Lesion-by-Lesion Comparison of Computerized Tomography and Indium-111-Labeled Monoclonal Antibody C110 Radioimmunoscintigraphy in Colorectal Carcinoma: A Multicenter Trial

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C110 is an anti-carcinoembryonic antigen murine IgG1 monoclonal antibody. Indium-111-labeled C110 radioimmunoscintigraphy (RIS) in colorectal cancer was studied in 51 presurgical patients at four institutions. Planar and SPECT images were obtained at least twice between 48 and 96 hr after injection of 5 mCi/5 mg of ^{111}In-C110. Fifty-one patients had 87 biopsy-proven lesions at surgery (57 hepatic, 30 extra-hepatic). Thirty-three patients (64.7%) had positive radionuclide scans, while 32 (62.8%) had positive CT scans (p = NS). While CT was better at overall lesion detection (62.1% versus 56%, $p < 0.05$), radionuclide scans were better than CT for extra-hepatic disease (60% versus 46.7%, $p < 0.01$). Hepatic metastases (52.6%) were visualized by Mab scans to selectively concentrate radioactivity. Uptake in draining lymph nodes was a significant limitation, making evaluation of these sites difficult. Indium-111-C110 shows selective uptake in metastatic colorectal cancer, including more than half of all hepatic lesions evaluated.

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Cancer of the large bowel ranks as one of the most common adult malignancies in the United States; there were an estimated 157,500 new cases diagnosed in 1991 (*1*). Numerous reports (*2–8*) have established the utility of radioimmunoscintigraphy (RIS) in detecting metastatic colorectal carcinoma, including so-called occult disease, i.e., disease not identified by conventional imaging modalities including computed tomography (CT). Radioiodine (^{131}I) and indium-111 (^{111}In) labeled to murine monoclonal antibodies (Mabs) have been the radionuclides most often utilized; most clinical trials have studied antibodies directed against carcinoembryonic antigen (CEA).

Indium-111 is a preferable nuclide for use in immunoscintigraphy with intact immunoglobulins due to its photon emission and half-life. However, a major drawback of ^{111}In-labeled antibodies in detecting metastatic colorectal carcinoma is the considerable nonspecific accumulation in the liver, precluding specific identification of hepatic lesions, which are the most common metastatic lesions in colon cancer. A recent study (*9*) underscored the poor detectability of RIS for hepatic metastases. There is therefore a clear need for an ^{111}In-labeled Mab that is capable of selectively localizing in hepatic metastases, in addition to lesions elsewhere in the body.

A murine IgG_1 monoclonal antibody that has a high affinity for CEA and can be chelated without significant loss of immunologic activity is C110 (*10*). An initial study by Griffin et al. (*11*) revealed that ^{111}In-C110 was capable of selectively localizing in hepatic metastases, being visualized as areas of increased radioactivity within the liver. We found similar results in patients with hepatic metastases from colorectal cancer (*12*).

A multicenter trial was carried out at four participating institutions* using a fixed dose (5 mg) of ^{111}In-C110 in patients with metastatic colorectal carcinoma. An important feature of trial design was that every patient had surgical exploration and tissue biopsy to confirm possible lesions within a week of antibody infusion. This made comparison much more meaningful. Lesion by lesion correlation with CT and surgery was carried out, and estimates of tumor uptake of radiolabeled antibody were made. The results of this study are presented.

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*Centers participating in the study were University of Massachusetts Medical Center, Worcester, MA; Michael Reese Medical Center, Chicago, IL; City of Hope Medical Center, Duarte, CA; and Memorial Sloan-Kettering Cancer Center, New York, NY.

TABLE 1
Regional Disease Distribution of Biopsy-Proven Patients

No. of patients (%)	
Total	51
Hepatic metastases	30 (58.8%)
Extra-hepatic disease	28 (54.9%)
Hepatic and extra-hepatic disease	7 (13.7%)
Radionuclide scan positive	33 (64.7%)
CT scan positive	32 (62.8%)
No. of lesions	
Biopsy-proven lesions	87
Concordance (both scan and CT positive)	35 (40.2%)
CT positive, scan negative	19 (21.8%)
CT negative, scan positive	14 (16.1%)
CT negative, scan negative	19 (21.8%)

MATERIALS AND METHODS

Patients

A total of 57 patients (age 29–75 yr, serum CEA 5.5–265 ng/ml) with previously treated colorectal carcinoma and a rising serum CEA level with or without known metastatic disease who were candidates for exploratory laparotomy were studied at the four participating centers. Requirements included a negative human anti-mouse antibody serum titer, no evidence of antibody cross-reactivity with the patient's granulocytes, a serum CEA between 5 and 500 ng/ml, and adequate renal, hepatic and hematopoietic function. Informed consent was obtained from all patients for the radioimmunolocalization study, the latter having been approved by the Institution Review Boards at the participating centers. All patients underwent standard imaging modalities including abdominal CT scans. Standard noncontrast and contrast CT scans were carried out in all patients; radiologist interpretation of the CT scans was not blinded in any way. The studies were reviewed at the individual centers prior to surgery. Three patients had extra-abdominal disease and did not undergo surgery; three had no evidence of disease at surgery (and negative standard workup and RIS). Fifty-one patients underwent biopsy of suspected lesion(s). These patients will be considered in this report.

The 51 biopsy-proven patients had a total of 57 hepatic and 30 extra-hepatic metastases from colorectal carcinoma proven by biopsy. Table 1 lists the overall lesion location and other disease distribution in these patients.

Indium-111-Labeled C110

Sterile conjugated Mab C110 (5 mg) was supplied by Abbott Laboratories (Abbott Park, IL) in a single-dose vial and stored at 4°C until use. Indium-111 (5 mCi) was shipped from Nordion Inc. (Toronto, Canada) to be available for radiolabeling on the day of patient administration. The ^{111}In was incubated with the conjugated antibody at room temperature for 30 min, and then tested for incorporation by thin-layer chromatography prior to injection. Aliquots of the final preparation were kept for use as standards and for determination of radioimmunoreactivity using CEA beads (Abbott Laboratories, Abbott Park, IL). The amount of radioactivity in the standards and in the injection syringe was assayed in a dose calibrator at the same time.

Administration of Radiolabeled C110

Patients received ^{111}In-C110 at least 72 hr prior to surgery. The radiolabeled Mab C110 was diluted in 30 ml normal saline (Abbott Laboratories, Abbott Park, IL) and administered as an intravenous infusion over 5 min. Patients were monitored for vital signs for at least 4 hr after completion of antibody infusion.

Pharmacokinetics and Radioimmunoscintigraphy

Blood was obtained for determination of radiolabeled Mab clearance immediately following antibody infusion and after 15, 30, 60, 120 and 240 min.

At two time points between 48 and 96 hr, anterior and posterior whole-body images were obtained. Additional anterior and posterior spot images of the thorax, abdomen, and pelvis were obtained, as was at least one single-photon computed tomograph (SPECT) of the abdomen. SPECT images were studied in the transverse, coronal and sagittal planes. At each imaging time point, blood was drawn for estimation of radioactivity.

In Vitro Studies

Samples of whole blood (0.5 ml each) were counted in a gamma counter along with appropriate dilutions of the standards and biopsy specimens where available. All blood, tissue and standard counts were obtained at the same time. Biopsy specimens were sectioned and histopathologically examined.

RESULTS

Fifty-one patients with known colorectal carcinoma and a rising serum CEA level with or without evidence of metastatic disease were studied. The labeling method was simple and efficient. The procedure reproducibly resulted in ≥90% incorporation of ^{111}In to antibody as determined by thin-layer chromatography using a solution of DTPA. Immunoreactivity of the radiolabeled C110 with CEA beads was ≥95%. None of the patients had any side effects during or after antibody infusion.

In a few patients, whole-body imaging was carried out on the day of infusion and showed blood pool images. This corresponded with pharmacokinetic analysis which demonstrated initial radioactivity confined to the vascular compartment, with a mean initial volume of distribution of 2.8 liters.

All radioimmunoscintigraphic scans (Mab scans) were brought as x-ray film copies to Memorial Sloan-Kettering Cancer Center and interpreted by the primary author as well as independently by two of the other authors (S.M.L., A.M.S.). Clinical information was provided to the observers, who were blinded only with respect to results of other imaging modalities. There was no significant interobserver difference in interpretation. Radionuclide scans were interpreted as positive if there were focal and persistent areas of *increased* tracer concentration in the liver. Extrahepatic areas of increased radiotracer concentration were interpreted as positive only if the uptake was very intense and persistent, or if (nondraining) mesenteric, mediastinal or supraclavicular nodes were involved. Figure 1 shows draining internal mammary nodal visualization in a patient with hepatic metastases. Similarly, bowel uptake was interpreted positive only if it was persistent in an area on consecutive images. In patients in whom hepatic metastatic disease was visualized, areas of increased tracer concentration were noted in the liver by 48 hr; relative uptake of radioactivity in these lesions increased over time.

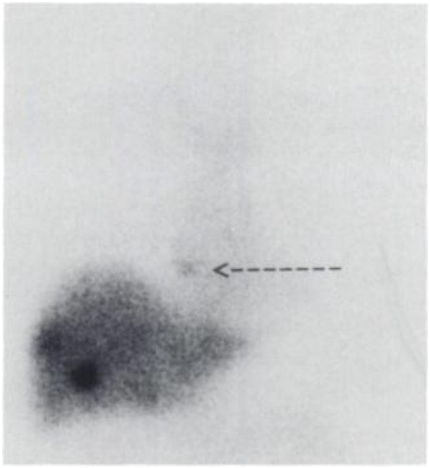

FIGURE 1. A 46-yr-old male (Patient 4/2) with prior right hepatic lobectomy for metastatic colon carcinoma presented with a rising serum CEA and a normal CT scan. Anterior thorax and upper abdomen planar image at 48 hr shows two hepatic lesions and internal mammary nodal uptake, considered normal nodal uptake. A chest CT showed no abnormality in the area.

SPECT delineated lesion extent better than the planar images by improving lesion-to-background ratios. However, only four of 30 hepatic lesions were detected only by SPECT, while all but one extrahepatic lesions seen on SPECT were seen, albeit occasionally more equivocally, on planar images. Larger hepatic lesions usually showed a "doughnut" pattern with a central photopenic area representing necrosis. If there was no peripheral rim of increased tracer uptake, the study was interpreted as negative.

Most patients showed a monoexponential clearance of blood radioactivity. The mean blood $T_{1/2}$ was 31.7 hr (range 8.7–66 hr). There was no statistically significant correlation between blood $T_{1/2}$ and disease extent; patients with more disease tended to have more rapid clearance. Table 2 shows the mean percent injected dose per gram (%ID/g) of tumor, blood and liver for a subset of 28 patients who had tissue counts available, arranged according to day of surgery. The mean tumor-to-nontumor ratios are also listed, as is the blood $T_{1/2}$ and Mab scan results for these lesions. The tumor-to-nontumor ratios were higher in those patients in whom lesions were identified preoperatively than in those whose images were negative. SPECT improved delineation of lesions especially in the liver.

Three patients had thoracic disease (two with lung lesions and one with mediastinal adenopathy) initially detected by RIS and confirmed by repeat CT scan. Fifty-four patients had exploratory laparotomy at up to a week after infusion of ^{111}In-C110. In three patients with negative RIS and equivocal CT scans, there was no evidence of disease at laparotomy. In general, tissue was sampled for biopsy if the imaging study or studies were positive, with the exception of macroscopically normal lymph nodes. Figure 2 graphically depicts mean tumor, blood and liver %ID/g at the day of surgery, obtained by calculations from gamma well counting. At all doses, tumor-to-blood ratios were considerable. Ratios in patients in whom scans were positive ranged from 1.1 to 67.5 (at various days of surgery). In a patient who had a positive scan with a tumor-to-nontumor ratio of less than 1, tumor tissue obtained was largely necrotic and the low ratio is considered a result of poor sampling.

Figures 3 and 4 detail the results of the RIS study in two patients. Two other patients are described here. Patient 4/17 had an 0.6-cm diameter hepatic lesion. Retrospective review of the SPECT and planar images failed to review

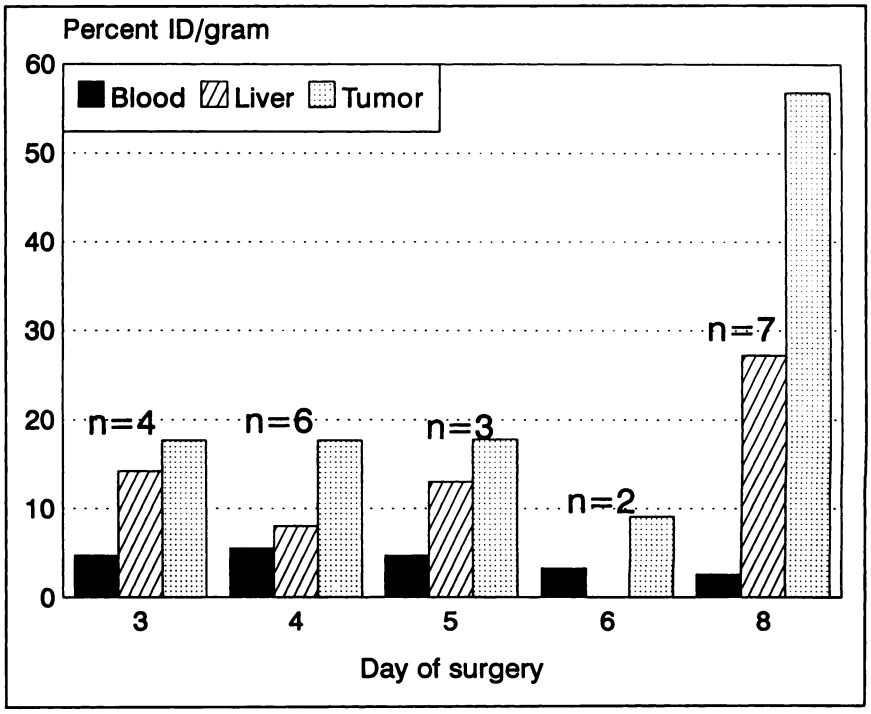

FIGURE 2. Graph showing mean percent injected dose per gram of tumor, normal liver and blood in patients who had surgery. The day of surgery and the number of patients studied at each time point are shown.

TABLE 2
Surgical Findings and Tumor Uptake

Patient no.	Blood half-life	Surgery day	Scan (±)	Percent ID/g × 10^3 (Mean)			Location	Tumor-to-nontumor
				Blood	Liver	Tumor		
4/8	19.3	3	+	9	18	36	Liver	3
4/10	26.3	3	+	0.4	0.3	0.2	Liver	0.6
2/10	64.2	3	+	—	—	17.1	Nodes	—
2/14	30.3	3	+	—	—	17.5	Colon	—
4/1	45.9	4	−	15	—	5	Nodes	0.3
4/3	21.1	4	+ (Liver)	1	—	1.1	Omentum	1.1
4/4	22.4	4	+	7	12	35	Liver	4
4/5	27.9	4	+	5	—	27	Liver	5.4
4/9	40.3	4	+	3	9	35	Liver	5.8
4/22	26.6	4	+	2	3.1	2.8	Liver	1.1
4/7	39.2	5	+	6	10	30	Liver	3.75
4/18	34.9	5	−	8	16	9.8	Liver	0.8
4/21	16.8	5	+	0.2	—	13.5	Liver	67.5
4/13	32.2	6	−	1.6	—	2.2	Presacrum	1.4
4/14	38.5	6	+	5	—	16	Rib	3.2
4/2	NA	8	+	0.2	—	2.9	Liver	15
4/15	27	8	+	1.8	36	180	Liver	9.1
4/17	51.3	8	−*	7.5	18.8	75	Liver	5.8
4/24	34.8	8	+	0.8	28	91.5	Liver	6.4
2/6	66	8	+	—	—	13.1	Colon	—
2/11	13.6	8	+	—	—	3.9	Presacrum	—
2/13	14.4	8	+	—	25.9	31.1	Liver	1.2
2/16	32.7	8	+	—	—	3	Colon	—
4/12	33.5	11	−	0.4	—	3.6	Omentum	9
2/8	26.2	—	+	—	—	3.2	Liver	—
5/1	8.7	—	+	—	—	0.6	Liver	—
5/2	37.5	—	+	—	—	3	Omentum	6†
5/6	23.3	—	+	—	—	3.4	Omentum	1.5†

*Liver lesion (0.6 cm) not seen on scan. See text for details.
†Ratios to tissue other than blood or liver.
$T_{1/2}$ = half-life.

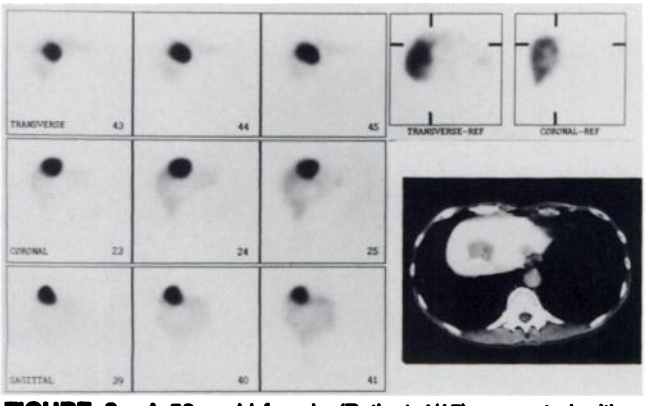

FIGURE 3. A 56-yr-old female (Patient 4/15) presented with a rising serum CEA. On CT (lower right), two lesions were seen in the superior right lobe and the caudate lobe of the liver. Only the superior right lobe liver lesion concentrated radioactivity selectively. The relevant CT slice is in the lower right. The caudate lobe liver lesion seen on CT was seen to be a hepatic cyst on intraoperative ultrasound and palpation. Representative 48-hr SPECT images (transverse, upper panel; coronal, middle panel; sagittal, lower panel) are shown. Reference planes are on the upper right.

the lesion which was found to have 0.075% %ID/g with a tumor-to-nontumor ratio of 5.8 at biopsy a week later. CT scans were also negative in this patient with a rising serum CEA and negative standard imaging workup. Patient 2/13 had a solitary right lobe lesion, measuring 3 cm in diameter. While the tumor uptake was high (0.031 %ID/g) at surgery a week later, tumor-to-nontumor and tumor-to-liver ratios were both less than 2. This patient's lesion was detected only on SPECT images, as were those of Patients 4/22 and 5/6 (the latter having an omental lesion).

Table 3 lists the numbers of biopsy-proven hepatic and extra-hepatic lesions that were detected by CT and Mab scan. While the number of hepatic lesions detected by CT was greater than that detected by Mab scan, the difference was not statistically significant (p = NS). The sensitivity of Mab scans for extra-hepatic disease was better than that of CT ($p < 0.01$). The total number of lesions detected by CT was greater than that detected by RIS ($p < 0.05$). However, the number of patients in whom disease was detected was comparable for both imaging modalities (p = NS).

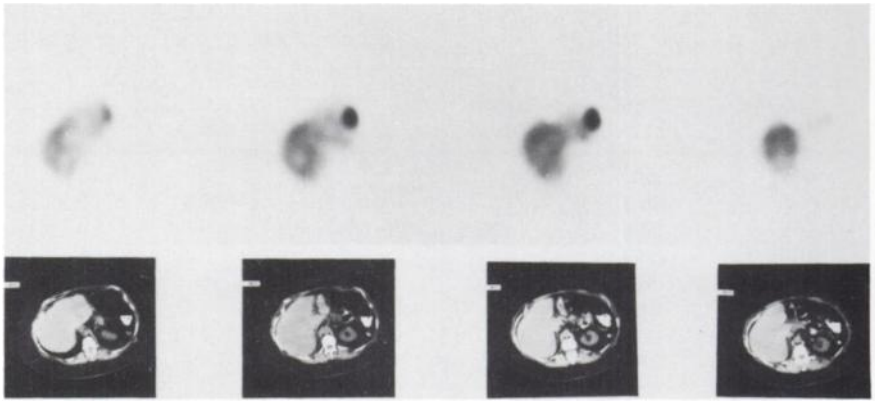

FIGURE 4. A 44-yr-old female (Patient 4/21) had a normal CT study and steadily rising serum CEA. The patient had a left hepatic lobectomy a year prior to this study. This patient was seen to have a 3-cm left lobe liver lesion at surgery. Representative transverse 72-hr SPECT (upper row) and CT slices (lower row) of the liver are shown.

DISCUSSION

Surgical exploration with biopsy is the only gold standard for diagnostic studies in cancer detection. Although a large number of clinical trials of radioimmunodetection with anti-CEA antibodies have been reported over the years, none with more than 50 patients have been surgically controlled. The reported high sensitivity and specificity of the nonsurgical studies is probably not accurate because false-negatives and false-positives will tend to be misclassified in a way that favors the noninvasive testing strategy.

In this study, 51 patients with biopsy-proven metastatic colorectal cancer were studied in a multicenter trial utilizing ^{111}In-C110, a murine IgG_1 Mab against CEA. Foci of increased activity were considered abnormal only if they were within the liver, or if they were detected in the abdomen in nodal areas that were "nondraining." There were 87 lesions detected in these patients, of which 78% (68 of 87) were identified by either CT or RIS. Of 57 hepatic lesions 48 (84%) were detected by either CT or RIS, while 30 (52%) were detected by RIS. CT was better than RIS at detection of abdominal (hepatic and extra-hepatic) disease ($p < 0.05$) while RIS was better ($p < 0.01$) than CT in the identification of extra-hepatic abdominal metastases, with a sensitivity of 60% (compared to 46.7% for CT).

The patients in Figures 3 and 4 serve to show that radioimmunoscintigraphy was useful in detecting disease in this group of patients. The patients detailed in the Results section serve to illustrate that both the size of the lesion and the tumor-to-surrounding tissue uptake ratio are important determinants of lesion detection. While no conclusions about specificity can be made from this limited series of patients, antibody uptake did appear to be specific especially for extra-nodal sites of disease. There was no correlation between serum CEA levels and detection rates.

TABLE 3
Lesion-by-Lesion Comparison of Computed Tomography and Radioimmunoscintigraphy in the Detection of Hepatic and Extra-Hepatic Abdominal Disease in 51 Patients with a Total of 87 Lesions

	CT scan	RIS study +	RIS study −	Total
Hepatic disease	+	22	18	40
	−	8	9	17
Total		30	27	57
Extrahepatic disease	+	13	1	14
	−	6	10	16
Total		19	11	30

NS = not significant. p = NS for hepatic lesions; $p < 0.01$ for extrahepatic disease.

Corbisiero et al. (*9*) studied 45 patients with colon cancer with ^{111}In-ZCE025, an anti-CEA Mab. In this study, the group studied individual lesion characteristics. Lesions were identified on the immunoscintigraphy studies only if there was persistent *increased* radioactive uptake. Of 121 biopsy-proven lesions, 40.5% were positive by immunoscintigraphy and 61.2% positive by CT. RIS was more useful in the detection of extra-hepatic disease, while CT was more suited for hepatic lesion detection. They found RIS disappointing in the evaluation of nodal disease and attributed it to the filtering effect of antigen-processing cells in nodes.

The detection of extra-hepatic abdominal disease (60%) was higher in our study than that reported (41.7%) by Corbisiero et al. with similar numbers of lesions (30 compared with 36). Our sensitivity for detection of hepatic disease (52%), however, is considerably higher than that (17.7%) reported by them, again with comparable numbers of lesions (57 versus 62).

As with Corbisiero et al., nodal uptake of radioactivity was a major limitation. We did note biopsy nodes that showed increased uptake on the scan but looked normal at surgery. The incidence of uptake in nonmetastatic nodes has been variously reported, and firm data using surgical confirmation is scarce. However, uptake in nonmalignant, CEA-containing nodes may well be a saturable compartment, and higher milligram doses of antibody may certainly result in more specific uptake in diseased nodes.

Corbisiero et al. used a higher dose of antibody than we did (40 mg versus 5 mg). While the initial work by Griffin et al. (*10*) did not show any improvement in tumor uptake with increasing antibody dose, we feel the question of saturability of binding sites in draining lymph nodes has not been adequately addressed with Mab C110. Accordingly,

we intend to study higher doses of Mab C110 in pre-surgical patients with metastatic colon cancer to determine whether false-positive nodal visualization will diminish with higher doses of ^{111}In-C110.

Earlier work by Patt et al. (*5*) with ^{111}In-ZCE025 demonstrated the effect of increasing antibody dose (2.5 mg to 80 mg) upon tumor visualization. They reported that with ^{111}In-ZCE025, the optimum dose was 40 mg. Their reported sensitivity at this dose was 77%; there was, however, no biopsy confirmation. Moreover, at all other doses (2.5, 5, 20 and 80 mg), the reported sensitivity was not more than 22%. At a 40-mg antibody dose, all 10 liver lesions were seen to concentrate radioactivity selectively. In contrast, we saw selective uptake in more than half of biopsy-proven hepatic lesions at a dose of 5 mg. While overall detection rate in our study was less than that reported by Patt et al., they did not have surgical confirmation of all lesions.

Abdel-Nabi et al. (*13*) studied B72.3, another ^{111}In-labeled Mab. They also did not find a relationship between doses ≥1 mg and tumor detection. RIS detected disease in 75% of patients. Only 2 of 18 biopsy-proven hepatic lesions were seen as "hot", i.e., selectively concentrated radioactivity. Four other lesions were seen as "cold". One out of nine lymph node metastases and 18 of 27 primary tumors were visualized to give total lesion detection rates of 52.8% for extra-hepatic abdominal disease. While our sensitivity for extra-hepatic abdominal disease is similar to that reported by Abdel-Nabi et al., ^{111}In-C110 appears to be far more sensitive for detection of hepatic disease.

We also quantified tumor uptake of ^{111}In-C110 in a subset of patients. By 72 hr after antibody infusion, mean tumor uptake was 0.017 %ID/g of tumor (Fig. 1). This stayed relatively stable through a week after infusion, and was as high as 0.18 %ID/g tumor in one patient a week after antibody infusion. While data regarding quantitative tumor uptake of ^{111}In-labeled Mab is sparse, we believe these numbers represent among the highest uptake of any antibody by metastatic colorectal cancer. This encourages us to believe that this antibody, labeled perhaps with yttrium-90 (^{90}Y), has potential utility in the treatment of metastatic colorectal cancer.

The relative virtues of ^{131}I and ^{111}In in the detection of solid tumors have been debated (*14*). However, ^{111}In does have better imaging and radiation dose characteristics. In this regard, some studies with ^{131}I-labeled Mabs are worthy of mention. Welt et al. (*8*), using ^{131}I-A33, carried out biopsy confirmation of abnormalities in 20 patients with metastatic colorectal cancer. Tumor uptake of radiolabel is comparable in both studies, although the tumor-to-liver ratios were far lower with ^{111}In-C110, perhaps due to the relatively greater retention of ^{111}In in liver.

Bischof-Delaloye et al. (*7*) imaged 57 patients with ^{123}I-labeled anti-CEA Mab fragments (Fab or F(ab')$_2$). Their study assessed regions of abnormal uptake and compared their findings with those on CT or MRI followed in some patients by biopsy. RIS had a very high sensitivity for regional disease detection (between 71% and 93%, depending upon the type of patient studied). Iodine-123 may be a preferable label for Mab fragments due to its optimum gamma emission characteristics and short half-life. However, a problem with detection rates based on regions is that in some cases, the number of lesions detected in a given region (e.g., in the liver or pelvis) may be less than those present, but the study will not reflect the less-than-optimum sensitivity.

CONCLUSION

We have found that RIS with ^{111}In-C110 is complementary to existing standard imaging modalities such as CT for the detection of metastatic colorectal carcinoma. RIS is better than CT in the detection of extra-hepatic abdominal metastases. Indium-111-C110 is the first antibody to show consistent selective localization in hepatic metastatic disease. Further studies to address relevant issues and improve detection of metastatic colorectal carcinoma with ^{111}In-C110 are underway.

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