Joint regional uptake quantification of thorium-227 and radium-223 using a multiple-energy-window projection-domain quantitative SPECT method

Supplementary Material

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I. Validating the SPECT simulation

A. Experiments

SIMIND is a Monte Carlo (MC) approach that has already been shown to model single-photon emission computed tomography (SPECT) imaging systems accurately [1]–[3], including when imaging other α-particle isotopes [4]. To demonstrate the accuracy of the SIMIND-based simulation approach for $^{227}\mathrm{Th}$-based α-particle radiopharmaceutical therapies (α-RPT) SPECT, we compared the projection data obtained with our simulation approach to that obtained on a physical scanner. For this purpose, we used a NEMA phantom (Data Spectrum$^{\mathrm{TM}}$, USA). The spheres of this phantom were filled with $^{227}\mathrm{Th}$ solutions with an activity concentration of 40 kBq/ml. The rest of the phantom was filled with water to simulate attenuation and scatter due to soft tissue. The phantom was scanned on a GE Discovery 670 SPECT/CT system with a medium energy general purpose (MEGP) collimator one day after purifying the $^{227}\mathrm{Th}$ isotope and filling the isotope in the phantom. Thus, at the time of scanning, a small portion of the $^{227}\mathrm{Th}$ had decayed to $^{223}\mathrm{Ra}$. During imaging, projections were acquired in two energy windows, corresponding to the two major photopeaks of $^{223}\mathrm{Ra}$ (66 - 98 keV) and $^{227}\mathrm{Th}$ (217 - 260 keV) at 60 angular positions spaced uniformly over 360°. The same image-acquisition process was modeled using our simulation approach (Sec. III B in the main manuscript). In the simulation, the concentration of $^{227}\mathrm{Th}$ and $^{223}\mathrm{Ra}$ were calculated theoretically, based on the filling and scanning time. The profiles of the projection data obtained with the physical scanner and with the simulation approach from the two energy windows were compared.

B. Results

Fig. 1 shows projections of the NEMA phantom in the two energy windows at the first angular position, acquired using simulated and physical SPECT systems. We also compared the profiles along the dashed line in the projections from the two approaches in both energy windows. To reduce the noise-related variation in this profile, each point in the profile was obtained by averaging the number of counts along five adjacent pixels on both sides of the dashed line. We observed that the profile of the simulated projection matched that acquired on the physical scanner in both energy windows. This provides evidence of the accuracy of the process to simulate isotope emission, the SPECT system, and the noise in this study.

II. Image reconstruction-based methods compared

A. Dual-isotope ordered subset expectation maximization image reconstruction (DOSEM)-based method

Based on analysis of the emission spectra of both isotopes, energy windows 66 - 96 keV and 217 - 260 keV (energy windows 1 and 3 in Fig. 1 of the main manuscript) were considered as the primary energy windows of $^{223}\mathrm{Ra}$ and $^{227}\mathrm{Th}$, respectively. We first reconstructed images of activity uptake of $^{227}\mathrm{Th}$ and $^{223}\mathrm{Ra}$ using projections from the corresponding two separate primary energy windows. In this step, we assumed there was no crosstalk contamination, i.e., the counts in the two energy

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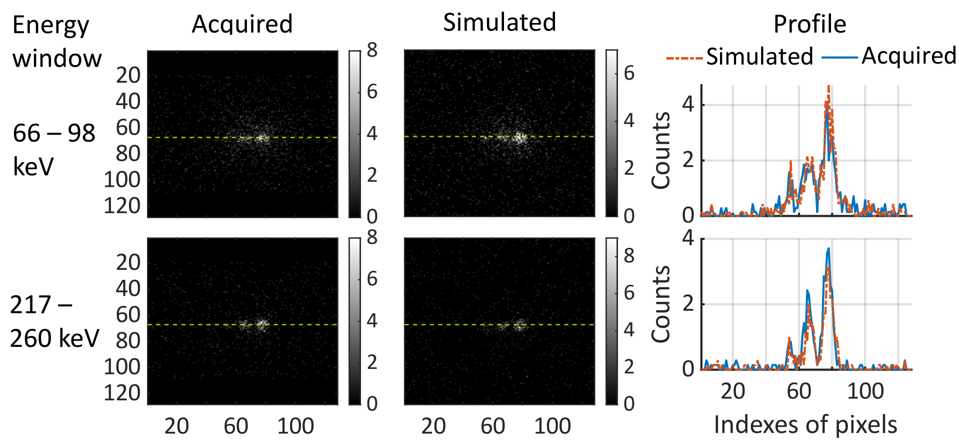

Fig. 1: Comparison of the simulated and physical-SPECT-system-acquired projections of the NEMA phantom in two different energy windows.

windows solely reflected emissions from $^{227}\mathrm{Th}$ and $^{223}\mathrm{Ra}$, respectively. The images were reconstructed using the ordered subset expectation maximization (OSEM) method, implemented using Customizable and Advanced Software for Tomographic Reconstruction (CASToR) software [5]. In this process, we compensated for attenuation, scatter, collimator-detector response, stray-radiation-related noise, and the complicated emission spectra of both isotopes. The scatter was compensated using effective scatter source estimation (ESSE) method, in which the scatter kernels were generated using SIMIND simulations [6]. Next, the reconstructed image of each isotope was forward projected to the photopeak energy window of the other isotope to estimate the crosstalk contamination in each photopeak energy window. In this forward projection, we modeled the emission spectra of both isotopes, attenuation, scatter, and collimator-detector response. In this step, the crosstalk contamination from primary photons was modeled from the emission spectrum, and the crosstalk contamination from scattered photons was modeled with the ESSE method. Then, the images of both isotopes were again reconstructed using the OSEM method, with the estimated crosstalk contamination as additive correction terms. Since the estimates of crosstalk contamination were not accurate due to the inaccurate reconstruction in the first step, we repeated these steps for multiple iterations.

More specifically, we denote the process of reconstructing and forward projecting the images of both isotopes to compensate for crosstalk as a 'joint iteration'. The iterations executed specifically for each isotope in the OSEM reconstruction are referred to as 'isotope-specific iterations'. For the purpose of fine-tuning the DOSEM-based method, we sought the optimal number of joint iterations and isotope-specific iterations. To this end, we generated 50 noise realizations of a representative patient phantom. Initially, image of each isotope was reconstructed from its corresponding photopeak energy window using the OSEM-based method, incorporating ideal crosstalk corrections. Through this process, we determined that the optimal number of isotope-specific iterations was 20, each comprising 6 subsets. With this number of isotope-specific iterations, the normalized root mean square error (NRMSE) between the true and estimated lesion uptake from the reconstructed images of both isotopes converged to its lowest value. Convergence was defined as a change in NRMSE of less than 1% over the next 10 iterations. Subsequently, we performed the DOSEM-based reconstruction from the crosstalk-contaminated SPECT projections as outlined above. The optimal number of joint iterations was established at 5, ensuring that changes in the mean estimated uptake of each isotope in each region were less than 0.1% with additional joint iterations.

B. Geometric transfer matrix (GTM)-based method

Partial volume effects (PVEs) are known to degrade quantification accuracy in SPECT [7]. The proposed method implicitly assumes constant uptake within each volume of interest (VOI). Under this assumption, PVEs can also be compensated for post-reconstruction. We compared our approach to the widely used geometric transfer matrix (GTM)-based method [8]. For each isotope, the elements of GTM were calculated from the reconstructed projections of the VOIs, obtained as described in Sec. III A of the main manuscript. Additional implementation details of this method are described in [8].

III. Figures of Merit

For a range of experimental conditions, we generated multiple instances of projection data for a single phantom, where each instance corresponded to separate noise realizations. Denote the total number of realizations by R. Considering one of the isotopes, denote the true activity uptake of the k^{th} VOI by λ_k and the corresponding estimate with the r^{th} noise realization by $\hat{\lambda}_{rk}$. In these experiments, the accuracy of the estimated uptake of this isotope was quantified using the normalized bias (NB), which, for the k^{th} VOI, is given by

$$\mathrm{NB}_k = \frac{1}{R}\sum_{r=1}^{R}\frac{\hat{\lambda}_{rk}-\lambda_k}{\lambda_k}. \tag{1}$$

TABLE I: The performance of the MEW-PDQ and LC-QSPECT methods on the task of quantifying regional uptake of ^{227}Th and ^{223}Ra in ^{227}Th-based α-RPTs.

	^{223}Ra				^{227}Th			
NB (%)	Background	Bone	Gut	Lesion	Background	Bone	Gut	Lesion
MEW-PDQ	-0.03	-1.2	0.05	0.8	0.01	1.1	-0.3	0.4
LC-QSPECT	250.8	178.8	154.4	450.0	6.3	2.9	7.9	1.8
NRMSE (%)	Background	Bone	Gut	Lesion	Background	Bone	Gut	Lesion
MEW-PDQ	2.0	9.5	1.1	18.9	0.9	4.7	0.8	3.6
LC-QSPECT	250.8	179.0	154.4	450.3	6.4	5.2	7.9	3.9

The precision of the estimated uptake of this isotope was quantified using the normalized standard deviation (NSD), which, for the k^{th} VOI, is given by

$$\mathrm{NSD}_k = \sqrt{\frac{1}{R-1}\sum_{r=1}^{R}\left(\frac{\hat{\lambda}_{rk}}{\lambda_k} - \frac{1}{R}\sum_{r'=1}^{R}\frac{\hat{\lambda}_{r'k}}{\lambda_k}\right)^2}. \tag{2}$$

Finally, the overall error in estimating the uptake was quantified by the normalized root mean square error (NRMSE). For the k^{th} VOI,

$$\mathrm{NRMSE}_k = \sqrt{NB_k^2 + NSD_k^2}. \tag{3}$$

Multiple experiments in this study were conducted across a plural number of patients. To evaluate the performance of the methods over a population of patients, each with one or multiple noise realizations, we used the ensemble NB and ensemble NRMSE. We denote the number of samples in the population by S and the number of noise realizations for each patient sample by R, and denote the true and estimated activity uptake of a particular isotope in the k^{th} VOI for the s^{th} sample from the r^{th} realization by λ_{sk} and $\hat{\lambda}_{skr}$, respectively. The ensemble NB for the k^{th} VOI is given by

$$\text{Ensemble NB}_k = \frac{1}{SR}\sum_{s=1}^{S}\sum_{r=1}^{R}\frac{\hat{\lambda}_{skr} - \lambda_{sk}}{\lambda_{sk}}. \tag{4}$$

The ensemble NRMSE for the k^{th} VOI is given by

$$\text{Ensemble NRMSE}_k = \sqrt{\frac{1}{SR}\sum_{s=1}^{S}\sum_{r=1}^{R}\left(\frac{\hat{\lambda}_{skr} - \lambda_{sk}}{\lambda_{sk}}\right)^2}. \tag{5}$$

Additionally, to quantify performance in cases where we had just a single estimate, we used normalized error, defined as the difference between the estimated and true uptake values, normalized by the true uptake value.

Finally, we also computed the Cramér-Rao lower bound (CRLB), which is the minimum variance that can be achieved by an unbiased estimator, as a benchmark for the precision of the activity estimated using the proposed method. The CRLB is given by the diagonal elements of the inverse of the Fisher information matrix for the estimated parameter. We denote the Fisher information matrix by $\boldsymbol{F}$ [9]. Since the task is to estimate regional uptake of ^{227}Th and ^{223}Ra at the same time, the Fisher information matrix needs to consider both isotopes. We denoted λ_l and $\hat{\lambda}_l$ as the true and estimated activity uptake respectively, where l ranges over the two isotopes in K VOIs. Thus the Fisher information matrix is a $2K$ by $2K$ matrix with elements given by

$$F_{l_1 l_2} = -E\left[\frac{\partial^2}{\partial\lambda_{l_1}\partial\lambda_{l_2}}\ln \Pr(\boldsymbol{g}|\boldsymbol{\lambda})\right], \tag{6}$$

where $E[x]$ denotes the expectation of a random variable x. We have already derived the likelihood of the measured data $\mathbf{g}$ in the main manuscript:

$$\Pr(\mathbf{g}|\boldsymbol{\lambda}) = \prod_{m=1}^{M}\exp[-(\boldsymbol{H\lambda})_m - \psi_m]\frac{[(\boldsymbol{H\lambda})_m + \psi_m]^{g_m}}{g_m!}. \tag{7}$$

Substituting Eq. (7) in Eq. (6) yields

$$F_{l_1 l_2} = \sum_{m=1}^{M}\frac{H_{ml_1}H_{ml_2}}{(\boldsymbol{H\lambda})_m + \psi_m}. \tag{8}$$

IV. Performance of the LC-QSPECT in $^{227}\mathrm{Th}$-based α-RPT

A. Experiments

In our previous studies [4], we proposed the low-count quantitative SPECT (LC-QSPECT) method to estimate the regional uptake of a single isotope from its photopeak energy window projections. The method has been observed to accurately and precisely estimate the regional uptake for patients administered with $^{223}\mathrm{Ra}$-based α-RPTs. Therefore, in this experiment, we evaluate the performance of the LC-QSPECT method on quantifying the regional uptake of $^{227}\mathrm{Th}$ and $^{223}\mathrm{Ra}$ for patients undergoing $^{227}\mathrm{Th}$-based α-RPT.

For this purpose, as described in Sec. III C of the main manuscript, we considered a patient phantom with average patient size, a 33.75 mm diameter lesion in the pelvis, standard total uptake, and regional uptake ratios as presented in Table 1 of the main manuscript. As described in Sec. III B of the main manuscript, we generated 50 noise realizations of that patient. We estimated the regional uptake of $^{227}\mathrm{Th}$ and $^{223}\mathrm{Ra}$ from those noise realizations using both the LC-QSPECT and the proposed multiple-energy-window projection-domain quantification (MEW-PDQ) methods. More specifically, the LC-QSPECT method was applied to individually estimate the regional uptake of $^{223}\mathrm{Ra}$ and $^{227}\mathrm{Th}$ from their respective photopeak energy windows, without accounting for crosstalk contamination. More implementation details of the LC-QSPECT method are described in [4]. The MEW-PDQ method was applied as described in Sec. III A of the main manuscript.

B. Results

Table I presents the NB and NRMSE values for the estimated regional uptake of $^{227}\mathrm{Th}$ and $^{223}\mathrm{Ra}$ obtained in this experiment. It was observed that the LC-QSPECT method yielded NB and NRMSE values exceeding 100% in the estimation of $^{223}\mathrm{Ra}$ uptake across all regions. Additionally, the proposed MEW-PDQ method significantly outperformed the LC-QSPECT method.

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