Why Is the Resolution of the Discovery PET/CT Camera So Poor?

TO THE EDITOR: Mawlawi et al. (*1*) present an excellent study documenting the performance of the new Discovery PET/CT camera (General Electric Medical Systems). However, as a designer of PET cameras, I am perplexed as to why the resolution of this new camera is so poor.

The Discovery PET camera uses design concepts similar to those pioneered by Mullani et al. in 1984 for the Posicam PET camera (Positron Corp.) (*2*) but, to increase its sensitivity, has a smaller detector ring diameter and shorter septa and uses more of the cross-coincidences between adjacent slices. The detector size in the Discovery, at 6.3 mm, is significantly smaller than the 8.5-mm detector in the Posicam. Therefore, the resolution should be better for the Discovery than for the Posicam. However, the resolution of the Discovery, at 6.09 mm in full width at half maximum, is slightly lower than the published resolution (5.8 mm in full width at half maximum) of the Posicam.

Perhaps the authors or the designers of the Discovery PET camera would like to explain to the readers why the resolution of their camera is lower than for a similar camera using larger crystals.

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Nizar A. Mullani, BSc
University of Texas–Houston Medical School
Sugar Land, Texas

REPLY: My coauthors and I appreciate the observation of Dr. Mullani regarding the measured resolution of the Discovery ST PET/CT scanner (General Electric Medical Systems) that was presented in our article (*1*).

The resolution of a PET scanner depends on several factors, including the detector element size and ring diameter. It has also been shown that detector decoding, such as that used in block detector designs, can affect the system resolution (*2*). For scanners that are designed with 1 detector per photomultiplier tube, the scanner resolution is approximately half the detector size. On the other hand, scanners with a block detector design have resolutions that are roughly equal to the individual crystal size in the block (*1*). In this regard, stationary ring cameras such as the Discovery ST, which has a block detector design, will have a transaxial image resolution similar to its detector size of 6.3 mm. Transaxial resolution measurements have been published for several scanners from several different manufacturers (*1,3–8*), including the Discovery ST measurements that were recently published in *The Journal of Nuclear Medicine* (*1*). Each of these scanners uses block detectors, except for the Allegro (Philips Medical Systems), which uses a modular detector design with many properties of a block detector. In each case the resolution is approximately equal to the crystal size.

PET systems using different detector designs, such as that in the Posicam 6.5 (Positron Corp.) (*9*), may achieve resolution results different from those achieved by a block detector with a comparable detector size. Nonetheless, the resolution of the Discovery ST is not "poor" but is consistent with the expected results for its type of detector design.

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Osama Mawlawi, PhD
M.D. Anderson Cancer Center
Houston, Texas

DNA Uptake of ^{131}I-Iododeoxyuridine

TO THE EDITOR: It was with great interest that we read the publication by Dr. Kwan-Hwa Chi et al. (*1*). They reported on the interesting approach of using antisense thymidylate synthase (TS) plasmids to improve the DNA uptake of ^{131}I-iododeoxyuridine (IdUrd). However, as interesting as this approach is, the presented data do not seem to fully support the authors' claim of improved uptake and improved antitumor activity for ^{131}I-IdUrd in the presence of these antisense TS plasmids. Moreover, we bring to the editor's attention a potentially dangerous procedure described and used by the authors to prepare the title reagent, ^{131}I-IdUrd.

The uncertainty in the in vitro uptake and toxicity studies and in the in vivo tumor growth evaluation arises from the method of ^{131}I-IdUrd preparation. For each 3.7 MBq of ^{131}I, the authors used 0.05 mg of the stannylated precursor in the synthesis of ^{131}I-IdUrd. The authors used no methods to purify ^{131}I-IdUrd of unreacted stannylated precursor and its byproducts. The removal in vacuo of the volatile components from the reaction mixture does not purge this mixture of stannylated derivatives. Incidentally, evaporation of unreacted ^{131}I with the aid of a vacuum is a dangerous practice and unless conducted with proper and efficient filters can result in air contamination and thyroid uptake of airborne ^{131}I.

The authors claimed that in vitro uptake of, and in vivo tumor response to, ^{131}I-IdUrd were significantly improved with antisense

TS plasmids. This may be an erroneous conclusion for the simple reason that each tumor was treated with 0.15 mg of the stannylated precursor and its byproducts, in addition to 11.1 MBq of ^{131}I-IdUrd. We have shown (unpublished data, 2003) that trialkylstannylated deoxyuridine is quite cytotoxic, even at concentrations 15–150 times lower than those in mixtures used by Chi et al. to treat mice. In the absence of the proper control—that is, tumors treated with stannylated precursors with or without antisense TS plasmids—a claim that tumor response to ^{131}I-IdUrd was improved is unsubstantiated. It is just as likely that tumors responded to a continuous supply of cytotoxic trialkylated tin derivatives. Similarly, the increased in vitro uptake of ^{131}IdUrd (Fig. 3 of Chi et al. (*1*)) could very well have been in response to repair of the DNA damage caused by the stannylated derivatives.

The decoupling of these two effects—radiotoxicity of ^{131}I-IdUrd and cytotoxicity of stannylated precursors/byproducts—is impossible in the experimental design presented in this paper.

The synthesis of any no-carrier-added radiopharmaceutical is exacting because molar quantities of the radiolabeled materials are often >15,000 less, as is the case here, than the molar quantities of nonradioactive precursors and byproducts. When these precursors or byproducts are cytotoxic in their own right, the information obtained with uncharacterized radioactive mixtures cannot be taken at its face value regardless of how exciting these results may seem.

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Janina Baranowska-Kortylewicz, PhD
Jessica Nearman, BSc
University of Nebraska Medical Center
Omaha, Nebraska

Blood Dosimetry and Dose-Rate Effects After Radioiodine Therapy of Differentiated Thyroid Cancer

TO THE EDITOR: In a recent article (*1*), Watanabe et al. demonstrated radiation damage to lymphocytes in thyroid cancer patients after ^{131}I therapy. The authors found that after administration of 3.7 GBq of ^{131}I, the damage to B lymphocytes in vivo may be equivalent to the damage after a mean external-irradiation dose of 0.45 Gy in vitro. Watanabe et al. did not, however, directly compare their data with blood or bone marrow absorbed dose values for patients receiving radioiodine therapy. A possible explanation for this fact is that a standardized protocol for the determination of the absorbed dose to the blood or to the bone marrow does not exist for radioiodine treatments of differentiated thyroid cancer (DTC). Moreover, almost no data on the absorbed dose to the blood after radioiodine have been published.

In a recent international multicenter study (*2*), we established such a standardized protocol for determination of the blood dose after administration of radioiodine to patients with DTC. Using this protocol, it is possible to compare absorbed blood doses directly with the results of biologic dosimetry and to observe whether the different calibration methods caused dose-rate effects.

In this study (*2*), we assessed the absorbed blood dose to 9 patients with DTC who twice received a tracer dose of 74 MBq of ^{131}I before ablation therapy. The activity concentrations in blood samples taken at 2, 6, 24, 48, and 120–144 h after administration of the ^{131}I tracer were used to generate blood time–activity curves and to determine the cumulated radioactivity concentration in the blood. Whole-body γ-camera scans ("conjugate views") were used to generate whole-body time–activity curves and to determine the cumulated radioactivity concentration in the remainder of the body. The blood dose was calculated as the sum of contributions from the cumulated radioactivity concentration in the blood, the residence time in the remnant, and the residence time determined for the remainder of the body, each weighted with adequate S values. In this approach, the residence time in the remainder of the body is defined as the whole-body residence time minus the residence time in the remnant and the residence time in the blood.

Blood dose values were calculated for vessel radii of 0.02 and 0.5 cm (*3*). For hypothyroid patients, the correspondent numbers are 0.09 ± 0.02 mGy/MBq (unpublished data, 2003) and 0.13 ± 0.03 mGy/MBq (*2*), respectively. If the kinetics of 74 MBq of ^{131}I are postulated to be equal to those of 3.7 GBq of ^{131}I, the expected blood dose range is between 0.32 ± 0.07 and 0.47 ± 0.10 Gy. The value of 0.45 Gy reported by Watanabe et al. (*1*) is well within this range.

Watanabe et al. (*1*) suspected that they underestimated the absorbed dose in radioiodine therapy because their calibration was based on high-dose-rate external-radiation exposure. After high-dose-rate irradiation, one would expect more pronounced biologic effects (*4*).

When the results of both dose assessment methods are compared, no difference in dose values is found within the margin of error. A dose-rate effect therefore is obviously not observed.

A multicenter ablation study of a large number of patients with DTC is under way. The results of that study, which includes blood dosimetry, will allow further comparison to the dose values given by Watanabe et al. (*1*).

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Michael Lassmann, PhD
Markus Luster, MD
Heribert Hänscheid, PhD
Christoph Reiners, MD
Universität Würzburg
Würzburg, Germany

Blood and Bone Marrow Dosimetry in Radioiodine Therapy of Thyroid Cancer

TO THE EDITOR: In a recent article by de Keizer et al. (*1*), the red marrow dosimetry model that I described in a previous

issue of *The Journal of Nuclear Medicine* (*2*) was used to estimate red marrow absorbed doses for patients receiving ^{131}I-NaI. The formulation I described was based on the expected distribution of antibodies. It does not apply to the much smaller NaI molecule.

The key difference is in the distribution volume of the 2 radiopharmaceuticals. Radiolabeled antibody is assumed to initially distribute in the plasma and extracellular fluid space of the red marrow, spleen, and liver—organs whose extracellular fluid space rapidly equilibrates with plasma. The total volume of this initial distribution space is 2.5–4 L. Correspondingly, the initial plasma percentage of injected activity per liter (%IA/L) for antibodies is in the range of 25–40 (i.e., the reciprocal of the initial distribution volume). The initial %IA/L for ^{131}I-NaI is in the range of 3–6, giving initial distribution volumes of 30–17 L. This means that the ^{131}I is not confined to the extracellular fluid of the red marrow but is most likely evenly distributed throughout a much larger volume that includes the blood and the red marrow. The concentration of ^{131}I in blood is, therefore, a better direct approximation of the concentration in red marrow. Use of a factor of between 0.2 and 0.4 to convert blood activity concentration to marrow activity concentration will underestimate the red marrow activity concentration (and, therefore, the absorbed dose) by between 5 and 2.5, respectively.

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George Sgouros, PhD
Johns Hopkins University
Baltimore, Maryland

Blood and Bone Marrow Dosimetry in Radioiodine Therapy of Differentiated Thyroid Cancer After Stimulation with rhTSH

TO THE EDITOR: In a recent article, de Keizer et al. demonstrated the radiation safety of radioiodine therapy with 7.4 GBq of ^{131}I after stimulation with recombinant human thyroid-stimulating hormone (rhTSH) in thyroid cancer patients (*1*). For 14 consecutive patients (17 treatments), they found that the red marrow dose was 0.16 ± 0.07 mGy/MBq, thus delivering a maximum total radiation dose of 1.91 Gy to the red marrow. The mean blood dose was 1.69 ± 0.34 Gy. In 4 of 17 treatments, the calculated blood dose exceeded the limit of 2 Gy. The authors did not observe a case of hematologic toxicity.

In a recent international multicenter study (*2*), we assessed the absorbed blood dose to 9 patients with differentiated thyroid cancer who twice received a tracer dose of 74 MBq of ^{131}I before ablation therapy. The blood dose was calculated as a sum of contributions using the measured residence times for the blood, remnant, and remainder of the body coupled with the appropriate S values. The blood residence time was determined through direct, sequential sampling, whereas the remnant and remainder residence times were obtained through sequential image analysis. The blood dose values for euthyroid patients after application of rhTSH were 0.08 ± 0.03 and 0.11 ± 0.03 mGy/MBq, assuming vessel radii of 0.02 and 0.5 cm, respectively (*2*).

Postulating that the iodine kinetics of 74 MBq of ^{131}I are equal to those of 7.4 GBq of ^{131}I, the expected blood dose range for 7.4 GBq of ^{131}I is between 0.60 ± 0.21 and 0.82 ± 0.22 Gy. The mean value of 1.69 Gy reported by de Keizer et al. (*1*) is approximately 2–3 times higher.

We believe that some aspects degrade the reliability of the blood and red marrow dose values published by de Keizer (*1*). The first of these aspects is that the median total body residence time (RT_{TB}) of 155 h (value recalculated from Table 2, column 1, not 132 h as stated in the text [fourth paragraph of "Results"]) would be high even for healthy subjects or in radioiodine therapy of benign thyroid disease. According to the International Commission on Radiological Protection (*3*), the RT_{TB} is expected to be an order of magnitude lower in athyreotic patients. An overestimation of the RT_{TB} results in blood dose values that are too high. The high value for RT_{TB} reported by de Keizer et al. cannot be explained by the residence times in residual thyroid tissue or neoplastic cells that were published recently (*4*). For none of the patients did the uptake in thyroactive tissue exceed 4%, and the median effective half-life was 2.7 d. The mean effective half-life in the remainder of the body must have been even longer (~4.5 d) to achieve an RT_{TB} of 155 h. Evaluations of residence time from direct measurements of whole-body activity over several days usually provide reliable data that are consistent with theory (e.g., in one study (*2*), the median RT_{TB} in euthyroid patients was 19 h). In the study of de Keizer, whole-body scintigraphy was performed at 24, 48, 120, 216, and 336 h after injection of the radioiodine (*4*). Although the 24-h scans might suffer from high-counting-rate dead-time effects and the accuracy of the extrapolation of the time–activity function to time zero might be degraded, it would be interesting to use the scans to recheck the RT_{TB} values given in (*1*).

A second aspect degrading the reliability of the values is that the authors do not list blood residence times. For ^{131}I therapy of thyroid carcinoma, the blood residence time correlates strongly with RT_{TB} (*2,5*). Knowledge of the cumulated activity in blood would enable the reader to evaluate the reliability of the RT_{TB} and blood dose values.

A third aspect is that the blood activity was fitted with a long decay component (biologic half-life, 80 d) for the second term of a biexponential decay function. The procedure is adequate for healthy subjects but, in conjunction with a short sampling period of not more than 72 h, might overestimate the blood residence time in athyreotic patients and patients with small amounts of residual thyroactive tissue with a mean effective half-life of 2.7 d. It would have been more appropriate to calculate a range of residence times using a long decay constant and continuing the last measured decay rate to infinity. The actual value is expected to lie within this range, and this approach would allow the reader to assess the uncertainty of the results.

A fourth aspect is that de Keizer et al. evaluated the red marrow dose using a method described by Sgouros (*6*) for bone marrow dosimetry in radioimmunotherapy. Sgouros stated stringent conditions under which the equations in his publication are valid. The authors have not demonstrated the validity of the theory for radioiodine. Because the biokinetics of radioiodine (sodium iodide) are not comparable to those of the much larger molecules used in radioimmunotherapy, the red marrow dose values might be substantially incorrect.

In summary, the dose values for red marrow and blood have to be reevaluated because they indicate that the commonly accepted blood dose limit of 2 Gy might be reached or even exceeded. The outcome is contrary to the expectation of a reduced blood dose due to higher renal clearance and reduced effective half-life in euthyroid patients. In the future, instead of giving uncertain bone marrow dose estimates, we should determine blood doses as accurately as possible to see if the limits of the traditional radioiodine therapy guidelines (i.e., a maximum blood dose of 2 Gy) can be further extended when using rhTSH.

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Michael Lassmann, PhD
Heribert Hänscheid, PhD
Christoph Reiners, MD
Universität Würzburg
Würzburg, Germany

Stephen R. Thomas, PhD
University of Cincinnati
Cincinnati, Ohio

REPLY: We appreciate the interest and comments expressed by Drs. Sgouros and Lassmann in their letters concerning our paper (*1*). The blood dose described by Luster et al. (*2*) for a small group of patients receiving low doses—just 74 MBq—after recombinant human thyroid-stimulating hormone (rhTSH) appears to be much lower than the result found by Benua et al. (*3*). We agree that blood doses are lower after rhTSH, but we doubt that rhTSH decreases blood dose by a factor of 2 or 3. Dr. Lassmann suggests that some aspects degrade the reliability of blood doses published in our article, causing an overestimation of blood dose and an underestimation of bone marrow dose. We would like to comment on those remarks.

Concerning blood dosimetry and total-body residence times (RTTB), it is stated that we probably overestimated RTTB. RTTB were reliably acquired by collecting all urine excreted by patients. The relatively high RTTB can be explained by the residence times in thyroid neoplastic tissue in patients. We disagree that according to the International Commission on Radiological Protection (*4*) the RTTB is expected to be lower. Our patients had metastatic thyroid cancer, and most had multiple metastatic lesions, thus increasing the RTTB. When a single lesion was measured, the highest uptake value was 4% (*5*). However, because multiple lesions were present, uptake in the whole body would be much higher. This is the obvious explanation for the relatively high red marrow dose. Furthermore, we believe that the dosimetry model used by Luster et al. (*2*) was designed for calculating absorbed doses to the blood and the walls of blood vessels, whereas more sophisticated bone marrow models formed the basis for our patient-specific method.

We agree with both Dr. Lassman and Dr. Sgouros that the volume of distribution of monoclonal antibodies may differ from the volume of distribution of ^{131}I. We also calculated the blood dose as described by Benua et al. (*3*) as a surrogate for the red marrow dose, with all activity distributed in the extracellular space. The mean value of this blood dose was 1.69 $\pm$ 0.34 Gy, whereas the red marrow dose according to the patient-specific method described by Sgouros (*5*) and Shen et al. (*7*) was 1.15 $\pm$ 0.52 Gy. When we correct red marrow for a blood concentration of 1 instead of the assumed factor of 0.32, the mean patient-specific red marrow dose is 1.35 $\pm$ 0.51 Gy. This slight increase is caused by the minor contribution to the red marrow dose from the circulating blood in comparison to the total-body contribution. We still believe that the patient-specific method can also be used to reliably estimate the red marrow dose of ^{131}I in patients with multiple thyroactive metastases.

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Bart de Keizer, MD, PhD
John M.H. de Klerk, MD, PhD
Utrecht University Medical Center
Utrecht, The Netherlands

Mark W. Konijnenberg, MsC
Mallinckrodt, Tyco Healthcare
Petten, The Netherlands