Published in final edited form as:

Acad Radiol. 2007 April ; 14(4): 476–485. doi:10.1016/j.acra.2007.01.008.

The Effect of Lung Volume on Nodule Size on CT

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Abstract

Rationale and objectives—To determine how measures of nodule diameter and volume on computed tomography (CT) vary with changes in inspiratory level.

Materials and Methods—CT scans were performed with inspiration suspended at total lung capacity (TLC) and then at residual volume (RV) in 41 subjects, in whom 75 indeterminate lung nodules were detected. A fully automated contouring program was used to segment the lungs; followed by segmentation of all nodules and the corresponding lobe using semi-automated contouring in both TLC and RV scans. The percent changes in lung and lobar volumes between TLC and RV were correlated with percent changes in nodule diameters and volumes.

Results—Both nodule diameter and volume varied non-uniformly from TLC to RV some nodules decreased in size, while others increased. There was a 16.8% mean change in absolute volume across all nodules. Stratified by size, the mean value of the absolute percent volume changes for nodules ≥ 5 mm and < 5 mm were not significantly different ($p = 0.26$). Stratified by maximum attenuation, the mean value of the absolute percent volume changes between the TLC and RV series for non-calcified (17.7%, SD = 13.1) and completely calcified nodules (8.6% SD = 5.7) were significantly different ($p < 0.05$).

Conclusion—Significant differences in nodule size were measured between TLC and RV scans. This has important implications for standardizing acquisition protocols in any setting where size, and more importantly, size change are being used for purposes of lung cancer staging, nodule characterization, or treatment response assessment.

Keywords

CT; lung nodule; volumetric measurement; reproducibility

Introduction

The lung is one of the predilection organs of metastases in the body, and also the site of the most frequently occurring cancer in the world (1). On CT, primary lung cancers and extrapulmonary metastatic lesions commonly present as non-calcified pulmonary nodules.

The measurement of pulmonary nodules can be made using unidimensional, bidimensional or volumetric techniques. Historically, size measurements derived from CT have been the mainstay in determining response assessment to cytotoxic therapies. Using bidimensional

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methods developed by the World Health Organization (WHO), measurements are achieved by multiplying a tumor's maximum diameter in the transverse plane by its largest perpendicular diameter on the same image, yielding a cross product. Pretreatment and post-treatment cross products are used to determine treatment response (2). Under these guidelines, tumor response to treatment is classified into one of four categories: complete response, partial response, stable disease, and disease progression (2). Response Evaluation Criteria in Solid Tumors (RECIST) criteria offers a simplified extraction of imaging data for wide application in clinical trials, presuming that linear measures are an adequate substitute for 2D methods (3). RECIST criteria represent a unidimensional method, which corresponds to the sums of nodules' longest diameters in pretreatment and post-treatment image sequences (3).

The third possibility, volumetric analysis, refers to using three-dimensional (3D) measurements for the calculation of the volume of the nodule in mm^3 , typically by semi-automated segmentation tools. The superiority of volumetric tumor measurements over simple diameter methods has been controversial; some studies have not supported the use of 3D measurement techniques in lieu of uni- or bidimensional measurements (4–6), while others have found a significant benefit of volumetric analysis (7,8). In a recent study, these three methods for tumor measurement showed fair to poor agreement in treatment response classification (9).

Pulmonary nodules that are stable during a radiological follow-up of at least two years are clinically diagnosed as benign (10); this clinical decision may sometimes also be based on pathology. Accurate size measurement of pulmonary nodules through radiological follow-up is imperative to determine the growth of the nodule over time. Theoretical advantages of using 3D volumetric measurements are: better quantification of total tumor bulk, more accurate assessment of tumor changes by adding a third dimension of measurement, and better measurement of irregular masses (9).

The TNM staging system of lung cancer (T stands for Tumor, N for Node, and M for Metastasis) takes into account the degree of primary tumor spread (T), the extent of regional lymph node involvement (N), and the presence or absence of distant metastases (M) (11). Accurate and reproducible measures of the primary lesion form part of the foundation for assigning a stage to the lung cancer. If the absence of nodal or metastatic involvement is evident, a primary lesion measuring ≤ 3 cm diameter (represented by T), is classified as Stage IA (T1N0M0); whereas a primary lesion > 3 cm diameter classifies the lesion as stage IB (T2N0M0). This difference significantly influences the estimated 5-year survival rates, which in the United States are: 61% for Stage IA and 38% for Stage IB ($p < 0.05$) (11).

Given the importance of measurement reproducibility when evaluating treatment response, characterizing indeterminate lung nodules over time, and/or staging lung cancer, our objective was to determine how the measure of nodule diameter and volume on CT varies with changes in total or lobar lung volumes resulting from different levels of inspiratory breathhold.

Methods and Materials

Nodule database

Image datasets were selected from participants in an ongoing emphysema-related clinical trial in which CT scans were first acquired at total lung capacity (TLC) and then at residual volume (RV) in the same setting; no participants were recruited exclusively for this study. This convenience sample was chosen because it provided two image series obtained in the same setting, at different levels of suspended respiration. Between March 2004 and October 2005, 41 participants with one or more nodules were identified, resulting in 75 indeterminate nodules that met inclusion criteria: 1) an average nodule diameter at least two times larger than slice

thickness, and 2) a maximum nodule diameter of 30 mm. All nodules that met our inclusion criteria were included in analyses. Nodules were defined as focal, roughly round opacities, at least moderately well marginated and no greater than 3 cm in maximum diameter, based on the definition of the Nomenclature Committee of the Fleischner Society (12), and irrespective of presumed histology (13). Nodules could be of ground glass (GG), solid, or mixed attenuation as well as partially or fully calcified. The use of the anonymized image datasets from the ongoing clinical trial was approved by our local institutional review board.

Imaging Protocol

Forty-one subjects were imaged on nine CT scanner models from three commercial vendors: General Electric (GE) LightSpeed 16 (n= 15) and LightSpeed QX/I (n=1) (GE Medical Systems; Waukesha, WI); Siemens VolumeZoom (n= 8), Siemens Emotion 6 (n= 4), Siemens Sensation 10 (n= 2), Siemens Sensation 16 (n=5) and Siemens Sensation 64 (n=2) (Siemens Medical Solutions; Forchheim, Germany); and Toshiba Acquillion Quad (n=3) and Toshiba Acquillion 16 (n=1) (Toshiba America Medical Systems; Tustin, CA). Image acquisition protocols varied based on scanner model, but were designed to maintain comparable image quality metrics across all scanners.

In the parent clinical trial, individual scans were acquired with the participants supine and in a single breathhold; scan time was taken into consideration in defining the acquisition parameters for scans. For the image series at TLC, participants were told to suspend breathhold after twice breathing deeply, then inhaling as deeply as possible. The RV series was obtained after instructing participants to breathe deeply twice, then exhaling as completely as possible before breathholding. Chest CT scans were acquired at 120 kVp using 140–300 mAs, a pitch of 1.375–1.5, and variable slice thickness ranging from 0.6–3.0 mm, as follows: 0.6 mm (3 nodules), 1 mm (3 nodules), 1.25 mm (26 nodules), 1.5 mm (12 nodules), 2 mm (12 nodules), 2.5 mm (8 nodules) and 3 mm (11 nodules).

Images were reconstructed with a display field of view spanning the widest cross-section of the lungs, using either medium or high spatial frequency reconstruction algorithms (e.g., GE Bone algorithm, Siemens B45 or B50, and Toshiba FC51 filters). Image quality and protocol adherence were assessed on each scan; in addition, machine performance was assessed bimonthly using a water phantom to ensure a mean water attenuation of 0 ± 4 HU, field uniformity within 7 HU as determined by three regions of interest (ROI), and acceptable image noise measurements based on ROI standard deviations of 15–40 HU.

Lung, Lobar, and Nodule Segmentation and Measurement

The CT data were transferred to an image analysis workstation for evaluation. The order of the participants' datasets was randomized for interpretation. All anatomic segmentation was performed using a non-commercial, semi-automated contouring program that has been previously validated (14). The lungs and lobes containing the nodules were segmented by one experienced thoracic radiologist (J.G.G; 12 years experience). The process involves initial lung segmentation using an automated, model-based algorithm (15). Manual editing is allowed to ensure that the trachea, airways of 5 mm or greater diameter, and central pulmonary arteries are excluded from the measurement of lung volume. The lungs are then subdivided into lobes by contouring the inter-lobar fissures with a semi-automated curve fitting tool. Nodules were segmented by a second experienced thoracic radiologist (D.R.A; 19 years experience) by selecting a seed point within the nodule, from which a 3D region growing algorithm was performed using adjustable attenuation thresholds for segmentation. This 3D ROI could be edited by the radiologist. Manual editing was applied only when needed based on visual inspection. The amount of editing was typically minimal and generally involved placing a

“wall” to prevent the inclusion of adjacent blood vessels or chest wall in the nodule segmentation.

For each image dataset of corresponding TLC and RV series, the lungs were segmented, and this step was followed by the segmentation of lobes and the nodules. The following measurements were performed automatically by our software: longest nodule axial diameter in a single plane (maximum distance between two boundary points), nodule volume, maximum nodule attenuation in HU, total lung volume, and volume of the lobe containing the nodule.

To determine whether attenuation influenced nodule volumes between TLC and RV scans, each nodule was classified into one of three attenuation categories based on the maximum HU in the nodule's ROI: (a) non-calcified nodules: maximum HU < 200; (b) partially calcified (containing partial volume averaged calcium): maximum HU $\geq$ 200 to < 1000 HU; and (c) completely calcified nodules: maximum HU $\geq$ 1000 HU.

For each subject, the percent change in nodule volume, total lung volume, and lung lobar volumes between TLC and RV were computed as follows:

$$\text{Percent change} = ((V_{\text{TLC}} - V_{\text{RV}}) / V_{\text{TLC}}) \times 100\%,$$

where V_{TLC} equals volume at TLC and V_{RV} equals volume at RV.

The absolute values of percent change in nodule size were also calculated to assess the magnitude of volume changes independently of the direction of change.

Statistical Analyses

Linear regression analysis was used to investigate the relationships between TLC lung volumes and RV lung volumes, between percent changes in nodule volume and percent changes in both total lung volume and lobar volume of the lobe in which the nodule was located. To evaluate the usefulness of nodule diameter, the correlation between nodule volume and the cube of the nodule diameter was compared across TLC and RV volumes, based on the geometric assumption that nodule volume is proportional to the cube of the diameter in a spherical object.

Simple linear regressions with clustering by subject between TLC and RV were used to compare nodule volumes, and the 95% confidence intervals of slopes in nodule volumes of TLC and RV were determined. Multiple linear regression with clustering by subject was used to better understand the absolute percent changes in nodule volume with covariates of the nodule size (< 5 mm, $\geq$ 5 mm) and the nominal variables of nodule maximum attenuation (< 200 HU, $\geq$ 200 HU to < 1000 HU, and $\geq$ 1000 HU). Results were stratified by size of nodule, nodule maximum attenuation, and lobar location of nodule.

Results

Among 41 participants, 75 nodules were identified, ranging in diameter from 3.2 to 22.4 mm (median 7.6 mm) at TLC and 3.4 to 22.5 mm (median 7.6 mm) at RV. Nodule volumes ranged from 30 to 2638 mm³ (median 165 mm³) at TLC and 25 to 2300 mm³ (median 156 mm³) at RV (Table 1). Nodules were of variable attenuations corresponding to: soft tissue (GG, solid, or mixed attenuation; n = 51), partially calcified (n = 16), and completely calcified (n = 8). Of the 67 nodules $\geq$ 5 mm, 45 were of soft tissue attenuation, 14 were partially calcified, and eight completely calcified. Of the eight nodules < 5 mm, six were of soft tissue attenuation and two were partially calcified. There were no completely calcified nodules < 5 mm in the dataset.

Nodules were located throughout the lungs bilaterally, including the right upper, right middle, and left upper lobes (n=44) and in both lower lobes (n=31).

Nodule diameters and volumes varied non-uniformly between TLC and RV series, meaning that some nodules decreased in size from the TLC to RV series (n = 40), while others increased in size (n = 35) (Figure 1). In Figure 1, nodule volume at TLC is plotted against nodule volume at RV; the solid line representing our results lies to the left of the line of identity (value of x axis = value of y axis). The fact that there are points on both sides of the identity line indicates a non-uniform direction of change in volume with varying lung volumes. The mean of the *absolute values* of percent changes in nodule volumes between TLC and RV scans was 16.8% (range 0.3%–69.2%). It provides a measure of the magnitude but not of the direction of change. There was no significant correlation between percent change in nodule volume and change in lobar volume ($r = 0.15$, $p > 0.05$). In Figure 2, the percent change in nodule volume is shown as a function of percent change in lobar volume; the fitted line is relatively flat which indicated the absence of correlation between percent change in nodule volume and lobar volume ($r = 0.15$, 95% confidence interval $[-0.1589, 0.4361]$).

Figures 3 and 4 represent examples of nodules that increased or decreased in volume size, respectively. The right upper lobe nodule shown in Figure 3 exhibited a 21% increase in nodule volume from TLC (815 mm³, Fig. 3A) to RV (987 mm³, Fig. 3B). Conversely, Figure 4 demonstrates a left upper lobe nodule in which there was a 24% decrease in volume from TLC (930 mm³) to RV (747 mm³). Differences in both size and shape of these nodules are visible on volume rendering between the two breathhold series. Noticeable change in shape of nodule was observed on axial images on Fig. 4(A and B).

Nodule diameter cubed in TLC and the TLC nodule volume were linearly correlated ($r = 0.86$; $p < 0.05$), as were nodule diameter cubed in RV and RV nodule volume ($r = 0.82$; $p < 0.05$). Percent changes of nodule diameter cubed and of volume showed moderate linear correlation ($r = 0.58$; $p < 0.05$).

Multiple regression analysis with clustering by subject showed several relationships. When stratified by nodule size, there was no significant difference ($p = 0.71$) between the mean of the absolute percent volume changes for nodules ≥ 5 mm (16.6%, SD = 15.1) and nodules < 5 mm (18.8%, SD = 13.4). Similarly, when stratified by maximum HU, there was no significant difference ($p = 0.94$) in mean of the absolute percent volume changes for non-calcified nodules (17.7%, SD = 13.1) and partially calcified nodules (18.1%, SD = 21.5) (Fig. 5). However, there was a significant difference ($p < 0.05$) between the means of the absolute percent volume changes for non-calcified on one side (17.7%, SD = 13.1) and of the completely calcified nodules on the other side (8.6%, SD = 5.7) (Figure 5, Table 2).

In nodules < 5 mm, the mean of the absolute percent volume changes of the nodules was 22.2% for soft tissue nodules (n = 6) and 8.4% for partially calcified nodules (n = 2). In our dataset, there were no completely calcified nodules with diameter < 5 mm. In nodules ≥ 5 mm, the mean of the absolute percent volume changes of the nodules was 17.1% for soft tissue nodules (n = 45), 19.4% for partially calcified nodules (n = 14) and 8.6% for completely calcified nodules (n = 8).

Finally, when stratified by anatomic region, nodule percent volume changes in the lower lobes tended to be in average 19 % larger in the TLC scans than in RV scans (confidence interval: 1.16 % to 1.22 %).

Discussion

In clinical practice, chest CT scans are routinely performed at suspended maximal inspiration, although expiratory breathholds are considered more reproducible (16). However, inspiratory volumes provide greater contrast between focal opacities and aerated lung, thus ensuring optimal delineation of pathology. Our results support the premise that the state of lung inflation influences the measure of nodule size. In our dataset of 75 nodules, we found that nodule size, measured by greatest axial diameter as well as by volume, varied between TLC and RV, albeit without a consistent direction of change. The variation in nodule size between TLC and RV scans were associated in our dataset with substantial changes in lung volume between TLC and RV. Patients commonly exhibit inconsistent lung volumes in non-respiratory gated CT series, which has the potential to influence the measure of nodule size independent of other factors. Variations in the size of nodules are likely to be multi-factorial, and may relate to the interplay between: (a) the characteristics of the nodule's attenuation and margins relative to its surround, (b) nodule anatomic location, (c) scan acquisition parameters and the resulting signal-to-noise characteristics, motion, and volume averaging effects in the image, (d) the quality of segmentation, (e) interscan variability and (f) variations due to the observer.

The effects of acquisition parameters on volumetric measurement reproducibility have been investigated in numerous phantom studies (17–19). Using 40 plastic nodules of known volume < 5 mm diameter, Ko et al. showed higher measurement reproducibility using high frequency reconstruction algorithms and diagnostic x-ray CT exposure (120 mAs) rather than low exposure CT techniques (18). In another phantom study, Winer-Muram et al. (19) showed that lung tumor volumes vary significantly with varying CT section width; hence, nodule volume is overestimated more on thick-section CT images than on thin-section images. Recognizing that slice thickness can strongly influence volumetric measurement reproducibility, one of the inclusion criteria in our study was an average nodule diameter at least two times larger than slice thickness.

We measured significant differences in nodule volume size between TLC and RV scans. In this study, there was significantly less size variation between series at different lung volumes in purely calcified lung nodules (8.6%) than in soft tissue or partially calcified nodules (17.7%) ($p < 0.05$). If one assumes that purely calcified nodules are structurally rigid and do not deform with variations in lung volume, then an 8.6% variation in size would represent the lower bound of measurement variation between scans, and could potentially relate to interscan variability independently of lung volumes. In a phantom study using deformable silicone nodules of 3–15 mm diameter, Yankelevitz et al. found < 3% variability in volume measurements; even when nodule shape was substantially altered, changes in volume could be determined to within a 3% error (17). We hypothesize that the 8.6% variability observed with calcified nodules is perhaps the lower limit of what we can expect for volumetric determinations *in vivo*.

We initially hypothesized that changes in the volumes of pulmonary nodules would exhibit a roughly linear correlation with changes in lung volumes; however, we found no such correlation (Fig 2). Rather, nodule volumes changed non-uniformly with changes in lung volumes: some nodules were larger at TLC, others at RV. To determine the potential impact of nodule size on volume differences between the two breathhold sequences (TLC and RV), we stratified nodules into two size categories. Initially, we expected larger variation in size in the group of small nodules. However, the means of the absolute percent volume changes for nodules ≥ 5 mm (16.6%, SD = 15.1, Table 2) and < 5 mm (18.8%, SD = 13.4) were not significantly different in our dataset ($p = 0.71$).

Interscan variability is a frequent factor influencing the reproducibility of volume measurements. Wormanns et al. assessed intra- and interobserver agreement between two

reviewers, followed by interscan agreement (20). In their study, intraobserver variability was 0.5% (95% CI, 0.2–1.6%) and interobserver variability was 0.5% (95% CI, –3.0% to 1.4%). Interscan variability, where two consecutive low-dose scans covering the whole lung were performed within 10 minutes, was approximately $\pm 20\%$ (20). Revel et al. (21) looked at 54 solid nodules evaluated three times by three reviewers during the same session. They reported intraobserver variability ranging from 2.4% to 3.1% and perfect interobserver agreement in 67% of cases. The small sample size of the remaining nodules limited further statistical analysis in their study. In another recent study evaluating interobserver agreement (repeatability) and interscan agreement (reproducibility) of lung nodule volume measurements, Goodman et al. used a fully automatic segmentation software program to compute the volumes of nodules scanned multiple times during the same session. The study was done on 50 nodules of less than 20 mm diameter (22). The authors reported a mean interobserver variability of 0.02% (SD = 0.73%), and concluded that interobserver variability was minimal (22). The interscan standard deviation of the mean was 13.1 % (confidence limits, $\pm 25.6\%$), signaling the important and predominant influence of this factor on measurement reproducibility. In this study, the authors acknowledged that lung volumes were not controlled between scans, which may have contributed to the interscan variability they observed (22).

In a recent study by Gietema et al., (23) Spearman correlation coefficient analysis revealed excellent interobserver agreement between two readers for the measure of nodule volumes using a semi-automated software program in which a spherical template is used to separate nodules from surrounding structures ($r=0.99$). The segmentation of small or irregularly shaped nodules was less reproducible. The authors determined that the poorer performance in very small nodules owes to volume averaging effects and the exclusion of the outer voxels; in irregularly shaped nodules, the software assumes a spherical shape and segmentation of the entire volume may be incomplete. They concluded that the observer should meticulously check *in vivo* segmentation results and may need to reposition initial seed points or manually correct segmented volumes to ensure visually complete segmentation.

One major challenge in determining the accuracy of CT volumetry of lung nodules is the variable methodology and statistical reporting used by different investigators, making it difficult to summarize the reported experience (22). Moreover, most current sophisticated nodule segmentation tools still require a small degree of human editing, such that performance reflects the interplay between the user and the software. Computer-aided diagnostic tools that reproducibly measure nodule volume are strongly needed (24,25). Standardized reporting of inter- and intraobserver observer variability, interscan variability, the degree of manual interaction, and the specific assumptions built into the segmentation routines would substantially advance our understanding of the differences in performance between available software programs.

There were several limitations in our study. First, our dataset was relatively small; this small sample size precluded sub-analyses to determine the possible contributions of anatomic distribution, attenuation, or other factors on breathhold induced differences in nodule volumes. Specifically, we had a greater percentage of nodules in the lower lobes and few were calcified. Moreover, our dataset included nodules of variable attenuations: GG, solid, and mixed attenuation, as well as nodules of partial and complete calcification. Since attenuation, as an indirect substitute of density, might influence volume changes at different inspiratory breathholds (18), we stratified our analyses according to three major attenuation groups: soft tissue non-calcified, partially calcified and completely calcified nodules. However, a larger dataset would have been required to enable greater discrimination between soft tissue nodules of solid, GG, and mixed attenuation. Some nodules were attached to the pleura; however, we could not segregate analyses by this factor given the relatively small dataset. We did observe that nodule volumes in the lower lobes tended to be larger in TLC relative to RV by a mean of

19% ($p < .05$). To verify this finding, we are currently in the process of collecting a larger dataset.

An additional, potentially confounding factor in our study is the fact that our cohort included patients with emphysema. In recent studies, malignant and benign nodules in patients with emphysema exhibited more overlap in CT features than did nodules in non-emphysematous lungs (26). While our objective was to assess the effects of varying lung volume on nodule volume and not to distinguish benign from malignant nodules, the presence of emphysema clearly influences lung compliance, airtrapping, and other variables that could impact changes in nodule morphology, nodule volume, and lung volumes. Future studies in patient cohorts with no associated disease are desirable.

Finally, the imaging protocol used in this study did not employ cardiac gating. It is well-known that the lungs are very dynamic organs that exhibit motion due not only to active breathing (although patients were instructed to breathold and scan times were less than 10 seconds), but also to cardiac motion. Boll et al. reported that cardiovascular motion was disproportionately conveyed to various pulmonary segments and led to changes in the volume of pulmonary nodules, especially in small pulmonary nodules (27). In their study, the authors concluded that precise volumetric assessment was therefore possible only if the cardiac phase was identified (27). In our study, the use of cardiac gating would have reduced this source of error, but would have required an increase in the radiation dose necessary to complete the study.

Measurement reproducibility is important when investigating the size of focal pulmonary nodules, particularly in oncology, where change analysis is a primary means of determining potential malignancy or treatment response. In the future, exploring all potential factors influencing variations in volume measurement will be essential to obtain reproducible measurements.

Conclusion

Significant differences in nodule volume were found between TLC and RV scans. Nodule size varied non-uniformly relative to lung volumes. This suggests that differences in breathhold between serial CT exams can affect the reproducibility of nodule size measurement and that significant attention must be paid to specifying and reproducing the level of suspended breathhold used to acquire CT scans in which change analysis is anticipated for clinical decision-making.

Acknowledgments

We thank Brandon Bigby, B.A. and Erin Angel, B.S. for providing editorial assistance, and Yang Wang M.S. and Sumit Shah Ph.D. for their assistance with figures procurement. Funded by the UCLA SPORC in lung cancer 5P50CA090388.

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Figure 1.

This graph plots nodule volume at TLC relative to nodule volume at RV. The dashed line is the line of identity, in which nodule volumes are equivalent between RV and TLC. The solid line represents our results and lies to the left of the line of identity (value of x axis = value of y axis). The fact that there are points on both sides of the identity line indicates a non-uniform direction of change in volume with varying lung volumes.

Figure 2.

The percent change in nodule volumes is plotted against the corresponding percent change in lobar volumes. Nodule volume varied non-uniformly between TLC and RV: some volumes decreased, while some increased. The flat line fits our dataset, indicating the absence of correlation between percent change in nodule volume and lobar volume.

Figure 3.

Volume rendering of a right upper lobe nodule shows a 21% increase in nodule volume in going from (a) value at TLC (815mm^3) to (b) value at RV (987mm^3). The rendering captures changes in both the size and shape of the nodule in two different breathhold conditions.

Figure 4.

(A, B) Axial images and (C, D) 3D volume rendering of a left upper lobe nodule. The axial images show the segmentation results through the nodule at its greatest diameter at TLC (panel A) and RV (panel B). The nodule exhibits a 24% decrease in volume when going from value at TLC (930mm^3) to the value at RV (747mm^3). The volume renderings at TLC (panel C) and RV (panel D) show that the nodule changes in both size and configuration between the two breathhold series.

Figure 5.

This graph plots maximum nodule attenuation vs. the absolute value of percent volume change. The non-calcified nodules are represented in this area of maximum HU < 200. The partially calcified nodules are visible in the area between maximum HU ≥ 200 and < 1000 HU, and completely calcified nodules are represented by attenuation ≥ 1000 HU.

Table 1

Size characteristics of the nodule dataset.

Value (75 nodules)	Maximum axial diameter (mm) at TLC	Maximum axial diameter	Nodule volume (mm ³) at TLC	Nodule volume (mm ³) at RV
Mean	9.3	9.3	390	377
Median	7.6	7.6	165	156
SD	4.6	4.7	559	516
Minimum	3.2	3.4	30	25
Maximum	22.4	22.5	2638	2300

TLC = Total lung capacity; RV = Residual volume

Table 2

Absolute value of % changes of nodule volume when the nodules are stratified by maximum HU (< 200, [200, 1000], 1000) and size of nodules (< 5mm and $\geq$ 5mm).

TLC maximum diameter	Nodule maximum HU at TLC				Total
	Variable	<200 HU	[200, 1000]	$\geq$ 1000 HU	
< 5 mm	N	6	2	0	8
	Mean	22.21	8.42	.	18.76
	SD	13.45	7.68	.	13.36
	Median	21.54	8.42	.	17.20
	Interquartile range	10.41	10.86	.	14.34
$\geq$ 5 mm	N	45	14	8	67
	Mean	17.14	19.44	8.55	16.60
	SD	13.09	22.65	5.65	15.12
	Median	14.00	9.37	6.89	11.95
	Interquartile range	13.93	12.87	9.01	13.36
Total	N	51	16	8	75
	Mean	17.74	18.06	8.55	16.83
	SD	13.10	21.51	5.65	14.87
	Median	15.84	9.37	6.89	13.06
	Interquartile range	17.56	12.65	9.01	13.42

TLC = Total Lung Capacity; N=number; HU = Hounsfield Units; SD = Standard Deviation; Interquartile range = 75th percentile-25th percentile