Development and evaluation of a model-based downscatter compensation method for quantitative I-131 SPECT

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Purpose: The radionuclide ^{131}I has found widespread use in targeted radionuclide therapy (TRT), partly due to the fact that it emits photons that can be imaged to perform treatment planning or post-therapy dose verification as well as beta rays that are suitable for therapy. In both the treatment planning and dose verification applications, it is necessary to estimate the activity distribution in organs or tumors at several time points. In vivo estimates of the ^{131}I activity distribution at each time point can be obtained from quantitative single-photon emission computed tomography (QSPECT) images and organ activity estimates can be obtained either from QSPECT images or quantification of planar projection data. However, in addition to the photon used for imaging, ^{131}I decay results in emission of a number of other higher-energy photons with significant abundances. These higher-energy photons can scatter in the body, collimator, or detector and be counted in the 364 keV photopeak energy window, resulting in reduced image contrast and degraded quantitative accuracy; these photons are referred to as downscatter. The goal of this study was to develop and evaluate a model-based downscatter compensation method specifically designed for the compensation of high-energy photons emitted by ^{131}I and detected in the imaging energy window.

Methods: In the evaluation study, we used a Monte Carlo simulation (MCS) code that had previously been validated for other radionuclides. Thus, in preparation for the evaluation study, we first validated the code for ^{131}I imaging simulation by comparison with experimental data. Next, we assessed the accuracy of the downscatter model by comparing downscatter estimates with MCS results. Finally, we combined the downscatter model with iterative reconstruction-based compensation for attenuation (A) and scatter (S) and the full (D) collimator-detector response of the 364 keV photons to form a comprehensive compensation method. We evaluated this combined method in terms of quantitative accuracy using the realistic 3D NCAT phantom and an activity distribution obtained from patient studies. We compared the accuracy of organ activity estimates in images reconstructed with and without addition of downscatter compensation from projections with and without downscatter contamination.

Results: We observed that the proposed method provided substantial improvements in accuracy compared to no downscatter compensation and had accuracies comparable to reconstructions from projections without downscatter contamination.

Conclusions: The results demonstrate that the proposed model-based downscatter compensation method is effective and may have a role in quantitative ^{131}I imaging. © 2011 American Association of Physicists in Medicine. [DOI: 10.1118/1.3590382]

Key words: radionuclide therapy, QSPECT, quantitative I-131 imaging, downscatter contamination, model-based compensation

I. INTRODUCTION

The radionuclide ^{131}I is widely used in therapeutic nuclear medicine, e.g., ^{131}I chloride is used to treat thyroid diseases, including thyroid cancer,¹ and targeted agents, including antibodies and peptides, labeled with ^{131}I have been used to treat a variety of other cancers.^{2–6} ^{131}I decay produces both a 364 keV photon used for imaging and beta particles with an

average energy of 192 keV (maximum energy of 606 keV)⁷ that provide a therapeutic effect.

As in all TRT, determining the appropriate administered activity (AA) is a critical part of optimizing therapy. One method to determine the appropriate patient-specific AA is the use of patient-specific dosimetry. In this case, the AA is calculated so that tumors or normal organs will receive a

certain specified target dose designed to kill the tumor or avoid normal organ toxicity. Estimating organ doses requires knowledge of the time activity curves of organs in the patient. In dose-based TRT treatment planning, this is accomplished with imaging studies acquired at a series of time points after administration of a planning dose of the agent. The activities in the organs of interest at each time point are estimated from the images, providing points on the organ time-activity curves. Thus, the reliability of the dose estimate is directly related to the reliability of the activity estimates obtained at each time point.

In the past, organ activities at the various time points have been estimated from planar scans quantified using standard planar image quantification methodologies.^{8–10} However, conventional planar quantification methods involve a series of approximate compensations for factors including attenuation, scatter, and overlap of organ projections with each other and the background. The use of SPECT projections combined with QSPECT reconstruction methods^{11–14} or more theoretically rigorous quantitative planar processing methods such as the QPlanar method¹⁵ has been shown to provide improved accuracy and precision compared to conventional planar quantification methods. For both QSPECT and QPlanar methods, the accuracy of activity estimates is directly related to the ability to accurately model the image formation process.

There has been a great deal of effort to model attenuation,^{8,16,17} the collimator-detector response,^{18–21} and scatter in the patient.^{22–26} However, ¹³¹I presents a set of unique challenges compared to other radionuclides used for TRT treatment planning such as ¹¹¹In. In addition to the imaging photon (364 keV), I-131 decay produces higher-energy photons, e.g., 637 keV (7.5%) and 722 keV (1.8%). The 637 and 722 keV photons can be scattered in the patient or interact in the collimator-detector system and be detected in the 364 keV photopeak energy window used for imaging. This component of the projection data will hereafter be referred to as downscatter contamination.

Downscatter contamination comprises a significant portion of the detected photons.²⁷ It tends to reduce the contrast and degrade the quantitative accuracy of ¹³¹I SPECT images. In most previous work the downscatter contamination for ¹³¹I SPECT was not treated separately and explicitly, but was combined with scattered 364 keV photons. For example, the triple energy window (TEW) method⁹ can compensate for the effects of both primary photons (364 keV) and high-energy photons (637 and 722 keV). This method has been used widely due to its ease of implementation. However, TEW approximates the shape of the scattered photon energy spectrum in the photopeak window by a line, and thus has limited accuracy.²³ In addition, the scatter estimate is based on the counts in two narrow auxiliary energy windows, which often have relatively few counts and thus high noise. This noise can propagate into reconstructed images, and, at a minimum, careful attention to low-pass filtering of the estimates is needed.²⁸ Monte Carlo methods are able to provide more accurate scatter estimates. However, due to their complexity and the time required for the Monte Carlo modeling,

this method is not routinely used in clinical practice. Dewaraja *et al.* have investigated a Monte Carlo based scatter compensation method to compensate simultaneously for both 364 keV photon scatter and downscatter.^{23,29} Although they performed the Monte Carlo simulation (MCS) only for a limited number of iterations to decrease computation time, MCS is still time consuming and the computations must be performed at least once for each patient and time point. In this paper, we propose a model-based downscatter compensation method that is faster than and provides accuracy comparable to MCS.

There has previously been a good deal of effort aimed at downscatter modeling and compensation for dual isotope imaging. Downscatter effects have been studied extensively in simultaneous Tl-201/Tc-99m cardiac SPECT.^{30–32} El Fakhri *et al.* and Du *et al.* developed downscatter compensation for simultaneous Tc-99m/I-123 brain SPECT.^{32–34} These methods provide an arsenal of methods for modeling object downscatter and collimator interactions and iterative reconstruction based compensation methods.

In this study we propose a model-based downscatter compensation method and evaluated it using MCS methods. The proposed compensation method is based on an adaptation of a previously developed model-based downscatter estimation method for ¹²³I SPECT (Ref. 35) combined with iterative reconstruction-based compensation for patient attenuation (A) and scatter (S) and the full (D) collimator-detector response (including septal penetration and scatter) of the 364 keV photons. In the evaluation, organ activities estimated from the SPECT images reconstructed with and without the addition of the proposed downscatter compensation method were compared to those estimated from images without downscatter contamination, i.e., simulated using only 364 keV photons.

II. METHOD

II.A. Downscatter model

In ¹³¹I imaging, a combination of scatter in the patient or collimator and partial deposition in the crystal can result in high-energy photons, such as the 637 and 722 keV photons, having a detected energy that lies in the 364 keV photopeak energy window. We have previously developed a method to model the contribution of high-energy photons in ¹²³I imaging.³⁵ The model proposed here for ¹³¹I is very similar: it uses the ESSE scatter model to estimate the number of photons incident on the collimator in both the photopeak energy window and a set of energy ranges above the photopeak, and uses a set of precomputed collimator-detector response functions to compute the fraction of those photons incident on the collimator that are detected in the photopeak energy window. However, there are also a number of differences: the ¹³¹I photopeak photon is higher in energy, the nonphotopeak photons have higher abundances, and a HEGP collimator is used. Thus, while the techniques are similar, it is not clear in advance that the method would work for this application. Thus, at a minimum, this paper represents adaptation and validation of those ideas for ¹³¹I.

In this project, similar to the work on ^{123}I , downscatter contamination was separated into three general categories based on where the energy is lost. The first category includes high-energy photons not scattered in the object but scattered in the collimator-detector. The second category includes high-energy photons scattered in the object but not in the collimator-detector. The third category includes photons scattered in both the object and collimator-detector. Note that in this taxonomy, scatter in the collimator-detector includes both septal scatter as well as scatter in the detector resulting in only a portion of the photon's initial energy being deposited in the crystal. The proposed model includes all these effects and is shown schematically in Fig. 1.

In this study, the effective scatter source estimation (ESSE) method³⁶ was used to model the scatter in the object. In the ESSE method, two object-independent scatter kernels are calculated by simulating a point source in a large water filled slab using Monte Carlo simulation, but in this case a modified version of the Simind code.³⁷ The method is exact for single scatter in a convex uniform attenuator and includes approximations for nonuniform attenuators and multiple scatter. One advantage of ESSE that is used in the present application is that it can estimate the number of scattered photons exiting the object in any specified energy range. This is accomplished using precalculated scatter kernels computed for emission at one energy or energies with detection in an arbitrary lower energy range. Thus, ESSE was used to model the scattering in the patient for photons in categories 2 and 3: in the former, scattering is modeled directly into the 364 keV photopeak energy window, while in the latter the photons are scattered in the body to an intermediate energy range.

The collimator-detector effects were modeled using precalculated collimator-detector response functions (CDRFs). The CDRF of a collimator-detector system refers to the image generated by a point source. The full CDRF models several factors including the effects of septal penetration, septal scatter, partial energy deposition in the crystal, and finite energy resolution of the detector. Since the CDRF is a function of the distance from the source to the collimator, we created tables of CDRFs comprised of the set of CDRFs generated for a set of distances from the collimator face. The CDRF at a specific distance was calculated using Monte Carlo simulations of an ^{131}I point source at that distance that modeled all the effects described above. The CDRF is also a

function of both the energy of incidence of the photon with the collimator-detector system and the detection energy range. Thus, we created a set of CDRF tables corresponding to the various set of input energy ranges as described in the following.

For photons not scattered in the body (category 1), we generated a CDRF table to model the collimator-detector system by simulating point sources emitting 637 and 722 keV photons with the appropriate abundance and recording the photons detected in the 364 keV photopeak window. In principal, these photons should be handled separately. However, the attenuation coefficients in water for 637 and 722 keV photons are very similar (differing by 0.005 cm^{-1}). Further, the abundance of the 722 keV photons is substantially lower than for the 637 keV photon. As a result, we combined the CDRFs, using abundance weighting, for these two photopeaks in order to eliminate the need to perform separate modeling of category 1 photons for these two energies. Since CDRF modeling is the most computationally intensive part of the downscatter model, this simplification results in approximately a 20% reduction in the computational cost.

Category 2 photons arrive at the collimator with energies in the same range as the detection window (328–400 keV). Since these photons have energies similar to the 364 keV photon, we used the same CDRF table for these as was used for scattered and unscattered 364 keV photons.

Category 3 photons arrive at the collimator with a wide range and continuous distribution of energies. To more accurately model the CDRF, we divided these photons into two smaller ranges: 400–650 keV and 650–740 keV and used a separate CDRF table for each range. The reason for this choice of energy windows is illustrated in Fig. 2, which shows the energy spectrum of scattered photons for the various emission energies from a point source at the center of a water cylinder with a diameter of 25 cm: the energy spectrum was relatively constant in each energy range. We generated CDRF tables for each of these input energy ranges using sources emitting photons with a constant probability density as a function of energy in each range. Using a single CDRF for each of these energy ranges computed using a flat input energy spectrum assumes that the energy spectrum for photons in these ranges is also flat. Using a larger number of energy ranges would make the approximation more exact, but would increase the computational burden. For each of these ranges we used scatter kernels for the ESSE method

FIG. 1. Flowchart of the model based downscatter estimation process. In this figure, the energy ranges in the circles indicate the energy ranges of the photons after the indicated interaction. Category 1: high-energy photons not scattered in the object but scattered in the collimator-detector. Category 2: high-energy photons scattered in the object but not in the collimator-detector. Category 3: high-energy photons scattered in both the object and collimator-detector.

FIG. 2. Energy spectrum of ^{131}I from a point source in a water cylinder simulated using Monte Carlo simulation.

that were created using the energies and abundances of the high-energy photons and output energies corresponding to each of the two ranges. These scatter kernels were used to estimate the photon flux incident on the collimator in the corresponding range.

II.B. Downscatter compensation method

We have incorporated the downscatter model into an iterative reconstruction based downscatter compensation method. Since the method is relatively time consuming compared to modeling the photopeak alone, requiring ESSE scatter modeling and CDRF modeling three times each, we did not model downscatter during each iteration of a conventional iterative reconstruction process. Instead, we modeled downscatter intermittently as shown in Fig. 3. The method is comprised of an initial reconstruction (recon. I) with no downscatter compensation, a number of repetitions of modeling the downscatter alternating with another iterative reconstruction (recon. II), and a final reconstruction (recon. III).

In all cases the reconstructions were performed using the ordered subsets-expectation maximization (OS-EM) algorithm³⁸ with A, S, and D compensations, where these compensations were for the 364 keV photons; reconstructions II and III included additive correction for downscatter using the downscatter estimate. We used 24 subsets per iteration (five angles per subset) in all cases.

FIG. 3. Flowchart illustrating the downscatter compensation method. Note that in the above the termination condition could be a fixed number of repetitions of recon. II or a numerical convergence criterion such as a specific level of change in the downscatter estimate. In the above A, D, S, and DS indicate compensation for attenuation, the full collimator-detector response, object scatter, of the 364 keV photons, and downscatter, respectively.

The projection images were first reconstructed using OS-EM with ADS compensations (recon. I). The compensations for A, S, and D were based on 364 keV photons since we assumed that all detected photons were from the 364 keV photopeak. This reconstructed image was used as the activity distribution for downscatter estimation. Because the reconstructed image was not the true activity distribution, we repeated the downscatter estimation process several times until the change in the downscatter estimate was small, as described in more detail below. This converged downscatter estimate was then used as an additive correction in the final reconstruction (recon. III). Note that in all cases the scatter kernels and CDRF tables were calculated with appropriate normalization so that no scaling of the downscatter estimate was needed before adding it to the projection computed to model the 364 keV photons.

There are four iteration parameters in this method: the number of iterations in reconstructions I, II, and III and the number of repetitions of the downscatter estimation in the loop containing reconstruction II. We used five iterations for reconstruction I and II and did not investigate optimizing this parameter. We used up to seven repetitions of the downscatter estimation/reconstruction II loop based on an investigation of the number of repetitions needed for convergence. Reconstruction III was performed using 50 iterations based on a study of mean square error as a function of iteration presented later in this paper.

II.C. Experimental design

II.C.1. Experimental validation of the Monte Carlo simulation method

In this study, we used Monte Carlo simulation to validate the method since it allowed us to obtain separate estimates of the downscatter, use more realistic organ shapes and activity distributions than with a physical phantom, and exactly know the true organ activities with perfect precision and accuracy. We used the SimSET/ARF MC code combination to model the model the propagation of the photons in the object, and the angular response function (ARF) method²¹ was used to model interactions in the collimator-detector.

A modified version of MCNP MC code,³⁹ previously validated for simulation of Tc-99m, Tl-201,⁴⁰ I-123 (including downscatter from high-energy photons),⁴¹ and In-111,¹¹

FIG. 4. Images and dimensions of the capsule and cylinder phantom used in the validation.

was used to calculate the ARF (angular response function) table used in the ARF method. To validate the modified version of the MCNP MC code for I-131 and the Philips camera simulated in this experiment, we compared the energy spectrum of a physical source with that from MCS. In the experiment, an I-131 capsule with dimensions of 2×1.4 cm (Fig. 4) was used as the source. A listmode file was acquired using a Philips Precedence SPECT/CT system by imaging the source at a distance of 25 cm from the collimator face. The activity in the I-131 capsule was 7.13 MBq. The projection images were framed into 512×512 matrices with a 1.166 mm pixel size using a 20% wide energy window centered at 364 keV. The acquisition time was 4 min. The energy spectrum generated from the listmode file was compared with that from the MCS code obtained by simulating a cylindrical source with the same dimensions and at the same distance from the collimator-detector system. We modeled an energy resolution of 9% at 140 keV and an inverse square root energy dependence in the simulation. This purpose of this experiment was to verify that the MCNP code, which was used to generate the ARF tables used for the SimSET/ARF simulation, provides a good model of photon interactions in the collimator and detector.

To validate the SimSET/ARF combination, we compared the projections of a hot sphere inside a cold cylinder phantom filled with water. A hollow sphere with a 2.6 cm inner diameter was filled with a solution containing 2.96 MBq of ^{131}I . The inner diameter of the cylinder phantom was 22 cm (Data Spectrum, NC, USA) (Fig. 4).

The sphere was mounted 3 cm away from the axis of the phantom. Projection images were acquired at 12 views over 360° and recorded into 512×512 matrices with a 1.166 mm pixel size using a 20% wide energy window centered at 364 keV. The acquisition time for each projection view was 5 min. A phantom and imaging system with same parameters

as in the experiment were simulated using the Simset/ARF MCS code using the same set of ARFs used in the phantom simulation described in the next section. Two projection views of the projection images from the physical experiment and MCS were compared.

II.C.2. Projection data simulation

The purpose of this study was to validate the downscatter model for a realistic object. In this simulation study we used the realistic 3D NCAT digital phantom⁴² to simulate patient anatomy. The activities in the organs were based on those from quantitative SPECT/CT reconstructions of a 5 mCi injection of In-111 Zevalin 24 h postinjection. We modeled the activity distribution from In-111 Zevalin because a similar activity distribution is expected for I-131 Bexxar since both target the CD-20 membrane protein of B cells. Table I lists the size and the simulated activity of each organ.

Low-noise projection images of seven organs (heart, lungs, liver, kidneys, spleen, bone marrow, blood vessels, and remainder) from emissions by photons at 364, 637, and 722 keV were separately simulated using the Simset/ARF code. In the simulation, we used ARF tables computed for the energy of each photopeak plus 16 energy ranges (284–300, 300–328, 328–350, 350–364, 364–380, 380–400, 400–440, 440–480, 480–520, 520–560, 560–600, 600–620, 620–637, 637–670, 670–700 and 700–722 keV) to model the energy dependence of the CDRF. A Philips Precedence camera with a 0.9525 cm thick NaI crystal and an HEGP collimator was simulated. Projections were simulated into 128×128 projection matrices with a 4.664 mm pixel size at 120 views over 360° using a 20% wide energy windows centered at 364 keV. We tracked a total of 4.1×10^{11} photons to generate low-noise projection data.

The low-noise projection data from the different photopeaks were scaled by the corresponding emission abundances (81.2% for 364 keV, 7.49% for 637 keV, and 1.8% for 722 keV) and a scale factor equal to the activity times the total acquisition time (120 projections times 30 s per view) divided by the number of photons simulated for that photopeak. The data were then summed to create datasets with (i.e., summing data from all three photopeaks) and without (i.e., using only data from the 364 keV photopeak) downscatter contamination. It was observed that downscatter contamination represented about 20% of the total counts in the projection images, demonstrating that downscatter is a significant effect and indicating that downscatter compensation is likely to be important for quantitative I-131 imaging. Since the organ activities were based on patient data and the simulation modeled a clinical acquisition time and the

TABLE I. Organ volumes and activities simulated in the NCAT phantom.

Organ	Heart	Lungs	Liver	Spleen	Kidneys	Bone marrow	Remainder
Volume (c.c.)	714.0	1847.6	1324.6	191.0	136.1	714.9	36770.6
Activity (MBq)	11.41	9.57	21.72	2.09	4.79	3.64	137.11

FIG. 5. The same coronal slice of the activity map (a) and attenuation map (b). Anterior projection views of the low-noise projection image with (c) and without (d) downscatter contamination and (e) the same as (c) but with simulated Poisson noise.

sensitivity of a real camera, the count level in the low-noise projection data was clinically realistic.

Noisy projection data were created by simulating 50 independent Poisson noise realizations using the low-noise data as the mean for a Poisson random number generator. Figure 5 shows sample images from the NCAT phantom, low-noise uncontaminated and contaminated projection images, and noisy contaminated projection images.

II.C.3. Image reconstruction

All the contaminated projections, including noisy and low-noise data, were reconstructed using the model-based downscatter compensation method described above. In the model-based compensation method, we used OS-EM with five iterations of 24 subsets per iteration for reconstructions I and II during the estimation process. These reconstructions modeled attenuation, scatter using ESSE (Ref. 36) and the full CDRF using a precalculated CDRF table for the 364 keV photons. To determine how many times the downscatter estimation process should be repeated, we investigated the convergence properties of the downscatter estimates as a function of repetition number. We calculated the average absolute change in pixel value, d , using the following formula:

$$d = \frac{\sum_{i=0}^{M-1} |a_{i,n} - a_{i,n-1}|}{M}, \quad (1)$$

where $a_{i,n}$ is the value of the i th pixel in the images of the downscatter estimated after the n th repetition, i is the pixel index, n is the repetition number, and M is the total number of the pixels in the image.

Figure 6 shows a plot of the average absolute change of the pixel value of the estimated downscatter averaged over the 50 noise realizations as a function of repetition number. Note that the average absolute change of pixel value converged ($d > 0.01$) after five to six repetitions. Based on these data, we used seven downscatter estimation repetitions in the remainder of the studies in this paper. The CPU time required to compute the downscatter from a $128 \times 128 \times 170$ image into hundred and twenty 128×170 projections for one repetition was 30 min on a single core of an AMD Opteron 275 CPU. The required memory was 176 MB.

After the downscatter estimates converged, the final SPECT image was reconstructed (recon. III) using OS-EM with 24 subsets per iteration. To determine the number of iterations needed for the final reconstruction, the root mean square error (RMSE) of activity estimates was calculated as a function of iteration number for each organ.

For comparison purposes, we reconstructed the projection data without downscatter contamination (i.e., from 364 keV photons only) using OS-EM and the same ADS compensation method described above. The errors in the organ activities estimated from the SPECT images reconstructed from the low-noise data with and without downscatter contamination were compared to evaluate the efficacy of the model-based downscatter compensation method. By this measure, perfect downscatter compensation would be achieved if the organ activity estimates from projection data with downscatter contamination reconstructed with downscatter compensation were the same as those reconstructed from projection data without downscatter contamination reconstructed without downscatter compensation. The mean error and standard deviation of organ activities estimated from the 50 sets noisy contaminated SPECT data were calculated to show the effects of statistical noise.

III. RESULT AND DISCUSSION

III.A. Validation experiment results

Figure 7 shows a comparison of measured and simulated energy spectra of the I-131 capsule in the range 300–730

FIG. 6. Plot of the average absolute change in pixel value of the estimated downscatter contamination averaged over 50 data sets as a function of repetition number.

Fig. 7. The measured and simulated energy spectra of a point source (capsule) at 25 cm from the collimator face.

keV. There was good agreement for the 364 keV peak and relatively small discrepancies for the 637 and 722 keV peaks. A likely reason for the residual discrepancies is that the assumed energy dependence of the energy resolution used in the MC simulation was not exact for higher energies. The percent RMSE between measured and simulated energy spectrum was 23.29%. Note that the errors come from not only spectral discrepancies but also statistical noise. To exclude the errors caused by noise, we also compared the simulated and measured total counts in energy a number of ranges (328–400, 610–650, 700–727 keV) to quantify the errors for the three energy peaks (Table II). The percent difference was 2.1% for 328–400 keV, 8.7% for 610–650 keV

TABLE II. Comparison of total counts in some energy ranges between measured and simulated energy spectra.

Energy range (keV)	328–400	610–650	700–727
Measured	1.36E+05	2.96E+04	5.20E+03
Simulated	1.39E+05	3.25E+04	7.60E+03

and about 30% for 700–727 keV. Considering the relatively low abundance of 722 keV photons, the agreement between measured and simulated spectra was considered good.

Figure 8 shows a comparison of images and profiles through the center of the hot sphere phantom from measured and simulated projection images at projection angles of 0° and 180°. The hot sphere was nearest to the collimator face at 0° and furthest from the collimator face at 180°. To demonstrate the agreement in the tails of the distribution, which represent scatter and penetration effects, the profiles are also displayed on a semi-log scale. Profiles are shown both between and along the septal penetration spokes of the CDRF. We can see that the agreement between the measured and simulated projections was excellent in all cases.

III.B. Downscatter model validation

To validate the downscatter estimation method for ^{131}I imaging, the downscatter contamination estimated from the

Fig. 8. Comparison of the projection images, linear and log scale profiles through the center of the hot sphere from the measured and simulated data using cylinder phantom. The projection angles 0° and 180° are that at which the hot sphere is the nearest and furthest from the detector surface, respectively.

true activity distribution was compared with the downscatter from the Monte Carlo simulation. However, in the proposed compensation method, the downscatter contamination was estimated iteratively using the SPECT image reconstructed after recon. II as the initial activity distribution instead of using the true distribution. Therefore, the downscatter estimate obtained using the reconstructed SPECT image was also compared to the estimate from MCS; for this comparison we used the mean of the downscatter estimates obtained from the 50 sets of noisy projection data that included downscatter contamination.

Figure 9 compares the profile in one view of the estimated and simulated downscatter contamination. There was relatively good agreement between the profiles of the two estimated downscatter projections, especially in the central area of the phantom. The percent RMSE of the two downscatter projections images was 1.8%. This illustrates that the proposed alternating downscatter estimation procedure produces a reconstructed SPECT image that can be used as a replacement for the activity map in downscatter estimation. All subsequent results were obtained using SPECT images as the input to the downscatter model. Larger disagreements between the estimated and MC downscatter estimates were observed outside the phantom. The larger errors outside the phantom were likely due to the fact that the combination of CDRF and attenuation is modeled as follows. Consider a plane in the activity distribution parallel to the collimator. Each voxel is first attenuated by an attenuation factor calculated along the ray from the voxel and perpendicular to the collimator. Then, the resulting attenuated activity distribution in the plane is convolved with the CDRF appropriate for that plane. The net effect is that attenuation is not modeled along the true photon path. This is a good approximation for photon directions almost perpendicular to the collimator face, corresponding to the central portion of the CDRF.

However, for photons with more oblique incident angles, corresponding to the tails, this approximation tends to overestimate the amount of attenuation for photons exiting the side of the object. Despite this error, the projections inside the object, for which the error is smaller, are more important in terms of the reconstructed activity distribution. Thus we expect that the effect on activity quantification will be small.

The MCS method we used allowed the detected higher-energy photons (637 and 722 keV) to be recorded in separate images according to whether they were scattered in patient body. Therefore, we could compare simulated and estimated downscatter components in category I and categories II and III (combined), respectively. The absolute percent differences over the whole projection image were 3.9 and 13.3% for category I and categories II and III, respectively. Since, the detected photons in categories II and III represented about 20% of the downscatter contamination. Therefore, their contribution to the overall error in the downscatter was relatively modest. Also note that the small error for the category I photons indicates that combining these two photons was an acceptable approximation.

Because the TEW method is simple to implement and commonly used for scatter compensation in ^{131}I imaging, we compared the downscatter component that would be obtained using the TEW method with that from MC simulation. Figure 10 compares the profile through the downscatter estimate obtained from the TEW method with that from MCS. The profile is from the same location and in the same projection view as the profiles in Fig. 9. Note that the TEW method significantly overestimated the downscatter component. The percent RMSE between the true MC simulated and TEW estimated downscatter projection was 33.2%.

To further investigate the disagreement between simulated and estimated downscatter contamination inside the phantom, we estimated the downscatter contamination for

FIG. 9. Top row: projection images of MC simulated downscatter contamination (a) and the model-based downscatter estimates from the true activity map (b) and the quantitative SPECT reconstruction (c). Bottom row: difference images from the images shown in the first row: the difference image (d) = (a)–(b) and (e) = (a)–(c). The graph at left shows a profile through the images in the top row at the position indicated. The inset in the graph shows a magnification of the profiles in the center of the phantom.

FIG. 10. Comparison between true MC simulated downscatter contamination (a) and the downscatter estimates from the TEW method (b) in the same location and the same projection view as Fig. 9, which shows a comparison to the model-based downscatter estimate.

each organ separately using both the proposed and TEW methods and compared the estimates with those from MCS. For these comparisons, only activity in the organ of interest was used in the activity map that served as the input for downscatter estimation. We compared the total counts in the estimated and MCS downscatter in the region of the projection data within the projected boundary of the phantom (Table III). For the TEW method, the estimated downscatter components for all the organs were highly overestimated, about 30% for heart, kidneys, and background, about 20% for lungs, spleen, liver, and bone marrow. For the proposed method, we observed that the magnitude of the error was less than 5% for all the organs except the lungs, where it was 10.20%, and the bone marrow, where it was 7.24%. The larger errors for these organs likely resulted from a difference in the attenuation factor as described above and approximations in the ESSE scatter estimation method. However, if we take into account the fact that the downscatter contamination represents about 20% in the measured projections, even the effect of these discrepancies on the organ activity estimates are expected to be relatively minor.

III.C. Efficacy of downscatter compensation

As mentioned above, one important issue in using the OS-EM iterative reconstruction algorithm is the optimal number of iterations. We used the RMSE of organ activity estimates as a figure-of-merit to find the optimal number of iterations. The RMSEs were calculated for each organ and are plotted in Fig. 11 as a function of iteration number. These show that a minimum was not reached even after 50 iterations of 24 subsets per iteration. However, the RMSEs were essentially converged for the heart and liver after 10–15 iterations and for the spleen, bone marrow and lungs after 25–30 iterations.

Based on the above convergence study, the SPECT images obtained after 50 iterations were used to calculate the organ activities in this study. Since we were interested in the effects of downscatter contamination, the results from the

low-noise uncontaminated SPECT images reconstructed using 50 iterations using OS-EM with A, S, and D compensations were used as the gold standard. This makes more sense in terms of evaluating the efficacy of downscatter compensation than comparing to the true activity since there are additional confounding errors. For example, partial volume effects are expected to have a significant effect on the accuracy of organ activity estimates due to the poor resolution of the HEGP collimator. Thus, without partial volume compensation, organ activities would tend to be underestimated. On the other hand, downscatter contamination would tend to result in overestimation. Thus, the accuracy depends on the relative balance of these two effects, and partial volume effects might make it difficult to judge the efficacy of downscatter compensation.

The percent differences in the estimated organ activities are shown in Table IV. For the low-noise data with downscatter compensation, the percent difference was less than 0.5% for all the organs except the lungs (3.35%) and bone marrow (2.86%). This demonstrates that the proposed model-based method provides accurate downscatter compensation. This phenomenon is consistent with the comparison of estimated and simulated downscatter contamination in the previous section. Note that the residual differences in organ activities due to imperfect downscatter compensation are smaller than the errors in downscatter estimates shown in Table III. Recalling that downscatter represents about 20% of the total projection data, we expect the error in activity estimates to be about 20% of the error in the downscatter estimates, and this is approximately what is observed in Table IV.

FIG. 11. Plot of RMSE as a function of the number of OS-EM iterations (24 subsets per iteration) for the various organs.

TABLE III. Percent error in the total counts of the downscatter estimates for each organ.

Error (%)	Heart	Lungs	Liver	Spleen	Kidneys	Bone Marrow	Background
Proposed	-1.88	-10.20	1.86	3.13	0.07	-7.24	-3.41
TEW	29.21	19.19	22.47	19.44	35.10	19.95	30.24

Percent error is calculated as $(\text{estimated} - \text{simulated}) / \text{simulated} \times 100\%$.

TABLE IV. Percent difference in organ activity estimates.

	Heart	Lungs	Liver	Spleen	Kidneys	Bone marrow	Background
*	−0.11	−3.35	−0.11	0.12	−0.31	−2.84	−0.07
**	6.65	8.55	6.08	7.82	7.20	15.08	14.96
***	−0.23 ± 1.11	−0.30 ± 1.92	−0.08 ± 0.94	−1.63 ± 3.06	−2.28 ± 2.02	−9.33 ± 3.00	0.07 ± 0.30

Percent difference is calculated as (estimated−standard)/standard × 100%. The gold standard for comparison was the SPECT reconstruction from data without downscatter contamination.

*: contaminated low-noise SPECT reconstructed using model-based downscatter compensation method.

**: contaminated low-noise SPECT reconstructed without downscatter compensation.

***: contaminated noisy SPECT reconstructed using model-based downscatter compensation method.

To show the effects of downscatter contamination on the organ activity estimates, we also calculated the percent difference in organ activities estimated without downscatter compensation from data that included downscatter contamination. We observed that, downscatter resulted in errors of 8% for the lungs, 6%–7% for heart, liver, spleen and kidneys, 15% for the bone marrow and background. This indicates the relative importance of downscatter compensation.

Table IV also shows the mean and standard deviation of the percent difference for organ activity estimates from the 50 sets of noisy data with downscatter contamination reconstructed with downscatter compensation. Compared to the results from low-noise downscatter-contaminated data, the statistical noise resulted in less than a 0.5% difference in the mean percent difference for the heart, liver, and background, about 2% for spleen and kidneys, about 3% for lungs, and about 6% for bone marrow. For all the organs except the bone marrow, these differences are within the estimated standard deviations. For all the organs the precision of the estimate was 3% or better. Note that the activity estimates for all the organs were underestimated compared to the reconstruction from data without downscatter. One possible explanation is that downscatter compensation slowed the convergence of the reconstruction algorithm, and thus resolution recovery. Therefore, the PVEs effects were more significant for SPECT images with downscatter compensation than those without downscatter compensation at the same iteration number.

Figure 12 shows the coronal slices (same slice as in Fig. 5) of the low-noise and noisy SPECT images reconstructed using the methods and parameters described in Sec. II C 2. These images demonstrate that the downscatter compensation method produced images very similar to those reconstructed from images without downscatter contamination.

In addition to knowing the efficacy of downscatter compensation, it is also desirable to know the overall accuracy and precision of I-131 QSPECT including downscatter compensation. Table V shows data analogous to Table IV, but where the true organ activities were used as the gold standard. We see that the accuracy was better than 5% for large organs but much poorer accuracy, about 15%, for smaller organs.

For large organs the accuracies were slightly worse than for corresponding organs when imaged using In-111 and an MEGP (medium energy general purpose) collimator.¹¹ For smaller organs the errors were much greater than for the In-111 case. These data suggest that the residual inaccuracy is largely due to partial volume effects resulting from the relatively poor resolution obtained with an HEGP collimator. Note that in He *et al.*¹¹ the errors for the lungs were much higher than in this work. This is due to the fact that, in that paper, blood vessels inside the lung boundaries were not treated as parts of the lung, but as a part of the blood vessel VOI. This resulted in very high spill-in effects in the lungs. In practice it would be very difficult to define lung VOIs that

FIG. 12. Coronal slices from the reconstructed SPECT images: (a) reconstructed from low-noise projections without downscatter contamination using OS-EM with attenuation, scatter and full collimator detector response compensations; (b) reconstructed from low-noise data using the proposed model-based downscatter compensation method; (c) reconstructed from noisy downscatter contaminated projections using the proposed model-based downscatter compensation method; (d) difference image obtained from (a)–(b). The maximum and minimum voxel values in the two groups of images are indicated in the grayscale bar at the right of each group.

TABLE V. Percent errors in organ activity estimates.

	Heart	Lungs	Liver	Spleen	Kidneys	Bone marrow	Background
*	-4.44	-4.71	-3.20	-14.86	-13.53	-13.38	0.97
**	4.12	1.81	5.03	-7.85	3.07	6.92	8.68
***	-4.10 ± 1.11	-1.66 ± 1.92	-3.17 ± 0.94	-16.60 ± 3.06	-15.50 ± 2.02	-19.85 ± 3.00	0.99 ± 0.30

Percent error is calculated as (estimated-true)/true × 100%.

*: contaminated low-noise SPECT reconstructed using model-based downscatter compensation method.

**: contaminated low-noise SPECT reconstructed without downscatter compensation.

***: contaminated noisy SPECT reconstructed using model-based downscatter compensation method.

excluded the blood vessels. So, in this work we included activity in blood vessels inside the lungs as lung activity.

As shown in Table V, the precisions were better than 3% for all organs, slightly worse than the precisions observed for In-111 using the same activity distribution and simulated acquisition time. The modestly reduced precision is likely due to the poorer sensitivity of the HEGP collimator but also partly due to the extra noise introduced by downscatter and extra imprecision induced by compensating for the broader CDRF. Note that the activity estimates for all the organs except the background were underestimated. This is because the PVE effects, which are significant for I-131 images obtained with HEGP collimators, result in organ activity spill out. This also explains why the background activity was overestimated: spill-in from higher activity organs resulted in spurious extra activity in the background.

In Table V we also showed the errors for the case of no downscatter compensation. For most of the organs, the SPECT images without downscatter compensation provided smaller errors than those with downscatter compensation. This is because, for these organs, not compensating for downscatter will offset errors due to partial volume effects, resulting in better overall accuracy. However, the degree to which these effects offset depends on patient dependent factors that modulate the magnitude of partial volume effects such as the proximity of organs and their relative activities. This phenomenon suggests that compensations for downscatter and PVEs should be implemented in combination to obtain the most reliable quantitative information from I-131 SPECT images.

IV. CONCLUSION

In this paper, we proposed a model-based downscatter compensation method and evaluated it using Monte Carlo simulation, after experimental validation of the Monte Carlo simulation code. We demonstrated that the proposed downscatter model used in the compensation method provided good agreement with Monte Carlo simulated downscatter estimates, while the TEW method significantly overestimated the downscatter component. We also demonstrated that, in the context of estimating organ activities in I-131 targeted radionuclide therapy, the proposed compensation method produced organ activity estimates comparable to those obtained from data without downscatter contamination, indicating the efficacy of the proposed compensation method. We observed that not compensating for downscatter

produced errors of 6%–15% in organ activity estimates. Combining the downscatter compensation method with model-based compensation for attenuation, scatter, and the collimator-detector response of 364 keV photons produced accuracies of better than 5% for larger and high uptake organs such as the background, heart and liver. Accuracies were poorer for smaller organs: biases for the spleen, bone marrow, and kidneys were on the order of 10%–15%. Compared to a previous study of In-111 QSPECT using an MEGP collimator, the accuracies were similar for large organs and poorer for small organs. These results indicate that partial volume effects may play a significant role and partial volume compensation may be beneficial. The precisions of the activity estimates were 3% or better for all the organs, indicating that shorter acquisition times may be acceptable if the images are used for organ activity quantification and organ VOIs are defined using, e.g., registered CT images.⁴³ These studies demonstrate that the proposed model-based downscatter compensation method is effective and may have a role in quantitative ¹³¹I imaging.

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¹J. Pineda, T. Lee, K. Ain, J. Reynolds, and J. Robbins, "Iodine-131 therapy for thyroid cancer patients with elevated thyroglobulin and negative diagnostic scan," *J. Clin. Endocrinol. Metab.* **80**, 1488–1492 (1995).

²O. W. Press, J. F. Eary, F. R. Appelbaum, P. J. Martin, W. B. Nelp, S. Glenn, D. R. Fisher, B. Porter, D. C. Matthews, T. Gooley, and I. D. Bernstein, "Phase-I trial of I-131 B1 (Anti-Cd20) antibody therapy with autologous stem-cell transplantation for relapsed B-cell lymphomas," *Lancet* **346**, 336–340 (1995).

³R. L. Wahl, K. R. Zasadny, D. MacFarlane, I. R. Francis, C. W. Ross, J. Estes, S. Fisher, D. Regan, S. Kroll, and M. S. Kaminski, "Iodine-131 anti-B1 antibody for B-cell lymphoma: An update on the Michigan phase I experience," *J. Nucl. Med.* **39**, 21s–27s (1998).

⁴G. L. DeNardo, K. R. Lamborn, D. S. Goldstein, L. A. Kroger, and S. J. DeNardo, "Increased survival associated with radiolabeled Lym-1 therapy for non-Hodgkin's lymphoma and chronic lymphocytic leukemia," *Cancer* **80**, 2706–2711 (1997).

⁵M. S. Kaminski, K. R. Zasadny, I. R. Francis, M. C. Fenner, C. W. Ross, A. W. Milik, J. Estes, M. Tuck, D. Regan, S. Fisher, S. D. Glenn, and R. L. Wahl, "Iodine-131 – Anti-B1 radioimmunotherapy for B-cell lymphoma," *J. Clin. Oncol.* **14**, 1974–1981 (1996).

⁶G. A. Yanik, J. E. Levine, K. K. Matthay, J. C. Sisson, B. L. Shulkin, B. Shapiro, D. Hubers, S. Spalding, T. Braun, J. L. M. Ferrara, and R. J. Hutchinson, "Pilot study of iodine-131-metaiodobenzylguanidine in combination with myeloablative chemotherapy and autologous stem-cell support for the treatment of neuroblastoma," *J. Clin. Oncol.* **20**, 2142–2149 (2002).

- ⁷D. A. Meier, D. R. Brill, D. V. Becker, S. E. M. Clarke, E. B. Silberstein, H. D. Royal, and H. R. Balon, Procedure guideline for therapy of thyroid disease with (131)iodine, *J. Nucl. Med.* **43**, 856–861 (2002).
- ⁸S. C. Moore, J. A. Brunelle, and C. M. Kirsch, An iterative attenuation correction for a single photon, scanning, multi-detector tomographic system, *J. Nucl. Med.* **22**, P65–P65 (1981).
- ⁹K. Ogawa, Y. Harata, T. Ichihara, A. Kubo, and S. Hashimoto, A practical method for position-dependent Compton-scatter correction in single photon-emission CT, *IEEE Trans. Med. Imaging* **10**, 408–412 (1991).
- ¹⁰S. R. Thomas, H. R. Maxon, and J. G. Kereiakes, In vivo quantitation of lesion radioactivity using external counting methods, *Med. Phys.* **4**, 253–255 (1976).
- ¹¹B. He, Y. Du, X. Y. Song, W. P. Segars, and E. C. Frey, A Monte Carlo and physical phantom evaluation of quantitative In-111SPECT, *Phys. Med. Biol.* **50**, 4169–4185 (2005).
- ¹²R. J. Jaszcak, R. E. Coleman, and F. R. Whitehead, Physical factors affecting quantitative measurements using camera-based single photon-emission computed-tomography (SPECT), *IEEE Trans. Nucl. Sci.* **28**, 69–80 (1981).
- ¹³M. S. Rosenthal, J. Cullom, W. Hawkins, S. C. Moore, B. M. W. Tsui, and M. Yester, Quantitative Spect Imaging – A review and recommendations by the Focus Committee of the Society-of-Nuclear-Medicine Computer and Instrumentation Council, *J. Nucl. Med.* **36**, 1489–1513 (1995).
- ¹⁴B. M. W. Tsui, E. C. Frey, X. Zhao, D. S. Lalush, R. E. Johnston, and W. H. McCartney, The importance and implementation of accurate 3d compensation methods for quantitative spect, *Phys. Med. Biol.* **39**, 509–530 (1994).
- ¹⁵B. He and E. C. Frey, Comparison of conventional, model-based quantitative planar, and quantitative SPECT image processing methods for organ activity estimation using In-111 agents, *Phys. Med. Biol.* **51**, 3967–3981 (2006).
- ¹⁶J. A. Malko, R. L. Vanheertum, G. T. Gullberg, and W. P. Kowalsky, Spect liver imaging using an iterative attenuation correction algorithm and an external flood source, *J. Nucl. Med.* **27**, 701–705 (1986).
- ¹⁷B. M. W. Tsui, G. T. Gullberg, E. R. Edgerton, J. G. Ballard, J. R. Perry, W. H. McCartney, and J. Berg, Correction of nonuniform attenuation in cardiac spect imaging, *J. Nucl. Med.* **30**, 497–507 (1989).
- ¹⁸A. R. Formiconi, A. Pupi, and A. Passeri, Compensation of spatial system response in spect with conjugate-gradient reconstruction technique, *Phys. Med. Biol.* **34**, 69–84 (1989).
- ¹⁹B. M. W. Tsui, H. B. Hu, D. R. Gilland, and G. T. Gullberg, Implementation of simultaneous attenuation and detector response correction in spect, *IEEE Trans. Nucl. Sci.* **35**, 778–783 (1988).
- ²⁰G. L. Zeng and G. T. Gullberg, Frequency-domain implementation of the 3-dimensional geometric point response correction in spect imaging, *Conference Record of the 1991 IEEE Nuclear Science Symposium and Medical Imaging Conference, 1991*, Vol. 1–3, pp. 1943–1947.
- ²¹X. Song, W. P. Segars, Y. Du, B. M. W. Tsui, and E. C. Frey, Fast modeling of the collimator-detector response in Monte Carlo simulation of SPECT imaging using the angular response function, *Phys. Med. Biol.* **50**, 1791–1804 (2005).
- ²²H. Zaidi and K. F. Koral, Scatter modelling and compensation in emission tomography, *Eur. J. Nucl. Med. Mol. Imaging* **31**, 761–782 (2004).
- ²³Y. K. Dewaraja, M. Ljungberg, and J. A. Fessler, 3-D Monte Carlo-based scatter compensation in quantitative I-131SPECT reconstruction, *IEEE Trans. Nucl. Sci.* **53**, 181–188 (2006).
- ²⁴E. C. Frey and B. M. W. Tsui, A practical method for incorporating scatter in a projector-backprojector for accurate scatter compensation in spect, *IEEE Trans. Nucl. Sci.* **40**, 1107–1116 (1993).
- ²⁵E. C. Frey and B. M. W. Tsui, A new method for modeling the spatially-variant, object-dependent scatter response function in SPECT, *IEEE Nuclear Science Symposium Conference Record 1997*, Vol. 1–3, pp. 1082–1086.
- ²⁶E. C. Frey, B. M. W. Tsui, and M. Ljungberg, A comparison of scatter compensation methods in spect – Subtraction-based techniques versus iterative reconstruction with accurate modeling of the scatter response, *Conference Record of the 1992 IEEE Nuclear Science Symposium and Medical Imaging Conference*, Vol. 1–2, pp. 1035–1037.
- ²⁷Y. K. Dewaraja, M. Ljungberg, and K. F. Koral, Characterization of scatter and penetration using Monte Carlo simulation in I-131 imaging, *J. Nucl. Med.* **41**, 123–130 (2000).
- ²⁸M. A. King, D. J. deVries, T. S. Pan, P. H. Pretorius, and J. A. Case, An investigation of the filtering of TEW scatter estimates used to compensate for scatter with ordered subset reconstructions, *IEEE Trans. Nucl. Sci.* **44**, 1140–1145 (1997).
- ²⁹Y. K. Dewaraja, M. Ljungberg, and J. A. Fessler, 3-d Monte Carlo-based scatter compensation in quantitative I-131SPECT reconstruction, *2004 IEEE Nuclear Science Symposium Conference Record*, Vol. 1–7, pp. 3653–3657.
- ³⁰H. Ando, T. Fukuyama, W. Mitsuoka, S. Egashira, Y. Imamura, H. Masaki, and T. Ashihara, Influence of downscatter in simultaneously acquired thallium-201/technetium-99m-PYP SPECT, *J. Nucl. Med.* **37**, 781–785 (1996).
- ³¹H. W. A. M. de Jong and F. J. Beekman, Rapid SPECT simulation of downscatter in non-uniform media, *Phys. Med. Biol.* **46**, 621–635 (2001).
- ³²W. T. Wang, B. M. W. Tsui, D. S. Lalush, C. Tocharoenchai, and E. C. Frey, Optimization of acquisition parameters for simultaneous Tl-201 and Tc-99m dual-isotope myocardial imaging, *IEEE Trans. Nucl. Sci.* **52**, 1227–1235 (2005).
- ³³Y. Du, B. M. W. Tsui and E. C. Frey, Model-based crosstalk compensation for simultaneous Tc-99m/I-123 dual-isotope brain SPECT imaging, *Med. Phys.* **34**, 3530–3543 (2007).
- ³⁴G. El Fakhri, P. Maksud, M. F. Kijewski, M. O. Habert, A. Todd Pokropek, A. Aurengo, and S. C. Moore, Scatter and cross-talk corrections in simultaneous Tc-99m/I-123 brain SPECT using constrained factor analysis and artificial neural networks, *IEEE Trans. Nucl. Sci.* **47**, 1573–1580 (2000).
- ³⁵Y. Du, B. M. W. Tsui, and E. C. Frey, Model-based compensation for quantitative I-123 brain SPECT imaging, *Phys. Med. Biol.* **51**, 1269–1282 (2006).
- ³⁶E. C. Frey and B. M. W. Tsui, A new method for modeling the spatially-variant, object-dependent scatter response function in SPECT, *IEEE Nucl. Sci. Symp.* **2**, 1082–1086 (1996).
- ³⁷M. Ljungberg and S. E. Strand, A Monte Carlo program for the simulation of scintillation camera characteristics, *Comput. Methods Programs Biomed.* **29**, 257–272 (1989).
- ³⁸H. M. Hudson and R. S. Larkin, Accelerated image-reconstruction using ordered subsets of projection data, *IEEE Trans. Med. Imaging* **13**, 601–609 (1994).
- ³⁹R. L. Harrison, D. R. Haynor, S. B. Gillispie, S. D. Vannoy, M. S. Kaplan, and T. K. Lewellen, A public-domain simulation system for emission tomography – photon tracking through heterogeneous attenuation using importance sampling, *J. Nucl. Med.* **34**, P60–P60 (1993).
- ⁴⁰W. T. Wang, E. C. Frey, B. M. W. Tsui, C. Tocharoenchai, and W. H. Baird, Parameterization of Pb X-ray contamination in simultaneous Tl-201 and Tc-99m dual-isotope imaging, *IEEE Trans. Nucl. Sci.* **49**, 680–692 (2002).
- ⁴¹Y. Du, E. C. Frey, W. T. Wang, C. Tocharoenchai, W. H. Baird, and B. M. W. Tsui, Combination of MCNP and SimSET for Monte Carlo simulation of SPECT with medium and high energy photons, *2001 IEEE Nuclear Science Symposium Conference Record*, Vol. 1–4, pp. 1358–1362.
- ⁴²W. P. Segars, B. M. W. Tsui, D. S. Lalush, E. C. Frey, M. A. King, and D. Manocha, Development and application of the new dynamic NURBS-based Cardiac-Torso (NCAT) phantom, *J. Nucl. Med.* **42**, 7P–7P (2001).
- ⁴³B. He and E. C. Frey, Effects of shortened acquisition time on accuracy and precision of quantitative estimates of organ activity, *Med. Phys.* **37**, 1807–1815 (2010).