Target definition of moving lung tumors in positron emission tomography: Correlation of optimal activity concentration thresholds with object size, motion extent, and source-to-background ratio

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(Received 26 October 2009; revised 11 January 2010; accepted for publication 21 January 2010; published 25 March 2010)

Purpose: Hardware integration of fluorodeoxyglucose positron emission tomography (PET) with computed tomography (CT) in combined PET/CT scanners has provided radiation oncologists and physicists with new possibilities for 3-D treatment simulation. The use of PET/CT simulation for target delineation of lung cancer is becoming popular and many studies concerning automatic segmentation of PET images have been performed. Several of these studies consider size and source-to-background (SBR) in their segmentation methods but neglect respiratory motion. The purpose of the current study was to develop a functional relationship between optimal activity concentration threshold, tumor volume, motion extent, and SBR using multiple regression techniques by performing an extensive series of phantom scans simulating tumors of varying sizes, SBR, and motion amplitudes. Segmented volumes on PET were compared with the “motion envelope” of the moving sphere defined on cine CT.

Methods: A NEMA IEC thorax phantom containing six spheres (inner diameters ranging from 10 to 37 mm) was placed on a motion platform and moved sinusoidally at 0–30 mm (at 5 mm intervals) and six different SBRs (ranging from 5:1 to 50:1), producing 252 combinations of experimental parameters. PET images were acquired for 18 min and split into three 6 min acquisitions for reproducibility. The spheres (blurred on PET images due to motion) were segmented at 1% of maximum activity concentration intervals. The optimal threshold was determined by comparing deviations between the threshold volume surfaces with a reference volume surface defined on cine CT. Optimal activity concentration thresholds were normalized to background and multiple regression was used to determine the relationship between optimal threshold, volume, motion, and SBR. Standardized regression coefficients were used to assess the relative influence of each variable. The segmentation model was applied to three lung cancer patients and segmented regions of interest were compared with those segmented on cine CT.

Results: The resulting model and coefficients provided a functional form that fit the phantom data

with an adjusted $R^2=0.96$. The most significant contributor to threshold level was SBR. Surfaces of PET-segmented volumes of three lung cancer patients were within 2 mm of the reference CT volumes on average.

Conclusions: The authors successfully developed an expression for optimal activity concentration threshold as a function of object volume, motion, and SBR. © 2010 American Association of Physicists in Medicine. [DOI: [10.1118/1.3315369](https://doi.org/10.1118/1.3315369)]

Key words: tumor contouring, PET/CT, lung cancer

I. INTRODUCTION

The use of fluorodeoxyglucose positron emission tomography (FDG-PET) in the treatment planning process for lung cancer has become popular in recent years due to evidence that data from PET imaging can significantly change various aspects of treatment. Several studies have found that incorporating PET information into computed tomography (CT) simulation can change treatment intent from curative to palliative,^{1–4} reduce interobserver variation,^{2,4–6} and alter gross tumor volume (GTV) delineation where PET effectively discriminates between malignant tissue and atelectasis.^{5,7–9}

Target volume delineation of lung cancer with PET/CT has been extensively reported in the literature,^{10–19} yet little consensus exists on exactly how to use PET to define a GTV.²⁰ Some studies recommend using a percentage threshold of maximum activity concentration (AC_{max}) or standardized uptake value (SUV) such as 42%,¹⁶ while others suggest an absolute SUV threshold such as 2.5 g/mL.²¹ Biehl *et al.*,¹⁰ however, have shown that a single threshold for lung lesions is inadequate and recommend thresholds varying from 15% for large tumors (>5 cm) and 42% for small tumors (<3 cm). Using phantom scans, Black *et al.*¹² developed a linear relationship for optimal thresholds as a function of mean SUV, which, in turn, is a function of background activity and target volume. Brambilla *et al.*¹³ determined that both target size and source-to-background ratio (SBR) were significant factors in determining appropriate activity concentration thresholds, and recommended that both variables be included in automatic segmentation algorithms. van Baardwijk *et al.*,²³ by way of thresholds determined by Daisne *et al.*,²² included both variables in their segmentation algorithm, applied the method to patients, and found good correlation with pathological specimen.

One significant variable many of these studies ignore is motion. Four-dimensional computed tomography (4D-CT) is the standard CT simulation technique at our institution for lung cancer patients undergoing radiation therapy, which allows physicians and physicists to incorporate patient-specific motion information into the target definition process. Typically, the “motion envelope” of a moving tumor is delineated on 4D-CT and margins are added for various other uncertainties. Though PET can also be acquired in a gated mode,²⁴ typically, PET is acquired in a static acquisition over several minutes per bed position. The effect of respiratory motion is a blurring of the tumor on the resulting image. Activity is spread out over voxels in the motion path of the tumor, lead-

ing to inaccurate quantification²⁵ and exaggerated tumor geometry (Fig. 1). Many of the aforementioned segmentation studies focused either on stationary objects in a phantom or moving targets in patient PET images compared to a free-breathing or breath-hold CT. Comparison of target volumes segmented on motion-blurred PET with free-breathing CT will most likely be inaccurate due to the possibility of motion artifacts in the CT,^{18,26} and comparison with breath-hold CT will be inappropriate because a breath-hold CT does not exhibit the same tumor motion as the PET data. It seems logical, then, to compare PET to 4D-CT to determine an optimal segmentation method. Indeed, a few of the studies comparing PET thresholds to CT volumes suggest that comparison to 4D-CT, rather than breath-hold or free-breathing scans, would be more appropriate.^{10,18,23} To date, however, no studies optimizing activity concentration thresholds using 4D-CT as the reference for phantoms or patients have been performed.

Some studies, however, have leaned to this direction. Caldwell *et al.*¹⁴ found that PET could indeed be used to determine internal target volume (ITV) for radiation therapy planning but that, as a result of their moving phantom study, conventional threshold values (acquired at rest) produced volumes that were too small. They reduced the threshold to 15% of maximum activity concentration to adequately capture the ITV. Similarly, Yaremko *et al.*²⁷ found that activity-filled spheres moving in air required a reduced threshold (25%) to capture the ITV.

The purpose of the present study was to investigate the dependence of activity concentration thresholds on object volume, motion amplitude, and source-to-background ratio for moving targets. We determined optimal PET activity concentration thresholds of the moving objects’ motion envelopes by comparing PET segmentation with cine CT segmentation using an extensive series of phantom scans at varying

FIG. 1. End inspiration phase of 4D-CT, end-expiration phase of 4D-CT, and PET images of moving lung tumor. All images are coronal slices. Note the blurred appearance of the moving tumor in the PET image, which is acquired over several breathing cycles.

FIG. 2. Experimental setup. (a) Motion platform and actuator were placed on a flat tabletop with controlling laptop. (b) Phantom is placed on the table flush against a piece of Lucite anchored to the table for reproducibility. Hatch marks were placed on pieces of tape on the base and moving parts of the platform to ensure motion is accurate from scan to scan.

object volume, motion, and SBR. We then developed an analytical expression for optimal threshold as a function of size, motion, and SBR using multiple regression techniques. We successfully applied this expression to three lung cancer patients who underwent 4D-CT and PET/CT simulation.

II. METHODS

The six spheres (inner diameters 10, 13, 17, 22, 28, and 37 mm) and background tank of a NEMA IEC thorax phantom (Data Spectrum, Chapel Hill, NC) were filled to six SBRs: 5:1, 10:1, 15:1, 20:1, 30:1, and 50:1. A motion platform capable of sinusoidal motion was placed on the flat tabletop of a General Electric Discovery VCT 64-slice PET/CT scanner with a LYSO detector ring (GE Healthcare, Waukesha, WI). The LYSO detector has been characterized by Kemp *et al.*²⁸ in 2-D and 3-D acquisition modes. At 1 cm from the center of the ring, the system has a spatial resolution of 5 mm. At 10 cm from the center of the ring, the spatial resolution is 5.9 mm in the radial direction and 5.2 mm in the tangential direction. The phantom was placed on the motion platform (Fig. 2) and moved sinusoidally with a 4 s period and a range of motion amplitudes (0, 5, 10, 15, 20, 25, and 30 mm peak-to-peak). The period and amplitudes were chosen to represent typical respiratory frequency²⁹ and motion extent.^{30,31} At each motion extent and SBR, coincidence data were collected for 18 min in 3-D mode and were recorded through list-mode acquisition. After the completion of the scan, the 18 min scan was split into three 6 min scans for repeatability using the volume imaging protocol replay feature. Images were reconstructed using OSEM reconstruction, 21 subsets, and two iterations at 50 cm field of view using a Gaussian postfilter of 4.29 mm FWHM. Using a 128×128 image matrix, voxel sizes were $3.9 \times 3.9 \times 3.3$ mm³. PET images were transferred to PINNACLE 8.1w (Philips Medical Systems, Madison, WI) for delineation of the six spheres.

To obtain the reference volume, the spheres were drained of liquid while keeping the background tank filled with water. The phantom was placed on the motion platform and cine CT scans were acquired for each motion extent. The scan protocol utilized cine CT at 120 kV, 100 mA, x-ray collimation of 8×2.5 mm², cine duration of 4.8 s, cine interval of

0.4 s, and gantry rotation of 0.4 s. In order to contour the maximum motion extent, the minimum intensity projection (min-IP, which takes the lowest pixel value in the image sequence) was produced from the cine CT data with in-house software.³² Because the spheres were empty and the background tank was full, the min-IP captured the motion path of the empty spheres. Furthermore, this method allowed us to capture the inner diameter of the moving sphere, which is identical to the activity-filled volume imaged by the PET scan. All min-IP images were transferred to PINNACLE 8.1w for contouring.

II.A. Target delineation

The motion envelopes of the six spheres on the min-IP images were autosegmented using seed-based 3-D region growing autosegmentation. A threshold of -425 HU was used to limit the region growing algorithm.^{33,34}

The motion-blurred spheres on each PET image set were segmented by determining AC_{max} in each sphere and creating ten to 20 regions of interest (ROIs), each corresponding to a different percentage threshold (in 1% intervals) of AC_{max} . These regions of interest were again formed by seed-based 3-D region growing autosegmentation on the PET image. PET acquisition occurred on different days for each SBR. Care was taken to reposition the phantom on the scanner bed. PET ROIs were registered with the CT regions of interest by matching centroids of each volume to mitigate the effects of repositioning the phantom.

When reference CT and PET threshold volumes were contoured for all spheres, motion extents, and SBRs, the ROIs were converted to mesh surfaces with a built-in PINNACLE 8.1w tool. The mesh surfaces were exported from PINNACLE and the separation between the surfaces was analyzed by a software program developed in-house for this study.

II.B. Analysis

II.B.1. Surface separation

To assess differences between the reference CT volume and each PET threshold volume, we developed an algorithm to measure the separation between the two surfaces similar to the method used by Pevsner *et al.*³⁵ which can assess concave volumes. This method, recently used by Rietzel *et al.*,³⁶ was a modification of the method put forth by Remeijer *et al.*³⁷ The main advantage of this method over simply comparing volume magnitudes^{17,19} or concordance³⁸ is that this method provides specific geometric information of where the volumes disagree.

A brief explanation of the surface separation analysis is provided here. First, slice-by-slice contours were converted to a triangular mesh by PINNACLE³ version 8.1 (this feature is commonly used in conjunction with model-based autosegmentation, but is convenient for our purposes as well). Triangular meshes were created for the reference CT volume and PET volumes for all threshold values. Meshes were then exported to a text file and provided the input for the surface separation algorithm which was developed in MATLAB (Mathworks, Natick, MA).

FIG. 3. Two spherical meshes are compared to the surface separation algorithm. From each sampling point on the “reference” mesh (in this case, the smaller sphere), the closest point on the other mesh surface is calculated.

The algorithm sampled the surface of the reference CT volume at regular angular intervals. In our study, the sampling interval was 5° in both the azimuthal and altitudinal directions. For each sampling point along the reference CT surface, the closest distance to the PET threshold mesh surface was calculated. Our algorithm was validated using a series of low and high resolution spherical meshes of varying sizes (Fig. 3).

For each sphere, motion extent, and SBR, the CT reference volume was compared to each PET threshold volume. The values of the deviations were squared and summed for each threshold volume and were plotted to determine which threshold produced the minimum sum of squares. We were, in essence, determining which threshold best “fit” the reference CT volume by a least-squares technique.

This surface separation algorithm was used to determine the optimal threshold for each combination of object volume, motion extent, and SBR. The algorithm was repeated for each of three image sets per experimental condition and the average optimal threshold was used for regression.

II.B.2. Multiple regression analysis

Multiple regression was employed to determine a three-dimensional function to best describe the relationship between three independent variables (size, motion, and SBR) and one dependent variable (optimal threshold). We first attempted to fit optimal threshold normalized to $AC_{\max}$, but quickly realized that $AC_{\max}$ was substantially degraded by partial volume averaging (related to object size) and motion blur (related to motion extent). The normalization factor of the dependent variable, therefore, was a function of two in-

dependent variables we were fitting against. In order to avoid unnecessary complication in the regression procedure, we normalized the threshold activity concentration values to a background measurement. The mean activity concentration (AC_{meanBG}) in a spherical ROI at the center of the phantom was used for the background measurement.

Partial volume averaging and motion blur also affected the measurement of SBR. We therefore measured the SBR for the largest sphere (where the effect of partial volume averaging was minimal) without motion and used this value for regression. A threshold of 80% of $AC_{\max}$ was used to segment a volume on the stationary sphere, and the ratio of mean activity concentration in the 80% threshold volume ($AC_{\text{mean80\%}}$) and the previously described background measurement was used for SBR. SBR was measured three times, once on each image set per experimental condition, and the average of the three SBR measurements was used for regression. Sphere volume was measured on PINNACLE using the segmented ROIs from the 0 mm motion condition. Nominal motion values were used in the regression.

To determine the relative influence of volume, motion, and SBR on optimal threshold, standardized regression coefficients were determined by transforming the variables such that the mean of each variable is 0 and the standard deviation is 1 and rerunning the regression.³⁹ The transformation is shown in Eq. (1), where x is the unstandardized variable, $\bar{x}$ and s_x are the mean and standard deviation of the unstandardized variable, respectively, and x_{std} is the standardized variable. The magnitude of the coefficients, denoted by β_n , represents the relative importance of each term in the regression function.

$$x_{\text{std}} = \frac{(x - \bar{x})}{s_x} \quad (1)$$

II.C. Patients

The accuracy of thresholds produced by the regression function was tested with two non-small-cell lung cancer patients and one small cell lung cancer patient with relatively small, solid tumors who underwent 4D-CT and PET/CT simulation. The motion envelope of the tumors was delineated with autosegmentation using seed-based 3-D region growing. A threshold of -425 HU was used to limit region growing (the same value as the phantom scan). Contours were reviewed by a thoracic radiation oncologist and adjusted if necessary.

To determine target volume, the tumor was autosegmented at end-expiration and volume was measured. Additionally, the tumor was autosegmented at end-inspiration and the measured distance between the centroids of the end-inspiration and end-expiration was taken as the motion extent. SBR was measured by taking the $AC_{\text{mean80\%}}$ and dividing by the background, determined by the mean activity concentration in the lung (subtracting the tumor and other physiological uptake).

As mentioned before, SBR was degraded by size and motion. In phantom studies, the true SBR was known. In patient

studies, unfortunately, the true SBR is unknown, so a recovery coefficient (RC) was applied to correct for activity degradation due to size and motion.⁴⁰ The RC was developed from the phantom data. $AC_{\text{mean80\%}}$ for each sphere size and motion condition was compared to the largest stationary sphere, such that the RC for each size and motion condition was defined as

$$RC(x,y) = \frac{AC_{\text{mean80\%}}(26.5,0)}{AC_{\text{mean80\%}}(x,y)}, \quad (2)$$

where x and y represent the different volumes and motions, respectively. ACs were averaged over the three phantom trials. “26.5” is the largest nominal sphere volume (in cm^3), and “0” is the static, no-motion scan condition. Recovered activity concentration is simply the product of the degraded activity concentration and the RC for the size and motion of the object of interest. Multiple regression was used to fit a function of volume and motion.

Volume, motion, and SBR (using *recovered* AC) were entered into the regression function and the resulting threshold was segmented on PINNACLE. The threshold ROI was converted to a mesh and the deviation between the cine CT volume and the PET threshold volume was calculated with the surface separation algorithm.

FIG. 4. Axial, sagittal, and coronal PET images of a moving sphere, inner diameter=37 mm, motion extent=20 mm, SBR=20:1. PET contours are volumes segmented at different percentages of maximum activity concentration. These contours are compared to the reference volume contoured on cine CT using the surface separation algorithm. The threshold volume which minimizes the sum of squared deviations is the optimal threshold for that sphere volume, motion extent, and source-to-background.

TABLE I. Nominal and actual volumes and SBRs.

Volume (cm^3)		SBR ^a (unitless)	
Nominal	Measured	Nominal	Measured
26.5	28.6	5	4.33 ± 0.02
11.5	12.7	10	8.12 ± 0.25
5.6	6.4	15	14.88 ± 0.22
2.6	3.1	20	19.91 ± 0.73
1.2	1.4	30	28.88 ± 1.40
0.5	0.7	50	52.15 ± 1.95

^aSBR: Source-to-background ratio measured in largest stationary sphere.

III. RESULTS

III.A. Segmentation model

By scanning six spheres of differing diameters at seven motion extents and six SBRs, 252 combinations of these variables were imaged and delineated to determine the optimal threshold. Approximately 20 thresholds ROIs were contoured for each volume/motion/SBR combination and were compared to the reference CT motion envelope volume (Fig. 4). Optimal thresholds were unable to be determined for 5 volume/motion combinations at SBR of 5:1 (13 mm inner diameter, 30 mm motion; 10 mm inner diameter, 15–30 mm motion) due to blurring of the sphere into the background. Nominal sphere volume and SBR versus measured values used for regression are shown in Table I. Note that sphere volumes segmented with a -425 HU threshold are within ± 1 mm variation (approximately 1 CT pixel) of the true inner radius.

A 3-D scatter plot of our phantom data is shown in Fig. 5. Since our data are four-dimensional, we illustrate motion, SBR, and optimal threshold on separate axes, with sphere inner diameter represented by different symbols and color for each value. There are clear patterns to the data, which suggest terms for an appropriate regression model. The relation-

FIG. 5. Optimal thresholds versus motion, source-to-background, and volume (denoted by different symbols). Threshold values are normalized to background. Error bars represent 1 standard deviation (3 measurements). Legend lists nominal sphere inner diameters.

FIG. 6. Optimal threshold versus source-to-background for stationary spheres. Each line represents a different sphere volume as denoted in the legend. Note the linear nature of the relationship. Error bars are 1 standard deviation (three measurements).

ship of optimal threshold with SBR, for example, is close to linear (Fig. 6). Optimal threshold versus motion and volume, however, are more complicated (Figs. 7 and 8). After trying several combinations of functions that were physically appropriate to the phenomena (a quadratic relationship, for example, would not make sense physically; there is no reason to expect maxima or minima), we settled on the model

FIG. 7. Optimal threshold versus motion for source-to-background=19.9. Each line represents a different sphere volume as denoted in the legend. Error bars are 1 standard deviation (three measurements).

FIG. 8. Optimal threshold versus volume for source-to-background=19.9. Each line represents a different motion extent (0–30 mm). Error bars are 1 standard deviation (three measurements).

shown in Eq. (3), where w is the threshold normalized to background, x is the volume in cm^3 , y is the motion in mm, z is the SBR (which is unitless), and B_n are the regression coefficients.

$$\ln(w) = B_1 x^{1/3} + B_2 y^{1/3} + B_3 \ln(z) + B_4 (x^{1/3} \ln(z)) + B_5 (y^{1/3} \ln(z)) + B_6 (xy)^{1/3} + B_7. \quad (3)$$

There are a few things of note in this equation. First, we took the natural logarithm of the threshold values w because the residuals increased with increasing SBR. Consequently, due to the linear relationship with SBR before taking the natural logarithm of threshold, we took the natural logarithm of SBR for the regression. For volume, the choice of cube root is not entirely surprising because volume is the cube of sphere radius. For motion, a logarithmic function would also have been appropriate except for the fact that logarithm is undefined at zero and we measured optimal thresholds at static or 0 mm motion extent. A cube root, therefore, was chosen because it behaves similarly to natural logarithm but is defined at zero. Interaction terms were included in the model because we found their inclusion created a substantially better fit to the data.

The regression equation with appropriate coefficients is shown in Eq. (4). This function produced an R^2 value of 0.96 and an adjusted R^2 value (which accounts for increasing R^2 due to additional terms in the fitting function) of 0.96. Several surfaces of the regression function (because the function is a family of surfaces) are shown in Fig. 9.

$$\begin{aligned} \ln(w) = & 0.0634x^{1/3} + 0.1202y^{1/3} + 0.7327(\ln(z)) \\ & + 0.0597(x^{1/3} \ln(z)) - 0.1221(y^{1/3} \ln(z)) \\ & - 0.0248(xy)^{1/3} - 0.9504. \end{aligned} \quad (4)$$

FIG. 9. Surfaces of regression function stated in Eq. (4). Each of the four surfaces displayed is calculated for (top) spheres of inner diameter 10, 17, 28, and 37 mm and (bottom) SBRs equal to 5:1, 20:1, 35:1, and 50:1.

The standardized regression coefficients, often denoted as β_n , are listed in Table II. Of the three independent variables, SBR was the most influential ($\beta_3=1.0606$), followed by motion ($\beta_2=0.2114$), then volume ($\beta_1=0.0841$). Both interaction terms with SBR, however, were more influential than motion and volume alone.

III.B. Application to patient studies

The RC function developed from phantom data is shown in Eq. (5) ($R^2=0.95$). Again, x is volume and y is motion extent.

TABLE II. Regression coefficients for regression model in Eq. (2).

Variable	B_n^a	β_n^b
Volume	0.0634	0.0841
Motion	0.1202	0.2114
SBR	0.7327	1.0606
Volume · SBR	0.0597	0.2750
Motion · SBR	−0.1221	−0.7251
Volume · Motion	−0.0248	−0.1101
Constant	−0.9504	−0.0321

^a B_n =Unstandardized regression coefficients.

^b β_n =Standardized regression coefficients.

$$RC = 0.1991x^{-1} + 0.0136y + 0.0725x^{-1}y + 0.8839. \quad (5)$$

Tumor characteristics, resulting threshold values, and average separation between PET and reference cine CT volumes are listed in Table III. The mean separation for all three patients was less than 2 mm. PET/CT and 4D-CT images and ROIs segmented with the threshold regression function are shown in Figs. 10 and 11 for patients 1 and 2, respectively. The segmented PET volumes were quite similar to the reference cine CT volumes, accurately including the tumor motion depicted in the 4D-CT end-inspiration and end-expiration images.

IV. DISCUSSION

We successfully developed an expression for activity concentration threshold as a function of object volume, motion, and SBR. The function, shown in Eq. (3), fit the data very well (adjusted $R^2=0.96$) and we found that SBR was the most influential variable in the expression. In applying this model to three lung cancer patients, we found the mean deviation between the model-produced threshold and the reference cine CT volume was less than 2 mm. The model is currently untested on a large number of patients, but an IRB-approved study comparing patient PET volumes segmented by model-predicted thresholds and motion-inclusive target volumes on 4D-CT is underway.

The current study is the most comprehensive investigation into threshold-based segmentation of PET imaging of moving targets to date. It is the first to investigate the relationship between motion, size, and SBR for a large range of motion (0–30 mm) and SBR (5:1 to 50:1). It is also the first to use the surface separation analysis to determine optimal threshold volume. Several studies have examined elements contained in the current study. Yaremko *et al.*²⁷ determined optimal thresholds for moving and static spheres in air, sizes ranging from 0.56 to 57.37 mL with 25 mm motion amplitude. Caldwell *et al.*¹⁴ investigated feasibility of using PET to delineate ITV by moving three spheres (inner diameters = 1.3, 2.9, and 6.6 cm) at three different motion extents (7, 16, and 27 mm), but did not determine optimal thresholds for each experimental condition. Black *et al.*¹² examined the influence of size and, indirectly, SBR by developing a linear function of mean SUV, but motion was not included.

There are several recent studies which are similar to the current work. Park *et al.*¹⁹ investigated the effects of target size, motion, and background activity on optimal thresholds in a phantom. The authors used the NEMA IEC phantom (sphere diameters identical to the current study), sinusoidal motion (adjusted with an exponential shaping parameter) with extents of 0, 10, and 20 mm, and SBRs of 4.0, 8.3, and infinite (no background) to determine optimal thresholds for these varying conditions. After renormalizing the threshold values in the current study to maximum activity concentration for comparison, we found that the optimal thresholds determined by Park *et al.*¹⁹ were generally higher than our results.

One significant difference between the current study and Park *et al.*¹⁹ is that the authors compared PET volumes to the

TABLE III. Application of threshold function to three lung cancer patients. Threshold is normalized to background measurement. Mean deviation is determined with surface separation algorithm.

Pt #	Volume (cm ³)	Motion (mm)	SBR ^a	Threshold	Mean separation (mm)	SD ^b (mm)
1	21.09	10.8	30.0702	4.37	1.03	0.08
2	0.98	6.6	19.6315	2.63	1.36	0.07
3	10.25	8.6	25.9020	3.73	1.44	0.09

^aSBR = source-to-background ratio.

^bSD = standard deviation.

known sphere volume, i.e., the *stationary* sphere, not the motion envelope of the moving sphere, in order to show that it is difficult to capture the “true target volume” without gated PET. This explains the large difference in thresholds at 2 cm motion (90% in Park *et al.*¹⁹ versus 18% in the current study for the smallest sphere with SBR=8). The goal of the current study was to match threshold volumes with motion-included target volume often used in 4D-CT-based simulation, not the volume of the spheres themselves. Our values, however, are lower for the stationary spheres as well, especially for the smallest sphere (75% in Park *et al.*¹⁹ versus 40% in the current study with SBR=8). This difference can most likely be explained by the fact that Park *et al.*¹⁹ compared volume magnitudes and we compared surfaces. Volume was estimated by summing the number of voxels above the threshold and multiplying by voxel volume, which, for Park *et al.*,¹⁹ was $4.7 \times 4.7 \times 3.27$ mm³. The width of one voxel (*x-y* plane) was almost one half the inner diameter of the smallest sphere, which causes partial volume averaging and inaccurate calculation of the volume. The surface separation algorithm essentially measures between meshes interpolated from the voxel-based contours. Though not technically higher resolution, the interpolated meshes give us a finer estimation of the best-fit threshold volume.

Brambilla *et al.*¹³ investigated target volume delineation in an NEMA IEC thorax phantom as a function of several variables, including SBR, sphere diameter, injected activity, and emission scan duration. Additional microspheres (inner diameters=4.1, 4.7, 6.5, and 8.1 mm) were added to the

phantom for analysis. Motion was not included in this study. Using multiple linear regression and standardized regression coefficients, the authors found that for sphere diameters less than 10 mm, sphere diameter, and SBR were significant predictors of optimal target threshold (as a percentage of maximum activity concentration), but, to a first approximation, SBR dependence could be neglected with little effect on optimal threshold. For sphere diameters greater than 10 mm, again, sphere diameter and SBR were significant predictors of optimal target threshold, but the opposite relationship between the two was observed: Sphere diameter was less significant and, to a first approximation, could be neglected. Injected activity and emission scan duration were both found to be nonsignificant predictors of optimal threshold, and, consequently, were not included in the current study.

The multiple regression techniques used in the current study are similar to those used in Brambilla *et al.*¹³ In selecting their regression model, the authors determined from previous studies that optimal threshold normalized to maximum activity concentration is related to $1/\text{SBR}$.⁴¹ In the present study, we found a nearly linear relationship between SBR and optimal threshold normalized to background. These findings are consistent: An inverse relationship between SBR and threshold normalized to “signal” is equivalent to a linear relationship between SBR and threshold normalized to “background.” Brambilla *et al.*¹³ also used standardized regression coefficients in their study and found that SBR is the

FIG. 10. PET/CT images of patient 1 with PET-segmented volume (thin contour) and reference cine CT volume (thick contour). (A) 4D-CT phase image at end-expiration. (B) 4D-CT phase image at end-inspiration. (C) Maximum intensity projection. (D) Coronal PET/CT image. (E) Transverse PET/CT image.

FIG. 11. PET/CT images of patient 2 with PET-segmented volume (thin contour) and reference cine CT volume (thick contour). (A) 4D-CT phase image at end-expiration. (B) 4D-CT phase image at end-inspiration. (C) Maximum intensity projection. (D) Coronal PET/CT image. (E) Transverse PET/CT image.

most influential variable for sphere diameters greater than 10 mm, which is consistent with the findings of the current study.

Okubo *et al.*¹⁸ used the NEMA IEC body phantom to examine optimal thresholds of moving spheres. The six spheres were identical to the spheres used in the current study. In a static phantom, optimal thresholds (expressed as a percentage of maximum SUV) were determined at SBRs of 10:1, 15:1, and 20:1. After excluding the smaller spheres (inner diameter 10–17 mm) due to partial volume averaging, they found 35% of maximum activity concentration to be a reasonable threshold. The phantom was then moved sinusoidally with a 4 s period to 10, 20, and 30 mm amplitudes (peak-to-peak) and PET images were segmented at 35% of maximum activity concentration at SBR=20:1 only. The authors found that a 35% threshold underestimated the actual sphere size in the axial plane and overestimated actual sphere size in the sagittal plane. The extent in the sagittal plane, however, was smaller than the ideal ITV. For comparison, we segmented the 28 mm inner diameter sphere, at 30 mm motion extent, and SBR=19.9, at 35% of maximum activity concentration. Figure 12 shows the 35% volume compared to the stationary sphere. Similar to the findings of Okubo *et al.*,¹⁸ the axial extent is underestimated but the sagittal extent overestimated compared to the stationary sphere. This threshold, however, is too high to match the motion envelope of the tumor, what the authors refer to as the “ideal ITV.”

An interesting finding in this work is the importance of interaction terms in the model, particularly the two terms related to SBR. In Fig. 5, one can observe the change in slope of the optimal threshold versus SBR relationship over different sphere volumes and motion extents, implying the interrelationship between these variables. This may be attributed to the substantial blurring caused by imaging objects similar in size to the point-spread function of the scanner or imaging objects moving at amplitudes similar to the size of

the object. In both cases, the spill-in and spill-out effects caused by blurring may couple the relative amount of background with the variables causing the blur, particularly for smaller objects where blur is substantial.

Segmentation by threshold is a common method of target delineation with PET, but gradient methods have been investigated as well. Drever *et al.*¹⁵ compared threshold-based segmentation with two gradient-based techniques, the first using a Sobel edge-detection filter and the second using a watershed technique. They found that both gradient techniques failed to accurately segment stationary targets in a phantom and that a threshold-based technique showed the most promise. Though not included in this study, we believe that investigation of gradient-based segmentation is important and should be pursued in future studies. For moving lung tumors, however, we anticipate that a gradient-based approach will be problematic. Motion blur substantially decreases the activity concentration gradient in the direction of motion, creating a situation where the edge of the tumor produces a high gradient in planes perpendicular to motion but a low gradient in planes parallel to motion. A single gradient threshold may be inadequate.

One of the strengths of the current approach is the simplicity of the tool. Only four measurements need to be made in order to calculate optimal threshold: Tumor volume, motion extent, mean activity concentration in the tumor, and background activity concentration. Once the four quantities are measured, it is simple to plug these values into the regression equation to determine the appropriate threshold normalized to background. One can obtain the activity concentration value by multiplying by the background measurement. Though portability of the model to different PET/CT scanners with different reconstruction algorithms may be a concern, we did apply the model to a set of phantom images acquired on a different PET/CT scanner under different acquisition and reconstruction parameters and

FIG. 12. Reference volume for stationary sphere (inner diameter=28 mm) compared to 35% maximum activity concentration of same volume sphere at 30 mm motion extent and source-to-background=19.9. Note that the 35% threshold underestimates the axial extent of the sphere and overestimates the sagittal extent of the sphere, consistent with the findings of Okubo *et al.* (Ref. 18). The 35% threshold, however, underestimates the full motion envelope of the tumor.

found good agreement between model-produced ROIs and CT contours (on the same order as if we had optimized PET volumes independent of the model).

This segmentation technique is theoretically not limited to lung cancer. Stationary tumors, such as PET avid head and neck tumors, could also be contoured using this approach simply by setting the motion parameter to zero. One significant caveat, however, is that the background surrounding head and neck tumors is substantially different than the lung, so choosing the appropriate background ROI may be complicated and will require further study before clinical application.

V. CONCLUSION

Using a comprehensive set of phantom experiments, the relationship among optimal PET activity concentration threshold, object volume, motion extent, and SBR was determined. The relationship, a model developed through multiple regression of the phantom data, produced an R^2 value of 0.96. SBR was found to be the most significant predictor of

optimal threshold. The validity of the model was tested with three lung cancer patients. The mean deviation between the segmented PET volume and reference cine CT volume was less than 2 mm. We are currently applying the regression function to a group of lung cancer patients and comparing optimal PET thresholds predicted with our regression function with motion envelope targets defined with 4D-CT. If successful, this will provide a relatively convenient target delineation technique for lung lesions that includes target volume, motion, and SBR.

ACKNOWLEDGMENTS

Financial support from Schissler Foundation MD Anderson Cancer Center Fellowship (A.C. Riegel), Presidents' Research Scholarship (A.C. Riegel), and Startup Fund M. D. Anderson Cancer Center.

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