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# Estimates of Radiation Absorbed Dose for Intraperitoneally Administered Iodine-131 Radiolabeled B72.3 Monoclonal Antibody in Patients with Peritoneal Carcinomatoses

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Using a newly available model for determining estimates of radiation absorbed dose of radioisotopes administered intraperitoneally, we have calculated absorbed dose to tumor and normal tissues based on a surgically controlled study of radiolabeled antibody distribution. Ten patients with peritoneal carcinomatosis received intraperitoneal injections of the murine monoclonal antibody B72.3 radiolabeled with  $^{131}\text{I}$ . Biodistribution studies were performed using nuclear medicine methods until laparotomy at 4–14 days after injection. Surgical biopsies of normal tissues and tumor were obtained. The marrow was predicted to be the critical organ, with maximum tolerated dose [200 rad (2 Gy) to marrow] expected at about 200 mCi (7.4 GBq). In patients with large intraperitoneal tumor deposits, the tumor itself is an important source tissue for radiation exposure to normal tissues. Local “hot-spots” for tumor-absorbed dose were observed, with maximum tumor-absorbed dose calculated at 11000 rad (11 Gy) per 100 mCi (3.7 GBq) administered intraperitoneal; however, tumor rad dose varied considerably. This may pose serious problems for curative therapy, especially in patients with large tumor burdens.

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**C**olorectal and ovarian cancers spread locally within the peritoneum and may stay confined within the peritoneal cavity for long periods of time before distant metastases occur (1,2). Radiolabeled monoclonal antibodies have been injected into body cavities including peritoneum

with the idea of locally delivering concentrated radioactivity to peritoneal tumor deposits for the purpose of radioimmunotherapy. Initial studies performed by Epenetos and colleagues were encouraging (3,4), and in a larger series of patients with locally advanced ovarian cancer, the use of radiolabeled antibody [ $^{131}\text{I}$ -anti-human milk fat globulin, 100 mCi (3.7 GBq) IP] was associated with apparent tumor response, especially in patients with low volume disease (5). Moreover, there is evidence that at least for some anti-tumor antibodies, including those included in this report, the intraperitoneal route of injection is superior to the intravenous route of injection, giving considerably better tumor-to-background ratios for intraperitoneal implants of tumor (6).

Current knowledge is incomplete regarding the tumor and normal tissue radiation-absorbed doses after intraperitoneal administration of radioisotopes. Estimates have been made for red marrow dose, using the assumption that the marrow is 25% of the total blood radiation absorbed dose, and thermoluminescent dosimeters have been used to estimate local serosal radiation absorbed dose (5). However, radiation absorbed doses to intraperitoneal organs have not been reported, and information on the dose actually delivered to tumor is not available. In large part, this is because surgical biopsies of tumor and normal tissues are rarely obtained in the course of such studies, and also, until quite recently, the MIRD schema did not include a systematic and general approach to the problem of intraperitoneally administered radioisotopes.

At the National Institutes of Health, we performed a surgically documented study of the biodistribution of the radiolabeled monoclonal antibody,  $^{131}\text{I}$ -B72.3, after intraperitoneal administration in a series of patients who were scheduled to undergo surgical resection of intraperitoneal carcinomatosis. These patients offered a unique opportu-

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nity to obtain extensive surgical specimens at multiple sites within the peritoneal cavity, for the measurement of concentrations of specific and nonspecific radiolabeled monoclonal antibodies in both tumor and normal tissues. Moreover, detailed kinetic studies were performed with computerized gamma cameras and probe systems, and direct blood sampling, to obtain information on tumor, tissue and organ clearances.

The biodistribution information obtained has served as the basis for several reports, these involve the correlation of immunohistochemistry and tumor localization after intraperitoneal administration (6) and the value of diagnostic imaging for the detection of occult tumor using an intraperitoneal administration for radioimmunoscintigraphy (7).

The Internal Radiation Dosimetry Center at Oak Ridge Associated University (ORAU) has recently published a method for calculating estimates of absorbed dose of radioactive material in the peritoneal cavity (8). In this report, we present normal tissue and tumor estimates of absorbed dose from the intraperitoneal injection of radiolabeled anti-tumor antibody,  $^{131}\text{I}$ -B72.3, based on the ORAU approach, and the tissue uptake and clearance data obtained during the course of nuclear medicine and surgical studies on a series of patients with peritoneal carcinomatosis. Doses for  $^{131}\text{I}$ , a therapeutically relevant isotope of iodine, have been included. An abstract describing this general method has been previously published (9).

## METHODS

### Antibody Preparation and Radiolabeling

B72.3, a murine monoclonal antibody IgG1, was labeled with  $^{131}\text{I}$  by the Iodogen method as previously described (6,7,12) to specific activities of 6.6 to 11.2 mCi (244 to 414 MBq) per mg with no detectable loss of immunoreactivity, when compared to unlabeled antibody in a competition assay (13).

### Patient Studies

Ten adenocarcinoma patients were enrolled in a pre-existing NCI Surgical Oncology Branch protocol and were found to be candidates for cytoreductive surgery. At surgery, the findings were metastatic colorectal (four patients) or appendiceal adenocarcinoma (six patients), confined to the intraperitoneal space. The patients ranged in age from 16–63 yr of age, with a median age of 36 yr.

The radiolabeled antibody preparation [10 mCi (370 MBq) of  $^{131}\text{I}$ -B72.3] was injected intraperitoneally through a Tenckhoff catheter placed in the intraperitoneal space at least 24 hr prior to the antibody administration. All patients had surgical exploration within 4–14 days (median 8 days) after the radiolabeled antibody infusion.

The patients were imaged within 2 hr of Mab administration, and then daily up to the day prior to surgery, using a General Electric 535 gamma camera and Hewlett Packard Scintigraphic data analyzer. No blood-pool or organ subtraction was performed. Scanning results were used to obtain quantitative information about organ, tumor, and peritoneal clearances which in turn were used to calculate the estimates of absorbed dose values presented below (7).

At the time of surgery, biopsies of tumor and normal tissue were weighed and counted in a gamma counter, and histologic and immunohistologic analysis was performed (6).

### Estimates of Absorbed Dose

*Normal Tissues: Region of Interest (ROI) Analysis.* Measurements of whole-body clearance with a thyroid probe positioned at a fixed distance from the patient, and urine radioiodine output, were used to obtain biologic parameters for calculating the cumulative activity of the radioisotopes in question. In principle, each patient's individual biodistribution values would give the most accurate estimates of absorbed dose, but for the purposes of this paper the data have been pooled, based on average values. It should be noted that the range of values was considerable, determined in part by the mass of intraperitoneal tumor and the long half-life of clearance from tumor. The following distribution values were used: biologic half-life of free antibody from peritoneum 30 hr (range 19–54 hr); based on the three patients with no detectable tumor uptake on scans in this series; tumor half-life of 120 hr based on ROI clearance values from large intraperitoneal tumor sites in two patients (both patients had the same half-life); clearance from the whole-body 72 hr (range 31–163 hr, based on the eight patients in this series who had adequate data for the measurement). Whole-body clearance was considered to be exclusively through the kidneys (transit time of 0.16 hr) with excretion via the bladder, which was considered to have been emptied every 4 hr. A model of the peritoneal cavity devised for estimating absorbed dose was used which was presented in detail elsewhere (8).

For dosimetry purposes, the peritoneum, whole body, kidney, and bladder were considered to be the source organs for the major organs and tissues. The "whole body" is actually the "remainder" of organs and tissues after the fractional radioactivity in the other source organs has been subtracted away. The time-dependent activity in each of these organs was derived from a series of differential equations. Uptake into tumor (if present) was considered to be instantaneous, and the clearance of the radioactivity from both peritoneum and tumor was thought to pass directly into the whole body, with clearance through the kidneys into the bladder. In addition, the dose to peritoneal surface was also computed, based on methods described in more detail in reference 8. Here the beta component dominates, and the distribution of antibody was assumed to be a "surface source" (See Table 7 of reference 8), for the absorbed dose constants used to compute estimates of dose (Table 1).

Because therapy was the major consideration, the data from  $^{131}\text{I}$ , a commonly employed therapeutic radionuclide, is presented. We found that unlike the situation that pertains to intravenous injection of radiolabeled antibody, in which case only a small amount of the total antibody is associated with the tumor, for intraperitoneal injections a large amount of the dose can be taken up by tumor. (See Figs. 2 and 3 where approximately 40% of the dose was localized to tumor.) For this reason, calculations were performed with the recognition that different fractions of the dose would be localized in the tumor, and estimates are shown for %dose in tumor = 20%, 40%, 60%, 80%, and 100% of the injected radioactivity, respectively.

S factors for normal tissue radiation absorbed dose from the fraction of the dose bound to tumor was assumed to be the same as for the peritoneum.

*Tumor Dosimetry.* Calculation of tumor dosimetry was based on the biologic half-life (120 hr) and the physical half-life of  $^{131}\text{I}$

**TABLE 1**  
Radiation Absorbed Dose Estimates to Sub-Peritoneal Tissue 100 mCi (37 MBq) Injected Intraperitoneally [Average Dose: rad (Gy)] at Various Depths for <sup>131</sup>I-B72.3 IgG

Distance below surface (cm)	% Injected radioactivity in tumor				
	0%	20%	40%	80%	100%
0.003	6900 (69.0)	6300 (63.0)	5800 (58.0)	4700 (47.0)	4200 (42.0)
0.006	5100 (51.0)	4800 (48.0)	4400 (44.0)	3600 (36.0)	3200 (32.0)
0.018	2700 (27.0)	2500 (25.0)	2300 (23.0)	1900 (19.0)	1700 (17.0)
0.030	1600 (16.0)	1500 (15.0)	1400 (14.0)	1100 (11.0)	1000 (10.0)
0.050	720 (7.2)	670 (6.7)	610 (6.1)	500 (5.0)	440 (4.4)
0.080	150 (1.5)	140 (1.4)	130 (1.3)	100 (1.0)	92 (.92)

to develop an effective half-life of 104 hr. The total mCi-hr was computed by utilizing the value for the content of radioactivity in the tumor at the time of injection (TO) for an injected dose of 100 mCi (3.7 GBq). Based on an absorbed dose constant of 0.4164 mCi-hr, an absorbed dose was calculated from the formula Dose (rad) = 1.44 × T1/2 (effective) × mCi/g of tumor × absorbed dose constant in rad-g/mCi-hr. Calculations were made for the minimum, average, and maximum doses and are listed in Tables 2 and 3. For the purposes of tumor dose, the gamma dose contributions were ignored, and the beta decay and all low-energy electrons less than 10 KeV were considered to be "non-penetrating".

**Dose Rate Calculations.** The dose rate to a given organ was computed from the known time-dependent distribution of radioactivity in the five source tissues and from the S values available from MIRDOSE (8,14). Calculations are shown for marrow, peritoneal surface, and for tumor, based on the maximum tumor concentration obtained at surgery (Patient 2 in Table 2). In regard to tumor dose, it is important to realize that this is the best dose rate that can be achieved, and that the dose rate generally will be less than this in most cases.

**TABLE 2**  
Tumor Content of Iodine-131-B72.3 IgG at Surgery Following Intraperitoneal Injection

Patient	Time of surgery (days)	No. of sites RI*	% injected activity/g (×E4)					
			TOS tumor			TO tumor		
			Min	Avg	Max	Min	Avg	Max
1	9	1	2	4	6	7	14	21
2	8	40	110	310	900	330	940	2700
3	4	16	30	40	47	52	70	82
4	7	44	40	150	320	110	410	870
5	14	17	4	7	17	26	49	120
6	6	6	26	74	250	59	170	570
7	8	15	11	83	110	33	120	330
8	7	32	9	67	190	23	180	500
9	7	6	3	9	17	8	24	45
10	10	10	1	2	4	2	10	14

Abbreviations: T,N = tumor and normal tissue sites; TOS = time of surgery; and TO: time of injection.

Tumor uptake is extrapolated back to time of injection, based on the values obtained at the time for surgery and the tumor clearance half-time rate of 120 hr.

\* RI = radiolocalization index (21).

## RESULTS

Figure 1 shows anterior whole-body images of the clearance of <sup>131</sup>I-B72.3 after intraperitoneal injection in a patient who had less than 10 g of TAG 72 negative tumor at surgery. This image represents the distribution of protein in the peritoneum with free flow in the pericolic gutters, up over the liver and spleen. By 24 hr, there is pooling in the pelvis. Gradually, the radiolabeled antibody is absorbed and a whole-body outline is seen. On the other hand in a patient with extensive peritoneal involvement, a very different pattern is seen (Fig. 2).

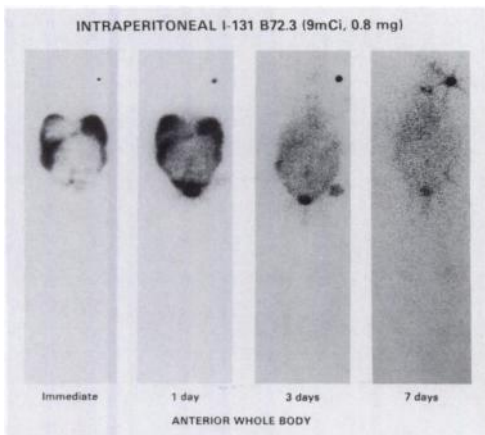
The patient was a 38-yr-old male with pseudomyxoma peritonei (Patient 3 in Table 3). Three days prior to surgery, the patient received 10 mCi (370 MBq) <sup>131</sup>I (1.1 mg B72.3) through a Tenckhoff catheter into the peritoneal space. There was rapid localization of antibody in a diffuse pattern throughout the peritoneum. At 24 hr, peritoneal lavage was performed through the Tenckhoff catheter, and a total of 49% of the injected radioactivity was removed in the lavage fluid. A total of 3% of the activity had been excreted in the urine, and the radioactivity retained in the body after the lavage was measured using a whole-body counter and found to be 47%.

Based on the images taken at 24 hr and at subsequent times, the radioactivity was localized on the tumor. Clearance from the peritoneum was much slower than that seen

**TABLE 3**  
Tumor Dose rad\*(Gy) for <sup>131</sup>I-B72.3 (100 mCi (3.7 GBq) Administered Intraperitoneally)

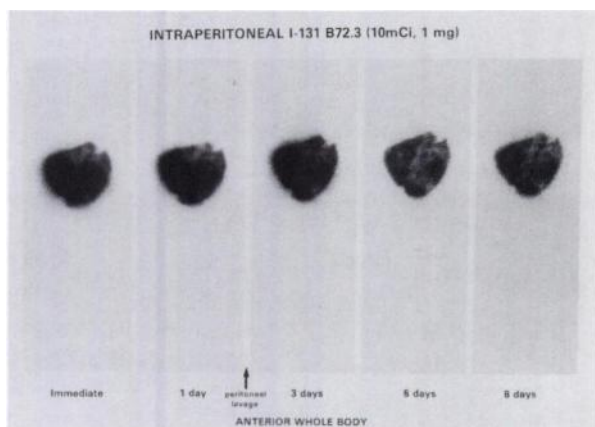
Patient	Minimum	Average	Maximum
1	30 (0.30)	60 (0.60)	91 (0.91)
2	1429 (14.29)	4071 (40.71)	11692 (116.92)
3	225 (2.25)	303 (3.03)	355 (3.55)
4	476 (4.76)	1776 (17.76)	3767 (37.67)
5	113 (1.13)	212 (2.12)	520 (5.20)
6	256 (2.56)	736 (7.36)	2468 (24.68)
7	143 (1.43)	519 (5.19)	1429 (14.29)
8	100 (1.00)	780 (7.80)	2165 (21.65)
9	21 (0.21)	104 (1.04)	195 (1.95)
10	10 (0.10)	42 (0.42)	61 (0.61)

\* Refer to Table 2, Patient 2 for biologic data.



**FIGURE 1.** Whole-body gamma camera images obtained after the intraperitoneal injection of  $^{131}\text{I}$ -B72.3 in a patient without antigen-positive tumor in the peritoneum. (See text for details.)

in subjects without intraperitoneal tumor. Whole-body probe measurements, obtained with a 4" diameter NaI crystal and thyroid collimator, of the percent retention as a function of time postinjection, using the immediate postinjection image as 100%, were as follows: 24 hr (pre-lavage), 88%; 48 hr (immediately post-lavage) 47%; 72 hr, 46%; 144 hr, 25%; 168 hr, 24%; 192 hr, 23%. Clearance half-life was estimated to be about 120 hr, taking the post-lavage counts (2 days) until the Day 8 count. The patient went to surgery 3 days later, where extensive tumor was found, replacing the omentum infiltrating the peritoneal surface. Tumor distribution corresponded to the diffuse uptake throughout the peritoneum that was seen on the scan. Because of the extensive tumor burden seen at surgery, only three biopsies were obtained and the patient was closed without undergoing significant resection of tumor. These combined data suggest that in this patient 40% or more of the  $^{131}\text{I}$ -B72.3 dose localized to his abdominal tumor.



**FIGURE 2.** Whole-body gamma camera images obtained at intervals after the intraperitoneal injection of  $^{131}\text{I}$ -B72.3 in a patient with extensive pseudomyxomatous peritonei.

### Time Course of Biodistribution of $^{131}\text{I}$ -B72.3

The measured parameters of clearance of  $^{131}\text{I}$ -B72.3 IgG was used to compute clearances from the five source organs and tissues: peritoneum ( $T_{1/2} = 30$  hr), tumor ( $T_{1/2} = 120$  hr), whole body ( $T_{1/2} = 72$  hr), kidney and bladder (empty q4h). Biodistribution, when 40% of the injected dose is bound to tumor, is shown in Figures 2 and 3. The maximum radioactivity in the kidney was only a few hundred microcuries, and the renal time-activity curve is plotted on the figure, but it is not readily distinguished from the x-axis line on this scale. The integral of the plotted activity in the source organs is the actual cumulative radioactivity, and loss from the compartments reflects the effects of both physical decay and biologic clearance. Similar data were also calculated for the case when 0%, 20%, 60%, 80%, and 100% of the injected dose were bound to tumor (data not shown). The area under each of these curves was calculated to provide the cumulated radioactivity in mCi-hr for the computation of dose to individual target organs by the MIRD method (14).

### Normal Tissue Dose After Intraperitoneal Injection

Calculation of the normal tissue dose by the absorbed dose fraction method is shown in Table 4, for several different fractional uptakes of  $^{131}\text{I}$ -B72.3, by tumor. Organs and tissues receiving the highest dose are thyroid, uterus, and pancreas. The thyroid received 2,600 rad (2.6 Gy)/100 mCi (3.7 GBq) injected, a dose at which some damage may be seen, indicating that patients' thyroid status should be followed in the post-treatment period even though acute effects are unlikely to occur. It should be noted that this dose is computed based on the fact that thyroid uptake of  $^{131}\text{I}$  in the fully suppressed thyroid gland is 0.25% of the injected dose at 24 hr (15) and an absorbed dose of 5.2 rad/mCi retained at 24 hr (16). Uterus and pancreas receive between 289 and 775 rad (2.87–7.75 Gy) per 100 mCi (3.7 GBq) injected, as a result of their location relative to the intraperitoneal contents. An increased fraction of activity in the tumor results in greater absorbed dose to these organs. These normal tissues are relatively radio-resistant, and such doses are unlikely to result in acute symptoms or sub-acute disturbance in function. Among organs receiving an intermediate dose, the small and large intestine and stomach deserve mention because of the known radiosensitivity of these organs. Acute doses of greater than 500 rad (5 Gy) would be expected to evoke some symptoms, but for single doses of 100 mCi (3.7 GBq), there appears to be some margin of safety for acute toxicity. Gonadal exposure is significant, with the ovaries receiving up to 228 rad (2.28 Gy) at the largest fraction of tumor uptake.

The organ most likely to suffer acute effects is the bone marrow, which may receive up to 120 rad (1.2 Gy) for the 100-mCi (3.7 GBq) dose at the highest fractions of tumor uptake. Such doses would be expected to have a myelosuppressive effect (17), but this should be tolerated without symptoms in patients with normal marrow function.

**TABLE 4**  
Radiation Absorbed Dose for Normal Tissues\*

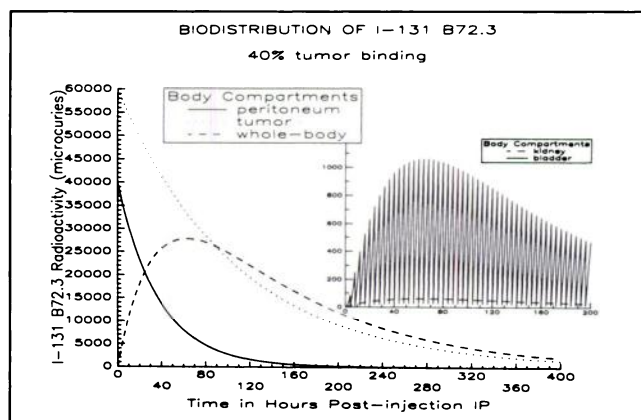
Target tissue	% ID taken up in tumor					
	0%	20%	40%	60%	80%	100%
Whole body	88 (0.88)	92 (0.92)	96 (0.96)	100 (1.0)	103 (1.03)	107 (1.07)
Uterus	332 (3.32)	421 (4.21)	509 (5.09)	598 (5.98)	687 (6.87)	775 (7.75)
Marrow	99 (0.99)	104 (1.04)	108 (1.08)	112 (1.12)	117 (1.17)	122 (1.22)
Liver	124 (1.24)	138 (1.38)	152 (1.52)	166 (1.66)	180 (1.80)	194 (1.94)
Spleen	106 (1.06)	113 (1.13)	120 (1.20)	127 (1.27)	134 (1.34)	142 (1.42)
Small bowel	167 (1.67)	196 (1.96)	226 (2.26)	255 (2.55)	285 (2.85)	314 (3.14)
Upper large intestine	152 (1.52)	175 (1.75)	199 (1.99)	223 (2.23)	247 (2.47)	271 (2.71)
Lower large intestine	99 (0.99)	102 (1.02)	105 (1.05)	109 (1.09)	113 (1.13)	117 (1.17)
Stomach	128 (1.28)	143 (1.43)	158 (1.58)	174 (1.74)	189 (1.89)	205 (2.05)
Pancreas	289 (2.89)	364 (3.64)	439 (4.39)	513 (5.13)	588 (5.88)	662 (6.62)
Testes	79 (0.79)	71 (0.71)	73 (0.73)	69 (0.69)	66 (0.66)	63 (0.63)
Ovary	138 (1.38)	177 (1.77)	174 (1.74)	192 (1.92)	210 (2.10)	228 (2.28)
Kidney	155 (1.55)	171 (1.71)	186 (1.86)	201 (2.01)	217 (2.17)	232 (2.32)
Bladder	259 (2.59)	260 (2.60)	261 (2.61)	262 (2.62)	263 (2.63)	264 (2.64)
Thyroid	2600 (26.0)	2600 (26.0)	2600 (26.0)	2600 (26.0)	2600 (26.0)	2600† (26.0)

\* Average dose rad (Gy) after intraperitoneal injection of 100 mCi (3.7 GBq) of I-131 B72.3 IgG.

† Based on blockade of the thyroid to 0.5% of the injected dose and considering the radiation dose to be 5.2 rad/mCi or 0.141 cGy/KBq.

### Tumor Dosimetry

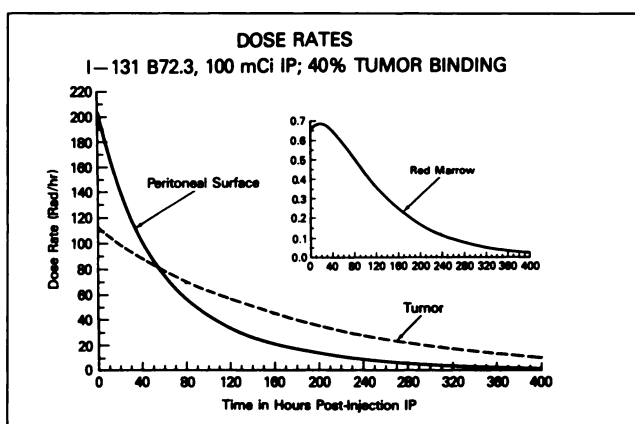
Based on the calculations shown in Table 3, there is considerable tumor radiation from 100 mCi (3.7 GBq) of injected <sup>131</sup>I-B72.3 in selected patients with disseminated intraperitoneal carcinomatosis. In this group of patients, about 40% had at least some lesions that would have received greater than 2,000 rad (20 Gy) to tumor. Radiation to sub-peritoneal tissue (Table 1) would be likely to give even greater radiation doses to tumor cells that are seeding the peritoneal surface. In fact, the exposure to these surfaces should be close to tumoricidal even with a single injection. However, the absorbed dose falls off very rapidly with depth, and the clinical relevance of microscopic dose rates is still a matter of conjecture.



**FIGURE 3.** Time-dependent biodistribution of <sup>131</sup>I-B72.3, assuming 40% tumor binding, after intraperitoneal injection of 100 mCi (3.76 GBq) of radiolabeled antibody (see text for details).

### Dose Rates to Selected Tissues

Dose rates can affect tissue response to radiation (18, 19). If the time-dependent distribution of radioactivity in the source organs is known, it is possible to compute the dose rates to target tissues. Using the distribution of radioactivity shown in Figure 3, the time-dependent dose rates were calculated for marrow and peritoneal surface and are shown in Figure 4. The peak dose rate to marrow from



**FIGURE 4.** Dose rates to tumor, peritoneum, and marrow as a function of time postinjection of 100 mCi (3.7 GBq) B72.3, with 40% tumor uptake. Dose rates are calculated from the biodistribution information in Figure 1. Peak rates are less than 0.7 rad/hr (cGy/hr) for marrow. For the peritoneum, the peak rates are high initially, at 210 rad/hour (2.1 Gy/hr). This dose is delivered to the most superficial 30 microns of peritoneal surface and falls off rapidly with depth. Dose rates to tumor of 110 rad/hr (1.1 cGy/hr) initially were calculated using the maximum concentration obtained from the surgical biopsies. (Patient 2 in Table 3.)



100 mCi (3.7 GBq) of  $^{131}\text{I}$  administered intraperitoneally occurs at about 20 hr postinjection because the whole body is the source organ that contributes most to the dose to marrow. For peritoneal surface, since the predominant radiation comes from the intraperitoneally distributed radioactivity, dose rate is at a maximum immediately after injection and declines rapidly thereafter. In this case, only the radiation from contained radioactivity within the tumor was considered in computing the dose and since the uptake was considered to be very rapid the dose rate was calculated to be highest immediately after injection.

## DISCUSSION

B72.3 is a monoclonal antibody that has been extensively studied after intravenous administration for targeting human tumors (6,13,20–22). This antibody recognizes a high molecular weight glycoprotein, termed TAG-72, with characteristics of a mucin (23).

One of the features of the tumor specimens removed at surgery, was the variability of concentration of radiolabeled antibody observed. A number of factors were examined to determine if there was a pattern to uptake differences, and multiple regression correlation was performed to evaluate the effect of antigen content, the proportion of the specimen that was tumor cells versus mucin, and whether the specimen appeared to be a hematogenous borne versus implanted tumor. As previously reported in a more formal analysis of the surgical specimen findings of these patients, the major factor that correlated best with uptake was the type of metastasis, i.e., implanted tumors had much greater uptake than hematogenously borne tumors after intraperitoneal injection (6). Multiple regression analysis showed that there was a positive correlation with antigen content and the fraction of the specimen that was tumor, but only about 16% of this variability could be explained. The distribution of the radiolabeled antibody solution in the peritoneum may be a variable that will be hard to determine from patient to patient. Adhesions, varying degrees of ascites, and the size and location of tumor masses may all play a role in the penetration of radiolabeled antibody into a given tumor deposit. (For a more detailed discussion of the distribution issue, please see reference 7, in which the diagnostic aspect of this study is presented.) The access of radiolabeled antibody to all the tumor sites after intraperitoneal injection may be limited in patients with advanced disease. This possibility suggests that patients should be treated relatively early in the course of their recurrence before multiple surgeries and caustic therapies render the physical distribution of the solution containing the radiolabeled antibody difficult.

In previous studies, we have reported a ten-fold or greater uptake in tumor in some patients, when the radiolabeled B72.3 is administered by the intraperitoneal route as compared to the intravenous route (6,7). The issue of concentration is important to estimates of absorbed dose because radiation dose delivered is directly proportional

to concentration, and for a half-life of 120 hr for clearance from tumor, a peak concentration of 0.058% ID/g of the injected radioactivity is required in order to obtain a total absorbed dose of 2100 rad (21 Gy). At this activity, as many as four repeated administrations of  $^{131}\text{I}$  IgG may be required to achieve the absorbed dose that cures the LS174T colon tumor xenograft animal model [about 8,000 rad (80 Gy)] (12). In view of the fact that a recombinant/chimeric B72.3 is now available (24), repeated injections with no or minimal human anti-murine IgG response may be feasible.

Absorbed dose to tumor will be a function of the total dose from non-penetrating radiation (from radioactivity concentrated in the tumor) and penetrating radiation (gamma rays) emitted by radioactivity in the source organs. The gamma dose contributions are dependent on the location and position of the tumor in relationship to the source organs. For tumor deposits with high uptake, the gamma component will be less than 10%, and this can be estimated by considering the dose to pancreas or other target organ in the retroperitoneum with the approximate shape and size of a "tumor" (see Table 4). Most of the dose to the pancreas occurs because of penetrating radiation. The maximum absorbed dose is 662 rads from the source tissues. On the other hand, maximum absorbed dose to tumor, as for example, Patient 2 in Table 4, is 11,692 rads or 17.8 times the absorbed dose contributed from penetrating radiation originating in the source organs.

The absorbed radiation doses calculated by the method reported in this paper for red marrow are in general agreement with the estimates of dose to hematopoietic marrow reported by others in a series of patients treated intraperitoneally with  $^{131}\text{I}$ -labeled anti-tumor antibodies (5,25). These investigators computed hematopoietic marrow exposures based on the assumption that all of the radiation is delivered to the marrow by radioactivity in the blood. Since the marrow weighs approximately 25% of the blood weight, for the purposes of calculating the dose to marrow, these investigators used the integrated radioactivity from zero to infinity in the blood (corrected for decay) and a specific absorbed dose constant for marrow of  $0.25 \times S$ , where  $S$  is the specific absorbed dose fraction for the non-penetrating radiation of  $^{131}\text{I}$ . The average value obtained in their patients was 1.5 rad per mCi (.0405 cGy/MBq) of  $^{131}\text{I}$ -labeled antibody injected. This included all patients with varying degrees of tumor involvement and is, on average, about 25% higher than the estimates that we calculated. These same investigators used thermoluminescent dosimeters (TLDs) to measure radiation absorbed dose in the abdomen and found an average of 2.85 rad per mCi (0.07695 cGy/MBq) of  $^{131}\text{I}$  injected (25). However, it is difficult to know how such data should be compared to the dose estimates to sub-peritoneal tissue reported here because the geometry of their dosimeters was such that much of radiation would be likely to have

been absorbed by the 1-mm plastic sheath covering the dosimeter. Otherwise no previous reports have included the normal tissue dose estimates that are included in our study.

A single exponential clearance approximates the data reasonably well, given the fact that a limited number of data points were available. More precise clearance curves and more detailed kinetics will probably require more quantitative imaging methods, such as positron emission tomography. In this regard, preliminary studies with  $^{124}\text{I}$ -labeled antibodies are underway here at MSKCC (Larson SM, personal communication).

## SUMMARY

Although useful for ascertaining general principles, the average clearance values used to calculate estimates of absorbed dose for Tables 1 and 4 have only limited relevance to individual patients. Clearance rates vary significantly, and these will have a major effect on the actual radiation dose to individual organs. For example, among the patients of this series, global clearance from the whole body varied from 31 hr to 162 hr (average 72 hr), which is a factor of 5. This correlated with the rate of clearance from the peritoneum, which showed a corresponding variation from 19 to 115 hr, although other factors, including varying renal clearance, also affected whole-body retention. Because of this, we recommend that individual estimates of absorbed dose be computed based on the clearance values obtained for each patient in order to correlate toxicity observed with computed radiation absorbed doses.

## REFERENCES

- Gilbert JM, Jeffrey I, Evan M, Mark AE. Sites of recurrent tumor after "curative" colorectal surgery: implications for adjuvant therapy. *Br J Surg* 1984;71:203-205.
- Barber HR, Kwon TH. Current status of the treatment of gynecologic cancer by site: ovary. *Cancer* 1976;38 (suppl 1):610-619.
- Hammersmith oncology group and the Imperial Cancer Research Fund. Antibody-guided irradiation of malignant lesions: three cases illustrating a new method of treatment. *Lancet* 1984;1:1441-1443.
- Epenetos AA, Nimmon CC, Arklie J, et al. Antibody-guided irradiation of malignant ascites in ovarian cancer: a new therapeutic method possessing specificity against cancer cells. *J Obstet Gyn* 1986;68:71-74.
- Stewart JSW, Hird V, Sullivan M, Snook D, Epenetos AA. Intraperitoneal radioimmunotherapy of ovarian cancer. *Br J Obstet and Gynecol* 1989;96:529-536.
- Colcher D, Esteban J, Carrasquillo JA, et al. Complementation of intracavitary and intravenous administration of a monoclonal antibody (B72.3) in patients with carcinoma. *Cancer Res* 1987;47:4218-4224.

- Carrasquillo JA, Sugarbaker P, Colcher D, et al. Imaging of peritoneal carcinomatosis with intraperitoneal injection of I-131-labelled B72.3 monoclonal antibody. *Radiology* 1988;167:35-40.
- Watson EE, Stabin MG, David J, Eckerman K. A model of the peritoneal cavity for use in internal dosimetry. *J Nucl Med* 1989;30:2002-2011.
- Larson SM, Carrasquillo JA, Colcher D, Reynolds JR, Sugarbaker P, Schlom J. Considerations for radiotherapy of pseudomyxoma peritonei with IP I-131-B72.3, a monoclonal antibody. *J Nucl Med* 1986;27:1021-1022.
- Stramignoni D, Bowen R, Atkinson BF, Schlom J. Differential reactivity of monoclonal antibodies with human colon adenocarcinomas and adenomas. *Int J Cancer* 1983;31:543-552.
- Anonymous. Points to consider in the manufacture of injectable monoclonal antibody products intended for human use in vivo. Office of Biologic Research and Review, Center for Drugs and Biologics, U.S. FDA. Revised Draft 6-11-84. Available from the U.S. Government Printing Office, Washington, D.C. 20402.
- Esteban JM, Schlom J, Mornex F, Colcher D. Radioimmunotherapy of athymic mice bearing human colon carcinoma with monoclonal antibody B72.3: histologic and autoradiographic study of effects on tumors and normal organs. *Eur J Cancer* 1987;23:643-655.
- Colcher D, Hand P, Nuti M, Schlom J. A spectrum of monoclonal antibodies reactive with human mammary tumor cells. *Proc Natl Acad Sci USA* 1981;78:3199-3203.
- Synder WS, Ford MR, Warner GG, Watson SB. "S" absorbed dose per unit cumulated activity for selected radionuclides and organs. In: *MIRD pamphlet 11*. New York: Society of Nuclear Medicine; 1-257.
- Moldofsky PK, Powe J, Mulhern CB, et al. Metastatic colon carcinoma detected with radiolabeled (Fab')<sub>2</sub> monoclonal antibody fragments. *Radiology* 1984;149:549-555.
- MIRD Dose Estimate Report No. 5. Summary of current dose estimates to humans from  $^{123}\text{I}$ ,  $^{124}\text{I}$ ,  $^{126}\text{I}$ ,  $^{130}\text{I}$ ,  $^{131}\text{I}$ , and  $^{132}\text{I}$  as sodium iodide. *J Nucl Med* 1975;16:857-860.
- Larson SM, Raubitschek A, Reynolds JC, et al. Comparison of bone marrow dosimetry and toxic effect of high dose I-131-labeled monoclonal antibodies administered to man. *Nucl Med Biol Int J Appl Radiat Instrum Part B* 1989;16:153-158.
- Buchegger F, Pelegrin A, Delaloye B, et al. Iodine-131-labeled MAb (Fab')<sub>2</sub> fragments are more efficient and less toxic than intact anti-CEA antibodies in radioimmunotherapy of large human colon carcinoma grafter in nude mice. *J Nucl Med* 1990;31:1035-1044.
- Humm JL, Chin LM, Macklis RM. Editorial: F(ab')<sub>2</sub> fragments versus intact antibody—an isodose comparison. *J Nucl Med* 1990;31:1045-1047.
- Thor A, Ohuchi N, Szpak CA, Johnston WW, Schlom J. The distribution of oncofetal antigen TAG-72 defined by monoclonal antibody B72.3. *Cancer Res* 1986;46:3118-3124.
- Esteban JM, Colcher D, Sugarbaker P, et al. Quantitative and qualitative aspects of radiolocalization in colon cancer of intravenously administered Mab B72.3. *Int J Cancer* 1987;39:50-59.
- Carrasquillo JA, Sugarbaker P, Colcher D, et al. Radioimmunoscintigraphy of colon cancer with I-131-B72.3 monoclonal antibody. *J Nucl Med* 1988;29:1022-1030.
- Johnson VG, Schlom J, Paterson AJ, Bennett J, Magnani JL, Colcher D. Analysis of a human tumor associated glycoprotein (TAG-72) identified by monoclonal antibody B72.3. *Cancer Res* 1986;46:850-857.
- Whittle N, Adair J, Lloyd C, et al. Expression of cos cells of a mouse-human chimeric B72.3 antibody. *Protein Engineering* 1987;1:499-505.
- Stewart JS, Hird V, Snook D, Sullivan M, Myers MJ, Epenetos AA. Intraperitoneal I-131- and Y-90-labeled monoclonal antibodies for ovarian cancer: pharmacokinetics and normal tissue dosimetry. *Int J Cancer* 1988;(suppl 3):71-76.