Biodistribution, Pharmacokinetic, and Imaging Studies with $^{186}\text{Re}$-labeled NR-LU-10 Whole Antibody in LS174T Colonie Tumor-bearing Mice

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ABSTRACT

Biodistribution, pharmacokinetic, and radioimaging studies were performed with $^{186}\text{Re}$-labeled NR-LU-10 whole antibody in athymic nude mice bearing the LS174T tumor growing either s.c. or in an experimental hepatic metastasis model. NR-LU-10 is an IgG2b murine monoclonal antibody (MAb) that reacts with virtually all human tumors of epithelial origin. NR-BC-1, an IgG2b murine MAb that reacts with normal human B-cell and B malignancies, was used as an isotype-matched control. These MAbS were radiolabeled with $^{186}\text{Re}$ (3.7-day physical half-life; 1.07-MeV $\beta$ particle and 137-keV $\gamma$, 9% abundance) by a preformed chelate approach by using the triamide thiolate ligand system. $^{186}\text{Re}$-labeled NR-LU-10 (50 $\mu\text{Ci}$) was injected into nude mice bearing LS174T tumors growing s.c. Biodistribution studies revealed that the LS174T tumor retained the highest concentration of $^{186}\text{Re}$-labeled NR-LU-10 (5.3% injected dose/g) at day 6. The tumor:blood ratio ranged from 0.1:1 to 10.8:1 by day 6, the last day of analysis. In contrast the tumor:blood ratio of $^{186}\text{Re}$-labeled NR-BC-1, the isotype-matched MAb control, was 1:1 on day 6. Pharmacokinetic analysis indicated that the $t_{1/2}\beta$ of NR-LU-10 for blood and other tissues ranged from 21 to 25 h, while the $t_{1/2}\beta$ for the LS174T tumor averaged 52 h. The area under the curve for tumor compared to blood was 2.8- to 5.7-fold higher than the area under the curve for all other tissues and organs. The mean residence time for NR-LU-10 in blood and all other organs ranged from 23 to 26 h, while the mean residence time for NR-LU-10 in the LS174T tumor was 72 h. Scintigraphic images revealed selective uptake of the $^{186}\text{Re}$-labeled NR-LU-10, but not of the $^{186}\text{Re}$-labeled NR-BC-1, at the LS174T tumor site. Studies in an experimental model of hepatic metastasis revealed a similar selective pattern of $^{186}\text{Re}$-labeled NR-LU-10 accumulation. Scintigraphic images of the LS174T tumor growing within the athymic nude mouse liver were obtained. The biodistribution, pharmacokinetic, and scintigraphic images suggest that $^{186}\text{Re}$-labeled NR-LU-10 shows promise as a therapeutic agent for gastrointestinal cancer.

INTRODUCTION

With the advent of monoclonal antibodies there has been a renewed interest in their use for targeted delivery (1). Drugs, toxins, and radionuclides have been coupled to MAbs to form immunolabeled conjugates with potential for more selective destruction of disseminated cancer. The impetus for treating malignant disease with antibody-targeted radionuclides is 3-fold. First, the deposition of $\beta$ emission from $^{186}\text{Re}$ spans multiple cell diameters, 90% deposition within 2 mm. Consequently, tumor cells devoid of antigen can be destroyed by the radiation cross-fire from adjacent antibody-bearing cells. Second, since the initial imaging studies (2, 3) with MAbs using $^{131}\text{I}$-labeled anticarcinoembryonic antigen, there have been improvements in radioimaging applications, using $\gamma$ and positron tumor imaging. These results indicate that several radionuclides can be stably labeled and can selectively concentrate in tumors. Third, clinical responses with antibody-targeted radionuclides by using $^{131}\text{I}$-labeled MAbs have been observed (4–7). These trials have demonstrated only modest therapeutic success and several factors have limited the therapeutic efficacy of $^{131}\text{I}$-labeled radioimmunoconjugates. Initial iodination radioiodinating used typical oxidative methods that can cause MAbs to lose immunoreactivity. In vivo, dehalogenation can also occur and results in nonspecific uptake of radiodine in both the thyroid and the stomach and reduces tumor retention. With the development of methods to attach metal chelating groups to proteins a wide range of $\beta$ emitting isotopes, including $^{67}\text{Cu}$ (8), $^{90}\text{Y}$ (9, 10), $^{153}\text{Sm}$ (11), and radioisotopes of rhenium ($^{186}\text{Re}$ and $^{188}\text{Re}$) can be attached to MAbs.

Wessels and Rogus (12) have suggested that $^{186}\text{Re}$ ($t_{1/2}$ = 3.68 days; $E_{\max}$ = 1.07 MeV) would be an excellent candidate radionuclide for radioimmunotherapy. The characteristics that make $^{186}\text{Re}$ an optimal radionuclide are a half-life of 3.7 days, which is long enough for tumor localization but short enough to minimize toxicity to whole body; a low abundance of 137 keV photons (9%) that allow imaging with a minimal nonspecific radiation dose; an intermediate energy $\beta$ emission comparable to $^{131}\text{I}$; and decay to stable daughters so that additional toxicity is of no concern. Rhenium has a structural chemistry similar to that of technetium and can be stably coupled to MAbs using the diamide-dimercaptide preformed chelate approach (13). MAbs are labeled by conjugation of a $^{186}\text{Re}$ mercaptacetetylglutaryl-glyglycyl-$\gamma$-aminobutyryl active ester agent. The stability of this radioimmunoconjugate is high with less than 2% loss over a 24-h period (14).

In this study $^{186}\text{Re}$ was chelated to NR-LU-10, a murine IgG2b MAb that recognizes a 40-kilodalton membrane glycoprotein expressed on most carcinomas of epithelial origin (15). To evaluate the potential of this RIC for cancer therapy, biodistribution and imaging studies were performed in nude mice bearing LS174T tumors growing s.c. as well as in experimental hepatic metastases in athymic nu/nu mice.

MATERIALS AND METHODS

Monoclonal Antibodies. NR-LU-10 is an IgG2b murine MAb reactive with the M, 40,000 glycoprotein which is expressed on most carcinomas of epithelial origin (15). NR-BC-1 is an IgG2b murine MAb reactive with a M, 35,000-43,000 Class II HLA-DR polymorphic variant expressed on normal B-cells and most B-cell lymphomas and leukemias (16). The antibodies were grown in airlift fermentators and were purified by anion exchange chromatography (InVitron Corp., St. Louis, MO). The antibody concentration was determined by absorbance measurements at 280 nm in 1-cm cuvets in a Spectronic 1201 (Milton Roy, Rochester, NY) spectrophotometer. The extinction coefficient of a 10-详情/毫升 solution was taken as 14.1.

Radiolabeling and Characterization of Labeled Antibodies. $^{186}\text{Re}$-Perrhenate was obtained from the Missouri University Research Re-
Fig. 1. Preformed chelate approach to antibody labeling. 186Re antibody labeling scheme including perrhenate reduction, complex formation, and coupling of the preformed chelate to the antibody.

actor in 2.5-3 Ci/mg rhenium. Targets containing nitric acid were purified following a slightly modified published procedure (17).

As outlined in the labeling schema shown in Fig. 1, perrhenate was then reduced with stannous ions in the presence of citric acid and chelated to a tetrafluorophenyl-activated ester derivative of the triamide thiolate (N,5) ligand system referred to as MAGG (18). The preformed 186Re-labeled chelate was coupled to the above intact MAb at pH 9.5 for 15 min at room temperature via site-specific linkage to lysine residues. The labeled MAbs were then purified by size exclusion gel chromatography or ion exchange chromatography to >95% as assayed by ITLC. Label stability was confirmed under multiple challenge conditions, including incubation at 37°C in serum and in 40 mM diethylenetriamine pentaacetic acid, 7 mM phosphate-buffered isotonic saline over 24 h (14). ITLC was used as a measure of radiochemical yield. The RIC (25 µl) was spotted on ITLC paper (ITLC SG, Gelman Science) and allowed to dry; 12% trichloroacetic acid was used as a solvent for chromatography. Following chromatography the strip was dried and cut into three regions (origin, middle, end) and placed into a gamma counter. Protein-bound radioactivity remained at the origin.

HPLC was used as a measure of RIC purity. HPLC analysis was performed on a Waters' Model 6000A solvent delivery system with a mobile phase of 0.2 M phosphate buffer (pH 6.8) (1 ml/min) on a 300 x 7.5-mm Bio-Sil TSK 250 (Bio-Rad Laboratory, Richmond, CA) size exclusion column; 0.5-ml fractions were collected on a FRAC 100 fraction collector (Pharmacia) and the amount of radioactivity in each fraction was determined on a Beckman 5500B gamma spectrophotometer.

Cell Lines. LS174T and HT29 are human colon adenocarcinoma cell lines and ASPC1 and SU86 are human pancreatic adenocarcinoma derived from patients with Burkitt's lymphoma. These cell lines were washed and subcultured at a dilution of 1:5.

Raji, Daudi, and EB3 are malignant B-lymphoblastoid cell lines derived from patients with Burkitt's lymphoma. These cell lines were grown in suspension culture and maintained at 37°C in a humidified atmosphere under 5% CO2. Cells were passaged every 2-3 days in RPMI 1640 supplemented with 10% FBS and penicillin-streptomycin-neomycin antibiotics. All cell lines were obtained from the American Type Culture Collection.

Indirect Immunofluorescence. Reactivity of NR-LU-10 and NR-BC-1 to the above cell lines was determined by flow cytometry analysis.

Table 1. Cell surface phenotype of established cell lines

<table>
<thead>
<tr>
<th>Cell line</th>
<th>Histotype</th>
<th>NR-LU-10* (% of positive cells)</th>
<th>NR-BC-1* (% of positive cells)</th>
<th>Total MFI</th>
<th>Total MFI</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASPC-1</td>
<td>Pancreatic adenocarcinoma</td>
<td>78.6</td>
<td>125.0</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>SU-86</td>
<td>Pancreatic adenocarcinoma</td>
<td>60.1</td>
<td>111.4</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>LS174T</td>
<td>Colon adenocarcinoma</td>
<td>86.1</td>
<td>131.3</td>
<td>2.7</td>
<td>90.2</td>
</tr>
<tr>
<td>HT-39</td>
<td>Colon adenocarcinoma</td>
<td>45.8</td>
<td>120.7</td>
<td>0.6</td>
<td>412</td>
</tr>
<tr>
<td>RAJ1</td>
<td>B-cell lymphoma</td>
<td>0.4</td>
<td>—</td>
<td>90.2</td>
<td>412</td>
</tr>
<tr>
<td>EB-3</td>
<td>B-cell lymphoma</td>
<td>1.5</td>
<td>—</td>
<td>77.3</td>
<td>109</td>
</tr>
<tr>
<td>DAUDI</td>
<td>B-cell lymphoma</td>
<td>4.7</td>
<td>44</td>
<td>93.9</td>
<td>403</td>
</tr>
</tbody>
</table>

* NR-LU-10, an IgG2b murine MAb that recognizes a PAN carcinoma antigen.

MFI, mean fluorescence intensity.

** NR-BC-1, an IgG2b murine MAb that recognizes a Class II HLA-DR variant on B-cell and B-cell lymphoproliferative disease.

—, none.
Table 2  Biodistribution of $^{111}$Re-labeled NR-LU-10 administered i.v. in athymic mice bearing LS174T colon carcinoma xenografts

<table>
<thead>
<tr>
<th>Tissue</th>
<th>$^{111}$Re-LU-10 (N = 4)</th>
<th>$^{111}$Re-LU-10 (N = 4)</th>
<th>$^{111}$Re-LU-10 (N = 4)</th>
<th>$^{111}$Re-LU-10 (N = 4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood</td>
<td>18.6 ± 2.80</td>
<td>22.6 ± 0.34</td>
<td>20.5 ± 0.98</td>
<td>18.6 ± 2.80</td>
</tr>
<tr>
<td>Skin</td>
<td>3.3 ± 1.00</td>
<td>4.8 ± 0.28</td>
<td>3.9 ± 0.45</td>
<td>4.1 ± 0.28</td>
</tr>
<tr>
<td>Heart</td>
<td>3.59 ± 0.29</td>
<td>0.23 ± 0.19</td>
<td>0.19 ± 0.38</td>
<td>0.12 ± 0.03</td>
</tr>
<tr>
<td>Lungs</td>
<td>2.91 ± 1.79</td>
<td>0.16 ± 0.12</td>
<td>0.21 ± 0.02</td>
<td>0.24 ± 0.07</td>
</tr>
<tr>
<td>Liver</td>
<td>4.70 ± 2.32</td>
<td>0.32 ± 0.13</td>
<td>0.35 ± 0.11</td>
<td>0.25 ± 0.01</td>
</tr>
<tr>
<td>Pancreas</td>
<td>0.63 ± 0.17</td>
<td>0.10 ± 0.17</td>
<td>0.07 ± 0.01</td>
<td>0.05 ± 0.01</td>
</tr>
<tr>
<td>Intestine</td>
<td>1.31 ± 0.56</td>
<td>0.07 ± 0.01</td>
<td>0.12 ± 0.01</td>
<td>0.05 ± 0.03</td>
</tr>
<tr>
<td>Stomach</td>
<td>1.58 ± 0.42</td>
<td>0.09 ± 0.05</td>
<td>0.11 ± 0.01</td>
<td>0.06 ± 0.02</td>
</tr>
<tr>
<td>Spleen</td>
<td>3.69 ± 1.13</td>
<td>0.18 ± 0.06</td>
<td>0.20 ± 0.03</td>
<td>0.19 ± 0.03</td>
</tr>
<tr>
<td>Kidney</td>
<td>2.89 ± 1.54</td>
<td>0.17 ± 0.11</td>
<td>0.26 ± 0.11</td>
<td>0.24 ± 0.11</td>
</tr>
<tr>
<td>Muscle</td>
<td>0.25 ± 0.25</td>
<td>0.03 ± 0.01</td>
<td>0.06 ± 0.02</td>
<td>0.03 ± 0.01</td>
</tr>
<tr>
<td>Bone</td>
<td>1.78 ± 0.20</td>
<td>0.16 ± 0.03</td>
<td>0.17 ± 0.01</td>
<td>0.09 ± 0.03</td>
</tr>
<tr>
<td>Tail</td>
<td>1.28 ± 0.31</td>
<td>0.32 ± 0.01</td>
<td>0.21 ± 0.05</td>
<td>0.12 ± 0.00</td>
</tr>
<tr>
<td>Tumor</td>
<td>1.95 ± 1.07</td>
<td>6.71 ± 0.75</td>
<td>5.97 ± 2.12</td>
<td>5.31 ± 2.24</td>
</tr>
</tbody>
</table>

Tumor wet weight: 1.2 ± 0.28 g

Table 3  Pharmacokinetic analysis of $^{111}$Re-labeled NR-LU-10 in LS174T tumor-bearing mice

<table>
<thead>
<tr>
<th>Tissue</th>
<th>AUC (cpm/g)</th>
<th>MRT (h)</th>
<th>$\tau_d$ (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood</td>
<td>1547 ± 10^5</td>
<td>24</td>
<td>0.995</td>
</tr>
<tr>
<td>Lungs</td>
<td>271 ± 10^4</td>
<td>26</td>
<td>0.929</td>
</tr>
<tr>
<td>Liver</td>
<td>406 ± 10^4</td>
<td>25</td>
<td>0.952</td>
</tr>
<tr>
<td>Kidney</td>
<td>316.6 ± 10^4</td>
<td>23</td>
<td>0.937</td>
</tr>
<tr>
<td>Spleen</td>
<td>316.6 ± 10^4</td>
<td>23</td>
<td>0.912</td>
</tr>
<tr>
<td>Tumor</td>
<td>1863.6 ± 10^4</td>
<td>77</td>
<td>0.934</td>
</tr>
</tbody>
</table>

$\tau_d$ and $\tau$ - terminal elimination half-life.

RESULTS

Radiolabeling of Monoclonal Antibodies and Characterization of Products. When 5-mg aliquots of NR-LU-10 and NR-BC-1 were labeled with 30 mCi of $^{111}$Re, the efficiency of incorporation of $^{111}$Re ranged from 30 to 40% with specific activities ranging from 0.5 to 2.5 mCi/mg. The radiochemical yield determined by ITLC was greater than 95%. By HPLC analysis, 97% of $^{111}$Re-labeled NR-LU-10 resolved as a single peak with an apparent molecular weight of 150,000. The immunoactive...
Fig. 4. Whole body scintigraphic image of athymic nude mice bearing s.c. LS174T tumors given injections i.v. of 50 μCi of 186Re-labeled NR-LU-10 or 50 μCi of 186Re-labeled NR-BC-1. Scanning was performed on day 6. Background subtraction was not utilized.

Flow Cytometric Analysis of NR-LU-10 and NR-BC-1 with Human Malignant Cell Lines. Reactivity of NR-LU-10 and NR-BC-1 on human malignant cell lines was determined by indirect immunofluorescence analysis. The results in Table 1 indicate that the epitope recognized by NR-LU-10 was highly expressed on gastrointestinal cell lines (LS174T, ASPC-1, SU-86, HT-29) but not on B-cell lines (Raji, EB-3, Daudi). Conversely, the epitope recognized by NR-BC-1 was highly expressed on B-cell lines but not on tumors of gastrointestinal origin.

Biodistribution and Pharmacokinetics of Radiolabeled NR-LU-10. The tissue biodistribution of 186Re-labeled NR-LU-10 was determined in athymic nude mice bearing s.c. LS174T tumors ranging in size from 1.2–1.9 g. The nude mice received 50 μCi i.v. of 186Re-labeled NR-LU-10 and were sacrificed at intervals up to 6 days. The results of the biodistribution study are shown in Table 2. By 24 h, the concentration of 186Re-labeled NR-LU-10 present in the tumor was 9.8% ID/g and in blood was 8.2% ID/g. All other organs had markedly lower concentrations of 186Re-labeled NR-LU-10 (<3.0% ID/g). The percentage of ID/g for blood declined from 8.2 to 0.49%, whereas the percentage of ID/g for the tumor declined from 9.8 to 5.3% on day 1 and day 6, respectively, resulting in a maximal tumor:blood ratio of 10.8 by day 6 (Fig. 2). All of the normal organs had retained less than 0.5% ID/g by 72 h. The tumor:tissue ratios for blood, lung, liver, kidney and spleen are shown in Fig. 3. With the exception of blood, peak tumor:tissue ratios were obtained 3 days after i.v. injection of 186Re-labeled NR-LU-10. They ranged from 20:1 to 40:1. Peak tumor:blood ratios were obtained on day 6 (10.8).

Pharmacokinetic parameters and noncompartmental calculations derived by regression analysis from the concentration versus time data are summarized in Table 3. Peak tissue concentrations of NR-LU-10 in normal tissues and organs occurred 4 h after i.v. injection, whereas peak levels in LS174T tumors occurred 24 h after injection. Terminal elimination (t½) half-lives of NR-LU-10 from blood and all normal organs ranged from 21 to 25 h while the t½ from the LS174T tumor was 52.5 h. The total AUC for LS174T tumor was 3.8–5.7 times the AUC of all other normal organs. The MRT of 186Re-labeled NR-LU-10 was 77 h in the LS174T tumor. The MRT in blood and other normal organs ranged from 23 to 26 h.

Selectivity of 186Re-labeled NR-LU-10 Localization. The relative tissue biodistribution of 186Re-labeled NR-LU-10 was compared to 186Re-labeled NR-BC-1 in mice bearing LS174T s.c. tumors. 186Re-labeled NR-BC-1 gave a different pattern of biodistribution than 186Re-labeled NR-LU-10 in nude mice bearing LS174T tumors. The tumor:tissue ratios of these two MAbs are presented in Table 4. The tumor:tissue ratios for 186Re-labeled NR-LU-10 ranged from 11:1 to 104:1. In contrast, the tumor:tissue ratios for 186Re-labeled NR-BC-1 ranged from 0.1:1.
Whole Body Scintigraphic Image

Fig. 6. Whole body scintigraphic image of athymic nude mouse bearing experimental LS174T hepatic metastases. The mouse was given an injection i.v. of 50 µCi of 186Re-labeled NR-LU-10. The image was obtained at day 6.

from 1:1 to 8:1, suggesting no preferential uptake of 186Re-labeled NR-BC-1 in the LS174T tumor system. These results were confirmed by whole body scintigraphic studies.

Imaging of Tumor-bearing Mice. The mice bearing LS174T s.c. tumors were given injections i.v. of 50 µCi of either 186Re-labeled NR-LU-10 or 186Re-labeled NR-BC-1 and whole body scintigraphic images were obtained 6 days later. The results in Fig. 4 indicate preferential uptake of NR-LU-10 at the s.c. tumor site with marginal uptake in the blood pool and normal tissues. As for the 186Re-labeled control (NR-BC-1), no difference in uptake was observed between the tumor site, the blood pool, and normal tissues.

Biodistribution Studies and Imaging Studies in Nude Mice Bearing LS174T Experimental Hepatic Metastasis. The relative biodistribution of 186Re-labeled NR-LU-10 was compared in mice bearing LS174T tumors growing either s.c. or as an experimental hepatic metastasis. The results in Fig. 5 indicate at day 6 a similar distribution pattern of 186Re-labeled NR-LU-10 in both xenograft models.

Scintigraphic images were also obtained with mice bearing LS174T hepatic metastases. The scintigraphic image in Fig. 6 reveals preferential uptake of 186Re-labeled NR-LU-10 at the tumor site.

DISCUSSION

The physical properties of 186Re make it an excellent candidate radionuclide for radioimmunotherapy when it is covalently attached to MAbs (13). A stable 186Re radiopharmaceutical has been prepared by conjugating a preformed 186Re active ester complex to NR-LU-10, an IgG2b murine MAb (14). A preliminary evaluation of 186Re-labeled NR-LU-10 therapeutic potential has been performed in nude mice bearing s.c. xenografts of SHT-1, a human small cell lung carcinoma cell line (22). Significant antitumor responses were observed with efficacious tumor growth control. While NR-LU-10 was generated against a human lung cancer cell line, it recognizes a variety of tumors of epithelial origin. Thus, the therapeutic potential of 186Re-labeled NR-LU-10 as a radiopharmaceutical can be evaluated in a variety of different tumor systems.

In this study we evaluated the therapeutic potential of 186Re-labeled NR-LU-10 for gastrointestinal cancer. These studies were performed with the LS174T tumor cell line growing both as a s.c. xenograft and as an experimental hepatic metastasis in athymic nu/nu mice. The nude mouse xenograft model can evaluate the potential of a radiopharmaceutical for both imaging and therapy of tumors, since it indicates the relative amount of radiopharmaceutical retained and its residence time in the tumor and normal tissues. The target:normal tissue relationship required for radioimmunotherapy is no greater than that for radioimmunoimaging if there is prolonged residence time of the radiopharmaceutical on the tumor cell (8).

Selective tumor accumulation of 186Re-labeled NR-LU-10 was observed, as the relative uptake in the LS174T tumor far exceeded highly vascularized tissues and organ concentrations. All normal tissues and organs with the exception of blood showed minimal uptake and more rapid clearance when compared to the LS174T tumor. While the AUC for the LS174T tumor and blood were comparable, both were 3.8–5.7 times higher than all other normal tissues and organs. However, the terminal elimination half-lives for the LS174T tumor and blood were different. The elimination half-life for blood was 2.4 times more rapid than for the LS174T tumor. Peak tumor:blood ratios appeared 5 days after i.v. injection, resulting in a tumor:blood ratio greater than 11:1. In contrast, the tumor:blood ratio for NR-BC-1 (the isotype-matched control) was only 1:1, indicating lack of selective concentration at the tumor site. The MRT (77 h) of the radiopharmaceutical was 3 times greater in the LS174T tumor than in all other normal organs and tissues. This extended MRT favorably compares to other radiopharmaceuticals that demonstrated control of tumor growth (8).

The radioimaging data also provided evidence of preferential
accumulation of the radiopharmaceutical at the tumor site. 18Re-labeled NR-LU-10 accumulated at the LS174T tumor site. In contrast, no significant accumulation was observed with the control MAb NR-BC-1 at the LS174T tumor site. The long accumulation and retention of the radiopharmaceutical is a desirable attribute for radioimmunotherapy, since prolonged contact with the radiopharmaceutical within the tumor cells dictates its effectiveness. However, the prolonged distribution of the radiopharmaceutical in the blood pool can result in a significant radiation dose delivered to all vascular organs. Potential toxic effects may be minimized if fractionated doses are delivered instead of a single activity dose.

Parallel studies were performed in athymic nude mice bearing LS174T experimental hepatic metastases. LS174T experimental hepatic metastases were established by implantation of LS174T tumor cells into the portal system through the ileocolic vein. This procedure has been successfully used to establish hepatic metastasis with MCA-38 colonic tumor cells in C57BL/6J mice (20). This model simulates the natural history of the development of metastases from colon cancer and provides a model that can more realistically assess the therapeutic potential of RIC.

The biodistribution pattern of 18Re-labeled NR-LU-10 in mice bearing LS174T experimental hepatic metastases was similar to the biodistribution pattern observed with mice bearing LS174T s.c. tumors of comparable size. Furthermore, LS174T tumors growing within the parenchyma of the nude mouse liver could be successfully imaged. The ability to image the uptake of a radiopharmaceutical in a tumor growing within a major internal organ is important for several reasons. Images can document uptake and distribution of a therapeutic dose of radiouclide. Furthermore, scanning can be used to document the effects of therapy. The availability of this model will enable us to pursue more realistic therapeutic evaluations of radiotherapeutics. These studies are currently under way.

ACKNOWLEDGMENTS

We wish to thank Norman Paolini, Jr., for his excellent technical assistance and Pat Arlandavo and Michelle Barbaro for their secretarial support.

REFERENCES

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