Preliminary findings in the evaluation of hepatic malignancies by radioimmunodetection, X-ray computed tomography, and magnetic resonance imaging*

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Abstract. In 12 consecutive patients with suspected metastatic carcinoma of the liver, we evaluated the sensitivity of radiolabeled antibodies to tumor antigens, magnetic resonance imaging, and X-ray computed tomography imaging in the detection of hepatic malignancies. Studies were performed with ¹³¹I labeled antibodies to CEA and/or CSAP; polyclonal, monoclonal and *F(ab')*₂ antibodies were used. Nontarget radioactivity was diminished by administration of ^{99m}Tc reagents simulating nontumor distribution and use of a computer subtraction method. In nine patients with confirmed liver neoplasms, radioimmunodetection disclosed the foci of hepatic malignancies. In three patients with suspected liver neoplasms, the antibody studies were positive, but at this time have not been confirmed. X-ray computed tomography each disclosed mass lesions in five patients and magnetic resonance in three. These findings suggest that radioimmunodetection provides greater accuracy in the detection and localization of cancer than other diagnostic modalities currently used.

Key words: Radioimmunodetection – Tumor detection – Antibodies

Although true tumor specificity has not been achieved in the isolation and characterization of tumor antigens, a number of tumor-associated products, or markers, have been used clinically for the in vitro monitoring of cancers that produce and release these substances into the bloodstream (Herberman and McIntire 1979). We therefore postulated that these tumor-associated markers could serve as useful targets for radiolabeled tumor-localizing antibodies administered in vivo, thereby permitting the external detection of cancers by radionuclide imaging (termed radioimmunodetection, or RAID) (Goldenberg 1980). After successful animal studies with radiolabeled antibodies against carcinoembryonic antigen (CEA) Primus et al. 1977, clinical trials were begun in 1977. We found that affinity purified goat anti-CEA antibodies labeled with ¹³¹I revealed CEA-producing tumors, some of which had not been discovered by other cancer detection methods (Goldenberg et al. 1978). Subsequently, antibodies against other tumor

markers, such as alpha-fetoprotein (AFP), human chorionic gonadotropin (HCG), prostatic acid phosphatase (PAP) and colon specific antigen protein (CSAP), were evaluated clinically, and it was found that tumors containing these substances were disclosed by RAID (Goldenberg and DeLand 1982). An important observation was that diagnostic examination with antimarker antibodies was successful despite the presence of high titers of these markers in the patients' blood (Primus and Goldenberg 1980). Several investigations have compared magnetic resonance imaging of the liver with other tumor detection modalities, such as ultrasound, radionuclide imaging, and computed tomography (Smith et al. 1981; Doyle et al. 1982). We report a study of 12 patients who had known or suspected liver tumors and who were examined by radiolabeled antibodies, computed tomography (CT), and magnetic resonance imaging (MRI).

Materials and methods

Subjects

Twelve consecutive patients capable of remaining motionless for the required MRI time entered the study. No patients were eliminated because of a negative antibody study. Each patient had been referred for RAID studies for the following reasons: (a) an evaluation of recurrent carcinoma; (b) a rising plasma titer of CEA without other diagnostic evidence of recurrent tumor; or (c) proven metastatic carcinoma from an unknown primary. In nine patients the primary tumor was from the colon, in one each from the breast and pancreas, and in one the primary neoplasm was unknown. Tumor sites were confirmed in nine patients – by histologic examination in seven, by sequential changes in X-ray tomography in three, and by a markedly elevated plasma CEA (>2,000 ng/ml) and abnormal liver function tests, including alkaline phosphatase, in one (Reynoso and Keane 1979; Zimmerman 1979). Each patient had one or more examinations by CT and one examination by MRI. Plasma levels of CEA were determined before and at the time of the RAID procedure by the Roche CEA radioimmunoassay method. Skin-testing was performed for hypersensitivity to the specific immunoglobulin preparation to be administered. To minimize thyroid sequestration of ¹³¹I, Lugol's solution (KI) was given orally, five drops twice daily for one week, beginning two days to three days before administration of the radioiodinated antibody.

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Table 1. Correlative results in patients with confirmed hepatic tumor

Patient No.	Diagnosis	Plasma CEA ng/ml	Liver findings			Confirmation
			CT	MRI	Antibody	
419	12/80 adca colon (11 pos nodes, large liver mets)	120	11/81 +		11/81 poly CEA + 11/82 poly CEA + 8/83 poly CEA +	surgery
462	7/82 adca rectum (10 pos nodes, multiple liver mets)	2.0 1.4	6/82 – 10/82 +		6/82 poly CEA + 9/82 $F(ab')_2$ + 11/82 CSAP + 3/83 mono CEA +	surgery
	11/83 30% liver replaced with tumor	0.19	3/83 + 10/83 + 9/84 –	3/83 –		surgery
485	6/82 adca sigmoid omental mets	17 7 46	11/82 – 2/83 – 4/83 +		11/82 poly CEA + 12/82 CSAP + 5/83 CSAP +	– to + CT
504	5/82 adca rectum (6 pos nodes, multiple liver mets)	1,024 (3/83)	3/83 – 6/83 +	4/83 +	4/83 CSAP +	surgery
505	10/82 adca sigmoid (recurrent)	2.9 (4/83)	11/81 – 6/83 +	4/83 –	4/83 mono CEA +	– to + CT
507	8/82 adca sigmoid (8 pos nodes)	461 900	2/83 – 5/83 –	4/83 –	4/83 mono CEA + 6/83 poly CEA +	surgery
	8/83 massive liver mets	> 2,000	8/83 +			
511	4/83 + CEA-source unknown	31	11/82 –	4/83 –	4/83 mono CEA +	– to + CT
	8/83 pancreatic ca (massive liver mets)	42	8/83 +			
517	6/83 met adca to bone (unknown primary)	26	7/83 –	7/83?	7/83 mono CEA +	
		> 2,000 (8/84)	8/84 –			↑LFT and alk PO_4
522	9/82 adca colon (pos nodes)	1.3 (7/83) 35 (8/83)	6/83 –	7/83 –	7/83 $F(ab')_2$ +	5/84 liver mets by arteriogram

met *mets*=metastases; *CEA*=carcinoembryonic antigen; *CT*=X-ray computerized tomography; *MRI*=magnetic resonance imaging; *AB*=antibody; *adca*=adenocarcinoma; *poly*=polyclonal; *FaB'*₂=fragment polyclonal CEA; *CSAp*=colon specific antigen protein; *mono*=monoclonal; *alk PO*₄=alkaline phosphatase

Written informed consent was obtained from all subjects after the procedures and risks were explained. Based on MRI patient restrictions, pregnant women and patients with cardiac pacemakers were excluded from the study, however, neither of these two categories was encountered.

Antibody preparations

The production of hyperimmune antisera to CEA, AFP, and CSAP has been reported (Goldenberg et al. 1978; Shochat et al. 1981; Zimmerman 1979). All CEA and CSAP preparations, polyclonal, monoclonal, and $F(ab')_2$ fragments, were prepared from the same source, the GW-30 tumor. In brief, after immunizing goats with purified antigen, the sera were subjected to extensive tissue adsorption and, in the case of CEA, affinity chromatography. The IgG fraction was isolated by ion-exchange chromatography. $F(ab')_2$ fragments of the goat anti-CEA IgG were prepared by proteolytic digestion with pepsin. The IgG preparation, at a concentration of 10 mg/ml to 20 mg/ml, was dialyzed against two changes of 50 volumes each of 0.1 M sodium acetate buffer, pH 4.0, at 4° C. Lyophilized pepsin (Sigma, St. Louis, MO) was dissolved in the same buffer, and added to the reaction mixture at a ratio of 1:100 w/w, pepsin:IgG.

The digestion was left to proceed at 37° C for 16 h, and was then terminated by dialysis against two changes of 50 volumes each of 0.1 M sodium phosphate, pH 7.5, containing 20% glycerol. The $F(ab')_2$ fragments were purified by gel filtration chromatography on a column of Sephadex G-150 (2.6 cm × 100 cm) equilibrated with the same buffer. The fractions containing the fragments were pooled and concentrated by means of ultrafiltration using Amicon YM-10 membranes. The purities of the preparations were determined by SDS-polyacrylamide electrophoresis, and the immunoreactivity by both radioimmunotitration and the analysis of a small aliquot of ¹²⁵I labeled fragments on a small column of CEA immunoadsorbent. The latter test established the fraction of anti-CEA immunoreactive $F(ab')_2$ fragments in the preparation.

The murine monoclonal antibodies (Mab) against CEA were prepared as described (Primus et al. 1983a). Briefly, female BALB/c mice were immunized with CEA in incomplete Freund's adjuvant, and the spleens from two mice demonstrating serum antibody against CEA were harvested for fusion with P3-X63-Ag8.653 murine myeloma cells. The Mabs of interest were purified from ascites fluid by precipitation with 40% ammonium sulfate, and then eluted from an ion-exchange column. The Mabs used for our studies

Table 2. Correlative results in patients with unconfirmed hepatic tumor

Patient No.	Diagnosis	Plasma CEA ng/ml	Liver findings		
			CT	MRI	Antibody
508	5/83 adca rectum (11 pos nodes)	3	4/83—	4/83—	4/83 CSAp+
519	6/83 adca colon (1 pos node)		6/83— 7/84—	6/83—	6/83 CEA $F(ab')_2$ +
521	10/82 adca breast (8 pos nodes)	2.5	6/83— 10/83—	7/83—	7/83 mono CEA +
	9/84 bone mets	17			

did not recognize any known cross-reacting epitopes other than CEA and meconium antigen (Primus et al. 1983b).

The specifications for the final products used clinically were as follows: (a) a single band in polyacrylamide gel electrophoresis, as stained with Coomassie Blue R or G; (b) a single component in gel filtration, co-eluting with reference goat or murine gamma-globulin; (c) immunoreactivity of 50%–90% for affinity-purified goat or murine monoclonal antibodies; (d) radiochemical purity greater than 90% with respect to gamma-globulin; and (e) specific activity of not less than 10 mCi/mg and not more than 20 mCi/mg IgG protein. In addition, the antibody preparations were shown to be safe for clinical use by microbiological, acute toxicity, and pyrogenicity testing.

Radionuclide imaging technique

After labeling the appropriate antibody preparations with ^{131}I by the chloramine-T method, (Greenwood et al. 1963) 75 MBq–110 MBq of the radiolabeled antibodies (2 ug/kg–3 ug/kg body weight) in 20 ml of 0.9% sterile saline solution were administered i.v. To minimize blood pool and background radioactivity, as well as that from free radioiodine in the stomach and urinary bladder, 19 MBq of $^{99\text{m}}\text{TcO}_4$ and 19 MBq of $^{99\text{m}}\text{Tc}$ labeled human serum albumin were given i.v. at 30 min and 5 min, respectively, before each scintigraphic examination. At 24 h and 48 h after administration of the radiolabeled antibody, gamma camera images of the chest, abdomen, and pelvis (standard protocol) were obtained. The data were obtained in two windows at 140 keV (+/–10%) and 364 keV (+/–10%), and stored in a minicomputer. Nontarget ^{131}I activity was subtracted using the $^{99\text{m}}\text{Tc}$ image. To further refine the technique of increasing target-to-nontarget ratios of radioactivity in the liver, $^{99\text{m}}\text{Tc}$ -sulfur colloid was administered i.v. after the routine ^{131}I and $^{99\text{m}}\text{Tc}$ images had been obtained. The region of the liver was imaged in the anterior, right lateral, and posterior projections, collecting data by means of windows set for the ^{131}I and $^{99\text{m}}\text{Tc}$ photon peaks. The images of the liver only were selectively extracted as regions of interest and the subtraction method used (^{131}I minus $^{99\text{m}}\text{Tc}$) to define the increased focus of activity of the radioactive antibodies. The radionuclide images were interpreted without knowledge of any clinical information or type of antibody used.

Magnetic resonance imaging

The MR instrument was of the resistive type, 0.15 Tesla (Technicare Corp., Solon, OH). Multiple image sections

were obtained in three modes: saturation recovery (SR), inversion recovery (IR), and spin echo (SE). Each section was 8 mm thick, with data acquired in a 256×128 matrix; a radiofrequency of 6.25 MHz was used; the body coil has an aperture of 53 cm. For the modified SR images, the repetition rates were 250 msec or 500 msec, and echo times were 30 msec. For the IR the repetition rates were 1,000 msec or 1,500 msec and the acquisition delay recovery times were 400 msec for 450 msec, respectively. For SE the repetition rate was 1,000 msec and the echo delay time was 60 msec. Each section examination required 4.5 min of instrument time to obtain sufficient averaging for an acceptable signal-to-noise ratio. The images were interpreted independently by three observers.

Transmission computed tomography

All patients received an examination of the liver by CT, (with and without contrast media), usually just before or after the radionuclide antibody study. The examinations were obtained with current instrumentation (General Electric 8800 and 9800, Technicare 2060, and Picker 600). Although more than half of the CT studies were performed by radiologists at other institutions, copies of the CT examinations were obtained and reviewed locally by two observers.

Results

Eight patients had one examination with radiolabeled antibodies; one had two examinations; two had three examinations; and one, four studies – a total of 20 RAID procedures in 12 patients. Six patients received ^{131}I labeled goat antibodies against CEA, five received goat antibodies against CSAp, six were studied with CEA monoclonal antibodies, and three with goat $F(ab')_2$ anti-CEA antibodies. Abnormal foci of increased radioactivity in the liver were found in all 20 studies. No variation in the results of the studies was observed, irrespective of the type of antibody used. For example, Patient 462 received four RAID studies, each with a different antibody (polyclonal CEA IgG, monoclonal CEA IgG, goat $F(ab')_2$ CEA antibody, and goat CSAp IgG), and abnormal foci of the radioactivity were observed in the liver with each preparation. As reported previously (Goldenberg et al. 1978), the level of plasma CEA, either low or high, (0.9 ng/ml–900 ng/ml) had no influence on the imaging results.

In nine of the patients the presence of hepatic cancer, either primary or metastatic, was confirmed by other methods (Table 1): by surgery in six, by a change in the CT

Table 3. Correlative results in patient with rectal carcinoma (.462)

Date	Clinical	Plasma	Liver findings			Therapy
		CEA ng/ml	CT	AB	MRI	
6/82	Adenocarcinoma rectum	2	—	poly CEA +		Radiation and chemotherapy
8/82	Dukes C; 10 of 11 mesenteric nodes positive-multiple liver metastases					Anteroposterior resection
10/82		1	+	CEA- <i>F(ab')</i> ₂ +		Chemotherapy
12/82		2	+	CSAp +		Chemotherapy
1/83		1	+			Chemotherapy
3/83		2	+	mono-CEA +	—	Chemotherapy
7/83		1	+			Chemotherapy
11/83	30% liver replaced with tumor-Celiac arteriogram negative	2	+			Surgery
6/84		2	+			Chemotherapy
9/84		1	—			Chemotherapy

in three, by hepatic arteriogram in one, and by a very marked elevation of plasma CEA (>2,000 ng/ml) plus abnormal liver function tests including serum alkaline phosphatase in one (Reynoso and Keane 1979; Zimmerman 1979). When the presence of hepatic tumors was first detected by the antibody method (Table 1), only three CT studies were positive. Subsequently, when the CT and MRI studies were performed concurrently in this group of patients, five were found to be positive by CT, and four positive and one questionable by MRI. Within 5 months of the combined CT-MRI studies of nine patients demonstrated evidence of mass lesions in the liver by X-ray tomography. In one patient (No. 511), the negative CT study preceded the RAID examination by 5 months, and a subsequent CT scan 4 months after the RAID study was positive for hepatic metastases.

The diagnosis of hepatic metastases by RAID was unconfirmed in three patients (Table 2). However, in two instances, Case No. 508 with extensive lymph node metastases to the mesentery and Case No. 521 with increasing plasma CEA level, the possibility of liver metastases was increased. Nevertheless, at this time with lack of confirmation by means of other standards, Cases Nos. 508, 519, and 521 are considered as false positives. In none of the patients who had positive antibody studies for hepatic tumor were false positive findings revealed by surgery.

Case study

Case No. 462

In June 1982 a 64-year-old man presented with a rectal mass that proved to be an invasive, moderately differentiated adenocarcinoma; his plasma CEA was 2 ng/ml. Table 3 summarizes the clinical course of this patient, and Fig. 1 illustrates the results. The first radioantibody study (6/82) demonstrated multiple foci of increased radioactivity, representing the antibody-antigen reaction in metastases, whereas an X-ray computed tomography study was negative for mass lesions. Two months later, surgery revealed multiple metastases in the liver. The patient received chemotherapy, and the CT and antibody studies were repeated 2 months after the anteroposterior resection. The computerized tomographic study revealed two metastases in the mid region of the liver, whereas the antibody study showed en-

largement of several metastases in the mid liver and left lobe and lesser sequestration of activity in the lesions of the right lobe. In December 1982 both the antibody and CT studies revealed the metastases, but the mass lesions were much more difficult to define by CT than in previous studies. The patient received his fourth series of treatment with chemotherapy. In March 1983 the fourth antibody study again revealed metastases. Each of the four CT examinations performed in 1983 revealed two mass lesions, but definition was faint. In November 1983, at exploratory laparotomy, 30% replacement of the liver by tumor was observed, and it is difficult to reconcile the surgical findings with the paucity of lesions seen on the CT study. Finally after eight chemotherapeutic treatments the CT study became negative in September 1984. The variance in the findings in this case reveals the difficulty in correlating the extent of metastases observed by CT and that found by antibody examination. An unusual finding was that the plasma CEA remained within normal limits for at least 27 months even though the metastases from this CEA-producing rectal adenocarcinoma were massive.

In this patient examinations with four different antibody preparations, the three directed against CEA and the antibody against CSAP, consistently disclosed lesions in liver. In this case and others in whom different antibodies were used, no one antibody appeared superior; however, the number of such cases is too small to draw any valid conclusions. At the time of the first antibody examination (June 1982), CT did not detect the hepatic or pelvic lesions, but 4 months later did show the liver metastases. MRI examination at the time of the fourth RAID procedure (9 months after the initial examination) did not show evidence of hepatic masses. In the five CT studies over a period of 18 months following the last positive antibody study the hepatic metastases were appreciably less well demarcated than previously, although surgery had revealed extensive replacement of liver parenchyma with metastatic tumor. The foci of sequestered radiolabeled antibodies varied somewhat in the four sequential studies during a period of 9 months (June 1982 to March 1983), while, the patient was undergoing intensive therapy. The changes in the location of the liver metastases were also reflected by the X-ray CT examinations. Eighteen months after the last antibody study, no evidence of hepatic metastases was detected by CT.

Fig. 1. When adenocarcinoma of the rectum was diagnosed in a 64-year-old man in June 1982, computed tomography and radionuclide liver study were negative, however, radiolabeled antibodies to CEA demonstrated several masses in liver (outlined). The CT was positive for mass lesions at the time of the second antibody study (Oct. 1982). In March 1983 CT and a fourth antibody study were positive for metastases, but magnetic resonance imaging was negative. After administration of ^{99m}Tc-macroaggregated albumin into the celiac artery (Nov. 1983), extensive masses were observed in the liver as was observed at surgery (see Table 3). Between June 1982 and March 1983 there was variability in the loci of the radioactively labeled antibody. Nine CT studies between June 1982 and November 1983 also demonstrated the same variability two of which were negative (Table 3). Apparently this changing phenomenon was related to the constant chemotherapy

Discussion

Since RAID, MRI, and CT procedures are available at our institution, the relative accuracy of these diagnostic technologies was compared in a series of 12 patients with

known or suspected malignant tumors in the liver. The antibody studies disclosed liver neoplasms in nine in which confirmation was obtained. In these cases with confirmed liver malignancies, the tumors were demonstrated by MRI in three and in another the diagnosis was diagnosis in one.

At the time of the initial antibody studies only three hepatic tumors had been diagnosed by CT, but later CT studies revealed liver masses in four other patients. It is possible that the CT studies may have demonstrated greater sensitivity if a bolus injection technique had been used. Thus, in these nine cases RAID showed a sensitivity of 100%, whereas that for MRI was 33% and for CT 22% (later 78%).

The successful detection by radiolabeled antibodies of carcinomas prior to subsequent confirmation by other diagnostic procedures has been documented (Goldenberg et al. 1978; Goldenberg and DeLand 1982; DeLand et al. 1982). In our experience RAID examinations have been requested when a rising plasma antigen titer associated with the particular carcinoma was present, yet other diagnostic evaluations did not indicate the location of the recurrent tumor. Previously we reported eleven cases of colorectal carcinoma, undetected by the usual methods of evaluation, but in which the tumor was defined by RAID and later confirmed by other means (Goldenberg et al. 1983). In one patient 40 weeks elapsed between the diagnosis by antibody imaging and subsequent confirmation by other studies. In these patients, elevated plasma CEA levels (9.0 ng/ml to 5,500 ng/ml) indicated recurrence of previously resected colorectal carcinoma, but other diagnostic procedures (radiographic, ultrasonic, and scintigraphic) failed to detect the site(s) of recurrence. The current method of selectively extracting the liver from the entire image and applying the subtraction technique to this region of interest only has improved the definition of abnormal foci of radioactivity to this organ and increased the confidence of interpretation. In a series of over 100 patients, false positive findings were less than 2% emphasizing the high specificity of immunodetection (Goldenberg et al. 1978).

Borokowski et al. reported a comparative study of imaging the liver by CT and by means of magnetic resonance using an instrument with a superconducting magnet (seven cases at 0.15T and ten cases at 0.30T) (Borokowski et al. 1983) by CT. All patients had SR and IR scans, and ten also had SE studies. In their series of 17 subjects, 10 were suspected of having metastatic liver disease – eight were detected by MRI (80%) and nine by CT (90%). In those patients with positive findings by MRI, all modalities (i.e., IR, SR, and SE) were positive. The authors observed that the most striking contrast was found with the IR technique and that the SR and CT images were quite similar. The reason for the lower detection rate of tumors in the same organ in our study is not known; however, Borokowski et al. (1983) used slightly longer repetition times, their patients had focal disease, and they did not prove conclusively that hepatic cancer was present in their subjects. As pointed out by Moss et al. (1984), studies obtained by the SE method with short repetition and echo intervals may result in primary and metastatic tumors appearing isodense with normal hepatic tissue. These authors found that some tumors were better demonstrated by IR and others by SE. This variation is probably due to tissue differences, but it underscores the fact that categories of pathologic processes do not necessarily correlate with fixed parameters for MR imaging. Moreover, it is important to note that Moss et al. (1984) using various MRI techniques, could not distinguish benign liver tumors from hepatocellular carcinoma.

With respect to CT, others have reported better results than we found in this series. For example, Knopf et al.,

using CT and a contrast agent, observed an overall accuracy of 94% for the detection of malignant lesions of the liver, either primary or metastatic (Knopf et al. 1982). In their study, all procedures were made with a current instrument (GE 8800), and were interpreted by one of their staff radiologists. In contrast, Grossman et al. (1977) concluded that CT was the least accurate imaging modality for detecting mass lesions of the liver. The instrument used by this group was not as sophisticated as that of Knopf et al. (1982), which may account for the difference. Also, in the study of Knopf and associates, the radiologists had knowledge of the clinical diagnoses at the time of their CT interpretations, which may influence the interpretation.

Of the 12 patients in our study, only five of the CT examinations were made at this institution, but the procedures on all patients were performed on state-of-the-art tomographic units. To ensure consistency in the interpretation, copies of all tomograms were obtained for review. Of the five patients whose CT studies revealed mass lesions of the liver at the time of the MRI examination, three were positive at the time of the first RAID study, one was positive at 2 months, and one at 5 months after the initial labeled antibody examination. Since the isodensity of tissues, which is a factor in CT lesion detection, does not enter into the RAID approach, it is reasonable to assume that the latter method should be more sensitive than CT.

This correlative examination of RAID, CT, and MRI procedures confirms our previous findings that radiolabeled antibodies to tumor-associated antigens have a high sensitivity for the detection of tumors. Greater accuracy with RAID should be forthcoming with improved antibody reagents, other radionuclide labels better suited for current instrumentation, and a more sensitive imaging method, such as the use of single-photon emission tomography. These advances are under development and will establish RAID as a reliable procedure for the detection of cancer, particularly for defining tumor sites (primary, metastatic, and recurrent), for tumor staging, and for resolving the difficult dilemma of identifying the unknown primary carcinoma (Goldenberg et al. 1983). The favorable results obtained with RAID support continued efforts towards achieving these goals.

References

1. Herberman RB, McIntire KR (1979) (eds) *Immunodiagnosis of cancer*, Vols 1 and 2. New York: Marcel Dekker, pp 1–1145
2. Goldenberg DM (1980) An introduction to the radioimmuno-detection of cancer. *Cancer Res* 40:2957–2959
3. Primus FJ, MacDonald R, Goldenberg DM, Hansen HJ (1977) Localization of GW-39 human tumors in hamsters by affinity-purified antibody to carcinoembryonic antigen. *Cancer Res* 37:1544–1549
4. Goldenberg DM, DeLand FH, Kim E, Bennett S, Primus FJ, van Nagell JR, Estes N, DeSimone P, Rayburn P (1978) Use of radiolabeled antibodies to carcinoembryonic antigen for the detection and localization of diverse cancers by external photocanning. *N Engl J Med* 298:1384–1388
5. Goldenberg DM, DeLand FH (1982) History and status of tumor imaging with radiolabeled antibodies. *J Biol Res Modif* 1:121–136
6. Primus FJ, Goldenberg DM (1980) Immunological considerations in the use of goat antibodies to carcinoembryonic antigen for the radioimmuno-detection of cancer. *Cancer Res* 40:2979–2983
7. Smith FW, Mallard JR, Reid A, Hutchinson JMS (1981) Nucle-

- ar magnetic resonance tomographic imaging in liver disease. *Lancet* 1:963-966
8. Doyle FH, Pennock M, Banks LM, McDonnell MJ, Bydder JM, Steiner RE, Young IR, Clark GJ, Pasmore T, Gilderday DJ (1982) Nuclear magnetic resonance imaging of the liver: initial experience. *Am J Radiol* 138:193-200
  9. Reynoso G, Keane M (1979) Carcinoembryonic antigen in prognosis and monitoring of patients with cancer. In *Immunodiagnosis of cancer, Part I*, Herberman RB, McIntire KR (eds). New York, Marcel Dekker, pp 239-254
  10. Zimmerman JH (1979) Evaluation of the function and integrity of the liver. In *Clinical diagnosis and management*. In: Henry JB (ed). Philadelphia, W.B. Saunders, pp 330-332
  11. Shochat D, Archey RL, Pant KD, Dahlman HL, Gold DV, Goldenberg DM (1981) Characterization of colon-specific antigen-p (CSAp) and isolation of immunologically active tryptic peptides. *J Immunol* 126:2284-2289
  12. Primus FJ, Newell KD, Blue A, Goldenberg DM (1983a) Immunological heterogeneity of carcinoembryonic antigen: 2. Antigenic determinants on carcinoembryonic antigen distinguished by monoclonal antibodies. *Cancer Res* 43:686-692
  13. Primus FJ, Freeman JW, Goldenberg DM (1983b) Immunological heterogeneity of carcinoembryonic antigen: 1. Purification from meconium of an antigen related to carcinoembryonic antigen. *Cancer Res* 43:679-685
  14. Greenwood FG, Hunter WM, Glover JS (1963) The preparation of ^{131}I -labeled human growth hormone of high specific radioactivity. *Biochem J* 89:114-123
  15. DeLand FH, Kim EE, Simmons G, Goldenberg DM (1980) Imaging approach in radioimmunodetection. *Cancer Res* 40:3046-3049
  16. DeLand FH, Kim EE, Casper S, Primis FJ, Dine ME, Goldenberg DM (1982) In vivo radioimmunodetection of occult recurrent colonic carcinoma. *Am J Roentgenol* 138:145-148
  17. Goldenberg DM, Kim EE, Bennett SJ, Nelson MO, DeLand FH (1983) Carcinoembryonic antigen radioimmunodetection in the evaluation of colorectal cancer and in the detection of occult neoplasms. *Gastroenterol* 84:524-532
  18. Borokowski GP, Buonocore E, George CR, Go RT, O'Donovan PB, Meaney TF (1983) Nuclear magnet resonance (NMR) imaging in the evaluation of the liver: A preliminary experience. *J Comput Assist Tomogr* 1:963-966
  19. Moss AA, Goldberg HI, Stark DB, Davis PL, Margulis AR, Kaufman L, Crooks LE (1984) Hepatic tumors: Magnetic resonance and CT appearance. *Radiology* 150:141-147
  20. Knopf DR, Torres WE, Fajman WJ, Sones PJ Jr (1982) Liver lesions: Comparative accuracy of scintigraphy and computed tomography. *Am J Radiol* 138:623-627
  21. Grossman ZD, Wistow BW, Bryan PJ, Dinn WM, McAfee JG, Kieffer SA (1977) Radionuclide imaging, computed tomography, and gray-scale ultrasonography of the liver: A comparative study. *J Nucl Med* 18:327-332

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