Simplifying volumes-of-interest (VOIs) definition in quantitative SPECT: Beyond manual definition of 3D whole-organ VOIs

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Purpose: We investigated the feasibility of using simpler methods than manual whole-organ volume-of-interest (VOI) definition to estimate the organ activity concentration in single photon emission computed tomography (SPECT) in cases where the activity in the organ can be assumed to be uniformly distributed on the scale of the voxel size. In particular, we investigated an anatomic region-of-interest (ROI) defined in a single transaxial slice, and a single sphere placed inside the organ boundaries.

Methods: The evaluation was carried out using Monte Carlo simulations based on patient indium ¹¹¹In pentetreotide SPECT and computed tomography (CT) images. We modeled constant activity concentrations in each organ, validating this assumption by comparing the distribution of voxel values inside the organ VOIs of the simulated data with the patient data. We simulated projection data corresponding to 100, 50, and 25% of the clinical count level to study the effects of noise level due to shortened acquisition time. Images were reconstructed using a previously validated quantitative SPECT reconstruction method. The evaluation was performed in terms of the accuracy and precision of the activity concentration estimates.

Results: The results demonstrated that the non-uniform image intensity observed in the reconstructed images in the organs with normal uptake was consistent with uniform activity concentration in the organs on the scale of the voxel size; observed non-uniformities in image intensity were due to a combination of partial-volume effects at the boundaries of the organ, artifacts in the reconstructed image due to collimator-detector response compensation, and noise. Using an ROI defined in a single transaxial slice produced similar biases compared to the three-dimensional (3D) whole-organ VOIs, provided that the transaxial slice was near the central plane of the organ and that the pixels from the organ boundaries were not included in the ROI. Although this slice method was sensitive to noise, biases were less than 10% for all the noise levels studied. The use of spherical VOIs was more sensitive to noise. The method was more accurate for larger spheres and larger organs such as the liver in comparison to the kidneys. Biases lower than 7% were found in the liver when using large enough spheres (radius ≥ 28 mm), regardless of the position, of the VOI inside the organ even with shortened acquisition times. The biases were more position-dependent for smaller organs.

Conclusions: Both of the simpler methods provided suitable surrogates in terms of accuracy and precision. The results suggested that a spherical VOI was more appropriate for estimating the activity concentration in larger organs such as the liver, regardless of the position of the sphere inside the organ. Larger spheres resulted in better estimates. A single-slice ROI was more suitable for activity estimation in smaller organs such as the kidneys, providing that the transaxial slice selected was near the central plane of the organ and that voxels from the organ boundaries were excluded. Under those conditions, activity concentrations with biases lower than 5% were observed for all the studied count levels and coefficients of variation were less than 9% and 5% for the 25% and 100% count levels, respectively.

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Key words: activity concentration estimation, quantitative accuracy, quantitative SPECT, volume-of-interest definition

1. INTRODUCTION

The introduction of commercial SPECT/CT cameras has led to renewed interest in quantitative SPECT since it provides the

means to rapidly and easily acquire the data needed for attenuation and scatter compensation.¹ In recent years, a growing number of investigators have demonstrated that, with appropriate SPECT acquisition, calibration, and compensation

techniques to correct for photon attenuation,^{2–7} photon scattering,^{8–16} collimator-detector response,^{17,18} and partial-volume effects,^{19–22} SPECT can provide accurate estimates of in vivo radioactivity distributions.^{23–28}

Among the applications that could benefit from accurate quantitation of the activity distribution are tumor detection, staging, and therapy response assessment in clinical oncology (examples of reviews for both PET and SPECT can be found in the literature^{29–33}). Another important application is individualized dosimetry for planning and monitoring of therapies with internally administered radionuclides.^{34,35} Further examples include applications in brain imaging, such as, iodine ¹²³I-ioflupane, also called DaTscan.³⁶ In all these applications, it is essential to determine the mean activity concentration in organs or regions. In tumor detection, the mean activity concentration in normal organs may be a useful metric for ensuring the comparability of images acquired at different times. For example, it may be useful to normalize quantitative values in tumors by the value in normal organs or to use normal organs to establish a threshold for uptake that represents malignancy.³⁷

The estimate of organ activity or activity concentration can be strongly dependent on the method used to define the organ VOIs. The most common method for determining mean organ activity concentration in clinical practice is using 3D whole-organ VOIs. However, defining full 3D organ VOIs can be very tedious and time consuming. For instance, in dosimetry, the additional effort required to define organ VOIs in SPECT compared to planar imaging has been used as a justification for the use of planar imaging in dosimetry applications. Furthermore, there is a real need to simplify the analysis pipeline in radiopharmaceutical therapy (RPT) dosimetry if it is to be routinely applied clinically.

As an alternative to manual definition, automatic or semi-automatic segmentation methods can be used. There are several strategies available such as edge detection,³⁸ thresholding,^{39–42} region growing,⁴³ and clustering.⁴⁴ These approaches have different levels of implementation complexity. In addition, none of these has been definitively shown to provide a general solution to segmentation of nuclear medicine images, and manual definition tends to be the dominant method in clinical practice.

The fact that the activity distribution in normal organs can reasonably be assumed to be uniform on the scale of the voxel size with many agents opens up the possibility of estimating the mean activity concentration in the organ using smaller VOIs that do not encompass the entire organ. In this work, we first investigated whether the activity concentrations in normal organs in patient images were consistent with uniform activity distributions in the case of ¹¹¹In pentetate. Having established this, we used the simulated images to investigate the accuracy and precision for two simpler alternatives to the full 3D organ VOI: estimating organ activity concentrations from an anatomic VOI in a single transaxial slice, and using a sphere placed inside the organ boundaries.

2. MATERIALS AND METHODS

2.A. 3D-SPECT data Monte Carlo simulations

Evaluating the reliability of quantitative imaging requires considering both the accuracy and precision of the estimated values. Estimating accuracy requires knowledge of the underlying truth, which is difficult to obtain in patient images. As a result, the evaluation of the proposed methods was carried out using SPECT images reconstructed from Monte Carlo simulated projections.

The simulations were performed using the SIMIND Monte Carlo code^{45,46} with parameters appropriate for a Precedence 16-slice SPECT/CT scanner (Philips) with a medium-energy general-purpose (MEGP) collimator. Projections were simulated based on patient ¹¹¹In pentetate images from a previously published retrospective study.²⁶ In that study, images were acquired approximately 24 h after intravenous injection of 229 ± 19 MBq (6.2 ± 0.5 mCi) of ¹¹¹In-pentetate. The acquisitions were performed with a 20%-wide energy window centered over each of the two photopeaks, i.e., at 171 and 245 keV. The duration of SPECT acquisitions was 48 min (45 s per view and 64 views acquired by each camera), and projections were stored in 128 transaxial and 128 axial projection bins at 128 views over 360° using a 4.664 mm projection bin size. The SPECT patient images were reconstructed as described in section 2.B of this paper and were quantified using a calibration factor, used to convert the reconstructed voxel values in the SPECT images to activity concentration values. The acquisition to obtain this factor, also described in the mentioned publication,²⁶ consisted of imaging a cylinder (diameter, 23 cm; height, 27.4 cm) filled with a solution containing 365.2 MBq (9.89 mCi) of ¹¹¹In using the same acquisition and reconstruction parameters as those used for the patients.

Voxel-based density and activity maps ($128 \times 128 \times 128$ cubic voxels with a side length of 4.664 mm) were used for the simulations (see Fig. 1). The density map was generated using the patient's CT-based attenuation map by segmenting the image into volumes corresponding to four materials using thresholding: bone, soft tissue, lung tissue, and air. In the simulations, these tissues were assigned density values of 1.85, 1.06, 0.35 (one-third of the soft tissue density), and

FIG. 1. Example of patient CT image (left) used to generate the activity map (center) and the density map (right) used in the simulations. [Color figure can be viewed at wileyonlinelibrary.com]

0 g/cm³, respectively. In SIMIND, the highest density was modeled using bone, while the lower density tissues were modeled using a material with the same composition as water but with the indicated densities. For the activity map, manually defined 3D whole-organ VOIs were drawn on the patient CT images by a nuclear medicine physician who defined liver, spleen, kidneys (cortex and medulla), and body background VOIs. Activity concentrations were estimated from these VOIs in the patient SPECT images. Each organ was simulated separately assuming constant activity concentrations.

Low-noise projections were generated for each organ. The organ projections were summed into a single set of projections (i.e., the complete simulation of the patient) and scaled to three different count levels, corresponding to 100, 50, and 25% of the product of the clinical administered activity and acquisition time. A Poisson-distributed pseudorandom number generator was used to simulate the acquisition quantum noise. We generated a total of 20 realizations for each count level (i.e., noise level) to estimate the uncertainties in the various measurements. We also show results for images reconstructed using the projections with no added Poisson noise, referred to as low-noise images.

We used this strategy for generating noisy projection data because SIMIND incorporates variance reduction methods to increase the simulation efficiency, and, as a result, the simulated projections are no longer Poisson-distributed. The number of simulated photons for each organ was determined using the relative Poisson effective count level.^{47,48} This technique provided a quantitative estimate of the true noise in the simulated projection data, including residual Monte Carlo simulation noise. The selected relative Poisson effective count level value was ≥ 0.95 for all the separated simulations, except for the body background where we set the factor to 0.92 to reduce the simulation time because we were not interested in quantifying precision in this region. In this way, the relative variance in the simulation was equivalent to the variance in a Poisson-distributed random number having 95 (or 92) percent of the photon histories actually simulated.

We performed an additional simulation to obtain the calibration factor, necessary to convert the reconstructed voxel values in the SPECT images to activity concentration, used in the analysis of the different methods. The phantom simulated was the same as that used experimentally to obtain the calibration factor for the patient images.

2.B. Image reconstruction

The projections were reconstructed using a 3D iterative ordered-subsets expectation-maximization (OSEM) algorithm with a rotation-based projector¹⁶ and compensation for attenuation, scatter, and the collimator-detector response (CDR) function. Scatter was modeled using the effective source scatter estimation (ESSE) method.¹² The CDR was estimated by Monte Carlo simulations of point sources at various distances from the face of the collimator including propagation of photons in the collimator and detector and included the effects of

penetration and scatter in the collimator-detector system. Both kernels were estimated using SIMIND.

The particular combination of reconstruction algorithm and compensation methods used in this work has been shown to be quantitatively accurate for a number of radionuclides including the one simulated here.²³ For example, we used the ESSE scatter compensation method, instead of the commonly used triple energy window (TEW) scatter compensation, because it has the advantage of not having free parameters such as the energy window width and low-pass filtering parameters of the scatter estimate. Optimizing these parameters would have added significant complexity to the paper, and it seems unlikely that results for optimized TEW would have been much different than for the ESSE-based scatter compensation method used in this work. Further information about the reconstruction method and its validation can be found in He *et al.*²³

Image reconstruction was performed with variable number of iterations and eight subsets per iteration, using $128 \times 128 \times 128$ cubic voxels with a side length of 4.664 mm. Convergence was assessed by comparing the quantification behavior as a function of iteration number in the organ VOIs. Negligible change was found after 30 iterations, and, therefore, 30 iterations were used in obtaining the results throughout the analysis.

No filtering was applied to the reconstructed images. While post-reconstruction low-pass filtering is often used clinically to control noise, it tends to increase partial-volume effects. Since this would have an especially negative effect on the kidneys, we did not use post-filtering in this investigation.

2.C. Image analysis

To evaluate the two proposed alternative methods for determining the mean organ activity concentration, we compared their performance with that of the true 3D whole-organ VOIs, which modeled perfect manual definition of the organs, e.g., using a perfectly registered CT image. The true 3D whole-organ VOIs were the same set of VOIs used to generate the activity maps in the simulations. Therefore, the 3D whole-organ VOIs method provided a gold standard for comparison of the organ activity concentration estimates obtained from other methods. These VOIs were used both to define the boundaries of the transaxial ROIs for the 2D method and as bounds for the region containing the spheres. For each of the three methods, we studied the inclusion or exclusion of voxels near the true organ edges, modeled by step-wise peripheral erosion of the VOIs.

The VOI activities were obtained by multiplying the average voxel value calculated in the VOI by the calibration factor obtained from the cylinder phantom simulation. The value of the calibration factor was calculated as the total measured counts in the image of the cylinder divided by the product of the known activity and the total acquisition duration. To reduce the impact of partial-volume effects on the calibration factor, the reconstructed voxel values were determined inside a cylindrical VOI defined larger than the cylinder size.

FIG. 2. CT images of the two patients simulated in this work. [Color figure can be viewed at wileyonlinelibrary.com]

In this work, we present the results for two patients, who will be referred to as Patient 1 and Patient 2 hereafter (see Fig. 2). Neither patient had lesions present in the organs of interest. Patient 1 was selected as a representative patient because the weight of this patient (72 kg) was similar to the average weight computed across the population of patients in the retrospective study.²⁶ Patient 2 was selected to explore the effects in large patients (patient weight: 115 kg) where attenuation, scatter, and the average radius of rotation are larger, and the count level was lower. The steps of the analysis are detailed in the subsections presented below.

2.C.1. Validation of activity distribution homogeneity

As discussed in section 2.A, the activity distributions in the simulations had a constant value inside each organ in the activity maps used in the simulations. However, in the reconstructed images the voxel values were non-constant for both the simulated and patient images. This inhomogeneous distribution could arise from a number of factors including noise, reconstruction artifacts due to the CDR compensation, and incomplete compensation for image degrading factors, e.g., partial-volume effects. We validated the assumption that the activity distribution inside the organs was homogeneous on the scale of the voxel size by comparing the distribution of voxel values inside the 3D whole-organ VOIs of the simulated data with those from the patient data.

It is important to mention that some potential misregistration was noted between the SPECT and CT images as acquired. Since the VOIs used in the analysis were drawn on the CT images, it was necessary to perform an explicit registration between the VOIs and the patient SPECT image prior to performing the analysis. We registered each VOI with the SPECT image separately using a rigid transformation. This introduced an extra uncertainty in the comparison since, for the simulations, we knew the true boundaries of the organ. However, for the patient data any misregistration between the functional and the anatomical images or misdefinition, i.e., deviations in the VOI outlines from the true (unknown) organ outlines, will lead to an imperfect estimate of the distribution of voxel values inside the 3D whole-organ VOIs,⁴⁹ making the comparison more difficult. These sources of non-

uniformity are not present in the simulated data. To take this into account, we studied different VOI definitions (i.e., using patient VOIs drawn on the CT or on the SPECT images) and several levels of dilation or erosion, which can eliminate voxels on the boundaries where there is mismatch due to misregistration or systematic misdefinition.

2.C.2 Study of the sources of non-uniformity

Our second goal was to understand the combination of the effects that make the reconstructed images non-uniform inside the various organs. To study these effects, we investigated the voxel-by-voxel activity error in the images. The error was obtained by calculating the difference between the reconstructed voxel value in one noise realization and the true value simulated in each organ relative to the true value. Since there were regions with positive and negative errors, we generated separate images for voxels with negative and positive error values. Negative values indicate underestimation compared to the true activity, while positive ones indicate overestimation.

We first investigated the voxel-by-voxel activity error in the considered organs using the reconstructed images of the low-noise projections. These images make it easier to see the effects of ringing artifacts and partial-volume effects, which can be obscured by noise. Next, we computed the voxel-by-voxel error for one noise realization with clinical-noise level (48-minute acquisition, 229 MBq administered activity, and imaged 24 h post injection).

2.C.3 Quantification using 3D whole-organ VOIs

As discussed before, we used the 3D whole-organ VOIs as a gold standard for estimating the mean activity concentration, since the organ 3D-VOIs were the same set of VOIs used to generate the activity maps in the simulations. We studied the bias (over 20 noise realizations) in the organ activity concentration estimate as a function of the number of steps of peripheral erosion to take into account the partial-volume effect. This was repeated for low-noise projections and for projections with noise levels corresponding to the 100, 50, and 25% of a typical clinical count level.

2.C.4. Quantification using an ROI in a single transaxial slice

One way to simplify activity concentration estimation is to find the average activity in a single transaxial slice using an ROI that encompasses the portion of the organ in that slice. We investigated this using the true organ VOI with or without erosion and evaluated the bias and standard deviation (over 20 noise realizations) in the mean activity concentration for each transaxial slice in the organ and 4 noise levels.

2.C.5. Quantification using a spherical VOI

The second proposed simplified method for estimating organ activity concentrations is the use of a spherical VOI placed

inside the organ boundaries. Key questions with regard to this method are the effects of the VOI size and position of the sphere inside the organ boundary. Sphere radii of 1 (4.6 mm) to 6 pixels (28 mm) were used in the evaluation. To study the effect of sphere placement we calculated the mean and standard deviation of the activity concentrations estimated from all possible placements of the sphere inside the organ boundary.

2.C.6. Impact on the precision of the activity estimates

To quantify the variability in the activity estimates, we calculated the coefficient of variation (COV), defined as the standard deviation divided by the mean, calculated over 20 noise realizations for the three methods and count levels. The smaller the COV, the better the precision of the estimates. The average was computed over the activity estimates for the different peripheral erosions of the VOIs (from 0 to 10 for the liver; from 0 to 3 for the kidneys) for the gold standard, over the different slices for the transaxial slices method, and over the spheres' positions for the spheres method. The voxels from the organ boundaries were not included in the transaxial slice ROIs and the two top- and bottom-most slices were excluded from the analysis for the single-slice-ROI method.

3. RESULTS

3.A. Validation of activity distribution homogeneity

Figure 3 shows an example of the comparison of the distributions of voxel values inside the different VOI definitions (i.e., using patient VOIs drawn on the CT or on the SPECT images) in the simulated and patient images for each of the considered organs for Patient 1. We focused on the liver and the kidneys in these studies, as they would be of most interest for either dosimetry or tumor normalization.

In the example shown in Fig. 3, we found good agreement for Patient 1 between the simulation and the patient data under the following conditions.

1. Liver:
  - a. Patient data: CT-VOI, 0 or 1 voxel erosion.
  - b. Simulated data: CT-VOI, 1 voxel dilation.
2. Left and right kidneys:
  - a. Patient data: SPECT-VOIs, 1 voxel erosion.
  - b. Simulated data: SPECT-VOIs, no erosion/dilation.

Similar results were found for Patient 2 (results not shown).

These data suggest that the inhomogeneities seen in the liver and kidneys in the images are consistent with a homogeneous activity distribution in normal organs. This indicates that the observed inhomogeneities in the images in these regions were due to factors including partial-volume effects at the boundaries of the organ, artifacts in the reconstructed image due to, e.g., CDR compensation, and noise. From this, we concluded that the MC simulated datasets with uniform activity distribution in the organs were reasonable surrogates for judging the accuracy and precision of methods for estimating the average activity in the VOIs.

3.B. Study of the sources of non-uniformity

To understand the combination of the effects that make the reconstructed images non-uniform inside the various organs, we present in Fig. 4 the positive and negative activity error images for the low-noise (left) and the clinical-noise (right) simulations in the liver and the left kidney (Patient 1). For better visualization, we show all error values less than 10% (in absolute units) using the same color (purple in the online version). This explains the fact that purple regions are present in both images (positive and negative activity bias). The results presented in the figure show, for the low-noise data, a negative error at the edge of the organ boundaries and a positive error for adjacent interior voxels. These are consistent with partial-volume effects and ringing due to CDR compensation, respectively. Similar behavior was observed for the kidneys, even for the noisy data, because the kidney reconstructed voxel values were high (~2000 counts/voxel), resulting in low noise in the kidney region of the image. In the liver, however, since the

FIG. 3. Histograms of the voxel values inside the VOIs (Patient 1). VOIs drawn on the CT image were used for the liver; SPECT-VOIs were used for the kidneys. [Color figure can be viewed at wileyonlinelibrary.com]

FIG. 4. Axial and coronal views of the positive and negative activity error (color in the online version) fused with the CT image (gray) calculated voxel-by-voxel (cubic voxel with a side length of 4.664 mm) for low-noise and clinical-noise simulations in the liver and the left kidney (Patient 1). The kidney images are zoomed by 1.6 $\times$ with respect to the liver image. The horizontal lines in the images denote the position of the slice shown in the other view. [Color figure can be viewed at wileyonlinelibrary.com]

reconstructed voxel values were lower (~ 230 counts/voxel), the noise was readily apparent. Thus, in addition to the previously discussed errors close to the edges, there are small clusters of negative and positive error values inside the liver. Note also that, due to spill-in effects from the right kidney into the liver, there is a high-positive error at the edge of the liver close to the kidney, which is visible for both noise levels.

The same behavior was observed for Patient 2 (images not shown), but clusters of error values were even more obvious. This is likely due to the higher attenuation by the body for

this patient, resulting in a decreased number of counts acquired for the same acquisition duration: 8.4×10^6 counts for Patient 1 versus 4.0×10^6 counts for Patient 2. Although attenuation compensation mitigates the effect on bias, it does not compensate for, and in fact amplifies, the noise, making the effects of the noise more visible.

Note that the error values calculated using the low-noise data are actually bias values since the voxel values are a good approximation to the mean values calculated over a large number of noise realizations. It was also verified that the bias values calculated using the 20 noise realizations were similar to the ones calculated using the low-noise data (results not shown).

3.C. Quantification using 3D whole-organ VOIs

Figure 5 shows the bias in the organ activity concentration estimate using the 3D whole-organ VOIs as a function of the number of steps of peripheral erosion. We observe that the lowest biases ($< 5\%$) were achieved for all organs and count levels with a peripheral erosion of 1 voxel. Larger erosions resulted in overestimation in both kidneys, likely due to ringing effects, with biases between 10 and 20%. This behavior in the kidneys was independent of count level, due to the high kidney uptake noted above. For the liver, there were some differences in bias as a function of count level, likely due to the effect of noise clusters that were more significant because of the relatively low liver uptake. Smaller VOIs (more erosion) resulted in greater variability (as evidenced by the larger error bars) in the activity concentration estimates for both organs. This is likely because there was less total activity in

FIG. 5. Quantification using 3D whole-organ VOIs after morphological erosion for 4 count levels for the MC simulations of Patient 1 (top) and Patient 2 (bottom). “Clinical” corresponds to the case where the number of counts for this patient was the same as for the clinical projection data; the curves labeled “0.5x” and “0.25xClinical” had a half and a quarter of the counts in the clinical projections, respectively. A negative bias indicates underestimation compared to the true activity. Error bars were calculated from the 20 noise realizations. Numbers labeling the data points are the number of voxels in the VOI after the indicated level of erosion. [Color figure can be viewed at wileyonlinelibrary.com]

FIG. 6. Bias in activity concentration estimates for the simulated Patient 1 using individual transaxial slices as a function of the slice number for the clinical-count level (8.4×10^6) using ROIs generated by 0, 1, or 2 pixels of peripheral erosion for (from left to right): the liver, the left kidney, and right kidney. The black objects in each graph are coronal slices through the indicated organs and are shown to illustrate the positions of the various transaxial slices in each organ. Negative signs indicate underestimation compared to the true activity. Error bars were calculated based on 20 noise realizations. [Color figure can be viewed at [wileyonlinelibrary.com](#)]

FIG. 7. (a), (b), (c): Bias in activity concentration estimates for the simulated Patient 1 using individual transaxial slices as a function of the slice number for the optimal peripheral erosion (1 pixel) and four noise levels for (from left to right): the liver, the left kidney, and right kidney. Negative signs indicate underestimation compared to the true activity. (d), (e), (f): standard deviation calculated based on 20 noise realizations in the same three organs. “Clinical” corresponds to the number of counts (8.4×10^6) for the SPECT clinical study, and “0.5x” and “0.25xClinical” had half and a quarter of this number of counts. [Color figure can be viewed at [wileyonlinelibrary.com](#)]

the organ VOI as it decreased in size, and thus less averaging out of the effects of quantum noise.

In Patient 2, there were smaller differences in bias and variability as a function of the number of erosions in the liver than in Patient 1. The bias was likely smaller because the biased voxels at the boundary represented a smaller fraction of the total liver volume than for Patient 1; the variability was likely lower because the effects of noise were averaged out over the larger volume.

3.D. Quantification using an ROI in a single transaxial slice

Figures 6 and 7 show the bias and standard deviation (over 20 noise realizations) in the mean activity concentration for each transaxial slice in the organ. The biases for this

method were similar to those for the whole-organ VOI for transaxial slices near the central plane of the organ: one voxel of erosion gave the lowest bias, which was less than 5% for all three organs (see Fig. 6). The variability was small for the clinical count level, but significantly larger for lower count levels (Fig. 7).

Similar results were observed for Patient 2 (not shown), but with slightly higher variability due to the lower total counts.

3.E. Quantification using a spherical VOI

Figures 8 and 9 illustrate the effects of VOI size and the position of the sphere inside the organ boundaries on the activity concentration estimate. The figures show the fraction of the spheres (vertical axis) with biases lower than a given

FIG. 8. The fraction of the spheres (vertical axis) within the boundary of the organ having a bias below the indicated percentage is plotted as a function of the percent bias (horizontal axis). Each figure shows curves for the low-noise and 100, 50, and 25% of clinical count level cases for the simulated Patient 1. The radius of the sphere used is shown in the inset of each graph along with a drawing to compare the sphere and the organ sizes; smaller spheres were used on the top row than the bottom. The error bars for the sphere fractions were calculated from 20 noise realizations. [Color figure can be viewed at wileyonlinelibrary.com]

FIG. 9. The fraction of the spheres (vertical axis) within the boundary of the organ having a bias below the indicated percentage is plotted as a function of the percent bias (horizontal axis) for the liver (left) and the left kidney (right). Each plot shows curves for the low-noise case and the 100, 50, and 25% of clinical count levels for the simulated Patient 2. The radius of the sphere used is shown in the inset of each graph along with a drawing to compare the sphere and the organ sizes. The error bars for the sphere fractions were calculated from 20 noise realizations. [Color figure can be viewed at wileyonlinelibrary.com]

bias value (horizontal axis) for Patient 1 and Patient 2, respectively. These demonstrate how sensitive the activity concentration estimate is to sphere placement. For the liver, we show the results for sphere radii of four (18.7 mm) and six pixels (28 mm); for the kidneys, spheres with radii of one (4.6 mm) and two pixels (9.3 mm) are shown.

The results shown in Fig. 8 demonstrate the importance of using a large sphere radius to provide a greater chance that a randomly placed sphere will have a small bias. This is partially due to the fact that larger spheres will contain, on average, a smaller fraction of their voxels near the edge of the organ, where partial volume and ringing effects are important. In addition, larger spheres average out the effects of noise.

The use of spherical VOIs provided a higher chance of low bias for spheres randomly placed in the liver than in the kidneys, with 100% of the 28 mm-radius-spheres that fit inside the liver having biases less than 7% for all the noise levels studied. For the kidneys, approximately 100% of the 9.3 mm-radius-spheres that fit inside the kidneys had biases lower than 20%, and 60% of the positions had biases lower than 10% for all the noise levels. This is because a very large fraction of the voxels in the kidney was near the organ boundary, so that a large fraction of spheres that fit was impacted by ringing and partial-volume effects.

In Fig. 9, we present the results for Patient 2 for the liver and the left kidney using the larger spheres (28 and 9.3 mm, respectively). The behavior for the low-noise data was not significantly different from that observed in Patient 1. However, the fractions of spheres above a given bias threshold for the noisy data were substantially lower than for the low-noise case due to the lower activity concentration, and thus larger relative noise fluctuations.

The results in Figures 8 and 9 illustrate that the effects of overall noise level on quantitation using a single spherical VOI were larger, especially for the kidneys, than for the other methods. For example, in the liver (Patient 1), shortening the typical clinical acquisition duration to a quarter of the time (“0.25xClinical” in the figures) reduced the percentage of the 28 mm-radius-spheres with biases lower than 7% from 100% to 80%. A similar reduction was observed in the kidneys with a bias threshold of 30% for the 9.3 mm-radius-spheres. Also, observe that the results obtained for Patient 2 for the clinical count level (“Clinical” in the figure) were very close to those obtained for the lower count levels with Patient 1, likely due to the overall lower activity concentrations in Patient 2 compared to Patient 1.

TABLE I. Coefficient of variation (COV) for Patient 1 for all the count levels and organs studied.

Organ	Method	Averaged COV [min–max] (%)					
		Clinical		0.5xClinical		0.25xClinical	
Liver	Gold standard	2.2	[0.3–9.4]	2.9	[0.6–12.9]	4.2	[0.6–16.6]
	Slices ^a	3.3	[2.0–8.5]	4.7	[1.9–9.3]	5.7	[3.3–10.6]
	Spheres (r = 28 mm) ^b	1.8	[1.1–2.9]	2.8	[1.6–4.8]	3.9	[2.4–6.6]
Left kidney	Gold standard	1.5	[0.5–3.1]	2.7	[0.8–6.4]	3.5	[0.8–9.1]
	Slices ^a	3.2	[2.4–4.1]	4.7	[3.0–6.1]	6.2	[4.7–7.9]
	Spheres (r = 9.3 mm) ^b	4.5	[2.8–6.3]	6.8	[5.0–9.6]	9.2	[4.7–11.6]
Right kidney	Gold standard	2.5	[0.6–6.4]	3.3	[0.8–8.9]	3.3	[1.1–7.6]
	Slices ^a	4.1	[3.3–5.2]	5.2	[3.7–8.2]	7.1	[5.3–9.3]
	Spheres (r = 9.3 mm) ^b	5.3	[3.8–6.0]	6.1	[4.9–7.1]	9.0	[6.1–12.1]

^aPixels from the organ boundaries were not included in the transaxial slice ROIs (1-pixel erosion) and the two top- and bottom-most slices were removed from the analysis.

^bSphere radius used in the method.

3.F. Impact on the precision of the activity estimates

In the previous sections, we have observed greater variability (as evidenced by the larger error bars in the figures or higher values of the standard deviation) with both the proposed methods compared to the gold standard. To quantify the impact on the precision of the activity estimates, we show in Table I a comparison, for Patient 1, of the average and range of the COV, calculated over 20 noise realizations for the three methods and count levels.

4. DISCUSSION

In this work, we analyzed two simplified methods for estimating activity concentrations in normal organs, i.e., when disease was not present. Typically, in clinical practice, mean activity concentrations would be obtained by defining 3D whole-organ VOIs, which can be very tedious and time consuming. Therefore, taking advantage of the fact that the activity distribution in normal organs can reasonably be assumed to be uniform on the scale of the voxel size with many agents (as was demonstrated here for the case of ¹¹¹In pentetate), we propose to estimate the mean activity concentration using smaller VOIs that do not encompass the entire organ. In particular, we investigated an anatomic ROI defined in a single transaxial slice, and a single sphere placed inside the organ boundaries.

We studied the impact on both accuracy and precision, measured by the bias and the variability in the activity estimates due to quantum noise, respectively. In terms of accuracy, we found that using an ROI drawn in a single transaxial slice produced similar biases compared to the gold standard, provided that the transaxial slice was near the central plane of the organ and that the voxels from the organ boundaries were not included in the ROI. Under those conditions, biases were less than 5% for both the liver and the kidneys for all the count levels studied. The spherical VOI method was more accurate when larger spheres were used and for larger organs such as the liver. Biases lower than 7% were found in the liver when

using large enough spheres (≥ 28 mm-radius) regardless of the position of the VOI inside the organ and of the count level. The biases were more position-dependent for smaller organs: only 60% of the sphere positions provided biases lower than 10% in the kidneys and biases were smaller than 20% for all the spheres positions. In the case of large patients, the sphere-method was less accurate for lower count levels.

In terms of precision, we observed that, as expected, the COV increased as the count level decreased. With exception only for the case of the spherical VOI in the liver, the COV was lower for the gold standard compared to the other methods, with averaged values around 5% or lower for the clinical count level, and around 9% or lower for the 25% count level for the three methods. The COV for the sphere-method was lower in the liver because the COV for the gold standard was calculated averaging over all the peripheral erosions of the VOIs, and, as shown in Fig. 5, the variation in the activity estimates was larger for smaller VOIs (higher levels of erosion). However, for moderate erosions of the liver VOI, the value of the COV was very low (e.g., COV = 0.3% for 1-voxel erosion).

While the results above demonstrate that both methods are suitable surrogates for the 3D whole-organ VOI in estimating the activity concentration, there are cases when one of the two methods is preferable. On the basis of the data, we recommend the use of the spherical VOI method for larger organs such as the liver, where using a 28 mm-radius-sphere produced a bias less than 7% and a COV lower than 7% even for the lowest count level and regardless of the position of the sphere inside the organ. In the case of activity estimates in smaller organs such as the kidneys, we suggest the use of the transaxial slice ROI method. With this method, providing that the transaxial slice was near the central plane of the organ and that the pixels from the organ boundaries were excluded from the ROI, biases lower than 5% and COVs less than 9% were obtained for the 25% count level.

It is worth mentioning that in this work, we evaluated two simplified methods for defining the VOI compared to whole-organ delineation, provided that the activity distribution in the organ can be considered uniform on the scale of the voxel size

and that appropriate compensation techniques are included in the reconstruction process. However, there are many ways to define a sub-organ-level VOI surrogate based on the same assumptions; for example, defining a different shape, such as a cubical VOI, or using a representative set of samples inside the organ avoiding voxels from the organ boundaries.

In addition, the investigation was performed using a specific combination of compensation methods. It might be possible that these simplified VOI definition methods would not be acceptable with other compensation methods. For example, scatter compensation using a sub-optimal method might result in poorer results for the simplified VOI definition methods, although it would also likely result in poorer quantitation for the 3D whole-organ VOIs. Thus, based on the data presented here, these simplified VOI definition methods should only be used with confidence with a reconstruction method that performs well in terms of whole-organ activity estimation. On the other hand, a different combination of compensations might be optimal for the simplified VOI definition methods. For example, CDR compensation resulted in ringing artifacts. While previous work²³ has showed that CDR compensation improves whole-organ activity estimates when used with 3D whole-organ VOIs, it might be possible that using simplified VOIs on images without CDR compensation would produce better results if the VOI were placed away from edges. However, this would not be optimal for determining the activity in small objects such as tumors, where CDR compensation would almost certainly provide the best results.²³

5. CONCLUSIONS

This work investigated the feasibility of using simpler methods than the 3D whole-organ VOI to estimate the organ activity concentration in SPECT in cases where the activity in the organ can be assumed to be uniformly distributed. In particular, the use of an ROI defined in a single transaxial slice or a spherical VOI placed inside the boundaries of the organ was investigated. The analysis was performed using simulated projections modeling the uptake of ¹¹¹In pentetate with activity concentrations and anatomies based on patient data. We first demonstrated that the activity in the liver and kidneys in the patient images were consistent with uniform activity distributions by comparing activity volume histograms in patient data with those from simulations with uniform distributions. We studied the effect of count level on the bias and precision, with count levels ranging from 100 to 25% of the clinical count level. Both of the methods were demonstrated to be suitable surrogates in terms of accuracy and precision. The results suggested that a spherical VOI was more appropriate for estimating the activity concentration in larger organs such as the liver. The placement of the sphere inside the organ was not critical, but larger spheres resulted in better estimates. However, a single-slice ROI was more suitable for activity estimation in smaller organs such as the kidneys, providing that the transaxial slice selected was near the central plane of the organ and that voxels from the organ boundaries were not

included in the ROI. For the cases investigated here, the bias and coefficient of variation in the activity concentration estimates were less than 10% when these methods were used, with values around 5% for clinical count levels.

Finally, since activity concentrations in uniform regions were estimated with comparable accuracy when measured over the whole organ, in a single transaxial slice, or spheres placed virtually anywhere in the organ, this work demonstrates the potential of SPECT as an accurate quantitative technique when appropriate compensation techniques are included in the reconstruction process.

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CONFLICT OF INTEREST

The images in this work were reconstructed using software licensed by Johns Hopkins University to GE Healthcare. One of the authors, E.C. Frey, receives a portion of the licensing revenue. The terms of this arrangement are being managed by the Johns Hopkins University in accordance with its conflict of interest policies.

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