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LROC Investigation of Three Strategies for Reducing the Impact of Respiratory Motion on the Detection of Solitary Pulmonary Nodules in SPECT

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Abstract

The objective of this investigation was to determine the effectiveness of three motion reducing strategies in diminishing the degrading impact of respiratory motion on the detection of small solitary pulmonary nodules (SPN) in single photon emission computed tomographic (SPECT) imaging in comparison to a standard clinical acquisition and the ideal case of imaging in the absence of respiratory motion. To do this non-uniform rational B-spline cardiac-torso (NCAT) phantoms based on human-volunteer CT studies were generated spanning the respiratory cycle for a normal background distribution of Tc-99m NeoTect. Similarly, spherical phantoms of 1.0 cm diameter were generated to model small SPN for each of 150 uniquely located sites within the lungs whose respiratory motion was based on the motion of normal structures in the volunteer CT

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studies. The SIMIND Monte Carlo program was used to produce SPECT projection data from these. Normal and single-lesion containing SPECT projection sets with a clinically realistic Poisson noise level were created for the cases of: 1) the end-expiration (EE) frame with all counts, 2) respiration-averaged motion with all counts, 3) one-fourth of the 32 frames centered around EE (Quarter-Binning), 4) one-half of the 32 frames centered around EE (Half-Binning), and 5) eight temporally binned frames spanning the respiratory cycle. Each of the sets of combined projection data were reconstructed with RBI-EM with system spatial-resolution compensation (RC). Based on the known motion for each of the 150 different lesions, the reconstructed volumes of respiratory bins were shifted so as to superimpose the locations of the SPN onto that in the first bin (Reconstruct and Shift). Five human-observers performed localization receiver operating characteristics (LROC) studies of SPN detection. The observer results were analyzed for statistical significance differences in SPN detection accuracy among the three correction strategies, the standard acquisition, and the ideal case of the absence of respiratory motion.

Our human-observer LROC determined that Quarter-Binning and Half-Binning strategies resulted in SPN detection accuracy statistically significantly below ($P < 0.05$) that of standard clinical acquisition, whereas the Reconstruct and Shift strategy resulted in a detection accuracy not statistically significantly different from that of the ideal case.

This investigation demonstrates that tumor detection based on acquisitions associated with less than all the counts which could potentially be employed may result in poorer detection despite limiting the motion of the lesion. The Reconstruct and Shift method results in tumor detection that is equivalent to ideal motion correction.

Index Terms

SPECT data quantification and correction methods; image quality assessment; image generation; simulation

I. Introduction

The best chance for long-term survival with lung cancer occurs when the disease presents as solitary pulmonary nodules (SPN). The current guidelines regarding the management of small SPN detected on CT scans have been published as a consensus statement by the Fleischner Society based on a review of the literature[1]. In this report SPN 9 mm or greater were considered as being the most suspicious. The development of radiotracers that are specific to particular antigens expressed on the cell surfaces of malignant SPN affords the opportunity to substantially assist in the classification task of identifying malignant from benign SPN [2–6].

Respiratory motion, however, is known to cause artifacts, decrease tumor detectability, and alter quantification of localization in medical imaging [7–9]. In single photon emission computed tomographic (SPECT) and positron emission tomographic (PET) imaging, acquisition times are too long to be accomplished in a single breath hold to negate the impact of respiratory motion. Various strategies based on respiratory gating have been proposed to improve tumor detection through reduced motion blurring by reconstructing

data acquired from only a portion of the respiratory cycle [10–15]. However, collecting events only during a portion of the respiratory cycle when little motion has occurred results in acquisitions with a decrease in total counts due to the omission of events from outside of the selected portion of the cycle. Thus using acquisitions obtained only during that portion of the respiratory cycle associated with minimal motion has the disadvantage of increased image noise, or requiring longer acquisition times with increased chances for the patient moving due to discomfort.

With the advent of gated CT imaging, it is now possible to obtain specific knowledge of the motion of small pulmonary lesions that are suspicious for malignancy [16–22]. It is therefore possible to apply such CT determined motion to SPECT and PET as a means of correcting for the motion of the lesion in question. Such an approach allows for the utilization of anatomical imaging to enhance functional imaging by SPECT and PET for tumor-avid radio-labeled agents. However, gated CT can involve an increase in radiation dose to the patient and a change from standard clinical protocols used for imaging. Thus it is not obvious that it or some variant is the preferred alternative.

Actual clinical studies in which the absence or presence of a lesion and its location are known is the ideal circumstance to assess a task-based comparison of lesion detection. However, acquiring the required number of image data sets is a time consuming and expensive undertaking. Alternatively, clinically realistic simulation studies offer an attractive alternative, at least for the initial evaluation of the potential benefit of these alternative correction strategies. In our previous investigations [23;24] we developed a simulation of the motion of solitary pulmonary nodules (SPN) during quiet supine respiration. This simulation employed the non-uniform rational B-spline cardiac torso (NCAT) anthropomorphic digital phantom [25;26] and was based on the movement of structures within the lungs during respiration as determined in breath-held CT images of a volunteer acquired at two different stages of respiration. Using this simulation we showed through human-observer localization receiver operating characteristic (LROC) studies that respiratory motion degrades tumor detection for four different iterative reconstruction strategies.

This follow-on investigation was designed to determine by human-observer LROC studies using our SPN respiratory-motion model, the effectiveness of three alternative strategies in reducing the degrading impact of respiratory motion on the detection of small SPN in comparison to standard clinical acquisition, and to the ideal case of the absence of respiratory motion. The three strategies were: 1) employing data from only one-fourth of the respiratory cycle centered on EE, 2) employing data from only one-half of the respiratory cycle centered of EE, and 3) employing data from the entire respiratory cycle that has been binned into eight states of respiratory motion and shifting in 3D the reconstructed slices of these states to align the SPN before summing the slices. The first two strategies traded a reduction in counts for a reduction in respiratory motion. The last strategy kept all counts in the slices shown to the observers, but required knowledge of the motion of the SPN between the eight motion states.

II. Materials and Methods

A. NCAT phantom generation

Two CT image sets were acquired on an electron beam CT scanner (EBCT: Imatron, South San Francisco) of a normal volunteer with lung inflation of 5% and 40% above residual volume with an in-plane pixel size of 0.78 mm and a slice thickness of 3.0 mm. Imaging was carried out at the University of Iowa under an IRB protocol associated with a separate study. With IRB approval the CT images were transferred to the University of Massachusetts after the removal of identifying information. A program was written in Interactive Data Language (IDL) which allowed the interactive display of the CT slices and the recording of the corresponding 3D location of 227 selected structures in the two slice sets by a radiation oncologist. The paired sets of points were then used to represent the respective end-points in the motion of SPN under the assumption that the presence of a small SPN would not alter the motion of the lung locally. Identified structures included proximal bronchi, secondary and occasionally tertiary bronchi, large diameter pulmonary vessels, and smaller diameter pulmonary vessels. Oftentimes, bifurcation or trifurcation points were used, and other times readily identifiable structures or patterns were selected.

In addition to marking points within the lungs, points associated with selected bones, heart, liver, spleen, stomach, and kidneys were marked at the two different states of respiration. These points were also chosen by the physician and only included those which were felt to be readily identifiable on the two sets of CT images. As detailed in [23;24] these organ boundary points were then used to adapt the structures in the standard NCAT resulting in two NCAT torso phantoms for this volunteer. The one for 5% of residual volume was modified to better represent end-expiration (EE), and the one for the 40% of residual volume was taken as end-inspiration (EI) with the two thus approximating normal tidal breathing of 500ml [27].

The set of equations we used to model the change in volume with respiration for time points between EE and EI were [23;24]

$$V(t) = -250\text{ml} \cos(\pi t/2) + 250\text{ml} \quad \text{for } 0 \leq t \leq 2 \quad \text{Eq.1}$$

$$V(t) = -250\text{ml} \cos(\pi(5-t)/3) + 250\text{ml} \quad \text{for } 2 \leq t \leq 5 \quad \text{Eq.2}$$

where $V(t)$ is the volume in ml and t is the time in seconds. With $t = 0.156$ seconds, a total of thirty-two NCAT torso phantoms were generated from the two initial NCAT's over one full 5 sec respiratory cycle, beginning with EE, going through EI, and ending again at EE according to Eq 1 and Eq 2. This created NCAT phantoms with the dynamic motion associated with breathing for the normal torso.

The pharmacokinetic data supplied by the manufacturer as well as actual clinical studies involving Tc-99m depreotide (NeoTect) [2], were used to define appropriate relative source distributions for the structures within these NCAT phantoms. The relative values were kidney 1.0, spleen 0.4, spine 0.16, sternum 0.16, liver 0.13, rib 0.10, and remainder of body including lung 0.02. Note that the relative uptake for the bones was set the same for both

bone and marrow. Based on these values, $256 \times 256 \times 256$ source maps for Tc-99m labeled depreotide were created with a voxel dimension of 0.208 cm for each of the 32 NCAT phantoms and for a respiration-averaged NCAT torso phantom (called Frame Ave hereafter). NCAT attenuation maps were also created for each of the NCAT phantoms for the 140.5 keV emitted photon energy of Tc-99m.

One hundred fifty points of the 227 paired points determined interactively by the physician to characterize the motion of similar anatomical structures in between the volunteer CT's were selected to represent the center of 1.0 cm diameter spheres to be used as simulated SPN sites for SPECT imaging. The 5% of residual volume points to be used to represent the EE location for SPN were modified similarly to that of the organ boundaries to better match EE [23;24]. A set of thirty-two NCAT sphere phantoms were generated over one complete respiratory cycle to similarly create the dynamic motion associated with breathing for each of the 150 separate nodules, also according to Eq 1 and Eq 2. In addition, a respiration-averaged sphere phantom was created for each of the 150 sites. The locations were equally divided between the right lung and left lung with seventy-five points in each. Of the 150 locations, fifty points were selected from the upper third of the lung (lung apices), fifty from the middle third, and fifty from the lower third (lung bases). The average (range) in three-dimensional (3D) motion between the points was: 0.67 (0.21–1.12) cm for the upper third of the lung; 1.59 (0.82–2.16) cm for the middle third, and 1.45 (0.57–2.69) cm for the lower third.

B. Projection simulation and combination into projection sets

With the NCAT source and attenuation maps as input, the SIMIND Monte Carlo program [28] was used to create low-noise SPECT projection data for each of the 32 frames and Frame Ave NCAT phantoms for use as normal backgrounds. The SIMIND Monte Carlo program was also used to produce low-noise SPECT projection data for the NCAT sphere phantoms for the 32 frames and Frame Ave for each of the 150 simulated tumor locations. Imaging simulated a clinical acquisition with low-energy high-resolution parallel-hole collimators on our two-headed Philips Prism2000 SPECT system. This is the system which is employed at our site for depreotide imaging. In each case 128×128 SPECT projection sets with a pixel size of 0.416 cm for 120 angles over 360 degrees for a photopeak window were produced.

The average total number of counts in the photopeak window for five clinical Tc-99m labeled depreotide studies was determined to be 22.5 million. The factor necessary to scale the SIMIND projections so that the photopeak window projections had this number of counts was then determined. One-hundred and fifty Poisson noise realizations were made for the EE frame projections and projections for each of the 32 frames of the respiratory cycle to serve as SPN absent projection sets. Another one-hundred and fifty noisy projection sets of each were made after adding the one-hundred and fifty SPN projection sets to the normal backgrounds after first scaling them to obtain the desired SPN contrast, as will be described later in the paper.

These projections served as the starting point for the creation of projection sets for the three strategies of motion correction, plus the clinical acquisition and the ideal case of the absence

of motion. Frame Ave with the total number of counts in a standard clinical acquisition served as our reference for SPN detection with standard clinical imaging. The EE Frame with the number of counts equal to that of a clinical acquisition served as the ideal for motion correction. The first of the correction strategies was Quarter Binning. This was the combination of the one-fourth of the 32 frames grouped around EE. Quarter Binning therefore had one-fourth of the motion of the respiratory cycle but also only one-fourth of the counts. This simulates gating SPECT acquisition about EE where humans typically pause slightly during respiration. The second was Half Binning in which one-half of the counts and motion are included in the acquisition. The third grouped the 32 frames into eight combined frames each occupying one-eighth of the respiratory cycle. The combining of sets of four simulated projections into one combined projection allowed simulation of a finite amount of motion as occurring within each respiratory frame. The eight combined projections were individually reconstructed, and then the eight reconstructed sets of slices shifted in 3D according to the known average motion of each SPN relative to EE. This simulated acquiring a respiratory binned SPECT acquisition and then correcting the SPN motion according to its motion as might be assessed in a low-dose gated CT. This method of motion correction is called “Reconstruct and Shift” hereafter. This method assumes that the site of a potential SPN has already been identified on CT and nuclear imaging is being performed to assist in distinguishing malignant from benign SPN or other non-cancerous anatomical structures.

C. Image reconstruction

The rescaled-block-iterative expectation-maximization (RBI-EM) algorithm was selected over other possible iterative algorithms for this study based on its convergence properties in the absence of subset balance [29], as well as its past LROC performance with simulated images [30]. Based on a previous study of RBI-EM [30], the 120 projections were broken up into 30 subsets with each containing 4 angles. The 4 angles were ordered to provide as large a difference in angles from angles in the current subset and the last subset as possible. No other subset variations were investigated herein. We selected from among the four variants of the RBI-EM algorithm we previously investigated which varied in the correction strategies included [23;24] the one in which solely system resolution compensation (RC) was included in RBI-EM reconstruction. That is no correction for attenuation or scatter is performed in the selected strategy. It was chosen because it had SPN detection accuracy almost as good as RBI-EM with all corrections (i.e., correction for attenuation, scatter and resolution), and a larger difference between motion present (Frame Ave) and motion absent (EE Frame) than RBI-EM with all corrections. This larger difference was appealing for usage within this study as it allowed for possible differentiation of strategies whose performance might be in between Frame Ave and the EE Frame results. The usage of solely RC also avoided issues regarding alignment between attenuation maps and emission data due to patient motion. Further although all manufacturers currently sell SPECT/CT systems, the majority of the installed base of SPECT does not have a CT with it, unlike with PET imaging. Thus our study is applicable to imaging being performed on any SPECT system, whether or not there is a CT present. Finally, the inclusion of RC within iterative reconstruction is now available from the manufacturers. Herein RC was performed by 3D modeling of the distance-dependent resolution inherent in SPECT imaging [31].

For the Reconstruction and Shift strategy of correction, the individual eight combined frames were reconstructed and shifted in 3D to align the volumes of bins two to eight back to the EE location of the SPN based on the average in plane and axial displacement of the SPN relative to its EE location. Following shifting they were then combined. One noise realization of the normal background studies was paired with each of the SPN present studies and had its eight sets of slices similarly shifted in 3D and combined to simulate the alignment of slices from cases in which the lesion seen on CT had no above background depreotide localization.

D. LROC human-observer studies

After the 3D reconstruction, transverse slices through the lesion centers were extracted from the SPN-present and paired SPN absent slices. The slice extracted varied slightly between the methods based on the location of the center-of-mass in the axial direction of the SPN counts in the slices with SPN. No interpolation in the axial direction was performed. The extracted slices were then adaptively thresholded specifically for each motion-correction strategy. The thresholding was needed as the apparent concentration of activity in structures such as the sternum, spine, and ribs was commonly significantly greater than that of lesions placed in the lungs. It simulated in a controlled manner the upper thresholding employed by the physicians when interpreting such studies. The thresholding was performed as previously reported in [23;24]. After thresholding, the slices were interpolated to 256×256 and then byte scaled for display. The size of the displayed pixels was thus 0.208 cm.

The observer studies were conducted in a darkened room using a monitor with a perceptually-linearized grayscale [32]. Each observer was allowed to adjust their viewing distance according to their preference, and could take as much time as they deemed necessary. The observers were not allowed to alter the display settings. Observer studies were conducted using a specifically written graphical user interface. Each image was rated by the observer on a discrete confidence scale of 1 to 6, with 1 denoting no confidence that a lesion was present, and 6 indicating high confidence that a lesion was present.

A reading session consisted of an initial training session followed by the test session. The image set for a given session consisted of images from just one of the five combinations of respiratory motion presence and correction investigated. The two-stage reading was intended to acclimatize the observer to the study environment and to characteristics of the simulated images as processed by a particular strategy. During the training, observers were given feedback as to lesion presence and location. This feedback was provided in the form of crosshairs centered on the lesion (if present). These cross-hairs could be toggled on or off to allow visibility of the lesion and surrounding region. No feedback was supplied to the observer during the test session, and only the ratings from the test session figured in the assessments of lesion detectability.

As described previously [23;24] preliminary human-observer LROC studies using the EE Frame based NCAT were conducted to determine the level of lesion contrast relative to the lung background. Also, pilot human-observer studies were conducted to optimize the reconstruction parameters for the reconstruction strategies. These studies employed the same five human-observers performing the same LROC task as in the actual test studies, but with

a different set of simulated cases. In this investigation only one of these reconstruction strategies was employed which was RBI-EM with resolution compensation. For it the parameters were 4 iterations of RBI-EM and $\sigma = 1.0$ for the 3D post-reconstruction Gaussian filtering. We did not vary the filtering as a function of correction strategy as we found detection accuracy to change little with post-filtering for this reconstruction strategy in the preliminary studies, and did not want to introduce extra smoothing which might counteract the correction of the blurring of respiratory motion inherent in the correct strategies.

The final comparison of lesion detection for the static EE Frame NCAT versus the Frame Ave and the three motion correction strategies was conducted using the same five observers as our previous studies [23;24]. Lesion contrasts relative to lung background were 6.5, 7.5 and 9 times the lung background, which were randomly assigned subject to there being an equal number of SPN with each contrast. The slices containing 102 lesion sites not employed previously in preliminary or pilot studies along with 102 matching slice locations with no lesion present were read by observers in two reading sessions of 102 slices each (51 abnormal / 51 normal). Dividing the slices into two reading sessions was done to diminish reader fatigue during a given reading session, and have a suitable number of slices being read for statistical analysis [33]. Additionally 48 of the images employed previously in preliminary or pilot studies (24 abnormal/24 normal) were used for the initial training. Each observer read the sets in an order designed to minimize reading order effects, and the order of the images within each set was randomized for each observer [33].

The confidence ratings and locations from each of the two reading sessions for each observer reading a given class of images were pooled, and the areas-under-the-LROC-curve (AUC_L) were computed using Swensson's algorithm [34]. The radius-of-correct-localization (rad_L) was determined as illustrated in the Results Section from the plot of AUC_L versus the radius from the true center of the SPN. The rad_L is used in LROC studies to determine whether an observer input location is scored as being a correct localization of the SPN, or not based on the radial distance for the true center [31].

To assess the statistical significance of regional differences in the lung at the $P < 0.05$ level, we performed a two-way ANOVA [35;36] on the AUC_L with source of slices (static, motion averaged, and one of three correction strategies) and region of the lung (upper, middle or lower third) as the factors. If there was a significant difference for a given factor, then Tukey's honest significant distance (HSD) test [35;36] was used to determine if there were pair-wise significance differences for that factor, again at the $P < 0.05$ level.

III. Results

A. Comparison of example slices

Figure 1 illustrates the appearance of the transverse slices reconstructed by RBI-EM with RC for the five alternative methods of respiratory motion presence and correction for an SPN with a contrast of 9:1 located in the upper third of the lung. The upper left slice is the noise-free case for the EE Frame and the arrow on it identifies the location of the SPN. The location of the tumor is the same in all six images. The upper right slice is the corresponding case for EE Frame with noise based on all counts within a typical clinical SPECT

acquisition. Note that the SPN is still readily seen, despite the presence of noise for the EE Frame, where there is no respiratory motion. The left slice in the middle row is for Frame Ave with a noise level equivalent to all counts being present. In this case which represents a standard clinical acquisition, the effect of simulated respiratory motion is apparent as the location of the tumor is now blurred. The middle right slice is the case for Quarter Binning with noise where one-fourth the motion and one-fourth the total counts are present. The large amount of noise in this image causes significant difficulty in determining the location of the tumor. The lower left slice is the case for Half Binning. The relative amount of noise in the image is less which causes the SPN to be more readily noticeable despite the increase in motion. The lower right slice is the case for shifting reconstructed slices in 3D to align the lesion and then combining them (Reconstruct and Shift). In this slice note that the structures other than the tumor have become blurred, the noise texture of the background has become more subtle, the tumor now appears much more spherical in shape, and its location is quite evident.

Similar results can be noted in Figure 2 which shows a comparable set of slices for an SPN with a contrast of 6.5:1 located in the middle third of the lung, and Figure 3 with an SPN of contrast of 7.5:1 located in the lower third of the lung.

B. Determination of the Radius-of-correct localization for use in LROC analysis

The human-observer results from the LROC studies were analyzed to determine the rad_L for use in determining AUC_L . Figure 4 shows the number of correct localizations plotted as a function of the radius in pixels from the center of the actual lesions for the Reconstruct and Shift and Quarter-Binning Strategies, which were the two extremes in observer performance. All three lesion contrasts were used in this analysis and the results shown are the average for all five observers. The total number of correct localizations is 102. Note that both curves reach an inflection point at approximately 11.5 pixels. Approximately the same inflection point was observed for the other three strategies. This value was therefore used as rad_L in our LROC analysis of the observer studies. With a displayed pixel size of 0.208 cm, this is equal to a radius of 2.39 cm.

C. Comparison of LROC SPN overall detection within the lung

The results of the human-observer LROC studies are shown in Table I. They are based on pooled data of five observers each reading two sets of 102 images. Values indicate the average area under the LROC curve $\pm$ the standard deviation for the five observers. Ideal motion correction corresponds to an acquisition obtained at EE using all counts and results in detection accuracy larger than that of Frame Ave which emulates a clinical acquisition. The results for Quarter-Binning and Half-Binning indicate that SPN detection based on acquisitions with less than all counts results in poorer detection than when all counts are included, even though the motion of the tumor is limited. Interestingly, the Reconstruct and Shift method results in SPN detection that is numerically larger than the ideal motion correction strategy.

The results summarized in Table I were statistically analyzed using two-way analysis of variance (ANOVA) with Tukey's honest significance difference test applied when significant

differences were observed in ANOVA. As shown in Table II a statistical significance at the $P < 0.05$ level was determined to be present between every paired comparison of the five cases of motion presence and correction strategies except the for difference between the ideal motion correction strategy (EE Frame) and the Reconstruct and Shift method.

D. Comparison of LROC SPN detection with lung location

The human-observer LROC results indicating the impact of lesion location on tumor detection for the five different comparison strategies are shown in Table III. Values indicate the area under the LROC curve $\pm$ the standard deviation. The results summarized in Table III indicate that tumor detection in the upper third of the lung is the lowest, whereas it is highest in the middle third of the lung. All 2-way comparisons of detection accuracy between the lung regions were determined to be statistically significant at $P < 0.05$ by Tukey's honest significance difference test.

E. Comparison of LROC SPN detection with contrast

The human-observer LROC results indicating the impact of lesion contrast on tumor detection for the five different comparison strategies are shown in Table IV. Values indicate the area under the LROC curve $\pm$ the standard deviation. The results summarized in Table IV indicate that the rank ordering of the strategies follows the same order at each contrast as that when all contrast were compared (Table I), with the exception that Reconstruct and Shift is second to EE Frame at the highest contrast.

IV. Discussion

As noted in the introduction, the greatest likelihood of cure for lung cancer occurs when the disease presents as an SPN. This situation occurs most commonly when the SPN is first detected on either plain film radiographs or on CT and have a size of 0.5 to 2 cm in diameter. According to the Fleischner Society recommendations [1], SPN 9 mm or greater are considered as being the most suspicious and require further evaluation which frequently involves a biopsy for tissue diagnosis. SPN of this small size typically move according to the local motion of the associated normal structures of the lung. Additionally, patients who present with an SPN, frequently lack other significant underlying pulmonary pathology and essentially fall into the category of being otherwise normal.

Because early detection is critical to improving the chances of long-term survival with lung cancer, this investigation was designed to determine the effectiveness of three alternative strategies in reducing the degrading impact of respiratory motion on the detection of small SPN in comparison to the ideal case of the absence of respiratory motion (EE Frame) and a standard clinical acquisition (Frame Ave). The basis of the first two strategies of Quarter-Binning and Half-Binning differed substantially from the methodology of the third strategy. The Quarter-Binning strategy was achieved by reconstructing the counts acquired during one-quarter of the respiratory cycle centered about EE, where patients have been found to typically pause briefly during respiration. For the Half-Binning strategy the counts for one-half of the respiratory cycle about EE were included. Both of these methods can be

accomplished clinically using just the SPECT (or PET) system with a device that tracks the respiratory motion of the individual patient [10–14].

The third strategy investigated was Reconstruct and Shift. Its application is clinically dependent on a dual-modality imaging system such as SPECT/CT (or PET/CT) where the motion of the SPN could be estimated in respiratory gated CT slices, and applied to correct the SPECT reconstructions [16;17;37]. Currently two separate imaging sessions are necessary with SPECT/CT in order to acquire both the lesion motion and SPECT data. Also CT involves an added radiation exposure, especially when performing a 4D study to estimate motion [16]. Based on the presumption that small SPN can be adequately imaged in thoracic MRI, a SPECT/MRI (or PET/MRI) system where both studies can be acquired simultaneously eliminates the need for prolongation of imaging time and the need for added radiation dose to the patient. However, the cost of adding a whole-body MRI system to a SPECT system is currently very considerable and is thus a significant barrier to the clinical adoption of this methodology. Alternatively, if the SPN is visible in the respiratory gated reconstructions, then its motion could be obtained from the emission data itself [38;39]. However if the objective of motion correction is to improve the detection of the SPN, then this approach is problematic. It is also possible that a model of lung motion perhaps coupled with some external surrogate could be developed and employed to correct for the motion of SPN to improve detection [40–43]. One could also determine the respiratory gating information for the emission data itself, bin the studies and then perform a filtering of the slices over the gated bins to reduce the impact of motion without knowing what the motion actually is [44]. However the motion is determined, our results show that SPN detection can be significantly increased by employing accurate knowledge of the SPN movement during respiration to correct for its motion without the need to reduce the counts by reconstructing only a portion of the respiratory cycle. Our Quarter-Binning and Half-Binning results show that this approach for reducing motion within the data employed in reconstruction can actually decrease the detection accuracy of SPN in SPECT due to the increased noise levels. These findings are of course limited to the experimental setup of this paper.

Herein we observed that reducing motion blurring by using events acquired for a portion of the respiratory cycle around EE without increasing acquisition time actually resulted in a decrease in AUC_L from the reduction in counts. However, Liu et al [15] observed that a reduction of 50% or less in counts for the same purpose resulted in no significant deterioration in activity quantification as judged by SUV_{MAX} . We believe this difference in the utility of reducing respiratory motion through employing events from only a portion of the respiratory cycle between our two studies is due in large part to the difference in the tasks being performed, as well as the difference in modalities employed. The human observers in our study were doing a task that required localization (determining where the SPN was if present) in addition to providing a rating as to their confidence that their selected location was an SPN. They were thus sensitive to the correlated noise (noise blobs) in the entire region of the lungs of the slice being displayed, and not just at the site of the SPN. As can be appreciated from the figures in our paper, as the count level decreased the noise texture changed such that it was harder for the human observers to correctly identify SPN as opposed to noise blobs at alternative locations, and even if they correctly localized the SPN they would likely be less confident which would result in a lower rating as to their

confidence. Another likely contributing factor to the difference in the two studies is that the contrast of the lesions in this study were selected to provide a challenge for the human observers performing the LROC task; whereas, the contrast in the study of Liu et al seemed to allow the lesions to be easily visualized. Also the slice counts in PET are generally higher than in SPECT. Thus our SPECT LROC task was count limited to begin with which resulted in a decrease in detection accuracy with decreased counts as illustrated in the studies of He et al [45]. Finally, as stated in the Material and Methods Section we did not adapt the post-smoothing for the reduced count-level strategies because of the stability seen in our preliminary LROC studies of detection accuracy as a function of post-smoothing with RC in reconstruction, and our desire not to introduce more smoothing to these studies which could counteract the reduction in SPN blurring with reduced motion which was the goal of these strategies. Thus this could also have been a factor in the significant reduction in detection accuracy for these strategies.

That the “Reconstruct and Shift” method might result in an improvement in the AUC_L to near that of our no-motion (EE) reconstructions was anticipated based on the previous work of a number of investigations of equivalent approaches in PET. For example, Nehmeh et al. [18] showed an increase in measured tumor SUV. As a further illustration, Qiao et al. [19] in a phantom study showed that this correction strategy reduced the error in quantification of activity by 95% compared to acquisition with no simulated motion. Also, Li et al. [20] in a phantom study showed that an equivalent reconstruction approach improved the signal-to-noise ratio over that of just 3D acquisition and reconstruction. In refinements of this method Lamare et al. [21] showed that a CT based affine-transformation which included accounting for scaling in 3D produced significant improvements in the lung and heart region in simulations, and Thorndyke et al. [22] used “retrospective stacking” which employed b-spline deformable image registration to correct for motion between respiratory amplitude-binned PET slices and saw large changes in the contrast-to-noise ratios compared to no correction in studies with phantoms. Thus our results are confirmatory to those just cited and others that the improvement in image quality to be gained by using CT estimated motion to correct lesion motion in emission imaging results in an increase in lung lesion detection accuracy by human observers. However, since CT acquisition is typically sequential with SPECT or PET acquisition, there is always the possibility that lung motion may differ between CT and emission imaging. Our work does not address the question of how accurate the CT motion model has to be to result in an improvement in detection by human observers when employed in emission reconstruction. Thus this remains an interesting open question.

Although not statistically significant, the Reconstruct and Shift strategy actually resulted in numerically better detection accuracy than the ideal case of the absence of motion (Tables I and II). This hint of better detection accuracy than that obtained with EE may be due to the smoothing of structures whose motion was not correctly modeled. With these structures thereby reduced in contrast they may have been less of a distracter to the observers.

The results of this investigation show that there are regional differences in the lung regarding tumor detection. The upper third of the lung is the region where detection of SPN was shown to be the worst, even though apical lesions were on average associated with less respiratory motion than in the other lung regions [23;24]. During performance of the training studies our

observers noted that SPN located at lung / soft tissue boundaries were hard to differentiate from positive noise correlations (noise blobs) occurring there. Due to the apical region having the smallest cross-section area, this distinction needed to be made most often in this region. That is SPN were on average more often located near the lung / soft tissue boundary in the apical region than far enough away to be more easily visualized. We believe this could be one possible explanation of the lowest detection performance being in the apical region.

One limitation of our work is that we did not assess comparing the accuracy of LROC to a location-known-exactly (LKE) strategy to see if one could obtain the same benefit in improved detection accuracy by just supplying the potential SPN location to the observer instead of employing it in reconstruction as could be available from a CT. Further limitations are we also did not assess the impact of errors in the estimated motion when used for correction, our study is based on the lung motion of a single volunteer's CT studies, and a simple model of SPN motion which did not include hysteresis between inspiration and expiration or the possible drifting in respiratory amplitude as can occur clinically.

Limitations aside, the results presented in this investigation can be expected to have future relevance in both medical imaging and radiotherapy. New imaging systems have now become available that feature dual-modality techniques consisting of the combination of PET/CT or SPECT/CT. These developments have led to the recognition of the importance that respiratory motion has on the detection of small lesions [14]. Due to the better spatial resolution in PET, the findings presented in this investigation are quite relevant to PET/CT in which the adverse effects of respiratory motion have already been reported as an important problem [14].

V. Conclusion

This investigation demonstrates that tumor detection based on acquisitions associated with less than all the counts which could potentially be employed can result in poor detection despite limiting motion of the lesion. That is, the standard clinical method of using a respiration-averaged acquisition (Frame Ave) resulted in tumor detection that is superior to either the Quarter Binning or Half Binning strategies herein. The Reconstruct and Shift method results in tumor detection that is equivalent to ideal motion correction (EE Frame). The effectiveness of the Reconstruct and Shift method is due to the use of all counts obtained in the acquisition, a sharpening of the SPN due to approximate correction of its motion, and a possibly additional subtle smoothing of structures in the slices whose motion was not the same as the SPN. Further investigations aimed at overcoming some of the limitations of this study and expanding it to investigating PET/CT imaging are warranted.

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Figure 1.

Six example transverse slices for an SPN with a contrast of 9:1 in the upper lung region. The upper left slice is the no noise added (ideal) case for End-Expiration (EE) Frame with SPN location indicated by the arrow, and the upper right slice is EE Frame having a noise level of a typical clinical acquisition. The middle left slice is Frame Ave which has the noise level and respiratory motion of a typical clinical study, and the middle right slice is quarter binning. The lower left slice is half binning, and the lower right slice is the case for shifting the reconstructions to realign the lesion.

Figure 2.
Six example transverse slices for an SPN with a contrast of 6.5:1 in the middle lung region. The layout of the slices is the same as Figure 1. Again SPN location indicated by the arrow on the upper left slice.

Figure 3.

Six example transverse slices for an SPN with a contrast of 7.5:1 in the lower lung region. The layout of the slices is the same as Figure 1. Again SPN location indicated by the arrow on the upper left slice.

Figure 4.

Number of correct localizations averaged for over the five human-observers for the 102 lesions plotted as a function of the radius in pixels from center of actual lesion for Reconstruct and Shift (solid line) and Quarter-Binning (dashed line) strategies which were the two extremes in observer performance. The result reveals that the curve reaches a first inflection point at approximately 11.5 pixels for both strategies. This distance was therefore

used as the radius of correct localization. With a pixel size of 0.208 cm, this is equal to 2.39 cm.

Table I

Human-observer LROC results indicating the effectiveness of the three alternative methods in reducing the degrading impact of respiratory motion on the detection of small SPN. The results presented are based on pooled data of five observers each reading two sets of 102 images. The values indicate the average area under the LROC curve rounded to two decimal places $\pm$ one standard deviation.

EE Frame (All Counts)	Frame Ave (All Counts)	Quarter Binning (1/4 Counts)	Half Binning (1/2 Counts)	Recons & Shift (All Counts)
0.76 $\pm$ 0.02	0.66 $\pm$ 0.03	0.37 $\pm$ 0.04	0.54 $\pm$ 0.04	0.81 $\pm$ 0.04

Table II

Statistical significance of 2-way comparisons of strategies by Tukey's honest significant distance test for the human-observer LROC results of Table I. NS is not significant and <0.05 mean significant at $P < 0.05$ level.

Strategy	Frame Ave	Quarter Binning	Half Binning	Recon. & Shift
EE Frame	<0.05	<0.05	<0.05	NS
Frame Ave	-	<0.05	<0.05	<0.05
Quarter Binning	-	-	<0.05	<0.05
Half Binning	-	-	-	<0.05

Table III

Human-observer LROC results indicating the impact of tumor location on detection for the five different strategies. The values indicate the area under the LROC curve rounded to two decimal places $\pm$ the standard deviation. Based on all strategies and observers all 2-way comparisons of location were statistically significantly different by Tukey's honest significant distance test at $P < 0.05$ level.

Location	EE Frame	Frame Ave	Quarter Binning	Half Binning	Recon. & Shift
Upper	0.69 $\pm$ 0.03	0.55 $\pm$ 0.07	0.32 $\pm$ 0.06	0.54 $\pm$ 0.05	0.72 $\pm$ 0.04
Middle	0.86 $\pm$ 0.03	0.80 $\pm$ 0.06	0.40 $\pm$ 0.04	0.52 $\pm$ 0.05	0.88 $\pm$ 0.05
Lower	0.75 $\pm$ 0.07	0.66 $\pm$ 0.09	0.42 $\pm$ 0.10	0.56 $\pm$ 0.08	0.84 $\pm$ 0.04

Human-observer LROC results indicating the impact of tumor contrast on detection for the five different strategies. The values indicate the area under the LROC curve rounded to two decimal places $\pm$ the standard deviation.

Table IV

Contrast	EE Frame	Frame Ave	Quarter Binning	Half Binning	Recon. & Shift
6.5	0.65 $\pm$ 0.05	0.54 $\pm$ 0.03	0.39 $\pm$ 0.04	0.42 $\pm$ 0.04	0.74 $\pm$ 0.04
7.5	0.77 $\pm$ 0.04	0.66 $\pm$ 0.06	0.40 $\pm$ 0.07	0.58 $\pm$ 0.04	0.85 $\pm$ 0.05
9.0	0.89 $\pm$ 0.02	0.81 $\pm$ 0.05	0.35 $\pm$ 0.04	0.61 $\pm$ 0.06	0.84 $\pm$ 0.03