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Radioimmunoassay for Carcinoembryonic Antigen as an Adjunct to Liver Scan in the Detection of Liver Metastases from Digestive-Tract Cancer

Tamio Aburano, Norihisa Tonami, and Kinichi Hisada

Kanazawa University, Kanazawa, Japan

In a series of 327 patients with primary GI malignancies, the occurrence of hepatic metastases was correctly detected in 70% of 113 cases by focal defects in the radiocolloid scintiscan. Only 1% of false positives were observed among the 214 patients without hepatic metastases. For these patients, the predictive value of the liver scan was 97%, and the overall accuracy, 89%. A composite test formed by disjoining focal radionuclide defects with the combination of elevated CEA and hepatomegaly, or elevated CEA and high alkaline phosphatase activity, exhibited a predictive value of 92% and an overall accuracy of 92%. Formation of such a composite test may be useful for preserving high accuracy when very strict scintigraphic criteria for metastases are employed.

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In 1965 carcinoembryonic antigen (CEA) was identified by Gold and Freedman (*1,2*) in carcinoma tissue from the epithelium of the human digestive tract and its entodermal derivates. This discovery was followed by the development of a radioimmunoassay by Thomson et al. (*3*) to measure plasma and urinary levels of CEA. Since then CEA radioimmunoassay has been introduced as a method for the detection of entodermally derived neoplasms. However, a recent study by Munro Neville and Laurence (*4*) showed that the nonspecificity of the CEA test greatly limited its value in the early diagnosis of cancer and that its major application lies in the followup of treated patients. According to Go (*5*), markedly increased serum CEA levels are highly suggestive of metastatic cancer, particularly hepatic metastases.

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For reprints contact: Tamio Aburano, Dept. of Nuclear Medicine, School of Medicine, Kanazawa University, Takara-machi 13-1, Kanazawa, 920 Japan.

Liver scanning has been widely used for the detection of hepatic metastases. However, this technique may give limited information when the need is to find small space-occupying lesions in the liver. According to the recent review by Brill and Patton (*6*), its detection rate is 83%. A simple radioimmunoassay method for measurement of CEA in serum by the use of the so-called "sandwich" method has recently been established in Japan (*7*). At present, CEA radioimmunoassay kits for this method are readily available and are used for the evaluation of cancer patients.

In the present project, the comparison between serum CEA levels and liver-scan findings was studied in patients with digestive-tract cancer in order to determine whether the combined use of the CEA test and a liver scan could provide more information than the liver scan alone in the detection of hepatic metastases.

PATIENTS AND METHODS

Both CEA radioimmunoassay and the liver scan were studied in a total of 327 patients with diges-

tive-tract cancer. The classification for the 327 patients (including, in parentheses, 113 patients with hepatic metastases) was: colorectal cancer, 114 (32); gastric cancer, 177 (58); pancreatic cancer, 17 (8); and cancer of the biliary system, 19 (15). In all patients the presence or absence of hepatic metastases was confirmed at laparotomy within 2 wk of these studies. Almost the entire surface of the liver was routinely explored visually and manually. In addition, a needle biopsy was made whenever the presence of hepatic metastases in a deep-seated portion was suspected from the manual examination.

Levels of CEA in human sera were measured using a radioimmunoassay based on the sandwich method, mentioned above. The levels obtained with this method were about half of those obtained with the Hoffman-La Roche method. In our method the normal CEA level was within 2.5 ng/ml, and CEA levels of over 5 ng/ml strongly suggested the presence of cancer, especially advanced cancer with distant metastases (*7*). Therefore, a CEA level of over 5 ng/ml was selected as being of significance where the possibility of hepatic metastases existed.

The liver scans were started 30–60 min after i.v. administration of 2–4 mCi of Tc-99m Sn colloid (Tc-99m stannous hydroxide). These were done immediately after taking a blood sample for the CEA assay. Either a rectilinear scanner with a 5-in. crystal and a 37-hole, 3-in. focussing collimator, or a gamma camera (intrinsic resolution using a lead bar phantom: 3.2 mm) with a high-resolution collimator having 42,000 parallel holes, was used. Anterior, right lateral, and posterior views were routinely obtained, and additional views were made when indicated. Only discrete focal defects in the liver (excepting physiologic shadows from the areas of the gall bladder, porta hepatis, hepatic vein, and right kidney) were adopted as criteria for diagnosing a positive liver scan. The findings of simple hepatomegaly, or of heterogenous uptake of radiocolloid in the liver, were not used.

The serum alkaline phosphatase (AP) determinations were performed with Bessey-Lowry's method. The normal level lies between 0.8–2.3 Bessey-Lowry units. These were also done on the same day as the liver scan.

In determining the diagnostic value of the present studies, the decision matrix of McNeil and Adelstein (*8*) was used, as follows.

1. The true-positive ratio (TP) is the proportion of positive studies in all patients with disease, and is the sensitivity of study.

2. The false-positive ratio (FP) is the proportion of positive studies in all patients without disease.

3. Accuracy is the proportion of correct outcomes (true positives and true negatives) to all outcomes (all patients with and without disease).

4. The prevalence ratio [P(D+)] of hepatic metastases is the proportion in the patient population under study, and is the prior probability of having disease.

5. The predictive value or posterior probability of a positive test [P(D+/T+)] is calculated from Bayes' theorem: $P(D+/T+) = TP \times P(D+)/[TP \times P(D+) + FP \times P(D-)]$.

RESULTS

Seventy-nine of 113 patients (70%) with hepatic metastases were correctly detected by focal defects in the radiocolloid liver scan. The types of carcinoma and the percentages of each detected of these 79 patients were: colorectal cancer, 22 (69%); gastric cancer, 40 (69%); pancreatic cancer, 5 (63%); and cancer of the biliary system, 12 (80%). However, 34 patients (30%) gave false-negative scans. Twenty-nine of these false-negative patients were associated with either small focal lesions (particularly less than 2–3 cm in a diameter) or with diffusely infiltrating lesions. The lesions in remaining five patients were falsely interpreted as physiologic impressions (one gall-bladder fossa, three porta hepatis, and one hepatic-vein indentation). Only three false positives (1%) were observed among the 214 patients without hepatic metastases. These could be explained by localized thinnings of the left lobe (two patients) and an unusual shape of the liver caused by right pleural disease (one patient).

High CEA levels of over 5 ng/ml were seen in 81 of 113 patients (72%) with hepatic metastases, and in 35 of 217 patients (16%) without hepatic metastases. Of the 34 false-negative scan images in the presence of hepatic metastases, 21 patients could be diagnosed correctly by a positive CEA. However, since 35 patients without hepatic metastases also showed positive CEA, the evaluation of hepatic metastases by CEA levels alone was less reliable. Most of these false-positive patients had advanced cancers.

When CEA levels over 5 ng/ml were combined with either hepatomegaly or increased serum alkaline phosphatase (AP) activity, 17 of 21 patients (81%) with hepatic metastases who were negative by only one test showed positive results with the combined test (hepatomegaly, 8; high AP, 15; and both 6). On the other hand, only five of 35 patients without hepatic metastases showed positive results (hepatomegaly, 2; high AP, 4; and both, 1). The evaluation of hepatic metastases by the combined test of high CEA with hepatomegaly or high AP was much more reliable than that by CEA assay alone.

TABLE 1. COMPARISON OF TESTS FOR DETECTION OF HEPATIC METASTASES IN 327 PATIENTS

Test or Composite	% True positives*	% False positives†	Predictive value	Overall accuracy
1. Focal defects	70	1	97	89
2. High CEA	72	16	70	80
3. Focal defects *or* high CEA	88	18	72	84
4. Focal defects *or* [(high CEA) with (hepatomegaly or high alkaline phosphatase)]	85	4	92	92

* 113 patients had metastases.
† 214 patients had no metastases demonstrable at laparotomy.

Table 1 shows the comparative evaluation of a) focal defects, b) high CEA, c) focal defects or high CEA, and d) a composite of focal defects, or high CEA with either hepatomegaly or high AP, for the detection of hepatic metastases in 327 patients with and without hepatic metastases. The predictive value of focal defects was 97%, and the overall accuracy 89%. On the other hand, a composite test formed by disjoining focal defects with the combination of high CEA and hepatomegaly, or CEA and high AP, exhibited a predictive value of 92% and an overall accuracy of 92%. The overall accuracy of the composite test was the best, although the predictive value of focal defects was the best. Therefore, formation of such a composite test may be useful for preserving high accuracy in the detection of hepatic metastases.

DISCUSSION AND CONCLUSION

As a diagnostic method in the detection of hepatic metastases, the routine liver scan with Tc-99m colloid has achieved widespread use with a high degree of accuracy. Because of the few false-positive results, the liver scan has been more reliable than liver function tests (*9,10*). False positives are usually due to either physiologic impressions such as gall-bladder fossa or porta hepatis, or extrinsic pressure caused by disease in adjacent organs and structures (*11,12*). Other space-occupying lesions in the liver—such as cyst or pseudomass in hepatic cirrhosis (*13*)—also caused false positives. The major deficiency of the liver scan is the relatively high incidence of false negatives. The main cause of false-negative liver scans is the insensitivity of the technique to small focal lesions less than 2–3 cm in diameter (*6*). As an adjunct to the liver scan in the detection of hepatic metastases, the usefulness of CEA assay was stressed by McCartney et al. (*15*) and Pompe et al. (*16*). They reported that diagnoses that were missed by scan could be detected by CEA levels. In their studies, however, the diagnostic accuracy of CEA assay in the detection of hepatic metastases was not fully discussed.

In our study, 30% of the 113 patients with hepatic metastases showed false-negative scans, and only 1% of the 214 patients without hepatic metastases gave false-positive scans. The 30% incidence of false-negative scans is relatively higher than the 17% false-negative ratio reported in the recent review by Brill and Patton (*6*). The primary cause of these relatively high false-negative and low false-positive ratios in our study, compared with their low false-negative ratio, is probably the adoption of discrete focal defects only (except for physiologic impressions) as the criterion for diagnosing a positive liver scan. An equivocal finding such as a small focal defect in the area of a physiologic shadow was not considered positive. Moreover, an abnormal scan on the basis of heterogenous uptake of radiocolloid in the liver, or simple hepatomegaly, was not adopted due to the low specificity for the detection of hepatic metastases (*14*). Five patients who showed small defects in the area of physiologic sites were falsely interpreted as negative. The remaining 29 false-negative patients were associated with small focal lesions or diffusely infiltrating lesions. As another cause of low false positives, no patient with hepatic cirrhosis was included in our study.

The positive CEA was seen in 72% of the 113 patients with hepatic metastases and in 16% of the 217 patients without hepatic metastases. These true-positive and false-positive ratios were close to those of Hirai: 71% and 16%, respectively (*7*). As an adjunct to the liver scan, 21 of 34 patients with hepatic metastases that were missed by liver scan could be detected by CEA levels. However, since 35 patients without hepatic metastases also showed positive CEA, and since most of these false-positive CEA patients had advanced cancers, the ruling out of hepatic metastases by CEA levels alone was less reliable than the negative scan.

In the combination of high CEA with simple hepatomegaly or abnormally high serum alkaline phosphatase (AP) activity, the evaluation of hepatic metastases by the combined test was much more reliable than that by CEA assay alone. Seventeen of 34 negative-scan patients with hepatic metastases could be correctly detected by the combined test. A composite test formed by disjoining focal defects with the combination of high CEA and hepatomegaly, or high CEA and high AP, exhibited a predic-

tive value of 92% and an overall accuracy of 92%. On the other hand, the predictive value of focal defects was 97%, and the overall accuracy, 89%. The overall accuracy of the composite test was the best, although the predictive value of focal defects was the best.

As a single test, the radionuclide liver scan was apparently superior to CEA assay, so the latter is not an adequate substitute for the liver scan. However, the composite test in our study could preserve high accuracy in the detection of hepatic metastases. Therefore, CEA radioimmunoassay may be useful as an adjunct to the liver scan in the evaluation of patients suspected of having hepatic metastases.

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