Simultaneous ^{99m}Tc -MDP/ ^{123}I -MIBG tumor imaging using SPECT-CT: Phantom and constructed patient studies

Yothin Rakvongthai, Georges El Fakhri, Ruth Lim, Ali A. Bonab, and Jinsong Ouyang^{a)}

Center for Advanced Medical Imaging Sciences, Division of Nuclear Medicine and Molecular Imaging, Massachusetts General Hospital, 55 Fruit Street, Boston, Massachusetts 02114 and Department of Radiology, Harvard Medical School, 25 Shattuck Street, Boston, Massachusetts 02115

(Received 8 May 2013; revised 26 August 2013; accepted for publication 27 August 2013; published 13 September 2013)

Purpose: Authors' goal is to evaluate the performance of simultaneous ^{99m}Tc -MDP/ ^{123}I -MIBG tumor imaging with fast Monte-Carlo (MC) based joint iterative reconstruction as compared to sequential ^{99m}Tc -MDP and ^{123}I -MIBG tumor imaging.

Methods: Noise-free ^{99m}Tc and ^{123}I SPECT projections were acquired separately using an anthropomorphic torso phantom modified to include a fillable tube around the lungs to mimic ribs. Additionally, ^{99m}Tc and ^{123}I projections were acquired separately using a 1-cm spherical "tumor" placed at various distances from one detector. Tumor-present data were generated by adding tumor projections to the torso phantom data, which were scaled to the total counts in typical clinical studies. Twenty-five noise realizations were generated by adding Poisson noise to the projection data for each radionuclide. Dual-radionuclide data were synthesized by summing the ^{99m}Tc and ^{123}I projections. Image reconstruction was performed using: (1) SR-OSEM, ordered subset expectation maximization (OSEM) without scatter correction (SC) using single-radionuclide (SR) data; (2) SR-MC-OSEM, OSEM with a fast MC-based SC using SR data; (3) DR-OSEM, OSEM without SC using dual-radionuclide (DR) data; and (4) DR-MC-JOSEM, joint OSEM with a fast MC-based SC using DR data. Ten ^{99m}Tc -MDP and ten ^{123}I -MIBG data sets, which had tumors mathematically inserted, were also used to evaluate the performance of authors' approach. For the phantom study, relative bias and relative standard deviation of tumor uptake were computed for each tumor using the tumor uptake in the noise-free single-radionuclide images, which were reconstructed by SR-MC-OSEM, as the gold standard. For both the phantom and constructed patient studies, mean contrast and standard deviation of contrast were computed for each tumor for both the single- and dual-radionuclide images. Additionally, contrast recovery was computed as the ratio between mean contrast and the mean contrast for SR-MC-OSEM.

Results: For the phantom study, DR-MC-JOSEM yielded 2.7% on average relative bias of tumor uptake using the images, which were reconstructed from the noise-free SR data with SR-MC-OSEM, as the gold-standard. For both the phantom and constructed patient studies, DR-MC-JOSEM yielded 94.7% and 95.2% tumor contrast recovery on average using SR-MC-OSEM as the reference, in the phantom and constructed patient studies, respectively. DR-MC-JOSEM yielded comparable relative standard deviation of bias and standard deviation of contrast to SR-MC-OSEM.

Conclusions: Simultaneous ^{99m}Tc -MDP/ ^{123}I -MIBG tumor imaging using authors' dual-radionuclide reconstruction approach yielded comparable image quality to sequential ^{99m}Tc -MDP and ^{123}I -MIBG imaging. For patients who need to undergo both scans, authors' approach offers perfectly registered dual-tracer images under identical conditions without compromising image quality, and reduces the imaging cost while increasing patient throughput. © 2013 American Association of Physicists in Medicine. [<http://dx.doi.org/10.1118/1.4820977>]

Key words: simultaneous dual-radionuclide imaging, MDP, MIBG, SPECT-CT, scatter correction

1. INTRODUCTION

Simultaneous $^{99m}\text{Tc}/^{123}\text{I}$ SPECT imaging allows the assessment of two physiological functions under identical conditions. A single SPECT scan produces both ^{99m}Tc and ^{123}I images, which are perfectly registered. There have been several reports on simultaneous $^{99m}\text{Tc}/^{123}\text{I}$ SPECT with many clinical applications, such as for brain,¹⁻⁴ parathyroid,^{5,6} and cardiac imaging.⁷ To our best knowledge, applying simultaneous $^{99m}\text{Tc}/^{123}\text{I}$ SPECT methodology to tumor imaging has not

been previously reported. In this work, we study the feasibility of using simultaneous ^{99m}Tc -methylene diphosphonate (MDP)/ ^{123}I -metaiodobenzylguanidine (MIBG) with SPECT-CT for imaging tumors, especially, neuroblastoma.

Neuroblastoma is the most common extracranial pediatric solid tumor and frequently metastasizes to bone, bone marrow, liver, lymph nodes, skin, and other organs.^{8,9} The treatment and prognosis of this disease varies with patient age and clinical stage. It is critical to have precise staging of the disease at diagnosis and follow-up to ensure the most

appropriate treatment plan. Bone-avid agents, such as ^{99m}Tc -MDP, have been shown to localize in osseous neuroblastoma deposits,^{10–15} particularly in cortical bone. Later, MIBG was found to be highly sensitive for the localization of neuroblastoma, particularly in soft tissues and bone marrow, and its use has become the standard of care.^{16–19} MIBG localizes in both primary and metastatic (most commonly bone marrow) deposits. MIBG studies were found to depict more bone marrow lesions than do conventional bone scans and far more soft-tissue deposits.²⁰ Bone scan, MIBG scan as well as CT scan are all routinely performed in clinical practice for accurate assessment of neuroblastoma.

Although the current clinical imaging tests for neuroblastoma described above have become the standard at most centers, they have a number of limitations. First, multiple scans are needed for each staging and restaging work-up. These scans are usually performed on different days, requiring multiple hospital visits, and sometimes multiple sedation or general anesthesia sessions. This can cause significant stress and risk to very young patients who have difficulty remaining motionless during imaging. Additionally, specialized pediatric anesthesiologists and nurses are required, which in most hospitals are a limited resource that must be shared with pediatric surgery and other departments. There is often a long wait time for scheduling for pediatric sedation or general anesthetic imaging studies due to the limited availability of these specialists. It is therefore very desirable to acquire all the scans at the same time on the same scanner, which will minimize the time spent in hospital, avoid repositioning the patient between scans, and eliminate the need for multiple sedations and general anesthesia. Second, planar images currently used for both MDP and MIBG scans do not offer the best sensitivity for lesion detection compared to tomographic images, especially for small tumors. Third, because the bone scan, MIBG scan, and CT scan are acquired on different days on different scanners, any attempt to coregister their respective images for anatomic localization would be technically difficult and inaccurate. Dual-radionuclide ^{99m}Tc -MDP/ ^{123}I -MIBG using SPECT-CT offers an ideal solution to overcome all of these limitations. Additionally, it has the advantage that a CT scan, which is registered to the SPECT scan, can be used for attenuation correction for SPECT.

SPECT images are degraded by statistical noise, attenuation, scatter, detector response, and limited spatial resolution. Simultaneous ^{99m}Tc / ^{123}I SPECT imaging is particularly challenging because the emission energies of ^{99m}Tc (140 keV) and ^{123}I (159 keV) are very close; not only are down-scattered ^{123}I photons detected in the ^{99m}Tc window, but, equally importantly, primary photons of each radionuclide are also detected in the wrong window (cross-talk), making the energy window based discrimination between the two radionuclides challenging.

Our group has previously developed a fast Monte Carlo (MC) simulation based joint ordered-subset expectation-maximization (JOSEM) algorithm, MC-JOSEM.²¹ First, two detected projections were used to reconstruct initial ^{99m}Tc and ^{123}I images, respectively, using the standard OSEM algorithm, while modeling the attenuation map and the de-

tector point spread function (PSF) in both the projector and back-projector. We estimated the scatter and cross-talk contributions to all energy windows using a fast MC algorithm based on these initial ^{99m}Tc and ^{123}I images. Instead of subtracting the low-noise estimate of the scatter and cross-talk contributions directly from the measured projections, we included the estimate when forward projecting to preserve Poisson statistics. We then used the JOSEM algorithm to reconstruct both ^{99m}Tc and ^{123}I images from both energy windows. This MC-JOSEM algorithm has been previously applied to cardiac SPECT imaging⁷ with satisfactory results.

The aim of this study was to apply MC-JOSEM algorithm to simultaneous ^{99m}Tc -MDP/ ^{123}I -MIBG tumor imaging using SPECT-CT and compare its performance with sequential ^{99m}Tc -MDP and ^{123}I -MIBG imaging using both phantom and constructed patient studies.

2. MATERIAL AND METHODS

2.A. Data acquisition

We used a dual-head Siemens Symbia system equipped with medium-energy low-penetration (MELP) collimators. The standard noncircular step-and-shoot protocol with a 180° detector configuration was used. For each acquisition, both detectors rotated 180° with 64 steps and acquired data for 30 s at each angle. As a result, there were a total of 128 views covering a 360° angular range in each acquisition. Each view had a 128×128 matrix with a pixel size of $4.7952 \times 4.7952 \text{ mm}^2$. The detected energy windows (DEWs) used for the acquisition of projection data were: 122–146 keV (^{99m}Tc window) and 146–169 keV (^{123}I window).

2.A.1. Phantom data

In the phantom study, an anthropomorphic torso phantom (Data Spectrum Corporation, Hillsborough, NC), which includes both left and right lungs, liver, spine, and soft-tissue compartments, was used. The phantom was modified to include a fillable tube around the lungs to mimic ribs. We investigated several ^{99m}Tc -MDP and ^{123}I -MIBG patient studies and filled the phantom with the concentration ratios observed in these patient studies. The phantom was always placed at the same position on the bed, which resulted in that the position of each detector was the same for a given angular view for all the acquisitions. The distance from the center of rotation to either detector ranged from 17.2 to 22.7 cm. Virtually, noise-free data were acquired for ^{99m}Tc and ^{123}I separately. To mimic a typical clinical study, the ^{99m}Tc (^{123}I) projection data were scaled so that the total counts within the ^{99m}Tc (^{123}I) detected energy window (DEW) was equal to seven million.

We also placed a 1-cm spherical “tumor,” which was filled with ^{99m}Tc and ^{123}I separately, at a distance ranging from 7.1 to 42.7 cm from the front end of the MELP collimator and acquired “noise-free” single-view data. Given a desired tumor location, the tumor projection data in each view were generated as follows. First, we computed the distance from the tumor location to the collimator for a given view. Second, the tumor projection for the view was computed by interpolation

using the acquired single-view tumor data according to the computed distance. Finally, we incorporated the attenuation into the tumor projections using the corresponding CT map of the torso phantom. The tumor projection data were first scaled to achieve the desired tumor-to-background contrast and then added to the torso phantom data to generate tumor-present phantom data. For the phantom study, we added the following tumors to the phantom: two tumors next to the spine (Tumors A and B), one tumor near the ribs (Tumor C), two tumors in the liver (Tumors D and E), and one tumor in the soft-tissue (Tumor F). Tumors A, B, and C (Tumors D, E, and F) were added to the scaled ^{99m}Tc (^{123}I) projections. Twenty-five noise realizations were generated by adding Poisson noise to the tumor-present projection data for each radionuclide. Dual-radionuclide projection data were then generated by merging ^{99m}Tc and ^{123}I projections.

2.A.2. Constructed patient data

For the constructed patient study, we used ten ^{99m}Tc -MDP and ten ^{123}I -MIBG patient scans. For each ^{123}I -MIBG scan, a registered CT scan was also acquired. To register a ^{99m}Tc -MDP bone scan to an ^{123}I -MIBG scan, we performed the following steps:

1. We identified the bones in the CT volume by applying a single threshold of 140 HU.
2. We created a bone CT by setting all the values for all the voxels other than the identified bones in the CT to -1000 HU.
3. We performed forward-projection of the bone CT for each view of the SPECT acquisition.

For each view, we registered the CT projection to the corresponding ^{99m}Tc -MDP projection using B-spine with mutual information data fidelity²² and topology-preserving priors.²³ For all the patients, very good registration was achieved and the reconstructed SPECT images using registered data were free of misregistration artifacts visually. After the registration, we had ten constructed-patient data sets, each of which had registered ^{99m}Tc -MDP and ^{123}I -MIBG data as well as a CT image volume. These data sets made it possible for us to combine ^{99m}Tc -MDP and ^{123}I -MIBG data to mimic simultaneous ^{99m}Tc -MDP/ ^{123}I -MIBG data. For the constructed patient study, we added tumors in the same organ locations in a similar way to the phantom study, i.e., Tumors A, B, and C (Tumors D, E, and F) were added to the ^{99m}Tc -MDP (^{123}I -MIBG) projections.

For this research work, our use of the data previously collected in the hospital's clinic for diagnostic purposes was approved by Massachusetts General Hospital (MGH) Institutional Review Board (IRB).

2.B. Reconstruction

For both the phantom and patient studies, we used the single- and dual-radionuclide reconstruction schemes for single- and dual-radionuclide data, respectively. These two reconstruction schemes were based on two different well val-

idated techniques, i.e., fast MC and multiple-radionuclide and multiple-energy-window OSEM reconstruction (denoted JOSEM), we developed previously.²¹ The fast MC algorithm was used to estimate scatter (for both single- and dual-radionuclide data) and cross-talk contribution due to limited energy resolution (for dual-radionuclide data only). The JOSEM algorithm was used to reconstruct dual-radionuclide data.

2.B.1. Single-radionuclide reconstruction

In case of single-radionuclide (i.e., sequential imaging), we performed the following two steps for ^{99m}Tc and ^{123}I data separately.

- (1) The detected energy window (DEW) projections of single-radionuclide data (122–146 keV for ^{99m}Tc and 146–169 keV for ^{123}I) were reconstructed independently using the standard OSEM algorithm, while modeling the attenuation map and the collimator-detector PSF but without scatter correction. This method is denoted SR-OSEM (for single-radionuclide OSEM).
- (2) For both radionuclides, the following reconstruction procedure was performed. The image after four iterations of SR-OSEM from the appropriate projection data was used as the initial image so that the fast MC algorithm could estimate scatter contributions to the appropriate energy window. The method was: First, two-hundred million photon histories were generated based on the image of the radionuclide to estimate the scatter contribution for all the 128 views. At each of the photon interaction points, the photon was forced to scatter while the photon history weight was multiplied by the probability that no photoelectric absorption would have occurred. In image space, each interaction point was used to update the scatter. For each object energy window (OEW) and projection angle, one scatter map was defined. OEWs were the set of energy windows covering the entire energy spectrum of the generated photons. Specifically, a photon would have a certain scattering angle if it scattered along the collimation direction at the interaction point; the scattered photon energy was then calculated given the scattering angle. The corresponding OEW was determined according to the calculated scattered photon energy, and the appropriate scatter map for this OEW was chosen accordingly. At the voxel where the interaction point was located, the weight was increased in the selected scatter map by adding the product of the current photon history weight and the probability per solid angle for a photon to scatter along the collimation direction. These scatter maps were then blurred by the PSFs. This blurring allowed the projection for the appropriate DEW to be formed from the counts in the OEWs. As a final step, the OSEM algorithm was carried out with 30 iterations for each noise realization. The simulated PSFs and attenuation

corrections were included in both the forward- and back-projections. The fast MC-estimated scatter contributions, which were calculated only once, were added to the estimates of primary photon projections during the forward-projection step of each iteration. This algorithm is denoted SR-MC-OSEM (for single-radionuclide OSEM with a fast MC based scatter correction). It should be emphasized that we performed this SR-MC-OSEM for the ^{99m}Tc data and the ^{123}I data separately.

For the phantom study, we also reconstructed ^{99m}Tc -only and ^{123}I -only noise-free data with SR-MC-OSEM. The reconstructed ^{99m}Tc and ^{123}I images after 30 iterations were used as the gold-standard images, which are denoted GS (for gold-standard).

2.B.2. Dual-radionuclide reconstruction

In case of dual-radionuclide (simultaneous imaging), we performed the following two steps for the mixed of ^{99m}Tc and ^{123}I data.

- (1) We performed the same procedures as Step 1 of the single-radionuclide reconstruction except that the dual-radionuclide data (i.e., the mixed data) were reconstructed. This method is denoted DR-OSEM (for dual-radionuclide OSEM).
- (2) We performed the similar procedures to Step 2 of the single-radionuclide reconstruction. Specifically, the ^{99m}Tc and ^{123}I images after four iterations of DR-OSEM were used as the initial images for the fast MC algorithm to estimate scatter and cross-talk contributions to both DEWs. Moreover, a joint OSEM incorporating two radionuclides and two DEWs was performed with 30 iterations for each noise realization. In this case, each forward-projection has contributions from both radionuclides, while each back-projection has contributions from both DEWs. This is different from the standard OSEM procedure, in which only one radionuclide and one DEW are involved in the reconstruction process. This algorithm is denoted DR-MC-JOSEM (for dual-radionuclide joint OSEM with a fast Monte-Carlo scatter correction).

2.C. Evaluation

For the phantom study, we compared the performance of the four methods described above based on the relative bias (RB) and the relative standard deviation (RSD) of the tumor activity as well as the mean and standard deviation (SD) of tumor contrast.

The relative bias (RB_i^k) and the relative SD (RSD_i^k) of activity in a given region of interest (ROI) i at iteration k were calculated using

$$\text{RB}_i^k = \frac{\bar{m}_i^k - g_i}{g_i}, \quad \text{RSD}_i^k = \frac{\text{SD}_i^k}{g_i},$$

where g_i is the average activity concentration for ROI i in the gold-standard image ($i = \text{A, B, C, or spine for } ^{99m}\text{Tc}$; and $i = \text{D, E, F, or liver for } ^{123}\text{I}$), $\bar{m}_i^k$ and SD_i^k are the mean and SD of the average activity concentration for ROI i at iteration k over all noise realizations, respectively.

To compare the performance in terms of both the mean and the SD of tumor contrast, for a given tumor, tumor-to-background contrast was computed as the ratio between the mean activity concentrations for using two ROIs: a 1.5-cm sphere centered at the tumor location (tumor-ROI) and a concentric 1.5-cm thick spherical shell outside the sphere (bck-ROI). For tumor i and iteration k , the mean (MC_i^k) and SD (SDC_i^k) of contrast were calculated over all N noise realizations using the following equations:

$$\begin{aligned} \text{MC}_i^k &= \frac{\sum_{n=1}^N \text{C}_{i,n}^k}{N}, \\ \text{SDC}_i^k &= \sqrt{\frac{\sum_{n=1}^N (\text{C}_{i,n}^k - \text{MC}_i^k)^2}{N-1}}, \\ \text{C}_{i,n}^k &= (m_{i,n}^{k,\text{tumor-ROI}} - m_{i,n}^{k,\text{bck-ROI}}) / m_{i,n}^{k,\text{bck-ROI}}, \end{aligned}$$

where $m_{i,n}^{k,\text{tumor-ROI}}$ and $m_{i,n}^{k,\text{bck-ROI}}$ are the average activity concentration values for tumor-ROI and bck-ROI, respectively. Additionally, we also computed the contrast recovery for tumor i , CR_i , using:

$$\text{CR}_i = 100 \times \frac{\text{MC}_i^{30}}{\text{MC}_i^{30,\text{SR-MC-OSEM}}},$$

where $\text{MC}_i^{30,\text{SR-MC-OSEM}}$ is the mean contrast of tumor i using SR-MC-OSEM after 30 iterations.

Similar to the phantom studies, we computed mean and SD of contrast as well as contrast recovery as described above for the constructed patient studies. However, we did not compute RB and RSD for the constructed patient studies because there is no noise-free patient data we can use as the gold standard.

3. RESULTS

3.A. Phantom data

Figure 1 displays the representative slices through one of the tumors in ^{99m}Tc and ^{123}I phantom images reconstructed using the methods described in Sec. 2. DR-MC-JOSEM yielded higher tumor-to-background contrast for both the ^{99m}Tc and ^{123}I images than both SR-OSEM and DR-OSEM. More importantly, DR-MC-JOSEM also yielded comparable tumor-to-background contrast to SR-MC-OSEM.

For each of the two radionuclides, Fig. 2 shows the bias and SD of tumor uptake as function of iteration number for one of the three tumors investigated. The results for other tumors are similar. For all the locations, SR-MC-OSEM and DR-MC-JOSEM yielded significantly low bias as compared to SR-OSEM and DR-OSEM. Moreover, DR-MC-JOSEM yielded comparable bias to SR-MC-OSEM. The similar trend was also realized for background quantitation shown in Fig. 3,

FIG. 1. Representative reconstructed phantom slice through a tumor in ^{99m}Tc and ^{123}I images. The arrows indicate the tumor locations.

FIG. 2. Relative bias and standard deviation of tumor uptake in ^{99m}Tc and ^{123}I images versus iteration number for the phantom study.

FIG. 3. Relative bias and standard deviation of the activity within the spine and liver ROIs in ^{99m}Tc and ^{123}I images, respectively, versus iteration number for the phantom study.

where a background ROI was drawn in the spine (liver) for ^{99m}Tc (^{123}I) images. The relative bias and SD for the tumor and background ROIs at the 30th iteration of reconstruction are shown in Table I. The average values of bias and SD over all tumors are also displayed. DR-MC-OSEM significantly outperformed DR-OSEM ($p < 10^{-8}$), and also yielded comparable relative bias and SD to SR-MC-OSEM. In summary, the mean bias with DR-MC-OSEM was a couple percentage points higher than that with SR-MC-OSEM.

Figure 4 displays the mean and SD of contrast at two locations for the phantom study. Table II shows the mean and SD of tumor contrast at the 30th iteration of reconstruction. The average values of relative contrast recovery using the mean contrast from SR-MC-OSEM as the reference are also displayed. DR-MC-OSEM significantly outperformed the DR-OSEM methods in terms of contrast ($p < 0.0005$), and also yielded comparable tumor-to-background contrast to SR-MC-OSEM.

TABLE I. Relative bias and standard deviation of uptake after 30 iterations for the phantom study.

Radionuclide	Location	Relative bias (RB) (%) $\pm$ relative standard deviation (RSD) (%)			
		SR-OSEM	SR-MC-OSEM	DR-OSEM	DR-MC-JOSEM
^{99m}Tc	Tumor A	24.9 $\pm$ 2.6	0.2 $\pm$ 2.3	31.5 $\pm$ 2.8	3.4 $\pm$ 2.3
	Tumor B	20.0 $\pm$ 2.0	−0.0 $\pm$ 1.8	33.9 $\pm$ 1.9	2.7 $\pm$ 1.5
	Tumor C	25.7 $\pm$ 4.5	−0.4 $\pm$ 3.8	34.8 $\pm$ 4.3	1.4 $\pm$ 3.3
	Tumor average	23.5 $\pm$ 3.0	−0.1 $\pm$ 2.6	33.4 $\pm$ 3.0	2.5 $\pm$ 2.4
	Bck ROI	17.7 $\pm$ 3.5	0.4 $\pm$ 3.1	22.7 $\pm$ 3.9	4.8 $\pm$ 3.2
^{123}I	Tumor D	24.7 $\pm$ 3.1	−0.7 $\pm$ 2.7	28.1 $\pm$ 2.9	0.9 $\pm$ 2.4
	Tumor E	26.5 $\pm$ 3.4	0.4 $\pm$ 3.2	30.6 $\pm$ 3.4	2.9 $\pm$ 3.2
	Tumor F	39.5 $\pm$ 8.8	−2.4 $\pm$ 8.0	48.7 $\pm$ 9.4	4.9 $\pm$ 8.9
	Tumor average	30.2 $\pm$ 5.1	−1.2 $\pm$ 3.0	35.8 $\pm$ 5.2	2.9 $\pm$ 4.8
	Bck ROI	33.3 $\pm$ 3.5	−0.3 $\pm$ 3.2	36.8 $\pm$ 3.5	0.5 $\pm$ 3.0

FIG. 4. The mean and standard deviation of tumor contrast versus iteration number for the phantom study.

3.B. Constructed patient data

Figure 5 shows the slices through tumors in ^{99m}Tc and ^{123}I patient images reconstructed using the methods described in Sec. 2. Both SR-OSEM and DR-OSEM, which do not include scatter and cross-talk corrections, yielded lower tumor-

to-background contrast than both SR-MC-OSEM and DR-MC-OSEM, which include scatter and cross-talk corrections. The tumor visibility in the images reconstructed by SR-MC-OSEM and DR-MC-JOSEM is approximately the same.

Figure 6 shows the mean and SD of contrast at two locations in ^{99m}Tc and ^{123}I images for the constructed patient

TABLE II. Mean and standard deviation of tumor contrast and relative contrast recovery after 30 iterations for the phantom study.

Radionuclide	Location	SR-OSEM	SR-MC-OSEM	DR-OSEM	DR-MC-JOSEM
^{99m}Tc					
Mean contrast (MC) $\pm$ standard deviation of contrast (SDC)					
	Tumor A	0.5 ± 0.0	0.6 ± 0.1	0.5 ± 0.0	0.6 ± 0.1
	Tumor B	0.2 ± 0.0	0.3 ± 0.0	0.2 ± 0.0	0.2 ± 0.0
	Tumor C	1.1 ± 0.1	1.5 ± 0.1	0.9 ± 0.1	1.4 ± 0.1
Relative contrast recovery (%)					
	Tumor A	85.5	100.0	79.0	96.8
	Tumor B	76.9	100.0	69.2	92.3
	Tumor C	74.2	100.0	62.3	92.1
	<i>Tumor average</i>	78.9	100.0	70.2	93.7
^{123}I					
Mean contrast (MC) $\pm$ standard deviation of contrast (SDC)					
	Tumor D	0.4 ± 0.0	0.5 ± 0.1	0.4 ± 0.0	0.5 ± 0.0
	Tumor E	0.4 ± 0.1	0.4 ± 0.1	0.4 ± 0.1	0.4 ± 0.1
	Tumor F	1.1 ± 0.2	2.4 ± 0.5	1.1 ± 0.2	2.1 ± 0.4
Relative contrast recovery (%)					
	Tumor D	81.1	100.0	79.3	96.2
	Tumor E	87.8	100.0	87.8	102.4
	Tumor F	47.5	100.0	45.0	88.3
	<i>Tumor average</i>	72.2	100.0	70.7	95.7

FIG. 5. Representative reconstructed patient slice through a tumor in ^{99m}Tc -MDP and ^{123}I -MIBG images. The arrows indicate the tumor locations.

study. Similar to the phantom study, both SR-MC-OSEM and DR-MC-JOSEM yielded higher tumor-to-background contrast than both SR-OSEM and DR-OSEM. Moreover, DR-MC-JOSEM yielded comparable contrast to SR-MC-OSEM. Table III shows the mean and SD of tumor-to-background contrast at the 30th iteration of reconstruction. The average values of relative contrast recovery using the mean contrast from SR-MC-OSEM as the reference are also displayed.

DR-MC-JOSEM outperformed DR-OSEM in terms of contrast, and also yielded comparable tumor contrast to SR-MC-OSEM.

4. DISCUSSION

Single-radionuclide imaging using ^{99m}Tc -MDP or ^{123}I -MIBG with standard OSEM reconstruction is used extensively in clinical practice to diagnosis tumor metastases in bone and soft tissue/bone marrow, respectively. The main purpose of this research is to assess the feasibility of using simultaneous ^{99m}Tc -MDP/ ^{123}I -MIBG dual-radionuclide with DR-MC-JOSEM as compared to sequential single-radionuclide imaging with SR-MC-OSEM. For both ^{99m}Tc and ^{123}I images, it is convincing from our phantom study that our dual-radionuclide imaging approach yielded less than 5% bias (see Fig. 2) and equivalent bias-standard deviation as compared to standard sequential single-radionuclide imaging. Our constructed patient study also clearly showed that our dual-radionuclide imaging approach had equivalent performance as compared to single-radionuclide imaging in terms of tumor contrast recovery (see Fig. 6). Therefore, we truly believe that dual-radionuclide imaging with DR-MC-JOSEM is feasible for clinical practice. Simultaneously ^{99m}Tc -MDP and ^{123}I -MIBG imaging has significant advantages over sequential single-radionuclide imaging for patients who need to undergo both ^{99m}Tc -MDP and ^{123}I -MIBG scans. Both ^{99m}Tc -MDP

FIG. 6. The mean and standard deviation of tumor contrast versus iteration number for the constructed patient study.

TABLE III. Mean and standard deviation of tumor contrast and relative contrast recovery after 30 iterations for the constructed patient study.

Radionuclide	Location	SR-OSEM	SR-MC-OSEM	DR-OSEM	DR-MC-JOSEM
^{99m}Tc	Mean contrast (MC) $\pm$ standard deviation of contrast (SDC)				
	Tumor A	1.7 ± 0.5	2.7 ± 1.1	1.6 ± 0.5	2.5 ± 1.0
	Tumor B	1.1 ± 0.3	1.5 ± 0.5	1.0 ± 0.3	1.4 ± 0.5
	Tumor C	1.3 ± 0.4	1.8 ± 0.5	1.1 ± 0.3	1.7 ± 0.5
	Relative contrast recovery (%)				
	Tumor A	62.0	100.0	59.0	93.0
	Tumor B	71.0	100.0	66.2	93.9
	Tumor C	70.7	100.0	58.0	91.7
	<i>Tumor average</i>	67.9	100.0	61.1	92.9
	Mean contrast (MC) $\pm$ standard deviation of contrast (SDC)				
^{123}I	Tumor D	0.6 ± 0.2	0.7 ± 0.3	0.5 ± 0.2	0.7 ± 0.2
	Tumor E	0.9 ± 0.3	1.2 ± 0.3	0.9 ± 0.3	1.2 ± 0.3
	Tumor F	1.1 ± 0.5	1.4 ± 0.6	0.9 ± 0.5	1.4 ± 0.6
	Relative contrast recovery (%)				
	Tumor D	82.6	100.0	75.4	94.2
	Tumor E	79.3	100.0	75.9	99.1
	Tumor F	76.1	100.0	68.1	99.3
	<i>Tumor average</i>	79.3	100.0	73.1	97.5

and ^{123}I -MIBG images are perfectly registered for identical patient conditions. Furthermore, it reduces the imaging cost and increases patient throughput.

For SR-OSEM and DR-OSEM, the region enclosed by the ribs in the MDP image and the region outside the liver in the MIBG image shown in Fig. 1 have the uptake caused by scatters and cross-talk. As expected, the scatter and cross-talk corrections, which were implemented in SR-MC-OSEM and DR-MC-JOSEM, removed such uptake. Similar effects can be seen in the constructed patient images shown in Fig. 5.

The results showed that our fast MC-based reconstruction algorithm corrected the scatters within each energy window, down-scatters from the high to the low energy window due to Compton scattering, and cross-talks between the two energy windows due to limited energy resolution of the SPECT detectors for dual-radionuclide imaging (Fig. 2 and Table I). The excessive bias of 23% on average in ^{99m}Tc images was caused by scatters in the ^{99m}Tc window itself (SR-OSEM vs SR-MC-OSEM). Additional bias of 9% on average was from down-scatters and cross-talk in the ^{123}I window (DR-OSEM vs SR-OSEM). Our approach not only corrects the scatters within the ^{99m}Tc window itself, but also corrects the down-scatters to the ^{99m}Tc window from the ^{123}I window as well as the cross-talk between these two energy windows. On the other hand, the excessive bias of 29% on average in ^{123}I images was caused by the scatters while cross-talk yielded additional 6% bias on average. Our fast MC-based algorithm corrected both scatters and cross-talks in ^{123}I images. Furthermore, the SD values were very close for all the methods.

Ideal goal of simultaneous dual-radionuclide imaging is to achieve the same image quality, quantified by, for example, tumor contrast, as sequential single-radionuclide imaging. As expected, DR-MC-JOSEM yielded slightly lower tumor contrast than SR-MC-OSEM due to the imperfect corrections. DR-MC-JOSEM was much better than both SR-OSEM and

DR-OSEM, which do not include the corrections. We also want to point out that the contrast improvement made by DR-MC-JOSEM was consistent with the improvement in the aspect of bias (Figs. 2 and 4). Moreover, the SD values of contrast for all the methods were very close.

For a given reconstruction algorithm, relative SD of activity uptake in a region typically increases as iteration number increases. However, I-123 relative SD for tumor F reached a plateau after several iterations (see Fig. 2). We believe that such difference was caused by the relative low I-123 activity concentration of tumor F. For a given region, the noise level in the reconstructed images has two different components. One is related to the activity concentration in the region and imaging time. This component is independent of the iteration number. The other, which is determined by the iteration number, contributes more to the overall noise level as the iteration number increases. Tumor F and its surrounding tissue had much lower I-123 activity concentration as compared to other tumors. The first component of the noise level described above for this tumor, therefore, dominates after the reconstruction converges. As a result, the overall noise level is flat at high iteration numbers. For other tumors, e.g., tumor A, however, the activity concentration was much higher. The second component of the noise level, which becomes higher as iteration number increases, dominates.

The contrast results in the constructed patient study were also consistent with those in the phantom study. The constructed patient data yielded equivalent performance of contrast recovery to the phantom study (see Figs. 4 and 6). As expected, the constructed patient data yielded much higher contrast SD than the phantom data due to the inter-patient background variations.

The future work includes incorporating the maximum *a posteriori* (MAP) with CT information, such as the boundaries of organs, and with smoothness of the images as priors

into our reconstruction algorithm. More importantly, we expect to perform both sequential single-radionuclide and dual-radionuclide studies for the same patient after this research protocol is approved by Massachusetts General Hospital's (MGH) Institutional Review Board (IRB). Given sufficient number of patients, we will be able to perform a localization receiver operation characteristic (LROC) analysis²⁴ on tumor assessment involving physicians. Such study will provide a complete and convincing evaluation of our approach in order to implement it in the clinical setting.

5. CONCLUSIONS

In this study, we have combined separately acquired ^{99m}Tc and ^{123}I data to mimic simultaneous $^{99m}\text{Tc}/^{123}\text{I}$ data for both our phantom and constructed patient studies. We have applied the MC-JOSEM algorithm to simultaneous $^{99m}\text{Tc}/^{123}\text{I}$ imaging and computed relative bias and standard deviation for various tumors and ROIs. The proposed simultaneous imaging method yielded equivalent performance as compared to the sequential ^{99m}Tc -MDP and ^{123}I -MIBG imaging. We have demonstrated that simultaneous ^{99m}Tc -MDP/ ^{123}I -MIBG is feasible in clinical practice. Our approach offers perfectly registered dual-tracer images under identical patient conditions without compromising image quality. Moreover, it reduces the imaging cost while increasing patient throughput and improving patient comfort.

ACKNOWLEDGMENTS

This work was supported in part by National Institutes of Health (NIH) Grant Nos. R21CA140771, R01HL110241, and R21EB012823.

^{a)} Author to whom correspondence should be addressed. Electronic mail: ouyang.jinsong@mgh.harvard.edu

¹ M. D. Devous, Sr., J. K. Payne, and J. L. Lowe, "Dual-isotope brain SPECT imaging with technetium-99m and iodine-123: Clinical validation using xenon-133 SPECT," *J. Nucl. Med.* **33**, 1919–1924 (1992).

² G. El Fakhri, S. C. Moore, P. Maksud, A. Aurengo, and M. F. Kijewski, "Absolute activity quantitation in simultaneous 123I/99mTc brain SPECT," *J. Nucl. Med.* **42**, 300–308 (2001).

³ S. Hapdey, M. Soret, and I. Buvat, "Quantification in simultaneous (99m)Tc/(123)I brain SPECT using generalized spectral factor analysis: A Monte Carlo study," *Phys. Med. Biol.* **51**, 6157–6171 (2006).

⁴ Y. Du, B. M. Tsui, and E. C. Frey, "Model-based crosstalk compensation for simultaneous 99mTc/123I dual-isotope brain SPECT imaging," *Med. Phys.* **34**, 3530–3543 (2007).

⁵ D. R. Neumann, C. B. Esselstyn, Jr., R. T. Go, C. O. Wong, T. W. Rice, and N. A. Obuchowski, "Comparison of double-phase 99mTc-sestamibi with

123I-99mTc-sestamibi subtraction SPECT in hyperparathyroidism," *Am. J. Roentgenol.* **169**, 1671–1674 (1997).

⁶ S. Shcherbinin, S. Chamoiseau, and A. Celler, "Quantitative image reconstruction for dual-isotope parathyroid SPECT/CT: Phantom experiments and sample patient studies," *Phys. Med. Biol.* **57**, 4755–4769 (2012).

⁷ J. Ouyang, X. Zhu, C. M. Trott, and G. El Fakhri, "Quantitative simultaneous 99mTc/123I cardiac SPECT using MC-JOSEM," *Med. Phys.* **36**, 602–611 (2009).

⁸ B. H. Kushner, "Neuroblastoma: A disease requiring a multitude of imaging studies," *J. Nucl. Med.* **45**, 1172–1188 (2004).

⁹ R. Howman-Giles, P. J. Shaw, R. F. Uren, and D. K. Chung, "Neuroblastoma and other neuroendocrine tumors," *Semin. Nucl. Med.* **37**, 286–302 (2007).

¹⁰ R. B. Howman-Giles, D. L. Gilday, and J. M. Ash, "Radionuclide skeletal survey in neuroblastoma," *Radiology* **131**, 497–502 (1979).

¹¹ R. A. Kaufman, J. H. Thrall, J. W. Keyes, Jr., M. L. Brown, and J. F. Zakem, "False negative bone scans in neuroblastoma metastatic to the ends of long bones," *Am. J. Roentgenol.* **130**, 131–135 (1978).

¹² F. W. Smith, D. L. Gilday, J. M. Ash, and R. H. Reid, "Primary neuroblastoma uptake of 99mtechnetium methylene diphosphonate," *Radiology* **137**, 501–504 (1980).

¹³ A. E. Podrasky, D. D. Stark, R. S. Hattner, C. A. Gooding, and A. A. Moss, "Radionuclide bone scanning in neuroblastoma: Skeletal metastases and primary tumor localization of 99mTc-MDP," *Am. J. Roentgenol.* **141**, 469–472 (1983).

¹⁴ M. Baker, A. R. Siddiqui, A. Provisor, and M. D. Cohen, "Radiographic and scintigraphic skeletal imaging in patients with neuroblastoma: Concise communication," *J. Nucl. Med.* **24**, 467–469 (1983).

¹⁵ I. Garty, A. Friedman, M. P. Sandler, and A. Kedar, "Neuroblastoma: Imaging evaluation by sequential Tc-99m MDP, I-131 MIBG, and Ga-67 citrate studies," *Clin. Nucl. Med.* **14**, 515–522 (1989).

¹⁶ M. Nakajo, B. Shapiro, J. Copp, V. Kalff, M. D. Gross, J. C. Sisson, and W. H. Beierwaltes, "The normal and abnormal distribution of the adrenomedullary imaging agent m-[I-131]iodobenzylguanidine (I-131 MIBG) in man: Evaluation by scintigraphy," *J. Nucl. Med.* **24**, 672–682 (1983).

¹⁷ B. Kimmig, W. E. Brandeis, M. Eisenhut, B. Bubeck, H. J. Hermann, and K. zum Winkel, "Scintigraphy of a neuroblastoma with I-131 metaiodobenzylguanidine," *J. Nucl. Med.* **25**, 773–775 (1984).

¹⁸ C. A. Hoefnagel, P. A. Voute, J. de Kraker, and H. R. Marcuse, "Radionuclide diagnosis and therapy of neural crest tumors using iodine-131 metaiodobenzylguanidine," *J. Nucl. Med.* **28**, 308–314 (1987).

¹⁹ C. J. Edeling, P. B. Frederiksen, J. Kamper, and P. Jeppesen, "Diagnosis and treatment of neuroblastoma using metaiodobenzylguanidine," *Clin. Nucl. Med.* **12**, 632–637 (1987).

²⁰ B. L. Shulkin, B. Shapiro, and R. J. Hutchinson, "Iodine-131-metaiodobenzylguanidine and bone scintigraphy for the detection of neuroblastoma," *J. Nucl. Med.* **33**, 1735–1740 (1992).

²¹ J. Ouyang, G. El Fakhri, and S. C. Moore, "Fast Monte Carlo based joint iterative reconstruction for simultaneous Tc-99m/I-123 SPECT imaging," *Med. Phys.* **34**, 3263–3272 (2007).

²² P. Thevenaz and M. Unser, "Optimization of mutual information for multiresolution image registration," *IEEE Trans. Image Process.* **9**, 2083–2099 (2000).

²³ S. Y. Chun and J. A. Fessler, "A simple regularizer for B-spline nonrigid image registration that encourages local invertibility," *IEEE J. Sel. Top. Signal Process.* **3**, 159–169 (2009).

²⁴ R. G. Swenson, "Unified measurement of observer performance in detecting and localizing target objects on images," *Med. Phys.* **23**, 1709–1725 (1996).