A Prospective Analysis of Laboratory Tests and Imaging Studies To Detect Hepatic Lesions

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A prospective study of the ability of laboratory tests and liver imaging tests to detect hepatic metastases was performed. Eighty patients at risk for hepatic metastases but without clinical evidence of disease were tested with 13 laboratory tests and three liver imaging tests. No single laboratory test had greater than 65% accuracy in the detection of hepatic lesions. No combination of the laboratory tests increased this accuracy. If the laboratory tests were used with one of the liver imaging tests, the accuracy was improved in some combinations to 76%. The CEA assay when analyzed in patients with colorectal primaries had an accuracy of 79%. The results show that the laboratory tests alone are not sufficiently accurate to detect liver metastases. Additional accuracy can be obtained by the combined use of a single liver imaging test and selected laboratory tests. Use of all the liver imaging tests and laboratory tests lowers the accuracy and increases the expense and thus is unnecessary.

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THERE IS NO ORGAN OR STRUCTURE that is more important than the liver for staging a wide variety of carcinomas, sarcomas, and lymphomas. Because of the large size and obscured location of this organ, determination of its involvement by disease remains a difficult clinical problem. Also, the early detection of metastatic disease has become of greater importance with the development of new techniques for the successful resection of hepatic metastases.[20] The optimal means for the efficient detection of the presence or absence of hepatic metastatic disease remains difficult to determine.

No previous study has attempted to determine the minimal number of hepatic diagnostic tests that is required to rule out metastases. In a prospective study of 80 patients, we have attempted to define those liver imaging studies and tests of hepatic function that are useful in the identification of patients with hepatic metastatic disease. A large number of hepatic tests were done on each patient in a prospective manner; a decision matrix for the presence or absence of lesions for single tests and composite tests was compared with the condition of the liver, which was determined at the time of exploratory surgery. Our hope, in performing this study, was to determine what single tests or what specific combination of tests was required to detect hepatic metastases; we hoped for the future to eliminate unnecessary tests and duplication of effort in order to increase the efficiency of hepatic testing.

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Materials and Methods

Patients who were being evaluated for primary or suspected recurrent malignancy and who were at risk for hepatic metastatic disease were eligible for this study; patients included in this study were those who had a laparotomy or laparoscopy to determine the presence or absence of disease in the liver. The average time from testing to definitive diagnosis was 10–17 days. At the laparotomy, patients included in the study had the entire liver palpated externally and bimanually examined for the presence of intraparenchymal metastatic disease. Patients who underwent laparoscopy were included if there was biopsy confirmation of suspected hepatic metastases at the time of endoscopy.

Each patient underwent three liver imaging studies: liver scintiscan, liver ultrasound, and liver computerized tomography (CT). Liver-spleen scans were obtained within one hour of an injection of technetium-99m sulphur colloid (99m Tc S.C.), 0.050 μCi/Kg of body weight. Large field of view (LFOV) gamma cameras were used (Raytheon Nuclear Diagnostics, Stamford, CT and Maxicamera CC, General Electric Medical Systems Division, Milwaukee, WI) to perform multiple image studies of the liver and spleen. Images were collected on clear nuclear medicine film (NMC-1 Eastman

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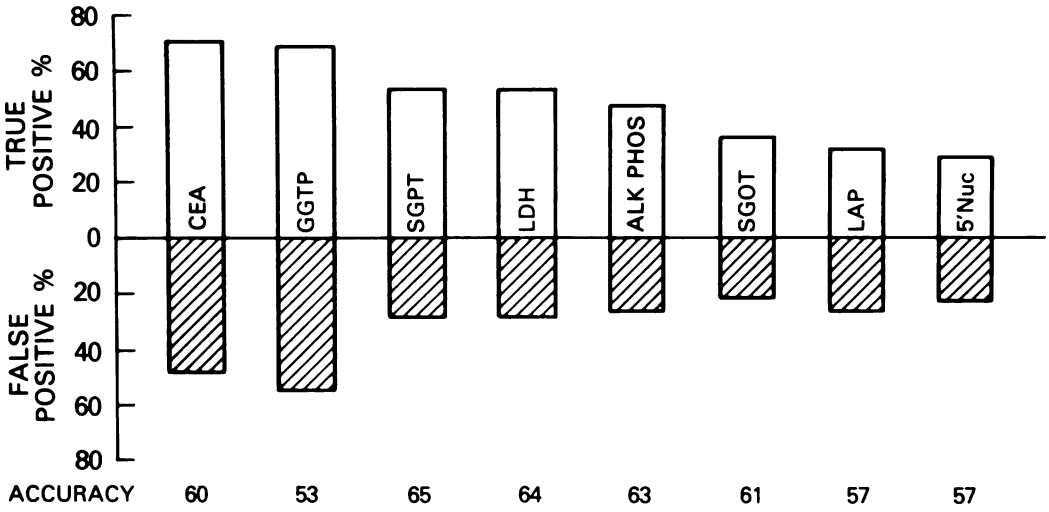

FIG. 1.

Kodak Co., Rochester, NY) 8 × 10 inches in size with six views on each sheet. The views obtained were anterior reclining with rib markers and five upright views: anterior, right lateral, right anterior oblique, posterior, and left lateral oblique. For the last view the patient was positioned to give the best view of the spleen.

Ultrasound examinations were performed with a Searle Digital Pho-sonic static B-scanner (Searle Diagnostic, Inc., Santa Clara, CA) employing 2.5 MHz or 3.5 MHz transducers, and with a mechanical sectoring real-time scanner (Advanced Technology Laboratories, Bellevue, WA) using a 3.0 MHz transducer. The liver was examined in the supine and left-lateral decubitus positions.

Computerized tomography scans of the liver were performed with the EMI 5005 body scanner (EMI, Northbrook, IL) with an 18-second scanning time. The slice thickness of the scans was 13 mm, performed at 15-mm intervals. In June 1980, a new General Electric 8800 body scanner was acquired, and thereafter patients were assigned randomly to either scanner for CT scans. A 9.8-second scanning time was utilized, with a 1-cm slice thickness and a 15-mm slice interval. The number of scans necessary to obtain visualization of the entire liver varied according to the size of the organ.

Each patient also had a series of laboratory tests that included alkaline phosphatase, LDH, SGOT, SGPT, prothrombin time, protein, albumin, and bilirubin. The majority of patients also had five additional tests that are often used to help determine the presence or absence of hepatic metastatic disease. These tests were carcinoembryonic antigen (CEA), leucine aminopeptidase (LAP), gamma-glutamyl transpeptidase (GGTP), 5′ nucleotidase, and alphafetoprotein (AFP). Tests were considered abnormal if they were outside the normal range as determined by the NIH clinical pathology laboratory.

Data from these tests were evaluated by standard statistical procedures.[21] Patients were classified as positive or negative for the presence of hepatic lesions, based on each test result. A decision matrix was constructed for the classification of patients based on test results according to their true disease status. For each single and composite test, an estimate of the true-positive ratio (sensitivity) was determined. This ratio is the proportion of patients with hepatic lesions who had an abnormal test result. The true-negative ratio (specificity) was also determined; this is the proportion of patients whose liver was not involved by hepatic lesions and whose tests were negative. Accuracy was defined as the number of tests that produced correct classification of the patient divided by the total number of tests that were scored.

Results

Use of Single Tests to Detect Hepatic Metastases

A comparison of individual laboratory tests for sensitivity, specificity, and accuracy revealed very few differences among these tests. Figure 1 shows that CEA and GGTP were the most sensitive laboratory tests, while SGOT and 5′ nucleotidase were the most specific. The accuracy ranged from 53–65%, with no significant differences seen between any of the tests.

If those patients with colorectal primary tumors were analyzed separately, the CEA test was more reliable. The sensitivity of the CEA as a single test was 86%[12,14] with a specificity of 60%[3,5] and an accuracy of 79%.[18,19] Use of the CEA test in this more restricted patient population increased the accuracy of the test from 60% to 79%.

Five tests that were analyzed but not included because there were so few abnormalities in these tests in the study patients are bilirubin, protein, albumin, alphafetoprotein, and prothrombin time.

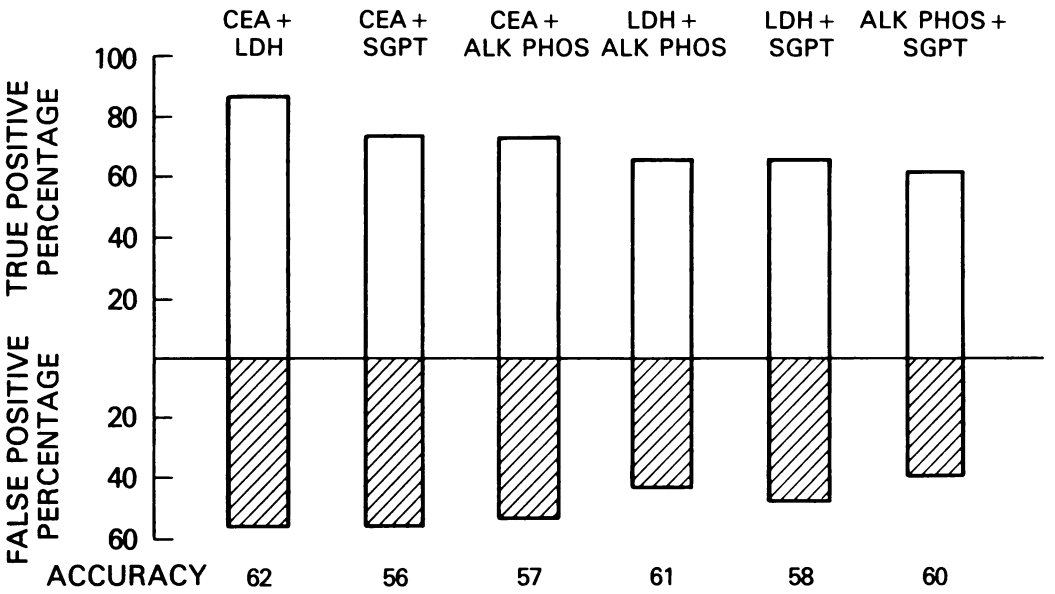

FIG. 2.

Detection of Hepatic Metastases Using a Composite Analysis of Laboratory Tests

A comparison of the results achieved with composite testing also showed a very close grouping of the test results. The test pairs were considered positive in a composite test if one of the two tests was positive; a test was considered negative if both the tests were negative. A pair of tests that looked at different aspects of hepatic function could complement each other as to accuracy. While CEA and LDH had an 87% sensitivity, the specificity was 44%; the resulting accuracy of 62% was less than that for LDH alone (64%). Other test pairs and their true-positive and true-negative ratios are shown in Figure 2.

Laboratory Tests and Liver Imaging Studies as a Composite Test

If results from laboratory tests of liver function and liver imaging studies are examined as composite tests, some improvement in the accuracy of these examinations is observed (Fig. 3). Again the true-positive ratio was defined as one of the two tests being positive in a patient with hepatic disease, and the true-negative ratio was defined as both tests being negative in a patient without hepatic metastases. (A false-positive test would equal one minus the true-negative ratio). If the CT scan was used as a composite test with 5′ nucleotidase or with SGOT, the accuracy was 76%. If the CT scan and CEA were used as a composite, the highest sensitivity

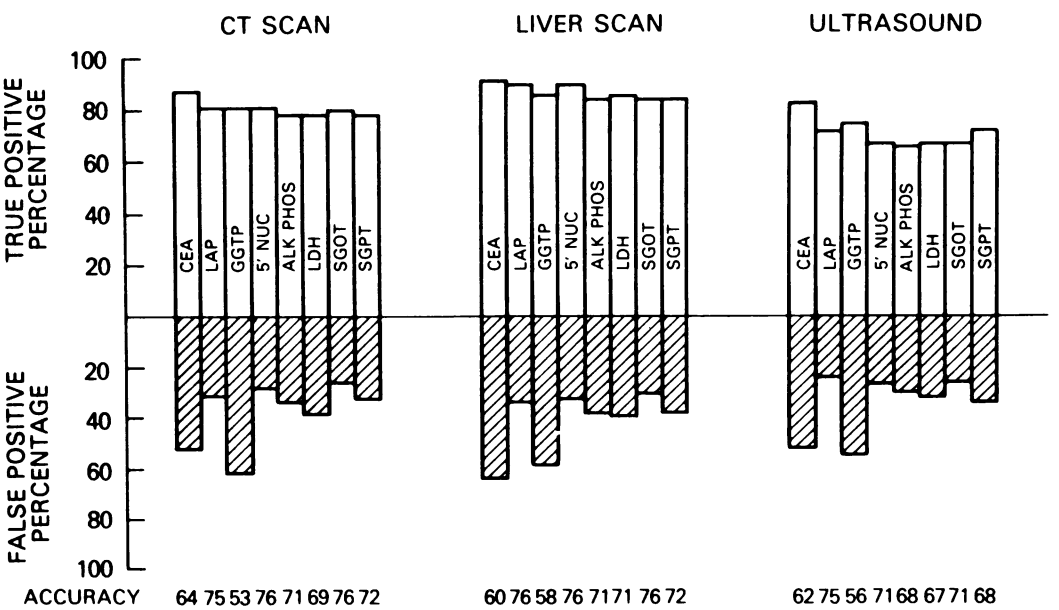

FIG. 3.

seen in this study, 87%, resulted; however, the accuracy of this composite test was only 64%. If liver scan and laboratory tests were used in combination, liver scan plus leucine aminopeptidase, liver scan plus 5′ nucleotidase and liver scan plus SGOT all had accuracies of 76%. Again CEA and liver scan had the greatest true-positive ratio, 91%.

Using ultrasound and laboratory tests, ultrasound plus leucine aminopeptidase had the highest accuracy at 75%. Ultrasound and CEA showed the greatest sensitivity, 83%.

There was no patient with a hepatic lesion and all normal laboratory and liver imaging tests.

Discussion

The best single test by which to determine the presence or absence of hepatic metastatic disease has not yet been determined. Different studies have advocated a wide variety of single best laboratory tests. For many years, alkaline phosphatase has been regarded as the best laboratory test by which to study a patient population to determine hepatic metastases.[9] Ranson, Adams, and Localio,[12] from their studies of colorectal cancer patients with hepatic metastatic disease, reported that LDH was the single best laboratory test. Baden[17] and coworkers, in studying GGTP and alkaline phosphatase, found both to be of little value in the preoperative diagnosis of hepatic metastases. Aronsen[15] and coworkers presented data to show that GGTP, with a 90% accuracy rate, was a better indicator of hepatic metastases than was alkaline phophatase, SGOT, or bilirubin. Cederqvist and coworkers[16] from Denmark found that SGOT and SGPT were both of low sensitivity for the detection of hepatic metastatic disease.

Our studies and those of Wanebo and coworkers[8] suggest that carcinoembryonic antigen is the best test by which to determine hepatic metastatic disease in patients with colorectal malignancy. In Wanebo's study, only four of 52 patients who had liver metastases failed to have an elevated CEA of 5 ng/ml or greater. In our studies, the true-positive ratio of CEA was very similar to that in Wanebo's work, 86%.

The use of composite tests to improve the accuracy of diagnostic procedures has been previously discussed.[18] Sugarbaker, Beard, and Drum[7] found that a composite test of CEA and liver scintiscan eliminated false-positive tests when attempting to identify liver metastases in patients with breast carcinoma. Other combinations of CEA, with barium enema and with liver scintiscan, have been reported by McCartney and Hoffer.[2] Recently Tartter et al.[1] studying alkaline phosphatase, CEA, and liver scan, reported low sensitivity for the liver scan (69%). The alkaline phosphatase had a sensitivity of 77%, and CEA was the best composite test, with 81%.

In this prospective study of 80 patients, no single laboratory test had a sensitivity of greater than 70% and none had an accurary of greater than 65%. The low scores on these tests is not surprising, for no patients with obvious gross hepatic metastatic disease as detected by physical examination were included in the patient population. Only those patients in whom the laboratory and radiologic diagnosis of metastases was important in patient management were included in this study. CEA, LDH, alkaline phosphatase, and SGPT were, in that order, the most accurate among the 13 laboratory tests we studied. Also, analysis of the data from laboratory testing as composites did not improve the accuracy in a statistically significant manner. However, when the laboratory tests and liver imaging studies were combined, the accuracy did improve. The combination of CEA with a liver imaging study in each instance increased the true-positive percentage; the same was seen when a combination of one of the other laboratory tests and a liver imaging study was used. Overall accuracy was best when leucine aminopeptidase or 5′ nucleotidase was combined with a liver imaging study.

Huguier and Lacaine[14] have recently published a study of hepatic metastases in patients with gastrointestinal malignancy. They compared alkaline phosphatase, GGTP, LDH, and SGOT. They found that alkaline phosphatase and GGTP were the most sensitive tests for detecting hepatic metastases.

Kowlessar et al.[11] in 1961 compared leucine aminopeptidase, 5′ nucleotidase, and alkaline phosphatase in patients with hepatic metastases from pancreatic cancer. They found 5′ nucleotidase and alkaline phosphatase to be more sensitive than leucine aminopeptidase.

Ranson, Adamson, and Localio,[12] in studying alkaline phosphatase, SGOT, SGPT, and LDH, found that LDH was the most accurate indicator of liver metastases. In their study in patients with subclinical hepatic metastases, alkaline phosphatase was not a useful examination.

The data from this study and from previous studies on liver imaging tests have led us to the following conclusions. The laboratory tests by themselves are not accurate enough to be screening tests for liver metastases. In a usual hospital or office setting, to evaluate a patient at risk for liver metastases, one liver imaging study, the standard liver function tests (alkaline phosphatase, SGOT, SGPT, LDH), and a CEA are all that need be done. The addition of the other liver imaging tests and all 13 laboratory tests will give no further accuracy and will markedly increase the expense. The choice of the liver imaging test used depends on the

availability of the tests at the specific hospitals. Important therapeutic decisions must be based on biopsy confirmation of the presence of disease. These liver imaging tests and laboratory tests can be used to detect a possible lesion, which would then have to be evaluated with laparotomy, laparoscopy, or closed liver biopsy. The accuracy of the combined laboratory and imaging tests is no greater than 76%. Thus, negative patients should be followed at regular intervals, since lesions of less than 2 cm will usually be missed at the first testing.[22]

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