Attenuation correction in 4D-PET using a single-phase attenuation map and rigidity-adaptive deformable registration

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Purpose: Four-dimensional positron emission tomography (4D-PET) imaging is a potential solution to the respiratory motion effect in the thoracic region. Computed tomography (CT)-based attenuation correction (AC) is an essential step toward quantitative imaging for PET. However, due to the temporal difference between 4D-PET and a single attenuation map from CT, typically available in routine clinical scanning, motion artifacts are observed in the attenuation-corrected PET images, leading to errors in tumor shape and uptake. We introduced a practical method to align single-phase CT with all other 4D-PET phases for AC.

Methods: A penalized non-rigid Demons registration between individual 4D-PET frames without AC provides the motion vectors to be used for warping single-phase attenuation map. The non-rigid Demons registration was used to derive deformation vector fields (DVF) between PET matched with the CT phase and other 4D-PET images. While attenuated PET images provide useful data for organ borders such as those of the lung and the liver, tumors cannot be distinguished from the background due to loss of contrast. To preserve the tumor shape in different phases, an ROI-covering tumor was excluded from nonrigid transformation. Instead the mean DVF of the central region of the tumor was assigned to all voxels in the ROI. This process mimics a rigid transformation of the tumor along with a nonrigid transformation of other organs. A 4D-XCAT phantom with spherical lung tumors, with diameters ranging from 10 to 40 mm, was used to evaluate the algorithm. The performance of the proposed hybrid method for attenuation map estimation was compared to (a) the Demons nonrigid registration only and (b) a single attenuation map based on quantitative parameters in individual PET frames.

Results: Motion-related artifacts were significantly reduced in the attenuation-corrected 4D-PET images. When a single attenuation map was used for all individual PET frames, the normalized root-mean-square error (NRMSE) values in tumor region were 49.3% (STD: 8.3%), 50.5% (STD: 9.3%), 51.8% (STD: 10.8%) and 51.5% (STD: 12.1%) for 10-mm, 20-mm, 30-mm, and 40-mm tumors, respectively. These errors were reduced to 11.9% (STD: 2.9%), 13.6% (STD: 3.9%), 13.8% (STD: 4.8%), and 16.7% (STD: 9.3%) by our proposed method for deforming the attenuation map. The relative errors in total lesion glycolysis (TLG) values were -0.25% (STD: 2.87%) and 3.19% (STD: 2.35%) for 30-mm and 40-mm tumors, respectively, in proposed method. The corresponding values for Demons method were 25.22% (STD: 14.79%) and 18.42% (STD: 7.06%). Our proposed hybrid method outperforms the Demons method especially for larger tumors. For tumors smaller than 20 mm, nonrigid transformation could also provide quantitative results.

Conclusion: Although non-AC 4D-PET frames include insignificant anatomical information, they are still useful to estimate the DVFs to align the attenuation map for accurate AC. The proposed hybrid method can recover the AC-related artifacts and provide quantitative AC-PET images. © 2016 American Association of Physicists in Medicine [https://doi.org/10.1002/mp.12063]

Key words: 4D-PET, CT-based attenuation correction, lung tumor, nonrigid registration

1. INTRODUCTION

Patient breathing is a well-known source of degradation in Positron emission tomography (PET) with fluoro-2-deoxy-D-glucose (FDG) integrated with computed tomography (PET/CT). CT images for lung tumors are typically acquired rapidly and with a breath-hold technique.¹ They represent an instantaneous snapshot during the breathing cycle. Respiratory motion in the chest region is inevitable during the slow PET imaging process as opposed to CT imaging. The displacement of organs (primarily lung and

liver) during imaging adversely affects the qualitative and quantitative accuracy of the final reconstructed PET images and subsequent diagnosis and treatment. The extent of respiratory motion varies depending on the different anatomical and physiological characteristics of each patient. The diaphragm typically moves of about 15–20 mm due to respiration² significantly degrading the effective spatial resolution of the thoracic PET images. In a clinical trial conducted on 20 patients, tumor motion in the lower lung lobes was found to be 12 ± 2 mm in the cranial-caudal direction.³

Final reconstructed PET images are degraded in two different ways as a consequence of respiratory motion: (a) Respiration causes lesion smearing, image blurring and quality degradation in PET images, and errors in the quantification of FDG uptake;^{4–8} and (b) The mismatch between PET and CT images results in incorrect AC and induces artifacts in the attenuation-corrected PET images.^{7,9,10}

Early attempts to reduce the mismatch between PET data and CT focused on generating respiratory-correlated PET images by monitoring breathing using either external markers and video cameras^{11–13} or external radioactive sources attached to the abdomen.¹⁴ With these methods, only data within a specific breathing phase correlated with the CT images were reconstructed, excluding all other information,^{12,14} and resulted in noisy PET reconstruction. Respiration-averaged CT (ACT) has been proposed as an alternative to motion-freeze helical CT to compensate for temporal resolution differences between PET and CT images. In a clinical trial, Pan et al. reported a significant reduction in the standard uptake values (SUV) error.¹⁵ Although using ACT can improve 3D PET images, the method may introduce some errors to 4D-PET; in addition, motion blur remains a challenge.¹⁵

The use of respiratory-correlated CT is another popular approach to reduce the mismatch between PET and CT, and relies on the dual gating of both techniques.^{11,16} In gated imaging, the acquisition time is split into several intervals, and the acquired image in each gate is assumed to be motion-freeze. The other advantage of gated 4D-CT imaging is that motion vectors can be estimated from high quality 4D-CT images.^{17–19} When motion vectors are available, motion correction is also possible by incorporating DVFs within the reconstruction algorithms, referred to as 4D reconstruction,²⁰ or by the post reconstruction registration (PRR) method that aligns individual reconstructed PET frames and calculates the average image.^{21,22} However, the use of 4D CT increases the patient dose that cannot be easily justified for all acquisitions.²³ In addition, the differences between the corresponding gated frames in 4D PET and 4D CT were also reported.^{24,25}

More sophisticated motion compensation methods jointly estimate activity distribution (PET image) and the attenuation map from the PET projection data only.²⁶ However, these methods require solving ill-posed problems in conventional PET. Improved results and reduced cross-talk have been reported in terms of joint-likelihood in time of flight PET.^{27–29} An alternative for these methods is the joint estimation of PET image and motion. Synthesizing 4D-CT can be achieved by applying the estimated motion model to a single CT. This can be done by including PET and the attenuation map in a cost function, where the probabilistic model accounts for an unknown motion applied to both activity and attenuation map.^{30–33} These methods typically consider a motion-aware acquisition model that relates projection data to a single motion-free image at different time frames. By optimizing this objective function, image and motion can be jointly estimated to fit into this model in the best way possible. In these methods, regularization is necessary for both image and motion.

Finding the best solution for this kind of optimization problems requires complicated mathematical calculations.

Another practical way to tackle the PET and CT mismatch issue is to estimate motion based on non-AC gated PET images and applying the motion model to move the single CT to match different PET frames.^{22,34} Nonrigid registration algorithms were used to estimate motion from gated PET images without attenuation correction. Therefore, gated CT acquisition is not needed. Dawood et al. used the optical flow method to estimate motion vectors between different PET frames for motion correction.^{21,22} Fayed et al. used the elastic software and B-spline method for nonrigid transformation between non-AC PET frames to estimate motion vectors in 4D-CT and PET-AC.³⁴ In their proposed method, investigators showed a good match between CT images in different phases and warped single CT. The method was evaluated in five patients and a Monte Carlo study using NCAT phantom,³⁴ but the study ignored the tumor's rigid nature and self-attenuation.

We developed a new hybrid method to generate 4D attenuation maps using a single motion-freeze CT for 4D-PET AC, available in clinical routine scans. The proposed method uses non-rigid registration between non-AC PET frames to calculate the DVFs and deform the CT image while preserving the tumor shape in different respiratory phases. We also compared the efficiency of our proposed method with similar methods that ignored tumor rigidity and tumor self-absorption in nonsmall lung cancer. We evaluated the improvement of tumor quantification in lung PET images.

2. MATERIALS AND METHODS

2.A. Four-dimensional XCAT phantom with respiratory motion

Simulation was performed using a 4D XCAT digital phantom, a realistic whole-body model that represents organ geometry and controls organ motion, based on nonuniform rational B-spline surfaces (NURBS).³⁵ A phantom representing a typical 74-kg male patient with normal FDG levels was generated based on human studies of FDG biodistribution.^{36,37} An attenuation phantom was generated based on 511 keV photons. Eight 3D activity phantoms were produced during one respiratory cycle. Each phantom corresponded to 0.625 s considering a normal respiratory cycle of 5 s. The first frame represented full exhalation with the maximum magnitude of respiratory motion (full inhale) occurring between the 4th and 5th frames. The deformation matrices were derived between all individual reconstructed frames (frames 2–8) and the corresponding full exhalation reconstructed frame (i.e., frame 1).

2.B. Tumor size, location, and activity

Lung spherical tumors with diameters ranging from 10 to 40 mm were simulated. Tumors were placed near the base of the lung right above the diaphragm where motion is higher

due to respiration. A lesion to background activity ratio of 4:1 was considered. This activity ratio is based on the reported SUV values of lung and lung tumors. According to several published papers $SUV > 2.5$ is the threshold for malignant lung tumors. Moreover, based on a research study on 38 patients the mean SUV value in lung is 0.6.³⁶ Each phantom was generated in eight different respiratory phases. In our study, tumor motion was up to 12 mm in superior–inferior (SI) direction and 6 mm in anterior–posterior (AP) direction when considering two most extreme phases (phase 1 and phase 4 as full exhalation and full inhalation, respectively). A single coronal slice from the XCAT activity and attenuation phantom with a 40-mm tumor in the lung is illustrated in Fig. 1.

2.C. Generating attenuated PET projections

A fast ray tracing algorithm was used to generate attenuated 3D-PET projections for a digital phantom by calculating the activity ray sum between different pairs of PET detectors.^{38,39} The dimensions and geometry of the PET simulator were based on a real PET scanner composed of 52 rings with 624 4×4 mm detectors per ring. Three-dimensional-PET projections of a time-varying digital phantom were considered as 4D-PET projections. Measured attenuated PET projections, $\mathbf{g}$ acquired by detector pair i , are related to activity distribution, λ , and attenuation distribution, μ , were calculated by the following equation:

$$\bar{g}_i = \sum_j l_{ij} a_i \lambda_j \quad \text{and} \quad a_i = \exp\left(-\sum_j l_{ij} \mu_j\right) \quad (1)$$

where l_{ij} is the weighting factor that represents the contribution of the j th cell to the i th ray sum. In this study, l_{ij} is equal to the fractional length of the j th image cell intercepted by the i th ray. Poisson noise was included to simulate noisy projections. We assumed 0.5 million registered lines of responses (LORs) in each time frame, resulting in a total of 4 million registered events in a total of eight phases, a typical 5-min data set for FDG-PET imaging of the chest region.

FIG. 1. A coronal slice of the XCAT attenuation map (left) and activity distribution (right) in the full exhalation phase with a 40-mm tumor in the lung.

FIG. 2. Reconstructed PET images of the lung with 40mm tumor without AC in two different phases; Left: phase 1 (full exhalation) and right: phase 4 (full inhalation). Tumors are not visible in non-AC PET images due to attenuation-induced loss of contrast.

2.D. PET image reconstruction

The number of measured counts in the projections is Poisson distributed. The most common algorithm for PET image reconstruction is the maximum likelihood expectation maximization (MLEM)^{40,41} or its faster version, the ordered subsets expectation maximization (OSEM).⁴² We used the OSEM algorithm with and without attenuation correction (two iterations and four subsets) to reconstruct the individual PET frames (Fig. 2).

2.E. Deformation vector fields (DVF) calculation

The Demons deformable registration between phase 1 (end-expiration) and all other phases was applied to obtain the DVFs.^{43,44} The optical flow equation is used as a basis of the Demon registration forces. For a given point p in a static image $\mathbf{F}$, the displacement $\mathbf{u}$ required for point p to match the corresponding point in moving image, $\mathbf{M}$, is estimated by:

$$\mathbf{u} = \frac{(m - f) \nabla f}{|\nabla f|^2 + (m - f)^2} \quad (2)$$

In this equation, f and m are intensities in static and moving images, respectively.

A free software for nonrigid image registration with the Demons algorithm was used to obtain initial forward and inverse DVFs.⁴⁵ The limited memory Broyden–Fletcher–Goldfarb–Shanno (LBFGS) optimization method was used with a normal line search.^{46,47} Termination tolerance on DVFs and the energy function value were both 10^{-6} . The maximum number of allowed iterations was 400, and the maximum number of allowed function evaluations was 100 times the amount of the unknowns.

2.F. Rigid transformation of the tumor

While attenuated PET images provide enough useful data for organ borders such as lung and liver, tumors are not distinguishable from the background due to loss of contrast. To

FIG. 3. The process of defining ROI 1 and ROI 2 for excluding lung tumors from nonrigid transformation; from left to right: CT image, tumor mask, and its blurred version for defining ROIs. [Color figure can be viewed at wileyonlinelibrary.com]

FIG. 4. Calculated DVFs using demons registration; from left to right in the x, y, and z directions with a spherical ROI with a constant value for rigid transformation of the tumor.

FIG. 5. Different attenuation maps used in this study; the reference attenuation map in phase 4 (left), derived attenuation maps from phase 1 used for AC-PET in phase 4 (middle column) and difference between the reference phase 4 map and other estimated attenuation maps (right column).

preserve the tumor shape in different phases, an ROI-covering tumor and neighboring voxels (ROI 1) was considered from the CT image. The voxels in the PET image, corresponding to those in the ROI 1, were excluded from nonrigid transformation. A single DVF value was instead assigned to all the voxels in the ROI 1. This single DVF value was calculated as the mean DVF in a smaller ROI covering only a few central voxels (ROI 2). To define ROI 1 and ROI 2, the extracted tumor mask was first blurred from the CT image using a 3D Gaussian filter with a standard deviation of 5 voxels. The voxels within thresholds of 2.5% and 98% of the maximum blurred tumor mask were considered for ROI 1 and ROI 2, respectively (Fig. 3). The x, y, and z components of the final DVFs calculated by our proposed hybrid method are shown in Fig. 4.

2.G. Evaluation parameters

The root-mean-square error (RMSE) is a frequently used measure of the differences between various sets of images. The normalized root-mean-square error (NRMSE) in the tumor region was used to evaluate the performance of different methods as compared to the perfect AC PET images. In perfect AC PET, every frame of 4D-PET was compensated for attenuation using its corresponding attenuation map. The NRMSE is often expressed as a percentage. A fixed $48 \times 48 \times 60 \text{ mm}^3$ ROI was used for all tumor sizes and the size was initially determined from the largest tumor for the NRMSE calculation. In general, the ROI was made large enough to encompass the largest 40-mm tumor in all eight phases.

FIG. 6. Effect of tumor size on different AC methods in reconstructed PET images using: (a) CT1, (b) Nonrigid transformed CT1, (c) Our proposed method, (d) Reference image. The phase 4 images with the highest mismatch and the most severe artifacts are shown.

FIG. 7. Difference between the reference phase 4 AC-PET frame and AC-PET images in phase 4 using different methods; from top to bottom: using CT1 for AC, using the Demons nonrigid transformed CT1 and using our proposed hybrid method.

$$RMSE = \sqrt{\frac{\sum_{i=1}^n (X_{obs,i} - X_{ref,i})^2}{n}} \quad (3)$$

$$NRMSE = \frac{RMSE}{\bar{X}_{ref}} \quad (4)$$

where $X_{obs,i}$ and $X_{ref,i}$ are the pixel values in the test and reference images within the ROI respectively, $\bar{X}_{ref}$ is the mean value in the reference image and n is the number of voxels in the ROI.

Dice coefficient (DC), a spatial overlap index, was used to quantitatively express the degree to which the tumor in different methods matches with the tumor in the reference image.⁴⁸ To calculate DC, tumors were segmented in both reference and test images, and the binary masks of the tumors were generated by assigning 1 to the tumor volume and 0

TABLE 1. Mean and standard deviation of NRMSE between the reference image and different AC methods in eight different phases.

Tumor size	AC-CT1	AC-demons	AC-hybrid
10 mm	49.3% (STD: 8.3%)	12.0% (STD: 2.6%)	11.9% (STD: 2.9%)
20 mm	50.5% (STD: 9.3%)	15.7% (STD: 4.1%)	13.6% (STD: 3.9%)
30 mm	51.8% (STD: 10.8%)	20.2% (STD: 7.4%)	13.8% (STD: 4.8%)
40 mm	51.5% (STD: 12.1%)	20.4% (STD: 11.4%)	16.7% (STD: 9.3%)

elsewhere. The value of DC ranges from 0, indicating no spatial overlap between the two sets of binary masks, to 1 in the case of complete overlap. For the two tumor masks, A and B, DC is calculated as:

$$DC(A, B) = \frac{2|A \cap B|}{|A| + |B|} \quad (5)$$

Tumor delineation for generating binary masks was performed based on a background-subtraction method that cancels out the additive effect of background on tumor activity. The equation has been reported as:^{49,50}

$$T = k \times (M - Bkg) + Bkg \quad (6)$$

In this equation, M is the region of interest (ROI) maximum, Bkg is the mean value in the background ROI, and k represents the required background-corrected relative threshold. For homogeneous structures and tumors more than twice as large as the reconstructed image spatial resolution, a fixed value of $k = 0.39$ (derived from calibration measurements in the phantoms) leads to the accurate delineation of the actual boundary; this is independent of the lesion's target to background contrast and shape.

Total lesion glycolysis (TLG) is a well-established quantitative parameter in PET-CT imaging for tumor delineation, evaluating tumor response to treatment and as a

reliable predictor of prognosis in soft tissue tumors.^{51–53} In this study, TLG was calculated for 30-mm and 40-mm tumors as a quantitative measure of different AC methods performance. TLG is calculated as the sum of the volume of voxels with specific uptake value (SUV) exceeding a certain threshold value in a tumor multiplied by mean SUV in that volume. The relative error in TLG values was plotted for different AC methods in different respiratory phases compared to TLG values in the perfect AC PET images. For the margin threshold, 40% of the maximum SUV (SUV_{max}) was used.

2.H. PRR of AC-PET frames

For every AC method, the Demons nonrigid registration was used to align all individual AC-PET frames to frame 1. The sum of all aligned frames was considered as a PRR volume. The purpose of this part was to evaluate how PRR volumes are affected by different AC methods. The Demons

code was used with the same parameters mentioned in 2–5. In contrast to section 2–5, here the Demons method aligns the AC-PET frames and generates a single PRR volume for each method.

3. RESULTS

3.A. Individual PET frames

Figure 5 compares the different attenuation maps used in this study, including phase 1 and phase 4 derived by deforming phase 1, along with reference phase 4 for 40-mm tumor in the lung. Phase 4 was chosen for display as the most extreme with severe, expected, AC-induced artifacts. As expected, the phase 1 attenuation map without any deformation was significantly different from the phase 4 map. Therefore, using the phase 1 attenuation map to correct the phase four PET images caused severe artifacts especially near the diaphragm and the tumor [Fig 6(a)]. The deformed phase 1

FIG. 8. Relative errors (NRMSE) between the reference frames and the different AC methods including a single CT (CT1), warped CT images using the Demons deformable registration and the proposed method for all phases and different tumor sizes. [Color figure can be viewed at wileyonlinelibrary.com]

FIG. 9. Relative errors on TLG values for different AC methods including a single CT (CT1), warped CT images using the Demons deformable registration, and the proposed method for all phases and different tumor sizes. [Color figure can be viewed at wileyonlinelibrary.com]

attenuation map using the Demons deformable registration has a near-perfect match in the diaphragm region but an artificially extended tumor. Since the 40-mm tumor has significant self-attenuation, using a Demons-derived attenuation map resulted in over-correction in the tumor region [Fig 6(b)]. This artifact can severely degrade tumor delineation and quantification. The proposed hybrid method for deforming the phase 1 attenuation map significantly reduced the bias in the tumor region, in addition to the diaphragm and lung–liver border [Fig 6(c)]. Figure 6 shows a coronal slice of the PET volumes in phase 4 after AC using three different attenuation maps and for four different tumor sizes with a tumor to background contrast of 4 in input phantoms. When the phase 1 attenuation map was used for AC, distortion was observed in the AC-PET images for large tumors. A 10-mm tumor could not be detected when the phase 1 attenuation map was used for AC of the PET image in phase 4. Besides visible artifacts, significant quantitative errors were observed for all tumor sizes when a single attenuation map was used for AC. Figure 7 displays the outcome of using three different attenuation maps for attenuation correction compared with the reference image by subtracting each AC-PET image from the reference AC-PET image at phase 4. Severe AC-induced artifacts were visible when the phase 1 attenuation map was used for AC. The Demons-derived attenuation map significantly reduced the artifacts except near the tumor. Improved results were observed by the deformed attenuation map using the proposed method for AC.

The mean (STD) of NRMSE values between the reference image and different AC methods are listed in Table 1. For all different tumor sizes, our proposed method for deforming the attenuation map results in the least amount of error compared to the other two methods. The error was higher in middle phases (4 and 5) where the mismatch was larger (Fig. 8). The difference between the Demons method and our proposed method for deforming the attenuation map was especially pronounced for larger tumors in middle phases. The Demons and our proposed method displayed a similar performance for 10-mm tumors (Fig. 8). This finding was expected since small tumors do not greatly contribute to total attenuation.

In terms of TLG values, the proposed method resulted in the lowest relative errors compared to two other AC methods (Fig. 9). The highest error was observed in the Demons method, especially in middle phases, where the tumor volume has been expanded artificially. The relative error in TLG values were -0.25% (STD: 2.87%) and 3.19% (STD: 2.35%) for 30-mm and 40-mm tumors, respectively, in proposed method. The corresponding values for Demons method were 25.22% (STD: 14.79%) and 18.42% (STD: 7.06%). DC values are shown as an overlap index comparing different AC methods to the reference images (Fig. 10). Among the different methods, our proposed hybrid method yielded higher values indicating a better match between tumor shape and position. When the phase 1 attenuation map was used for AC, the DC values were 0.34 (STD: 0.18), 0.47 (STD: 0.18), 0.62 (STD: 0.16) along all the phases for 20 mm, 30 mm, and 40 mm, respectively. The corresponding values increased

to 0.69 (STD: 0.10), 0.77 (STD: 0.08), and 0.85 (STD: 0.06) using Demons method and further increased to 0.72 (STD: 0.09), 0.82 (STD: 0.08), and 0.87 (STD: 0.04) using proposed method.

3.B. PRR of AC-PET frames

The Demons deformable registration was used to align all individual gated AC-PET images. Phase 1, which has the true corresponding attenuation map, was considered as the fixed image, and all other frames were aligned to

FIG. 10. DC values between the tumor mask in the reference frames and the tumor mask in different AC methods including using a single CT (CT1), warped CT images using the Demons deformable registration and the proposed hybrid method for all phases and different tumor sizes. [Color figure can be viewed at wileyonlinelibrary.com]

FIG. 11. (a) nongated 3D-PET corrected for attenuation using CT1 and three-dimensional-PET images after PRR to align all 4D-PET frames to phase 1 after AC using different methods. (b) CT1, (c) Nonrigid transformed CT1, (d) Our proposed method, (e) Reference image.

FIG. 12. Image difference between the reference PRR volume in phase 1 and different methods after PRR calculated by subtraction; from top to bottom: using CT1 for AC, using Demons nonrigid transformed CT1 and our proposed method.

it. Figure 11 displays a coronal slice of the nongated 3D-PET and PRR volumes for different AC methods and different tumor sizes generated by summing all deformed individual AC-PET images. As opposed to individual frames, nongated 3D-PET image and the PRR volumes are less influenced by AC-induced artifacts; however, hot spot artifacts were visible when a single attenuation map was used for AC [Figs. 11(a) and 11(b)]. Both the Demons and our proposed method can successfully generate PRR volumes comparable to the reference PRR volume. A slightly reduced bias was observed in the tumor region using the proposed method (Fig. 12). A quantitative comparison between different methods is illustrated in Fig. 13. Although both the Demons and the proposed method outperformed using a single attenuation map for AC, the difference was much less in the PRR volumes

FIG. 13. Relative errors (NRMSE) between the reference PRR volume in phase 1 and other PRR volumes from individual frames after AC using different methods including CT1, warped CT images using the Demons deformable registration and the proposed method. [Color figure can be viewed at wileyonlinelibrary.com]

as compared to individual frames (Fig. 8). DC values after PRR are reported for different AC methods (Table 2). Again, the maximum overlap between tumors in the reference image and tumors in different methods was observed in the hybrid method.

4. DISCUSSION

We introduced and evaluated a new algorithm to derive 4D attenuation maps from a single phase CT for AC in gated PET. The proposed method considered a deformable registration for organs with visible borders in non-AC 4D-PET frames. A rigid displacement was considered for lung tumors. The idea is that lung tumors with mechanical rigidity greater than the surrounding lung tissue would show no significant

TABLE 2. DCs between the tumor mask in the reference frames and the tumor mask in different AC methods after PRR.

Tumor size	AC-CT1	AC-Demons	AC-Hybrid
20 mm	0.591	0.847	0.881
30 mm	0.912	0.933	0.939
40 mm	0.920	0.934	0.958

changes in shape during respiration, in agreement with a previous clinical study.⁵⁴ The proposed method requires two non-AC PET frames along with the tumor mask extracted from a single phase CT image to exclude it from nonrigid transformation. A single vector was instead assigned to all tumor voxels for rigid tumor displacement. The assumption made in the current study was that the lung tumor behaves in a fully rigid manner. This assumption is in accordance with a previous study, where the analysis on 4D-CT of 30 early stage nonsmall cell lung cancer patients showed that deformation of lung tumors during normal respiration was minimal.⁵⁴ In more general case, the level of rigidity depends on the tumor, so that each voxel will have its own DVF. In this case we may need a more sophisticated approach to apply constraints on deformable registration, to account for tumor rigidity in tumor region from CT side data. To consider for blending DVF edges in tumor region to the background we examined the effect of blurring DVF borders into our final AC-PET frames. However, for lung tumor quantification, we did not observe any change because of the relatively uniform attenuation coefficients of the lung surrounding the tumor (Fig. 14).

When the proposed method was used for AC, we observed a significant improvement in image quality for individual 4D-PET frames as compared with the two other methods. The inefficiency of nonrigid transformation using the Demons algorithm in preserving the tumor shape was also addressed. The Demons method tends to change the tumor shape depending on the respiratory phase. In this study, we used the end-exhalation phase as reference, therefore all other phases resulted in tumor extension mostly in the axial direction where the highest lung deformation takes place. This occurs because of a lack of contrast in the internal lung structures, including tumors, in non-AC PET frames.

FIG. 14. The minimal effect of smoothing DVFs borders on final AC-PET frames; AC-PET frames using attenuation maps derived from the proposed combined method with and without smoothing DVF borders and the line profile along the tumor. [Color figure can be viewed at wileyonlinelibrary.com]

We demonstrated that while individual PET frames are highly sensitive to the selection of a correct attenuation map, the PRR volumes are less influenced by this selection. To construct the PRR volumes, all the PET frames were aligned with those that had a true corresponding attenuation map. Since the fixed image was not affected by AC, the Demons can efficiently align the other frames to it. However, if we consider other PET frames that are highly influenced by AC-induced errors we should also expect incorrect PRR volumes.

Fast helical CT provides high quality imaging free of respiration-induced blurring and artifacts. This method can be successfully applied to all 4D PET images for AC. All 4D-PET frames can be later aligned to the same phase as the CT image using the Demons registration and the PRR method. Therefore, we can have motion-freeze PET imaging along with breath-hold CT. Since both PET and CT are motion-free and in the same temporal phase, their fusion provides high quality metabolic-anatomical data for effective diagnosis and quantification. Controversial results have been reported on the use of breath-hold versus free-breathing CT for better PET quantification.^{15,55} However, the ideal situation is having motion-freeze PET images using all LORs along with motion-free CT images.

5. CONCLUSIONS

We demonstrated the promising use of non-AC-FDG-PET frames for the derivation of attenuation maps in different phases from a single-phase attenuation map. We showed that the deformable Demons registration alone does not provide a good solution for lung tumor displacement because of a lack of contrast in non-AC-PET lung images. Improved performance of the proposed method was observed as compared with two other methods on simulated datasets. This method is practical and easy to implement, making it an attractive alternative to standard 4D-CT imaging characterized by excessive patient exposure and complicated imaging protocol and processing. A comparison between the AC-PET frames with deformed 4D attenuation map series and AC-PET with the original 4D attenuation map series demonstrated the efficiency of our proposed approach.

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CONFLICT OF INTEREST

None.

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