Dosimetry in a Myeloablative Setting

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In clinical therapy trials using high dosages of systemically administered radioactivity to treat cancer, myeloablation may occur. This is either an effect of the circulating radioactivity labeled to antibodies exposing the bone marrow to radiation, or it may occur because malignant cells in the bone marrow are targeted. Bone marrow cells may be targeted through antigens expressed on cells in the bone marrow or because radioactivity is targeted to the skeleton. Assessment of radiation absorbed dose to the marrow may be useful for dose escalation or individualized patient treatment planning. With successful preservation of marrow function with autologous marrow or peripheral blood stem cell transplantation, other normal organs may also receive sufficient radiation to show toxicity. Accurate dose estimates to these organs is important for the design of future studies in order to minimize or avoid toxicity. This paper reviews internally administered high dose radiation therapy studies, and examines the radiation absorbed dose estimates reported from these studies.

INTRODUCTION

Radiation doses over 1.5 Gy to the whole body may be associated with myeloablation. When the exposure is from accidental external exposure, the effects will depend on the whole body dose. The dose to the marrow, the other organs and the whole body are essentially the same. Doses of >100 Gy will cause death within 24–48 hours of exposure from cardiovascular and central nervous system failure. Whole body doses of 10–100 Gy cause death from gastrointestinal syndrome, within 3–10 days of exposure. Doses of 1–10 Gy can cause death by marrow ablation. With modern supportive treatment, patients may survive having been exposed to up to ~8 Gy. With death occurring from gastrointestinal syndrome at doses greater than 10 Gy, the window where bone marrow transplants is most useful is when the absorbed dose is in the range of 8–10 Gy to the whole body.

Total-body irradiation (TBI) for treatment of radiosensitive malignancy is dose limiting from bone marrow failure. The LD_{50} is presumed to be 3–4 Gy at approximately 30 days. With successful engraftment of hematopoetic progenitor cells, substantially higher doses of TBI can be safely administered. With supportive therapy to reduce complications from damage to other organs, doses as high as 10 Gy can be administered as a single fraction, and or 15.75 Gy in dose fractionated schemes, although transplant related complications are increased at these levels.

When exposed to high doses of radioactivity from internal administration of radionuclides, the effects and toxicities will depend on the biodistribution of the radiopharmaceutical. One must consider the dosimetry to both the specific tissue targeted, generally the tumor, where the aim is to deliver the highest possible dose to the tumor to achieve a response, and to the normal organs. The normal organs may be exposed to high doses of radioactivity because of cross-reactivity of antibody with antigen expressed in normal organs, from radioactivity in circulation, and from metabolism and excretion of the radioactivity. The toxicity will therefore depend on the biodistribution and metabolism of the radiopharmaceutical.

High doses of radionuclides administered sys-
temically are labeled either to large or to small molecules. Antibodies are large protein molecules, 150 kD molecular weight and have a long circulation time. When radiolabeled, they expose the marrow to high doses of radiation. Radiolabeled small molecules are now being evaluated for therapeutic purposes because maximal uptake at the target occurs very rapidly, sometimes within minutes, as opposed to 24–48 hours for intact antibodies, and non-targeted radioactivity is rapidly excreted through the urinary system. Radiolabeled peptides such as somatostatin analogues and gastrin are in clinical trials for treatment of tumors bearing the appropriate receptors; and radiolabeled biotin is used for pretargeted antibody therapy. Because of the rapid pharmacokinetics of the small molecule, myeloablation is avoided. Radioactive phosphonates are being evaluated to treat bone and bone marrow disease in patients with multiple myeloma in conjunction with stem cell rescue.

Estimates of radiation dosimetry can be useful to anticipate toxicity and efficacy, and clinical trials can be designed considering potential organ radiation toxicity. The usefulness of these estimates depends on establishing a dose response model that would depend on accurate pharmacokinetic data and an accurate dosimetric model. The MIRD methodology is commonly used, with quantitative gamma camera imaging techniques to estimate biodistribution of the radiopharmaceutical and doses estimated to a MIRD phantom. Accuracy is limited both because of the difficulties of accurately measuring radioactivity in the patient by current quantitative imaging methodology, and because of the use of standard man phantoms as a surrogate for the patient.

When imaging data are not available, mathematical models may be useful to estimate dose from limited pharmacokinetic data, such as data from external whole body counting or blood clearance. With successful marrow rescue technology, and the administration of higher doses of radioactivity, we must continue to improve the specificity of the dose estimation to individual patients so that risks of toxicity can be anticipated and dosages adjusted accordingly for patient safety.

Myeloablation from Non-Targeted Radiation
Radioimmunotherapy (RIT) has been evaluated in clinical trials for treatment of cancer for the past two decades. Bone marrow toxicity is invariably the first dose limiting tissue from internally administered radioactivity. As the dosage of radioactivity is increased, the hematological toxicity occurs earlier and the blood count nadirs are lower. As the radiation dose increases to the point where stem cell replacement is necessary for marrow recovery, at between 1 and 4.5 Gy (by external beam radiation criteria), the granulocyte count typically shows an initial increase, as peripheral cells move into the vascular system followed by a permanent drop in cell count within 4–6 days, unless marrow or stem cells are replaced (Figure 1). This is consistent with severe but reversible injury to the hematopoietic system as described by Fliedner.

The development of marrow and peripheral blood stem cell rescue techniques has allowed higher dosages of radioactivity to be administered in an attempt to deliver sufficient radiation to tumor to achieve response. Antibodies labeled with $^{131}$I, $^{90}$Y- and $^{186}$Re have been administered, fol-

![Figure 1](image-url)
owed by marrow rescue for treatment of patients with non-Hodgkin’s lymphoma (NHL) and adenocarcinomas and also in association with total body irradiation for leukemia. The majority of trials used $^{131}$I-labeled antibodies in patients with relatively radioresistant disease, and these studies were often discontinued before the second organ of toxicity was identified because of lack of response. With the improved stability of $^{90}$Y-labeled antibodies using newer chelates, the current area of most interest with myeloablative RIT is with $^{90}$Y, particularly in patients with breast cancer where encouraging responses have been observed.

Press et al. were the first investigators to report on high dose RIT in a myeloablative setting. Dosimetric evaluation played an essential part in those trials for patient selection and for the dose escalation aspect of the protocol. The design of the myeloablative trials using $^{131}$I-B1 antibody for treating NHL is such that the patient selection and dose to be administered is based on quantitative gamma camera imaging from a tracer dosimetry study with 5 mCi $^{131}$I-antibody. Predicted tumor dose estimates must be higher than normal organ dose estimates for patients to be eligible for therapy. In the initial phase I high dose radiolabeled B-1 antibody trial for NHL, the organ system of radiation toxicity that proved dose limiting was cardiopulmonary at radiation absorbed doses of greater than 27 Gy to the lungs. In the current studies, the dosimetry study must determine that tumor will receive a higher dose than any normal tissue, and a predicted dose of 27 Gy to lungs is set as the limit from which to base the dosage for each patient. Other toxicities observed have been thyroid suppression and gastrointestinal toxicity.

This trial design was adopted by others when using myeloablative doses for RIT. Juweid used this approach and set limits to kidney (initially 9 Gy), and lung and liver (initially 12 Gy), when treating patients with medullary thyroid cancer with $^{131}$I-MN14(Fab')$_2$. In general, the kidney doses determined the dosage limit. One of eight patients had dose limiting gastrointestinal toxicity, and minor toxicities were variable, including pulmonary, cardiac, neurological, hepatic, but not renal. Dose escalation was as a 3 Gy increased limit and no further toxicity identified at the next dose level. Responses were considered encouraging, with one partial response and all other patients with stable disease. The study was discontinued because a new humanized antibody became available.

Tempero et al. carried out a high-dose therapy with $^{131}$I-labeled CC49 antibody in patients with gastrointestinal cancers. Mucositis has been dose limiting in this study and has been significant in several of these trials. Local radiation absorbed dose associated with mucositis cannot be determined.

The DeNardos have taken the approach that as with chemotherapy, a higher dose can be delivered to tumor associated with less toxicity when the dose is fractionated. This approach however is limited by the fact that anti-antibodies (HAMA, HACA) develop in most patients with adenocarcinomas, thus multiple doses cannot always be administered. Two trials were reported by Richman using high dose RIT for breast cancer patients. $^{131}$I-chimeric L6 was administered, beginning at a dose level 2.5 times the maximum tolerated dose without marrow rescue. Because of HACA, only the one patient who received cyclosporin to suppress HACA was able to receive three cycles RIT. Dosimetry estimates in this one patient suggested that with dose fractionation, lung tolerance was higher than with a single high dose of radiation, lung radiation absorbed dose estimate was 31 Gy without toxicity. Richman reported results from another high dose study for breast cancer patients, using $^{90}$Y170H.82 antibody. In-111 was used as a tracer to define the therapy dose for the $^{90}$Y-antibody. The limit to normal organs was defined as 8 Gy per cycle to the liver, lungs or kidneys. With this radiomunonoconjugate, the tracer study indicated the liver defined the dosage to be administered, but no significant non-hematological toxicity was observed. For various reasons, more than one cycle was not administered. With the availability of humanized antibodies, this approach may become more feasible for treating patients with solid tumors.

**MYELOABLATION WHEN BONE MARROW IS THE TARGET**

**Targeting malignant marrow cells with radiolabeled antibodies**

Radiolabeled antibodies directed against myeloid and lymphomatous malignancies have been administered in conjunction with 12 Gy total body irradiation, and different regimens including cyclophosphamide, busulfan, and/or thiopeta, followed by allogenic or autologous bone marrow transplant or stem cell transplant.
I-anti-CD33 antibodies have been used to ablate the marrow and to target acute myelogenous leukemia (AML) in the bone marrow in order to prevent relapse of leukemia.\textsuperscript{21,22} Anti-CD33 antibodies were also labeled with \textsuperscript{90}Y and \textsuperscript{212}Bi but in both cases insufficient radiation dose was delivered to the leukemia cells to achieve a long lasting response, necessitating stem cell rescue.\textsuperscript{23,24}

I-131-anti-CD45 antibodies have been similarly used to treat AML, acute lymphocytic leukemia and advanced myelodysplasia in conjunction with autologous marrow or stem cell rescue. Based on biodistribution studies with a tracer dose of \textsuperscript{131}I-anti-CD45, using identical methods as for the myeloablative B1 antibody treatment for NHL, dose escalation was carried out with the liver radiation absorbed dose estimates being used to limit the administered dose, because from quantitative imaging the liver was the organ estimated to receive the highest radiation dose. With this radioimmunoconjugate, 84\% of 44 patients had favorable dosimetry.\textsuperscript{25} Although mucositis was the dose limiting toxicity in this study, at a liver dose level of 12 Gy, one patient experienced grade III hepatic toxicity at 10.5 Gy, determined to be the maximum tolerated dose (MTD). In this study with a heterogenous group of patients, 30\% survived disease free for 26–100 months.

\textsuperscript{188}Re anti-CD66c was used to treat myeloid or lymphoid malignancies in 43 patients in conjunction with 12 Gy TBI and autologous or allogenic stem cell transplantation, with median dosages of 289 mCi, without a second organ of toxicity identified.\textsuperscript{26} Anti-CD66c targets myeloid cells thus the blast cells are irradiated as a bystander effect. Doses to the liver ranged from 2–11 Gy, mean 4.5 Gy. With consideration of the 12 Gy TBI, these livers were estimated to receive up to 23 Gy. Mean additional dose to the marrow and spleen were both 13.5 Gy, and 5.7 Gy to kidneys. No additional toxicity due to the\textsuperscript{188}Re-anti-CD66c was noted. At six months, disease free survival was 63\%.

**Skeletal Targeted Radiotherapy**

\textsuperscript{166}Ho-DOTMP\textsuperscript{5} and \textsuperscript{153}Sm-EDTMP\textsuperscript{6} are radiophosphonates that are being used as vehicles to target bone for treatment of multiple myeloma in the bone and bone marrow. They are small molecules and thus behave differently to the radiolabeled antibodies. The primary consideration is the urinary system, as that is the route of excretion of the unbound radiophosphonates. Targeted doses as high as 48 Gy \textsuperscript{166}Ho-DOTMP to bone marrow followed by peripheral blood stem cell infusion have been administered successfully. Aspects of the\textsuperscript{166}Ho-DOTMP study are described below, as limited data from \textsuperscript{153}Sm-EDTMP has been published only in abstract form.

A phase I/II study was carried out in 83 patients with multiple myeloma. Patients were treated with melphalan 140 or 200 mg/m\textsuperscript{2} alone or 140 mg/m\textsuperscript{2} with 8 Gy TBI, and a peripheral blood stem cell transplant in conjunction with the \textsuperscript{166}Ho-DOTMP. Dose escalation was based on a targeted marrow dose that was determined from a tracer study with 30 mCi \textsuperscript{166}Ho-DOTMP. Target marrow dose ranged from 20–40 Gy to attempt to eradicate all myeloma cells within the skeleton and bone marrow. High dosages of \textsuperscript{166}Ho-DOTMP were administered to achieve these marrow doses, 460–4476 mCi (17–166 GBq). With the small molecule pharmacokinetics there was rapid targeting to skeleton and rapid excretion of non-bound \textsuperscript{166}Ho-DOTMP through urinary system. Skeletal uptake varied from 15 to 55\% and resulted in high exposure to the kidneys and to the bladder from the high doses of non-targeted radioactivity; the non-skeletal dose was inversely proportional to skeletal uptake. Methods for estimating radiation absorbed dose differed from standard dosimetry methods used with radiolabeled antibodies, because \textsuperscript{166}Ho is a difficult radionuclide to image and quantitative gamma camera imaging was not performed.

**Marrow Dose Estimates**

The primary objective of the study was to determine whether engraftment would be impacted by the high marrow radiation absorbed doses. The re-engraftment was normal in all but one patient. Median time for both granulocyte and platelet engraftment was 10 days, range 4–28 days.

The method to estimate the marrow dose evolved during the course of the trials. The method assumes that all activity remaining in the patient after 18 hours is deposited in skeleton. Based on gamma camera imaging and cumulative urinary excretion, this is a reasonable assumption. Whole body counts from 20 to 48 or 72 hours are used to derive a time-activity curve for the skeleton. The intercept of the curve is assumed to represent the initial skeletal uptake and the slope represents the skeletal disappearance time. Sixty-two percent of the skeletal activity is assumed to be bound to the trabecular bone sur-
face, based on the relative surface area of the skeleton according to ICRP 70. The S-values for $^{166}$Ho were calculated at Oak Ridge National Laboratory and obtained from Stabin at Oak Ridge Associated Universities. The adult S-value is used for all patients because the 15-year-old MIRD phantom model has a marrow distribution and marrow mass probably more representative of a growing teen than a low weight adult. The question of correcting marrow mass according to body size, rather than relying on the adult phantom mass was examined.

Figure 2a shows the marrow absorbed doses for all patients from Phase I/II studies estimated using the above methods. Adjusting the S-value by a patient specific marrow mass on the basis of body size results in markedly different dose estimates if the patient is much different to the MIRD model size (Figures 2b-d).

Figure 3 demonstrates the differences in dose estimates observed in the smallest and largest patients on the trials using the above adjustments. All the marrow dose estimates are shown from these selected patients to demonstrate the degree of alteration in the dose estimation when marrow mass is adjusted according to patient size.

The greatest variation from the standard model is with the weight correction because the largest variation from the standard model, 70 Kg, is patient weight. This approach gave a difference in marrow dose estimate as high as 20 Gy total marrow dose. The least variation is with height-based adjustments. Active marrow mass would not be expected to correlate directly with patient weight. Only about 70% of the marrow of a normal adult is located in the long bones, thus a direct correlation with height is probably not valid either. If there is truly a difference in cellularity or active marrow mass that is related to body size, the smallest and largest patients will have the greatest error in marrow dose estimate by relying on the standard MIRD phantom for the dose estimate. The body surface area (BSA) correction is a compromise between height and weight. Not shown is the lean body mass correction, which is similar to the BSA correction. The most accurate means of correcting for active marrow mass is not known, thus at the present time body surface area and lean body mass adjustments are under consideration.

**Bladder Dose**

The tolerance of bladder tissue to radiation is higher than that of the kidney, 65 Gy vs 15 Gy by external beam criteria. The accumulation of radioactivity in the bladder between voiding results in a higher radiation exposure to the bladder wall than the kidneys. It is important that the patient be hydrated to lower the concentration of urine in the bladder, and that the patient void frequently. Because bladder wall surface dose is so dependent on the concentration of radioactivity in the bladder, ideally the radioactivity should be administered when there is already non-radioactive urine in the bladder, so the radioactivity can be quickly diluted. Obtaining gamma camera counts from the bladder by counting bladder regions of interest is not practical because of the rapidly changing amount of radioactivity entering the bladder, and the frequent voiding during hydration. Several models for estimating bladder dose have been developed.

The revised Dynamic Bladder Model MIRD 14 was used to estimate the dose to the bladder wall surface. This model is the most physiological of the bladder models and considers the urine entry rate, radioactivity entry rate, initial bladder volume, residual bladder volume, and voiding intervals. The initial bladder volume and the void volumes and intervals can be varied with this model. The model was adapted for hydration, with an increased rate of urine entry into the bladder and also for increased fluid in the bladder from continuous bladder irrigation (CBI) through a bladder catheter.

This model assumes that the entry rate into the bladder is equal to clearance rate from the whole body. The assumptions used for the non-irrigated bladder when patients were hydrated with 200 ml/hr (for the therapy dose), were that the urine flow rate is 4.3 ml/min. Initial urine volume was assumed to be 300 ml, and after voiding, residual volume is 10 ml. Patients were encouraged to void hourly for the first 8 hours.

The assumptions were modified for the catheterized and irrigated bladder. Patients were hydrated with 200 ml/hr and irrigated with CBI of 200 ml/hr fluid. Urine flow rate was assumed to be 8 ml/min and the residual volume assumed to be 50 ml.

In the $^{166}$Ho-DOTMP trials, bladder toxicity was observed in several patients. Using the Bearman criteria, this is classified as microscopic hematuria or macroscopic hematuria/hemorrhagic cystitis. It occurred between 1 and 18 months following treatment, thus is a late toxicity, typical of radiation toxicity from vascular damage. Bladder toxicity occurred in 22 of the
Figure 2a. Marrow dose estimates for all patients.

Figure 2b. Marrow dose estimates when marrow mass is adjusted according to patient weight.

Figure 2c. Marrow dose estimates when marrow mass is adjusted according to patient height.

Figure 2d. Marrow dose estimates when marrow mass is adjusted according to patient body surface area.
53 patients at all dose levels who received IV hydration only. Two of 30 patients with both IV hydration and CBI had hematuria, but this was attributable to other causes, unrelated to the $^{166}$Ho-DOTMP treatment.

Dose estimates to the bladder wall for all patients are shown in Figure 4. There was a difference in the dose estimates between those patients with and without bladder toxicity. No patient who received continuous bladder irrigation with a high dose of $^{166}$Ho-DOTMP experienced bladder toxicity related to the treatment. At doses below 40 Gy to the bladder wall surface, no bladder toxicity was observed. The model indicated that continuous bladder irrigation reduced the bladder wall dose by about two-thirds. The overlap of patients with and without toxicity at dose estimates higher than 40 Gy is most likely due to the assumptions used in the model, described above. The same urine flow rate was assumed for all patients. With the differences in urine volume produced by different patients, this assumption increases the uncertainty in the patient specific dose estimates. Because of radiation safety concerns, urine cannot be collected following the therapy dose to derive improved dose estimates. To prevent or reduce hemorrhagic cystitis in future patients, lower dosages will be administered and all patients will be catheterized with continuous bladder irritation.

**Thrombo-Microangiopathic (TMA) nephropathy** was another late toxicity occurring on this trial in 8% of the patients. Although the patients who experienced the syndrome were patients at the highest dose level according to the targeted marrow dose, correlation with radiation absorbed dose to kidneys was poor, and the histological changes on renal biopsy from TMA cannot be differentiated from radiation nephritis. Whether this was due to the effects of the treatment, or from other causes present in this population group, including drugs and the transplant itself, or immunological factors is unknown at this time.

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**Figure 3.** Changes in marrow dose estimates with size adjustments.

**Figure 4.** Bladder wall surface dose for all patients. The effect of the irrigation of the bladder on both the dose estimates and the toxicity is shown.
Kidney Dosimetry

Traditionally regions of interest are drawn around the kidneys with a nearby background region of interest. Following attenuation correction and correction for camera calibration, a time-activity curve is produced. In studies where the kidneys are clearly visualized this is relatively simple, but questions on the reliability of the methodology still arise:

1) Background subtraction. The kidneys occupy up to approximately a third the width of the abdomen, thus background subtraction from a region close to the kidney that does not consider the thickness of the kidneys relative to the whole body, will overestimate the background activity in the overlying and underlying areas, and will underestimate kidney dose.30

2) In situations where there is intestinal activity overlying the kidneys, the kidneys are not visualized from the anterior images, and a posterior approach with an effective point source correction is more valid for attenuation correction than the geometric mean approach.28,31

3) The actual organ mass should be accounted for if known. As mentioned above in relation to marrow dose, assumptions for the mass of the target organs cause great uncertainty in the dose estimates. For diseases known to cause enlarged organs, patients’ organ mass is often considered and the mass of the organ is derived from a CT scan or using organ fusion techniques. Examples include spleen measurement in patients with non-Hodgkin’s lymphoma,31 liver masses for patients with colon cancer who have metastases to the liver.27 Kidney mass is generally not measured, but is important if kidney dose is of clinical concern. The masses of the right and left kidneys in the MIRD adult phantom are each 150 g. In a small series of cancer patients in whom we estimated kidney mass by drawing regions of interest on CT slices and then adding the area of the slices to obtain the kidney volume, the size of one kidney ranged from 75 to 300 g, although the average size remained 150 g. Thus, without considering kidney size, patients with large kidneys will have their kidney dose underestimated, and those with smaller kidneys will have the kidney dose overestimated.

For all radioactive small molecules, the urinary system is of concern for radiation toxicity from high dosages. To estimate the kidney dose in this situation, multiple early time points must be acquired so as not to miss the time of highest activity in the kidney. For radioactive antibody fragments and peptides, retention in the kidney is a problem and with high administered dosages, the region of interest approach is important.

Another approach for kidney dose is to use a mathematical model. A model was described in ICRP 5332 that considers blood and urine traversing the kidney. This uses information from blood perfusing the kidney and urine being excreted through the kidneys. This model appears to be a reasonable approach when there is no retention of activity by binding to normal kidney tissue. This approach uses the blood content of the kidney, assuming the kidney contains 2% of the blood volume, and thus a residence time of blood in the kidney can be assumed to be 2% of the blood residence time. Urinary excretion must be measured, either from counting urine, or it can be estimated from the decrease in whole body counts when there is no hepatobiliary metabolism or excretion through the intestinal tract. The transit time of the radioactivity moving from the blood into the urine is included in the model, with the probability of decay occurring during the transition through the kidney factored into the calculation. This is a useful approach for radionuclides that have poor imaging characteristics. Dose estimates from these two methods has not yet been compared.

DISCUSSION

For treatment of cancers other than NHL, with conventional radiolabeling of antibodies it appears that stem cell rescue will be required because dosages in the myeloblastic range are probably necessary to achieve meaningful tumor responses. Radiolabeled antibodies directed at tumor within the marrow are in clinical trials, used as a boost to total body irradiation with stem cell transplants, and these trials for lymphoid and myeloid malignancies show encouraging results. Another new field of high dose therapy is emerging with the bone-seeking agents to target the skeleton, at present for treatment of multiple myeloma.

With these high dosages of radioactivity administered, it is important to continue monitoring for late onset toxicity for several months, because vascular radiation damage does not present clinically early on. With high doses radioactivity administered in conjunction with other therapeutic approaches, unusual syndromes may develop, as mentioned above. Assessing the relationship of unexpected clinical findings with radiation is
important but a degree of confidence in the dose estimates is essential before one can conclude that radiation is or is not a cause or contributing factor. Dosimetry studies must be as patient specific as possible to provide meaningful dose estimates, because radiation absorbed dose estimates to the MIRD models from patient pharmacokinetic data have not been shown to have a high correlation with toxicity in patients. It is important to try to obtain an accurate assessment of the mass of the target organs, by direct measurement if possible, or otherwise perhaps from adjustments according to the size of the patient, if there is evidence of a meaningful correlation of organ mass with body size. The use of the MIRD phantom masses may be one of the assumptions causing the largest error in dose estimation, and is one aspect of the dosimetry estimation methodology that can be improved with current technology. Treatment planning dosimetry studies will continue to be important when the biodistribution of the radiopharmaceutical varies between patients, so that the highest safe therapy dose can be administered. With improved accuracy of radiation absorbed dose estimates, the dosimetry studies will continue to be essential in phase I/II trials in the development of new therapies.

REFERENCES


