Adsorption of metallic radionuclides on plastic phantom walls

Mi-Ae Park,^{a)} Ashfaq Mahmood, Robert E. Zimmerman, and Naengnoi Limpa-Amara
Brigham and Women's Hospital and Harvard Medical School, 75 Francis Street, Boston, Massachusetts 02115

G. Mike Makrigiorgos
Dana-Farber Cancer Institute and Harvard Medical School, 44 Binney Street, Boston, Massachusetts 02115

Stephen C. Moore
Brigham and Women's Hospital and Harvard Medical School, 75 Francis Street, Boston, Massachusetts 02115

(Received 27 February 2007; revised 24 January 2008; accepted for publication 24 January 2008; published 27 March 2008)

Metal radionuclide solutions at neutral *pH* adhere to plastic containers. Adsorption of radionuclides on the walls of phantoms leads to a nonuniform activity distribution, which could adversely affect imaging studies, as well as phantom-based validations of absorbed dose calculations used in radioimmunotherapy, requiring accurate knowledge of the underlying activity distribution. In the work reported here, the authors determined the degree of metal chelation required to minimize metallic radionuclide oxide formation and adsorption on phantom walls in order to yield more reliable experimental data for validating image-based dosimetry. Using hollow spherical plastic phantoms, the authors evaluated three different radionuclides, I-131, In-111, and Y-90, in solutions containing three different concentrations of the chelator, ethylenediaminetetraacetate (EDTA). Adsorption to plastic walls was determined using μ SPECT imaging and/or by counting aliquots of solutions. Reconstructed images and measurements of I-131 activity showed that it was uniformly distributed within all spheres; however, images of In-111 in 0.25- μ M EDTA indicated that the activity concentration near the wall was much higher than that in the middle of the sphere. The decrease in activity concentration near the center of the spheres was $\sim 47\%$. Y-90 in 0.25- μ M EDTA behaved similarly; the activity concentration of Y-90 decreased by 46%. For an In-111 or Y-90 radioactivity concentration of 0.74 MBq/mL, a 2.5- μ M EDTA solution was required to achieve a uniform distribution, suggesting that, under our experimental conditions, ~ 700 EDTA molecules were required for each radiometal atom to prevent precipitation and adsorption on poly(methylmethacrylate). For certain radiometals, e.g., In-111 or Y-90, adequate chelation is essential to achieve uniform activity concentration values and homogeneous distribution within the phantom compartments. © 2008 American Association of Physicists in Medicine.
[DOI: [10.1118/1.2871191](https://doi.org/10.1118/1.2871191)]

Key words: radioactivity distribution, internal dosimetry, plastic phantom

I. INTRODUCTION

Improved estimates of radiation absorbed dose from various radionuclides used in radioimmunotherapy should translate into more effective patient treatment. Unfortunately, however, direct dose measurements in individual patients are currently not feasible; therefore, indirect, image-based, patient-specific dosimetry has been proposed and widely studied in recent years.¹⁻³ In this technique, images of the biodistribution of a therapeutic (or surrogate) radionuclide are first obtained—often at several different times over a few days—using SPECT, PET, or planar imaging. For example, Y-90 ibritumomab tiuxetan is a therapeutic radiopharmaceutical while In-111 ibritumomab tiuxetan is an imaging surrogate for treatment planning in relapsed *B*-cell non-Hodgkin lymphoma.⁴ I-131 labeled tositumomab is also used for lymphoma therapy.⁵ Total absorbed doses in tumors and normal tissues and organs are then estimated from the time integral of the biodistribution data, using spatial convolution techniques with simulated dose-point kernels, especially for anatomic regions of uniform density.⁶ In less homogeneous re-

gions, direct Monte Carlo simulation of charged particle and photon dose deposition may be performed. In both approaches, because the computed values of dose ultimately depend on computer simulation, validation of the methodology is crucial.

Most dose validation and imaging studies make use of phantoms and require very accurate knowledge of the injected activity distribution within the phantoms, as well as of the material composition and density within the various walls and compartments of the phantoms. In-111 is not only used as an imaging surrogate for Y-90, but it is also an important imaging agent in its own right, and can be labeled to several different radiopharmaceuticals.⁷⁻⁹ Phantom measurements are also used for quantification of activity and for evaluation of reconstruction algorithms. Therefore, for both diagnostic and therapeutic applications, it is important to have accurate knowledge of the radionuclide's activity distribution within phantoms.

It has been previously observed by others that certain radiopharmaceuticals appear to stick to the inside of plastic syringes.^{10,11} Using these radiolabeled compounds, it was

TABLE I. Summary of the size of phantoms and activity concentration for each EDTA concentration.

EDTA concentration (μM)	I-131		In-111		Y-90	
	I.D. (cm)	MBq/mL	I.D. (cm)	MBq/mL	I.D. (cm)	MBq/mL
25	1.2	0.32	1.2	0.69	1.2	0.75
2.5	1.2	0.70	1.0	0.73	1.0	0.64
0.25	1.0	0.43	1.2	0.61	1.2	0.83

perceived that the residual activity measured in a syringe after injecting its contents into a phantom or patient was more than one would expect, based on experience with other radionuclides. In solutions at neutral $p\text{H}$, unchelated metal-chloride radionuclides—such as In-111 and Y-90—can form metal oxides over a time scale consistent with the decay of the radioactivity due to the hydrolysis of the metal-aqua complex in solution.¹² This causes the metal ions to form precipitates which adhere to the walls of the container. To prevent this oxide formation and precipitation of M^{3+} ions, radiometals are maintained and shipped as MCl_3 in 0.04–0.05-N HCl from the manufacturer. For example, indium and yttrium are stored as metal chlorides in a 0.04-N HCl solution of InCl_3 and YCl_3 , as are SmCl_3 , GaCl_3 , and LuCl_3 . This acidic condition prevents the hydrolysis of metal-aqua $[\text{M}(\text{H}_2\text{O})_n]^{3+}$ species, thereby preventing precipitation and adsorption on container walls.

However, when imaging and dosimetry validation experiments are performed with these radionuclides in solutions, they are frequently carried out using solutions at or near neutral $p\text{H}$, thus increasing the possibility of inhomogeneous distribution. This necessitates the elucidation of a method to perform such measurements with these M^{3+} radionuclides under such conditions. We have investigated the utility of a general metal chelator, ethylenediaminetetraacetate (EDTA), for chelating these M^{3+} radiometals to produce a uniform radioactivity distribution throughout the phantom compartment under neutral $p\text{H}$ conditions. We also determined the degree of such chelation necessary for In-111, Y-90, and I-131 to minimize adsorption of these radionuclides on the walls of various plastic phantoms and containers.

II. METHODS

II.A. Solution and phantom preparation

Normal phosphate-buffered saline at $p\text{H}$ 7.3 ($1\times\text{PBS}$ = phosphate buffer—0.01 M, NaCl—0.137 M, and KCl—2.7 mM), which contained 0.25-, 2.5-, and 25- μM EDTA, was prepared and used for making various solutions. For the work reported here, different phantoms were assembled, each containing a solution of one of the radionuclides I-131, In-111, or Y-90. Each radionuclide was withdrawn from its original solution received from the manufacturer and added directly into the $1\times\text{PBS}$ containing the appropriate EDTA concentration. We did not attempt to systematically study the effects of temperature and $p\text{H}$ of the solution; hence, a $p\text{H}$ of 7.3 was fixed for all experiments, which were performed in a 20 °C temperature-controlled environment.

Activity-concentration values ranged from 0.37 to 0.93 MBq/mL. The values of I-131 activity concentration in the phantom were (a) 0.32, (b) 0.7, and (c) 0.43 MBq/mL, while the corresponding values of EDTA concentration were (a) 25, (b) 2.5, and (c) 0.25 μM . Each solution was prepared separately; therefore, the activity in each phantom was not exactly the same across all of the phantoms. The phantom size and activity concentration for each EDTA concentration are summarized in Table I. The specific activity of In-111 provided by the manufacturer, MDS Nordion, was 1.85 GBq/ μg , while those of Y-90 and I-131 were 20 and 0.74 GBq/ μg , respectively. The In-111 solutions contained several impurities including Fe, Cd, Cu, Pb, Zn, and Ni; these amounts were each less than 2.7 $\mu\text{g}/\text{GBq}$, according to the manufacturer. For the Y-90 solutions, the total of all impurities was less than 0.81 $\mu\text{g}/\text{GBq}$; the possible impurities included all of the metals listed above except nickel. The MCl_3 radionuclides were received in diluted form, 0.9–3.7 GBq/mL in 0.04-N HCl solution.

Each solution was injected into a hollow spherical phantom from Data Spectrum, Inc. The spheres, which were made of poly(methylmethacrylate) (PMMA), had inside diameters of either 1 or 1.2 cm. The average plastic wall thickness of all phantoms was 1 mm. Three 50- μL aliquots of each radionuclide solution with each EDTA concentration were pre-stored in glass tubes to provide activity reference values. We later measured the activity of the solutions in the three tubes for each condition using a sodium-iodide well counter, and the mean value was taken to be the reference activity for the solution. Phantoms were stored for about 24 h before we measured the activity distribution.

II.B. SPECT imaging and gamma counting

The uniformity of the different activity distributions was investigated by examining reconstructed μSPECT images and/or by measuring a solution's activity concentration directly using a well counter. For Y-90, a pure beta emitter, the activity of each known solution volume was measured only with the well counter. Approximately 24 h after the phantom preparation, the phantoms with I-131 and In-111 were imaged using our μSPECT imaging system at Harvard Medical School (TRIONIX, Twinsburg, OH). This system is comprised of three standard gamma cameras, each of which has two tungsten pinhole collimators.¹³ The diameter of the pinholes used for our experiments was 0.8 mm. This system provides very high-resolution images suitable for measuring the activity distributions in small phantoms. Conventional

SPECT systems used for patient imaging would not be capable of imaging with adequate accuracy an activity gradient within the 1- to 1.2-cm-diameter spheres because the spatial resolution of these clinical SPECT systems is usually not better than ~ 5 mm. For example, a dual-head SPECT system equipped with high-resolution parallel-hole collimators has ~ 7 mm resolution for imaging an object 10 cm away from the detector, while the μ SPECT system yields 0.9 mm average reconstructed resolution. The radius-of-rotation from the center of each sphere to the center of the pinhole aperture plate was 3 cm. We used a 20% energy window for both In-111 photopeaks (171 and 245 keV), and for the main I-131 photopeak (364 keV).

The images were reconstructed using a three-dimensional-ordered-subsets expectation-maximization algorithm¹⁴ with 20 subsets, six projections/subset, and three iterations. The slice thickness of the reconstructed image was 0.4 mm and the pixel size in each slice was $0.4 \text{ mm} \times 0.4 \text{ mm}$. We did not apply attenuation or scatter correction since the phantoms were very small. For the 1.2-cm-sphere phantom, the average attenuation path length over 360 deg was 6 and 7.6 mm, respectively, for the source at the center and at the periphery. The difference in attenuation for these path lengths is $<2\%$ for photons with energies near the photopeaks mentioned above. Similarly, the detected scatter fractions are very low for such small phantoms.

We estimated the activity concentration in the middle of the spheres using ten regions of interest (ROI) positioned well inside of each sphere; these ROI were chosen on all slices through the sphere, to avoid the “hotter” ring region; the size of each ROI was 8×8 pixels, i.e., $3.2 \text{ mm} \times 3.2 \text{ mm}$. The ROI measurements were then converted into values of activity concentration in MBq/mL using a calibration factor determined previously for a uniform In-111 or I-131 source distribution. One count/pixel in reconstructed In-111 or I-131 images corresponds to 0.028 or 0.01 MBq/mL, respectively.

Additionally, after 24 h of exposure, three 50- μL aliquots of In-111 and Y-90 solutions were carefully withdrawn from the center of the phantom using a 100- μL Hamilton syringe (The manufacturer, Hamilton Co., indicated that 50- μL volume in a 100- μL syringe measures $50 \pm 1 \mu\text{L}$), and each sample's activity was measured using a gamma well-counter system (Perkin Elmer-1480 WIZARD). We recorded the number of detected counts per minute and then calculated the mean and standard deviation over the three samples which had been drawn from the same phantom. These values were compared with the count rate expected using the reference

FIG. 1. μ SPECT reconstructed images of I-131 in PMMA phantoms with (a) 25-, (b) 2.5-, and (c) 0.25- μM EDTA concentrations. The diameter of the phantom was 1.2 cm for (a) and (b) and 1.0 cm for (c).

aliquots, obtained from the starting solution and stored in glass vials, which were counted at the same time.

III. RESULTS

The central slice of the reconstructed images of I-131 solutions within three different PMMA spherical phantoms is shown in Fig. 1. ROI measurements (Table II) and visual comparison indicated that the I-131 in all spheres was uniformly distributed; the average standard deviation over all ROI was 4.5% of the average activity.

We obtained similar results for I-131 activity distributions from samples using the gamma well-counter measurements. The average difference between the measured activity of the reference solution and that from phantoms was $3.2 \pm 0.2\%$. Not surprisingly, the results indicate that I-131 (not being a M^{3+} metal ion) does not precipitate in neutral solutions and, therefore, does not require chelation for use in PMMA phantom compartments. This observation is consistent with some of our earlier studies,¹⁵ in which we showed that experimentally measured dose values, using I-131 solutions contained in the same phantom material (PMMA), agreed well with simulated doses—for both self- and target-dose values.

Transverse images of the phantoms containing In-111 with EDTA concentrations (a) 25, (b) 2.5, and (c) 0.25 μM are shown in Fig. 2. The bright ring on the periphery in (c) clearly represents a nonuniform activity distribution. The ROI values throughout the volume of the spheres are summarized in Table II. The average and standard deviation over ten ROI were then converted into values of activity concentration. With 0.25- μM EDTA, the activity concentration in the solution was only $\sim 45\%$ of the initial In-111 concentration in the starting solution (Table III). We estimated the total activity around the periphery by subtracting the activity in the center from the total activity. At EDTA concentrations of 2.5 μM and higher, there was no sign of any activity pre-

TABLE II. ROI values for I-131 and In-111 reconstructed images within $8 \text{ pixels} \times 8 \text{ pixels}$. The background count, 0.41 for In-111 and 1.35 for I-131, was subtracted from each ROI.

ROI (counts/pixel)	I-131			In-111		
	25 μM	2.5 μM	0.25 μM	25 μM	2.5 μM	0.25 μM
Average	35.3	60.0	37.8	24.4	26.4	12.3
Standard dev.	1.4	3.6	1.3	0.6	0.3	0.2

FIG. 2. μ SPECT reconstructed images of In-111 in PMMA phantoms with (a) 25-, (b) 2.5-, and (c) 0.25- μ M EDTA concentrations. The diameter of the phantom was 1.2 cm for (a) and (c) and 1.0 cm for (b).

cipitation from the solution, as observed in the images and the solution sampling and direct activity measurements.

In Fig. 3, we show line profiles across the center of the slices in Figs. 1 and 2. These demonstrate graphically that the voxel values around the periphery were higher than those in the middle of the phantom in Fig. 2(c). The average voxel value was two times higher at the periphery than in the middle, but this ratio ranged from 1 to 5. The higher activity rings which we also observed in many of the other slices of the same phantom indicate that the nonuniformity covered most of the plastic sphere's inner surface. In Table III, we summarized the mean and standard deviation of the estimated values of activity concentration (over the ten ROI) and the corresponding values measured directly by gamma well counting after the imaging. The reference activity listed was the initial activity concentration in each sphere.

The measured In-111 activity concentration in the spheres containing 25- and 2.5- μ M EDTA solutions was very close to the reference value. However, the activity concentration in the sphere containing 0.25- μ M EDTA solution decreased from 0.61 to 0.34 MBq/mL, based on image analysis, and to 0.31 MBq/mL, based on gamma well counting. This indicates that 40%–50% of the total In-111 activity present in the solution was redistributed via precipitation and adherence to the PMMA container walls, thereby creating the “hot” ring seen in the images.

Because Y-90 does not emit gamma rays useful for imaging, we investigated the activity distribution using only the gamma well-counter measurements. In Table III, we have also summarized the average and standard deviation over three samples of Y-90 in the phantoms with different values of EDTA concentration. A significant activity difference was observed only for the sample from the spherical phantom containing 0.25- μ M EDTA solution. The activity was 54%

FIG. 3. Line profiles of the images shown in Figs. 1 and 2. The pixel size is 0.4 mm.

of the total activity in the 1.2-cm-diameter sphere. This implies that 46% of the total activity had adhered to the plastic walls, which is consistent with the result of the adsorbed percentage we measured for In-111 (above) in a similar phantom, also using a 0.25- μ M EDTA solution.

IV. DISCUSSION AND CONCLUSIONS

We have found that phosphate-buffered saline at pH 7.3 containing 2.5- μ M EDTA was sufficient to maintain a uniform activity distribution when using phantoms containing ~ 0.74 MBq/mL Y-90 or In-111. In a 2.5- μ M EDTA solution containing 0.74 MBq/mL In-111 with specific activity, 1.85 GBq/ μ g, there would be 3.6×10^{-12} mol/mL of In-111 and 2.5×10^{-9} mol/mL of EDTA, giving an ~ 700 molar concentration excess of EDTA over In-111, under these experimental conditions.

TABLE III. Activity measurements of In-111 and Y-90 solutions of various EDTA concentrations from spherical PMMA phantoms. The reference activity was stored in glass tubes and used to define the true activity concentration. All values were corrected for decay.

EDTA concentration (μ M)	In-111 (MBq/mL)			Y-90 (MBq/mL)	
	Reference	ROI	Gamma counting	Reference	Gamma counting
25	0.69 ± 0.01	0.68 ± 0.03	0.68 ± 0.00	0.75 ± 0.04	0.69 ± 0.02
2.5	0.73 ± 0.02	0.74 ± 0.02	0.72 ± 0.01	0.64 ± 0.04	0.66 ± 0.03
0.25	0.61 ± 0.04	0.34 ± 0.01	0.31 ± 0.00	0.83 ± 0.01	0.45 ± 0.01

Without sufficient chelation, we observed that as much as 50% of the total activity may precipitate and adhere to the plastic walls of the phantom, leading to a highly nonuniform activity distribution. This can result in localized activity concentration values as much as five times greater in image voxels closest to the walls than in voxels in the middle of the sphere in a 1.2-cm-diameter sphere. Both M^{3+} metal ions displayed similar behavior, i.e., measurements obtained with In-111 solutions were quite consistent with those from Y-90 solutions, as expected. We believe that the somewhat increased activity that appears to be in the center of the I-131 spheres is attributable to pinhole penetration and scatter by high-energy I-131 contaminant photons; however, this effect is certainly not large enough to change our observations about the degree of adsorption of I-131 on the PMMA walls of these spheres.

Because most dose-validation studies are performed using plastic phantoms, it is crucial to know whether the radioactivity may be adhering to the plastic walls of the phantom before proceeding with an experiment. As we have shown in this article, the metal radionuclide atoms could be chelated more strongly to eliminate their precipitation and adherence to the plastic phantom walls.

ACKNOWLEDGMENT

This work was supported in part by the National Institutes of Health under Grant Nos. R01-EB001989, R01-CA119334, and S10-RR017224.

^{a)}Electronic mail: miaepark@bwh.harvard.edu

¹K. S. Kolbert *et al.*, "Implementation and evaluation of patient-specific three-dimensional internal dosimetry," *J. Nucl. Med.* **38**, 301–308 (1997).

²Y. K. Dewaraja, S. J. Wilderman, M. Ljungberg, K. F. Koral, K. Zasadny, and M. S. Kaminiski, "Accurate dosimetry in ¹³¹I radionuclide therapy

using patient-specific, 3-dimensional methods for SPECT reconstruction and absorbed dose calculation," *J. Nucl. Med.* **46**, 840–849 (2005).

³M. de Jong, W. A. P. Breeman, R. Valkema, B. F. Bernard, and E. P. Krenning, "Combination radionuclide therapy using ¹⁷⁷Lu- and ⁹⁰Y-labeled somatostatin analogs," *J. Nucl. Med.* **46**, 13S–17S (2005).

⁴T. E. Witzig, "Radioimmunotherapy for patients with relapsed B-cell non-Hodgkin lymphoma," *Cancer Chemother. Pharmacol.* **48**, S91–S95 (2001).

⁵M. S. Kaminski *et al.*, "¹³¹I-tositumomab therapy as initial treatment for follicular lymphoma," *N. Engl. J. Med.* **352**, 441–449 (2005).

⁶W. E. Bolch *et al.*, "MIRD pamphlet no. 17: The dosimetry of nonuniform activity distributions—Radionuclide S values at the voxel level," *J. Nucl. Med.* **40**, 11S–36S (1999).

⁷C. J. Palestro, C. Love, G. G. Tronco, M. B. Tomas, and J. N. Rini, "Combined labeled leukocyte and technetium 99m sulfur colloid bone marrow imaging for diagnosing musculoskeletal infection," *Radiographics* **26**, 859–870 (2006).

⁸D. B. Sodee *et al.*, "Preliminary imaging results using In-111 labeled CYT-356 (Prostascint) in the detection of recurrent prostate cancer," *Clin. Nucl. Med.* **21**, 759–767 (1996).

⁹E. Bombardieri *et al.*, "¹¹¹In-pentetreotide scintigraphy: Procedure guidelines for tumour imaging," *Eur. J. Nucl. Med. Mol. Imaging* **30**, BP140–BP147 (2003).

¹⁰J. A. Kennedy and G. S. Besses, "Comparison of adsorption of iodine-131-thyroxine to glass and plastic containers," *J. Nucl. Med.* **8**, 226–228 (1967).

¹¹B. A. Jansson, M. B. Goransson, and B. N. Agren, "Adsorption of some technetium-99m radiopharmaceuticals onto disposable plastic syringes," *J. Nucl. Med. Technol.* **26**, 196–199 (1998).

¹²F. A. Cotton and G. Wilkinson, *Advanced Inorganic Chemistry*, 4th ed. (Wiley, New York, 1980), pp. 152–153, 333–334, and 990–992.

¹³S. C. Moore, R. E. Zimmerman, A. Mahmood, R. Mellen, and C. B. Lim, "A triple-detector, multiple-pinhole system for SPECT imaging of rodents," *J. Nucl. Med.* **45**, 97P–98P (2004).

¹⁴H. M. Hudson and R. S. Larkin, "Accelerated image reconstruction using ordered subsets of projection data," *IEEE Trans. Med. Imaging* **13**, 601–609 (1994).

¹⁵M.-A. Park, S. C. Moore, N. Limpa-Amara, R. E. Zimmerman, A. Mahmood, and G. M. Makrigiorgos, "Y-90 and I-131 dosimetry using coumarin-3 carboxylic acid in phantoms of different size and shape," *J. Nucl. Med.* **46**, 86P–87P (2005).