Generating lung tumor internal target volumes from 4D-PET maximum intensity projections

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Purpose: Positron emission tomography (PET) of lung tumors suffers from breathing-motion induced blurring. Respiratory-correlated PET ameliorates motion blurring and enables visualization of lung tumor functional uptake throughout the breathing cycle but has achieved limited clinical use in radiotherapy planning. In this work, the authors propose a process for generating a gated PET maximum intensity projection (MIP), a breathing-phase projection of the 4D image set comprising gated PET images, as a technique to quantitatively and efficiently incorporate respiratory-correlated PET information into radiotherapy treatment planning.

Methods: 4D-CT and respiratory-gated PET using [¹⁸F]fluorodeoxyglucose (FDG) were acquired of three patients with a total of four small (4–18 cc), clearly defined lower-lobe lung tumors. Internal target volumes (ITVs) for the lung tumors were generated by threshold-based segmentation of PET-MIP images and ungated PET images (ITV_{PET-MIP} and ITV_{3D-PET}, respectively), and by manual contouring of CT-MIP and end-exhale and end-inhale phases of 4D-CT (ITV_{CT-MIP}) by a radiation oncologist. Because of the sensitivity of tumor segmentation to threshold value, several different thresholds were tested for ITV generation, including 40%, 30%, and 20% of maximum standardized uptake value (SUV_{max}) for FDG as well as absolute SUV thresholds of 2.5 and 3.0. The normalized overlap and relative volumes of ITV_{PET-MIP} and ITV_{3D-PET} with respect to ITV_{CT-MIP} were compared. The images were also visually compared. ITV_{CT-MIP} was considered a gold standard for these tumors with CT-visible morphology.

Results: The mean and standard deviation normalized overlap and relative volumes between ITV_{PET-MIP} and ITV_{CT-MIP} were 0.68 ± 0.07 and 1.07 ± 0.42 , respectively, averaged over all four tumors and all five threshold values. The mean and standard deviation normalized overlap and relative volumes of ITV_{3D-PET} and ITV_{CT-MIP} were 0.47 ± 0.12 and 0.69 ± 0.56 , respectively.

Conclusions: PET-MIP images better match CT-MIP images for this sample of four small CT-visible tumors as compared to ungated PET images, based on the metrics of volumetric overlap and relative volumes as well as visual interpretation. The PET-MIP is a way to incorporate 4D-PET imaging into the process of lung tumor contouring that is time-efficient for the radiation oncologist and involves minimal effort to implement in treatment planning software, because it requires only a single PET image beyond contouring on CT alone. © 2011 American Association of Physicists in Medicine. [DOI: 10.1118/1.3633896]

Key words: PET, 4D-PET, lung cancer, radiotherapy treatment planning

I. INTRODUCTION

Positron emission tomography (PET) using [^{18}F]fluorodeoxyglucose (FDG) has been shown to be useful in the definition of radiation therapy treatment volumes of lung tumors.¹ Lung cancer PET image is degraded because PET images are acquired over several minutes and breathing motion causes image blurring. In addition, respiratory motion creates artifacts in the computed tomography (CT) images used for PET attenuation correction. Therefore, this motion blurring causes distortion of the imaged tumor shape and decreases the apparent FDG uptake in the PET image, thereby degrading PET quantitation. Several authors have demonstrated that respiratory gating techniques for PET imaging hold promise for improving the quality of PET imaging of lung cancer by reducing motion blurring and subsequently improving uptake quantitation by reducing averaging effects.^{2–5} These techniques often generate a series of respiratory-correlated PET images (“4D-PET”), each at a selected breathing phase. Using the multiple gated images directly presents an increased workload to the radiation oncologist and, furthermore, may not be readily incorporable into the treatment planning workflow using commercial software. A single PET image that represented the entire breathing cycle would improve the efficiency of PET-guided radiation therapy treatment planning in cases where the tumor or its motion envelope was not readily visualized using CT.

The maximum intensity projection (MIP) of respiratory-correlated CT images has been shown to effectively capture the motion of well-isolated tumors for radiation therapy treatment planning.^{6–8} In this work, we investigate a process for generating a gated PET MIP as a technique to quantitatively and efficiently incorporate respiratory-correlated PET information into radiotherapy treatment planning. The gated PET-MIP is a breathing-phase projection of the 4D image set comprising gated PET images and is defined in analogy to the CT-MIP: each PET-MIP voxel value is the maximum intensity value of an input set of gated PET images spanning the full breathing cycle, where the PET image intensity at each phase represents the tumor and normal tissue FDG uptake at each breathing phase without motion blurring. It provides complementary metabolic information in a matched format that facilitates direct comparison to the CT-MIP. In this study, we demonstrate PET-MIP application in a small sample of tumors and show that it can provide a superior match to anatomically defined target volumes.

TABLE I. Size and motion of tumors studied.

Tumor number		1	2a	2b	3
Volume (cc)		18	7	9	4
Dimension (mm)	L-R	40	25	25	17
	A-P	33	25	31	23
	S-I	29	22	33	23
Motion amplitude (mm)	L-R	2	4	5	2
	A-P	6	5	11	5
	S-I	19	41	16	19

II. MATERIALS AND METHODS

A total of four lung tumors in three patients were studied. The sizes and motion of the tumors are summarized in Table I. Tumors were contoured in all 4D-CT phases, and the tumor motion was defined as the motion of the center of mass of the contours. Patients were imaged using a hybrid PET/CT scanner (Biograph TruePoint/TrueView 40; Siemens Medical Solutions). The PET system is a multiring LSO scanner operating in 3D acquisition mode and is characterized by a 67 cm axial field-of-view by 21.6 cm in the longitudinal direction. The CT system is a 40-slice scanner with 40 detector rows and a rotation time of as low as 0.37 s. The scanning protocol included a helical CT scan, an axial 4D-CT, a PET list-mode acquisition, and a second, identical axial 4D-CT, which was used to test consistency of breathing motion and to check for nonrespiratory induced patient motion. The CT scans were performed from the dome of the liver to the apex of the lungs.

II.A. PET imaging

All patients fasted for at least 4 h. PET list-mode data were acquired approximately 60 min after intravenous administration of approximately 10 mCi of FDG. A single 21.6 cm bed position was imaged for 12 min over the upper chest of the patient to include the dome of the liver. An abdominal bellows signal was used as the respiratory surrogate and was recorded synchronously with PET data acquisition using an external data acquisition system (DAQ). The DAQ is briefly described as follows. The bellows signal was recorded using a personal-computer based analog-to-digital conversion board (Labview; National Instruments Corporation). Digital trigger signals, originated with the Labview system, were sent simultaneously to the respiratory-trigger input of the PET scanner and to the analog-to-digital converter. The PET scanner recorded the triggers in the list-mode file. The scanner’s respiratory-trigger functionality is intended to enable phase-based PET gating by Siemens proprietary reconstruction software, but the triggers were not used for that purpose. Instead, the triggers were sent at random uniformly distributed time intervals in the range of 1–4 s. By matching the trigger intervals in the list-mode file and in the data file recording the bellows signal, time synchronization between the two data files was achieved.

II.B. 4D-CT imaging

4D-CT scans were acquired according to a protocol of 25 low-dose cine-mode scans per couch position (15 mAs per scan at 120 kVp).⁹ The respiratory surrogate used for the 4D-CT scanning was the same as was used for the PET imaging, namely, the abdominal bellows. Twelve transverse slices of 2.4 mm thickness were acquired at each couch position. Between 9 and 11 couch positions were sufficient to image the entire lungs. While images of the entire lungs were not necessary to compute either CT-MIPs or PET-MIPs, whole lung image datasets were useful for other parallel research. The fastest available rotation time of 0.37 s was used in order to minimize intrarotation breathing motion.

FIG. 1. Breathing trace of patient 2 showing voltage levels defining gating windows (horizontal dotted lines).

Cycle time was 0.56 s for a total scan time of 14 s per bed position. Twenty-five axial scans were acquired in order to adequately sample the breathing cycle and to be robust to the presence of an atypical breath during acquisition. Ten amplitude-sorted full-lung images were constructed, evenly spaced in percentile breathing amplitude from the 5th through the 95th percentiles. A MIP image was constructed from the ten full-lung images.

II.C. PET image reconstruction

List-mode data were gated into six windows according to the amplitude of the abdominal bellows signal. Custom software written in the MATLAB environment was used for this preprocessing step (Mathworks; Version 2008a). Human restful breathing patterns are asymmetric, with the majority of the breathing cycle spent near end-exhalation. Gating windows were chosen allowing each to subtend a different ranges of breathing amplitude so that every gated PET image had sufficient coincidence-event statistics for low image noise (see Fig. 1). If gating windows had been chosen to subtend equal amplitude ranges, end-inhalation images would have been produced with reduced statistics and thus increased noise.¹⁰ Gated list-mode files were reconstructed into emission images using Siemens reconstruction software with the same algorithms used for clinical image reconstruction (AW-OSEM, four subsets, eight iterations). The voxel size was $4.07 \times 4.07 \times 2.03 \text{ mm}^3$. Gated PET images were corrected for 511 keV photon attenuation using the 4D-CT phase that most closely matched the PET gating windows' median bellows signal amplitude. In addition to gated images, an ungated PET image was reconstructed for each patient using the first 2 minutes of list-mode data, providing equivalent breathing-induced blurring and approximately equivalent coincidence-event statistics to a routine clinical PET scan. For the ungated image, the attenuation correction was computed using a helical breath-hold CT scan (111 mAs effective; 120 kVp; 5 mm slice thickness). Patients were instructed to hold their breath

at a midventilation state during the breath-hold CT. A PET MIP image was constructed from the gated PET images.

II.D. Internal target volume generation

Internal target volumes were generated from the CT-MIP (ITV_{CT-MIP}), from the PET-MIP ($ITV_{PET-MIP}$), and from the ungated PET (ITV_{3D-PET}). ITV_{CT} was generated by manual contouring of the CT-MIP images by a radiation oncologist. The MIP-derived contours were checked against the peak-exhale and peak-inhale 4D-CT phases to verify correct boundaries between the tumor and the diaphragm or tumor and chest wall, as necessary. $ITV_{PET-MIP}$ and ITV_{3D-PET} were segmented by thresholding the images inside a manually drawn region-of-interest surrounding the tumor. Multiple thresholding schemes were investigated because of the sensitivity of tumor volume delineation to threshold value.¹¹ Thresholds of an absolute standardized uptake value (SUV) greater than 2.5 and 3 were used, as well as thresholds of 40%, 30%, and 20% of tumor maximum standardized uptake value (SUV_{max}). In tumor 2b, a small section of tumor had to be contoured manually in the PET MIP image due to the overlap between tumor and a normal structure exhibiting elevated uptake, however, there was little ambiguity in that process.

II.E. Data analysis

Normalized volumetric overlap and relative volumes were computed between $ITV_{PET-MIP}$ and ITV_{CT-MIP} and between ITV_{3D-PET} and ITV_{CT} . The ITV_{CT-MIP} was considered the gold standard of tumor volume and motion against in which the PET images were compared. Normalized overlap volume was defined as two times the intersection volume of ITV_{PET} with ITV_{CT-MIP} , divided by the sum of the volumes of ITV_{PET} and ITV_{CT-MIP} , and thus ranged from 0 to 1, with one indicating complete overlap. Relative volume was defined as the volume of $ITV_{PET-MIP}$ or ITV_{3D-PET} divided by the

TABLE II. Normalized overlap volumes between PET and CT-MIP tumor contours. The coefficient of variation (CV), defined as the standard deviation of a distribution divided by its mean, is used to indicate the relative dispersion of overlap volumes with respect to choice of threshold.

	Tumor	1	2a	2b	3
Threshold					
SUV > 2.5	PET-MIP	0.61	0.71	0.76	0.75
	Ungated	0.46	0.32	0.61	0.41
SUV > 3	PET-MIP	0.59	0.72	0.78	0.71
	Ungated	0.40	0.24	0.56	0.23
>0.4 · SUV_{max}	PET-MIP	0.55	0.61	0.67	0.72
	Ungated	0.44	0.35	0.44	0.59
>0.3 · SUV_{max}	PET-MIP	0.59	0.70	0.75	0.75
	Ungated	0.51	0.47	0.57	0.63
>0.2 · SUV_{max}	PET-MIP	0.61	0.7	0.78	0.57
	Ungated	0.50	0.52	0.67	0.50
Mean	PET-MIP	0.59	0.68	0.75	0.69
	Ungated	0.46	0.40	0.56	0.49
CV (σ/mean)	PET-MIP	0.04	0.07	0.06	0.12
	Ungated	0.10	0.32	0.17	0.37

TABLE III. Relative volumes of internal target volumes from PET-MIP and ungated PET contours (relative to volumes from CT-MIP contours). The coefficient of variation (CV), defined as the standard deviation of a distribution divided by its mean, is used to indicate the dispersion of relative volumes with respect to choice of threshold.

	Tumor	1	2a	2b	3
Threshold					
SUV > 2.5	PET-MIP	1.17	1.27	1.34	0.95
	Ungated	0.58	0.25	0.56	0.31
SUV > 3	PET-MIP	0.98	1.00	1.17	0.70
	Ungated	0.42	0.16	0.45	0.15
>0.4-SUV _{max}	PET-MIP	0.74	0.52	0.56	0.74
	Ungated	0.49	0.30	0.31	0.61
>0.3-SUV _{max}	PET-MIP	1.00	0.82	0.75	1.18
	Ungated	0.83	0.59	0.46	1.27
>0.2-SUV _{max}	PET-MIP	1.49	1.45	1.07	2.42
	Ungated	1.69	1.25	0.74	2.37
Mean	PET-MIP	1.08	1.01	0.98	1.20
	Ungated	0.80	0.51	0.50	0.94
CV (σ /mean)	PET-MIP	0.26	0.36	0.32	0.59
	Ungated	0.65	0.87	0.32	0.96

volume of ITV_{CT-MIP}. Relative volumes of greater than or less than 1 indicated that the PET-derived volume was greater or smaller than the CT-derived volume, respectively. Note that the ITV volume was not the physical volume of the tumor, but rather the volume of the shape encompassing the tumor motion envelope throughout the breathing cycle. The images were also visually compared.

FIG. 2. CT-MIP image of tumor 2a, with ITV_{PET-MIP} and ITV_{3D-PET} from thresholding at 0.2-SUV_{max} shown by solid blue and dashed green lines, respectively. ITV_{CT-MIP}, manually drawn from the CT-MIP and individual 4D-CT phases, is shown for reference by the dashed black line.

III. RESULTS

Normalized overlap volumes are shown in Table II. Relative volumes are shown in Table III. The mean and standard deviation normalized overlap and relative volumes between ITV_{PET-MIP} and ITV_{CT-MIP} were 0.68 ± 0.08 and 1.07 ± 0.42 , respectively, averaged over all four tumors and all five threshold values. The mean and standard deviation

FIG. 3. Sagittal slices of tumor 3. Upper row: (a) CT-MIP; (b) PET-MIP fused with CT-MIP; (c) ungated PET fused with CT-MIP. Middle row: (d) end-inhale phase of 4D-CT; (e) PET-MIP fused with end-inhale 4D-CT; (f) ungated PET fused with end-inhale 4D-CT. Lower row: (g) end-exhale phase of 4D-CT; (h) PET-MIP fused with end-exhale 4D-CT; (i) ungated PET fused with end-exhale 4D-CT. The manually drawn CT-MIP contours are shown in blue on the fused PET/CT slices.

FIG. 4. Coronal slices of tumor 2a. Upper row: (a) CT-MIP; (b) PET-MIP fused with CT-MIP; (c) ungated PET fused with CT-MIP. Middle row: (d) end-inhale phase of 4D-CT; (e) PET-MIP fused with end-inhale 4D-CT; (f) ungated PET fused with end-inhale 4D-CT. Lower row: (g) end-exhale phase of 4D-CT; (h) PET-MIP fused with end-exhale 4D-CT; (i) ungated PET fused with end-exhale 4D-CT. The manually drawn CT-MIP contours are shown in blue on the fused PET/CT slices.

normalized overlap and relative volumes of ITV_{3D-PET} and ITV_{CT-MIP} were 0.47 ± 0.12 and 0.69 ± 0.56 , respectively. The $ITV_{PET-MIP}$ showed a greater normalized overlap volume with ITV_{CT-MIP} than did ITV_{3D-PET} for all the thresholding values. In addition, $ITV_{PET-MIP}$ was less sensitive to threshold value than was ITV_{3D-PET} : The coefficients of variation of overlaps and relative volumes across the five threshold values, listed in Tables II and III, respectively, were smaller in the case of $ITV_{PET-MIP}$ than ITV_{3D-PET} for every tumor, except for the relative volume of tumor 2b, in which case the coefficients were equal. The normalized overlap was greatest for PET-MIP segmented with a threshold of $SUV > 2.5$, which in turn was superior to all five of the thresholds for the ungated PET images. Likewise, in the majority of cases, the relative volume was closest to one for PET-MIP images compared with the ungated PET images. The only circumstances where the ungated PET images were found to have improved relative volumes were tumor 2a and 3 when segmented with a threshold of $>0.2 \cdot SUV_{max}$. In these cases, the tumor was over-segmented in both the ungated and MIP images by this particular threshold. The ITV_{3D-PET} , though smaller than $ITV_{PET-MIP}$, did not cover the areas of the ITV_{CT-MIP} arising from the end-inhale position of the tumors (for example, see Fig. 2), as is consistent with the fact that the normalized overlap volumes with ITV_{CT-MIP} are higher for the PET-MIP than the ungated PET.

Figures 3(b) and 3(c) show sagittal slices of PET-MIP and ungated PET images, respectively, of tumor 3 overlaid

on the CT-MIP image, while Figs. 3(e) and 3(f) show the PET images overlaid on the end-inhale phase of 4D-CT. Because of the breathing cycle bias toward exhalation, the ungated PET image appears to extend only within the superior portion of the tumor motion envelope as seen in the CT-MIP image, whereas the PET-MIP image extends throughout the entirety of the anatomical location of the CT-MIP tumor. Figure 4 shows the PET-MIP and ungated PET images of tumor 2a overlaid on the CT-MIP image and on the peak-inhale 4D-CT phase. For this highly mobile tumor located just above the patient's diaphragm, the ungated PET image is poorly matched to the tumor's anatomical location in the higher-amplitude phases of breathing.

IV. CONCLUSION

We have demonstrated a respiratory-correlated PET maximum intensity projection (PET-MIP), defined in analogy to the familiar CT-MIP. Internal target volumes extracted from PET-MIP images are shown to be quantitatively and qualitatively well-matched to internal target volumes determined using CT-MIP images for a set of small, mobile tumors, especially when compared to ungated PET.

The ability to generate a PET-MIP could have several implications for radiotherapy treatment planning. For instance, the PET-MIP should be particularly useful in the planning of treatment for patients, whose tumors are both highly mobile and CT-ambiguous. For tumors located

adjacent to highly mobile normal structures such as diaphragm, heart, and chest wall, the ability to integrate the functional information from PET should lead to more accurate target delineation. This is well demonstrated by Fig. 4. In this circumstance, if the diaphragm at exhalation overlaps the tumor position at inhalation, using the CT-MIP leads to an ambiguous determination of the ITV, necessitating contouring on specific breathing phases. In many cases, the MIP overlap between the diaphragm and tumor is clear, so the treatment planner may elect not to use the MIP to segment the ITV. However, some cases are subtle and the treatment planner may not recognize that the tumor overlaps the diaphragm on the MIP image. Unlike CT, the PET image will provide differentiation between diaphragm and tumor tissues, so the overlap between the two tissues throughout the breathing cycle will not negatively impact the ITV determination when using the PET-MIP. Furthermore, for tumors adjacent to postobstructive atelectasis, respiratory-corrected PET images may enhance the ability to distinguish tumor from collapsed lung.

There is also ongoing interest in integrating the functional information derived from PET into determinations of dose and fractionation.^{12–14} Certainly, accurate representation of SUV for FDG uptake would be a critical component of any protocol exploring this as a viable therapeutic strategy, and the use of a PET-MIP could be a simple means to integrate this functional information into the treatment planning process. As seen in Figs. 3–4, the PET-MIP presents tracer uptake throughout the full range of tumor motion in a single volumetric image, which could be easily thresholded for purposes of graded radiotherapy treatment planning.

From a practical standpoint, the gated PET image could be used to generate an ITV directly, by delineating the images on each phase of the respiratory cycle. However, as with CT-MIP, use of a single image set to segment tumor has the ability to reduce complexity at the level of the treatment planning system as well as decrease the work load on the radiation oncologist.

Of course, in the small, well-encapsulated lung tumors studied here, a high degree of overlap between FDG-avid malignant tissue and CT-visible morphology is expected. Furthermore, a limitation of this study is the small number of tumors studied. Further work is planned to confirm the results presented here, and to study the value of this technique on patients with CT-ambiguous tumors. As such, patients are currently being enrolled to ongoing prospective trials at Washington University in St. Louis and UCLA in Los Angeles, exploring the use of respiratory-correlated PET for patients with at least one biopsy-proven or suspected malignant lung lesion.

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