The effects of mismatch between SPECT and CT images on quantitative activity estimation – A simulation study

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Abstract

Background: Quantitative activity estimation is essential in nuclear medicine imaging. Mismatch between SPECT and CT images at the same imaging time point due to patient movement degrades accuracy in both diagnostic studies and target radionuclide therapy dosimetry. This work aims to study the mismatch effects between CT and SPECT data on attenuation correction (AC), volume-of-interest (VOI) delineation, and registration for activity estimation.

Methods: Nine 4D XCAT phantoms were generated at 1, 24, and 144 h post In-111 Zevalin injection, varying in activity distributions, body sizes, and organ sizes. Realistic noisy SPECT projections were generated by an analytical projector and reconstructed with a quantitative OS-EM method. CT images were shifted, corresponding to SPECT images at each imaging time point, from -5 to 5 voxels and also according to a clinical reference. The effect of mismatched AC maps was evaluated using mismatched CT images for AC in SPECT reconstruction while VOIs were mapped out from matched CTs. The effect of mismatched VOI drawings was evaluated using mismatched CTs to map out target organs while using matched CTs for AC. The effect of mismatched CT images for registration was evaluated by registering sequential mismatched CTs to align corresponding SPECT images, with no AC and VOI mismatch. Bi-exponential curve fitting was performed to obtain time-integrated activity (TIA). Organ activity errors (%OAE) and TIA errors (%TIAE) were calculated.

Results: According to the clinical reference, %OAE was larger for organs near ribs for AC effect. For VOI effect, %OAE was larger for small and low uptake organs. For registration effect, %TIAE were larger when mismatch existed in more numbers of SPECT/CT images, while no substantial difference was observed when using mismatched CT at different imaging time points as registration reference. %TIAE was highest for VOI, followed by registration and AC, e.g., 20.62%±8.61%, 9.33%±4.66% and 1.13%±0.90% respectively for kidneys.

Conclusions: The mismatch between CT and SPECT images poses a significant impact on the accuracy of quantitative activity estimation, attributed particularly from VOI delineation errors. It is recommended to perform registration between emission and transmission images at the same time point to ensure diagnostic and dosimetric accuracy.

Keywords: Misregistration; Targeted radionuclide therapy; SPECT/CT; Attenuation correction; Segmentation

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1 Introduction

Targeted radionuclide therapy (TRT) is an effective therapy for various types of cancers [1], uses radionuclide labeled molecules to kill cancer cells with ionizing radiation by destroying their DNA in the cell nucleus and by “bystander” effects [2], resulting in tumor shrinkage. Compared to conventional chemotherapy, TRT aims to specifically deliver a lethally absorbed dose targeting cancerous cells with minimal collateral toxicity to the surrounding normal organs or tissues, requiring accurate drug biodistribution information prior to and post-treatment. Such information can be obtained by planar imaging or emission computed tomography, i.e., SPECT and PET [3]. Given the sequential quantitative activity images at different time points post-injection, or sometimes at single time point post-injection for Y-90 radioembolization, the estimation of time-integrated activity (TIA) for critical organs and tumors, used for further absorbed dose conversion, is obtained by fitting the time-activity curves (TACs) and sum the area under the curve.

Integrated CT in SPECT/CT can be used for attenuation correction (AC) in SPECT reconstruction to improve quantitative accuracy and provide an anatomical reference for the activity uptakes in general. For TRT dosimetry, CT data can be further used for segmentations of tumors and critical organs and registrations to reduce the misalignments among serial scans [4,5]. However, the accuracy of registration between SPECT and CT data is limited by certain voluntary and involuntary motions since CT scans take a couple of seconds while SPECT imaging needs at least several minutes. Voluntary variables are mainly due to the patient movement between SPECT and CT scans as the patient position may change during two acquisitions. Involuntary movements are mostly physiological activities, such as the beating of the heart, the peristalsis of the bowel [6], and the respiratory movements of the lungs and adjacent organs [7]. Respiration cause organ movement or deformation, particularly in the upper abdominal [8], and lower thoracic regions [9,10]. The SPECT and CT mismatch may manifest from different respiratory position as patients practice breath-holding during CT scans and free-breathing during SPECT scan. Such movements alter the appearance of organ shape, size, and location contributing to the minor mismatches between the SPECT and CT imaging sessions. Voluntary and involuntary mismatch errors not only cause artifacts in the SPECT data due to the use of misaligned CT for AC [11,12] but also mislead anatomical localization for later segmentation required for dosimetric calculations. He et al. [13] have studied the impact of SPECT/planar and CT misregistration at the same imaging time point, and misdefinition of volume-of-interest (VOI) from manual segmentation on activity estimation. In their study, VOI misregistration errors were generally larger than misdefinition errors, producing a considerable source of errors on activity estimations. For planar images, the quantitation error could be up to 8% for kidneys activity with a one voxel VOI mismatch in the superior-inferior direction between planar and CT images. The error was about -5% for the spleen if SPECT and CT images had one voxel VOI mismatch in the anterior-posterior direction. This study claimed that SPECT images were less sensitive to the VOI misregistration errors than the planar images, which could possibly due to the reduction of organs overlapping in SPECT. One limitation of their study is that only mismatch within 1 voxel, i.e., 4.42 mm, between SPECT and CT is evaluated, whereas about two thirds of the clinical cases showed more than one voxel of misregistration, and the mean misregistration for integrated SPECT/CT at the same time point could reach 8.6±3.8 mm for three directions, with a range of 0-22.4 mm [14].

Moreover, for serial imaging sessions, CT images are usually used for registration and the resultant motion field will be used to align the corresponding SPECT images to reduce the misalignments at different time points [15]. Thus, a mismatch of SPECT and CT at the same time point would lead to TIA estimation errors when using CT images for registration reference. All the aforementioned errors will propagate to the final TIA estimation, and are expected to accumulate for more number of imaging time points.

This study aims to systematically evaluate the impact of mismatch between CT and SPECT images using simulations at the same imaging time point in the following aspects: (i) AC; (ii) VOI definition; and (iii) registration among sequential SPECT/CT images.

2 Materials and Methods

2.1 Phantom Population

A population of nine 4D digital extended cardiac torso (XCAT) phantoms was used [16]. The XCAT phantoms with highly detailed body anatomies and physiological functions were generated using non-uniform rational B-spline (NURBS) and subdivision surfaces based on the segmentation of patient datasets. The phantoms used in this study varied in three anatomical variations with different representative In-111 Zevalin activity distributions (Figure 1), modeling an axial respiratory motion of 20 mm and 5 s period as well as normal cardiac motion. The activity distribution in the background remainder, kidneys, spleen, liver, heart, bone marrow, and blood vessel was uniform except for the lungs since there was no airways activity. The time-varying activity and effective half-life of each organ were based on a set of clinical patient data [17] to
simulate whole-body SPECT scans covering from the thorax to the abdomen at three imaging time points, i.e., 1, 24, and 144 h post-injection. Table 1 shows the measured organ activities for the simulated phantom population from the clinical patient data [17].

### 2.2 Simulation and Quantitative Reconstruction

An analytical projector [18] of a medium energy general-purpose (MEGP) collimator modeling attenuation, scatter, and geometric collimator-detector-response (GCDR) was used for the simulations based on a GE Discovery VH Hawkeye SPECT/CT system with a crystal thickness of 2.54 cm. Considering two photopeaks of In-111, i.e., 171 keV and 245 keV with abundances of 90.2% and 94%, respectively, the attenuation maps with abundance weighted average energy of 210 keV for AC in reconstruction were generated [19]. The scatter was modeled by the effective source scatter estimation (ESSE) method [20] and the GCDR was performed using an analytic formulation proposed by Metz et al. [21].
The simulated SPECT projections were generated in 128 transaxial and 170 axial bins with 4.42 mm voxel size and 128 views over 360° acquisition, using phantoms with a voxel size of 2.21 mm. A system calibration factor of 1.43×10⁻⁴ counts s⁻¹Bq⁻¹ was used to scale the noise-free projections to a clinical SPECT count level of 30 s/view acquisition time, which were then added with Poisson noise to obtain realistic noisy projections. The data were reconstructed using the OS-EM algorithm (8 iterations and 16 subsets, i.e., 128 updates) with attenuation, ESSE and GCSR compensation. The size of the SPECT reconstruction image was 128×128×170, with a voxel size of 4.42 mm. No post-filtering was applied. CT projections were generated by an analytical projector from the respective attenuation maps, which were then modeled with Gaussian noise based on the clinical data [22]. The noisy projections were reconstructed using the in-house filtered back-projection algorithm provided by Johns Hopkins Division of Medical Imaging Physics to obtain the noisy CT images. The reconstruction matrix and voxel size of the CT reconstruction image were the same as those in SPECT.

2.3 Experimental Design

2.3.1 The AC Map Effect

To evaluate the effects caused by using mismatched AC maps, mismatched CT images were employed for AC in SPECT reconstruction while VOIs were mapped out from matched CTs. SPECT and the corresponding CT images at 24 h post-injection were used for assessing the AC errors from SPECT and CT mismatch in the organ activity estimation. Images at 1, 24, and 144 h post-injection were analyzed for the AC errors from SPECT and CT mismatch in the TIA estimation.

2.3.1.1 Organ activity estimation. The CT image was first shifted between 0 to 5 voxels (0-22.1 mm) in anterior-to-posterior (y-), superior-to-inferior (z-) and lateral (x-) directions, respectively as compared to the corresponding SPECT image. The shifts were 0.1 voxel for 0 to 1 voxel, 0.2 voxel for 1 to 2 voxels and 1 voxel for 2 to 5 voxels, respectively. We also evaluated the random mismatch between CT and SPECT images where CT images were shifted randomly with the mean distance of 8.3 ± 3.0 mm (1.87 ± 0.68 voxels) and a maximum range of 22.1 mm (5.01 voxels) as compared to the corresponding SPECT images according to the clinical reference [14] mentioned in the introduction. The noisy projections were reconstructed using the mismatched CT maps for AC (Figure 2). VOIs of the target organs, i.e., kidneys, spleen, liver, and lungs were segmented from the matched CT images semi-automatically using an open-source software application ITK-SNAP [23] to map out the corresponding organs from the SPECT images to measure the organ activities. It works based on a binary decision when a VOI crosses a voxel.

\begin{equation}
A(t) = A_1 e^{-\lambda_1 t} + A_2 e^{-\lambda_2 t} \tag{1}
\end{equation}

where \( A_1 \) and \( \lambda_1 \) were the magnitude and kinetic components for the uptake phase, and \( A_2 \) and \( \lambda_2 \) were the coefficients for the clearance phase. Four parameters \((A_1, A_2, \lambda_1, \text{and } \lambda_2)\) at each voxel were fitted over four imaging time points \((t = 0, 1, 24, \text{and } 144 \text{ h})\), assuming zero activity at \( t = 0 \). Based on our previous study, bi-exponential fitting delivers lower normalized sum of squares for error compared to mono-exponential method [24]. A nonlinear least-squares method was used for curve fitting to obtain the TIA images.

Table 1

| Patient # | Activity (MBq) |
|-----------|----------------|
|           | Heart | Lungs | Liver | Kidneys | Spleen | Marrow | Blood vessels | Whole body |
| 1         | 8.86  | 9.74  | 27.87 | 2.28    | 7.12   | 9.58   | 5.97         | 201.87     |
| 2         | 15.96 | 18.87 | 44.65 | 4.39    | 6.11   | 7.41   | 5.97         | 222.42     |
| 3         | 10.11 | 12.20 | 17.75 | 1.49    | 3.77   | 3.68   | 5.97         | 152.94     |
| 4         | 11.82 | 13.34 | 41.58 | 3.26    | 4.03   | 6.33   | 5.97         | 194.01     |
| 5         | 13.64 | 16.30 | 25.79 | 3.96    | 7.41   | 4.66   | 5.97         | 174.36     |
| 6         | 13.14 | 12.97 | 26.27 | 1.99    | 4.66   | 3.58   | 6.54         | 208.05     |
| 7         | 16.33 | 11.77 | 22.54 | 2.18    | 3.27   | 2.77   | 4.94         | 170.84     |
i.e., area under the curves by integration using MATLAB v.9.6 (The MathWorks Inc., Natick, USA). VOIs segmented from the matched CT images were used to map out the target organs from the TIA images. Figure 3 shows the experimental design for the mismatched AC map effect.

2.3.2 The VOI Delineation Effect

To evaluate the effects of mismatched VOI delineation, mismatched CT images were used to map out target organs, and matched CT maps were employed for AC in SPECT reconstruction. Similar to the previous section, the mismatched effect on VOI delineation was investigated on organ activity and TIA estimation errors.

2.3.2.1 Organ activity estimation. The simulated SPECT projections were reconstructed using the matched CT maps for AC. Then the target organs on SPECT images were mapped out using mismatched VOIs which were obtained from the shifted CT (Figure 4), generated as described in Section 2.3.1.1, to obtain the organ activities.

2.3.2.2 TIA estimation. The simulated noisy projections at three imaging time points were reconstructed with corresponding matched CT maps for AC. Misalignments were not modeled among SPECT images at different time points. Mismatched CT were obtained at each imaging time point as described in Section 2.3.1.2. Then, mismatched VOIs from 24 h post-injection were used to map out target organs from the TIA images directly. Curve fitting and integration were then performed as described in the previous section to obtain the TIA images. Figure 5 shows the experimental design for the mismatched VOI delineation effect.

2.3.3 The Registration Effect

To evaluate the mismatched registration effect, sequential mismatched CTs were registered by non-rigid method to align corresponding SPECT images, with no AC and VOI mismatch errors. The registration effect was investigated by aligning images at different imaging time points for TIA estimation. To model the common misalignments among sequential scans, the local organ deformation was
modeled on the original phantoms for kidneys, spleen, liver, and stomach at 1 and 144 h post-injection since images at 24 h post-injection were used as reference. The organs were translated and rotated randomly within ±5 pixels (11.05 mm) or degrees, when using the phantoms of 24 h post-injection as the reference. The volume change was held within 5% for each organ except the stomach while the stomach varies greatly for different patients, in the range of 4%-62%. The boundaries of the lungs were defined by the deformation of surrounding organs, i.e., liver and heart. Aside from the local organ deformation, a rigid transformation within ±5 pixels or degrees of translation or rotation was also modeled [25,26] in SPECT images at 1 and 144 h post-injection respective to the reference images to simulate the whole body movement between scans.
2.3.3.1 Accumulative Registration Effect. Here we aim to determine the accumulative TIA quantification error when images of one, two or three imaging time points were shifted and registered to images at one single time point (24 h image). Sequential CT images of the nine phantoms were shifted randomly according to the clinical reference [14]. These images were then compared with the corresponding SPECT images at one imaging time point (at 24 h post-injection), two imaging time points (at 1 and 24 h post-injection) and three imaging time points (at 1, 24 and 144 h post-injection), respectively. CT images were then non-rigidly registered to the “reference image”, i.e., CT images at 24 h post-injection, using the rigid plus B-spline framework under the open-source program “Elastix” [27]. The resultant motion vectors were then applied to align the corresponding SPECT images with matched CT AC. The TIA images were derived by curve fitting and integration of the SPECT images over three imaging time points, using the same method described in the previous sections. Matched VOIs were segmented on CT images at 24 h post-injection to map out the target organs from the TIA images.

2.3.3.2 Registration Effect on Mismatched Reference Images. Here we aim to determine TIA quantification error when images at each imaging time point (1, 24, and 144 h) were used as a registration reference for other two imaging time points. Sequential CT images of the nine phantoms were shifted randomly as compared to their corresponding SPECT images on 1, 24 or 144 h post-injection separately. The shifted CT images at three different imaging time points were used as the “reference image” respectively for registrations. The resultant motion fields were then used to align the corresponding SPECT images with matched CT AC. Curve fitting and integration were performed on the “registered” images to obtain the TIA images, and TIAs for target organs were then mapped out using matched VOIs at the reference time point.

Figure 6 shows the experimental design for the mismatched registration effect.

The TIA estimation results from the aforementioned mismatched effects, i.e., AC map effect, VOI delineation effect, and registration effect, obtained from Sections 2.3.1.2, 2.3.2.2 and 2.3.3.1 (mismatch at all three imaging time points) were compared to demonstrate their corresponding error magnitudes.

2.4 Data Analysis

For AC map and VOI delineation effect at one imaging time point, the target organ ($A_{w/mismatch}$) was compared to the reference organ activity ($A_{ref}$), obtained with no SPECT/CT mismatch, in order to calculate the relative errors in organ activity estimation introduced by mismatched SPECT and CT images, i.e., the organ activity relative errors (%OAE):

$$%OAE = \frac{A_{w/mismatch} - A_{ref}}{A_{ref}} \times 100\%$$

Positive values indicate overestimation and negative values indicate underestimation of the organ activity. %OAE was calculated as the average of nine phantoms for all organs.

For the errors in TIA estimation caused by sequential mismatched SPECT and CT images, the relative TIA error (%TIAE) for the target organs ($TIA_{w/mismatch}$) was defined as the following equation, using sequential SPECT and CT images with no SPECT/CT mismatch and no misalignment among different imaging time points for registration as reference ($TIA_{ref}$):

$$%TIAE = \frac{TIA_{w/mismatch} - TIA_{ref}}{TIA_{ref}} \times 100\%$$
\[ \%TIAE = \left( \frac{|TIA_{ac/mismatch} - TIA_{ref}|}{TIA_{ref}} \right) \times 100\% \]  

\( \%TIAE \) was calculated as the average of nine phantoms for all organs. Statistical analysis was performed using the paired t-test with Bonferroni correction by SPSS Version 24 (IBM Corp., Armonk, NY, USA) for %TIAE. A p-value < 0.05 was defined as significantly different.

3 Results

3.1 The AC Map Effect

Figure 7 shows the %OAE for target organs by the mismatched AC map effect for Phantom #2A. The %OAE for the mismatch between SPECT and CT images along x- and z-directions were larger than y-direction for all target...
3.2 The VOI Delineation Effect

Figure 8 shows the %OAE for the mismatched VOI delineation effects for Phantom #2A. The %OAE for VOI effect was larger on small organs, i.e., kidneys and spleen, and organs with lower activity uptake, e.g., lungs. The results show that the mismatch errors were proportional to the magnitude of the CT mismatches. The %OAE results of nine phantoms were consistent (Table 2). The errors are generally <3% for mismatch according to the clinical reference.

3.3 The Mismatched Registration Effect

Figure 9 shows the %TIAE results for different numbers of SPECT and CT mismatch existed in a study with three imaging time points. For sequential imaging sessions, as the number of the mismatch in three imaging time points increases, the calculated error increases. For example, %TIAE for kidneys was 1.99% ± 1.45%, 6.14% ± 3.98%, and 9.33% ± 4.66% respectively for SPECT/CT mismatches existed in one imaging time point (at 24 h post-injection), two imaging time points (at 1 and 24 h post-injection) and three imaging time points (at 1, 24 and 144 h post-injection). Sig-
significant differences were observed among mismatches at one, two, and three imaging time points for all target organs.

Figure 10 shows the results of using CT images at different time points as the “reference image” for registration when applying sequential CT images to register the corresponding SPECT images. There was no statistically significant difference among %TIAE for the CT reference at different time points.

Table 2
Mean %OAE and standard deviation of nine phantoms for the mismatched AC map effect.

|                | kidneys | spleen     | liver      | lungs      |
|----------------|---------|------------|------------|------------|
| x-shift        | -1 voxel| -0.11% ± 0.06% | -4.01% ± 0.35% | 2.73% ± 0.20% | 1.17% ± 0.18% |
|                | -2 voxels| -0.32% ± 0.12% | -8.00% ± 0.71% | 5.46% ± 0.41% | 4.25% ± 0.56% |
|                | -5 voxels| -1.61% ± 1.25% | -20.20% ± 1.60% | 13.43% ± 1.10% | 17.30% ± 2.40% |
| y-shift        | -1 voxel| -0.20% ± 0.07% | -0.37% ± 0.19% | 0.20% ± 0.04% | 0.19% ± 0.10% |
|                | -2 voxels| -0.40% ± 0.13% | -0.83% ± 0.33% | 0.31% ± 0.08% | 1.06% ± 0.49% |
|                | -5 voxels| -0.96% ± 0.25% | -2.28% ± 0.76% | 0.55% ± 0.19% | 4.38% ± 2.29% |
| z-shift        | -1 voxel| 1.54% ± 0.35% | 3.43% ± 0.17% | -0.20% ± 0.15% | 0.41% ± 0.09% |
|                | -2 voxels| 2.30% ± 0.58% | 5.62% ± 0.54% | -0.62% ± 0.30% | 1.67% ± 0.14% |
|                | -5 voxels| 3.03% ± 1.21% | 11.84% ± 1.38% | -3.90% ± 0.84% | 9.86% ± 1.35% |
| Mismatch according to clinical reference | -0.72% ± 0.50% | 2.13% ± 1.34% | -2.58% ± 0.81% | 1.54% ± 0.28% |

Figure 11 compares the %TIAE results for SPECT and CT mismatch for AC, VOI and registration effects. The %TIAE for the AC map effect was the smallest while the VOI delineation effect was the largest for all organs, e.g., 1.13% ± 0.90%, 20.62% ± 8.61% and 9.33% ± 4.66% respectively for mismatched AC, VOI, and registration effects for kidneys. Significant differences were observed among different effects.
4 Discussion

In this work, the errors of mismatches caused by patient movement between CT and SPECT scans at the same time point were evaluated systematically, including the %OAE for AC map and VOI delineation effects at one imaging time point and the %TIAE from sequential images taken at different time points post-injection. All results showed that the mismatches between CT and SPECT images influence activity estimation and further affect the TIA estimation.

Goetze et al. [14] demonstrated the misregistration frequently occurred between SPECT and CT images in myocardial perfusion SPECT/CT, i.e., about two thirds of the clinical cases showed more than one voxel of misregistration. They observed that the mean misregistration was $8.6 \pm 3.8$ mm, with a range of $0–22.4$ mm. Thus, aside from a fixed range of mismatch, given a voxel size of $4.42$ mm in this study the CT images were shifted randomly in three directions with the mean (1.87 voxels, i.e., 8.3 mm) and the maximal range (5.01 voxels, i.e., 22.1 mm) with respect to the SPECT images according to their study. Other studies

![Figure 8. %OAE introduced by shifting CT images from -5 to 5 voxels in the three directions for the mismatched VOI delineation effects.](image)

|                   | kidneys | spleen       | liver      | Lungs    |
|-------------------|---------|--------------|------------|----------|
| **x-shift**       |         |              |            |          |
| −1 voxel          | −1.08% ± 1.24% | −2.22% ± 0.92% | −1.47% ± 0.24% | 0.59% ± 0.31% |
| −2 voxels         | −3.17% ± 1.65% | −10.02% ± 3.00% | −4.86% ± 0.54% | 1.42% ± 0.93% |
| −5 voxels         | −16.37% ± 3.24% | −42.83% ± 7.94% | −19.79% ± 2.01% | 4.82% ± 3.07% |
| **y-shift**       |         |              |            |          |
| −1 voxel          | −4.07% ± 1.16% | −1.81% ± 0.94% | −1.21% ± 0.37% | 4.77% ± 1.41% |
| −2 voxels         | −9.58% ± 1.86% | −6.43% ± 1.80% | −3.88% ± 0.83% | 12.01% ± 3.97% |
| −5 voxels         | −30.97% ± 4.14% | −26.43% ± 3.57% | −14.98% ± 2.07% | 42.81% ± 6.38% |
| **z-shift**       |         |              |            |          |
| −1 voxel          | −1.94% ± 0.45% | −3.65% ± 1.00% | −0.84% ± 0.23% | −1.86% ± 0.47% |
| −2 voxels         | −7.15% ± 1.71% | −13.64% ± 2.69% | −3.11% ± 0.45% | −3.25% ± 1.24% |
| −5 voxels         | −32.46% ± 8.03% | −55.93% ± 6.58% | −13.83% ± 1.06% | −6.00% ± 3.94% |
| **Mismatch according to clinical reference** | −9.14% ± 8.47% | −11.94% ± 10.34% | −4.38% ± 2.88% | 5.97% ± 4.36% |
documented the mismatch distance between SPECT or PET and CT in the clinical situation as well. Nakamoto et al. discovered that more than 10% cases showed the mismatch between PET and CT could be greater than 20 mm [8]. Cohade et al. verified the mismatch could be up to 26.2 mm for the lesions in PET/CT [28]. Another SPECT/CT study demonstrated the maximum mismatch for neck and upper abdomen could be up to about 20 mm with the mean range of 6.8 ± 3.3 mm in abdomen [29]. The five-voxel shifted distance in our study could be the worst-case scenario as given this large shift magnitudes, the mismatch could be found and manually corrected from visual assessment during a clinical study.

The %OAE results revealed the trends and magnitude of errors in activity estimations caused by AC map and VOI delineation mismatch effects. The AC errors of the organs near ribs showed a larger impact compared with the organs far from the ribs. This could be attributed to the larger attenuation coefficient of bone as compared to the soft tissues. For instance, when the CT maps are shifted to the right, the ribs could be moved into the liver region and would cause over attenuation compensation which led to activity overestimation in the liver. On the contrary, if the CT is shifted to the left, the background could move into the liver, leading to the underestimation of the liver activity. Moreover, there are less rib movement in anterior-posterior direc-

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**Accumulative Registration Effect**

![Accumulative Registration Effect](image)

Figure 9. %TIAE for target organs with SPECT/CT mismatch existed in one, two, and three imaging time-points. All results represent the average of nine phantoms and error bars show the standard deviation.

**Registration Effect on Reference Images**

![Registration Effect on Reference Images](image)

Figure 10. %TIAE for target organs when using mismatched CT image at different time points as registration reference. All results represent the average of nine phantoms and error bars show the standard deviation.
tion. Thus, the %OAE is relatively smaller for the AC mismatch effect in this direction.

For the VOI delineation mismatch effect, %OAE was larger for small organs, such as kidneys and spleen, and low uptake organs that are close to the high uptake organs, e.g., the lungs. For example, according to the clinical reference, VOI delineation mismatch causes the spleen %OAE to reach -11.94% ± 10.34%. All target organs except the lungs showed activity underestimation since the adjacent region had lower activities. Overestimation in lungs was expected, due to higher activities in surrounding organs, i.e., heart and liver. These results were in accordance with another study [13].

For the registration effect, we evaluated errors by using mismatched CT images at different imaging time points as the “reference image” and by calculating the numbers of mismatch occurred in sequential SPECT/CT. No significant difference was observed when using mismatched CT images as registration reference at different imaging time point (Figure 10), probably attributed to the fact that CTs at different imaging time points possess similar image intensity while this is different in sequential SPECT images for SPECT-based registration [5]. For a study with three imaging time points, %TIAE is >6% for all target organs when SPECT and CT mismatch accumulates for three SPECT/CT sessions (Figure 9). The VOI delineation errors were generally largest, followed by registration and AC map errors in TIA estimation (Figure 11).

Simulation provides an effect means for evaluation with known truth, i.e., organ activity and TIA in this study. Moreover, different mismatch schemes can be modeled based on the clinical reference [14]. We used a well validated analytical SPECT simulation tool for this study while Monte Carlo-based simulations can provide full physics modeling yet with intensive computational time [30,31]. Considering the purpose of our study is to investigate the SPECT/CT mismatch effects, full MC simulation is not employed. The simulated CTs used in this study were with better image quality as compared to the clinical low dose CT images for SPECT/CT as the attenuation maps from the XCAT phantoms were used [7]. In this study, we generated the CT images with the same voxel size as with SPECT images directly without down sampling. The interpolation error from the real CT images with a larger matrix size could be reduced in this simulation study.

In this study, rigid mismatch is modelled between SPECT and CT, which should be a legitimate assumption for voluntary motion happened between the same time point of SPECT and CT due to the relatively short time gap. However, nonrigid motion deformation may exist from involuntary motion, e.g., respiratory motion, between the same time point of SPECT and CT, causing inaccuracy in dosimetry. For example, liver and lungs mis-registration between the mismatched SPECT/PET and CT due to respiration in Y-90 microsphere treatment planning or dose verification for primary or metastatic cancers in the liver is commonly observed in clinics, posing uncertainties for the dosimetric calculations. Associated results are published in our recent study [32]. However, registration between mismatched SPECT and CT due to respiration could be chal-
lenging due to the substantially inherent motion blur, leading to unclear organ boundaries from the static emission images. Respiratory gating and motion compensation could be a possible solution [33]. Although restraints and careful positioning could reduce patients’ movement, our results indicate that non-negligible mismatches between SPECT and CT images at the same time point could affect the accuracy up to \( \sim 20\% \) especially for small and low uptake organs (Figure 11). Also, the accuracy of organ activity estimation for quantitative SPECT is 90% with appropriate compensation [34]. Thus, alleviating the mismatch between transmission and emission images by registration is necessary to improve the AC map, VOI delineation, and then CT-based registration among serial scans for TRT dosimetry. Evaluation of the registration accuracy between SPECT and CT is usually achieved by visual assessment in the clinic, while more quantitative evaluation can be obtained by physical metrics such as mutual information, dice similarity coefficient (DSC), correlation analysis and kappa statistic, which is beyond the scope of this study. The impact of mismatch with higher resolution SPECT images is expected to be more significant as we observed that the mismatch between PET and CT caused more quantification errors as compared to that between SPECT and CT based on our previous research experience [10].

Lesions are not simulated in this study, as for the maximal tolerated dose regime, absorbed dose for critical organs are more important. Recent studies showed that lesion absorbed dose is also a key index for the success of the therapy [35]. However, SPECT and CT mismatch impact on lesions are expected to be similar or even more severe to small organs, i.e., spleen in this study. Mismatch effects on lesions with different characteristics, e.g., size, activity uptake, and locations, are being covered in another upcoming paper for Y-90 microsphere radioembolization [36]. The simulation set up is based on existing literature [17,26] for further cross comparisons. Thus, this study is based on simulations with In-111 Zevalin which has fallen out of use, and lymph nodes were not assessed as target organs though Zevalin is mainly for non-Hodgkin lymphoma (NHL). Although NHL usually starts in the lymph nodes, it is common to be found in the neck, liver or spleen as well. The conclusion should be applicable to other common clinical applications such as Lu-177 and Y-90 tracers nowadays, and the mismatch impact to lymph node is also expected to be similar to small organs.

5 Conclusion

This work studied the mismatch effects between SPECT and CT scans at the same time point, including the activity estimation errors caused by the AC map and VOI delineation, and TIA estimation errors, caused by AC map, VOI delineation and registration from sequential SPECT/CT scans. Our results showed that activity estimation errors increase as the mismatch magnitude increases. It was observed that the VOI delineation errors were the largest, followed by registration and AC maps errors, especially for the small organs and low uptake organs in this study. Quantitative TIA errors could reach \( \sim 20\% \) for SPECT and CT mismatch modeled according to a clinical reference with the mean mismatch of \( \sim 2 \) voxels considering the worst-case scenario. Registration between SPECT and CT at the same time point is recommended to enhance the diagnostic and dosimetric accuracy.

Abbreviations

SPECT/CT: Single photon emission computed tomography/computed tomography
SPECT: Single photon emission computed tomography
CT: Computed tomography
AC: Attenuation correction
VOI: Volume-of-interest
GCDR: Geometric collimator-detector-response
TIA: Time-integrated activity
OAE: Organ activity relative error
TIAE: relative time-integrated activity error
TRT: Targeted radionuclide therapy
TAC: time-activity curve
XCAT: 4D digital extended cardiac torso
MEGP: Medium energy general purpose
ESSE: Effective source scatter estimation
OS-EM: Ordered subset expectation maximization

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Authors contributions

YQ LYU and G Mok were both the primary writers of the manuscript. YQ LYU was responsible for phantom generation, data collection and analysis. GF CHEN and ZL LU were responsible for data collection. Y CHEN was responsible for providing clinical advice for the study, while G Mok and Y CHEN were responsible for the simulation design, data interpretation and study integration.
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Availability of data and materials

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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