Differences in Biodistribution of Indium-111- and Iodine-131-Labeled B72.3 Monoclonal Antibodies in Patients with Colorectal Cancer

Kunihiko Yokoyama, Jorge A. Carrasquillo, Alfred E. Chang, David Colcher, Mario Roselli, Paul Sugarbaker, William Sindelar, James C. Reynolds, Patricia Perentesis, Otto A. Gansow, Barbara Francis, Richard Adams, Ronald Finn, Jeffrey Schlom, and Steven M. Larson

Department of Nuclear Medicine, Warren G. Magnuson Clinical Center; NCI-Surgery Branch; Laboratory of Tumor Immunology and Biology; Radiation Therapy Branch, NCI National Institutes of Health, Bethesda Maryland; Department of Nuclear Medicine, Kanazawa University, Kanazawa 920, Japan

We have compared the biodistributions of [^{131}I]B72.3 and ^{111}In-SCN-Bz-DTPA B72.3 monoclonal antibody (MoAb) in patients with metastatic colon cancers. B72.3 is an IgG_1 that recognizes a mucin-like colon cancer associated antigen. Eight patients were infused with 3–5 mCi and 0.36–20 mg of ^{111}In-labeled B72.3 prepared with a bifunctional chelate, isothiocyanatobenzyl-DTPA (SCN-Bz-DTPA). The biodistribution was compared with that of 13 patients previously studied as part of a separate trial, with 1–10 mCi and 0.16–1.35 mg of [^{131}I]B72.3. The Beta $T_{½}$ in serum was 63 ± 5 hr for ^{111}In-SCN-Bz-DTPA B72.3 and 52 ± 10 hr for [^{131}I]B72.3. Whole-body retention of the ^{111}In ($T_{½}$ = 11.8 days) was significantly longer than for [^{131}I] B72.3 ($T_{½}$ = 3.3 days), $p < 0.000001$. The ^{131}I was excreted primarily through the urine. Urinary excretion of ^{111}In was low and gamma camera images confirmed that some ^{111}In was excreted in the bowel. Tumor localization was seen in one of seven evaluable patients receiving ^{111}In-SCN-Bz-DTPA B72.3. Gamma camera images showed that the liver concentrates ^{111}In but not ^{131}I. We conclude that ^{111}In-SCN-Bz-DTPA B72.3 is metabolized in a different manner from the iodinated B72.3. The high concentration and prolonged retention of ^{111}In by the liver interferes with tumor imaging of metastases.

J Nucl Med 30:320–327, 1989

There has been a great interest in the use of radiolabeled antibodies for tumor imaging (*1–22*). Most of this work has focused on the uses of iodinated antibodies (*1–6,9,12,15,19–21*) that have resulted in variable degrees of success for tumor detection. The use of iodine-131 (^{131}I) for labeling antibodies is not ideal (*23*). Alternate methods for labeling monoclonal antibodies (MoAb) using bifunctional chelates that can then be labeled with indium-111 (^{111}In) have been developed (*24–26*) and tested in animal models (*26,27*). The advantages of ^{111}In-labeled antibodies include: (a) more favorable energy for imaging; (b) a 2.8 day half-life; (c) suitability for kit formulation; and (d) the stability of radiolabeled antibodies over their iodinated counterpart (*23*).

Several clinical trials with ^{111}In-labeled MoAb have shown encouraging imaging results (*13,17*). A drawback to these clinical trials utilizing ^{111}In was the large amount of ^{111}In concentrating in the liver that interfered with detection of liver metastases. Although the mechanisms that result in concentration of ^{111}In in the liver are not completely known, the expectations were that by utilizing a stronger chelate, release of ^{111}In from the chelate with translocation into transferrin and concentration in the liver could be avoided.

We have previously reported detection of metastatic colon cancer lesions in 42.7% to 51.9% of patients, using intravenous injection of [^{131}I]B72.3 (*9,10*). Correlation with surgical findings documented the specificity of tumor uptake (*9,11*). B72.3 has been labeled with ^{111}In using the bifunctional chelate, 1(p-isothiocyana-

Received Apr. 27, 1988; revision accepted Oct. 11, 1988.

For reprints contact: Jorge A. Carrasquillo, MD, Dept. of Nuclear Medicine, National Institutes of Health, Bldg. 10/Rm 1C401 20892.

tobenzyl) diethylenetriaminepentaacetic acid (SCN-Bz-DTPA), which form a more thermodynamically stable complex with ^{111}In than the mixed or cyclic anhydride of diethylenetriaminepentaacetic acid (DTPA) (*26*). Animal studies with ^{111}In-SCN-Bz-DTPA B72.3 resulted in less liver uptake than other routinely used bifunctional chelate methods (*26*).

In this report, we present imaging and biodistribution data obtained from eight patients who received ^{111}In-SCN-Bz-DTPA B72.3 and compare these results to data from 13 patients previously studied (*9–11*) with ^{131}I-labeled B72.3 IgG.

MATERIALS AND METHODS

Monoclonal Antibodies

B72.3, is a IgG_1 murine monoclonal antibody, that recognizes a high molecular weight (>10^6 D) colon cancer associated antigen (TAG-72) expressed in ~85% of colorectal carcinomas but in virtually no normal adult tissues (*29*). The generation (*28*), production, and purification has been previously published (*30*).

Radiolabeling

The iodogen method (*31*) was used to label B72.3 with ^{131}I at specific activity of 2.2 to 13.1 mCi/mg and four preparations were labeled with iodine-125 (^{125}I) at specific activities of 2.4 to 4.0 mCi/mg using a similar method. The bifunctional chelate, SCN-Bz-DTPA was conjugated to B72.3 MoAb IgG at a ratio of 3:1. One milligram of conjugated coupled antibody was allowed to react with 13 to 56 mCi of ^{111}In for 60 min. Excess DTPA was then added to complex unreacted ionic ^{111}In, and the protein bound fraction were separated by size exclusion high performance liquid chromatography (HPLC) (TSK3000). The specific activities of the final radiopharmaceutical ranged from 0.25 to 13.9 mCi/mg. All products passed sterility and pyrogen testing. A mean of 95% of the ^{111}In in the final product was bound to the antibody as determined by instant thin layer chromatography using plastic-backed silica gel plates (10% ammonium formate/methanol/citric acid 0.2*M*).

Immunoreactivity

The immunoreactivity of each radiolabeled antibody preparation was tested in a solid phase radioimmunoassay (RIA). The solid phase RIA showed that both the iodinated and ^{111}In-labeled B72.3 IgG retained their immunoreactivity (*28*). In addition, [^{131}I] B72.3 and ^{111}In-SCN-Bz DTPA B72.3 have been tested in competitive radioimmunoassay and have shown competition that is indistinguishable from unlabeled antibody (unpublished data).

Patients

These studies were performed under a protocol approved by the Human Research Committee of the National Cancer Institute. Each patient gave informed consent. Thirteen patients with metastatic disease from a previously resected primary colorectal carcinoma were studied with [^{131}I]B72.3 and eight were studied with ^{111}In-SCN-Bz-DTPA B72.3 (Table 1). The mean age for patients studied with [^{131}I]B72.3 was 55 yr old and for those studied with ^{111}In-SCN-Bz-DTPA B72.3 was 59 yr. The patients staging studies included computed tomography of the chest, abdomen and pelvis, liver and spleen scan, bone scan and chest x-ray. All but two patients underwent exploratory laparotomy for clinical indications.

Immunohistology with B72.3 was performed in tumors from 17 of the 21 patients. All 17 expressed the TAG-72 antigen.

The patients studied with ^{111}In-SCN-Bz-DTPA B72.3 were participating in a protocol that selected patients with radiographic evidence of metastatic disease limited to the liver. The patients receiving [^{131}I]B72.3 included a broad population with either liver metastases or other sites of intraperitoneal involvement. We have previously reported scan and clearance data on the 13 patients receiving [^{131}I]B72.3 as part of a larger dose esclation trial (*9–11*).

Eight patients received ^{111}In-SCN-Bz-DTPA B72.3 (3–5 mCi/0.36-0.78 mg). To determine whether the mass of MoAb had an effect on clearance or biodistribution three patients received coinfusion of unmodified B72.3 for a total of 20 mg. The pharmacokinetics of ^{111}In-SCN-Bz-DTPA B72.3 were compared with that of 13 other patients who received [^{131}I] B72.3 (1–10 mCi/0.16–1.35 mg). In four of the patients receiving ^{111}In-SCN-Bz-DTPA B72.3 a direct comparison was made to iodinated B72.3 by coinfusing them with [^{125}I]B72.3. All antibodies were infused intravenously over 1 hr. The thyroid of patients receiving [^{131}I]- or [^{125}I]B72.3 was blocked (*10*).

Biodistribution

Following MoAb administration, blood samples were collected at 5, 30, 60, 120, and 240 min daily for 3 days and occasionally at later times until the patients underwent surgery. Urine was collected daily for 3 days postinfusion. For the clearance studies, aliquots of the plasma and urine were counted in a well-type gamma counter along with an aliquot of the injected standard. The dose retained in serum was calculated from the concentration of radioactivity (% dose/ml) multiplied by the patients' estimated plasma volume (*32*). Whole-body clearance was assessed daily using a NaI crystal probe detector (*10*).

Patient Imaging

Serial scintiphotos were acquired with a 530-mm large field-of-view gamma camera (General Electric 535, General Electric, Milwaukee, WI) within 2 hr of MoAb administration, and then daily up to the time of surgery. The ^{111}In-SCN-Bz-DTPA B72.3 images were obtained with a medium-energy collimator using a 20% window centered over the 173-keV and 247-keV photopeaks. The [^{131}I]B72.3 images were obtained with a high-energy collimator using a 20% window over the 364-keV photopeak. Anterior and posterior whole-body images as well as multiple spot views (5 to 10 min each) were obtained. In addition to analog images, digital images were also recorded with an on-line computer (Hewlett Packard Scintigraphic Data Analyzer or Elscint). Typical spot views for the ^{111}In images had 300,000 to 1 million counts while those for ^{131}I had 100,000 to 500,000 counts. No image subtraction technique was utilized. Serial images were analyzed by manually drawing regions of interest (ROIs) over the anterior and posterior heart, liver, spleen, kidney, bone marrow, and tumor. The geometric mean was obtained after

TABLE 1
Summary of the Patients Receiving B72.3

Name	Sex	Injected dose mg	Injected dose mCi	S.A.	Scan result	Tumor location	Tumor size (cm)	Tumor antigen status
^{131}I B72.3*								
1	M	0.16	2.1	13.13	+	Rectum	4.5 × 5	+
2	F	0.17	2.0	11.76	−	Rectum, pelvis	4 × 3	+
3	M	0.18	2.0	11.11	−	Liver, lung, LN	NK	+
4	F	0.22	1.6	7.27	−	Rectum, LN	3.7 × 3.2	+
5	M	0.26	2.0	7.69	+	Liver	NK	NK
6	M	0.26	2.0	7.69	+	Orbit, bone	NS	+
7	M	0.27	2.0	7.41	+	Liver	2.5	+
8	M	0.36	0.8	2.22	−	Omentum	2.5 × 4	+
9	F	0.40	1.9	4.75	+	Liver, peritoneum	0.2–3 × 3	+
10	M	1.08	10.0	9.26	−	Lung	1 × 0.8	NK
11	M	1.18	9.4	7.97	+	Liver, LN	2.5 × 2	+
12	M	1.32	10.0	7.58	+	Diffuse peritoneum	10 × 4	+
13	F	1.35	10.0	7.41	−	Liver	3 × 2.5	+
^{111}In B72.3								
14	F	0.36	5.0	13.89	−	Lung, liver	7 × 7	+
15	F	0.41	4.6	11.22	+	Liver, LN (portal)	3 × 2	+
16	M	0.50	5.0	10.00	−	Liver, LN (portal)	14 × 15	+
17	M	0.77	2.7	3.51	−	Liver	6 × 5	+
18	M	0.78	3.4	4.36	−	Lung, liver	1.5 × 1.5	NK
19†	M	0.46	2.2	4.78	−	Liver	2.5 × 1.5	+
20†	M	0.46	2.2	4.78	−	Liver	6.5 × 4	+
21†	M	0.56	5.0	8.93	−	Liver, LN (ileum)	5 × 3, 5 × 4	NK
^{125}I B72.3								
16	M	0.50	1.2	2.44				
19†	M	0.55	2.2	4.00				
20†‡	M	0.55	2.2	4.00				
21†	M	0.71	2.0	2.82				

S.A., specific activity mCi/mg; LN, lymph node; NK, not shown; NS, no surgery.
* Portions of the ^{131}I B72.3 data have been previously published (Reference 9, 10).
† Patients coinfused with ^{111}In and ^{125}I B72.3 and unlabeled B72.3 for a total of 20 mg.
‡ Patient had partial subcutaneous infiltration of his antibody dose.

correction for physical decay. Values were expressed as counts per pixel per injected radioactivity (mCi).

The scans were interpreted by three nuclear medicine physicians who had available the results of the patients clinical staging. The images were interpreted as positive when focal areas of increased uptake were seen in the analog images not corresponding to sites of physiologic uptake (blood pool, bladder, and thyroid). As a "gold" standard, scan results were compared to surgical and radiographic findings.

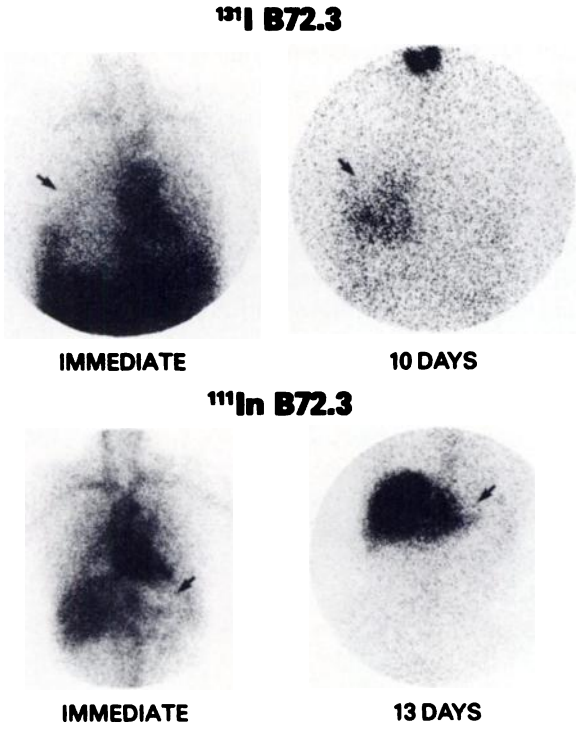
RESULTS

Representative scintiphotos are depicted in Figure 1. The early images showed biodistribution of ^{111}In-SCN-Bz-DTPA B72.3 that was very similar to that of [^{131}I] B72.3, showing predominant blood-pool activity in the heart, liver, and spleen while large tumor sites in the liver appeared as a cold defect. With time, the biodistribution of the two preparations diverged. The [^{131}I] B72.3 cleared from blood pool and normal organs resulting in improved tumor to nontumor contrast at delayed time points. In contrast, ^{111}In-SCN-Bz-DTPA B72.3 accumulated in the normal liver and was retained. As a result, in all but one patient liver metastases were not seen to concentrate the MoAb in amounts greater than the normal liver. Three patients with liver metastases and no radiographic evidence of extrahepatic metastases were found to have lymph node involvement at the time of laparotomy. The ^{111}In-SNC-Bz-DTPA B72.3 scintiphotos failed to detect portal lymph nodes (two patients) and a mesenteric lymph node (one patient).

The serum clearance of the two preparations were not significantly different, the Beta $T_{½}$ for ^{111}In-SCN-

Bz-DTPA B72.3 was 63 ± 5 hr and for [^{131}I]B72.3 it was 52 ± 10 hr (Fig. 2). The whole-body clearance curves of ^{111}In-SCN-Bz-DTPA B72.3 had a biologic $T_{½}$ of 11.8/days compared to a $T_{½}$ for [^{131}I]B72.3 of 3.3 days ($p < 0.000001$) (Fig. 3). The cumulative urinary excretion of ^{111}In and ^{131}I was significantly different (Table 2) with much less excretion of ^{111}In at every time point ($p < 0.0001$). The whole-body excretion (probe counts) of ^{131}I correlated well with the urinary excretion of ^{131}I indicating that the whole-body clearance was almost exclusively through this route. In contrast, the cumulative urinary excretion of ^{111}In was significantly lower than the whole-body loss of ^{111}In over the period of observation ($p < 0.01$), suggesting another route of excretion in addition to the urinary. The pharmacokinetics of ^{111}In and ^{125}I were directly compared in three of four patients receiving coinfusion of ^{111}In-SCN-Bz-DTPA B72.3 and [^{125}I]B72.3. The mean Beta $T_{½}$ in serum for ^{111}In was 62.3 hr, and that of ^{125}I was 58.4 hr ($p = 0.25$). At 96 hr, a mean of 14% of the ^{111}In and 45% of the ^{125}I had been excreted in the urine ($p < 0.0001$).

Figure 4 shows data from the region of interest for ^{111}In and ^{131}I patients. The ROI analysis showed that the blood-pool activity represented by a ROI over the left ventricle gradually decreased at a similar rate for both preparations. These determinations correlated with the plasma activity measured directly in a gamma



The arrows indicate the tumor sites.

FIGURE 1
Representative scintiphotos of ^{111}In-SCN-Bz-DTPA B72.3 and [^{131}I]B72.3 in patients with liver metastases from colon cancer. Initial biodistribution of the two preparations was similar (left panel). With time a difference in liver retention of radioactivity was noted (right panel). The arrows indicate the sites of metastatic liver disease. In the lower panel the tumor did not concentrate the antibody.

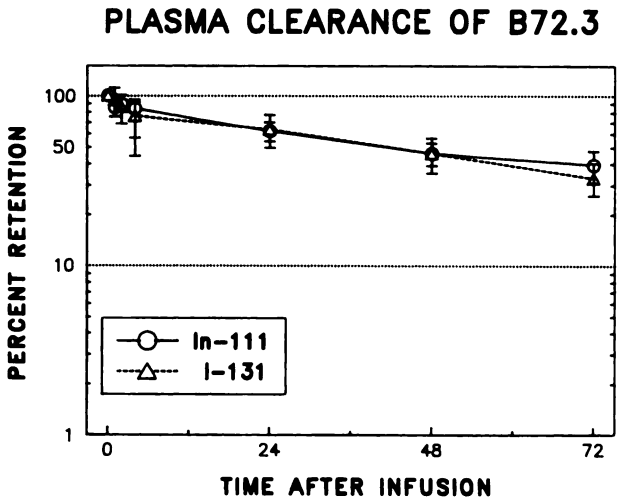


FIGURE 2
Plasma clearance of B72.3. There are no significant differences in the retention (mean ± s.d.) of ^{111}In-SCN-Bz-DTPA B72.3 and [^{131}I]B72.3 in serum.

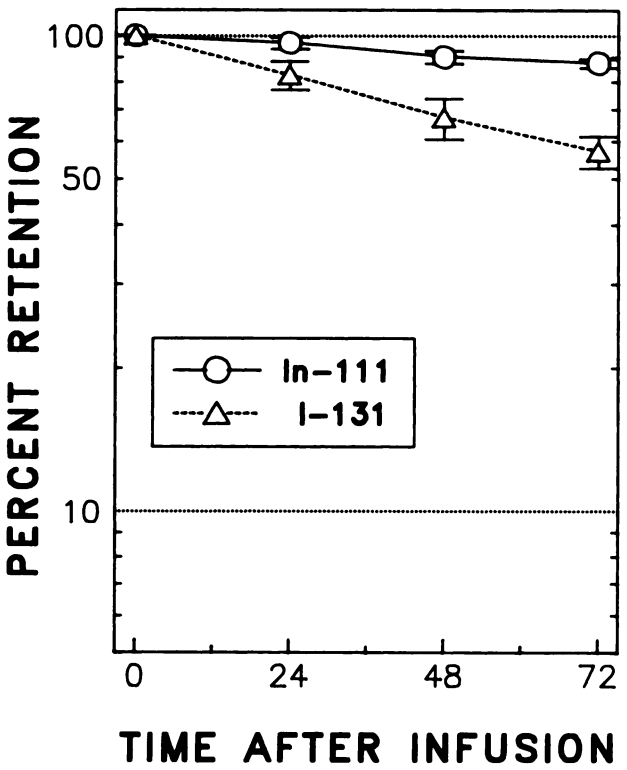


FIGURE 3
The whole-body retention (mean ± s.d.) of patients receiving ^{111}In-SCN-Bz-DTPA B72.3 was significantly prolonged when compared to that of patients receiving radioiodinated B72.3.

TABLE 2
Urinary Excretion and Whole-Body Excretion

Time (hr)	^{131}I Mean	± s.d.	Urine excretion ^{111}In		Whole-body excretion* ^{131}I		^{111}In	
0–24	15.9	4.94	3.0	0.80†	17.5	6.00	5.9	1.65†
0–48	31.9	9.54	5.3	1.26‡	32.9	7.00	10.0	3.44‡
0–72	42.3	12.5	7.9	1.35§	43.0	4.83	12.6	2.56§

* Fraction of radioactivity excreted from the body was determined by using a NaI probe (see text).

p values for differences between ^{131}I and ^{111}In excretion (n = 13 for ^{131}I and n = 7 for ^{111}In): †$p < 0.002$, ‡$p < 0.01$, §$p < 0.002$.

TABLE 3
Liver to Heart Ratio

Time (hr)	^{131}I Mean	Sd	^{111}In Mean	Sd
0	0.65*	0.14	0.70*	0.10
24	0.67†	0.14	1.19†	0.34
48	0.73†	0.17	1.43†	0.45
72	0.74†	0.29	1.85†	0.50

Comparison of ^{131}I (n = 6) and ^{111}In (n = 5) liver to heart ratios using ROI data: * Not significantly different, † $p < 0.01$.

counter ([^{131}I]B72.3, r = 0.900, ^{111}In-SCN-Bz-DTPA B72.3, r = 0.903, $p < 0.05$). There was a striking difference between the ^{111}In and ^{131}I liver activity. With ^{111}In-SCN-Bz-DTPA B72.3, liver activity increased throughout the study indicating a steady accumulation of ^{111}In. In contrast, ^{131}I liver activity was greatest in the first images and declined thereafter. This change in the ^{131}I liver activity also paralleled the gradual reduction of the blood-pool activity.

Comparisons of liver to heart (blood pool) ROI radioactivity are shown in Table 3. For the [^{131}I]B72.3 preparation the liver to heart ratio was nearly constant throughout the study. With ^{111}In-SCN-Bz-DTPA B72.3, the initial liver to heart ratio was not significantly different from that of ^{131}I; thereafter this ratio increased and was significantly greater than for the ^{131}I preparations. Radioactivity in the spleen and bone marrow were slightly greater with ^{111}In-SCN-Bz-DTPA B72.3 than with ^{131}I. The ^{111}In activity in these organs and kidney plateaued after 24 hr. The ^{131}I activity in these organs remained constant for 24 hr and thereafter diminished slightly, paralleling the drop in blood-pool activity.

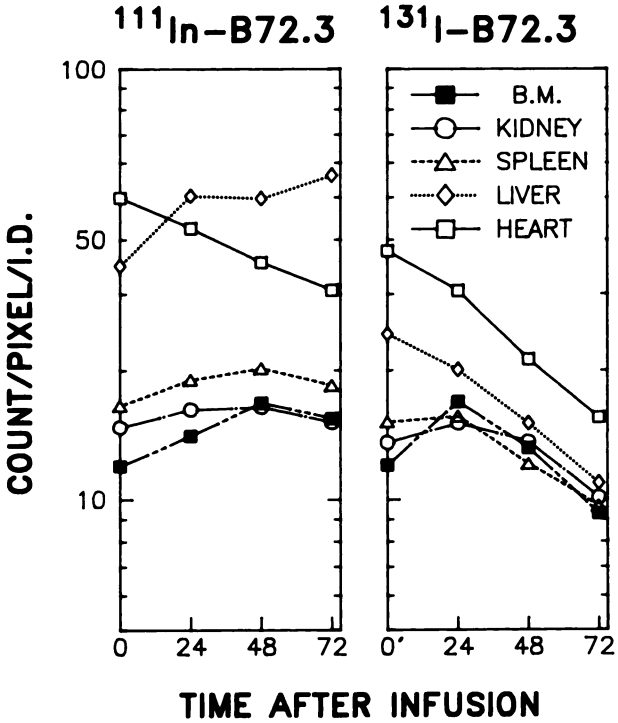


FIGURE 4
The sequential changes (mean) in concentration of ^{111}In and ^{131}I in normal organs was determined from the ROI analysis of gamma camera images. The ROI data was expressed as counts per pixel normalized to the mCis administered.

In seven of 13 patients who received [^{131}I]B72.3, tumor was identified by scanning (Table 1). Four of the six patients with hepatic metastases had lesions identified on scan. Only one of eight patients with liver metastases who received ^{111}In-SCN-Bz-DTPA B72.3 had a positive scan for hepatic metastases. In this patient, faint tumor concentration was identified in the computer acquired images. In the other patients with hepatic metastasis, tumor uptake of ^{111}In-SCN-Bz-DTPA B72.3 was not detected and occasionally lesions appeared to have less activity than the normal liver.

Figure 5 shows plotted ROI data from three patients with hepatic metastasis. In Patient A-11, who received [^{131}I]B72.3, initial hepatic activity was greater than tumor activity. Clearance of activity from normal liver, however, was faster than from the tumor, and images at delayed times clearly showed positive uptake in the tumor (Fig. 1).

In Patient B-1, who was given ^{111}In-SCN-Bz-DTPA B72.3, both hepatic and tumor activity increased with time and ROI analyses showed tumor to nontumor ratios <1.0. Therefore, the tumor always appeared as a "cold" defect.

In Patient B-2, who also received ^{111}In-SCN-Bz-DTPA B72.3, the liver and tumor activity remained relatively constant throughout the study. Unlike the other ^{111}In-SCN-Bz-DTPA B72.3 cases, this patient had a tumor to liver ratio of >1.0. The digital images showed that activity was slightly more concentrated in the tumor than in normal liver.

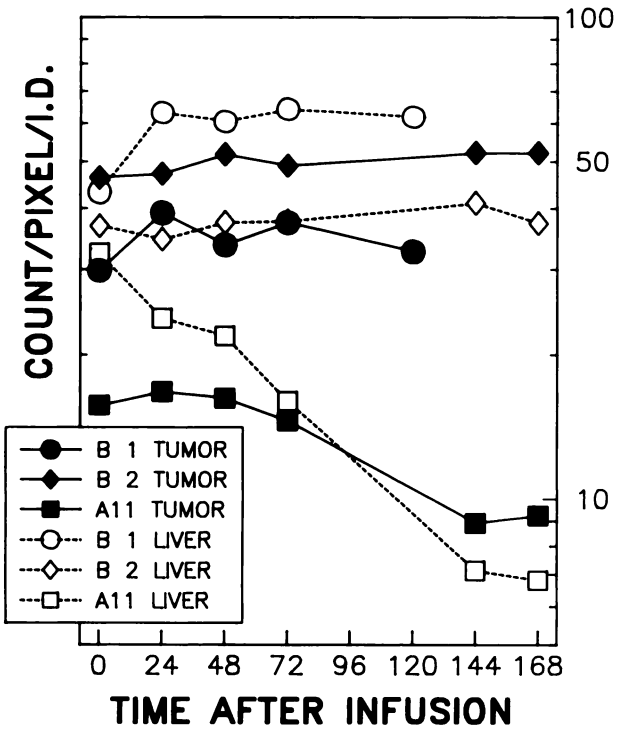


FIGURE 5
The serial differences in concentration of ^{111}In (two patients) or ^{131}I in the normal liver and in liver metastases of patients receiving radiolabeled B72.3 was obtained from ROI analyses.

DISCUSSION

This study demonstrates major differences in biodistribution of [^{131}I]- and [^{111}In]B72.3 MoAb. The most prominent differences were the prolonged whole-body retention of ^{111}In, its high liver uptake and its excretion into bowel. Several mechanisms could be responsible for these differences between the ^{131}I- and ^{111}In-labeled MoAb (*18,33,34*). Although a slow release of ^{111}In could not be excluded, rapid release did not occur since a comparison of ^{111}In and ^{131}I or a direct comparison of ^{111}In with ^{125}I showed similar plasma clearance. Others have reported similar clearance of ^{111}In and radioiodinated MoAb from blood and longer retention of ^{111}In than iodine in tumor and normal tissue (*18,33*). This suggests that once the MoAb has been metabolized, the differences in retention of ^{111}In and iodine are secondary to differences in their handling, rather than differences in the handling of the antibody. We speculate that the liver represents a normal route of metabolism for murine MoAb and both of our radiolabeled preparations are handled similarly and the differences observed are secondary to differences in the handling of the ^{131}I or ^{111}In. The ^{131}I is not retained intracellularly but rapidly excreted from the body. In contrast, ^{111}In binds to intracellular sites and is retained for long periods of time (*35*). Alternatively, the lack of concentration of ^{131}I by the liver and the fact that hepatic and plasma clearance of ^{131}I closely parallel one another, could also be explained by small differences in metabolism of the ^{111}In and ^{131}I antibody. It is unlikely that uptake of ^{111}In in the liver is secondary to colloid formation, because the MoAb was purified by HPLC and analysis prior to injection shows no evidence of colloid formation. Had colloids been formed, liver uptake would occur quickly rather than in the gradual mode observed in our patients.

Although the TAG-72 antigen circulates and can be detected in serum (*36*) we could not detect a correlation between the level of circulating antigen and liver uptake.

The urinary excretion of ^{111}In was smaller than that of ^{131}I. This was confirmed by measuring the excretion of ^{111}In and ^{125}I from patients receiving coinfusion of both tracers. Comparison of the urinary excretion of ^{111}In with the probe counts and visualization of the gastrointestinal tract by gamma scintigraphy suggested that half of the excreted ^{111}In could be excreted through the gut. No stools were obtained to quantitate this or determine the form in which the ^{111}In was excreted. Gastrointestinal excretion represents a significant problem for detection of peritoneal implants or local recurrence.

Our results show several similarities with other work using ^{111}In-labeled antibodies prepared with the mixed anhydride or bicyclic anhydride of DTPA that have shown liver uptake and variable amount of bowel activity. While [^{131}I]B72.3 shows little accumulation in the liver, other ^{131}I-labeled MoAb have demonstrated liver uptake (*13–15,18*). Since radioiodine does not concentrate in the liver, this accumulation may be due to the binding of cross-reacting antigens in the liver to receptors in the liver such as Fc receptors or binding to circulating cells which then clear into the liver (*17*).

Our findings suggest that the accumulation of the ^{111}In in the liver, spleen, and bone marrow is lower with our preparation. However, we cannot determine whether this is due to the greater stability of the chelate or to a characteristic of the MoAb.

There are limitations in our comparison of ^{131}I and ^{111}In-SCN-Bz-DTPA MoAb. The patients injected with ^{111}In-SCN-Bz-DTPA B72.3 represented an extremely difficult test for the technique since the series was biased toward patients with liver metastases whereas the [^{131}I] B72.3 patients had a broader spectrum of metastatic sites. The high concentration of ^{111}In in the liver resulted in poor detection of metastases in the liver and in lymph nodes adjacent to the liver. In contrast, ^{131}I did not concentrate in the liver and hepatic metastases were frequently visualized when the ^{131}I blood-pool activity cleared (*10*).

The current study indicates that although the radiolabeled antibodies behaved similarly in vitro, in vivo handling of the antibodies and/or radionuclides may result in significantly different biodistribution.

Further studies should be directed at elucidating the mechanism of liver uptake and attempting to eliminate this "nonspecific" uptake in order to take advantage of the superior physical properties of ^{111}In.

ACKNOWLEDGMENTS

The authors acknowledge the expert technical assistance of Margarita Lora, Patrick Maloney, and Diane Simpson in handling patient samples and assays; Marge Cawley, Susan Lange, Susan Kummer, and Penny Yolles for imaging the patients, and Karen Anderson and Lori Byrne for preparation of this manuscript.

REFERENCES

1. Goldenberg DM, DeLand FH, Kim E, et al. Use of radiolabeled antiantibodies to carcinoembryonic antigen for the detection and localization of diverse cancers by external photoscanning. *N Engl J Med* 1978; 298:1384–1386.
2. Mach J-P, Carrel S, Forni M, et al. Tumor localization of radiolabeled antibodies against carcinoembryonic antigen in patients with carcinoma. *N Engl J Med* 1980; 303:5–10.
3. Mach J-P, Buchegger F, Forni M, et al. Use of radiolabeled monoclonal anti-CEA antibodies for the detection of human carcinomas by external photoscanning and tomoscintigraphy. *Immunol Today* 1981; 2:239–247.
4. Mach J-P, Chatal JF, Lumbroso JD, et al. Tumor localization in patients by radiolabeled monoclonal antibodies against colon carcinoma. *Cancer Res* 1983; 43:5593–5600.
5. Chatal JF, Saccavini JC, Funoleau P, et al. Immunoscintigraphy of colon carcinoma. *J Nucl Med* 1984; 25:307–314.
6. Moldofsky PJ, Powe J, Mulhern CB, et al. Metastatic colon carcinoma detection with radiolabeled F(ab') 2 monoclonal antibody fragments. *Radiology* 1983; 149:549–555.
7. Hnatowich DJ, Griffin TW, Kusciuczyk C, et al. Pharmacokinetics of an indium-111-labeled monoclonal antibody in cancer patients. *J Nucl Med* 1985; 26:849–858.
8. Fairweather DS, Bradwell AR, Dykes PW, et al. Improved tumor localization using indium-111 labeled antibodies. *Br Med J* 1983; 287:167–170.
9. Colcher D, Esteban JM, Carrasquillo JA, et al. Quantitative analyses of selective radiolabeled monoclonal antibody localization in metastatic lesions of colorectal cancer patients. *Cancer Res* 1987; 47:1185–1189.
10. Carrasquillo JA, Sugarbaker P, Colcher D, et al. Radioimmunoscintigraphy of colon cancer with iodine-131-labeled B72.3 monoclonal antibody. *J Nucl Med* 1988; 29:1022–1030.
11. Esteban JM, Colcher D, Sugarbaker D, et al. Quantitative and qualitative aspects of radiolocalization in colon cancer patients of intravenously administered MoAb B72.3. *Int J Cancer* 1987; 29:50.
12. Renda A, Salvatore M, Sava M, et al. Immunoscintigraphy in the follow up of patients operated on for carcinoma of the sigmoid and rectum: preliminary report with a new monoclonal antibody-B72.3. *Dis Colon Rectum* 1987; 30:683–686.
13. Halpern SE, Dillman RO, Witztum KF, et al. Radioimmunodetection of melanoma utilizing ^{111}In-96.5 monoclonal antibody: a preliminary report. *Radiology* 1985; 155:493–499.
14. Larson SM, Brown JP, Wright PW, et al. Imaging of melanoma with ^{131}I labeled monoclonal antibodies. *J Nucl Med* 1983; 24:123–129.
15. Murray JL, Rosenblum MG, Sobol RE, et al. Radioimmunoimaging in malignant melanoma with ^{111}In-labeled monoclonal antibody 96.5. *Cancer Res* 1985; 45:2376–2381.
16. Colcher D, Esteban J, Carrasquillo J, et al. Complementation of intracavitary and intravenous administration of a monoclonal antibody (B72.3) in patients with carcinoma. *Cancer Res* 1987; 47:4218–4224.
17. Carrasquillo JA, Bunn PA, Keenan AM, et al. Imaging of cutaneous T-cell lymphoma with ^{111}In T101 monoclonal antibody. *N Engl J Med* 1986; 315:673–680.
18. Carrasquillo JA, Mulshine JL, Bunn PA, et al. Indium-111 T101 monoclonal antibody is superior to iodine-131 T101 in imaging of cutaneous T-cell lymphoma. *J Nucl Med* 1987; 28:281–287.
19. Sullivan DC, Silva JS, Cox CE, et al. Localization of I-131 labeled goat and primate anti-carcinembryonic antigen (CEA) antibodies in patients with cancer. *Invest Radiol* 1982; 17:350–355.
20. Larson SM, Carrasquillo JA, Krohn KA, et al. Localization of ^{131}I labeled p97 specific Fab fragments in human melanoma as a basis for radiotherapy. *J Clin Invest* 1983; 72:2101–2114.
21. Larson SM, Carrasquillo JA, McGuffin RW, et al. Use of I-131 labeled, murine Fab against a high molecular weight antigen of human melanoma: a preliminary experience. *Radiology* 1985; 155:487–492.
22. Epenetos AA, Shepherd J, Britton KE, et al. ^{123}I radioiodinated antibody imaging of occult ovarian cancer. *Cancer* 1984; 1:55 984–987.
23. Halpern SE. The advantages and limits of indium-111 labeling of antibodies. Experimental studies and clinical applications. *Int J Rad Instrum [B]* 1986; 13:195–201.
24. Krejcarek GE, Tucker KL. Covalent attachment of chelating groups to macromolecules. *Biochem Biophys Res Commun* 1977; 77:581–585.
25. Hnatowich DJ, Childs RL, Lanteigne D, et al. The preparation of 1) DTPA-coupled antibodies radiolabeled with metallic radionuclides: an improved method. *J Immunol Meth* 1983; 65:147–157.
26. Esteban JM, Schlom J, Gansow OA, et al. New method for the chelation of indium-111 to monoclonal antibodies: biodistribution and imaging of athymic mice bearing human colon carcinoma xenografts. *J Nucl Med* 1987; 28:861–870.
27. Halpern SE, Hagan PL, Garver PR, et al. Stability, characterization and kinetics of ^{111}In-labeled monoclonal anti-tumor antibodies in normal animals and nude mouse-human tumor nodels. *Cancer Res* 1983; 43:5347–5355.
28. Colcher D, Hand P, Nuti M, et al. A spectrum of monoclonal antibodies reactive with human mammary tumor cells. *Proc Natl Acad Sci USA* 1981; 78:3199–3203.
29. Johnson VG, Schlom J, Paterson AJ, et al. Analysis of a human tumor-associated glycoprotein (Tag 72) identified by monoclonal antibody B72.3. *Cancer Res* 1986; 46:850–857.
30. Colcher D, Keenan AM, Larson SM, et al. Prolonged

binding of a radiolabeled monoclonal antibody (B72.3) used for onsite radioimmunodetection of human colon carcinoma xenografts. *Cancer Res* 1984; 44:5755–5751.
31. Fraker PJ, Speck JC, Jr. Protein and cell membrane iodinations with a sparingly soluble chloroamide, 1,3,4,6-techrachloro-3a, 6a-diphenylglycoluril. *Biochem Biophys Res Commun* 1978; 80:849–857.
32. International Committee for Standardization in Hematology. Recommended methods for measurement of red cell and plasma volume. *J Nucl Med* 1980; 21:793–800.
33. Khaw BA, Cooney J, Edgington T, et al. Differences in experimental tumor localization of dual-labeled monoclonal antibody. *J Nucl Med* 1986; 27:1293–1299.
34. Perkins AC, Pimm MV. Differences in tumour and normal tissue concentrations of iodine- and indium-labeled monoclonal antibody. *Eur J Nucl Med* 1985; 11:295–299.
35. Thakur ML, Segal AW, Louis WL, et al. Indium-111-labeled cellular blood components: mechanism of labeling and intracellular location in human neutrophils. *J Nucl Med* 1977; 18:1022–1026.
36. Klug TL, Sattler MA, Colcher D, et al. Monoclonal Antibody immunoradiometric assay for an antigenic determinant (Ca 72) on a novel pan carcinoma antigen (TAG-72). *Int J Can* 1986; 38:661–669.