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Modeling the respiratory motion of solitary pulmonary nodules and determining the impact of respiratory motion on their detection in SPECT imaging

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Abstract

The objectives of this investigation were to model the respiratory motion of solitary pulmonary nodules (SPN) and then use this model to determine the impact of respiratory motion on the localization and detection of small SPN in SPECT imaging for four reconstruction strategies. The respiratory motion of SPN was based on that of normal anatomic structures in the lungs

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determined from breath-held CT images of a volunteer acquired at two different stages of respiration. End-expiration (EE) and time-averaged (Frame Av) non-uniform-B-spline cardiac torso (NCAT) digital-anthropomorphic phantoms were created using this information for respiratory motion within the lungs. SPN were represented as 1 cm diameter spheres which underwent linear motion during respiration between the EE and end-inspiration (EI) time points. The SIMIND Monte Carlo program was used to produce SPECT projection data simulating Tc-99m depreotide (NeoTect) imaging. The projections were reconstructed using 1) no correction (NC), 2) attenuation correction (AC), 3) resolution compensation (RC), and 4) attenuation correction, scatter correction, and resolution compensation (AC_SC_RC). A human-observer localization receiver operating characteristics (LROC) study was then performed to determine the difference in localization and detection accuracy with and without the presence of respiratory motion. The LROC comparison determined that respiratory motion degrades tumor detection for all four reconstruction strategies, thus correction for SPN motion would be expected to improve detection accuracy. The inclusion of RC in reconstruction improved detection accuracy for both EE and Frame Av over NC and AC. Also the magnitude of the impact of motion was least for AC_SC_RC.

Index Terms

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

I. Introduction

The greatest likelihood of cure for lung cancer occurs when the disease presents as a solitary pulmonary nodule (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 the most suspicious. It is recommended that these lesions be followed radiographically over short intervals of time, and it may also be advised that the patients undergo a biopsy. The development of radiotracers that are specific to particular antigens expressed on the cell surfaces of malignant SPN affords the unique opportunity to substantially assist in the classification task of identifying malignant from non-malignant SPN. Moreover, the ability to identify malignant SPN through emission imaging can be further leveraged to determine which patients should undergo a transthoracic percutaneous needle biopsy for tissue diagnosis and which should proceed directly to either a video-assisted thoracoscopic surgery or open resection by thoracotomy.

Respiratory motion, however, has been known to cause artifacts and decrease tumor detectability in medical imaging for some time [2;3]. In single photon emission computed tomographic (SPECT) imaging, acquisition times may be 20 minutes or longer. Under these circumstances, breath holding techniques to reduce the impact of respiratory motion are neither practical nor possible. It is thus of interest to systematically investigate potential methods designed to improve tumor detection by diminishing or correcting respiratory motion. Carrying out such an investigation with simulated SPECT acquisitions based on a

humanoid digital phantom provides the investigator the ability to know the truth as to lesion presence and location, as well as the extent of motion. Thus comparisons of tumor detectability can be made for the case of no motion versus realistically modeled respiratory motion. This would allow for assessment of the impact of motion, and investigation of the possible effectiveness of strategies to decrease it.

One of the most widely used humanoid digital phantoms for defining source and attenuation maps for simulated imaging is the non-uniform rational B-spline cardiac torso, or NCAT phantom [4;5]. The NCAT is designed by the “warping” of the spline surfaces to correctly fit the shape of anatomic structures as imaged by magnetic resonance imaging (MRI) or computed tomographic (CT) imaging techniques. Four-dimensional (4D) NCAT phantoms which model respiratory motion can be created by generating two or more individual three-dimensional (3D) NCAT phantoms each being rendered at a specific time point within the respiratory cycle such as end-expiration (EE) or end-inspiration (EI). One then interpolates between these to create a set of NCAT phantoms spanning the entire respiratory cycle at the desired temporal sampling using a model of the motion of structures with respiration[4;5].

There were two objectives of this study. The first was to develop a 4D NCAT phantom modified to match the anatomy and respiratory motion exhibited in CT slices of a human volunteer, with the motion of SPN within the lungs modeled on that of anatomical structures within the lungs of the volunteer. The second objective was to use this modified NCAT phantom to investigate the impact of the respiratory motion of the SPN with human-observer localization-receiver-operating-characteristic (LROC) studies [6] for selected reconstruction strategies. In the following Methods Section we first detail our development of a modified 4D NCAT with realistic modeling of the motion of SPN throughout the lungs. We next detail our creation of photopeak and scatter-window SPECT projection sets from the modified NCAT phantoms using the SIMIND Monte Carlo package [7]. This is then followed by defining the four reconstruction strategies in which we will compare the impact of respiratory motion and the selection of the reconstruction parameters to be employed by them through human-observer lesion-detection studies. Finally we detail the methodology for our LROC human-observer studies to assess the impact of motion, and our statistical analysis of these studies. In the Results Section we illustrate the 3D motion of the anatomical sites within the lung which served to model the motion of SPN. We then show EE and EI NCAT phantoms based on the volunteer CT studies. We then document how the range of lesion contrasts employed in the study was determined, as well as the radius of correct localization for LROC analysis. This is followed by specification of the reconstruction parameters we determined in human-observer studies to result in the best detection accuracy for each reconstruction strategy. Finally our global and regional LROC results for the four reconstruction strategies, both with and without simulated respiratory motion, are presented. We conclude with a discussion of our findings, study limitations, and the conclusions we believe that can be drawn from our results.

II. Materials and Methods

A. Determination of information for modeling respiratory motion of SPN and structures of torso from CT slices

Residual volume (RV) of the lungs is defined as the volume of air remaining in the lungs after maximum expiration[8]. Sets of CT images were acquired in a normal volunteer during apnea with total lung volume held at 5% above RV, and 40% above RV as determined by the use of a pneumotachometer and high frequency balloon valve which prohibited air flow at the mouth when lung volume reached the desired level on the expiratory limb [9]. These CT images were acquired on an electron beam CT scanner (EBCT: Imatron, South San Francisco) 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. The CT images were studied to serve as models for the motion of SPN in patients whose lungs were otherwise normal under the assumption that the presence of a small SPN would not significantly modify the local motion within the lung.

A program was written in Interactive Data Language (IDL) which allowed the interactive display of the CT slices and the recording of the 3D location of selected structures in the slices. A radiation oncologist marked identical anatomic structures on the two CT data sets corresponding to volumes of 5% above RV and 40% above RV in the respiratory cycle. 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. Again our assumption in using these sites was that the presence of a small SPN would not alter the motion of the lung locally.

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. They were used to adapt the structures in the standard 4D NCAT to the anatomy of this volunteer as detailed in the following section.

B. Generation of a modified 4D NCAT phantom and SPN with respiratory motion based on that determined from CT

The surfaces of the standard NCAT were altered to conform to the specific anatomy of the healthy volunteer using the CT images acquired at 5% and 40% above RV. The change in lung volume between these corresponded to 1610 *ml*. The limitation of using these two modified NCAT phantoms to represent EE and EI was recognized since they do not accurately represent the anatomic position and volume associated with average tidal breathing within the normal respiratory cycle. To compensate for this discrepancy, the modified NCAT phantom that was derived at 5% above RV was secondarily modified to better approximate EE. The scaling of this phantom was accomplished by using simple

linear interpolation in redefining its anatomic surfaces at locations between 5% above RV and 40% RV to create locations corresponding to 19% above RV. The surfaces of the modified NCAT phantom derived from the CT images acquired at 40% above RV were employed to represent EI locations. These two modified NCAT phantoms correspond to a volume change in the lungs of 952 *ml*. Normal tidal volume is 500 *ml* and occurs at lung volumes between 24% and 35% above RV [8]. We employed the increased tidal volume of 952 *ml* as it might easily correspond to the respiratory volume of an apprehensive patient confronting the diagnosis of cancer and undergoing his or her first SPECT study. As detailed in the Discussion Section the magnitude of the resulting motions of SPN we employed agreed well with those reported in clinical imaging.

We used the assumption that structures transform between the two different states along the x, y, and z directions according to the same rate of change as that of the volume. Thus the change in the 3D positions of the points that define a structure or surface for a 5 second respiratory cycle with inspiration occurring during the first 2 seconds and expiration during the subsequent 3 seconds were taken to be

$$\Delta x, y, z(t) = -\frac{1}{2}\Delta_{x,y,z}^{\text{Exp} \rightarrow \text{Insp}} \cos(\pi t/2) + \frac{1}{2}\Delta_{x,y,z}^{\text{Exp} \rightarrow \text{Insp}} \text{ for } 0 \leq t \leq 2 \quad (1)$$

$$\Delta x, y, z(t) = -\frac{1}{2}\Delta_{x,y,z}^{\text{Insp} \rightarrow \text{Exp}} \cos(\pi(5-t)/3) + \frac{1}{2}\Delta_{x,y,z}^{\text{Insp} \rightarrow \text{Exp}} \text{ for } 2 \leq t \leq 5 \quad (2)$$

where $\Delta_{x,y,z}^{\text{Exp} \rightarrow \text{Insp}}$ represents the change in the 3D position of points from end-expiration to end-inspiration and $\Delta_{x,y,z}^{\text{Insp} \rightarrow \text{Exp}}$ represents the change in the 3D position of points from end-inspiration to end-expiration. The cosine function was used in agreement with the findings reported by George et al.[10]. We generated thirty-two modified NCAT torso phantoms over one full respiratory cycle beginning with EE through EI and ending again at EE according to (1) and (2) to create the dynamic motion associated with breathing for the normal torso. This results in thirteen modified phantoms between EE and EI, and nineteen modified phantoms between EI and the return to EE. Additionally, a respiration-averaged modified NCAT torso phantom was generated as well.

One hundred and fifty pairs of points were selected from the 227 initially marked in the CT slices to represent the center of 1.0 cm diameter spheres to be used as simulated SPN. The 1.0 cm diameter agrees with criteria of the Fleischner Society of SPN of 9 mm or larger representing the most suspicious. Also our past experience in lesion detection studies was that for lesions smaller than the SPECT system FWHM variations in lesion size were manifested more as changes in contrast than apparent size in the reconstructed slices. Thus instead of altering size, the contrast of the 1.0 cm lesions was varied to fall within a range which provided areas under the LROC curves suitable for conduction of the human observer studies as detailed in following section II.E. Using the NCAT software, 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 spheres also according to equations (1) and (2). In addition, a respiration-averaged sphere phantom

was created as the average of the spheres at the 32 time points of respiration for each of the 150 simulated tumor sites. The 150 locations were equally divided between the right 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).

C. Projection data simulation

The radiopharmaceutical selected for investigating the impact of respiratory motion on the detection of small SPN in SPECT imaging was Tc-99m labeled depreotide (NeoTect). Tc-99m labeled depreotide is a low molecular weight polypeptide capable of binding to the somatostatin receptor which is often expressed on the cell surface membrane of both small cell and non-small cell lung carcinomas[11;12]. Tc-99m labeled depreotide is approved by the US Food and Drug Administration for use in the evaluation of suspicious SPN. The relative concentrations of Tc-99m labeled depreotide within the various tissues and organs contained within the 4D modified NCAT phantoms were obtained from pharmacokinetic data supplied by the manufacturer. These 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. 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 the EE Frame which is the first of the 32 modified NCAT phantoms, and for the respiration-averaged modified NCAT phantom (called Frame Av hereafter). Based on the emitted photon energy of 140.5 keV, EE and Frame Av attenuation maps were also created.

With the above source and attenuation maps as input, the SIMIND Monte Carlo program [7] was used to create low-noise SPECT projection data for the EE Frame and Frame Av modified phantoms for use as normal backgrounds. The SIMIND Monte Carlo program was also used to produce low-noise SPECT projection data for the two NCAT sphere phantoms for the EE Frame and Frame Av for each of the 150 simulated tumor locations. In both cases, this corresponded to simulating clinical acquisition with a low-energy high-resolution parallel-hole (LEHR) collimator on our Philips Prism2000 SPECT system which is the system employed at our site for depreotide imaging. The radius-of-rotation between the collimator face and the axis-of-rotation was 25 cm which was approximately the average radius employed in clinical imaging. With this radius the system FWHM was 1.44 cm at the axis of rotation for acquisition. 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 and a scatter window for use in Triple Energy Window (TEW) scatter correction[13] were produced.

Five clinical Tc-99m labeled depreotide studies were analyzed to determine the total number of counts to be used in the simulated acquisitions. The average total number of counts in the photopeak window was determined to be 22.5 million. Thus the normal background photopeak projection sets were scaled such that when the random Poisson noise sets were produced from them, the expected number of counts was 22.5 million. The same factor was used for the TEW scatter window projections which resulted in an average expected number of counts of 4.5 million in them. The same scaling factor was applied to the projections sets in which the SPN were present prior to the noisy version of them being produced. For the

purposes of this study, the same total counts were assigned to the modified NCAT phantoms corresponding to the EE Frame and to the respiration-averaged NCAT phantoms (Frame Av). Thus the EE Frame slices were selected to represent the ideal case of acquisition in the absence of respiratory motion. Against this ideal case we compared the detection accuracy in the Frame Av reconstructions that contained the combined motion of the 32 frames covering the respiratory cycle.

D. Image reconstruction strategies

The second objective of this investigation was to determine the impact of respiratory motion on SPN detection both globally and regionally within the lung, and if this impact varied with reconstruction strategy. For this task four variants of the rescaled-block-iterative expectation-maximization (RBI-EM) algorithm[14] were chosen for investigation. These four were: 1) RBI-EM with no correction (NC), 2) RBI-EM with attenuation correction (AC), 3) RBI-EM with resolution compensation (RC), and 4) RBI-EM with attenuation correction, scatter correction, and resolution compensation (AC_SC_RC). NC was selected as the standard baseline against which to compare the others which included compensation for one or more of the physical degradations inherent in SPECT imaging. NC was also investigated as it was of interest to determine if AC alone would deteriorate or improve detection accuracy in comparison to it. AC was investigated because of its demonstrated success in improving detection accuracy in SPECT myocardial perfusion imaging [15;16]. Thus it was of interest to determine if it may have a similar impact in SPN imaging. RC was included because the inclusion of system spatial resolution in reconstruction has now become available from all the manufactures of SPECT systems, and had the potential to improve detection accuracy of the small SPN employed in this study. We were also particularly interested in determining RC's utility even in the presence of the additional blurring of respiratory motion. Further due to the potential for a mismatch between attenuation during clinical imaging and that measured during sequential CT imaging, we were interested in determining if RC alone could improve detection accuracy thereby avoiding this potential problem of attenuation mismatch clinically. AC_SC_RC was included as the strategy with full modeling of the physical degradations of imaging, aside from motion, and thus had the expectation of proving most beneficial in SPN detection.

The RBI-EM algorithm was selected over other possible iterative algorithms based on its convergence properties in the absence of subset balance[14], as well as its past LROC performance with simulated images[17]. Based on our previous study of RBI-EM[17], 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. Each of the RBI-EM variants employed a 3D post-reconstruction Gaussian filter which was optimized for that strategy for human-observer lesion detection. The reconstruction parameters of number of iterations and post-reconstruction 3-D Gaussian filter σ were subsequently optimized by human-observer LROC studies for each of the variants as detailed below in the section on human-observer LROC studies.

AC transmission imaging on our Philips Prism2000 SPECT system is performed using a scanning-line source. Note that this system which employs simultaneous transmission / emission imaging diminishes the potential for attenuation mismatch between the derived attenuation maps and emission data compared to sequential imaging. To approximate this process simulated transmission projection data were generated using an analytic projector modeling our scanning Gd-153 line source[18] from the original modified NCAT attenuation distributions for both EE Frame and Frame Av. The two sets of projection data were scaled to match clinical count levels after which random Poisson noise realizations were generated. A single noise realization was created for each set of projections; however, prior to post-filtering the noise in each slice was independent of the others. With the above projection data as input, two attenuation maps were reconstructed using the block-iterative transmission AB (BITAB) reconstruction algorithm[19]. This results in a clinically realistic and noisy attenuation map corresponding to the source distribution of EE Frame and to the source distribution of Frame Av.

For SC the two-energy window (TEW) variant of the triple-energy window method was employed in determining an estimate of the scatter contribution in the acquired projection data from the scatter window data[13]. The scatter estimate was added in RBI-EM reconstruction to the result of the projection of the current estimate prior to being divided into the simulated projection data. This avoids corrupting the Poisson noise nature of the projection data and the question of how to incorporate negative values[20].

RC was performed by 3D modeling of the distance-dependent resolution inherent in SPECT imaging. In past LROC studies we have determined such modeling to significantly improve image quality[21]. Thus we investigated RC alone, as well as in combination with AC and SC.

E. Human-observer LROC studies

After the 3D reconstruction, transverse slices through the lesion centers were extracted from the tumor-present cases. The slices were then adaptively thresholded specifically for a given reconstruction 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 by determining the maximum count in the circular cross-sectional region of each lesion in each transverse slice for a given reconstruction strategy for the set of reconstruction parameters used to reconstruct the slices. The maximum and standard deviation of the maxima was then determined. The upper threshold for the strategy and reconstruction parameter combination was then taken as the maximum of the maxima plus one standard deviation. This sets a buffer above the highest pixel count among all the lesions for a given strategy and reconstruction parameter combination equal to the standard deviation among the pixel counts. Thus no lesion pixels are altered by this process. This upper thresholding procedure was chosen to increase lesion contrast but leave unaffected the noise structure in the region of the lesion. The lesion-absent slices for a given reconstruction strategy and parameter combination were thresholded at the same level as the lesion present

slices. The lower threshold in all cases was zero. 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[22]. Each observer was allowed to adjust his viewing distance according to his preference, and could take as much time as he 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 reconstruction strategy. 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 unobscured 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.

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 prior to the human-observer LROC studies employed to select (optimize) the reconstruction parameters. The preliminary studies employed two observers from our medical physics group who had significant past experience in performing LROC studies. Each performed an LROC evaluation on sets consisting of 96 slices. Of these 48 were with lesion present and 48 were from matching transverse levels with no lesion present. The first 32 of the slices presented to the observers were training slices. The remaining 64 were test slices, 32 of which had lesions. The goal was to determine the levels of lesion contrast in which the lesion is neither so faint that it is very difficult to detect nor so bright that it is almost always identified. In our experience this corresponds to areas-under-the-LROC-curve (AUC_L) that range between 0.6 and 0.9. Note that the AUC_L can go below 0.5 unlike in ROC. The two different representative reconstruction strategies used in determining the lesion contrast were RBI-EM reconstruction with AC and RBI-EM with RC. These were selected as representative of strategies whose performance (AUC_L) would likely be in the mid-range of the four being compared. In each strategy, a single combination of the number of iterations and σ of the 3D post Gaussian filter was used. The selection of these initial reconstruction parameters was based on a visual assessment of image quality. For the RBI-EM with AC strategy, the reconstruction parameters of two iterations with σ of 1.0 were used. For the RBI-EM with RC, the reconstruction parameters of six iterations with σ of 1.0 were used. The human-observer LROC results from the contrast determination studies were also used in defining the radius-of-correct-localization (rad_L) for use in subsequent work. The rad_L is used in LROC studies to determine whether this is scored as being a correct localization of the lesion, or not [21]. The number of iterations and standard deviation (σ) of the 3D post-

Gaussian filtering investigated for determination of optimum values were based on previous experience in optimizing these parameters for thoracic tumor detection and detection of perfusion defects [16;21;23–26]. The selected parameters for NC and AC were 2 and 4 iterations, and for σ were 0.5, 0.75, 1.0, 1.5, or 2.0. For RC and AC_SC_RC they were 4, 6, and 8 iterations and σ 's of 0.5, 0.75, 1.0, and 1.5.

Pilot human-observer studies using the EE Frame based NCAT were conducted to optimize the reconstruction parameters for each strategy. Five observers from our medical physics group performed the study by rating sets consisting of 32 training slices (16 abnormal and 16 normal) followed by 64 test slices (32 abnormal and 32 normal) as with the preliminary studies. The lesion contrasts in this study were 6.5 and 9 times background as these were determined in the preliminary LROC studies to have average AUC_L within the desired range in the preliminary LROC studies. Separate optimizations were performed for each strategy. Each of the five observers read the sets in an order designed to limit reading order effects [21]. The order of the images within each set was randomized for each observer.

The final comparison of lesion detection for the static EE Frame NCAT versus the Frame Av NCAT slices was conducted using the same five observers. Lesion contrasts relative to lung background were 6.5, 7.5 and 9 times the lung background. For each reconstruction strategy and static or motion average NCAT, the remaining 102 lesion sites and an equal number of normal cases from matching transverse levels were read by the observers in two reading sessions. For a given reading session, 48 images (24 abnormal/24 normal) were used for the initial training, while 102 images (51 abnormal/51 normal) were evaluated in the test session. Again 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.

The confidence ratings and locations from each of the two reading sessions for each observer reading a given reconstruction strategy and motion state were pooled, and the AUC_L was computed using Swensson's algorithm[6] and the rad_L determined from the preliminary LROC studies. To assess the statistical significance of the differences at the $P < 0.05$ level, we performed a three-way ANOVA[27;28] on the AUC_L with motion state (static or motion averaged), reconstruction strategy (NC, AC, RC, or AC_SC_RC), 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 difference (HSD) test[27;28] was used to determine if there were pair-wise significance differences between the levels for that factor, again at the $P < 0.05$ level.

III. Results

A. Respiratory motion model

An appreciation of the variation in direction and magnitude of motion for the anatomical structures determined in the CT slices acquired at 5% RV and 40% RV from the healthy volunteer can be gained from the three summed projections shown in Figure 1. The transverse summed projection shows the posterior / anterior and medial /lateral motion of the sites. The coronal summed projection shows the superior / inferior and medial / lateral motion of the sites. The sagittal summed projection shows the superior / inferior and

posterior / anterior motion of the sites. The origin of each arrow indicates a selected point in one of the lungs at 5% RV, and the tip of arrow indicates the same point at 40% RV. Note that the greatest extent of inferior motion occurs in the region of the lung bases. However, it was also seen that there is a significant anterior (sagittal view) and medial /lateral motion (transverse view) of structures with inspiration. Note also that this especially occurs in the central portions of the lungs that include the region of the hilum and portions of the heart. Recall that as described in the methods section, the motion illustrated in Figure 1 was reduced so as to better represent that of a patient during SPECT imaging. A total of 227 pairs of matching anatomical sites were determined in the CT slices. Of these 150 were selected with which to perform the LROC studies.

B. Modified NCAT phantom

In the top row of Figure 2 is an anterior-posterior shaded surface display of modified NCAT phantoms generated at EE (19%RV) and at EI (40%RV) as detailed in the Methods Section showing the change in location of the surfaces of the anatomic structures in going from EE to EI. It is demonstrated that the sternum and rib tips move superiorly while the heart, liver, stomach, and spleen move inferiorly. Included in the figure are two potential locations of SPN modeled as 1.0 cm diameter spheres. The change in location of the SPN in going from EE to EI can be seen as the difference in the location of the sphere at EI indicated by the symbol $\bigcirc$ relative to the $\bullet$ symbol indicating its location in EE. It is shown that there is both inferior and medial motion. In the bottom row of Figure 2 are cranial-caudal shaded surface displays of the NCAT phantoms at EE and EI including the SPN. This view of the phantoms and SPN looking down through the shoulders demonstrates the anterior and medial change in location of the SPN in going from EE to EI, which is again seen as the difference in the location of the sphere at EI relative to its location in EE.

Table 1 summarizes the extent and variability of simulated respiratory motion of the 150 SPN in the total lung and each of the three thirds. Notice that the average motion in the superior / inferior (SI) direction increases from the apex to base of lungs in agreement with the visual impression in Figure 1. Also note that on average the greatest extent of motion is in the middle third of the lung due to the larger AP motion there than in the lower third.

C. LROC human-observer studies

The LROC results from the contrast determination studies were analyzed to determine rad_L for giving the observer credit for correct localization [21]. Figure 3 shows the number of correct localizations plotted as a function of the radius in pixels from the center of the actual lesion. Lesion contrasts of 6.5, 9, and 11.5 times the background and the reconstruction strategies of RBI-EM with AC and RBI-EM with RC were used in this analysis. The top two curves correspond to a contrast of 11.5 for RBI-EM with AC and RBI-EM with RC. The middle two curves correspond to a contrast of 9 for RBI-EM with AC and RBI-EM with RC. The lowest two curves correspond to a contrast of 6.5 for RBI-EM with AC and RBI-EM with RC. All curves reach an inflection point at approximately 8.5 pixels which was subsequently used as the rad_L in our investigation. With a pixel size of 0.208 cm after being interpolated from 128×128 to 256×256 for display, this is equal to a rad_L of 1.77 cm.

From these preliminary LROC studies, lesion contrasts of 6.5 and 9 were determined to provide suitable areas under the LROC curves for the stationary tumors (EE Frame) as reconstructed by two of the reconstruction strategies investigated. These two selected contrasts were then employed in the reconstruction parameter optimization studies from which the results are shown in Table II. For NC there was a large range in the average AUC_L of the 5 observers from 0.50 to 0.83. The largest variation in AUC_L was between different values of σ , with less variation occurring with iteration number. Similar results were observed for AC with AUC_L there varying between 0.42 and 0.79. For RC the variation in AUC_L with reconstruction parameters was much less being between 0.83 and 0.89. For AC_SC_RC the variation in AUC_L was again small being 0.85 to 0.90. For both RC and AC_SC_RC it was difficult to say whether variation in iteration number or σ had a larger impact. Full results of the optimization study can be found in [29]. From these investigations it was determined that for each of the reconstruction strategies the optimal value of σ was 1.0. For the NC and AC strategies, the optimal number of iterations was two. For the RC and AC_SC_RC strategies, the optimal number of iterations was four in line with our past observations that a larger number of iterations are required when RC is included in reconstruction [21].

Figures 4 and 5 demonstrate the impact of σ of the 3-D Gaussian smoothing filter on lesion appearance versus noise, as well as the impact of respiratory motion. In Figure 4, the upper left image corresponds to two iterations and $\sigma = 0.5$ while the upper right image corresponds to two iterations and $\sigma = 1$ for the reconstruction strategy of RBI-EM with AC. The images shown in this figure correspond to the no motion case of stationary tumors (EE Frame) in which all the counts are assigned to EE Frame NCAT. This represents ideal motion correction. Reconstructions of the SIMIND projections before the Poisson noise was added are shown beneath each of the top two images. The images shown in Figure 5 are for the exact same tumor as seen in Figure 4 and correspond to the respiration-averaged case which represents an actual clinical acquisition. Again, the upper left image corresponds to two iterations and $\sigma = 0.5$ while the upper right image corresponds to two iterations and $\sigma = 1$ for the reconstruction strategy of RBI-EM with AC. With motion, the location of the tumor is not apparent except in the noise-free case which is shown beneath each. The influence of the number of iterations and σ of the 3-D Gaussian smoothing filter was similarly as significant for the reconstruction strategy of RBI-EM with NC. However, the influence of the number of iterations and σ of the 3-D Gaussian smoothing filter was less significant for RBI-EM with RC and least for RBI-EM with AC_SC_RC.

Figures 6 and 7 show example transverse slices for two lesion present locations for each of the four reconstruction strategies for end-expiration (EE) and motion averaged cases. A lesion contrast of 9 is shown in both figures to facilitate visualization of the lesions whose location is indicated in the first slice by an arrow.

The human-observer LROC results for EE Frame versus Frame Av indicating the impact of simulated respiratory motion on detection of SPN for the entire lung and each of the three sub-regions are shown in Table III. The results presented are based on five observers each reading two sets of 102 test images (204 images in total). Sixty-eight of these were from each of the three sub-regions of the lung. Listed in the table are the average AUC_L for the 5

observers $\pm$ the standard deviation in observer AUC_L . The differences in the magnitude of the AUC_L suggest that simulated respiratory motion adversely affects tumor localization and detection in all four of the reconstruction strategies for the entire lung, and that the magnitude of this effect seems dependent on the particular reconstruction strategy that was evaluated. For example, AC_SC_RC has numerically the largest average of AUC_L for both EE Frame and Frame Av among the four strategies, but it also shows the least difference between these two motion states.

The results summarized in Table III were analyzed for the presence of statistically significant differences as described in the methods section. When comparing column-wise between the stationary tumors (EE Frame) and the tumors blurred out by simulated respiration (Frame Av), these were determined to be statistically different at the $P < 0.05$ level by Tukey's HSD test[27;28]. All three of the pair-wise comparisons between the sub-regions of the lung were also significantly different with the upper third having the lowest average AUC_L and the middle third the highest. It is interesting to note in Table III that the largest variation between NC and AC occurs in the lower third of the lung. However we do not have an explanation for why this occurs.

Table IV shows the results of pair-wise comparison across reconstruction strategies by Tukey's HSD test[27;28]. As can be seen from this table all pair-wise comparisons were determined to be statistically significant at the $P < 0.05$ level except NC to AC. Thus AC by itself was not observed to be either harmful or beneficial in terms of localization and detection of the SPN.

IV. Discussion

The analysis of the motion of anatomical sites shown in Figure 1 and Table I illustrate the three-dimensional nature to the motion of structures within the lung, and that the magnitude and direction of motion vary based on the specific anatomic region of the lung. Thus a reasonable approach to the correction of the impact of SPN motion could consist of first mapping the motion of questionable lesions seen in the initial CT of patients through hybrid imaging and then using this data to apply an individualized motion model for each specific patient [30–33]. Since it was determined herein that respiratory motion can significantly impact detection of SPN in SPECT, the incorporation of lesion-specific correction of motion in image reconstruction has the potential to improve detection accuracy. This supports further research in development and testing of such correction strategies for SPECT as well as PET.

In this study we investigated the impact of respiratory motion on the detection of small SPN in SPECT imaging as a function of reconstruction strategy. As shown in Tables III and IV modeling system spatial resolution in reconstruction (RC) with or without correction for lesion respiratory motion can significantly impact the detection of small SPN. Thus RC alone without the inclusion of AC, which is susceptible to mismatch between CT and SPECT, can be used to improve detection accuracy for SPN. This is important because all major manufacturers now include the option for usage of RC as part of iterative reconstruction on their systems.

The inclusion of attenuation and scatter compensation with RC (AC_SC_RC) can further improve detection accuracy over that of RC alone. Also as seen in Table III, the combined compensation resulted in by far the least difference in detection accuracy between without respiratory motion (EE Frame) and with motion (Frame Av) for the entire lung of the four strategies investigated. Thus the need for motion compensation to improve detection accuracy might actually be decreased through usage of combined correction for the small size lesions investigated herein. However in our study we had an exact match between the attenuation map used in simulating imaging and that used during reconstruction. Thus we are unable to comment on the possible degradation in detection accuracy of a mismatch between these as is likely to occur during sequential SPECT/CT imaging. The attenuation maps modeled did have an elevated noise level compared to ones obtained from CT. This could have been a factor in the lack of a significant improvement with attenuation correction compared to no correction. However, it was determined in a study of the impact of noise in attenuation maps on detection accuracy for Ga-67 thoracic lesions that such noise would have an impact on detection accuracy only at levels significantly higher than those in this investigation [18]. Still the lesions in that study were in the mediastinum and not the lungs. Thus there is the possibility that usage of properly aligned attenuation maps derived from CT may have resulted in a significant difference with AC.

It is interesting to note that it was the apex (upper third of the lung) where detection accuracy was the lowest (Table III) despite there being the least motion there (Table I). This result was found for all four of the reconstruction strategies both for the tumors blurred out by simulated respiration (Frame Av) and for the stationary tumors at end-expiration (EE Frame). Our SPN were constrained to remain within the lung, whereas sites of positive noise correlation (noise blobs) could occur anywhere in the slices, even just outside the lung boundary. In judging candidate SPN locations the readers had to subjectively evaluate whether the candidate was just inside or just beyond the lung boundary, without knowing the exact location of this boundary as could be obtained from hybrid imaging with CT. Due to the apical region having the smallest cross-section area, this decision needed to be made most often in this region. Thus it could be one possible explanation of the lowest detection performance being in the apical region. This difficulty is illustrated for a high contrast lesion in the upper third of the lung near the lung boundary in Figure 5. Thus the usage of the CT anatomy to identify the lung boundary with SPECT or PET imaging would seem to be especially beneficial as the general consensus among thoracic radiologists is that SPN of the malignant phenotype are mostly located peripherally throughout the lungs.

By using the NCAT phantom and clinically acquired CT data, a model of the motion of SPN in the lungs was developed. However there are a number of limitations to this model, and our study. Although based on CT studies from a single volunteer, which needed to be interpolated to be closer to the changes expected during quiet supine breathing, we do not believe this is a major limitation. This is because we determined the motion for simulating the SPN at 150 locations distributed throughout the lungs. Thus we investigated a population of 150 possible motions which varied greatly in magnitude and direction as illustrated in Figure 1 and quantified in Table I. Adding more volunteers would certainly have modified this population. In particular as documented in Table I and illustrated in Figure 1 the volunteer we based motion on showed a mix of transverse motion (“chest breathing”) and

axial motion (“abdominal breathing”). The ratio of transverse to axial motion would vary as the volunteer being modeled varied from being primarily one of these to the other. The full range of variation in this ratio was not represented by our usage of a single volunteer upon which to base the modeling of motion. However, since the volunteer employed herein had a mix of the two types of motion, the motion modeled herein does represent a compromise between the two extremes.

Further the motions employed are supported by published reports. The extent of diaphragmatic excursion during normal respiration was described as early as 1954[34]. In the supine position and with normal tidal breathing, the mean movement of the left leaf of the diaphragm was 17.8 mm and the mean movement of the right leaf was 17 mm. The respiratory movement of sixteen small lung tumors in thirteen patients has also been assessed by imaging[30]. Upper and middle lobe tumors moved on average of 6.2 mm in the superior-inferior direction while lower lobe tumors moved on average of 9.1 mm in the superior-inferior direction. The largest amount of movement was found to be 24 mm in the superior-inferior direction for one tumor located in the lower lobe. Another image-based study involving small lung tumors in a total of twelve patients demonstrated anterior-posterior movement of more than 10 mm in two patients while seven patients were found to have superior-inferior movement of greater than 10 mm[35]. In that study, the largest amount of movement was found to be 25 mm in the superior-inferior direction for one tumor that was also associated with 13 mm of movement in the anterior-posterior direction. Several studies have been reported in which the motion of lung tumors was based on gold fiducial markers ranging in size from 2 to 4 mm that were implanted in or near lung tumors[31;36;37]. In one of these studies, lung tumor trajectories were not found to be simple and were felt to require complete three-dimensional mapping[31]. The superior-inferior motion was found to be greatest at 12 ± 2 mm for tumors located in the lower lobe while anterior-posterior motion was small at 2 ± 1 mm for tumors in the upper lobe and lower lobe[37]. However, for two patients in whom the tumor was located in the anterior aspect of the middle of the thorax, movement in the anterior-posterior direction was more than 5 mm[37]. More recently a fluoroscopic study of the superior-inferior motion of lung tumors as correlated with that of the diaphragm in ten patients observed average variations of between 12 to 24 mm [38]. Kyriakou and McKenzie [39] used sagittal slices from respiratory-gated CT studies in six patients to develop a finite element model of the lung. This model included a decrease in the magnitude of tumor motion with increased distance away from the diaphragm as was determined herein.

As noted in the introduction, the greatest likelihood of cure for lung cancer occurs when the disease presents as a SPN. This situation occurs most commonly when the SPN is first detected on either plain film radiographs or on CT and has 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. Thus we believe our usage of small normal structures throughout the lung of a normal volunteer is not a significant

limitation to our investigations. However, as reported elsewhere we similarly investigated the motion of anatomical sites in CT scans of six volunteers with various types of significant lung pathology[29]. In those volunteers, the motion of anatomical sites inside the lung varied significantly from what we observed for the normal volunteer reported herein. Our modeling of the motion of SPN assumed that small (1 cm) tumors would move as does the normal anatomy in the volunteer we studied, and thus would be expected to be increasingly at variance with the motion of actual SPN as their size increased or if the patients have other significant pulmonary disease.

The use of a cosine function in this investigation to model the respiratory cycle is supported as a useful approximation by an extensive analysis [10]. While cosine and cosine-squared were both favored in that study, cosine was preferred over cosine-squared due to its simplicity. However we did not include location dependent phase delays in tumor motion relative to the diaphragm which have been documented to occur [38;40]. Also all simulated lung tumors were modeled as moving along the same straight-line path from end-expiration to end-inspiration and from end-inspiration back to end-expiration. Actual lung tumors have been found to demonstrate differences in this path between inspiration and expiration [35;37;39]. Nor did we include the possibility of changes in tumor shape during respiration [41]; however, given the small size of the SPN we modeled this lack of variation in size is not believed to be a major limitation. Another possible limitation is that the motion was done by a physician expert instead of an automated process; but typically automated processes are validated against physician experts [42].

All observers in this study were members of our medical physics group and had participated previously in other human-observer LROC studies. None of the observers were nuclear medicine physicians. In past studies with simulated[43;44] and even hybrid[45] images when we mixed scientists from our laboratory with nuclear medicine physicians we have not observed any significant difference between the two populations of observers. We believe this is due to the extensive training we do of observers before they start the actual study and the lack of usage of clinical information beyond that of the transverse slice itself. Thus we do not believe this is a significant limitation to the results of this study. We also did not allow the observers to vary the display settings as physicians are able to when reading clinical studies. Had we done so, results may have been altered quantitatively.

Finally this investigation was initially designed when Tc-99m depreotide was the radionuclide imaging procedure of choice for the clinical evaluation of suspicious SPN using SPECT imaging [11;12]. However, the use of positron emission tomographic (PET) imaging with 18F-2-fluoro-2-deoxy-d-glucose (FDG) has replaced it within the United States in large part for clinical cases in which SPN are suspected to be malignant. Nonetheless, Tc-99m depreotide is still available and has shown favorable performance compared to PET using FDG in Europe [46–48]. Also SPECT has been found to be superior to PET in terms of specificity for the detection of SPN in the lungs for patients with tuberculoses (TB) as PET is unable to differentiate malignancy in these cases [49]. Further Tc-99m remains a label of choice for radiopharmaceuticals due to the favorable energy of the emitted photon and the widespread availability of SPECT imaging systems. Thus new radiopharmaceuticals are being developed which may expand the usage of SPECT imaging of Tc-99m labeled

pharmaceuticals for SPN. An example of one such imaging agent currently in Phase III trials is Tc-99m-ethylenedicycysteine-deoxyglucose (Tc-99m-ED-DC) [50]. The biodistribution of this agent is similar to that of depreotide [51]. The results and observations regarding respiratory motion from this investigation are thus applicable to Tc-99m-ED-DC and any Tc-99m labeled imaging agent that becomes available for thoracic SPECT. Our findings may also be extrapolated to the impact of motion on the detection and quantification of localization of SPN imaging by FDG in PET to the extent that both are trying to detect small, moving tumors of low apparent contrast in the lung background [52].

V. Conclusion

The motion of internal pulmonary structures is complex in association with volume expansion inside the thoracic cavity. Using clinically acquired CT data, a model of the motion of SPN in the lungs was developed consistent with these observations. Simulated respiratory motion adversely affects tumor detection in the four reconstruction strategies that were part of this investigation. The magnitude of this effect is greatest for RBI-EM with NC, with AC, and with RC, and least for RBI-EM with AC_SC_RC. Also the combination of RBI-EM with AC_SC_RC has been shown to result in the best detection accuracy (highest AUC in Table III) whether respiratory motion is present or not. There are regional differences in tumor detection both for the tumors blurred out by simulated respiration (Frame Av) and for the stationary tumors at end-expiration (EE Frame). The upper third of the lung is the region where detection of SPN was shown to be the worst, even though lesions in the apex are associated with little respiratory motion.

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Figure 1.

Shown are the sum over all transverse slices (top), coronal slices (middle), and sagittal slices (bottom) of the 3D movement vectors indicating motion of the selected anatomical structures within the lungs in the healthy volunteer. The origin of each arrow indicates a selected point in one of the lungs at 5% RV, and the tip of arrow indicates the same point at 40% RV. The length of the arrow indicates the relative magnitude and direction of motion of the selected point.

Figure 2.

Illustration of motion for two SPN (sphere) locations. Top row are anterior-posterior views of the two NCAT torso phantoms at end-expiration (EE) on the left and end-inspiration (EI) on the right. The extent of inferior and medial motion can be seen as the difference in the location of the sphere at EI relative to the • symbol indicating its location in EE. Bottom row are cranial-caudal views of the two NCAT torso phantoms at EE on the left and EI on the right. The extent of anterior and medial motion of the same two SPN can be seen in this “through the shoulders” view as the difference in the location of the sphere at EI relative to the • symbol indicating its location in EE.

Figure 3.

Number of correct localizations for 32 lesions at each contrast plotted as a function of the radius in pixels from center of actual lesion. The top two curves correspond to a contrast of 11.5 for RBI-EM with AC and RBI-EM with RC. The middle two curves correspond to a contrast of 9 for RBI-EM with AC and RBI-EM with RC. The lower two curves correspond to a contrast of 6.5 for RBI-EM with AC and RBI-EM with RC. Note that all curves reach an inflection point at approximately 8.5 pixels.

Figure 4.

Example of the impact of 3D Gaussian smoothing for a lesion with a contrast of 9 within the middle third of the lung. Image A corresponds to two iterations and $\sigma = 0.5$ while image B corresponds to two iterations and $\sigma = 1$ for RBI-EM with AC reconstruction of noisy projection data. The images shown correspond to the ideal case of no motion (EE Frame) and the location of the 1.0 cm tumor is readily seen in both images as pointed to by the arrows. The without added Poisson noise cases are shown beneath each of the top two images as C and D.

Figure 5.

Example of the impact of 3D Gaussian smoothing and motion on tumor visibility in comparison to Figure 4 for a lesion with a contrast of 9 within the middle third of the lung. Image A corresponds to two iterations and $\sigma = 0.5$ while image B corresponds to two iterations and $\sigma = 1$ for RBI-EM with AC reconstructed from noisy projection data. The images shown correspond to the respiration-averaged case which represents clinical acquisition. The location of the tumor is not apparent in the top row of images but can be seen in the second row with no added Poisson noise as images C and D, and is again indicated by the arrows.

Figure 6.

Example transverse slices scaled as per display in the LROC study with a lesion of contrast 9 in the upper right lung at position indicated by arrows. Images A–D are for EE Frames where no simulated respiratory motion is present, and images E–H are for the average of data acquired over the respiratory cycle. Images A and E are for NC, B and F for AC, C and G for RC, and D and H for AC_SC_RC.

Figure 7.

Example transverse slices scaled as per display in the LROC study with a lesion of contrast 9 in the lower left lung at position indicated by arrows. Images A–D are for EE Frames where no simulated respiratory motion is present, and E–H are for the average of data acquired over the respiratory cycle. Images A and E are for NC, B and F for AC, C and G for RC, and D and H for AC_SC_RC.

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Summary of the extents of motion of the 150 lesion sites used in LROC studies for the total lungs, and 3 regions the lungs were divided into for analysis of detection accuracy. Tabulated are the average and standard deviation of the components of motion in the lateral (Lat), anterior / posterior (AP), and superior /inferior (SI) directions as well as the overall total magnitude and range of motion (Total).

Table I

Lung Region	Lat Ave $\pm$ SD (mm)	AP Ave $\pm$ SD (mm)	SI Ave $\pm$ SD (mm)	Total Ave $\pm$ SD (mm)	Total range (mm)
Entire Lung	2.5 $\pm$ 2.0	12.1 $\pm$ 4.7	5.5 $\pm$ 2.9	13.9 $\pm$ 4.8	2.1 – 26.9
Upper third	1.0 $\pm$ 0.8	6.5 $\pm$ 2.6	0.9 $\pm$ 0.9	6.7 $\pm$ 2.7	2.1 – 11.2
Middle third	3.1 $\pm$ 2.1	14.5 $\pm$ 3.2	5.3 $\pm$ 0.2	15.9 $\pm$ 2.9	8.2 – 21.6
Lower third	2.5 $\pm$ 1.9	11.3 $\pm$ 4.7	7.9 $\pm$ 2.9	14.5 $\pm$ 4.6	5.7 – 26.9

Table II

Results for reconstruction parameter optimization human-observer LROC studies.

Reconstruction Strategy	NC	AC	RC	AC_SC_RC
3D Post-Recon Gaussian Filter	$\sigma = 1.0$	$\sigma = 1.0$	$\sigma = 1.0$	$\sigma = 1.0$
Number of RBI Iterations	2 Iterations	2 Iterations	4 Iterations	4 Iterations

Table III

Average $AUC_L \pm$ standard deviation for EE Frame (no respiratory motion simulated) versus Frame Av (simulated with respiratory motion) for five observers rating 204 test slices in each case for entire lung, and 68 for each of the three sub-regions of the lung. The overall difference between EE Frame and Frame Av was statistically significant at $P < 0.05$ by Tukey's HSD test. All three of the pair-wise comparisons between the sub-regions of the lung were also significantly different with the upper third having the lowest average AUC_L and the middle third the largest.

Motion type - Lung Region	NC	AC	RC	AC_SC_RC
EE Frame - Entire Lung	0.60 ± 0.03	0.61 ± 0.08	0.75 ± 0.02	0.80 ± 0.04
EE Frame - Upper third	0.52 ± 0.05	0.49 ± 0.08	0.66 ± 0.06	0.67 ± 0.07
EE Frame - Middle third	0.72 ± 0.03	0.62 ± 0.12	0.86 ± 0.01	0.89 ± 0.02
EE Frame - Lower third	0.56 ± 0.06	0.72 ± 0.08	0.71 ± 0.03	0.83 ± 0.05
Frame Av - Entire Lung	0.47 ± 0.04	0.50 ± 0.07	0.62 ± 0.02	0.74 ± 0.06
Frame Av - Upper third	0.41 ± 0.06	0.40 ± 0.08	0.50 ± 0.03	0.64 ± 0.07
Frame Av - Middle third	0.57 ± 0.05	0.50 ± 0.11	0.77 ± 0.06	0.85 ± 0.07
Frame Av - Lower third	0.43 ± 0.10	0.61 ± 0.04	0.60 ± 0.08	0.75 ± 0.07

Table IV

Statistical significance of pair-wise comparison of reconstruction strategies for entire lung by Tukey's HSD test. NS is not significant at $P < 0.05$.

	AC	RC	AC_SC_RC
NC	NS	<0.05	<0.05
AC	-	<0.05	<0.05
RC	-	-	<0.05