Original Article

Evaluation of the 95% limits of agreement of the volumes of 5-year clinically stable solid nodules for the development of a follow-up system for indeterminate solid nodules in CT lung cancer screening

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Background: This study sought to evaluate the 95% limits of agreement of the volumes of 5-year clinically stable solid nodules for the development of a follow-up system for indeterminate solid nodules.

Methods: The volumes of 226 solid nodules that had been clinically stable for 5 years were measured in 186 patients (53 female never-smokers, 36 male never-smokers, 51 males with <30 pack-years, and 46 males with ≥30 pack-years) using a three-dimensional semiautomated method. Volume changes were evaluated using three methods: percent change, proportional change and growth rate. The 95% limits of agreement were evaluated using the Bland-Altman method.

Results: The 95% limits of agreement were as follows: range of percent change, from ±34.5% to ±37.8%; range of proportional change, from ±34.1% to ±36.8%; and range of growth rate, from ±39.2% to ±47.4%. Percent change-based, proportional change-based, and growth rate-based diagnoses of an increase or decrease in ten solid nodules were made at a mean of 302±402, 367±455, and 329±496 days, respectively, compared with a clinical diagnosis made at 809±616 days (P<0.05).

Conclusions: The 95% limits of agreement for volume change in 5-year stable solid nodules may enable the detection of an increase or decrease in the solid nodule at an earlier stage than that enabled by a clinical diagnosis, possibly contributing to the development of a follow-up system for reducing the number of additional Computed tomography (CT) scans performed during the follow-up period.

Keywords: Computed tomography (CT); lung cancer screening; indeterminate solid nodule; volumetry; follow-up

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Introduction

With the implementation of computed tomography (CT) lung cancer screening, numerous indeterminate nodules have been detected and their follow-up is crucial. Among several CT lung cancer screening projects, the Dutch-Belgian randomized lung cancer screening trial (NELSON) introduced the management of lung nodules based on volume doubling times (VDT) derived from nodule volumetry using computer software (1-3). Briefly, the volume of solid nodules determined the screening result: <50 mm^3 was considered negative, 50–500 mm^3 was considered indeterminate, and >500 mm^3 was considered positive; if the volume growth (percent volume change) was <25%, the screening result was considered negative, and if the volume growth was ≥25%, the VDT of the nodule was calculated and a VDT <400 days was considered to be a positive result (4). In contrast to NELSON, the National Lung Screening Trial (NLST) used nodule diameter to assess nodule size; participants with nodules of 4 mm or larger in maximal diameter were considered positive (5). Although many volumetry studies have evaluated pulmonary solid nodules (6-18), the standard for the follow-up of pulmonary solid nodules in CT screening in the US and in daily clinical practice is still the measurement of pulmonary nodule size using electronic calipers (19,20). A review article concluded that accumulating evidence indicates that semi-automatic volume measurements have a higher accuracy and reproducibility than diameter measurements (21). To our knowledge, only one article has reported volume changes in clinically stable solid nodules with long-term CT follow-up (14). To develop a dedicated follow-up system for solid nodules, we attempted to evaluate the 95% limits of agreement for volume changes in nodules that had been clinically stable for 5 years in not only smokers, but also in never smokers as the first step in the developing of such a system. Regarding the assessment of pulmonary solid nodule volumes, several methods have been reported, such as the percent change (6,17), proportional change (17), growth rate (14), and monthly volumetric growth index (6). In the present study, we aimed to evaluate the volume change using the following three methods: the percent change, the proportional change, and the growth rate.

The purpose of this study was to evaluate the 95% limits of agreement for the volumes of 5-year clinically stable solid nodules for the development of a follow-up system for indeterminate solid nodules.

Methods

CT scanning and image reconstruction in CT lung cancer screening

The CT lung cancer screening protocol of the Research Center for Cancer Prevention and Screening has been described elsewhere (22). The scanning protocol from February 2004 to June 2010 was as follows: tube potential, 120 kVp; tube current, 30 mA; collimation, 1 mm × 16 rows; 0.5 second per rotation; pitch, 0.69; standard reconstruction kernel. The scanning protocol after July 2010 was the same for the tube potential, tube current, and rotation speed, but the collimation was 1 mm × 32 rows. CT images were reconstructed using 5 mm thick sections obtained at 5 mm intervals and 2 mm thick sections obtained at 2 mm intervals between February 2004 and November 2011; after December 2011, the CT images were reconstructed using 5 mm thick sections obtained at 5 mm intervals and 1 mm thick sections obtained at 1 mm intervals. If a solid nodule examined using volumetry in this study had been scanned before December 2011, the CT images of the solid nodule were reconstructed in contiguous 1 mm thick sections using the raw CT data.

Patients with 5-year stable nodules

To evaluate the 95% limits of agreement for the volumes of 5-year stable solid nodules, patients with 5-year stable solid nodules with a longest diameter of between 5 mm or larger and less than 10 mm were selected sequentially among a baseline cohort of CT lung cancer screening cases at the Research Center for Cancer Prevention and Screening between February 02, 2004, and March 31, 2007. Information on the smoking status was obtained using a questionnaire at the time of the baseline CT screening. The location of each nodule (lung lobe and distance from the pleura), the shape of the nodule (oval or polygonal), and the presence of contacting vessels were documented. A representative solid nodule imaged at five time points during a 5-year period is shown in *Figure 1*.

Volumetry of pulmonary solid nodules

Volume measurement of the solid nodules was performed using commercially available software [Lesion Management Solutions (LMS), MEDIAN Technologies, Valbonne, France], as described elsewhere (23). In brief, the software can detect, segment, and quantify pulmonary solid nodules; after

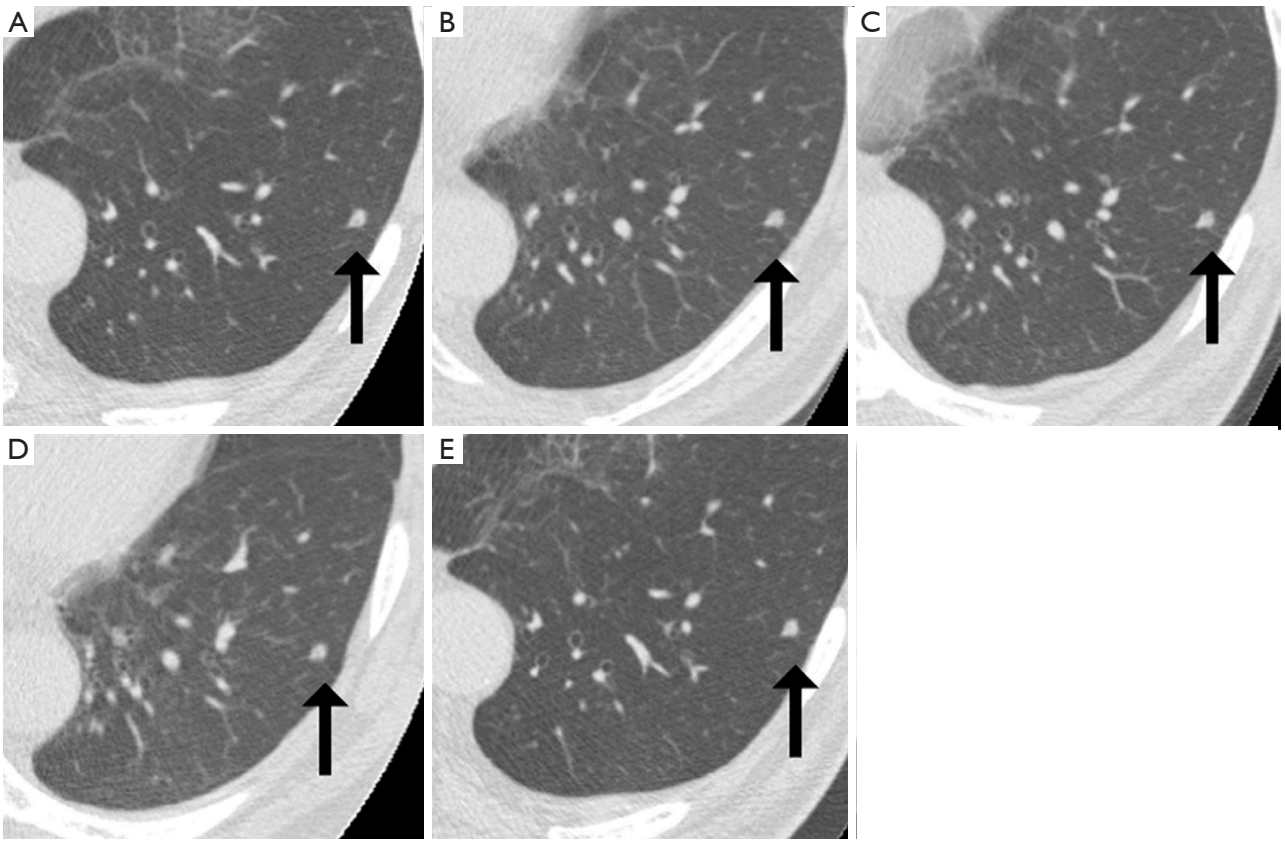

Figure 1 Axial chest CT images of the representative stable nodule in segment 9 of the left lower lobe. The nodule was imaged at five time points (left to right) between September 2004 and September 2009. (A) September 2004; (B) January 2005; (C) January 2006; (D) January 2007; (E) September 2009.

segmentation, the longest diameter, perpendicular diameter, and volume of each nodule were extracted automatically (*Figure 2*). Readers were able to make manual adjustments to the contour of the lesion as necessary. One thoracic radiologist (Kakinuma R, 33 years' experience in reading chest CT) measured the volumes of all the solid nodules.

Methods for evaluating volume change

Percent change

The percent change between scans at two time points was calculated as the ratio of the difference in the second volume estimate (V_2) and the first volume estimate (V_1) relative to the first volume estimate (6,17).

Percent change (%) = $100 \times (V_2 - V_1) / V_1$

Proportional change

The proportional change was calculated as the ratio of the difference between the V_2 and the V_1 to the average between the first and second volume estimates (17).

Proportional change (%) = $100 \times (V_2 - V_1) / [(V_2 + V_1) / 2]$

Growth rate

The growth rate measured at any two points in time (T_1, T_2) was computed as follows (14).

Growth rate (%) = $100 \times (V_2 - V_1) / [V_1 (T_2 - T_1)]$

A power function, $\sigma = a(\Delta T)^{-b}$, with two free parameters, a and b, was used to model the dependence of the standard deviation (SD) (σ) of the growth rate on the time interval ($\Delta T = T_2 - T_1$) (14).

Intra- and Inter-reader variability of nodule volume measurements

One thoracic radiologist (Kakinuma R) re-measured the volumes of 52 solid nodules that had been randomly

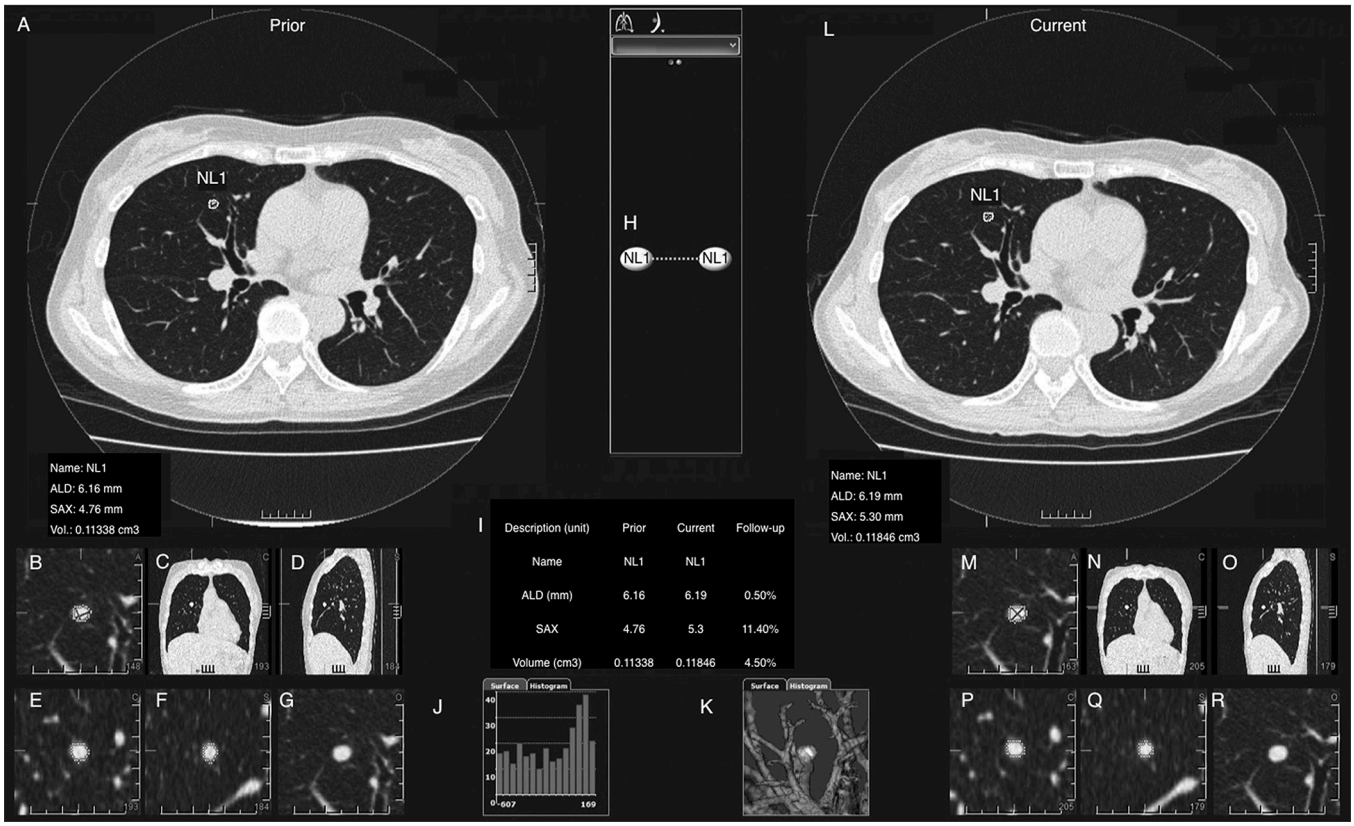

Figure 2 User interface of the LMS. A solid nodule was located in segment 5 of the right middle lobe. The axial CT image on the left (A) was taken 1 year prior to the axial CT image on the right (L); the measurement results were shown in left lower corner of each axial CT image; (B,M) axial zoom with diameter measurements; (C,N) coronal view; (D,O) sagittal view; (H) matching of CT slices on which the nodule exists; (I) table for results of analyses; (E,P) coronal zoom of the nodule; (F,Q) sagittal zoom of the nodule; (G,R) axial zoom of the nodule; (J) histogram of the nodule in *Figure 2L*; (K) three-dimensional visualization of the nodule. NL1, nodule number; ALD, axial largest diameter; SAX, short axial diameter; Vol., volume; LMS, Lesion Management Solutions.

selected from the study cohort at an interval of 1 month. The other radiologist (Muramatsu Y, 37 years of experience) independently measured the volumes of the 52 solid nodules. The intra-reader (Kakinuma R) and inter-reader variability (Kakinuma R *vs.* Muramatsu Y) were evaluated with Bland-Altman methods.

Evaluation of an increase or decrease in volume of solid nodules based on the 95% limits of agreement for the volumes of 5-year stable solid nodules

A clinical diagnosis of whether a nodule has shown growth or not is based on manual diameter measurements (21). The cutoff-value for evaluating an increase or decrease in the longest diameter in a clinical setting was set as 1.73 mm in the present study, based on the 95% limits of small non-calcified pulmonary nodules (24). For a "clinical diagnosis" in the present study, nodule stability was defined as a difference of less than 1.73 mm in the longest diameter of a solid nodule between the baseline screening CT examination and the final repeat screening CT examination. The longest diameter and the perpendicular diameter were measured using electronic calipers and the results were entered into a nodule database prospectively during the screening process. The 5-year stability of the nodules was determined retrospectively based on the data in the database. Images of each nodule that had been obtained at multiple time points were reviewed by a thoracic radiologist (Kakinuma R) to confirm stability.

To evaluate the increase or decrease in volume, solid nodules with a longest diameter of 5 mm or larger but less than 10 mm, other than 5-year stable solid nodules

that showed an increase or decrease in diameter, were chosen sequentially from the baseline cohort of subjects undergoing CT lung cancer screening at the Research Center for Cancer Prevention and Screening between February 02, 2004, and March 31, 2010 (the period for selecting solid nodules with an increase or decrease in diameter was longer than the period for selecting 5-year stable solid nodules because the number of solid nodules with an increase or decrease in diameter was relatively small). An increase or decrease in volume was evaluated using the 95% limits of agreement for each evaluation method.

Statistical analysis

The median and interquartile range (IQR) for age, and the volumes were calculated; the medians of the volumes at baseline for the four smoking statuses were evaluated using the Kruskal-Wallis rank sum test. The mean number and median number of follow-up CT examinations per patient were calculated. The means of days until change detection in the solid nodules were calculated. A Bland-Altman analysis was performed to assess the 95% limits of agreement of the volume changes determined using each evaluation method (25). The relationship between the SD of the growth rate and a power of the time interval was evaluated. The agreement between readers was assessed for the measured volumes using an intraclass correlation coefficient (ICC). The time of the detection of a change between the volume and diameter was evaluated using the Mann-Whitney U test. R software, version 3.1.2 (The R Foundation, Vienna, https://www.r-project.org) was used for the statistical analysis. A P value less than 0.05 was considered statistically significant.

Results

Characteristics of the patients

The total numbers of patients and pulmonary solid nodules with a longest diameter between 5 mm or larger and less than 10 mm were 243 and 305, respectively. Among them, 79 solid nodules in 57 patients were less than 50 mm^3 after volume measurement; solid nodules with a volume of less than 50 mm^3 were excluded from this study because such lesions were considered to be negative results in the NELSON trial. Therefore, 186 patients (median age: 62 years old, and IQR: 56.3–67 years old), and 226 solid nodules (median volume: 70.7 mm^3, IQR: 58.0–93.4 mm^3) were analyzed in this study. Long-term CT follow-up was performed for a mean of 5.3±0.5 years (range, 5–8.1 years; median, 5.2 years) after the baseline examination. The mean number of follow-up CT examinations per patient was 4.0±0.6 examinations (range, 3–6 examinations; median, 4 examinations). Among the 186 patients, 53 females and 36 males were never-smokers, 51 males were smokers with less than 30 pack-years, and 46 males were smokers with 30 pack-years or more. The volumes of the nodules at baseline, the locations of the nodules, the distances from the pleura, and the shapes of the nodules are shown in *Table 1*. The medians of the volumes of nodules at baseline for the four smoking statuses were not significantly different (Kruskal-Wallis chi-squared =2.3174, df =3, P=0.5092). Seventy-seven percent (174 out of 226) of the solid nodules were in contact with pulmonary vessels.

The 95% limits of agreement for volumes in 5-year stable solid nodules

The 95% limits of agreement for volumes in 5-year stable solid nodules are shown in *Table 2*: range of percent change, from ±34.5% to ±37.8%; range of proportional change, from ±34.1% to ±36.8%; and range of growth rate in overall estimate ["overall estimate" means that the SD was calculated across all observations (14)], from ±39.2% to ±47.4%. The SD of the growth rate was well approximated by a power of the time interval (*Figure 3*), while the SD of the percent change and the proportional change were independent of the time interval (*Figures 4,5*).

The differences in the mean of the volume change between female never-smokers and patients with other smoking statuses were not statistically significant, although the range of the 95% limits of agreement in the male smokers with 30 pack-years or more was slightly larger than those in the patients with other smoking statuses (*Tables 2*,*S1*,*S2*).

Evaluation of an increase or decrease in volume of solid nodules based on the 95% limits of agreement for the volumes of 5-year stable solid nodules

The results for ten nodules evaluated in ten patients are shown in *Tables 3-6*. The age of the patients ranged from 41 to 68 years old (median, 65.5 years old); the smoking statuses were female never-smoker (n=1), male never-smoker (n=3), male smoker with <30 pack-years (n=2),

Table 1 Characteristics of the patients

Characteristics	Female never-smokers (%)	Male never-smokers (%)	Male <30 pack-years (%)	Male ≥30 pack-years (%)	Total (%)
Number of patients	53	36	51	46	186
Age (years)					
Median	59.5	62	61	64	62
IQR	56.0–64.3	59.0–67.5	56.0–67.0	58.0–67.0	56.3–67.0
Number of nodules	60	43	66	57	226
Volume of nodules at baseline (mm^3)					
Median	71.3	71.5	65.8	76.2	70.7
IQR	57.6–94.0	61.7–84.0	56.7–90.7	63.3–98.8	58.0–93.4
Location					
Right upper lobe	12 (20)	5 (12)	7 (11)	14 (25)	38 (17)
Right middle lobe	9 (15)	3 (7)	12 (18)	9 (16)	33 (15)
Right lower lobe	9 (15)	9 (21)	14 (21)	9 (16)	41 (18)
Left upper lobe	12 (20)	11 (26)	9 (14)	11 (19)	43 (19)
Left lower lobe	18 (30)	15 (35)	24 (36)	14 (25)	71 (31)
Distance from the pleura					
≥1 cm	14 (23)	14 (33)	24 (36)	21 (37)	73 (32)
<1 cm	39 (65)	28 (65)	41 (62)	32 (56)	140 (62)
Attached	1 (2)	0	1 (2)	0	2 (1)
Perifissural	6 (10)	1 (2)	0	4 (7)	11 (5)
Shape					
Oval[¶]	32 (53)	26 (60)	35 (53)	26 (46)	119 (53)
Polygonal[§]	28 (47)	17 (40)	31 (47)	31 (54)	107 (47)
Contacting vessel					
Yes	41 (68)	34 (79)	54 (82)	48 (81)	174 (77)
No	19 (32)	9 (21)	12 (18)	11 (19)	52 (23)

[¶], oval shape includes round and spindle shapes; [§], polygonal shape includes triangular and rectangular shapes; IQR, interquartile range.

and male smoker with ≥30 pack-years (n=4). Median volume of the ten solid nodules at the baseline examination was 166.6 mm^3 (IQR, 77.1–213.8 mm^3). Among the six nodules that showed an increase in diameter, two nodules (No. 9 and 10) were resected and diagnosed as adenocarcinomas. The remaining eight nodules were not resected and had not been diagnosed as lung cancers as of March 2014. Although 4 nodules (No.1, 3, 4, 5) did increase in size, we suspected that these nodules were benign nodules. Among the ten nodules, the 95% limits of agreement for the percent change, the proportional change, and the growth rate enabled volume changes to be detected in ten, nine, and ten nodules, respectively. The numbers of nodules detected at an earlier stage than the clinical diagnosis (i.e., an increase or decrease in diameter) were 8, 5, and 7 nodules when evaluated based on the percent change, the proportional change, and the growth rate, respectively (*Table 6*). The percent change-based,

Table 2 SD and 95% limits of agreement for each evaluation method according to sex and smoking status

Evaluation method	Female never-smoker	Male never-smoker	Male smoker with <30 pack-years	Male smoker with ≥30 pack-years
Percent change				
SD (%)	17.8	17.6	18.3	19.3
95% limits of agreement (%)	34.9	34.5	35.9	37.8
Proportional change				
SD (%)	17.4	17.4	17.7	18.8
95% limits of agreement (%)	34.1	34.1	34.7	36.8
Growth rate				
SD (%)	$\sigma = 1.18734 \times (\Delta T)\ \hat{}\ (-0.80893) \times 100$	$\sigma = 1.09439 \times (\Delta T)\ \hat{}\ (-0.77890) \times 100$	$\sigma = 1.49312 \times (\Delta T)\ \hat{}\ (-0.89270) \times 100$	$\sigma = 1.00624 \times (\Delta T)\ \hat{}\ (-0.71827) \times 100$
95% limits of agreement (%)	$1.96\times\sigma$	$1.96\times\sigma$	$1.96\times\sigma$	$1.96\times\sigma$
Growth rate				
Overall estimate of SD (%)	20.6	20.7	24.2	20
95% limits of agreement (%)	40.4	40.6	47.4	39.2

σ, standard deviation of growth rate; (ΔT), time between exams (months). Overall estimate means that standard deviation for each smoking status was calculated across all observations for each smoking status (13). SD, standard deviation; 95% limits of agreement, 1.96 SD.

proportional change-based and growth rate-based diagnoses of an increase or decrease in the solid nodules were made at a mean of 302±402 (n=10), 367±455 (n=9), and 329±496 days (n=10) from the baseline scan, respectively, whereas the clinical diagnosis was made at 809±616 days (n=10) (P<0.05, Mann-Whitney U test) (*Table 6*).

Intra-reader variability based on percent and proportional changes

One thoracic radiologist (Kakinuma R) measured the volumes of 52 nodules in 41 patients twice at an interval of 1 month. The 95% limits of agreement were as follows: –2.4±26.5% for percent change; –3.5±30.0% for proportional change (*Figure 6*); the ICC was 0.990 (95% CI, 0.982–0.994).

Inter-reader variability based on percent and proportional changes

Two radiologists (Kakinuma R, Muramatsu Y) measured the volumes of 52 nodules in 41 patients within the study cohort for the evaluation of inter-reader variability. The 95% limits of agreement were as follows: 32.9%±62.3% for percent change; 25.4%±42.5% for proportional change (*Figure 7*); the ICC was 0.869 (95% CI, 0.783–0.922).

Discussion

The present study examined whether the 95% limits of agreement for volume changes in solid nodules that were stable for 5 years differed when software other than that used in the NELSON trial was applied to detect nodule changes earlier than that possible using diameter measurements, such as in the NLST. The results showed that the 95% limits of agreement for volume changes in 5-year stable solid nodules may enable the detection of an increase or decrease in solid nodules at an earlier stage than that enabled by a clinical diagnosis

In Japan, lung cancer screening is presently conducted using chest X-rays for population-based screening (26), and low-dose CT lung cancer screening is conducted as an opportunistic screening for not only smokers, but also never-smokers. Lung cancer deaths in never-smokers rank as the fifth most common cause of death in men and the third in women, reflecting a relatively high estimated rate (31% of male patients and 80% of female patients) of lung cancers that are unrelated to smoking in Japan (27).

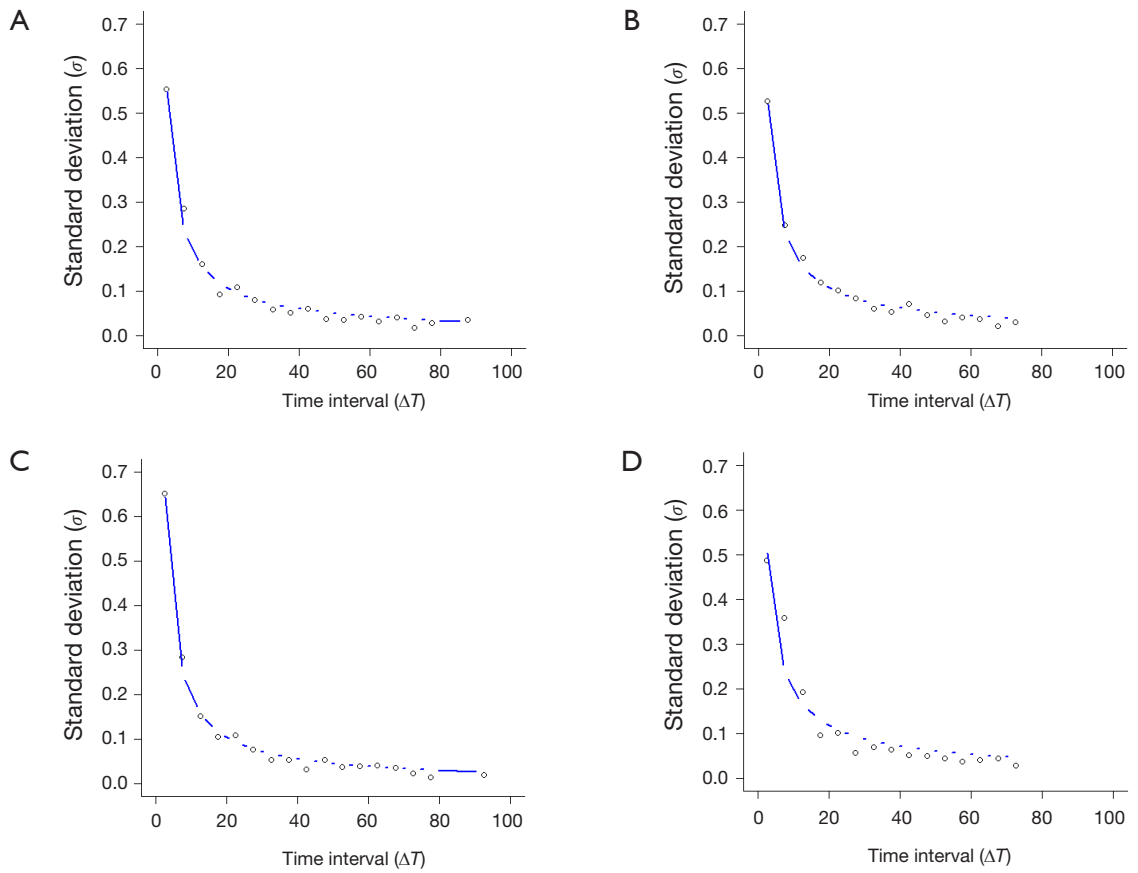

Figure 3 Plot shows that the standard deviation (σ) of the growth rate (GR) is approximated by a power of the time interval (ΔT; months). (A) Female never-smokers, $\sigma = 1.18734 \times (\Delta T)$ ^ (–0.80893); (B) male never-smokers, $\sigma = 1.09439 \times (\Delta T)$ ^ (–0.77890); (C) male smokers with <30 pack-years, $\sigma = 1.49312 \times (\Delta T)$ ^ (–0.89270); (D) male smokers with ≥30 pack-years, $\sigma = 1.00624 \times (\Delta T)$ ^ (–0.71827). Small open circle, measured data; Line, model.

Therefore, the present study evaluated the 95% limits of agreement of the volumes of 5-year clinically stable solid nodules not only in smokers, but also in never-smokers.

With respect to CT scans for the volumetry of solid nodules, several protocols have been reported as follows: one standard-dose CT scan (7,16); two standard-dose CT scans (6); three standard-dose CT scans (9); one low-dose CT scan (10); two low-dose CT scans (8,11); three low-dose CT scans (12); a range from two to seven low-dose CT scans (14); one standard-dose CT scan and one ultra-low-dose CT scan (13); one low-dose CT scan and one ultra-low-dose CT scan (18). The present study used several low-dose CT scans (range, 3–6 scans).

Regarding the CT scan intervals for the volumetry of solid nodules, same-day CT scans (8,9,11,13,17,18) and different-day CT scans (6,12,14,16) have been reported: the shortest intervals were within 10 minutes (8,11,13) and the longest interval was 8.5 years (14). The smallest inter-scan variability of the volume change for same-day CT scans ranged from –20% to 20.4% (18), whereas the largest inter-observer variability for same-day CT scans (two scans within 15 minutes) was 7.4%±44.2% (mean percent difference ± SD) (17).

In the NELSON trial, nodule growth was defined as a change in the volume of at least 25% between two subsequent examinations based on validation studies with repeated low-dose CT examinations performed on the same days, in which the measurement error was maximally 25% (3). However, optimization of the VDT cutoff for fast-growing nodules in lung cancer screening revealed that lowering the VDT cutoff could reduce false-positive referrals (28).

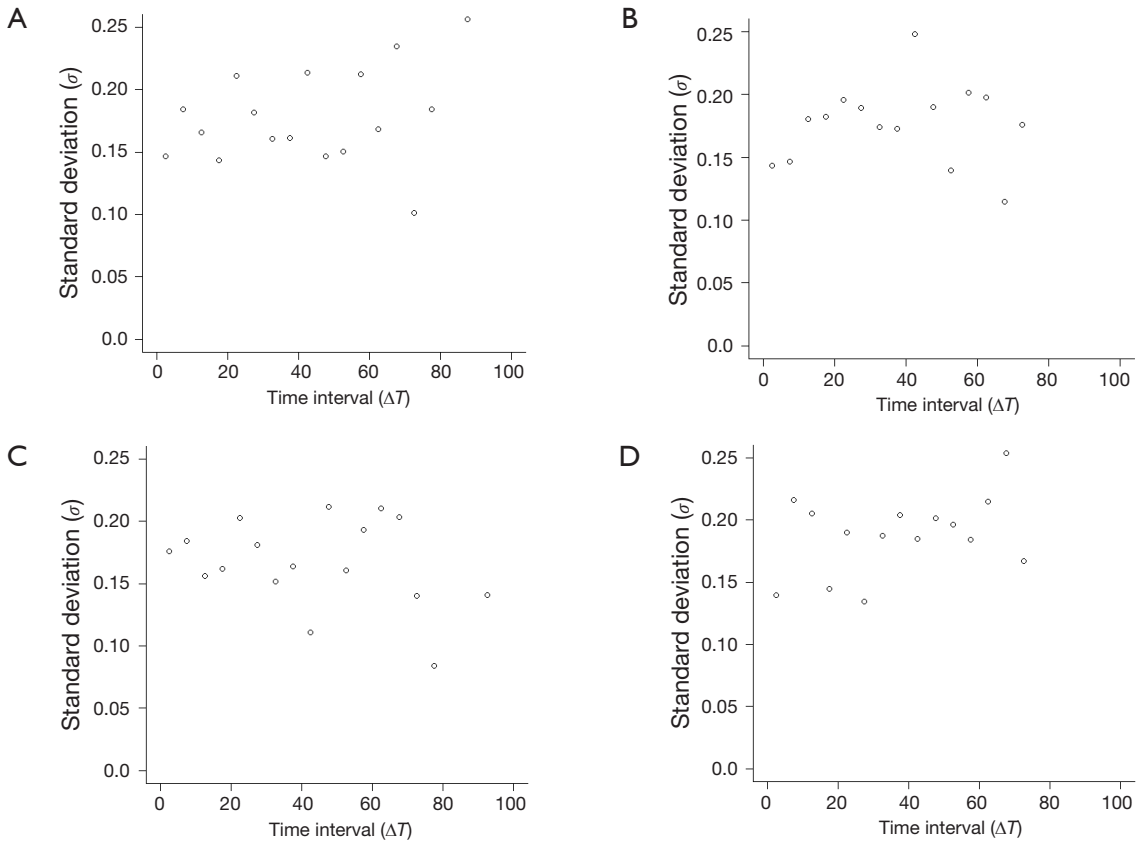

Figure 4 Plot shows that the standard deviation of the percent volume change is independent of the time interval (ΔT; months). (A) Female never-smokers; (B) male never-smokers; (C) male smokers with <30 pack-years; (D) male smokers with ≥30 pack-years.

Not all CT screening facilities can use the software that was used in the NELSON trial. Comparison of three software systems for semi-automatic volumetry of pulmonary nodules showed that significant difference was found in measured volume between software in the NELSON trial and the other two software packages (29). The software that we used in the presently reported study has been used and validated in clinical trials (23), but the 95% limits of agreement for the volumes of solid nodules detected during CT screening have never been evaluated. Therefore, we performed the presently reported study.

Which method is more appropriate for evaluating volume changes when developing a follow-up system for indeterminate solid nodules? Although each of the evaluation methods can be implemented using computer software, the percent change might be optimal for implementation in clinical settings because of its simple cutoff value and the finding that in our very small cohort, the number of earlier-detected nodules was larger when the percent change method was used, compared with the other methods that were evaluated. Moreover, the mean number of days until a change was detected was shorter for the percent change method than for the other methods; however, the mean number of days until a change was detected was not significantly different for the percent change method, compared with the other evaluation methods. A prospective study is warranted.

The present study had several limitations. First, only one radiologist (Kakinuma R) retrospectively reviewed the solid nodules on serial CT images, confirmed the clinical stability of the nodules, and performed the volumetry studies for the solid nodules. The radiologist had 33 years of experience in reading chest CT images and 22 years of experience in reading lung cancer screening CT images, although an inherent intra-reader variability exists for the measurement of nodules. Second, although this study utilized a semiautomated quantification of the solid nodule volumes, manual correction of the contour of a nodule

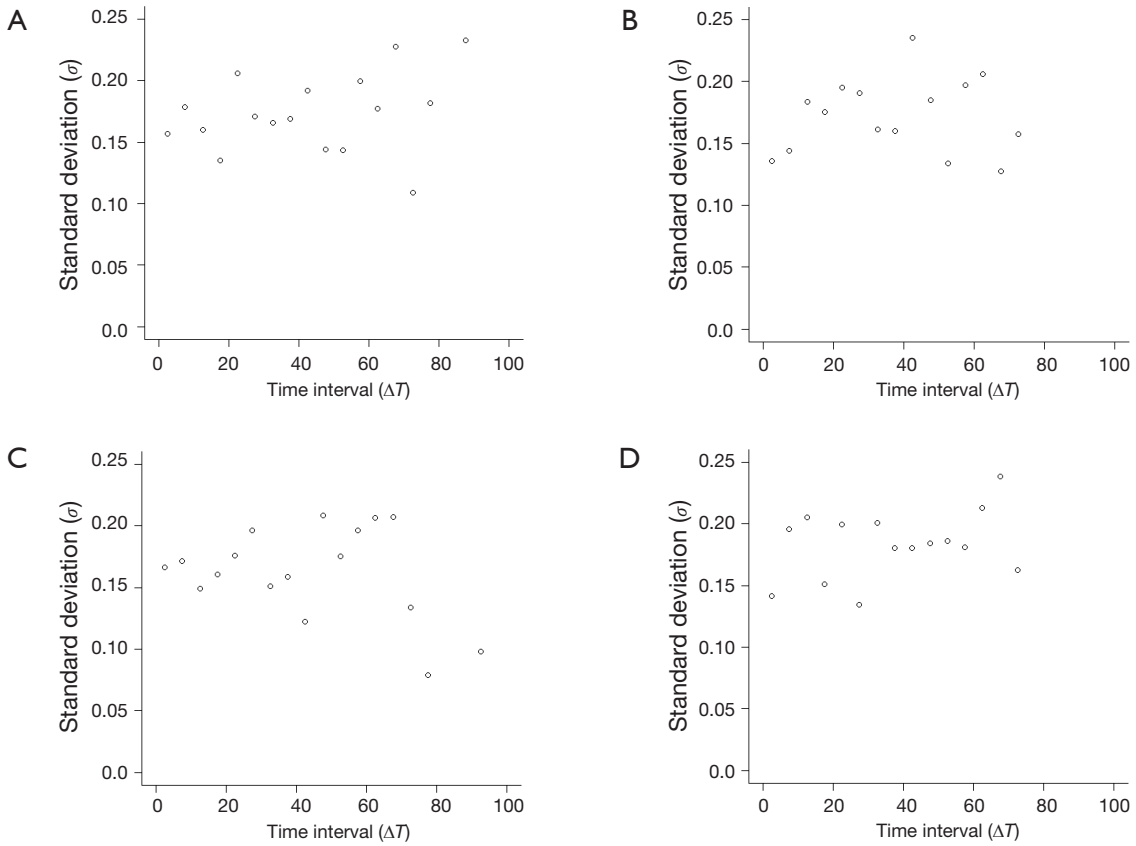

Figure 5 Plot shows that the standard deviation of the proportional volume change is independent of the time interval (ΔT; months). (A) Female never-smokers; (B) male never-smokers; (C) male smokers <30 pack-years; (D) male smokers ≥30 pack-years.

Table 3 Maximal diameter of solid nodules for evaluation

Nodule no.	T0	T1	T2	T3	T4	T5	T6	T7	Sex and smoking status	Change in diameter
1	7	8.6	8.4	8.6	8.4	8.6	8.8**	9.4**	M <30	Increase
2	6	5.7	4.2*	3.5*	3.9*	3.5*	3.9*	3.9*	M-n	Decrease
3	6.5	7.3	7.3	7.9	7.9	8.5**	8.9**	9.1**	M ≥30	Increase
4	8	8.2	8.8	8.6	9.5	9.9**	11.9**		M-n	Increase
5	9	9.7	9.8	10.1	10.1	11**	11.5**		M ≥30	Increase
6	7.5	6.9	6.1	4.8*	4.8*	3.9*	2.7*		M ≥30	Decrease
7	7.5	8.5	6.4	5.5*	5.5*	4.8*			M-n	Decrease
8	7.5	4.8*	3.9*	3.6*	3.9*				M ≥30	Decrease
9	8	8.6	8.6	11.5**					M <30	Increase
10	8	8.2	10.3**						F-n	Increase

*, indicate a diameter decrease of more than 1.73 mm; **, indicate a diameter increase of more than 1.73 mm. T0, date of the baseline CT scan; T1, date of the second CT scan; T2, date of the third CT scan; T3, date of the fourth CT scan; T4, date of the fifth CT scan, T5, date of the sixth CT scan; T6, date of the seventh CT scan; T7, date of the eighth CT scan; M ≥30, male smoker with ≥30 pack-years; M <30, male smoker with <30 pack-years; M-n, male never-smoker; F-n, female never-smoker. Definition of "change" was defined as an increase or a decrease of more than 1.73 mm in maximal diameter based on the maximal diameter on the baseline CT.

Table 4 Changes in volumes of solid nodules relative to the baseline CT scans

Methods	Nodule no.	T1-T0	T2-T0	T3-T0	T4-T0	T5-T0	T6-T0	T7-T0	Sex and smoking status
Percent change (%)	1	19.6	16.1	29.5	41.4**	37.3**	14.4	19.4	M <30
	2	–53.2*	–81.9*	–85.3*	–87.5*	–90.2*	–93.6*	–95.8*	M-n
	3	44.4**	54.1**	100.5**	124.5**	158.2**	204.1**	228.1**	M ≥30
	4	39.9**	54.1**	43.0**	64.5**	91.1**	156.8**		M-n
	5	4.1	19.5	34.5	38.5**	49.7**	57.2**		M ≥30
	6	–24.0	–49.4*	–74.7*	–82.1*	–88.0*	–85.4*		M ≥30
	7	–37.7*	–36.6*	–29.5	–41.5*	–41.0*			M-n
	8	–54.0*	–73.7*	–82.8*	–77.8*				M ≥30
	9	40.1**	37.7**	318.4**					M <30
	10	5.0	61.9**						F-n
Proportional change (%)	1	17.9	14.9	25.7	34.3	31.4	13.4	17.7	M <30
	2	–72.5*	–138.7*	–148.7*	–155.7*	–164.3*	–175.9*	–184.1*	M-n
	3	36.3	42.6**	66.9**	76.7**	88.3**	101.0**	106.6**	M ≥30
	4	33.2	42.6**	35.4**	48.8**	62.6**	87.9**		M-n
	5	4.0	17.8	29.4	32.3	39.8**	44.5**		M ≥30
	6	–27.3	–65.7*	–119.3*	–139.3*	–157.2*	–149.1*		M ≥30
	7	–46.5*	–44.8*	–34.6*	–52.4*	–51.5*			M-n
	8	–74.0*	–116.8*	–141.4*	–127.3*				M ≥30
	9	33.4	31.7	122.8**					M <30
	10	4.9	47.3**						F-n
Growth rate (%)	1	78.7	21.6	16.9	15.1**	9.8**	2.9	3.6	M <30
	2	–215.8*	–96.1*	–45.1*	–30.3*	–23.2*	–19.1*	–16.3*	M-n
	3	151.4**	67.4**	55.8**	44.5**	41.7**	42.5**	39.2**	M ≥30
	4	159.9**	75.7**	36.0**	29.4**	28.5**	31.6**		M-n
	5	14.1	18.9	16.5	12.6	12.2**	11.3**		M ≥30
	6	–178.7*	–129.8*	–90.9*	–62.2*	–37.7*	–23.7*		M ≥30
	7	–137.6*	–46.6*	–16.2	–14.7*	–8.2			M-n
	8	–216.8*	–61.2*	–37.6*	–15.7*				M ≥30
	9	160.9**	50.4**	175.6**					M <30
	10	19.2	120.2**						F-n

*, indicate a volume decrease of more than the 95% limit of agreement; **, indicate a volume increase of more than the 95% limit of agreement. T0, date of baseline CT scan; T1, date of second CT scan; T2, date of third CT scan; T3, date of fourth CT scan; T4, date of fifth CT scan; T5, date of sixth CT scan; T6, date of seventh CT scan; T7, date of eighth CT scan; M ≥30, male smoker with ≥30 pack-years; M <30, male smoker with <30 pack-years; M-n, male never-smoker; F-n, female never-smoker. Definition of "change" is defined as an increase or decrease of more than 1.96 SD in each volume change parameter relative to the volume on the baseline CT. SD, standard deviation.

Table 5 Time until detection of a change in volume

Nodule No.	No. of time points	Days until detection of a change[¶]				Sex and smoking status	Change in diameter
		Clinical diagnosis [diameter]	Percent change	Proportional change	Growth rate		
1	8	1,834 [7]	1,002 [5]*	NA[§]	1,002 [5]*	M <30	Increase
2	8	311 [3]	90 [2]*	90 [2]*	90 [2]*	M-n	Decrease
3	8	1,386 [6]	107 [2]*	293 [3]*	107 [2]*	M ≥30	Increase
4	7	1,165 [6]	91 [2]*	261 [3]*	91 [2]*	M-n	Increase
5	7	1,483 [6]	1,120 [5]*	1,483 [6]	1,483 [6]	M ≥30	Increase
6	7	300 [4]	139 [3]*	139 [3]*	49 [2]*	M ≥30	Decrease
7	6	665 [4]	100 [2]*	100 [2]*	100 [2]*	M-n	Decrease
8	5	91 [2]	91 [2]	91 [2]	91 [2]	M ≥30	Decrease
9	4	662 [4]	91 [2]*	662 [4]	91 [2]*	M <30	Increase
10	3	188 [3]	188 [3]	188 [3]	188 [3]	F-n	Increase

[¶], data in parentheses are time points; [§] No change detected; *, indicate a nodule that was detected earlier than the clinical diagnosis. M ≥30, male smoker with ≥30 pack-years; M <30, male smoker with <30 pack-years; M-n, male never-smoker; F-n, female never-smoker. NA, not available.

Table 6 Summary of detected changes in volume

Variables	Clinical diagnosis (diameter)	Percent change	Proportional change	Growth rate
No. of change-detected nodules	10	10	9	10
No. of earlier-detected nodules	NA	8	5	7
Days until change detection (mean ± SD)	809±616	302±402	367±455	329±496
P value (*vs.* diameter)*	NA	0.0151	0.0496	0.0206

*, Mann-Whitney U test. SD, standard deviation; NA, not available.

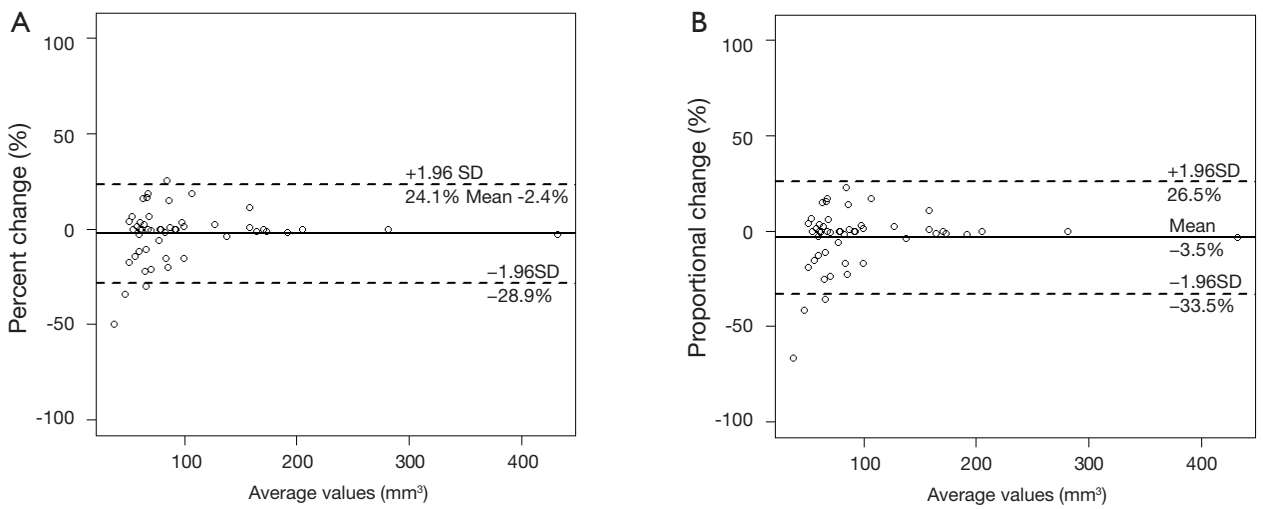

Figure 6 Intra-reader variability. (A) 95% limits of agreement for percent change; (B) 95% limits of agreement for proportional change.

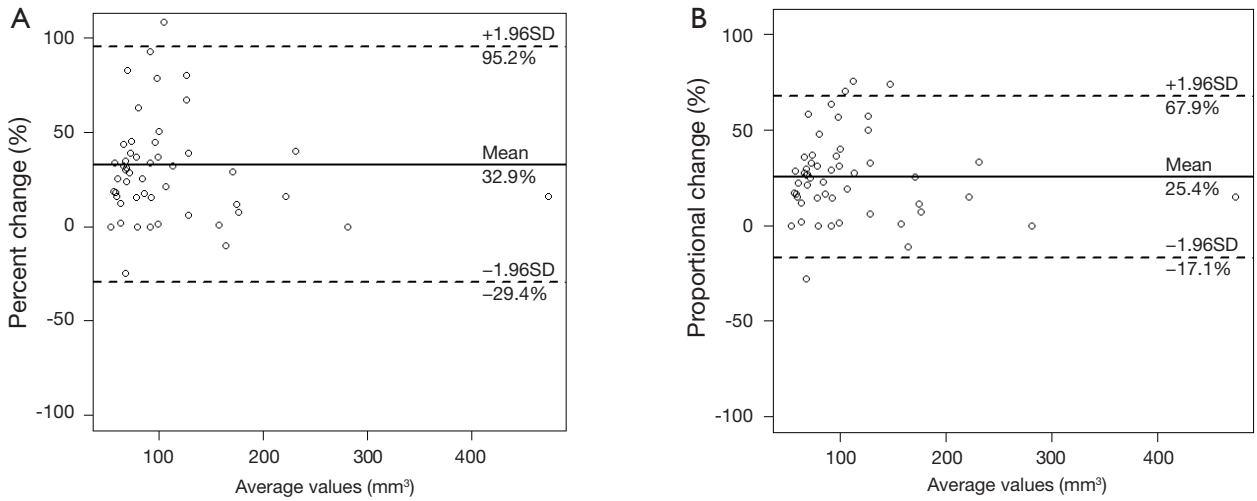

Figure 7 Inter-reader variability. (A) 95% limits of agreement for percent change; (B) 95% limits of agreement for proportional change.

was allowed for better segmentation of the nodule because 77% of the solid nodules were in contact with pulmonary vessels; this procedure might have affected the results of this study. Other studies have also reported results with manual correction (14,30). Third, the NELSON lung nodule management system used the percent volume change and the VDT for assessments (1-3). However, the present study did not evaluate the VDTs because of the very small cohort that was used for the evaluation. Fourth, female smokers were not included in this study because the number of female smokers was very small. Finally, regarding the evaluation of the progression of indeterminate solid nodules, the number of solid nodules that showed an increase in the longest diameter was very small because the number of solid nodules with a longest diameter of less than 10 mm that showed an increase in the longest diameter was quite limited. Further evaluation with larger patient and nodule numbers is needed to develop a follow-up system for solid nodules with more significant findings.

Conclusions

The 95% limits of agreement for volume changes in 5-year stable solid nodules may enable the detection of an increase or decrease in solid nodules at an earlier stage than that enabled by a clinical diagnosis, possibly contributing to the development of a follow-up system for reducing the number of additional CT scans performed during the follow-up period. Validation of our findings in a study with larger patient and nodule numbers is required.

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Footnote

Conflicts of Interest: Mr. Yamamichi is an employee of Canon Inc., Japan and was a visiting researcher of the Cancer Screening Division, Research Center for Cancer Prevention and Screening, National Cancer Center, and Dr. Oubel is an employee of MEDIAN Technologies, France. The other authors have no conflicts of interest to declare.

Ethical Statement: The institutional review board in the National Cancer Center approved this study (approval number: 2012-345) and informed consent was obtained from all the patients.

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Supplementary

Table S1 Summary of percent changes

Nodule volume ≥50 mm^3	Never-smokers		Smokers	
	Female never-smokers	Male never-smokers	Male smokers, <30 pack-years	Male smokers, ≥30 pack-years
No. of patients	53	36	51	46
No. of nodules	60	43	66	57
No. of pairs for measurements	598	430	715	580
Mean percent change	0.009	0.020	0.023	0.007
Standard deviation	0.178	0.176	0.183	0.193
P value* (*vs.* female never-smokers)	NA	0.7925	0.5377	0.05317
No. of patients	89[¶]		97[†]	
No. of nodules	103[§]		123[‡]	
Mean percent change	0.014		0.016	
Standard deviation	0.177		0.187	
P value*	0.06182			

*, F-test; [¶], subtotal of number of female never-smokers and male never-smokers; [§], subtotal of number of nodules in female never-smokers and male never-smokers; [†], subtotal of number of male smokers with <30 pack-years and male smokers with ≥30 pack-years; [‡], subtotal of number of nodules in male smokers with <30 pack-years and male smokers with ≥30 pack-years.

Table S2 Summary of proportional changes

Nodule volume ≥50 mm^3	Never-smokers		Smokers	
	Female never-smokers	Male never-smokers	Male smokers, <30 pack-years	Male smokers, ≥30 pack-years
No. of patients	53	36	51	46
No. of nodules	60	43	66	57
No. of pairs for measurements	598	430	715	580
Mean proportional change	–0.006	0.005	0.007	–0.011
Standard deviation	0.174	0.174	0.177	0.188
P value* (*vs.* female never-smokers)	NA	0.9957	0.6517	0.05216
No. of patients	89[¶]		97[†]	
No. of nodules	103[§]		123[‡]	
Mean proportional change	–0.001		–0.001	
Standard deviation	0.174		0.182	
P value*	0.1097			

*, F-test; [¶], subtotal of number of female never-smokers and male never-smokers; [§], subtotal of number of nodules in female never-smokers and male never-smokers; [†], subtotal of number of male smokers with <30 pack-years and male smokers with ≥30 pack-years; [‡], subtotal of number of nodules in male smokers with <30 pack-years and male smokers with ≥30 pack-years.