The impact of audio-visual biofeedback on 4D PET images: Results of a phantom study

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Purpose: Irregular breathing causes motion blurring artifacts in 4D PET images. Audiovisual (AV) biofeedback has been demonstrated to improve breathing regularity. To investigate the hypothesis that, compared with free breathing, motion blurring artifacts are reduced with AV biofeedback, the authors performed the first experimental phantom-based quantification of the impact of AV biofeedback on 4D PET image quality.

Methods: The authors acquired 4D PET dynamic phantom images with AV biofeedback and free breathing by moving a phantom programmed with AV biofeedback trained and free breathing respiratory traces of ten healthy subjects. The authors also acquired stationary phantom images for reference. The phantom was cylindrical with six hollow sphere targets (10, 13, 17, 22, 28, and 37 mm in diameter). The authors quantified motion blurring using the target diameter, Dice coefficient and recovery coefficient (RC) metrics to estimate the effect of motion.

Results: The average increase in target diameter for AV biofeedback was 0.6 ± 1.6 mm ($4.7 \pm 13\%$), which was significantly ($p < 0.001$) smaller than for free breathing 1.3 ± 2.2 mm ($9.1 \pm 19\%$). The average Dice coefficient for AV biofeedback was 0.90 ± 0.07 , which was significantly ($p < 0.001$) larger than for free breathing (0.88 ± 0.10). The RCs for AV biofeedback were consistently higher than those for free breathing and comparable to those for stationary targets. However, for RCs the impact of target sizes was more dominant than that of motion. In addition, the authors observed large variations in the results with respect to target sizes, subject traces and respiratory bins due to partial volume effects and respiratory motion irregularity.

Conclusions: The results indicate that AV biofeedback can significantly reduce motion blurring artifacts and may facilitate improved identification and localization of lung tumors in 4D PET images. The results justify proceeding with clinical studies to quantify the impact of AV biofeedback on 4D PET image quality and tumor detectability. © 2012 American Association of Physicists in Medicine. [DOI: 10.1118/1.3679012]

Key words: audiovisual biofeedback, 4D PET, motion blurring artifacts, phantom, lung cancer

I. INTRODUCTION

The use of PET images has become increasingly popular and important for radiotherapy planning tasks such as gross tumor volume (GTV) delineation and dose painting.^{1–5} PET images are usually acquired for 3–5 min per bed position. The images are time-averaged over many respiratory cycles causing motion blurring artifacts, particularly in thoracic and abdominal images. The motion blurring artifacts are dependent on both the displacement and pattern of respiratory motion. From a phantom study, the recovery coefficient (RC) of a 4 ml

sphere decreases from 83% in a stationary mode to 78% and 58% with a 1 and 2 cm motion range, respectively.⁶ Thus, the motion blurring artifacts result in loss of contrast.^{7,8} In addition, surrounding normal tissues (e.g., lung) can be unnecessarily irradiated due to the overestimation of tumor volumes induced by the blurring artifacts. Therefore, respiratory motion management techniques need to be implemented to increase the accuracy of tumor volume delineation.^{9–14}

There are four broad classes to reconstruct PET images to reduce artifacts in the presence of motion:¹⁵ (1) hardware-based gating,^{7,9–11,13,16–19} (2) software-based gating,^{20–27} (3)

incorporated-motion-model (IMM) based algorithms,^{28–30} and (4) joint estimation.^{31–34}

The hardware-based gating is based on the assumption that external respiratory motion is a surrogate for motion of internal structures. Investigators have used different respiration tracking systems such as pressure sensors,¹⁷ spirometers,¹⁷ temperature sensors,¹¹ and optical tracking^{7,9,10} to monitor the respiratory motion and simultaneously generate a trigger signal at a user-predefined phase^{7,10,11,16} or displacement.^{19,35} Gated PET or four dimensional (4D) PET retrospectively correlates a respiratory signal with the PET data acquisition to allow reconstruction at different phases or displacement of the respiratory cycle. The drawbacks of gated PET are (1) the reduction in the signal-to-noise ratio (SNR) due to the short acquisition time per gated bin, (2) possible weak correlation between internal tumor motion and external respiratory motion (dependence on the size and location of the tumor) (Refs. 36 and 37) (3) inaccurate trigger positions due to irregular respiratory motion.^{7,9,16} A way to improve the low SNR in gated PET images is by registering (rigid and/or deformable registration) and then combining the gated bins after the image reconstruction process.^{38,39} The disadvantage of this approach is that new uncertainties may be caused due to the manipulation of the data during the registration process. Another hardware-based approach is the deep-inspiration-breath-hold (DIBH) technique to collect PET data in one single time bin by coaching the patient to hold the breath at predefined breathing displacement.¹³ However, DIBH-PET does not provide any information on tumor motion and may not be tolerable for patients who have compromised respiratory function.

The software-based gating is not a clinical protocol, but has the potential to extract accurate motion information from PET data itself. Therefore, it is called data-driven gating. The purpose of this approach is to perform gating with the motion information of internal structures extracted from PET data itself without using external hardware such as a pressure belt or an optical camera. The data-driven gating algorithms are categorized into sinogram-based and image-based algorithms. Both sinogram and images with a short time frame have motion information due to the geometrical fluctuation of coincidence events emitted from a tumor with respiratory motion. The sinogram-based method is efficient in processing time,^{20,22–26} but only estimates motion in the superior–inferior direction. The image-based method can track tumor motion in three dimensional directions, although the reconstruction is time-consuming.^{21,27} The concept of data-driven gating enables the possibility of using PET for real-time tumor motion tracking.

IMM-based methods employ a motion model coupled to the image reconstruction process.^{28–30} The advantages of these approaches are (1) images are generated in a single optimization process with regard to both acquired data and motion information and (2) all acquired data, instead of data from only one time bin, are used to reconstruct the images. Thus, the IMM-based methods are more-time consuming than standard reconstruction methods. Qiao *et al.* and Li *et al.* proposed a motion model constructed by performing nonrigid registration on 4D computed tomography (CT)

data.^{28,29} Similarly, Reyes *et al.* presented a respiratory motion model built from magnetic resonance imaging (MRI) data.³⁰ The main drawback of constructing motion models based on other imaging modalities is the mismatch of respiratory motion between PET and other modalities.

The joint estimation method is simultaneous estimation of motion parameters and images. Cao *et al.* Gilland *et al.*, Gravier *et al.* proposed a maximum-*a posteriori* (MAP) framework in which motion information is incorporated through a temporal prior/penalty.^{31–33} The parameter associated with the prior/penalty term often needs to be selected with careful consideration since it plays an important role in the reconstructed images. Jacobson and Fessler incorporated parameters to describe the effects of motion into the statistical model of the projections, whereby joint maximum likelihood estimation of image and motion parameters is carried out.³⁴

In the four classes above, the hardware-based gating is only a clinical protocol, and the other methods are yet to be implemented clinically. As mentioned above, irregular respiratory motion prevents inaccurate trigger positions in the hardware-based gating. Nehmeh *et al.* found that irregular breathing (motion amplitude and period) deteriorates the accuracy of 4D PET.^{7,9,10,16} Also, they have mentioned that only bin #1 is reproducible because of the irregularity of breathing^{7,9} and the effect of gating should be dependent on the size and site of lesion and the amplitude and period of motion.⁷ Thus, they used verbal breathing instructions to reduce irregularities of breathing during the scan and they suggested that visual prompting might improve the regularity of breathing amplitude.¹⁶ However, the previous articles have not analyzed quantitatively the correlation between breathing regularity and motion blurring artifacts. Several independent studies have shown that audiovisual (AV) breathing training methods have demonstrated an ability to improve respiratory reproducibility.^{14,40–43}

To summarize, irregular respiration causes motion blurring artifacts in 4D PET images and AV biofeedback has been demonstrated to improve respiratory regularity. Therefore, the purpose of this work was to investigate the hypothesis that compared with free breathing, motion blurring artifacts are reduced with AV biofeedback. To achieve this we performed the first experimental phantom-based quantification of the impact of AV biofeedback on 4D PET image quality.

II. METHODS

We designed a phantom study to experimentally test our hypothesis. A schematic of the design is shown in Fig. 1. In PET images, there are large uncertainties caused by the combination of several parameters, such as spatial resolution, statistical errors, respiratory motion, tumor size and shape, etc.^{8,44} These parameters may vary from patient to patient and from one scan to the next in the same patient, and thus it is complicated to distinguish the impact of each parameter separately in 4D PET images. Therefore, due to the uncertainties of PET images, it is difficult to conclude that the improvement of respiratory regularity guarantees the reduction of motion blurring artifacts even though we could expect the

FIG. 1. The flowchart for phantom experiments: the respiratory motion traces of ten healthy subjects were reproduced by the 4D phantom during PET scans. The amount of motion blurring (MB) artifacts in 4D PET images with motion (AV biofeedback or free breathing) was quantified with respect to images without motion (stationary).

reduction of motion blurring artifacts through the improvement of respiratory regularity. Moreover, for scientific investigation, it is necessary to quantify the impact of AV biofeedback on 4D PET images. The advantage of a phantom study compared to a clinical study is that “ground truth” is known, which accurate quantitative analysis possible. Evaluation and clinical validation of algorithms developed to improve image quality is inherently difficult and sometimes unconvincing, particularly when applied to clinical data in the absence of ground truth.

II.A. Respiratory motion traces for our phantom study

AV biofeedback is performed by guiding the patient to follow a waveform with period and displacement determined by averaging the patient’s own free breathing respiratory cycles. Currently, AV biofeedback is implemented using the Real-time Position Management (RPM) system (Varian Medical Systems, Palo Alto, CA) to obtain breathing data, i.e., abdominal displacement. The AV biofeedback system is in clinical use for radiotherapy imaging and treatment sessions at two institutions. In a previous study by Venkat *et al.* from which the data for the current study was taken,¹⁴ compared with free breathing, AV biofeedback reduced cycle-to-cycle variations in displacement by greater than 50% and variations in period by over 70%. We used the respiratory motion traces of ten healthy subjects acquired in the Venkat study¹⁴ to reproduce AV biofeedback and free breathing traces with a programmable motion phantom (4D phantom). The AV biofeedback traces consisted of the recorded respiratory motion with AV biofeedback guidance. Corresponding to the current standard of care for PET image acquisition, the free breathing traces

consisted of the recorded respiratory motion under normal conditions without any breathing instructions.

Based on a review of the respiratory motion literature, the AAPM Task Group 76 report states that there are no general patterns of respiratory behavior that can be assumed for a particular patient prior to observation and treatment (Ref. 12, page 13).¹² The many individual characteristics and the many motion variations associated with tumor location and pathology lead to distinct individual patterns in displacement, direction and phase of tumor motion. Therefore, the breathing traces of healthy subjects may be comparable to those of lung cancer patients. In order to avoid the bias that the ability of healthy subjects to respond to AV guidance might be more superior to lung cancer patients, we compared the breathing traces of healthy subjects to those of George’s data (24 lung cancer patients).⁴⁰ For quantification of breathing irregularity, a method is to compute the standard deviation (SD) of displacement of each bin. This method is (1) simple and (2) well-matched to the principle of phase-based gating, which collects all the events according to phase in cycle-to-cycle. In other words, the SD of each bin is computed with all points corresponding to the bin. The SDs are 2.7 ± 0.9 mm and 3.1 ± 1.1 mm for the healthy subjects and patients, respectively, demonstrating similar averages and variations of respiratory motion between data from lung cancer patients and that of the subjects used in this study. The variation of displacement is patient-specific and subject-specific and both mean and SD of displacement variation have similar quantitative values. Note that respiratory cycles were distinguished by phase information in both data sets.

II.B. 4D and stationary PET data acquisition

Using a 4D phantom, we acquired 4D PET images of a cylindrical phantom for both AV biofeedback and free breathing motion traces. We also obtained stationary PET images as the reference for quantifying motion blurring artifacts. In all the three kinds of scans, the initial spatial position of the phantom was maintained to prevent other errors caused by PET system limitations, such as detector size and spacing.⁴⁵ The parameters for reconstruction were also maintained for consistency.

II.B.1. Cylindrical Phantom

The cylindrical phantom consisted of six hollow spheres (10, 13, 17, 22, 28, 37 mm in diameter and 0.5, 1.2, 2.6, 5.6, 11.5, 26.5 ml in volume) of a NEMA ICE body phantom and a cylinder (20.8 cm in inside diameter, 17.5 cm in inside height and 3100 ml in volume) of a Hoffman 3D brain phantom (Fig. 1). A cylinder of a NEMA ICE body phantom was not used as it exceeded the weight limit of the 3D motion stage of the 4D phantom. We positioned the six hollow spheres symmetrically in the cylinder. We injected ¹⁸F-FDG into the six hollow spheres as targets and the cylinder as background. The standard background activity concentration (5.18 kBq/ml) was determined with a typical injection dose (370 MBq) into a 70 kg patient. The target to background ratio was 8:1.⁸

II.B.2. 4D Phantom

We used the 4D phantom to reproduce tumor motion and abdominal displacement due to respiration for simulating clinical 4D PET scans. The 4D phantom was a programmable motion platform consisting of a 3D motion stage and a 1D motion stage (Fig. 1) that simulate tumor motion and abdominal displacement, respectively.⁴⁶ We placed the cylindrical phantom on the 3D motion stage and scanned it. We placed an infrared reflective marker box on the 1D motion stage and measured the vertical motion of the marker box by the RPM system throughout a scan. Here, we assumed a linear one-to-one correlation between the internal tumor motion (3D motion stage) and external respiratory signals (1D motion stage) and used the same respiratory traces for both the 3D and 1D motion stages to reproduce AV biofeedback and free breathing motion. We based this assumption on the combined optical monitoring and fluoroscopic analysis of the abdominal wall and diaphragm motion by Vedam *et al.*³⁷ They found a correlation of 0.82–0.95 in 60 measurements from five patients. This correlation can be used to predict diaphragm motion, based on the respiration signal to within 0.1 cm. Diaphragm motion is dominant in the superior–inferior (SI) direction and lung motion is strongly dependent on the diaphragm motion, so the assumptions, (1) a linear correlation between target motion and external motion and (2) SI direction only for tumor motion, are reasonable in this phantom study. In general, abdominal organ motion is predominantly in the SI direction, with no more than a 2-mm displacement in the AP and lateral directions.¹² Based on the general characteristics

of lung tumor motion, we made the simplification in this study of only SI motion. For this reason, we moved the 3D motion stage in the SI direction only. The SI phantom motion was synchronized with the 1D motion stage, whose motion was only in the anterior–posterior direction. We placed the 4D phantom outside the scanner, rather than on the scanner bed (Fig. 1), as it could not be positioned in the scanner bore due to its height.

II.B.3. 4D PET Acquisition

We obtained 4D PET scans with AV biofeedback and free breathing by acquiring a list-mode file in synchronization with breathing cycles from the RPM system using a PET/CT scanner (Discovery ST 16, GE Medical Systems, Waukesha, WI) in 2D scan mode.⁴⁷ According to the scanner specifications, the PET system has a transaxial field of view (FOV) of 70 cm and an axial FOV of 15.7 cm. The slice thickness (axial sampling interval) is 3.27 mm. The transaxial full width at half maximum (FWHM) is 6.2 mm at 1 cm and 6.8 mm at 10 cm, and the axial FWHM is 4.8 mm at 1 cm and 5.9 mm at 10 cm from the center of FOV. For each subject trace, we performed three scans: (1) 4D PET with AV biofeedback, (2) 4D PET with free breathing, and (3) stationary PET sequentially in the same order and consistently. The acquisition time for the first scan was 20 min. For clinical scans, a 3 min PET scan is usual for tumor detection, and a 5 min PET scan is usual for treatment plan. For this phantom study, however, 5 min was not enough based on the standard background activity concentration (5.18 kBq/ml) determined with a typical injection dose (370 MBq) into a 70 kg patient. Instead of increasing activities, the scan time was increased to 20 min as used by Park *et al.*⁸ The acquisition time for the first scan increased for the other two scans in order to maintain approximately the same total counts (true + random + scatter). In other words, the increased scan time was calculated based on exponential decaying and half life of ¹⁸F-FDG considering the initial amount of injection and waiting time between the scans. Volume imaging protocol (ViP) was used for respiratory gating. The RPM system sent trigger signals into the scanner at peak-inhalation. Data were retrospectively collected into one of five bins (phases) of the breathing cycles which were determined by the trigger signals. Park *et al.* concluded that the 5 bin gating method gives the best temporal resolution with acceptable image noise.⁸ The same time duration was maintained for every bin of each cycle to ensure near uniform counts in each bin. It is reasonable to assume that each bin has approximately the same amount of coincidence events in that each cycle of respiratory traces is equally divided by the number of bins (phase-based gating). These procedures were equivalent to those described by Nehmeh *et al.*⁷

II.B.4. Stationary PET Acquisition

We acquired the stationary images as ground truth of the true target image. As the images had the smallest statistical errors and no motion blurring artifacts with the given scan time and activity concentration, we used them to find

optimal percentage thresholds for target segmentation. We also used the stationary images as a reference to quantify the motion blurring artifacts of 4D PET images with AV biofeedback and free breathing.

II.B.5. Reconstruction

We reconstructed the PET images with the protocol that was used clinically in our radiation oncology department. The ordered subset expectation maximization (OSEM) algorithm (21 subsets, 2 iterations, and 5.14 mm FWHM Gaussian post filter) was applied for 2D reconstruction. The corrections for random coincidences and dead time were included in the reconstruction procedure. However, we did not perform the CT attenuation correction as the 4D phantom was placed outside the scanner as described above. The matrix size for an image slice was 128×128 with a 4.68×4.68 mm pixel size. The number of image slices was 47 and the slice thickness was 3.27 mm.

II.C. Quantification of motion blurring artifacts and statistical analysis

We quantified motion blurring using the target diameter, Dice coefficient and recovery coefficient (RC) metrics as described in detail below for the targets segmented by thresholding. For each target size, we determined the threshold value using the method described by Soret *et al.*,⁴⁴ i.e., a percentage of the maximum pixel value in a volume of interest (VOI), which gave the closest volume to the real volume for stationary images. A 3D PET image consisted of 47 slices with a slice thickness of 3.27 mm and pixel width of 4.68 mm. For quantification, the 3D images were interpolated by a voxel size of $1 \times 1 \times 1$ mm³. An algorithm for the 3D image analysis was developed and implemented using MATLAB (MathWorks, Natick, MA). To test the hypothesis, we compared motion blurring artifacts with AV biofeedback and free breathing using the paired *t* test with $p < 0.05$ considered to be statistically significant.

II.C.1. Target diameter

The blurring was quantified as an increase in target diameter by subtracting the segmented diameter of a stationary target volume from that with motion (AV biofeedback or free breathing). The target diameter was the length (mm) of a segmented line through the center of mass (COM) of each segmented volume in the SI direction.

II.C.2. Dice coefficient

The Dice coefficient is a metric of the degree of overlap between two volumes and is quantified as the ratio of twice the volume of intersection to the sum of the two volumes. In this study, we calculated Dice coefficients for overlap between the target volumes with motion (AV biofeedback or free breathing) and stationary target volumes, representing shape distortion of a moving target with respect to the corresponding stationary target. Prior to calculation, the two vol-

umes were registered to each other by matching the COM positions.

II.C.3. Recovery coefficient

In PET images, signal intensity of small targets is usually lower than its true activity due to limited spatial resolution of PET scanners. Thus, RC was defined as a ratio of observed activity and true activity.^{6,8} The signal intensity can be further deteriorated by respiratory motion. In this study, in order to emphasize the effect of respiratory motion, we modified the RC as a ratio between the observed maximum counts (signal intensity) of each target with motion (AV biofeedback and free breathing) and the largest (37 mm) stationary target.

II.C.4. Target trajectory

Given that irregular breathing could lead to inaccurate triggers during scanning, we evaluated the trajectory of a target volume to investigate whether the positions of a target in 4D PET images were consistent with the real motion of the target. The trajectory was quantified as the displacement of the COM of each target volume in the SI direction from five respiratory bins.

III. RESULTS

III.A. Comparison of blurring artifacts for one example subject trace

Figure 2 shows the comparison of blurring artifacts of the 13 mm target with AV biofeedback and free breathing for subject-1. The unit of y-axis in the profiles is the proportional counts per second (PROPCPS) multiplied by scan time (second), i.e., total counts without attenuation correction. In bin-1 (peak-inhale phase), the target profile and segmented volume of AV biofeedback were less blurred than those of free breathing [Fig. 2(A)]. The increase in diameter was 1 mm for AV biofeedback, much smaller than the 9 mm increase for free breathing. However, in bin-4 (transition from exhale to inhale), the target profile and segmented volume of AV biofeedback were comparable to those of free breathing, with an increased diameter of 0 mm for AV biofeedback and 1 mm for free breathing [Fig. 2(B)]. The probability distribution of displacement of free breathing was spread in bin-1. As a result, the maximum signal intensity of images for free breathing decreased, as observed in the corresponding profiles [Fig. 2(A)]. However, the probability distribution of displacement of AV biofeedback was similar to that of free breathing in bin-4 and the signal intensities were also similar [Fig. 2(B)]. These results indicate the correlations between the blurring artifacts and respiratory variations.

III.B. Comparison of blurring artifacts for all subject traces

Figure 3 shows AV biofeedback reduced motion blurring artifacts compared with free breathing. The average increase in diameter of the six targets was 0.6 ± 1.6 mm ($4.7 \pm 13\%$)

FIG. 2. Comparison of blurring artifacts in (A) bin-1 (peak-inhalation) and (B) bin-4 (transition from exhalation to inhalation) of 4D PET images with motion (AV biofeedback and free breathing) for the 13 mm target of subject-1: (1) profile, (2) volume, and (3) histogram of respiratory displacement indicating the correlation between the blurring artifacts and respiratory variations. PROPCPS = proportional counts per second.

for AV biofeedback, which was significantly ($p < 0.001$) smaller than 1.3 ± 2.2 mm ($9.1 \pm 19\%$) for free breathing [Fig. 3(A)]. The average Dice coefficient of the six targets was 0.90 ± 0.07 for AV biofeedback, which was significantly ($p < 0.001$) larger than 0.88 ± 0.10 for free breathing [Fig. 3(B)]. However, there were large variations in the results with respect to target sizes. In general, the larger improvements were observed in smaller targets. Figure 3(C) shows that loss of signal intensity was caused by target sizes and irregular motion. For all targets, the RCs for AV biofeedback were

consistently higher than those for free breathing and comparable to those for stationary, which indicates that AV biofeedback decreased signal loss. For the largest target, the RCs were 1.00 ± 0.04 , 0.97 ± 0.04 , and 1.00 ± 0.00 by definition) with AV biofeedback, free breathing and stationary, respectively. Whereas, for the smallest target, the RCs were 0.36 ± 0.05 , and 0.39 ± 0.03 with AV biofeedback, free breathing and stationary, respectively. These results indicate that the impact of target size was more dominant than that of motion. Figure 3(A) has large error bars which means a wide

variation between the subjects is observed. In other words, the results are subject-specific (Fig. 4).

Figure 3 indicates that motion blurring artifacts were sensitive to target size. Thus, the motion blurring artifacts of the 13 mm target (second smallest) were compared with those of 28 mm target (second largest) for all subject traces and all bins (Fig. 4). For both target spheres, AV biofeedback reduced the average increase in diameter in 8/10 subject traces [Fig. 4(A)]. Moreover, AV biofeedback reduced the standard deviation in 6/10 subject traces and 7/10 subject traces for the 13 mm target [Fig. 4(A.1)] and 28 mm target [Fig. 4(A.2)], respectively. In subject-6 and subject-7, AV biofeedback did not improve respiratory irregularity. This resulted in larger displacement variations than in free breathing. For the 13 mm target, the average increase in diameter was $9.9 \pm 16\%$ for AV biofeedback, which was significantly ($p = 0.006$) smaller than $19 \pm 20\%$ for free breathing. However, for the 28 mm target, the average increase in diameter was $1.2 \pm 3.3\%$ for AV biofeedback, which was not significantly ($p = 0.080$) smaller than $2.3 \pm 4.4\%$ for free breathing. Even for the 13 mm target, there were remarkable

variations in the results among subject traces: the respiratory trace of subject-1 demonstrated average increases in diameter of $11 \pm 12\%$ and $39 \pm 40\%$ for AV biofeedback and free breathing, respectively. Whereas, subject-9 demonstrated $1.5 \pm 8.4\%$ and $3.0 \pm 8.8\%$ for AV biofeedback and free breathing, respectively. High standard deviations in each subject trace indicate that there were large variations for the blurring artifacts of respective bins. In all bins except bin-4, which was the transition period from exhalation to inhalation, AV biofeedback reduced the motion blurring artifacts [Fig. 4(B)]. In bin-1 (peak-inhalation), the average increases in diameter were $15 \pm 17\%$ and $30 \pm 20\%$ for AV biofeedback and free breathing, respectively. Whereas, in bin-3 (peak-exhalation), the average increases in diameter were $0.8 \pm 6.8\%$ and $6.5 \pm 12\%$ for AV biofeedback and free breathing, respectively.

The relationship between respiratory parameters and PET blurring metrics, computed over each patient, phantom sphere diameter and respiratory bin, are quantified in Table I. This table, computed for AV biofeedback, free breathing and both dataset combined, yields several insights:

FIG. 3. Comparison of blurring artifacts (mean $\pm$ SD) for respective target sizes of 10 subjects with respect to (A) diameter, (B) Dice coefficient, (C) Recovery coefficient for 4D PET images with motion (AV biofeedback and free breathing). Note that the increase in diameter was determined by subtracting the segmented diameter of a stationary target volume from that with motion (AV biofeedback or free breathing). RC was defined as a ratio of the maximum signal of a target to that of the largest (37 mm) stationary target. Note that the error bars indicate standard deviation (SD).

FIG. 4. Comparison of blurring artifacts (**mean**±**SD**) for 13 and 28 mm targets in respect to (A) subjects and (B) bins for 4D PET images acquired with motion (AV biofeedback and free breathing). Note that the subject traces are sorted by the increases in diameter for the 13 mm target and the y-axis scales are different. Note that the error bars indicate standard deviation (SD).

- PET blurring in general is strongly correlated with the respiratory signal variations.
- The diameter increase is more strongly correlated with the respiratory signal variations than the Dice coefficient.
- The respiratory signal variations are more highly correlated with blurring artifacts than breathing period variations.
- Free breathing correlations are higher than those of AV biofeedback.
- The latter point can be explained that, as the respiratory variations overall are smaller with AV biofeedback than

the other sources of experimental variations such as resolution and noise, the other sources contribute more significantly to the overall uncertainty.

III.C. Comparison of target trajectories for one example subject trace

Figure 5 shows the trajectories of the 37 mm target for AV biofeedback and free breathing of subject-10. From visual inspection, the trajectory for AV biofeedback [Fig. 5(A)] was consistent with the corresponding motion trace [Fig. 5(B)] and the displacement of each respiratory cycle was

TABLE I. The correlation coefficients between respiratory parameters and PET image diameter increase and Dice coefficient computed over each patient, phantom sphere diameter and respiratory bin. CC = correlation coefficient; AV = audiovisual biofeedback; FB = free breathing; SD = standard deviation.

Respiratory parameter	Diameter increase CC (p-value)			Dice coefficient CC (p-value)		
	AV	FB	Combined	AV	FB	Combined
SD of respiratory signal	0.50 (<0.001)	0.68 (<0.001)	0.64 (<0.001)	-0.19 (<0.001)	-0.22 (<0.001)	-0.24 (<0.001)
SD of breathing period	-0.32 (0.36)	0.55 (<0.001)	0.38 (0.006)	0.08 (<0.001)	-0.15 (<0.001)	-0.14 (<0.001)

similar to the overall displacement, which ranged from -4 to 3 mm. However, the trajectory for free breathing [Fig. 5(A)] was considerably different from the corresponding motion trace [Fig. 5(C)]. The displacement of each respiratory cycle was less than the overall displacement, which ranged from approximately -2 – 4 mm due to the baseline shift. Therefore, for free breathing, the trajectory of targets on 4D PET images in five bins did not match with the corresponding motion trace. Four out of ten subject traces of free breathing (including subject-10) had baseline shifts.

IV. DISCUSSION

We investigated the impact of AV biofeedback on 4D PET images in a phantom study for the first time. AV biofeedback resulted in significantly ($p < 0.001$) smaller increases in the target diameter (4.7% vs 9.1%) and significantly ($p < 0.001$) larger Dice coefficients (0.90 vs 0.88) and RCs compared to free breathing. The results indicate that AV biofeedback can significantly reduce motion blurring artifacts.

However, there were large variations in the results relating to target sizes, subject traces and respiratory bins due to partial volume effects and respiratory motion irregularity. Figure 3 shows that the motion blurring artifacts of smaller targets were more reduced by AV biofeedback. It is important to consider that Figs. 3(A) and 3(B) were averaged results, which resulted in standard deviations larger than mean values. For this reason, Fig. 4(A) shows the result of each subject for 13 mm target. There are large variations between the subjects, which means that each subject has a different amount of improvement. For example, the improvement of subject-1 is 20% larger than that of subject-10. Moreover, Fig. 2 shows that each bin of the same subject has a different amount of improvement. This observation is also important for radiation treatment planning based on 4D PET images.

IV.A. Radiotherapy planning

PET images have been shown to influence the selection of target volumes for nonsmall cell lung cancers because PET has better sensitivity and specificity than CT.^{1–5} In addition, the development of intensity-modulated radiotherapy (IMRT) has enabled dose painting for which a high-uptake subvolume (i.e., biological target volume) needs to be derived from PET images.⁴⁸ Accurate quantification and localization of tumor volumes or high-uptake subvolumes are limited by respiratory motion during image acquisition. Thus, motion management techniques are necessary to reduce uncertainty in defining heterogeneous dose distributions and improve efficacy of image-based dose painting.⁴⁹ 4D PET is a widely used solution to reduce the blurring artifacts caused by respiratory motion. However, a prior condition during data acquisition must be regular respiration.¹⁶ Irregular respiration can also cause misalignment of PET and CT images which results in inaccurate quantification of images and mislocalization of tumors.^{18,50–52} Under these limitations of 4D PET, the results of this study indicate that AV biofeedback can provide two advantages for future radiotherapy treatment planning. First, AV biofeedback may increase image quality by reducing motion blurring arti-

Fig. 5. Comparison of (A) trajectories of the 37 mm target for AV biofeedback and free breathing of subject-10. The trajectory indicates the center of mass (COM) of the target. The actual motion displacements of the target in the SI direction with time for (B) AV biofeedback and (C) free breathing are also shown. Note that bin-1 corresponds to peak-inhalation.

facts. Second, AV biofeedback may improve the accuracy of CT-based attenuation correction and consequently quantification of PET data, through using AV biofeedback in both CT and PET scans. This second possibility comes from the

observation that the trajectories of targets did not exhibit baseline position shifts with time for AV biofeedback (Fig. 5).

IV.B. Partial volume effect (PVE)

Figure 3 shows that the results were statistically significant, but the clinical impact for large tumors is questionable in that the absolute and relative improvement of large targets (≥ 17 mm) was small. We attributed this result to PVE as it strongly depends on spatial resolution and target size. The spatial resolution (axial FWHM) of the PET scanner used in this study was 4.8 mm at 1 cm and 5.9 mm at 10 cm from the center of FOV. In general, the lesions smaller than two or three times the FWHM suffer from PVE around the boundary of hot lesions.^{44,53} The RC results indicate that (1) signal loss is higher for small targets due to limited spatial resolution and (2) signal intensity of small targets is further degraded due to respiratory motion [Fig. 3(C)]. Therefore, the results of this study demonstrate that AV biofeedback could increase the quality of imaging small tumors, which are vulnerable to motion due to PVE by improving respiratory regularity.

IV.C. Respiratory motion patterns and displacement

Motion patterns and displacement are significant factors that influence the motion blurring artifacts. In Fig. 4(A), the blurring artifacts of all subjects had large variations, as each subject trace had different motion patterns and displacement. Thus, the motion blurring artifacts reduced by AV biofeedback were dependent on the improvement of respiratory regularity. Typically, inhalation requires active participation of respiration muscles, but exhalation is passive for quiet breathing.¹² For this reason, exhalation is generally more stable than inhalation. Figure 4(B) shows this trend. Therefore, AV biofeedback improved the regularity of inhalation more than that of exhalation.

IV.D. Trajectory of target motion in 4D PET images

Respiratory bins allow the time-averaged trajectory of the lesion in 4D PET images to be estimated.¹⁸ However, in Fig. 2, the positions of the target with free breathing were inconsistent with expected locations: in bin-1, an expected location of the target was a negative position in an inferior direction, as bin-1 was around peak-inhalation. In addition, as bin-4 was in the transition period from exhalation to inhalation, an expected position had to be located around zero. This mistracking was caused by incorrect binning due to irregular free breathing. Moreover, the baseline shift of respiration (exhale fluctuation) is not a rare phenomenon and needs to be taken into consideration for individualized precise 4D radiotherapy.^{54,55} Therefore, AV biofeedback can be a solution to reduce the baseline shift (Fig. 5).

IV.E. Limitations

Three limitations in this study were

1. We assumed full correlation between the internal tumor motion and external respiratory signals and used the same RPM traces (i.e., abdominal displacement) in order to

reproduce internal and external motion in the 3D and 1D motion stages, respectively. However, several previous studies have shown variable correlations between internal and external motion for lung cancer patients (see, e.g., Table III in Ref. 12). Variable correlations are likely to reduce the overall 4D image quality and therefore reduce the difference between AV and free breathing images. Current clinical 4D PET imaging and AV biofeedback use an external marker only, though an internal marker could potentially be used. Lu *et al.*⁵⁶ proposed the use of an internal tumor signal (Calypso) for 4D CT imaging and, by inference, 4D PET imaging.

2. We acquired the respiratory motion traces used in this study from healthy subjects, not lung cancer patients. Many lung cancer patients have compromised pulmonary function and can have difficulties in self-regulating their breathing using AV biofeedback. We will investigate this issue in the future through a clinical patient study. The only other known paired dataset of free breathing and AV biofeedback in which the data are publically available is that of George *et al.*⁴⁰ The dataset includes 24 lung cancer patients. However, the AV biofeedback method used had simple audio instructions rather than biofeedback and the visual display only showed upper and lower limits of motion without guiding the patient on how to breathe during intermediate states. Therefore, we chose to use the healthy volunteer data for this study.
3. We did not perform CT attenuation correction as the motion phantom did not fit into the PET/CT bore (Fig. 1). We did not consider attenuation correction as a significant factor influencing the results of this study for three reasons: (1) the only variable for this study was a breathing trace; (2) all the targets were positioned symmetrically in the cylinder, and hence, experienced similar attenuation during scanning; and (3) the segmented targets were almost the same with and without attenuation correction in stationary images. The locations of edges of targets were preserved without attenuation correction even though the edges closest to the center of the cylinder were more attenuated.

Despite these limitations, our phantom study has the advantage over a patient study because the ground truth target motion is known, along with images of the target in the stationary state for comparison, from which our quantitative analysis was performed.

V. CONCLUSIONS

We performed the first investigation of AV biofeedback on 4D PET images in a phantom study using measured respiratory traces of healthy subjects, who had similar motion variations to a cohort of lung cancer patients. The results indicate that AV biofeedback can significantly reduce motion blurring artifacts in 4D PET images compared with free breathing. As a result of this study, we expect that AV biofeedback will facilitate improved identification and localization of lung tumors in 4D PET images and enable accurate PET-based radiotherapy treatment planning. In addition,

as AV biofeedback can preserve the trajectory of tumor motion in PET images, the accuracy of alignment with CT images for attenuation correction may be increased. Our phantom study results support proceeding with clinical patient studies to quantify the impact of AV biofeedback on 4D PET image quality.

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