Quantitative simultaneous $^{111}\text{In}/^{99\text{m}}\text{Tc}$ SPECT-CT of osteomyelitis

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Purpose: A well-established approach for diagnostic imaging of osteomyelitis (OM), a bone infection, is simultaneous SPECT-CT of $^{99\text{m}}\text{Tc}$ sulfur colloid (SC) and ^{111}In white blood cells (WBC). This method provides essentially perfect spatial registration of the tracers within anatomic sites of interest. Currently, diagnosis is based purely on a visual assessment—where relative discordance between $^{99\text{m}}\text{Tc}$ and ^{111}In uptake in bone, i.e., high ^{111}In and low $^{99\text{m}}\text{Tc}$, suggests OM. To achieve more quantitative images, noise, scatter, and crosstalk between radionuclides must be addressed through reconstruction. Here the authors compare their Monte Carlo-based joint OSEM (MC-JOSEM) algorithm, which reconstructs both radionuclides simultaneously, to a more conventional triple-energy window-based reconstruction (TEW-OSEM), and to iterative reconstruction with no compensation for scatter (NC-OSEM).

Methods: The authors created numerical phantoms of the foot and torso. Multiple bone-infection sites were modeled using high-count Monte Carlo simulation. Counts per voxel were then scaled to values appropriate for ^{111}In WBC and $^{99\text{m}}\text{Tc}$ SC imaging. Ten independent noisy projection image sets were generated by drawing random Poisson deviates from these very low-noise images. Data were reconstructed using the two iterative scatter-compensation methods, TEW-OSEM and MC-JOSEM, as well as the uncorrected method (NC-OSEM). Mean counts in volumes of interest (VOIs) were used to evaluate the bias and precision of each method. Data were also acquired using a phantom, approximately the size of an adult ankle, consisting of regions representing infected and normal bone marrow, within a bone-like attenuator and surrounding soft tissue; each compartment contained a mixture of ^{111}In and $^{99\text{m}}\text{Tc}$. Low-noise data were acquired during multiple short scans over 29 h on a Siemens Symbia T6 SPECT-CT with medium-energy collimators. Pure $^{99\text{m}}\text{Tc}$ and ^{111}In projection datasets were derived by fitting the acquired projections to the sum of $^{99\text{m}}\text{Tc}$ and ^{111}In contributions, using the known half-lives. Uncontaminated data were scaled and recombined into six datasets with different activity ratios; ten Poisson noise realizations were then generated for each ratio. VOIs in each of the compartments were used to evaluate the bias and precision of each method with respect to reconstructions of uncontaminated datasets. In addition to the simulated and acquired phantom images, the authors reconstructed patient images with MC-JOSEM and TEW-OSEM. Patient reconstructions were assessed qualitatively for lesion contrast, spatial definition, and scatter.

Results: For all simulated and acquired infection phantoms, the root-mean squared-error of measured $^{99\text{m}}\text{Tc}$ activity was significantly improved with MC-JOSEM and TEW-OSEM in comparison to NC-OSEM reconstructions. While MC-JOSEM trended toward outperforming TEW-OSEM, the improvement was only found to be significant ($p < 0.001$) for the acquired bone phantom in which a wide range of $^{111}\text{In}/^{99\text{m}}\text{Tc}$ concentration ratios were tested. In all cases, scatter correction did not significantly improve ^{111}In quantitation.

Conclusions: Compensation for scatter and crosstalk is useful for improving quality, bias, and precision of $^{99\text{m}}\text{Tc}$ activity estimates in simultaneous dual-radionuclide imaging of OM. The use of the more rigorous MC-based estimates provided marginal improvements over TEW. While the phantom results were encouraging, more subjects are needed to evaluate the usefulness of quantitative $^{111}\text{In}/^{99\text{m}}\text{Tc}$ SPECT-CT in the clinic. © 2013 American Association of Physicists in Medicine. [<http://dx.doi.org/10.1118/1.4812421>]

Key words: SPECT, quantitative imaging, scatter, dual-radionuclide, infection

1. INTRODUCTION

In single-photon emission-computed tomography (SPECT), two radionuclides can be simultaneously imaged and discriminated from one another based on the energies of the emitted

photons, thereby allowing two different biological functions to be imaged with perfect temporal and spatial registration. This technique has proven useful for diagnostic imaging of osteomyelitis (bone infection) and coronary artery disease, as well as other pathologic processes. In 1999, Hachamovitch

reviewed the state of dual-radionuclide imaging for clinical cardiac studies, saying that “recent publications have demonstrated the efficacy of this imaging approach for both the identification of the presence of coronary artery disease and risk stratification.”¹ More recently, other authors have shown that newer dedicated cardiac SPECT systems equipped with CZT detectors, which have excellent energy resolution, offer even greater advantages for simultaneous dual-radionuclide heart studies.² For assessment of prosthetic infections, it is widely accepted that dual-radionuclide imaging is superior to both labeled leukocyte imaging alone and FDG PET.^{3,4} In other papers, dual-radionuclide imaging has been shown to exhibit high specificity for osteomyelitis in comparison to three-phase bone scans, or leukocyte imaging.^{5,6} Furthermore, many studies have demonstrated that the use of combined SPECT-CT imaging adds value to nuclear-medicine infection images by helping to localize sites of suspected infection.⁶⁻⁹

One successful combination of radiotracers used in dual-radionuclide imaging of osteomyelitis is technetium-99m ($^{99\text{m}}\text{Tc}$)-labeled sulfur colloid (SC) and indium-111 (^{111}In)-labeled white blood cells (WBC).¹⁰ Diagnosis of osteomyelitis is currently based purely on a visual assessment of the images. When a lesion is characterized by increased count density on the ^{111}In WBC image and decreased $^{99\text{m}}\text{Tc}$ SC uptake, and additionally the lesion can be localized to bone on CT, active osteomyelitis is highly probable.¹¹ Other combined patterns of uptake could indicate processes such as cellulitis or a neuropathic joint. The physician’s interpretation of the relative uptake of In-111 and Tc-99m within a region of interest is, by definition, quite subjective. Furthermore, without scatter and crosstalk correction, the ratio of ^{111}In and $^{99\text{m}}\text{Tc}$ is expected to vary considerably with depth and location of the region within the body. More accurate estimates of the activity concentration of both radionuclides should, therefore, substantially reduce the subjectivity of clinical assessments, reduce inter-observer variability, and increase observer confidence when interpreting these studies.

In order to produce quantitative image reconstructions, the limitations of dual-radionuclide SPECT must first be addressed; these are primarily photon scatter, crosstalk, and image noise. Scatter occurs within the patient as well as the imaging table and the system detectors. In particular, for simultaneous $^{111}\text{In}/^{99\text{m}}\text{Tc}$ imaging, the 171- and 245-keV primary photons from ^{111}In can downscatter and lose energy such that they are detected in the $^{99\text{m}}\text{Tc}$ 140-keV energy window. Compensating for scatter and crosstalk, by eliminating or reducing the effect of these downscattered photons, is one important way of improving quantitation.

In this study, we compared two methods that have both been found to be clinically translatable and beneficial for improving image quality: the triple-energy window (TEW) method and Monte Carlo-based scatter estimation.¹² Scatter estimates achieved using each of these methods were incorporated into an iterative reconstruction program to compensate for collimator and detector spatial resolution and to further reduce noise in the images. Simulated and acquired phantom data were then evaluated on the basis of absolute ac-

tivity quantitation and lesion visualization. Finally, the same reconstruction approaches were applied retrospectively to 12 patient datasets.

The TEW method conventionally estimates scatter using narrow 3-keV scatter windows placed on both sides of the photopeak windows.¹³⁻¹⁵ A trapezoidal estimate of the scattered photons in the photopeak window is then made based on the two scatter windows. However, clinical SPECT systems often limit the number of independent energy windows that can be acquired simultaneously to a maximum of six, which would not be sufficient for imaging more than two primary photopeak energies. Therefore, we opted to use TEW scatter- and photopeak-windows previously designed for simultaneous $^{111}\text{In}/^{99\text{m}}\text{Tc}$ planar imaging on a clinical system.¹⁶ In this approach, wide scatter windows placed between photopeaks are used to correct for scatter in both of the adjacent photopeaks.

While TEW scatter compensation is appealing due to its straightforward implementation, it is limited in that it is not based closely on the underlying physics so, for example, it cannot estimate collimator penetration, or coherent scatter in the patient, collimator, or detectors.¹⁷ An alternative method of scatter compensation uses Monte Carlo (MC) methods to fully model these effects. Many groups have published methods for MC-based scatter and crosstalk compensation, including fully 3D approaches, and acceleration techniques.¹⁸⁻²¹ We have used our MC-based joint ordered subsets expectation maximization (OSEM) algorithm (MC-JOSEM), which has previously been shown to reduce bias and improve precision for ^{111}In SPECT alone and for $^{99\text{m}}\text{Tc}/^{123}\text{I}$ brain and cardiac SPECT.²²⁻²⁵ This program was modified for simultaneous $^{111}\text{In}/^{99\text{m}}\text{Tc}$ imaging on a Siemens Symbia T6 SPECT-CT system (Siemens Medical Solutions USA, Inc., Knoxville, TN).

The accelerated MC scatter modeling uses the unbiased Delta Scattering method to determine the photon interaction points in the simulated patient for each of the emitted photon energies.²² The algorithm forces all photons to scatter through a forward angle such that they then have a high probability of being geometrically collimated and arriving at the detector. In order to account for those photons that would not have been detected, the weight of each photon scattering in the patient is multiplied by the probability that the photon would not have scattered through the chosen angle or undergone photoelectric absorption in the patient. The sums of these photon history weights at all scatter points in the patient and for all projection angles simulated define the so-called “scatter-maps.”^{26,27} These weighted scatter-maps are then included during the forward-projection step of JOSEM, based on convolution-forced detection (CFD), followed by the correction step in which the ^{111}In and $^{99\text{m}}\text{Tc}$ images are simultaneously updated. In the work reported here, we evaluated whether direct modeling of all physics interactions in the patient and detector using our accelerated Monte Carlo-based scatter compensation significantly improves the quantitative values of images in comparison to TEW, as well as to OSEM without scatter correction.

2. METHODS

TEW-OSEM and MC-JOSEM scatter-compensation methods were evaluated quantitatively through simulations and a phantom acquisition. Additionally, patient image data were retrospectively reconstructed and evaluated. Simulated and acquired data were reconstructed identically using iterative scatter-compensation techniques. Furthermore, since it is common for clinics not to correct for scatter in dual-radionuclide imaging, all data were reconstructed by OSEM with no compensation for scatter (NC-OSEM).

2.A. Monte Carlo simulations

Non-identical Monte Carlo techniques were used for both simulations of the numerical phantoms and as part of the MC-JOSEM scatter compensation. The simulated data were generated by a full Monte Carlo program²⁸ which models all details of photon transport through the object, the collimator, and the detector, whereas the Monte Carlo-based scatter estimates were highly accelerated by convolution forced detection techniques. To modify these programs for this (previously unsimulated) combination of radionuclides, we acquired energy spectra from $^{99\text{m}}\text{Tc}$ and ^{111}In . Point sources of these radionuclides in air were separately acquired on a Siemens Symbia T6 SPECT-CT system equipped with medium-energy low-penetration (MELP) collimators. Energy spectral photopeaks were fitted to Gaussian functions, whose widths were then included in the latest version of our Monte Carlo code.

The point spread functions (PSFs) used for CFD and resolution modeling were precomputed by Monte Carlo simulation of point sources in air, located at each of 34 source-collimator distances, with emission energies spanning the range from 115 to 245 keV, in 10-keV increments. These energy values were chosen to match the mean values of the energy bins used to store scatter maps (S-maps) during the joint Monte Carlo-based reconstruction of a raw projection dataset. Each PSF is the image of a point source that would be obtained from emitted photons within a certain energy range, located at a given distance from the collimator, and detected within one of the three defined primary photopeak energy windows. The PSFs included all collimator and detector-related physical effects, i.e., geometrically collimated photons, as well as photons penetrating through or scattering within the collimator and/or detector. The PSFs were stored in a five-dimensional array, consisting of 34 source-collimator distances $\times$ 14 scatter-map energy bins $\times$ 3 detected photopeak energy windows $\times$ (16 $\times$ 16) detector pixels, representing one quadrant of the symmetric detector kernel. The pixel size was 0.4795 cm.

During each forward-projection step of MC-JOSEM, the object-scatter contributions to the detector data that would be measured from the current image estimate were obtained by summing over all S-map energy bins and voxels. Each voxel's contribution was first attenuated along the path-length from the voxel to the boundary, using a linear attenuation coefficient appropriate for the energy of the given S-map bin. The ray's contribution to the projection image pixels was then

rapidly computed by CFD using the appropriate prestored PSF. The contribution of the primary photons emitted from the object was calculated in a similar manner, using a PSF precomputed for just the three primary photopeak energies, i.e., 140, 171, and 245-keV.

2.B. Numerical phantom simulations

Numerical phantoms of the foot and lower torso were designed to model multiple regions of normal and infected bone. To create each of these phantoms a CT image volume was first re-sampled to 128 $\times$ 128 $\times$ 80 voxels to match the SPECT voxel size (0.4795 cm). A CT-number thresholding approach was used to segment the CT into regions of bone, soft tissue, and air. The liver, spleen, and bladder were also segmented in the torso phantom. Multiple regions of infection were evaluated within the phantom bones: eight such regions in the foot phantom, and ten in the torso phantom. These regions were created to be as large as possible (greater than 2.5 cm) while still being confined within bone and spaced at least 2 cm from other nearby regions of infection. Normal bone regions were located throughout the phantoms and were similarly spaced at least 2 cm from regions of infection. Voxel values for each of the compartments were scaled to count levels that emulated the activity distributions of $^{99\text{m}}\text{Tc}$ and ^{111}In seen in patients being evaluated for suspected OM. The distribution within each compartment was assumed to be uniform.

Data were generated by a full Monte Carlo simulation for a dual-head SPECT-CT system with detectors configured 180° apart; 128 projection views were simulated over 360°. The high-count simulated data were then scaled down to be in the range we have observed clinically in these typically very low-count patient studies. After scaling, in the foot phantom, the total number of counts detected in the photopeak windows was 2×10^5 for $^{99\text{m}}\text{Tc}$, and 7×10^4 for ^{111}In . In the pelvic phantom, 4×10^5 and 2×10^5 photopeak counts were used, respectively, for $^{99\text{m}}\text{Tc}$ and ^{111}In . Poisson noise was generated from simulated datasets to create ten different datasets of each simulated phantom. "Scatter-free" data, containing only detected primary photons, were also simulated and reconstructed. The average of ten scatter-free noise-generations served as the true image.

2.C. Numerical phantom reconstructions

All iterative reconstruction methods described below modeled CT attenuation correction (CTAC) and resolution recovery. The attenuation map and collimator-detector PSFs were modeled within the projector and the backprojector. The fundamental difference between these three algorithms, therefore, is only the manner in which scatter and crosstalk are estimated and included within the OSEM reconstruction (or not included, in the case of NC-OSEM).

2.C.1. NC-OSEM

The 15% energy-window data were reconstructed iteratively with CTAC but no compensation for scatter (NC-OSEM). To determine the number of iterations to be

used for the analysis, data were reconstructed for as many as 15 iterations and eight subsets. The minimum root-mean-square error (RMSE) with respect to reconstructions of scatter-free simulations for the same number of iterations was then calculated to determine the appropriate reconstruction parameters for the duration of the study.

2.C.2. MC-JOSEM

The 15% energy-window data were also used for the MC-JOSEM reconstructions. To begin MC-JOSEM, an initial estimate of the scatter had to be created based on a starting estimate of the activity. We reconstructed the raw data for two iterations of OSEM without scatter correction (equivalent to NC-OSEM) to arrive at this starting image. Based on this initial activity estimate, starting S-map estimates were rapidly simulated for 64 projection views and then interpolated to obtain 128 views over 360° . These first S-maps were then incorporated additively during the forward-projection of JOSEM for two iterations. Based on the MC-JOSEM reconstructions, improved S-map estimates were simulated. The joint MC-based reconstruction then began anew using these second S-maps, incorporating the scatter estimate during the forward projection of the source distribution with each iteration. The S-maps were not used during the backprojection. This process was repeated for up to four scatter-map estimates, beginning the reconstructions anew with each scatter-map estimate. As with NC-OSEM, up to 15 iterations and eight subsets of MC-JOSEM were initially completed to determine the appropriate number of iterations.

2.C.3. TEW-OSEM

Photopeak windows, scatter windows, and scatter weights were previously optimized by Xhu *et al.*¹⁶ to achieve the lowest RMSE of activity estimates for planar imaging of ^{111}In and $^{99\text{m}}\text{Tc}$; these energy parameters and weights were also used for our TEW-OSEM simulations. Scatter windows were placed (1) below the 140-keV $^{99\text{m}}\text{Tc}$ photopeak, (2) between the 140-keV and 171-keV photopeak windows, and (3) between the 171-keV and 245-keV photopeak windows. These scatter windows were contiguous with the photopeak windows such that the entire energy spectrum from 99 to 265-keV was covered (see Table I). As described above for MC-JOSEM, TEW scatter estimates were also incorporated into the reconstruction by addition to the projections of the current image estimate. Images were reconstructed using eight subsets and up to 15 iterations of OSEM.

2.D. Simulation analysis

Simulated foot infections were analyzed using small $2 \times 2 \times 2$ -voxel volumes of interest (VOIs). VOIs were located centrally within the eight infection locations based on their known locations. The mean counts per voxel in each infection of each reconstruction (represented by C_{measured} in Eqs. (1) and (2)) were measured and averaged over all noise

TABLE I. Photopeak (PP) and scatter (SC) energy window limits for simulations and acquisitions. 15% PP windows were used for both NC-OSEM and MC-JOSEM.

Emitted photon energy (keV)	15% PP window (keV)	TEW PP window (keV)	TEW SC window (keV)
140 ($^{99\text{m}}\text{Tc}$)	130–150	130–150	99–129
171 (^{111}In low)	158–183	166–182	151–165
245 (^{111}In high)	227–262	229–265	183–228

deviates ($\bar{C}_{\text{measured}}$). The standard deviation over all infection regions and noise deviates was also calculated (σ_{measured}). Due to the larger bones in the pelvis and torso, $3 \times 3 \times 3$ voxel VOIs were used to measure the mean counts per voxel of the required locations in the torso phantom. In addition to the ten infection regions evaluated, seven normal bone marrow regions were also measured in each phantom. Larger VOIs were also placed in the spleen ($5 \times 3 \times 3$), liver ($4 \times 4 \times 4$), and bladder ($4 \times 4 \times 4$) of the torso phantom. The relative bias [Eq. (1)], precision [Eq. (2)] and RMSE with respect to scatter-free reconstructions ($\bar{C}_{\text{true}}$) were calculated for each of the regions:

$$\% \text{bias} = \frac{\bar{C}_{\text{measured}} - \bar{C}_{\text{true}}}{\bar{C}_{\text{true}}} * 100, \quad (1)$$

$$\% \text{precision} = \frac{\sigma_{\text{measured}}}{\bar{C}_{\text{measured}}} * 100. \quad (2)$$

One-way ANOVA tests, performed in MATLABTM, were used to determine whether the performance of the three methods differed. Paired Student *t*-tests were then used to evaluate whether one scatter compensation method was more successful than the other.

2.E. Bone phantom design

Phantom acquisitions were performed using a three-compartment phantom (Fig. 1) designed to model an anklebone infection. Two cylindrical 1-liter bottles represented adult ankles; a bone infection was mimicked in one of these ankles using methods described by Xhu.¹⁶ The activity-concentration values injected in the bone marrow, infection, and soft tissue compartments were designed to reproduce uptake values similar to those observed in a retrospective review of osteomyelitis patient images.

The phantom was filled with a mixture of water and activity at the time of the first acquisition, as follows:

- To imitate osteomyelitis, a small “infection site” (2.4 mL capsule) was filled with 145 kBq of ^{111}In and 228 kBq of $^{99\text{m}}\text{Tc}$. This capsule was secured within a 30 mL bone marrow compartment.
- In the bone marrow compartment, 0.304 MBq of ^{111}In and 4.870 MBq of $^{99\text{m}}\text{Tc}$ were added to water. The bone marrow compartment was then inserted into a hollow cylinder with attenuation properties matching those of cortical bone. The lesion-containing bone marrow

FIG. 1. A CT slice of the acquired three-compartment anklebone infection phantom.

compartment and the bone attenuator were both secured within a larger 1-liter, cylindrical, soft-tissue container that was approximately the same diameter as an adult ankle.

- (c) A mixture of 2.492 MBq ^{111}In and 36.220 MBq $^{99\text{m}}\text{Tc}$ was added to the ankle soft tissue compartment as background activity.
- (d) A “normal” (nonlesion containing) ankle was filled with a uniform mixture of water, 2.539 MBq of ^{111}In and 47.431 MBq of $^{99\text{m}}\text{Tc}$ to represent a second leg.

2.F. Bone phantom acquisition and processing

High-count, low-noise data were acquired on a Siemens Symbia T6 SPECT-CT system with medium-energy low-penetration (MELP) collimators. Image data were acquired for both radionuclides simultaneously in 24 thirty-minute scans over 28 h. The same parameters and energy windows used for the simulation study were also used for the phantom acquisitions. Energy-window sets were alternated between acquisitions such that 12 scans each were acquired with the 15% photopeak windows, and another 12 with the TEW windows. A CT scan was also acquired and used for attenuation correction, as well as for the Monte Carlo-based scatter correction in MC-JOSEM.

For each of the two sets of energy windows, all projection pixel values were temporally fitted to the sum of two contributions, one from $^{99\text{m}}\text{Tc}$ and the other from ^{111}In , using their known half lives (6.01 and 67.31 h, respectively). The fitting problem was thereby reduced to a simple, two-parameter lin-

ear fit for the initial activity concentration of each radionuclide in every detector pixel. This allowed us to create essentially separate radionuclide datasets. The average of the residuals between the fitted vs experimentally acquired data ranged from 0.014% at the earliest acquisition to 1.2% at the later acquisitions. The fitted pure projections of $^{99\text{m}}\text{Tc}$ and ^{111}In were then scaled down to count levels typical of patient imaging and recombined to create six different ratios of $^{99\text{m}}\text{Tc}$ to ^{111}In activity. A constant number of background counts, measured with a blank acquisition, was added to the scaled data to simulate natural background from various sources, and Poisson noise deviates were then generated to create ten statistically independent raw datasets for each activity ratio. The reconstruction methods used for the acquired datasets were identical to those used for the simulations.

2.G. Bone phantom analysis

Acquired data were evaluated in terms of absolute activity quantitation. VOIs were drawn in the infection, normal bone marrow, and soft tissue compartments. The VOI placements were based on scatter-corrected MC-JOSEM reconstructions as well as on prior knowledge of the location of the infection. The mean values of activity concentration (counts per voxel) of ^{111}In and $^{99\text{m}}\text{Tc}$ in each compartment were estimated and evaluated for bias with respect to the same regions in high-count separated images of ^{111}In and $^{99\text{m}}\text{Tc}$. We chose to evaluate each method's bias [Eq. (1)] with respect to the reconstructed images, rather than to the absolute activity, to minimize the impact of partial-volume effects on our

TABLE II. Percent bias $\pm$ precision of simulated foot-phantom activity estimates, averaged over all eight infection (inf.) regions and all seven normal bone regions after ten noise-realizations.

Reconstruction method	$^{99\text{m}}\text{Tc}$ inf.	$^{99\text{m}}\text{Tc}$ bone	^{111}In inf.	^{111}In bone
NC-OSEM	85.1% $\pm$ 16.3%	34.0% $\pm$ 20.7%	12.6% $\pm$ 13.1%	69.7% $\pm$ 30.4%
MC-JOSEM	12.8% $\pm$ 11.9%	-3.1% $\pm$ 10.2%	1.6% $\pm$ 9.5%	31.0% $\pm$ 26.9%
TEW-OSEM	16.4% $\pm$ 12.1%	3.8% $\pm$ 11.9%	11.8% $\pm$ 10.5%	60.6% $\pm$ 20.0%

analysis. The relative precision of all methods was calculated from the standard deviation of activity in a given region over all noise realizations using Eq. (2). The RMSEs were also calculated to determine the overall performance of each method. One-way ANOVA and paired Student t -tests were used again here to evaluate statistical significance.

2.H. Human subject reconstructions

Data for our human-subject reconstructions were retrospectively acquired through a search of patients who received an ^{111}In WBC/ $^{99\text{m}}\text{Tc}$ SC SPECT-CT scan between 2009 and 2012. Patients first underwent SPECT or planar imaging of ^{111}In WBC alone. If the ^{111}In WBC was positive for infection and the lesion appeared to localize to bone, then the patient would be asked to return for simultaneous $^{99\text{m}}\text{Tc}$ SC and ^{111}In WBC SPECT-CT. For the 12 cases included in our study, patients were injected with 13.3–20.3 MBq (360–550 μCi) ^{111}In WBC 24 h prior to imaging, and 140.6–222.0 MBq (3.8–6.0 mCi) $^{99\text{m}}\text{Tc}$ SC the day of imaging.

All subjects were reconstructed with the same three iterative methods used for the simulated and acquired phantom data. The subjects' data were acquired under mostly the same conditions as the phantom data; however, SPECT scatter-window data were not always available. Therefore, in most cases the TEW reconstructions were completed by using the acquired 15% photopeak window data and scatter-window data simulated by full Monte Carlo simulations. The human-subject data were reconstructed using two iterations and eight subsets to obtain images of comparable noise level to our phantom results. As stated earlier, the Monte Carlo techniques used within the MC-JOSEM reconstruction were highly accelerated and quite a bit different than the detailed Monte Carlo program used to simulate the scatter-window data.

3. RESULTS

3.A. Numerical foot phantom

The most accurate and precise activity estimates were found after the third MC scatter estimate followed by a single iteration of JOSEM with eight subsets. For TEW-OSEM, the smallest RMSE of activity concentration for normal and infected bone (regions of equal importance in osteomyelitis imaging) also occurred after one iteration and eight subsets. While bias improved with additional numbers of iterations, precision worsened leading to an overall increase in the RMSE of activity estimates with increasing iteration number. The bias and precision of activity estimates in infected and

normal bone regions after one iteration of each method are summarized in Table II.

By a one-sided paired Student t -test, the RMSE of activity for the foot phantom-simulation was significantly reduced for $^{99\text{m}}\text{Tc}$ reconstructions with scatter compensation ($p < 0.001$), i.e., from 65.3% with NC-OSEM, to 16.7% with TEW-OSEM, and 13.2% with MC-JOSEM. While MC-JOSEM trended toward lower RMSE than TEW-OSEM, the difference was not significant ($p = 0.20$). For ^{111}In reconstructions, no significant difference in RMSE was found between the three methods by a one-way ANOVA test. Additionally, there were no significant differences found in the precision of the three methods for either $^{99\text{m}}\text{Tc}$ or ^{111}In .

3.B. Numerical torso phantom

The performance of the scatter-compensation methods in the torso phantom were consistent with those found in the numerical foot phantom. We chose to compare the three methods at two iterations and eight subsets because while the minimum RMSE was found at one iteration, the bias improved dramatically between iterations 1 and 2 [see Figs. 2(a) and 2(b)]. Therefore, the trend toward increasing RMSE [Figs. 2(c) and 2(d)] with more iterations was largely due to worsening precision, which may be further improved through longer acquisitions or larger radiotracer injections. As with the foot-phantom simulations, for MC-JOSEM the third scatter-map estimate was used. The results for normal and infected bone regions (both of great importance in osteomyelitis evaluation) at two iterations are summarized in Table III.

Quantitation in $^{99\text{m}}\text{Tc}$ images, as measured over all of the VOIs, including infections, normal bone, liver, spleen, and bladder, was greatly improved for both the TEW and MC-based methods with respect to NC-OSEM ($p < 0.001$). The overall RMSE in $^{99\text{m}}\text{Tc}$ images was reduced from 44.8% with NC-OSEM, to 16.5% using TEW-OSEM, and 15.6% using MC-JOSEM [see Fig. 2(d)]. The performance for ^{111}In did not differ between methods by one-way ANOVA test. The RMSE of ^{111}In , shown in Fig. 2(c), was observed to be 32.3% with NC-OSEM, 31.0% with TEW-OSEM, and 19.1% with MC-JOSEM. While a statistically significant difference between MC-JOSEM and TEW-OSEM was not observed, MC-JOSEM trended toward most accurately reconstructing $^{99\text{m}}\text{Tc}$ images ($p = 0.38$). Precision was again found to be similar across all methods for both radionuclides.

Scatter was also visibly reduced in the torso-phantom reconstructions, particularly in normal bone regions close to

FIG. 2. Percent bias and percent RMSE of activity estimates with increasing iteration number, averaged over ten noise-realizations in the torso phantom and over all regions of interest. Error bars on the percent bias graphs represent the precision of the estimates.

simulated infections for scatter-compensated $^{99\text{m}}\text{Tc}$ reconstructions [see arrows in Fig. 3]. The lower-activity $^{99\text{m}}\text{Tc}$ lesions in the vertebrae were also better defined in scatter-compensated images than in the NC-OSEM images with no scatter compensation. For the ^{111}In images, differences between the compensated and uncompensated images were not visibly detectable.

3.C. Three-compartment phantom

Consistent with the numerical phantom results, both scatter compensation methods outperformed NC-OSEM for quantitation in the bone infection phantom images (Table IV). As observed in other simulated phantom reconstructions,

precision of uncorrected $^{99\text{m}}\text{Tc}$ and ^{111}In reconstructions matched that of scatter corrected reconstructions. The absolute improvement in ^{111}In activity estimates across all three compartments was not significant and unsurprisingly, a more dramatic improvement was seen in $^{99\text{m}}\text{Tc}$. The improvements in RMSE of $^{99\text{m}}\text{Tc}$ with MC-JOSEM, at 9.8%, and TEW-OSEM, at 16.6%, were highly significant ($p < 0.001$) when compared to NC-OSEM, 41.9%, by one-sided paired Student t -tests. Additionally, the RMSE of $^{99\text{m}}\text{Tc}$ was significantly lower for MC-JOSEM than for TEW-OSEM ($p < 0.001$). Visual improvements were also most evident in $^{99\text{m}}\text{Tc}$ reconstructions where the bone-infection contrast was worse for NC-OSEM than for either TEW-OSEM or MC-JOSEM (Fig. 4).

TABLE III. Percent bias $\pm$ precision of simulated torso-phantom activity estimates, averaged over all ten infection (inf.) regions and all seven normal bone regions after ten noise realizations.

Reconstruction method	$^{99\text{m}}\text{Tc}$ inf.	$^{99\text{m}}\text{Tc}$ bone	^{111}In inf.	^{111}In bone
NC-OSEM	62.5 $\pm$ 15.0%	22.5% $\pm$ 12.5%	7.3% $\pm$ 11.9%	59.0% $\pm$ 23.4%
MC-JOSEM	-5.6 $\pm$ 17.1%	-7.9% $\pm$ 12.7%	-2.6% $\pm$ 12.1%	23.8% $\pm$ 24.3%
TEW-OSEM	7.7 $\pm$ 19.0%	0.5% $\pm$ 14.4%	6.8% $\pm$ 11.9%	54.1% $\pm$ 25.3%

FIG. 3. These images present results of the simulated torso phantom, with multiple lesions. The first two columns display coronal average reprojections through six slices of the ^{111}In and $^{99\text{m}}\text{Tc}$ reconstructions, respectively. The “true image” (top row) is an average reprojection through the same slices of the torso phantom. In the third column, the anterior projection frame of the MC and TEW-based scatter estimates is shown for the Tc-99m energy window. Both scatter estimates are windowed identically. Estimated total scatter and crosstalk counts represent 31.33% (MC) and 37.61% (TEW) of the counts detected in the primary $^{99\text{m}}\text{Tc}$ photopeak window.

3.D. Human subject reconstructions

Data from 12 subjects were retrospectively reconstructed using the same three iterative methods described previously. For all cases, background scatter and noise were suppressed with scatter compensation, which was clearly visible in

maximum-intensity reprojections of the scatter-compensated reconstructions (Fig. 5). More subtle improvements were observed in slice-by-slice comparisons. For example, in reconstructed images of a knee with a confirmed bone infection, shown in Fig. 6, improved $^{99\text{m}}\text{Tc}$ image quality can be seen in the joint space between the femur and tibia in

TABLE IV. Percent bias $\pm$ precision of activity estimates in the acquired ankle phantom, averaged over all six $^{111}\text{In}/^{99\text{m}}\text{Tc}$ ratios, after ten noise-realizations.

Reconstruction method	$^{99\text{m}}\text{Tc}$ inf.	$^{99\text{m}}\text{Tc}$ bone	^{111}In inf.	^{111}In bone
NC-OSEM	$44.0\% \pm 6.4\%$	$38.5\% \pm 5.8\%$	$5.1\% \pm 5.1\%$	$6.8\% \pm 6.7\%$
MC-JOSEM	$-4.4\% \pm 6.8\%$	$-8.3\% \pm 5.9\%$	$-3.1\% \pm 5.4\%$	$-2.9\% \pm 7.3\%$
TEW-OSEM	$-13.5\% \pm 6.5\%$	$-14.7\% \pm 8.5\%$	$1.3\% \pm 6.5\%$	$2.8\% \pm 8.8\%$

FIG. 4. Maximum intensity images, reprojected through three slices of the ankle phantom, for an $^{111}\text{In}/^{99\text{m}}\text{Tc}$ ratio of 1.4. The arrow identifies the simulated infection site, which is more clearly separated from the normal bone marrow on both the scatter corrected $^{99\text{m}}\text{Tc}$ images (d) and (f) compared to the uncorrected reconstruction (b).

scatter-compensated reconstructions. Additionally, greater contrast can be observed between the infected medial aspect of the distal femur and the normal lateral aspect for the MC-JOSEM and TEW-OSEM $^{99\text{m}}\text{Tc}$ images than for the NC-OSEM image.

FIG. 5. Maximum intensity images of a subject evaluated for suspected osteomyelitis of the knee. The background noise in MC-based scatter corrected reconstructions was reduced by 91% in $^{99\text{m}}\text{Tc}$ images and by 96% in ^{111}In images relative to uncorrected reconstructions (NC-OSEM). The matched distribution of ^{111}In WBC and $^{99\text{m}}\text{Tc}$ SC is not indicative of osteomyelitis. Blood and knee fluid cultures later confirmed inflammation rather than bone infection.

FIG. 6. Single slice views of reconstructions of a subject with confirmed osteomyelitis in the knee. Suppressed $^{99\text{m}}\text{Tc}$ counts on the medial portion of the infected knee (arrows) in comparison to the contra-lateral side, are more evident with MC-JOSEM and TEW-OSEM than NC-OSEM. Additionally, background noise in the ^{111}In images is suppressed in scatter compensated reconstructions. The discordance between ^{111}In and $^{99\text{m}}\text{Tc}$ reconstructions indicates that this subject has osteomyelitis.

4. DISCUSSION AND CONCLUSIONS

We have shown that quantitation in simultaneous $^{111}\text{In}/^{99\text{m}}\text{Tc}$ SPECT-CT imaging of bone infection can be improved through the use of scatter compensation methods with iterative reconstruction. Improvements were mostly gained in the accuracy of $^{99\text{m}}\text{Tc}$ estimates; however, some qualitative improvements were also observed for both radionuclides. The relative bias of ^{111}In in normal bone was one case in which the scatter and crosstalk compensation methods appeared to be less successful (Tables II and III). However, the bias only seemed to be worse here than in other regions because the simulated activity concentration of ^{111}In in normal bone (the denominator of the relative bias) was very low. Still, we observed that MC-JOSEM's performance was best even in these very low count regions. Furthermore, for all simulated and acquired results, TEW was not much different than uncorrected reconstructions for ^{111}In . One possible explanation for this is that the effects of downscatter are minimal with ^{111}In and therefore, comparable results can be achieved without scatter compensation for this radionuclide.

In $^{99\text{m}}\text{Tc}$ reconstructions of our acquired ankle-phantom data with no scatter compensation, we also observed that, over the range of activity ratios assessed, as the ratio of ^{111}In to $^{99\text{m}}\text{Tc}$ increased, the bias and RMSE of the $^{99\text{m}}\text{Tc}$ measured activity increased [Fig. 7(b)]. If the downscatter from higher energy ^{111}In into $^{99\text{m}}\text{Tc}$ is the greatest source of bias of in $^{99\text{m}}\text{Tc}$ images, then as the ratio of ^{111}In to $^{99\text{m}}\text{Tc}$ in a given region increases, the bias should also increase.

FIG. 7. RMSE of activity estimates in the normal and infected marrow regions for the ankle phantom reconstructions as a function of the ratio of ^{111}In to $^{99\text{m}}\text{Tc}$ activity concentration. For the $^{99\text{m}}\text{Tc}$ uncorrected reconstructions (b), the RMSE increases as the ratio of ^{111}In to $^{99\text{m}}\text{Tc}$ increases. This trend is suppressed in the scatter-compensated reconstruction methods TEW-OSEM and MC-JOSEM.

However, TEW-OSEM and MC-JOSEM were both successful in greatly reducing this bias. The RMSE of ^{111}In activity estimates improved with increases in the ratio of ^{111}In to $^{99\text{m}}\text{Tc}$ for all methods [Fig. 7(a)].

An improvement in the overall appearance of images was observed in both phantom and human-subject scatter-compensated reconstructions. Quantitative improvements could not be demonstrated in reconstructions of human-subject data, for which the true activity distribution was unknown. Assessment of the clinical value of the scatter compensation approaches would require acquisition of substantially more patient studies with known infection status.

Added computation time remains a limitation for incorporating Monte Carlo-based scatter correction methods into the clinic. For this study, each MC-based scatter estimate took between 30 min and 2 h depending on the number of counts acquired for that patient. Therefore, a MC-JOSEM reconstruction that incorporated the third scatter estimate took several hours longer than TEW. It should be noted, however, that these reconstructions were completed on a dual-processor PC and were not fully optimized for speed. Incorporating methods such as the multiple-projection simulation method,²¹ is

one way in which computation time for MC-JOSEM could be improved.

The degree with which MC-based scatter compensation outperformed TEW in this study was analogous to that observed by Dewaraja *et al.* for iodine-131.¹² In simulations, the accuracy gained by MC-based scatter compensation over TEW was not statistically significant. However, in the bone infection phantom acquisition, for which a wider range of ^{111}In to $^{99\text{m}}\text{Tc}$ activity concentration values was tested, MC-JOSEM appeared to perform better than TEW-OSEM for $^{99\text{m}}\text{Tc}$ reconstructions. Additionally, in simulated regions of very low activity—such as ^{111}In in normal bone—MC-JOSEM performed the best (Tables II and III). These results may indicate that MC-JOSEM is the more appropriate scatter-compensation method, particularly for low-count studies. However, in general, the performance of the modified TEW-OSEM was also excellent and the further accuracy gained with MC-JOSEM was incremental.

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