Radioimmunodetection of Occult Carcinoembryonic Antigen-Producing Cancer

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This study evaluates the ability of ^{111}In-labeled anti-carcinoembryonic antigen (CEA) monoclonal antibody (Mab) ZCE-025 to detect sites of occult cancer in patients with elevated serum CEA who have negative or equivocal CT scans. One hundred forty patients suspected of having occult cancer were evaluated. Except for elevated CEA levels, all had negative work-ups, including negative or inconclusive CT scans. Eighty-two patients (59%) had positive scans and 58 (41%) had negative scans. Seventy-five of the 82 patients with positive scans had confirmation of at least one Mab-positive lesion (91% positive predictive value). Thirty-eight of the 58 patients with negative scans had negative follow-up (66% negative predictive value). The Mab scan correctly identified at least one site of tumor in 75 of the 95 patients with recurrent or metastatic disease (79% sensitivity) and correctly predicted the absence of disease in 38 of 45 patients (84% specificity).

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Despite years of innovative research and occasional major scientific advances in diagnosis and therapy, cancer is exceeded only by cardiovascular disease as the leading cause of death in the United States. It is estimated there will be 1,100,000 new cancer diagnoses and 514,000 cancer deaths in the United States in 1991 (*1*).

It is generally acknowledged that early diagnosis is the key to successful cancer therapy. Unfortunately, current imaging techniques are frequently unable to detect cancer at an early enough stage to permit successful therapy. This is particularly true for recurrent or metastatic colorectal cancer. The CT scan, which in this setting is the most accurate diagnostic imaging procedure currently available, is often negative in patients with an elevated serum carcinoembryonic antigen (CEA) who have a high probability of recurrent disease. Not uncommonly, these patients are found to have recurrent or metastatic disease that was inapparent by CT scanning, even in retrospect. If it can be shown that earlier and more accurate diagnosis will lead to improved salvage of these patients, then it follows that a better diagnostic test will have a favorable impact on patient management.

During the past several years, radiolabeled monoclonal antibodies (Mabs) have been used successfully to image a wide variety of malignant tumors (*2–6*). Encouraging results have been obtained, although some problems must yet be overcome as this technique approaches routine clinical use (*5,7*). Several Mabs targeted to CEA have been evaluated in patients with colorectal cancer and other CEA-producing tumors (*8–19*).

The purpose of this study was to investigate the ability of ^{111}In-labeled anti-CEA Mab, ZCE-025, to detect occult cancer in patients with elevated serum CEA levels who have otherwise negative evaluations.

MATERIALS AND METHODS

Study Design

One hundred seventy-three patients (74 men, 99 women) with a mean age of 65 yr (range 31–92 yr) were studied. All but 7 had a prior history of CEA-producing cancer: 104 colon, 46 rectum, 7 lung, 3 metastatic disease from unknown primary sites, 2 lung plus colon and one each breast, cervix, anus and stomach. The seven patients with no prior history of cancer were entered into the study on the basis of a persistent unexplained serum CEA elevation. Serum CEA levels were elevated in all but three patients (mean 90). The three patients with normal CEA levels were referred because of equivocal findings on follow-up CT scans after prior resection of colorectal cancer. All patients had CT scans of the abdomen and pelvis that were read as either negative or equivocal for recurrent or metastatic cancer and many had negative CT scans of the chest. CT scans interpreted as equivocal showed either tissue thickening consistent with scar tissue but impossible to differentiate from recurrent cancer, or lymph nodes that subjectively were felt to be prominent yet measured less than 1 cm in diameter. All other tests that were obtained were negative. This analysis is limited to 140 of the 173 patients who had sufficient follow-up to allow definitive assessment of tumor status.

Not included among the 140 patients analyzed were 6 patients with equivocal Mab scan findings due to persistent colon activity which interfered with scan interpretation. Although attributed to excreted material within the contents of the colon, its failure to clear over time, often despite bowel cleansing, resulted in an equivocal scan report.

This study was conducted under investigational new drug applications issued to Hybritech Incorporated of San Diego, CA. All patients signed an informed consent approved by the Insti-

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tutional Review Committee of Sutter Community Hospitals of Sacramento, CA.

Post-scan follow-up was obtained until tumor was documented or for a minimum of 3 mo (average 21 mo). Positive confirmation of disease was considered definitive when one or more of the following were obtained at any time during the follow-up period: surgical demonstration of cancer, positive biopsy or enlarging mass seen on sequential CT or MR scanning. Recurrent or metastatic cancer was arbitrarily considered to be absent if all tests except CEA remained negative for at least 3 mo. When follow-up was negative at or beyond 3 mo but subsequently became positive, the patient was reclassified as positive for disease regardless of the elapsed time between the Mab scan and definitive tumor diagnosis.

These patients were accrued between April 1987 and February 1990 under investigational protocols that evolved over time. The patients entered early in the course of this investigation received ascites-derived Mab, whereas the more recently studied patients received Mab produced in cell culture. The Mab dose also varied depending on the specific protocol open at the time of patient accrual.

Mab Preparation

Radiolabeling of the Mab conjugate was accomplished by adding approximately 5 mCi of ^{111}In-citrate to the reaction vial, incubating at room temperature for 30 min, then quenching with neutralizing buffer. Thin-layer chromatography was used prior to injection to measure the percentage of ^{111}In bound to the Mab. The radiolabeled Mab was not utilized if the labeling efficiency was less than 80%. Vital signs were obtained immediately preinfusion and at 15-min intervals during and 2 hr following infusion.

ZCE-025

ZCE-025 is an intact murine IgG_1 with high affinity for CEA (*20–27*). It was originally produced by Haskell et al. (*20*) and subsequently licensed to Hybritech and renamed Hybri-CEAker®. ZCE-025 can be produced in cell culture or isolated from mouse ascites. It was provided in vials containing DTPA-conjugated ZCE-025 in kit form ready for labeling with ^{111}In and in vials containing 40 mg of unconjugated ZCE-025. One hundred twenty-seven patients received 42 mg of ascites-derived Mab consisting of a mixture of 2 mg of ^{111}In-labeled ZCE-025 and 40 mg of unconjugated, unlabeled ZCE-025 diluted in 100 cc of normal saline given as an intravenous infusion over 30 min. Forty-four patients received 5 mg of cell culture-derived ^{111}In-labeled ZCE-025 without additional unlabeled Mab given as a slow intravenous push over 3–5 min. Two patients received 2 mg of ascites-derived ^{111}In-labeled ZCE-025 without additional unlabeled Mab given as a slow intravenous push over 3–5 min.

Gamma Camera Imaging

All patients underwent gamma camera imaging at 3 days and 7 days after Mab infusion. A minimum of six 450-sec planar images were obtained on both days, consisting of anterior and posterior views of the thorax, abdomen and pelvis. Typical counts per image obtained over the chest, abdomen and pelvis were 900K, 1.3M and 500K on Day 3 and 300K, 400K and 170K on Day 7, respectively. Right anterior oblique views of the liver were obtained in most patients, and a few patients had delayed imaging between 8 and 10 days postinfusion.

At the discretion of the nuclear medicine physician, SPECT imaging was also obtained in many of the patients, but was not required by the protocol. All images were obtained on large field of view gamma cameras equipped with medium-energy collimators and interfaced to nuclear medicine computers. Both photopeaks of ^{111}In were utilized with 20% windows. SPECT images were acquired in 64 × 64 × 16 bit format with 360° rotation employing 64 views of 25 sec each. Routine uniformity and center of rotation corrections were applied. All images were interpreted by a nuclear medicine physician who had full knowledge of all available clinical and radiological data.

Follow-up and Mab Scan Correlation

Follow-up was obtained through direct patient contact, review of medical records and consultation with referring physicians. All relevant radiographs and medical records were reviewed by the principal investigator and correlated with the original Mab scan reports.

The Mab scans were given one or more of the following classifications as determined by follow-up: true-positive, true-negative, false-positive and false-negative. The Mab scan was classified true-positive if at anytime during follow-up tumor was determined to be present in an area identified as abnormal by the Mab scan. If tumors were identified during follow-up in any area not considered abnormal by the Mab scan, the scan was classified false-negative. The scan was classified false-positive if an area identified as abnormal was found to be negative at surgery, on biopsy or by CT scanning for a minimum of 3 mo. The scan was classified true-negative if CT scans and all other follow-up studies except CEA remained negative for a minimum of 3 mo. When a patient with a true negative classification at or beyond 3 mo developed cancer on subsequent follow-up, the scan was reclassified false-negative.

RESULTS

The findings are summarized in Figure 1. Of the 140 patients with definitive follow-up, 82 (59%) had positive scans and 58 (41%) had negative scans. Of the 82 patients with positive scans, 75 had confirmation of at least one Mab-positive lesion (91% positive predictive value) and 7 did not (9% false-positive). Three of the patients classified as false-positive, however, continue to have slowly rising CEAs. In the 82 patients with positive scans, definitive

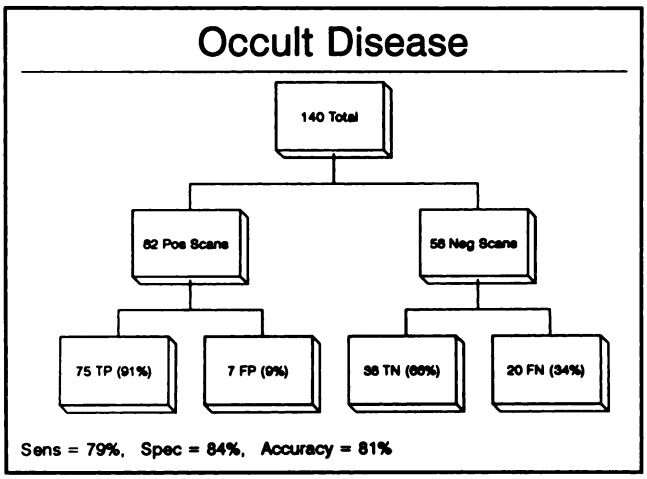

FIGURE 1. Summary of Mab scan findings and follow-up correlation. TP = true-positive; FP = false positive; TN = true-negative; FN = false-negative.

determination of tumor status was achieved by surgery in 39 (48%), biopsy in 12 (15%) and sequential CT or MR scanning in 29 (35%). Two (2%) of the patients with positive scans were determined to be false-positive by negative follow-up through 12 mo. Of the 75 patients with true-positive scans, 53 had no identification of tumor elsewhere, 16 were found to have additional lesions that were missed by the Mab scan and 6 had true-positive plus false-positive findings. The per-patient sensitivity of the Mab scan for correct identification of at least one lesion was 79% (75/95). The average time between the positive Mab scan and confirmation of tumor was 3 mo (range 0–18 mo).

Of the 58 patients with negative scans, 38 had negative follow-up and some also had negative surgery or declining CEAs (66% negative predictive value). Patients classified as true-negative were followed for an average of 12 mo (range 3–24 mo). The remaining 20 patients were found to have CEA-producing cancer detected by surgery, biopsy and/or sequential CT scanning (34% false-negative). The average time between the negative Mab scan and demonstration of tumor was 4 mo (range 0–22 mo). The per-patient specificity of the Mab scan was 84% (38/45).

The Mab scan correctly identified occult liver metastases in 19 of 32 patients (59%). These hepatic metastases were seen as hot spots in 14 patients, cold defects in 2 patients and cold defects with hot rims in 3 patients. The average time between the positive Mab scan and confirmation of a liver metastasis was 2 mo (range 0–8 mo). The average time between the negative Mab scan and demonstration of a liver metastasis was 5 mo (range 0–17 mo).

The impact of SPECT imaging on the accuracy of the Mab scan was not systematically studied. In several patients, however, SPECT helped to clarify equivocal findings on planar images and provided more certain identification of anatomic location, particularly in the abdomen, retroperitoneum and mediastinum. There were a few patients in whom SPECT identified liver metastases that were not clearly seen on planar images.

Serum CEA levels did not correlate with scan accuracy nor was there a subjective difference in the biodistribution of Mab in patients grouped by serum CEA levels. The study, however, was not designed to address these questions in a systematic or prospective manner.

Adverse Events

All 173 patients were evaluated for adverse events. Five patients (3%) experienced allergic-type adverse events that could reasonably be attributed to the Mab infusion. Two of these patients had no prior history of exposure to murine antibodies. Both developed mild urticaria that resolved without treatment. One of these patients subsequently had a second ZCE-025 scan with no adverse event. The other three patients with adverse events had a prior history of exposure to murine Mabs: two had previous ZCE-025 scans and one was previously scanned with another anti-CEA Mab (CEM-231, Hybritech). One experienced fever, chills and pruritus 4 hr postinjection, which resolved spontaneously the following day; the second experienced generalized erythema and anxiety during infusion, which resolved within 10 min after termination of the infusion and administration of intravenous benadryl; and the third experienced a serum sickness type reaction with mild hypotension and joint swelling that responded to intravenous fluids and steroids. No long-term sequelae were observed.

There were 17 patients in this study with prior history of murine Mab injections. Eleven patients received second injections of ZCE-025, two patients received third injections of ZCE-025 and four patients with prior CEM-231 injections received ZCE-025. The adverse reaction rate on repeat injections was 18% (3/17) compared to 1% (2/156) on first injections, indicating an increased risk with repeated Mab exposure. Nevertheless, all of the reactions were mild and easily controlled. Measurements of human anti-murine antibodies (HAMA) were not obtained.

Dose Comparison

The sensitivity, specificity and accuracy of the Mab scans done with 42 mg of ascites-derived ZCE-025 were not statistically significantly different than the scans done with 5 mg of cell culture-derived ZCE-025 (Fig. 2). Although the predictive values of the two doses were significantly different, this difference can likely be explained by the significant ($p < 0.001$) difference in disease prevalence between the two groups. The difference in disease prevalence is probably due to the fact that the CEA levels in patients scanned with 5 mg of Mab (mean = 33) were significantly lower than in those patients scanned with 42 mg (mean = 109). This was a result of protocol design (a higher CEA elevation was required in the earlier investigations done with 42 mg of ascites-derived ZCE-025 than in the later studies done with 5 mg of cell culture-derived ZCE-025).

Occult Disease

	42mg ZCE-025 (ascites)	5mg ZCE-025 (cell culture)	Overall
PPV	96% (67/70)	67% (8/12)	91% (75/82)
NPV	60% (25/42)	81% (13/16)	66% (38/58)
Sens*	80% (67/84)	73% (8/11)	79% (75/95)
Spec*	89% (25/28)	76% (13/17)	84% (38/45)
Accuracy*	82% (92/112)	75% (21/28)	81% (113/140)
Prevalence**	75% (84/112)	39% (11/28)	69% (96/140)

* NS ($p > 0.20$), ** $p < 0.001$

FIGURE 2. Comparison of 42 mg of ascites-derived ZCE-025 with 5 mg of ZCE-025 produced in cell culture. PPV = positive predictive value; NPV = negative predictive value; Sens = sensitivity; Spec = specificity.

DISCUSSION

Other investigators have demonstrated the ability of ^{111}In-labeled ZCE-025 to identify occult metastases in patients with elevated serum CEA levels and negative CT scans (*12,15,21*). However, there have been no previous reports dealing with comparable numbers of patients followed for a comparable length of time. Duda et al. (*15*) reported results in 10 patients with occult colorectal cancer scanned with 40 mg of ZCE-025 prior to second-look surgery. The Mab scan accurately predicted the presence or absence of disease in 62% of these patients. Patt et al. (*12*) reported results in 20 patients with occult CEA-producing cancer (18 colon, 1 breast and 1 Hodgkin's disease) scanned with 40 mg of ZCE-025. Tumor was confirmed by surgery (10 patients), biopsy (2 patients) or radiography (7 patients) in all 19 patients with positive scans, yielding a positive predictive value of 100%. Doerr et al. (*21*) reported results in 13 patients with occult colorectal cancer scanned with 10–40 mg of ZCE-025. The Mab scan correctly identified occult cancer in 11 of 12 patients (92%) with recurrent or metastatic disease. One patient had a true-negative scan and one patient with a metachronous cecal primary had a false-negative scan.

In this study of 140 patients followed for an average of 21 mo after Mab infusion, the scan correctly identified at least one site of occult cancer in 75 of 95 patients (79%) who were ultimately found to have cancer. It should be noted, however, that at the time of definitive diagnosis, 16 of these patients were found to have one or more additional lesions not identified by the Mab scan and 6 had at least one Mab avid focus not confirmed to be cancer. By comparison, the CT scan identified none of the lesions.

It was not possible to analyze the data on the basis of individual lesions since many of the patients with multiple focal abnormalities on the Mab scan had histopathologic or radiographic correlation obtained at only one site. Instead, the data were analyzed on a per patient basis. The conservative approach was employed of classifying as false-negative any patient with a negative scan who developed cancer at any time during follow-up, regardless of the elapsed time between the Mab scan and definitive tumor diagnosis.

The Mab scan correctly predicted the absence of occult cancer in 38 of 45 patients (84%) who had negative follow-up.

There is concern regarding the ability of ^{111}In-labeled Mabs to detect hepatic metastases in the presence of high background levels of isotope within the liver. This is important in patients with a history of colorectal cancer since the liver is a common site of metastatic disease and surgical salvage of patients with limited hepatic metastases is feasible. The CT scan is accurate for detection of hepatic metastases. Nevertheless, it may fail to detect lesions that exhibit x-ray attenuation similar to surrounding hepatic parenchyma. In this study, the CT scan correctly identified none of the lesions in the 32 patients with occult liver metastases, whereas the Mab scan correctly identified hepatic metastases in 19 (Fig. 3). Despite the presence of high background levels in the liver, 17 of these 19 patients had metastases identified as either hot spots or cold spots with hot rims. One might argue that the other two patients with cold liver metastases should be classified false-negative. They were classified true-positive, however, since any focal abnormality in Mab uptake within the liver should be viewed as potential tumor in patients with no focal abnormalities on CT scan to suggest an alternative explanation.

The requirement of a negative CT scan for entry into this study resulted in a preponderance of small lesions in those patients with hepatic metastases. The smallest that was correctly identified measured 9 mm in diameter at the time of surgical confirmation. It is likely that more of the lesions would have appeared cold relative to surrounding liver if larger metastases had been present.

Some nonspecific activity was identified within the colon in the majority of patients in this study. This colonic

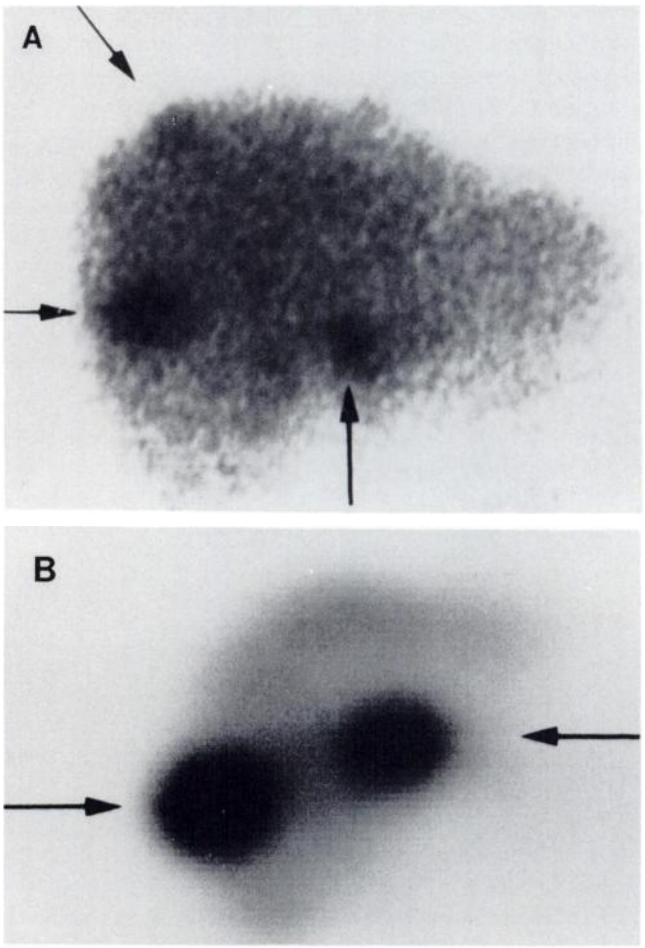

FIGURE 3. Anterior planar (A) and coronal SPECT (B) images of the liver 7 days postinjection of 5 mg of ^{111}In-labeled ZCE-025 demonstrating hepatic metastases that were subsequently confirmed at surgery. Note that the metastases are seen as "hot spots" despite relatively high background levels in the liver.

activity rarely interfered with scan interpretation, and in this study resulted in an equivocal result in only 6 patients (3%). Colonic activity tends to clear or at least change position over time whereas tumor uptake tends to become more intense relative to background; thus the value of imaging on multiple days. Bowel cleansing is often helpful. In ongoing studies, mild laxatives are being utilized in many patients and enemas are occasionally given.

It was not possible to objectively assess the ability of the Mab scan to accurately predict the extent of recurrent or metastatic disease. One should be cautious, therefore, when using the results of the Mab scan to determine whether or not tumor is resectable. When multiple extrahepatic lesions are seen, however, the scan findings might be utilized to avoid futile surgery (Fig. 4).

Focal isotope uptake was observed in hilar or mediastinal lymph nodes in several patients with Mab-avid lung metastases. Lymph node metastases were confirmed in some (Fig. 5), but others were not confirmed at surgery (Fig. 6). This may be secondary to accumulation of shed CEA within lymph nodes. It is also possible that micrometastases within lymph nodes may be inapparent both to the surgeon (Fig. 4) and pathologist. Caution is recommended in using such scan results as conclusive evidence of hilar or mediastinal lymph node metastases, particularly in the absence of lymphadenopathy on CT scanning. This phenomenon was also observed in groin lymph nodes in patients with recurrent rectal or rectosigmoid cancer (Fig. 7).

The Mab scan proved particularly accurate in differentiating recurrent disease from post-surgical or post-radiation scar tissue in the pelvis or presacral space in patients

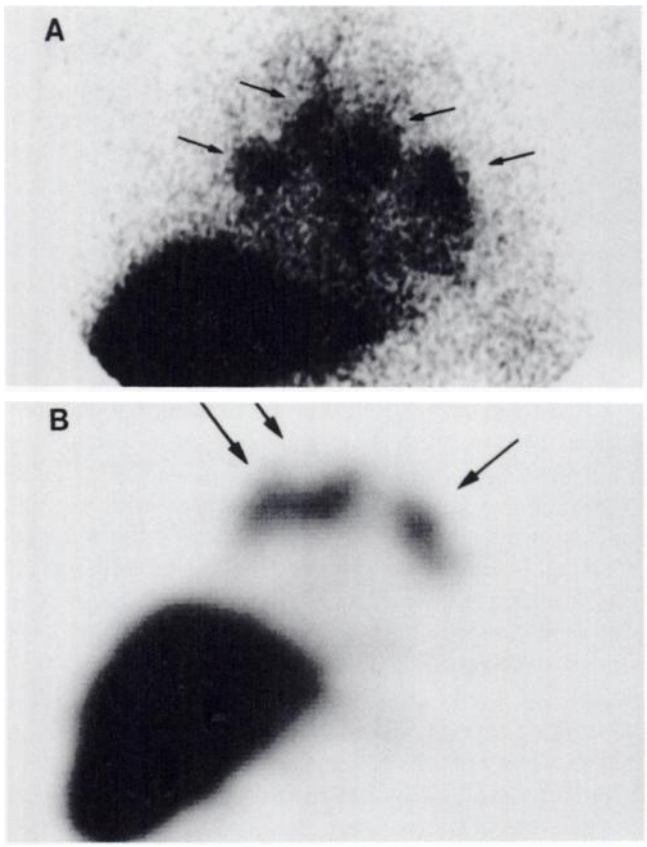

FIGURE 5. Anterior planar (A) and coronal SPECT (B) images of the thorax obtained 7 days after injection of 5 mg of ^{111}In-labeled ZCE-025 showing focal Mab accumulation in hilar and mediastinal metastases subsequently confirmed on follow-up MR scan and biopsy.

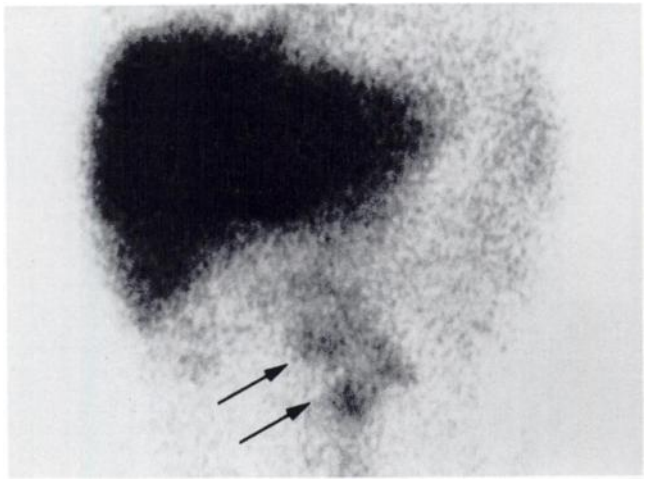

FIGURE 4. Anterior planar images of the abdomen obtained 7 days postinjection of 5 mg of ^{111}In-labeled ZCE-025 showing focal uptake in the central abdominal region (same patient as in Fig. 3). No lesions were identified in this area at surgery done 4 wk after imaging. Repeat surgery done 4 mo after imaging, however, demonstrated multiple mesenteric and peritoneal metastases in the central abdominal region, confirming the scan findings.

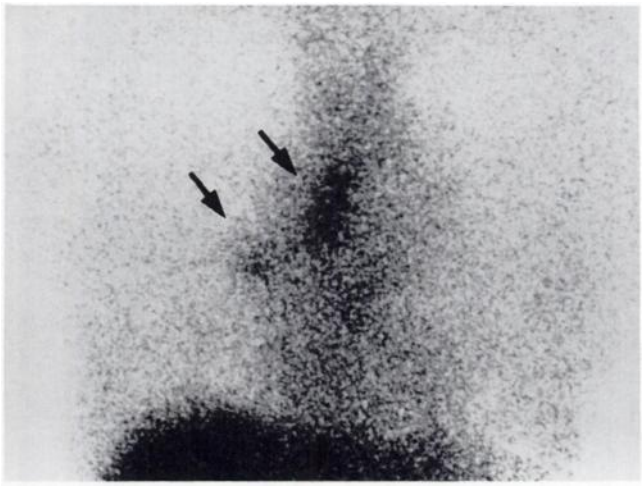

FIGURE 6. Anterior planar image of the thorax obtained 7 days postinjection of 42 mg of ZCE-025 showing focal Mab accumulation within a right hilar (lower arrow) pulmonary metastasis. The pulmonary lesion was confirmed, but the apparent mediastinal lymph node metastasis (upper arrow) was not confirmed.

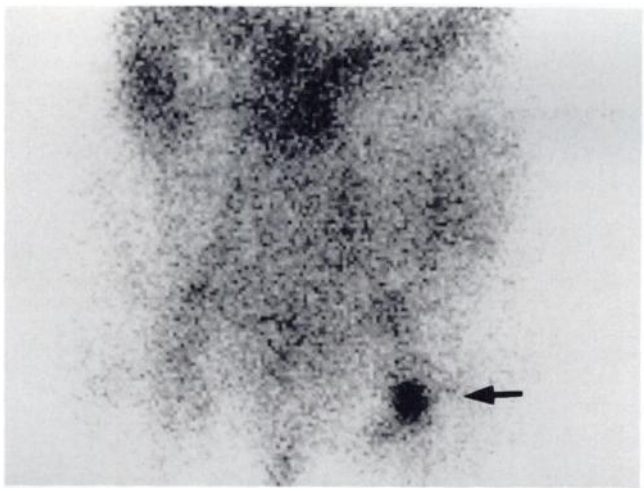

FIGURE 7. Anterior planar image of the pelvis obtained 7 days postinjection of 5 mg of ^{111}In-labeled ZCE-025 showing focal Mab accumulation within a groin lymph node in a patient with prior history of rectal cancer. Metastatic disease was subsequently confirmed by biopsy. Unconfirmed Mab accumulation in groin lymph nodes has also been observed.

with prior history of rectosigmoid or rectal tumors (Fig. 8), thus enabling early surgical intervention in several cases.

CONCLUSIONS

Patients with elevated serum CEA, negative CT scan and prior history of CEA-producing cancer pose a formidable diagnostic challenge. These data indicate that anti-CEA Mab scanning contributes significantly to the accurate diagnosis of these difficult to manage patients. By detecting otherwise occult lesions, the Mab scan may permit earlier surgical intervention in some patients and avoidance of unnecessary surgery in others. In this study, the Mab scan correctly identified at least one site of recurrent or metastatic disease in 75 of the 95 patients with occult cancer—disease not identified by CT scanning, which in this clinical setting is the best diagnostic imaging procedure currently available. More work needs to be done to determine if the improved diagnostic information provided by Mab scanning will have a positive impact on patient management and, ultimately, survival.

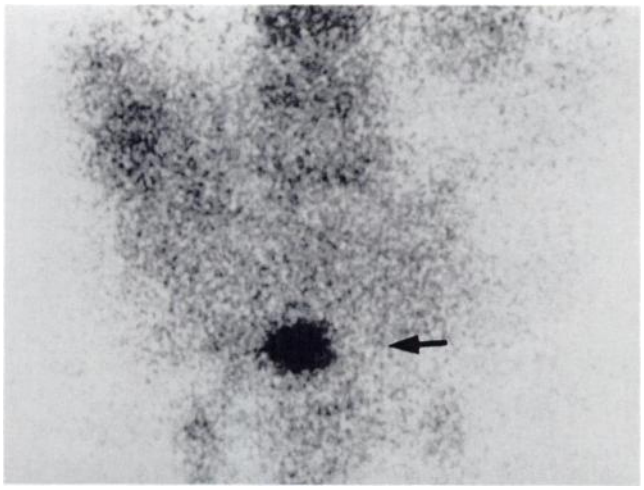

FIGURE 8. Posterior planar image of the pelvis obtained 7 days postinjection of 42 mg of ZCE-025 showing focal Mab accumulation where subsequent surgery confirmed recurrent colorectal cancer. The pelvic CT scan was negative.

ACKNOWLEDGMENTS

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EDITORIAL

Immunoscintigraphy of Colorectal Carcinoma and the Loch Ness Monster

What has Nessie, the legendary animal supposedly living in Loch Ness in the Scottish Highlands, in common with immunoscintigraphy? At first glance, there is no obvious relationship, but if one looks a bit closer one will notice that both are supported by firm believers on one side and attacked by convinced skeptics on the other. Who is right, who is wrong? I do not feel competent to give a definite answer to this question, but I shall try to discuss some reasons for the uncertainty of the status of immunoscintigraphy in the diagnostic work-up of patients with colorectal carcinoma.

First experiments in animals bearing human colon carcinoma grafts with excellent uptake of ^{131}I-labeled polyclonal antibodies directed against carcinoma-embryonic antigen (CEA) raised the hope of approaching the legendary concept of the magic bullet set up by Paul Ehrlich. The images obtained in patients with CEA-producing tumors were much less clear. The average nuclear medicine physician had some difficulties in accepting that a few white, red or yellow dots on a scan represent significant tumor uptake; and I guess that it was even more difficult for the average surgeon to accept. These pictures need the faith of the pioneers of immunoscintigraphy to be accepted in the same way that pictures of the Loch Ness Monster need the faith of those who have shot them to be interpreted.

The monoclonal antibody technique described by Köhler and Milstein in 1975 aroused the interest of the medical community in radioimmunodetection, which was expected to be followed very rapidly by efficient radioimmunotherapy. Again, we had to learn that even specific antibodies were still not magic bullets able to detect, visualize and destroy tumor cells wherever they were located in the body. Faith was confronted with the reality that macromolecules must first cross the capillary membrane before reaching the antigen on the tumor cells while swimming against the stream of high interstitial pressure (*1*). It is really magic that some of these antibodies finally reach their target! And they do: the article published by Haseman et al. in this issue of the *Journal*, as well as numerous other articles, which were reviewed extensively by Goldenberg and Larson (*2*), show that the faith in immunoscintigraphy of colorectal carcinomas was justified, even if many problems remain to be solved. Haseman et al. detected at least one tumor deposit in 75/95 patients (79%) whose clinical and radiological work-up was negative or equivocal at the time immunoscintigraphy was performed. This confirms the opinion of most of researchers involved in the field that immunoscintigraphy is able to visualize tumor foci before they are large enough to be shown by other methods. The technique takes advantage of the fact that uptake per gram tumor tissue in percent of injected activity is higher in smaller than in larger tumors. It thus has the potential to narrow the gap between the first doubts about a possible recurrence raised by subtle changes in a patient's symptoms or laboratory tests and treatment.

Despite many encouraging results, skepticism concerning the future of immunoscintigraphy and radioimmunotherapy remains. In fact, immunoscintigraphy is not yet considered a routine nuclear medicine procedure. Even if we know that antigens need not necessarily be tumor-specific as long as they are more abundant in tumor than in nontumor tissue or that antigen shed into circulation does not prevent from successful tumor imaging, it is not always easy to distinguish

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