Radiation Dosimetry for Indium-111-Labeled Anti-CEA-F(ab')$_2$ Fragments Evaluated from Tissue Distribution in Rats

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Accurate dosimetric investigations are important to be able to fulfill the ambition of radiation protection in nuclear medicine and to minimize the radiation burden to the patient. This paper presents human radiation absorbed dose estimates following an administration of an ^{111}In-labeled anti-CEA-F(ab')$_2$ (BW431/31) based on detailed biodistribution and elimination data in a rat model. Animals were followed from the time of injection up to 28 days after injection. A significant initial uptake of ^{111}In in the bone marrow, 25% of injected activity, was evident after 6 hr. The kidneys showed a maximal uptake of 20% at 24 hr. At the end of the study, 27% of the activity was still retained in the whole body. The estimated humans absorbed dose to the kidneys, testes, spleen and bone marrow was 2.27, 0.80, 0.51 and 0.37 mGy MBq^{-1}, respectively. The effective dose was estimated to 0.27 mSv MBq^{-1}. The tissue distribution in rats was comparable to that in humans, which was confirmed by whole-body scintigrams and human biopsies.

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Carcinoembryonic antigen (CEA) is a high molecular-weight (MW180000) glycoprotein and is probably the most studied oncofetal antigen. CEA was first reported to be associated with colorectal carcinoma cells (*1*), but has later been found in numerous malignancies of epithelial origin (*2*). The use of different ^{111}In-labeled murine anti-CEA monoclonal antibodies (CEA-Mabs) for the imaging of gastrointestinal carcinomas in animal models and in humans is well documented, using both intact antibody and the fragments Fab and F(ab')$_2$ (*3–5*). Apart from uptake in malignant tissues, ^{111}In activity accumulates in normal tissues such as the liver, spleen, bone marrow, kidneys, bladder and colon (6,7). It has also been shown that male patients with colorectal cancer had an unexpected uptake of ^{111}In-CEA-Mab in the testes (*8*). Because of the usually low uptake of radiolabeled antibodies in tumors, single-photon emission computed tomography (SPECT) has become an appropriate tool in tumor imaging (*9,10*). A sufficiently high activity must be administered to the patient to obtain good image statistics. Consequently, several normal tissues, e.g., bone marrow, liver and kidneys, may receive an undesirable radiation exposure, thus limiting the administered activity. Accurate dosimetric investigations are of the utmost importance in order to fulfill radiation protection requirements and to minimize radiation burden to the patient (*11*). This is of special importance if radiolabeled tumor- and nontumor-specific antibodies are used for screening tests, in pediatric nuclear medicine or volunteers in research.

In this paper, the long-term biokinetics and biodistribution of ^{111}In-labeled anti-CEA-F(ab')$_2$ BW431/31 fragment were studied in normal rats. The biokinetics and tissue distribution from the animal model were scaled to man utilizing absorbed dose fractions compiled by the MIRD committee. Absorbed doses to humans were estimated for ^{111}In and for radionuclide impurity of ^{114m}In. The biodistribution results in the animals were compared to published human data, i.e., scintigrams and tissue biopsies from patients who received the same F(ab')$_2$ fragment.

MATERIALS AND METHODS

Radiopharmaceuticals

A F(ab')$_2$ fragment of the murine anti-CEA Mab BW431/31 (*12,13*) was prepared from an intact antibody and supplied as a commercial freeze-dried kit containing 1 mg F(ab')$_2$ BW431/31 (Scintimun®, Behringwerke, Marburg, Germany). The F(ab')$_2$ fragment is coupled to diethylenentriaminepentaacetic acid (DTPA) using cyclic DTPA dianhydride (c-DTPAA) according to the method by Hnatowich et al. (*14*). The F(ab')$_2$ kit was labeled with sterile, ultra pure and carrier-free $^{111}InCl_3$ (Amersham International plc., Buckinghamshire, England) in 0.04 *M* HCl, made up to 1 ml isotonic saline solution, and was allowed to incubate for 45 min. The activity concentration at this step was 120 MBq ml^{-1} (3.2 mCi ml^{-1}). After the termination of the incubation, 0.1 ml sterile EDTA (0.01 *M*) was added to scavenge any free ^{111}In.

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Radiochemical and Radionuclide Quality Control

The labeling yield of the prepared ^{111}In-anti-CEA F(ab')$_2$ solution was determined by gel filtration chromatography using a 1.5 × 30 cm Sephacryl HR S-100 column (Pharmacia, Uppsala, Sweden) and 10 ml 0.9% NaCl as eluant. Commercial $^{111}InCl_3$ contains small amounts of ^{114m}In as a radionuclide impurity, which should be checked regularly. Indium-114m may contribute to an increase in the absorbed dose to the patient if its activity level is not minimized. Thus, measurement of ^{114m}In in the ^{111}In solutions was carried out by means of a 40-cm^3 high purity germanium semiconductor detector (HPGe) (Canberra Industries Inc., Meriden, CT). Detailed studies of the immunoreactivity, antigen binding and in-vivo behavior of the CEA-BW431/31 have been published, and the F(ab')$_2$ has proved to be unaffected with different excess amounts of c-DTPAA (*12*). The affinity constant of the CEA-BW431/31 to tissue-associated CEA has been reported to be $K_a = 1 \cdot 10^8$-$8 \cdot 10^8$ (*13*). No measurements of these parameters were performed in the present experiment.

Animals

Thirty-two male Wistar rats (Moellegard Breeding Center Ltd, Denmark) were used in these studies. Prior to the experiment, the animals were allowed to acclimatize in the laboratory. The rats weighed 230 ± 14 g (mean ± s.d.). The animals had access to standard laboratory food and tap water ad libitum. During invasive procedures light ether anesthesia was used. An intravenous injection of 7.0 ± 1.0 MBq (0.19 ± 0.03 mCi) of ^{111}In-F(ab')$_2$ fragments in a volume of 0.20 ml (approximately 80 μg 431/31-F(ab')$_2$ was given into the vena femorales. After the administration of the radiopharmaceutical all rats, except those that were killed on Day 1, were individually housed in metabolic cages (Techniplast Gazzada, Buguggiate, Italy) to monitor all urinary and fecal excretion of ^{111}In. The excretion products were determined daily during the first week, and then every third day until the termination of the experiment. On every third day, the residual urine on the wall of the separation cone was rinsed off and collected for activity measurements in order to correct urine activity.

Whole-blood samples were collected from the orbita plexus. An aliquot was taken for the measurement of whole-blood activity, and the rest was centrifuged for separate measurements of the activity in plasma and blood cells. Euthanization and dissection were performed at 0 (< 2 min), 3, 6, 24 hr and 5, 8, 15 and 28 days. Three rats were used at 0 and 3 hr and at 8, 15 and 28 days; six rats were used at 6 and 24 hr and at 5 days. Resected tissues included the heart, liver, spleen, lungs, kidneys, testes, muscle, thyroid, red bone marrow and the gastrointestinal tract (which was further separated into its different parts). The red bone marrow was taken from both shafts of the femur. The tissue samples were removed, carefully washed in saline, blotted dry and placed in preweighed plastic tubes. All tissues were weighed wet prior to the activity measurements.

Activity Measurements

All tissue samples were measured in a pre-calibrated NaI(Tl) detector system. In addition, some tissues (bone marrow, spleen, liver, kidneys and testes) were subjected to a second measurement on the HPGe detector for ^{114m}In activity. Sufficient counting times were used to keep the statistical error below 1% for ^{111}In and below 5% for ^{114m}In (normally near 2%). All activity measurements were corrected for background and physical decay, and if necessary for physical decay during counting. Samples measured for ^{111}In at the end of the experiment (i.e., 28 days) were also corrected for the contribution from ^{114m}In impurities due to the long half-life of ^{114m}In (49.51 days). The activity in the organs is expressed as the percentage of injected activity per total organ. Thus, all concentration figures were multiplied by the actual organ weights, or for those organs not weighed whole, tabulated normal weights were used (*15–17*).

Human Absorbed Dose Calculations

Residence times in all organs studied were calculated from the biological data obtained in the animals. Human absorbed dose calculations were performed according to the methods outlined by the MIRD committee (*18*) and the ICRU (*19*) using the computer program MIRDOSE2 developed at Oak Ridge Associated Universities (*20*). Because ^{114m}In is not included in this computer code, absorbed doses from this radionuclide were calculated with the corresponding ICRP 53-computer code (*21*). The procedures for the calculations are summarized in Appendix 1. Effective dose was determined as described in ICRP Report 60 (*22*).

RESULTS

Quality Control

The labeling yield of the BW431/31-F(ab')$_2$ was measured by gel filtration chromatography after 45 min of incubation and was found to be 95%. The remaining 5% was detected as unreacted ^{111}In-EDTA complex. Gel filtration chromatography also made on samples from plasma and urine 24 hr after injection indicated that the main activity was detected in one single peak localized at the same place as the freshly labeled ^{111}In-BW431/31-F(ab')$_2$. The impurity of ^{114m}In on the reference day (i.e., the injection day) was measured to be 0.03% of the ^{111}In activity, corresponding to an injection of 1.58 kBq ^{114m}In.

Biokinetics and Biodistribution in the Rat

Initially, a small but fast urinary excretion takes place, probably due to free ^{111}In chelated by EDTA at the time of preparation. Seventeen percent of the injected activity was excreted during the first 24 hr, mainly through the urine. During the entire study period, 61% of the ^{111}In-fragments was eliminated by the urine and only 12% by the feces (Fig. 1). The whole-body retention was calculated from the elimination data, giving a two-component retention curve with a shorter half-life of 2.83 days and an intercept corresponding to 58% of the administered activity with a longer half-life of 49 days corresponding to 42% of the activity.

The elimination of the ^{111}In-F(ab')$_2$ fragments in rat blood was rapid and the amount retained decreased to 10% within 6 hr. Less than 1% of the activity was found in the red blood cell fraction. The biodistribution of ^{111}In in resected tissues showed a bone marrow uptake that was initially substantial, with a peak of 25% at 6 hr, but decreasing significantly during the first 5 days (Fig. 2). The maximum uptake in the liver of 12% was reached within 24 hr, after which the activity declined slowly to 7% 5 days after injection. The activity in the spleen was less

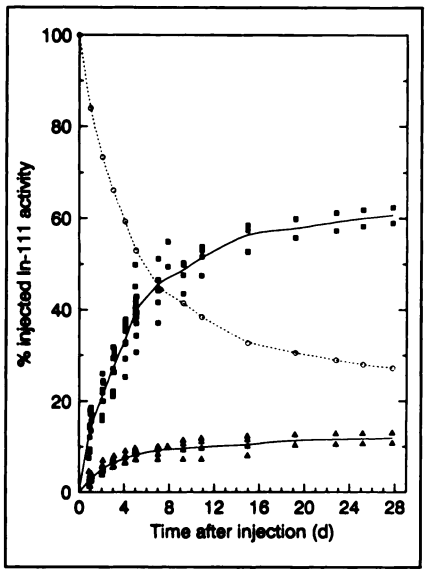

FIGURE 1. Cumulated activity in urine (squares) and feces (triangles). Each point corresponds to an individual animal. During 28 days, a total of 61% activity was eliminated in the urine and 12% in the feces. The curves reach plateaus with only minor excretion after 1 wk. The dashed line displays the whole-body retention calculated from the excretion data.

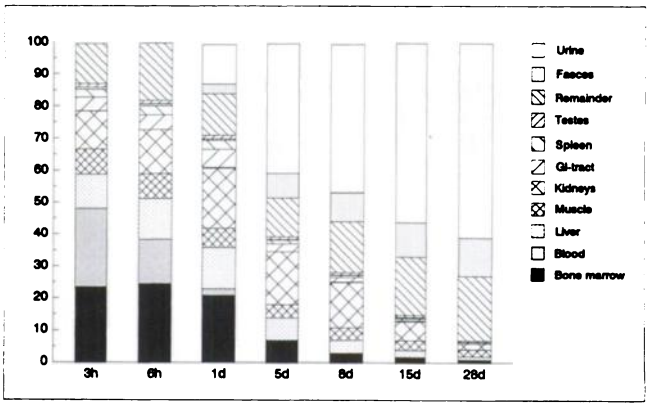

FIGURE 3. Measured percentage of injected ^{111}In in rat tissues at various times after i.v. injection of ^{111}In-CEA-F(ab')$_2$ BW431/31. The remainder includes uncollected organs (e.g., fat, skin, skeleton and lymph nodes). See Appendix 2 for the biological parameters used for the absorbed dose estimates.

than 2%. As anticipated, the organs containing most activity, apart from the red bone marrow, were the kidneys with a maximum uptake of 20% of the injected ^{111}In activity at 24 hr. The percentage of injected ^{111}In in the animal organs at various time points is shown in Figure 3. The carcass, including the skeleton, fat, fur, skin and other uncollected organs and excluding bone marrow, muscle and blood, accounted initially for 11% of the injected activity. These organs were called the *remaining tissues* in the absorbed dose calculations. The elimination of ^{114m}In followed that of ^{111}In in the organs studied (data not shown). For all organs investigated, the biokinetic curves were fitted by the least squares method and resolved into multicomponent exponential functions. The fractional distribution coefficients and the elimination constants for all tissues studied are given in Appendix 2. The cumulated activities obtained from these data and used in the absorbed doses calculations are given in Table 1.

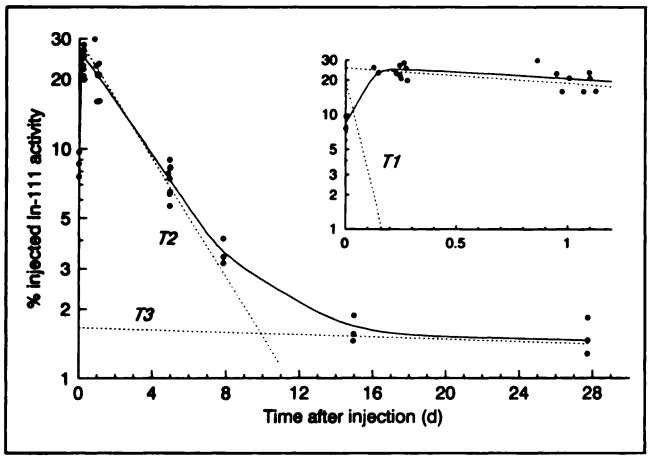

FIGURE 2. Bone marrow retention of ^{111}In activity up to 28 days postinjection. The uptake in the bone marrow is characterized by a significant rapid accumulation of about 25% of the injected activity. The retention curve was resolved and characterized as a difference and sum of three exponential functions. Elimination constants (T1-T3) are given in Appendix 1.

Estimation of Human Absorbed Doses

The estimated absorbed doses to humans are presented in Table 2. The organs receiving the highest absorbed doses of ^{111}In are the kidneys, spleen, testes and bone marrow, with 2.27, 0.51, 0.80 and 0.37 mGy MBq^{-1},

TABLE 1
Comparison of Residence Times in Organs After Single Intravenous Injection of ^{111}In-anti-CEA-F(ab')$_2$ BW 431/31 in Rats and ^{114m}In*

Source organ	Residence time, τ (hr)	
	^{111}In	^{114m}In
Bladder contents†	0.33	1.23
Blood (whole)	3.22	4.16
Bone marrow	12.60	39.56
Heart wall	0.20	0.65
Kidneys	15.88	58.26
Kidneys (excretion process)†	0.016	0.039
Liver	6.07	23.90
Lungs	0.32	0.94
Muscle (other tissue)	5.43	22.77
Spleen	1.52	3.74
Testes	0.90	5.01
Remainder	9.48	45.84
GI-tract	3.04	9.49
Stomach (wall)	0.13	0.31
Small intestine (wall)	1.30	4.71
Cecum (wall)	0.93	2.50
Colon (wall)	0.55	1.44

* The amount of impurity of ^{114m}In in the administered activity is usually only 0.04%–0.08% of the injected ^{111}In activity.

† Calculated from the whole-body data and the fraction excreted through the kidneys (61%) according to ICRP 53 (*21*).

respectively. The contamination of ^{114m}In in the administered ^{111}In-activity (i.e., 0.03%) contributes with absorbed doses less than 0.9 μGy and 6.3 μGy per MBq injected ^{111}In to the bone marrow and kidneys, respectively. The effective dose was estimated to be 0.27 mSv MBq^{-1} for ^{111}In.

DISCUSSION

In this study, human radiation absorbed doses have been estimated based on radiopharmacokinetic data from rats. For appropriate calculations of the absorbed dose to different organs, detailed studies of biokinetics and biodistribution of radiopharmaceuticals are a prerequisite. Such studies are, however, often difficult to carry out in patients, and long-term repeated measurements cannot be performed. Measurements using a scintillation camera have limited applicability for detailed distribution studies in smaller or overlapping organs and spread tissues such as the red bone marrow. Thus, it is often necessary to perform pharmacokinetic studies in an animal model for an accurate evaluation of distribution throughout the organs of the body and scale the animal data to man utilizing the MIRD human absorbed fractions. Although several attempts to characterize interspecies differences have been evaluated (*23,24*), no extrapolation method which yields more accurate results than the direct application of organ residence times from animal to human has been recognized. In the present study, we assume that the fractions of the injected activity remaining in organs and tissues are similar in rat and man. What is notable in the present study is the significant early uptake of activity in the red bone marrow, which is consistent with previous reports (*25–27*). It has been reported that several normal tissues contain measurable CEA that may be responsible for the nonspecific accumulation of ^{111}In-F(ab')$_2$ (*28*). It has also been shown that the germ cells of the normal male testes contain small concentrations of CEA which may be responsible for a specific accumulation of ^{111}In in the testes after injection of anti-CEA-Mabs (*8*).

The estimated human absorbed dose values given in Table 2 are calculated solely from pharmacokinetics obtained in rats and should be used with their inherent limitations. We believe, however, that the present study has identified the critical organs and gives reasonably good estimates of the expected macroscopic absorbed doses to the patient. The biodistribution in rats is preliminarily confirmed by human data presented by Ingvar et al. on patients with primary or secondary colorectal cancer (*29*). In spite of an expected difference between man and rat for ^{111}In activity in circulating blood, the accumulation in the liver, bone marrow and muscle is surprisingly similar between man and rat, although there are apparent differences within this small patient group (Table 3). Human organ uptake is expressed as the percentage of injected ^{111}In taken up and is compared to interpolated rat data at the corresponding times. The cumulated urinary excretion

TABLE 2
Absorbed Dose Estimates (mGy MBq^{-1}) for the Adult Human from Single Intravenous Administration of ^{111}In-anti-CEA-F(ab')$_2$ BW 431/31*

Organ	$\bar{D}$ (mGy MBq^{-1})	
	^{111}In	^{114m}In/^{114}In
Adrenals	0.24	0.27
Bladder wall	0.091	2.03
Bone surfaces	0.19	8.70
Brain	0.065	0.036
Breasts	0.054	1.93
Stomach wall	0.12	0.24
SI wall	0.18	2.40
ULI wall	0.21	5.81
LLI wall	0.15	4.76
Kidneys	2.27	100.30
Liver	0.29	6.65
Lungs	0.070	0.75
Bone marrow	0.37	18.14
Muscle (other tissue)	0.061	0.28
Ovaries	0.11	1.96
Pancreas	0.20	2.03
Skin	0.044	1.91
Spleen	0.51	10.87
Testes	0.80	65.80
Thymus	0.057	1.92
Thyroid	0.038	0.90
Uterus	0.10	1.95
Total body	0.092	1.55
Heart wall	0.096	0.41
Gall bladder wall	0.19	2.03
Effective Dose (mSv MBq^{-1})	0.27	12.81

* The absorbed doses of ^{111}In were estimated using MIRDOSE2 (Oak Ridge), while the absorbed doses of ^{114m}In were estimated using ICRP53 computer code (Malmö).

from the patients, redrawn in Figure 4, is also roughly comparable to that in rats. In addition, scintigrams showing the biodistribution of ^{111}In-activity in these patients after intravenous injection of ^{111}In-labeled anti-CEA-F(ab')$_2$ BW 431/31 fragments from the same batch (Fig. 5) confirm a similar biodistribution between man and rat.

Radiation doses given by the manufacturer of the ^{111}In-labeled anti-CEA-F(ab')$_2$ BW431/31 are 0.39 mGy MBq^{-1} for the liver, 0.46 mGy MBq^{-1} for the spleen, 0.36 mGy MBq^{-1} for bone marrow, 1.27 mGy MBq^{-1} for the kidneys and 0.11 mGy MBq^{-1} for the whole body (*30*). Human distribution data were used for the liver, kidney and whole body, while rat data were used for the spleen and bone marrow. Benz et al. have published biodistribution and radiation dose data in patients receiving the intact anti-CEA antibody BW431/26 labeled with either ^{111}In or ^{99m}Tc (*31*). BW431/26 has other properties than BW431/31 that nevertheless result in a fairly similar radiation dosimetry for ^{111}In. The absorbed dose to the liver, spleen, kidney and whole body was estimated to be 0.69, 0.54, 0.29 and 0.1 mGy MBq^{-1}, respectively. The absorbed dose to the kidneys is lower mainly due to different metabolisms of

TABLE 3
Indium-111 Activity in Surgical Samples from CEA Patients in Comparison to Data from Rats

	(%Injected ^{111}In)								
	Patients* (n = 6)						Rats†		
Days p.i.	(2 d) m	(3 d) m	(3 d) m	(4 d) f	(4 d) f	(4 d) f	(2 d)	(3 d)	(4 d)
Organ									
Blood	7.5	4.9	5.9	3.2	4.6	3.3	1.0 ± 0.2	0.5 ± 0.1	0.2 ± 0.1
Liver	7.0	12.0	11.2	47.8	7.4	1.6	10.7 ± 2.0	9.1 ± 1.9	7.8 ± 1.7
Marrow	19.9	n/a	8.0	6.5	7.3	3.9	15.6 ± 3.7	12.1 ± 3.0	9.3 ± 2.5
Muscle	4.5	4.9	9.9	5.3	5.9	3.5	5.6 ± 1.8	4.9 ± 1.7	4.3 ± 1.6

* Figures recalculated and given as percentage of the injected activity using normal organ values for ICRP standard man and woman, respectively (ICRP 1975). Patient data were obtained from (*29*).

† Interpolated values in the retention curves obtained in the present animal study. The uncertainty of the values given is estimated from the standard error in the declination coefficients.

m = man and f = female.

intact antibodies and fragments. The above dose data are not very different from the estimations in the present investigation. The effective dose for ^{111}In-anti-CEA-F(ab')$_2$ was estimated to be 0.27 mSv MBq^{-1}, which is the same as the published figure for ^{111}In-transferrin, i.e., 0.26 mSv MBq^{-1} (*21*).

Most radiopharmaceuticals used for routine diagnostic procedures give absorbed doses that have been considered acceptable for adult patients. The absorbed doses are well below the dose thresholds at which deterministic effects can occur. There is, however, no recognized dose threshold for stochastic effects, and even a small absorbed dose may theoretically increase the risk of cancer or produce serious inherited disorders. In general, even if an established nuclear medical examination is considered safe, every increment of absorbed dose to an individual may carry some risk, according to the philosophy of radiation protection (*22*). In nuclear medicine, including the use of radiolabeled antibodies, the health benefit outweighs the potential ra-

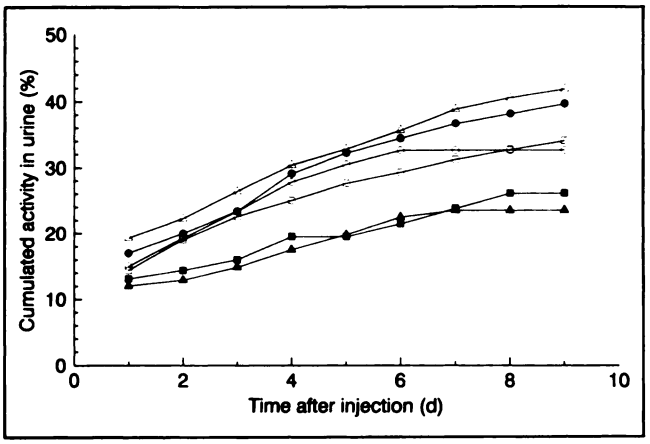

FIGURE 4. Cumulated activity in urine for six patients (solid markers:male, open markers:female) 0 to 9 days after injection of ^{111}In-labeled anti-CEA-F(ab')$_2$ BW 431/31 [reprinted with courtesy of (*29*)].

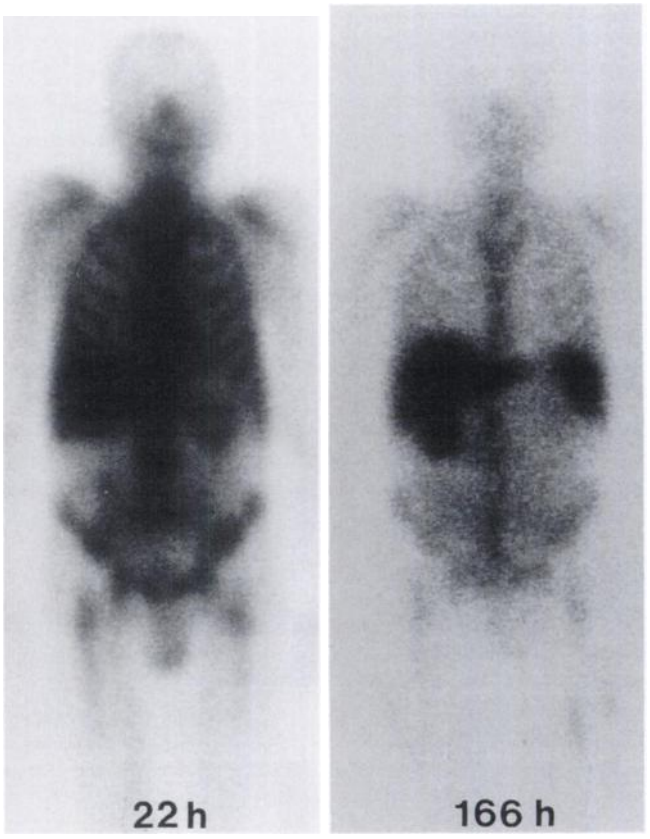

FIGURE 5. Anterior-posterior whole-body scans show tracer biodistribution in a male patient with suspected metastasis in the liver of carcinoembryonic origin. Left scintigram is taken 22 hr after injection, and the right is a postoperative scintigram 166 hr after injection of 135 MBq ^{111}In-labeled anti-CEA-F(ab')$_2$ 431/31. The biodistribution is very similar to that found in the present animal experiment, with notable activity accumulation in several tissues [reprinted with courtesy of (*29*)].

diation risks, but these should nevertheless be weighed seriously, both for tumor- and nontumor-specific agents, and especially for pediatric patients, breast-feeding women, women of child-bearing age and research uses. Since the hazards of radiation increase with absorbed dose, optimization of the administered activity as well as the imaging equipment is of prime importance.

In conclusion, the biodistribution data obtained in rats for ^{111}In-labeled anti-CEA-F(ab')$_2$ BW431/31 have been used for human absorbed dose estimations. The major proportion of the administered activity was retained in the red bone marrow and the kidney. The organs with the highest radiation burden are the kidneys, the reproductive system and red bone marrow. Of further importance is information on inhomogeneous activity distribution at the cellular level in these tissues because of the emission of low energy electrons from ^{111}In. In parallel studies, it has been found that ^{111}In activity accumulation is heterogeneous, distributed in various tissues (*32,33*). These observations will become more significant when cellular dosimetry is considered (*34,35*). Thus, information of the detailed activity biodistribution in animals together with important human biokinetic data may give us the necessary information for accurate radiation dosimetry at macro- and microscopic levels.

APPENDIX 1

Dosimetric Calculations

Several methods of calculating the absorbed dose to an organ from radionuclides have been described. The calculations reported in this paper are based on the method described in (*18*) with:

$$\bar{D}(r_k) = \sum_h \tilde{A}_h(0, \infty)S(r_k \leftarrow r^h), \qquad \text{Eq. 1}$$

where $\bar{D}(r_k)$ is the mean absorbed dose to any target organ r_k from cumulated activity in any source organ r_h $\tilde{A}_h(0, \infty) = \int_0^\infty A_h(t)dt$ is the cumulated activity in the source organ and $S(r_k \leftarrow r_h)$ is the absorbed dose in r_k per unit cumulated activity in r_h.

The cumulated activity $\tilde{A}_h$ in the source organ r_h over an infinite period is given by integrating the fractional distribution function (i.e., α_{h_j} is the *j-th* fractional uptake in r_h):

$$A_h(t) = A_0 \sum_j \alpha_{hj}e^{-\lambda_j t}, \qquad \text{Eq. 2}$$

which has the solution $\tilde{A}(0, \infty) = A_0 \sum_j \alpha_{hj}/(\lambda_j + \lambda)$, where λ_j is the biological elimination constant of the j-*th* exponential component and λ is the physical decay constant of the radionuclide.

$\tilde{A}$ usually is expressed relative to the administered activity, A_0. The ratio $\tilde{A}/A_0$ is defined by the MIRD method as the *residence time*, τ, which has the dimension of time (hr). Multiplication of τ by S yields the absorbed dose per unit cumulated activity.

ACKNOWLEDGMENTS

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APPENDIX 2

Biological Parameters of the Fractional Distribution Function $\alpha_h(t)$ of ^{111}In-CEA-F(ab')$_2$ in Wistar Rats (n = 32)

$$\alpha_h(t) = \sum_j \alpha_{hj}e^{-\lambda_j t}$$

Source organ	α_{h1}	λ_1 (d^{-1})	α_{h2}	λ_2 (d^{-1})	α_{h3}	λ_3 (d^{-1})	α_{h4}	λ_4 (d^{-1})
Blood	0.565	36.481	0.402	4.587	0.0319	0.767	0.00107	0.0248
Liver	−0.0457	0.693	0.0896	0.267	0.0508	0.0588	—	—
Spleen	−0.0282	6.112	0.0256	0.303	0.00584	0.0638	—	—
Bone marrow	−0.184	19.416	0.252	0.297	0.0166	0.00578	—	—
Lungs (both)	0.0056	0.706	0.00232	0.0601	—	—	—	—
Muscle	0.0576	0.648	0.0459	0.0393	—	—	—	—
Heart wall	0.00243	0.5065	0.00145	0.0507	—	—	—	—
Kidneys (both)	−0.254	1.643	0.254	0.090	—	—	—	—
Testes (both)	0.0106	0.0368	—	—	—	—	—	—
Thyroid	0.00004	0.338	0.00003	0.0216	—	—	—	—
Gastrointestinal tract	−0.0441	3.788	0.0524	0.303	0.0136	0.0408	—	—
Stomach	0.0014	0.3505	0.0014	0.0514	—	—	—	—
Small intestine	−0.0320	1.3368	0.0278	0.3293	0.0042	0.0221	—	—
Cecum	−0.0174	6.7624	0.0128	0.2566	0.0047	.0672	—	—
Colon	−0.0167	1.9827	0.0157	0.4642	0.0010	0.0206	—	—
Remainder*	0.1120	0.0462	—	—	—	—	—	—
Total body†	0.584	0.245	0.416	0.0143	—	—	—	—

* Remainder is approximated to be tissues not included above, i.e., the carcass including for example adrenals, fat, skeleton and skin. The half-life was assumed to be the same as for muscle.

† Total body includes all tissues (calculated from excretion data).

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