Screening for Liver Metastases from Colorectal Cancer with Carcinoembryonic Antigen and Alkaline Phosphatase

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A sensitive and economic method of screening for liver metastases in patients with colorectal cancer was developed using serum alkaline phosphatase and carcinoembryonic antigen. The upper limit of normal for alkaline phosphatase and carcinoembryonic antigen did not represent the optimal levels for use in predicting liver metastases. However, with alkaline phosphatase greater than 135 I.U., and/or carcinoembryonic antigen greater than 10 ng/ml, sensitivity was 88%: 23 of 26 patients with liver metastases fulfilled either or both criteria. The false-positive rate was 12%. Liver scanning, alone, demonstrated metastases in only 69% of 35 patients with liver metastases. The combination of alkaline phosphatase and carcinoembryonic antigen can be used economically to screen for liver metastases, and to determine which patients should undergo a liver scan.

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THE PRESENCE OF LIVER metastases influences the therapy and prognosis of patients with colorectal cancer. The most commonly used tests for predicting the presence of liver metastases include the serum alkaline phosphatase,[1-6] liver scan,[2-10] and, more recently, carcinoembryonic antigen.[11-13] Many studies have demonstrated the superiority of liver scan in the detection of liver metastases before operation.[2-4,6,8,9] Unfortunately, the expense, inconvenience, and radioisotope exposure associated with liver scanning detract from its use as a screening test.

Several investigators have tried to use serum tests to identify a group of colorectal cancer patients with a high probability of having liver metastases.[1,5,6,10,13] They have met with limited success, because colorectal cancer patients without liver metastases often have high-normal and, in many cases, abnormal values for the serum test being evaluated.[14] We attempted to identify a group of patients with high probability of having liver metastases using alkaline phosphatase and carcinoembryonic antigen. The records of patients who had undergone laparotomy for colorectal cancer were reviewed in an effort to develop an economically feasible screening test for the preoperative detection of liver metastases, using a combination of alkaline phosphatase and carcinoembryonic antigen.

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Materials and Methods

The records of 327 patients who underwent operations for cancer of the colorectum at the Mount Sinai Hospital, and who had either preoperative liver scanning or carcinoembryonic antigen determination between July 1977 and September 1979, were reviewed. Serum alkaline phosphatase had been routinely determined in all patients when they were admitted to the hospital. One hundred seventy-nine patients had undergone preoperative liver scanning, and carcinoembryonic antigen was available in 190 patients.

Alkaline phosphatase was determined with a Technicon® computer-controlled biochemical analyzer, using the method of Bessey, Lowry, and Brock[14] and modified for automation by Morgenstern, Kessler, Auerbach, Flor, and Klein.[15] The upper limit of normal in our laboratory is 90 I.U. (mμ/nl). Liver scans were performed using 3 mCi of intravenous technitium-99m (^{99m}TC) sulfur colloid followed in 15 minutes with anterior, posterior, and right lateral projections to 300,000 counts. Serum carcinoembryonic antigen was determined by immunoassay using the CEA-Roche® Test Kit. The upper limit of normal is 5 ng/dl. The presence of liver metastases at laparotomy was determined by palpation and inspection. Biopsy specimens were obtained only when gross findings were questionable.

The tests were evaluated by calculating the sensitivity, false-positive, and false-negative rates (Table 1). Sensitivity, A/A + C, is the proportion of patients with liver metastases testing positive. The false positive rate, B/A + B + C + D, is the proportion of patients testing positive, but found at laparotomy to be free of metastases. The false negative rate, C/A + B + C + D, represents the proportion of patients testing negative in the presence of metastases.

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TABLE 1.

	Liver Metastases	
	Present	Absent
Positive test	A	B
Negative test	C	D

Sensitivity rate: A/A + C.
False-positive rate: B/A + B + C + D.
False-negative rate: C/A + B + C + D.

TABLE 3.

	Liver Metastases	
	Present	Absent
Alkaline phosphatase >90	43	110
Alkaline phosphatase ≤90	13	161

Sensitivity rate: 43/43 + 13 = 77%.
False-positive rate: 110/43 + 110 + 13 + 161 = 34%.
False-negative rate: 13/43 + 110 + 13 + 161 = 4%.

Results

Thirty-five (20%) of the 179 patients who underwent liver scanning were subsequently proved to have liver metastases at laparotomy (Table 2). Only 24 of these 35 liver metastases had been detected by preoperative liver scanning, for a sensitivity rate of 69%. The 11 patients with metastases not predicted by the liver scan determined the false-negative rate of 6%. Three patients with liver scans indicative of metatases were subsequently found to be free of metastatic disease, for a 2% false-positive rate.

In the 327 patients for whom alkaline phosphatase levels were determined, 56 (17%) were subsequently shown at laparotomy to have liver metastases (Table 3). The alkaline phosphatase levels were elevated in 43 of the 56 patients, for a sensitivity rate of 77%. But, it was also elevated in 110 of the patients without metastases, for a false-positive rate of 34%. The 13 patients with liver metastases and normal alkaline phosphatase levels determined the false-negative rate of 4%. If alkaline phosphatase had been used as the sole criterion to determine which patients should undergo liver scanning, 153 patients would have been scanned in order to detect 43 liver metastases. Thirteen patients, 23% of the patients with liver metastases, would have undergone laparotomy without the benefits of preoperative liver scanning.

In the group of patients in whom CEA was available, 26 were found to have liver metastases at surgery (Table 4). Twenty-one of the patients with metastases had CEA values greater than 5, for a sensitivity rate of 81%. Forty-six of the patients without liver metastases also had an elevated CEA, a false-positive rate of 24%. The false-negative rate, determined by the five patients with normal CEA in the presence of metastases, was 2%. If CEA had been used as a criterion for preoperative liver scanning, 67 patients would have been scanned in order to detect the 21 liver metastases, and five patients, 19% of the patients with liver metastases, would have undergone operations without preoperative liver scanning.

In an effort to improve the sensitivity of CEA and alkaline phosphatase as possible criteria for liver scanning and reduce the excessive number of patients without liver metastases subjected to preoperative scanning, we plotted the values of CEA and alkaline phosphatase for patients with and without liver metastases (Fig. 1). Increasing the levels of CEA or alkaline phosphatase required before scanning a patient decreases the sensitivity of the screening test. Decreasing these levels increases the false-positive rate, increasing the number of patients without metastases who would be scanned. The best compromise between the decreasing sensitivity and increasing the false-positive rates is reached when the combination of CEA greater than 10 and/or alkaline phosphatase level greater than 135 are chosen as criteria for liver scanning. Twenty-three of the 26 patients with liver metastases fulfilled these criteria, for a sensitivity rate of 88% (Table 5). The false-negative rate of 2% equalled that for alkaline phosphatase or CEA alone. The false positive rate of 12% is acceptable for a screening test because only 46 patients would be scanned in order to indentify the 23 patients with liver metastases.

Discussion

Shortly following the development of serum alkaline phosphatase, Gutman et al.[12] found elevated levels in

TABLE 2.

	Liver Metastases	
	Present	Absent
Positive liver scan	24	3
Negative liver scan	11	141

Sensitivity rate: 24/24 + 11 = 69%.
False-positive rate: 3/24 + 11 + 3 + 141 = 2%.
False-negative rate: 11/24 + 11 + 3 + 141 = 6%.

TABLE 4.

	Liver Metastases	
	Present	Absent
CEA >5	21	46
CEA ≤5	5	118

Sensitivity rate: 21/21 + 5 = 81%.
False-positive rate: 46/21 + 46 + 5 + 118 = 24%.
False-negative rate: 5/21 + 46 + 5 + 118 = 2%.

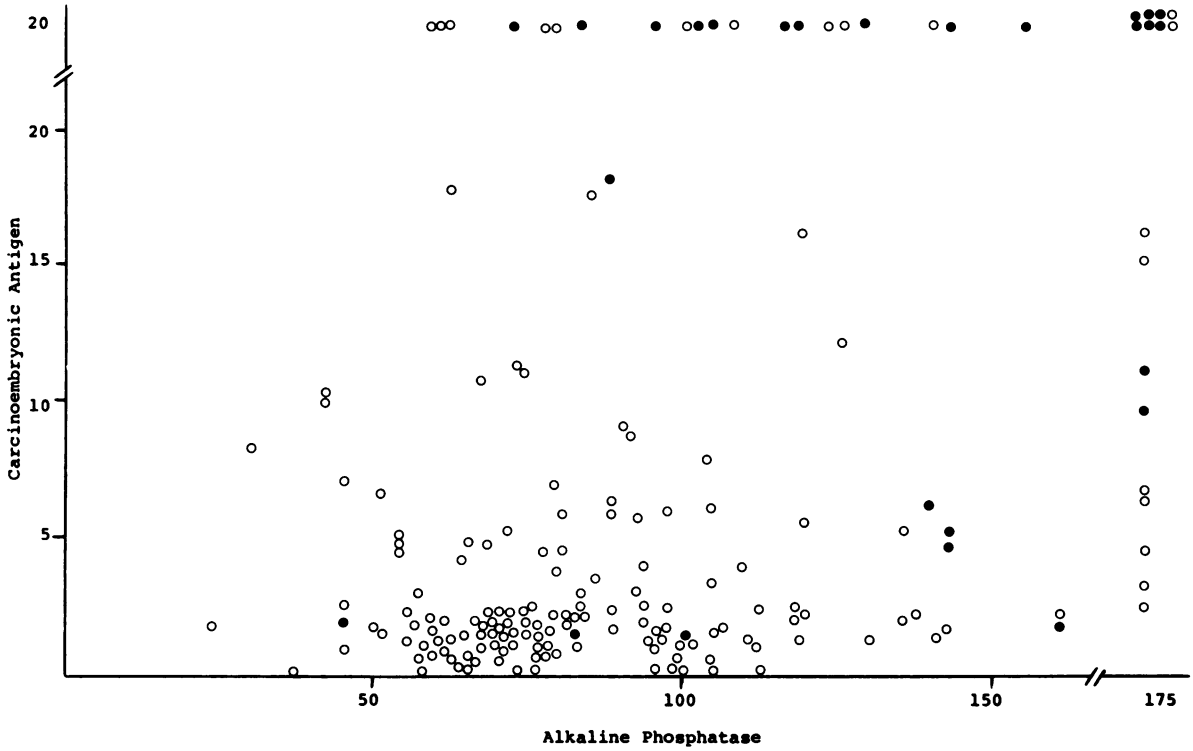

FIG. 1. Distribution of alkaline phosphatase and carcinoembryonic antigen in patients with (●) and without (○) liver metastases.

30 patients with metastatic liver disease. Mendolsohn and Bodansky[16] demonstrated the surperiority of alkaline phosphatase to BSP retention in the diagnosis of liver metastases, and this remained the best noninvasive test for metastases until the application of scintillation scanning to the liver by Stirret et al., in 1954.[17] Since that time, liver scanning has been considered the most accurate noninvasive test in the diagnosis of metastatic disease to the liver.[2,5,8,9,18] Liver scans also have value in directing transcutaneous liver biopsy.[3,19] Alkaline phosphatase has been combined with BSP retention,[4,8,10] serum bilirubin,[20] and gamma-glutamyl transpeptidase[1,13] in attempts to improve its accuracy. However, liver scan remains the standard to which all other noninvasive tests are compared. The results obtained by liver scan in detecting metastatic disease in our study—69% sensitivity rate, 6% false-positive rate, and 2% false-negative rate—are similar to those obtained in several previous studies.[2-4,6-9,11,12]

Refinements in the diagnostic value of alkaline phosphatase have followed the realization that the sensitivity, false-negative and false-positive rates are determined by the prevalence of liver metastases in the population tested.[1,6,7,16,21] Baden et al.[1] examined alkaline phosphatase and gamma-glutamyl transpeptidase, relative to liver metastases discovered at laparotomy, in a population of colon cancer patients with a low prevalence of metastases. They concluded that alkaline phosphatase alone or combined with gamma-glutamyl transpeptidase was no better than the simple assumption that liver metastases were absent in all patients.

Other investigators have found elevated levels of alkaline phosphatase in 58–85% of patients with liver metastases from all primaries,[2-5,10,13,20,22,23] and in 65–77% of patients with liver metastases from colon cancer.[1,6,13] Forty-three of 56 patients with liver metastases in our series had serum alkaline phosphatase levels greater than the upper limit of normal for our laboratory (90), for a 77% sensitivity rate. Unfortunately, 110 of 271 patients without liver metastases (34% false-negative rate) also had serum alkaline phosphatase levels above 90. The normal limits for alkaline phosphatase are not helpful in deciding which patients should or should not be scanned.

TABLE 5.

	Liver Metastases	
	Present	Absent
CEA >10 and/or alkaline phosphatase >135	23	23
CEA ≤10 and alkaline phosphatase ≤135	3	141

Sensitivity rate: 23/23 + 3.
False-positive rate: 23/23 + 23 + 3 + 141 = 12%.
False-negative rate: 3/23 + 23 + 3 + 141 = 2%.

Carcinoembryonic antigen was first described by Gold and Freedman in 1965,[24] with high hopes that a screening test for colon cancer had finally been developed. These early hopes were not realized, but carcinoembryonic antigen is useful in the management of patients with colorectal cancer.[11-13,25,26] Levels of carcinoembryonic antigen correlate with stage,[26] and high levels are found in patients with liver metastases.[11-13,26] In fact, carcinoembryonic antigen had been suggested as an adjunct to liver scanning, and it has been used as an indicator of metastases with sensitivity rates ranging from 36 to 96%.[11-13] In our study, 21 of 26 patients with liver metastases had carcinoembryonic antigen levels greater than 5, for a sensitivity rate of 81%. Forty-six per cent of the patients without liver metastases also had carcinoembryonic antigen levels greater than five. This represents a false-positive rate of 24%, which is unacceptably high for a screening test: an excessive number of patients without liver metastases would be subjected to liver scanning.

Screening has traditionally been used for the early detection of disease in an otherwise healthy population.[27] The same criteria used to evaluate mass screening programs also apply to tests on patients with colon cancer for detecting metastases.[18] Although carcinoembryonic antigen and alkaline phosphatase are both simple, acceptable, low cost, and relatively sensitive, neither is acceptable as a screening test for detecting liver metastases preoperatively, because both tests have high-false positive rates.

We combined carcinoembryonic antigens greater than 10 and/or alkaline phosphatase greater levels than 135 in order to increase the selectivity for patients with liver metastases. Twenty-three of 26 patients with liver metastases fulfilled these criteria, for a sensitivity rate of 88%. An equal number of patients without liver metastases also fulfilled the criteria, but this represents only 14% of the 164 patients without liver metastases. This 12% false-positive rate is acceptable for a screening test. Patients with a carcinoembryonic antigen greater than 10 or an alkaline phosphatase level greater than 135 would subsequently undergo a liver scans to verify a suspected metastases. This would reduce the expense, inconvenience, and radioisotope exposure associated with detecting liver metastases in patients with colon cancer.

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