remetastasis" from established hepatic metastases.[4] In a study of 117 patients treated with hepatic artery infusional chemotherapy, Fortner and coworkers[10] found a 42 percent incidence of intra-abdominal extrahepatic disease. They similarly found that a majority (36 of 50) of patients had abdominal lymph-node involvement. Kemeny *et al.*[11] evaluated CT scanning in the identification of extrahepatic disease. They found that in 68 of 100 patients, the CT scan accurately reflected the presence or absence of disease outside

the liver, for a 32 percent error rate, comparable to that which was observed in the present series.

While several factors that were highly associated with the presence of extrahepatic disease were found, none was predictive. A logistic regression model developed was insufficient to be useful as a predictive tool. A considerable proportion of patients with isolated hepatic metastases documented after an extensive radiologic evaluation will have extrahepatic disease at laparotomy. New imaging modalities such as magnetic resonance require evaluation in the prediction of the presence of extrahepatic metastatic disease. The authors concur with Kemeny,[11] that accurate identification of extrahepatic disease requires surgical assessment.

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