Pulmonary Nodules: Volume Repeatability at Multidetector CT Lung Cancer Screening[1]

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Purpose: To assess in vivo volumetric repeatability of an automated software algorithm in pulmonary nodules detected during a lung cancer screening trial.

Materials and Methods: This study was approved by an institutional review board. Written informed consent was obtained from all participants. Data were collected from the Multicentric Italian Lung Detection project, a randomized controlled lung cancer screening trial. The first 1236 consecutive baseline computed tomographic (CT) studies performed at the Istituto Nazionale Tumori of Milan were evaluated. Among the enrolled participants, those who underwent repeat low-dose CT after 3 months and had at least one indeterminate nodule with a volume of more than 60 mm^3 (diameter of 4.8 mm or greater) were considered. Nonsolid, part-solid, and pleural-based nodules were excluded from this study. A descriptive analysis was performed by calculating means and standard deviations of nodule volumes at three assessment times (at baseline and 3 and 12 months later). The volume measurement repeatability was determined by using the approach described by Bland and Altman.

Results: One hundred one subjects (70 men, 31 women; mean age, 58 years) with 233 eligible nodules (mean volume, 98.3 mm^3; range, 5–869 mm^3) were identified. The 95% confidence interval for difference in measured volumes was in the range of ±27%. About 70% of measurements had a relative difference in nodule volume of less than 10%. No malignant lesions were registered during the follow-up of these subjects.

Conclusion: Semiautomatic volumetry is sufficiently accurate and repeatable and may be useful in assisting with lung nodule management in a lung cancer screening program.

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The number of small pulmonary nodules incidentally detected increased with the introduction of multidetector computed tomographic (CT) scanners (1). These findings had a great effect on early lung cancer screening programs. In fact, lung cancer screening with low-dose CT revealed a detection rate of asymptomatic cancer in high-risk individuals of 1% per year, but the detection of benign lesions was 50 times higher (2–5). The frequency of benign pulmonary lesions in heavy smokers is directly related to the sensitivity of spiral CT and has proved to be very high with the use of latest-generation equipment. Nonetheless, the effect of sensitivity on the overall performance of early detection programs in high-risk populations largely depends on the selected diagnostic algorithm (5). The challenge for the radiologist is to correctly identify the few malignant lesions among the numerous benign nodules.

Diagnostic evaluation of such small, probably benign but indeterminate pulmonary nodules frequently involves serial CT scanning to depict growth as evidence of possible malignancy (6). With modern multidetector CT, it is now possible to acquire thin-section (<1-mm section thickness) CT image data for the whole thorax within a single breath hold. The advent of thin-section data from advanced dedicated software has enabled fully automated three-dimensional segmentation; immediate three-dimensional reconstruction along axial, coronal, and sagittal planes; and highly consistent volume measurement of lung nodules for subsequent assessment of growth (7).

It has been suggested that the use of volumetric measurements, by using automatic segmentation to define nodule margins on thin-section CT images, is the optimal method to assess nodule growth (8). Most of these investigations were performed as in vitro studies that involved scanning lesions in air without absorbing phantoms or with chest CT phantoms that did not include native lung tissue (9).

The purpose of our study was to assess in vivo volumetric repeatability of an automated software algorithm in pulmonary nodules detected during a lung cancer screening trial.

Advances in Knowledge

- Within the cutoff value of 25% indicating a suspicious relative dimensional change, we found almost 95% of benign nodules; moreover, about 70% of all measurements had a relative difference in nodule volume of less than 10%.
- No malignant lesions were registered during follow-up in these subjects.
- Although computer-aided detection system performance may not be optimal at this time, semiautomatic volumetry is sufficiently accurate and repeatable and may be useful in assisting lung nodule management in a lung cancer screening program.

Materials and Methods

This retrospective study was approved by our institutional review board at the Istituto Nazionale Tumori of Milan. Data were collected from the Multicentric Italian Lung Detection (MILD) project, a randomized lung cancer screening trial in the Italian population conducted by three centers located in the Lombardy region. The project was supported by a research grant from the Italian Ministry of Health, the Italian Association for Cancer Research, and the Cariplo Foundation. MILD primary end points are the assessment of smoking cessation rate among participants and the real possibility to prevent mortality in heavy smokers with early detection with annual chest CT. MILD includes subjects aged 50–75 years who are current or former (having quit < 10 years previously) smokers of 20 pack-years or more with no history of cancer within the previous 5 years. The individuals recruited were randomly assigned into two groups: A control group underwent a program of primary prevention with pulmonary function test evaluation and blood sample collection, and an early detection group underwent the same program with the addition of low-dose spiral CT. The early detection group was further randomized into two arms: yearly low-dose CT versus low-dose CT every 2 years. The MILD project was approved by the institutional review boards, and written informed consent was obtained from all participants.

Within the MILD project, all solid pulmonary nodules were prospectively recorded in a database, with a maximum limit of four nodules for each subject. Completely calcified nodules were excluded. We deemed solid lesions with a volume of less than 60 mm^3 (diameter of 4.8 mm or greater) to be nonsuspicious and scheduled repeat low-dose CT at 1 or 2 years. Nodules with a volume of 60–250 mm^3 (about 5–8 mm in diameter, respectively) underwent repeat CT examination after 3 months. Subjects with nodules greater than 250 mm^3 in volume were referred for a more differentiated work-up, including fluorine 18 fluorodeoxyglucose positron emission tomography (PET) or lung biopsy. We adopted a computer-aided detection volumetric growth of 25% or higher after a 3-month interval as the

Implication for Patient Care

- A software algorithm for the assessment of volumetric changes in pulmonary nodules at follow-up CT may play an important role in the evaluation of heavy smokers in lung cancer screening trials.

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Abbreviation:
MILD = Multicentric Italian Lung Detection

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threshold indicative of malignant growth (10). No further evaluation was required until the next follow-up for nodules showing no growth (Fig 1).

In the present study, we evaluated baseline CT images in the first 1236 consecutive MILD project participants (418 women, 818 men) obtained between September 2005 and September 2006 at the Istituto Nazionale Tumori of Milan. We included 112 subjects with at least one indeterminate nodule greater than 60 mm^3 in volume that was considered stable and who underwent repeat chest CT 3 and 12 months after baseline CT. Nonsolid, part-solid (five cases), and pleural-based (six cases) nodules were excluded because the automated segmentation algorithm showed limitations in the identification and separation of the nodule mass from the surrounding tissue structures. We registered the nodule volumetric measurement at baseline, as well as at 3 and 12 months.

CT Imaging

CT was performed with a 16-detector CT scanner (Somatom Sensation; Siemens Healthcare, Forchheim, Germany) without contrast material (0.75-mm collimation, 0.5-second rotation time, 1.5 pitch, 30 effective mAs, and 120 kVp). The acquisition field of view ranged from 300 to 400 mm. The same parameters were adopted for each repeat scan.

The entire chest was scanned in full inspiration in about 10 seconds by using a craniocaudal scanning direction. For each examination, images were obtained from the raw data by using the following parameter settings: 1-mm-thick sections at 1-mm increments (reconstruction kernel B50f) and 5-mm-thick sections at 5-mm increments (one with kernel B50f and one with kernel B30f). The data from all scanners were stored and transferred to a separate workstation (Leonardo or Syngo MMWP VE20A SL08P62–2006; Siemens Healthcare). The scanner was calibrated daily to allow reliable measurements and comparison between examinations. Each CT study was examined by two of seven alternating radiologists (A.M., E. Civelli, G.D.T., L.F.F., and C.M., senior radiologists with 15–20 years of experience; F.T. and E.F., junior radiologists with 1 year of experience). Whenever discordance occurred between the two examiners in the identification of lesions to be assessed volumetrically, a final decision was reached by consensus. Only one of the two radiologists performed the software-automated volume measurements (LungCare; Siemens Healthcare).

The graphical user interface is divided into four segments: two axial views, of which one displays the original 1-mm-thick section and the other represents a slab maximum intensity projection of adjustable thickness; a coronal view (slab reference segment); and one view that shows the select volume of interest. After the data set (1-mm thickness) is loaded, a computer-aided detection feature automatically depicts nodules; a marker appears, and the candidate nodule then can be accepted or discarded. If the lesion is accepted, automated volume measurement is performed. No manual postprocessing of the segmentation result was performed. The software calculated the volume and the x-, y-, and z-axis diameters. At the end of the analysis, all data were recorded in the dedicated central database. This routine procedure was performed for all nodules on MILD project CT scans.

Statistical Analysis

A descriptive analysis was performed by calculating means and standard deviations of nodule volumes at distinct assessment times (baseline and after 3 and 12 months). The repeatability of volume measurements for the same nodule was determined by using the approach described by Bland and Altman (11). With this approach, by using one-way analysis of variance with the nodule as the factor, we could estimate the within-nodule standard deviation, from which the repeat-

Figure 1

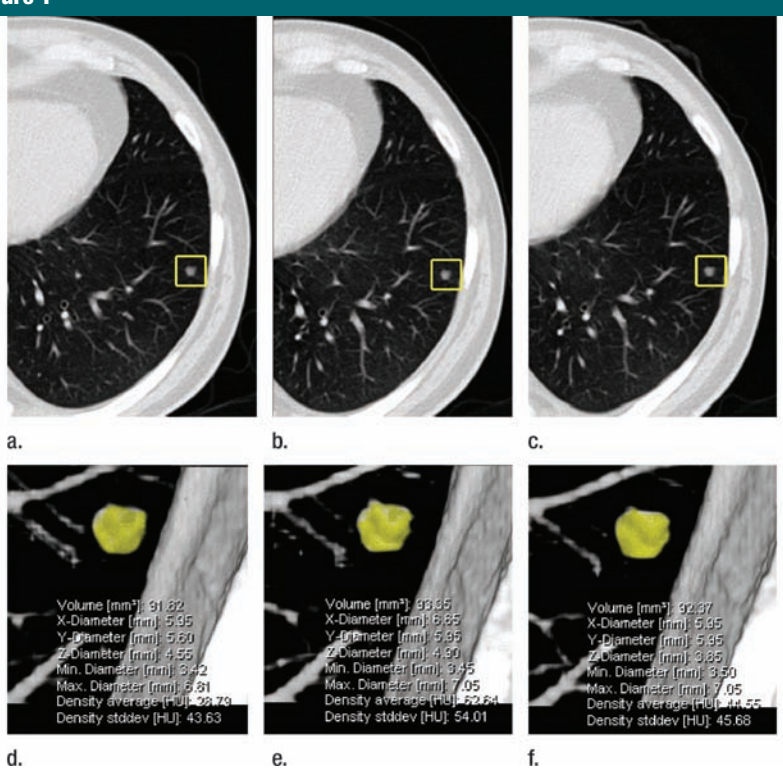

Figure 1: **(a–c)** Axial maximum intensity projections without contrast material at baseline, 3-month follow-up, and 12-month follow-up CT, respectively, and **(d–f)** respective volume-rendered images of 6-mm stable pulmonary nodule. Volume and diameter measurements were almost identical. Green boxes in **a–c** indicate nodules. Green areas in **d–f** indicate volume measurements.

ability coefficient was obtained. This coefficient is useful for defining the limits within which two readings are expected to vary for 95% of the nodules as an effect of method imprecision and is calculated as 2.77 times the within-nodule standard deviation. Because of increasing variability in volume with increasing volume, volume measurements were previously log transformed and then used for analysis of variance. Such a transformation allowed the implied assumptions of independence between measurements and variance homogeneity to be fulfilled. The calculations were performed by using software (SAS, release 8.2; SAS Institute, Cary, NC).

Results

We recruited subjects who were enrolled in the MILD project and who underwent the first 1236 baseline CT studies performed in our hospital. We recalled 133 subjects at the 3-month repeat CT examination (recall rate, 10.7%). We excluded from this analysis subjects without nodular parenchymal lesions (20 cases), those with no solid or those with part-solid nodules (five cases), and those with nodules attached to the costal pleura (six cases). One subject underwent surgical resection after substantial growth of a nodular lesion at repeat 3-month CT (T1N0M0 adenocarcinoma with a bronchioloalveolar component) (Fig 2).

Therefore, within the cohort, we identified 101 subjects (70 men, 31 women; mean age, 58 years; range, 49–73 years; 74 current and 27 former smokers; men: mean age, 58.6 years; range, 49–73 years; women: mean age, 57.3 years; range, 50–68 years) with 233 eligible nodules (mean volume, 98.3 mm^3; range, 5–869 mm^3). Thirty-five subjects had one nodule, 21 had two nodules, 24 had three nodules, and 21 had four nodules. Automated volume measurements were evaluated in all nodules. One hundred seven (45.9%) nodules had a volume less than 60 mm^3, 111 (47.6%) had a volume between 60 and 250 mm^3, and 15 (6.4%) had a volume greater than 250 mm^3.

The mean volume of the 233 nodules at baseline was 99.1 $mm^3 \pm 127.5$ (standard deviation), and the median volume was 67 mm^3 (range, 5–839 mm^3). The mean volume at 3 months was 97.6 $mm^3 \pm 129.3$, and the median volume was 64 mm^3 (range, 5–869 mm^3). The mean volume at 12 months was 98.2 $mm^3 \pm 127.6$, and the median volume was 63 mm^3 (range, 5–866 mm^3).

The plots in Figure 3 show, for each nodule, the differences in volume calculated by subtracting the nodule volume at the first CT scan (baseline) from the volume measured at the second scan (namely, after 3 or 12 months), relative to the mean of the two measurements and the differences in volume calculated by subtracting the nodule volume at 3 months from the volume at 12 months, relative to the mean of the two measurements.

The plots show that these differences, both after 3 and after 12 months from baseline, were centered around zero and that their scatter was homogeneous along the x-axis, indicating that variability on a relative scale was not affected by nodule volume. The within-nodule standard deviation was 0.0977,

Figure 2

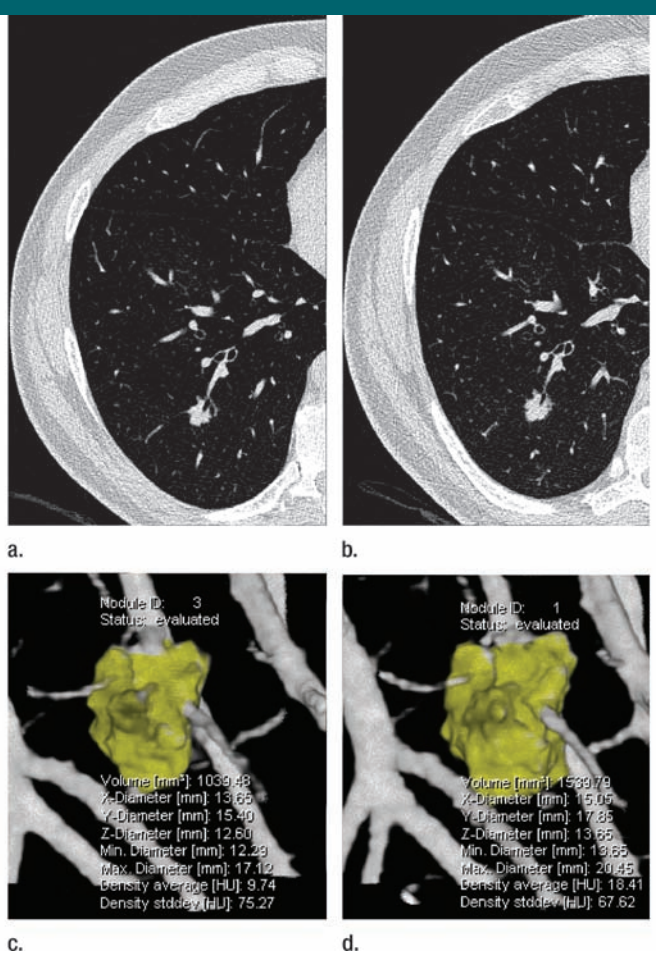

Figure 2: **(a, b)** Axial CT images without contrast material and **(c, d)** respective volume-rendered images. **(a)** Solid lung nodule with spiculated margins detected during first low-dose CT study. PET performed a few days later had a negative finding (not shown). **(b)** Patient underwent further low-dose CT for growth assessment within 3 months. Nodule measurement (green areas) varied from **(c)** 1039 mm^3 at baseline to **(d)** 1539 mm^3 at 3 months. Pathologic diagnosis was T1N0M0 adenocarcinoma with a bronchioloalveolar component.

Figure 3

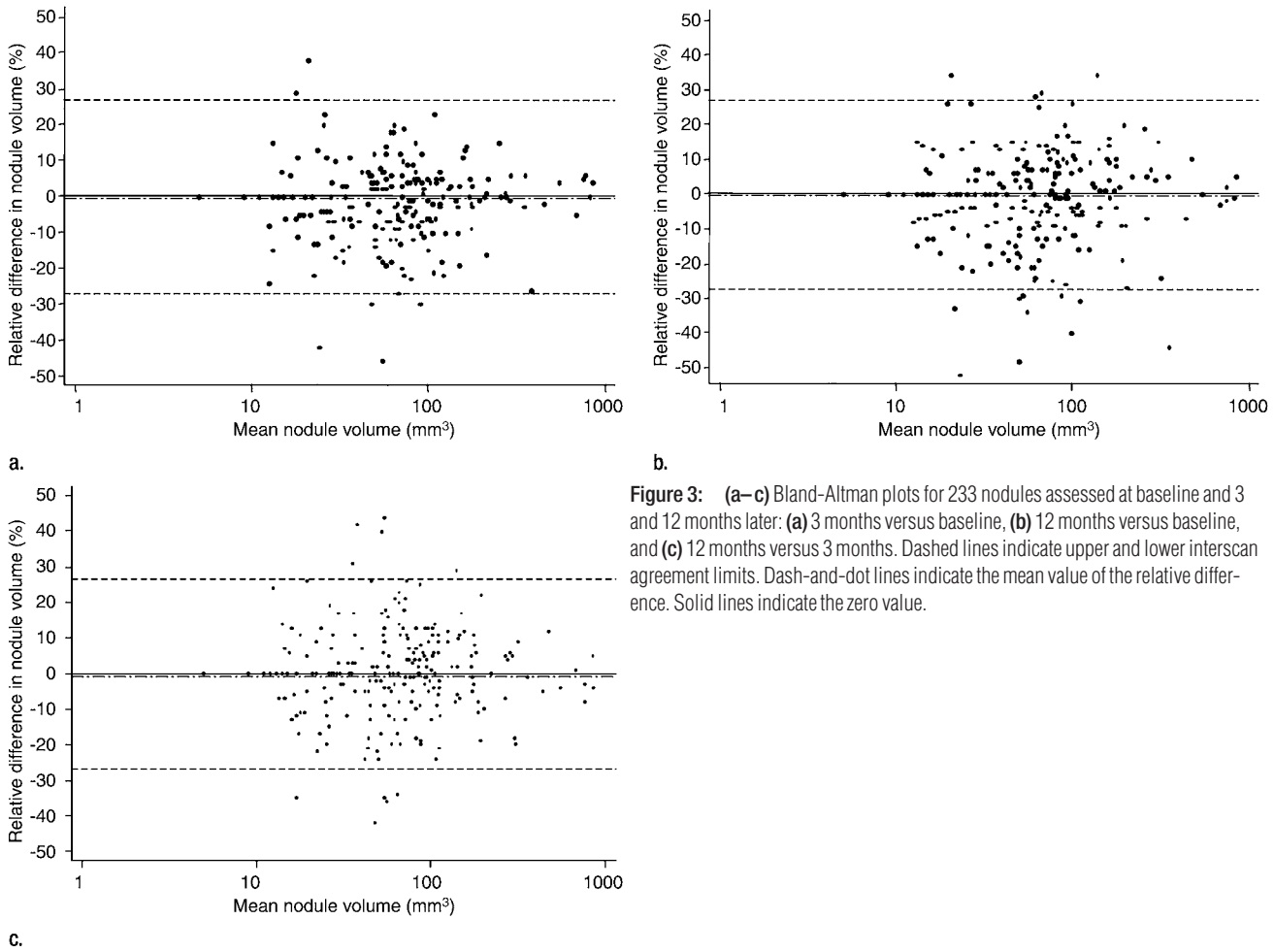

Figure 3: **(a–c)** Bland-Altman plots for 233 nodules assessed at baseline and 3 and 12 months later: **(a)** 3 months versus baseline, **(b)** 12 months versus baseline, and **(c)** 12 months versus 3 months. Dashed lines indicate upper and lower interscan agreement limits. Dash-and-dot lines indicate the mean value of the relative difference. Solid lines indicate the zero value.

and the repeatability coefficient was equal to 0.27. This means that the relative difference between two volume readings was expected to vary for 95% of the nodules in the range of ±27%.

The Table shows the relative difference in nodule volumes at 3 and 12 months. With the consideration of the positive and negative relative differences, at 3 and 12 months, the percentage of measurements with a relative difference in nodule volume of less than 10% was 70.4% and 61.8%, respectively. The percentage of nodules with a relative difference between 10% and 25% was quite similar for negative and positive variations. In the extreme classes (relative difference, >25%), data points were too small in number to allow any reliable assessment. Two of 233 nodules (volume of 15 and 17 mm^3 at baseline) revealed an increase in nodule volume of more than 25% after 3 months.

Relative Difference in Nodule Volume Assessed 3 and 12 Months after Baseline CT

	3 Months after Baseline CT		12 Months after Baseline CT	
Relative Difference	No. of Nodules	Percentage	No. of Nodules	Percentage
Increase < 10%	78	33.5	71	30.5
Decrease < 10%	86	36.9	73	31.3
Increase 10%–25%	23	9.9	32	13.7
Decrease 10%–25%	34	14.6	38	16.3
Increase > 25%	2	0.8	7	3.0
Decrease > 25%	10	4.3	12	5.2

PET was required in five individuals with at least one lesion greater than 250 mm^3, and the result was negative in all cases.

None of the nodules showed malignant characteristics at the first annual repeat examination. Until December

2008, depending on the time of recruitment, 98 subjects underwent a second annual repeat examination. Findings from this additional follow-up imaging study revealed that one lesion increased in volume over 2 years (78 mm^3 at baseline, 85 mm^3 at 12 months, and 141 mm^3 at 24 months). The patient refused additional watchful waiting and underwent video-assisted thoracoscopic surgical resection at another institution. (This lesion was diagnosed as an intrapulmonary lymph node.) No histologic proof was available for other nodules included in this study.

Discussion

Pulmonary nodules are a common finding at lung cancer screening trials. The majority of pulmonary nodules with diameters less than 10 mm detected in such a setting are benign (5,12), and experiences with long-term follow-up of lesions smaller than 5 mm suggest that these nodules require no additional work-up. Indeterminate lesions with a size between 5 and 10 mm frequently lead to a diagnostic dilemma (13). Unlike in larger nodules, the use of additional investigations, such PET or the measurement of CT contrast enhancement, is controversial. Few data exist to evaluate the sensitivity of PET for detection of malignant nodules with diameters less than 10 mm (14), while minimally invasive procedures (15) or invasive surgical approaches often seem unjustified for probably benign lesions.

Therefore, repeated size assessment to detect nodule growth is the most widely used method to distinguish between benign and malignant lesions, especially for nodules with diameters up to 10 mm (16). Surveillance of nodule growth is usually performed with assessment of maximum lesion diameter with physical or digital calipers. Nevertheless, it has been demonstrated that three-dimensional volumetry was more sensitive in detecting growth than diameter measurement because volume doubling is equivalent to an increase in diameter of only 26%. Such small changes in dimension are difficult to detect with manually guided diameter measurements. In addition, Revel et al (17) observed poor two-dimensional measurement reliability in an interobserver study. Therefore, asymmetric growth may also impair correct lesion measurement, and lesion growth may be missed (18). On the other hand, computer-aided three-dimensional volumetry gives rise to a number of questions. Phantom experiments have been used to determine the precision of computer-based volumetric analysis (19,20). They yielded good reproducibility with a measurement error of less than 10% (9). In vivo, nodule measurement error is expected to be greater than in phantoms, because greater partial-volume effects, motion artifacts, and irregular shapes of nodules play important roles (20,21).

Available in vivo data applicable to a current clinical scenario with full-field scan reconstruction, instead of targeted reconstruction of the nodule, are rather scarce. Because real nodule volumes cannot be determined, an almost unavoidable approach is to perform two consecutive CT scans, analyzing the standard deviation of repeated measurements, to estimate a measurement error.

Repeatability of commercially available software was evaluated by performing two consecutive low-dose CT scans within 10-minute intervals in patients with lung metastases (22). Those authors examined a total of 151 nodules in two consecutive scans with a low-dose CT protocol, with 95% limits of agreement from −20.4% to 21.9%.

Gietema et al (23) applied a similar study design by using the same type of semiautomated software. A thinner collimation was used and a higher number of nodules was detected; nevertheless, the authors found comparable limits of agreement (−21.2% to 23.8%). In this experience, the precision of nodule segmentation was highly dependent on nodule shape and was weakly related to inspiration level, while mean nodule volume showed no effect.

We assessed in vivo volumetric repeatability in pulmonary nodules detected in 101 subjects during long-term follow-up by using consecutive spiral CT at 3 and 12 months during a screening trial. We observed that variation in volume estimation of nonmalignant nodules fluctuated for 95% of the nodules in the range of ±27%. These results were quite comparable with other analyses performed with the identical software. We evaluated nodules detected at lung cancer screening, where lesions have no regular shape and smooth margins, as they do in the case of lung metastases considered in previous studies. The choice of an appropriate detection threshold for volume change is important for practical purposes. We selected a 25% increase in volume after 3 months as the threshold of suspicious malignancy because, as reported in previous studies, after this period a malignant nodule with a volume doubling time of 300 days will have increased 23% in volume (10). Therefore, within the cutoff value of 25% indicating a suspicious volumetric relative change, we found almost 95% of the nodules. Moreover, in our study, about 70% of all measurements had a relative difference in nodule volume of less than 10%. Only two of the 233 nodules had an increase of more than 25%. These two outliers were nodules of a few millimeters associated with the main nodules for which the subject was recalled after 3 months. No malignant lesions were registered during the follow-up of these subjects.

We found comparable limits of agreement in measurements at 3 and at 12 months, and this suggests that the spreading interval is a consequence of method imprecision.

Semiautomated measurement without any observer-induced postprocessing is not reproducible in all circumstances for all nodules, but, on the other hand, manual diameter measurement of the nodules is a tedious task and operator dependent. In our experience, systematic use of widely applied commercial semiautomated software expedites the diagnostic work-up.

There were limitations of this study. First, the authors have assumed that all nodules considered stable at three consecutive low-dose scans with a follow-up of 12 months were not malignant; but because of the lack of pathologic correlation, this assumption cannot be con-

firmed. Nevertheless, 98 subjects underwent a second annual repeat examination, and none of the nodules showed malignant characteristics. Traditionally, stability in nodule size during a 2-year period has been considered a sign that a lesion is benign (24), although bronchoalveolar cell carcinomas and typical carcinoids occasionally appear to be stable for 2 years or more (6,25). On the other hand, hamartomas, benign tumors, and other benign lesions may increase (26), and this might contribute to system inaccuracies.

Another potential limitation was that this study was based on one specific software program; thus, our results may not apply to other systems. Finally, our study did not consider nonsolid, part-solid, and pleural-based nodules. The observation suggests that there is a subset of nodules for which volumetric measurement is not reproducible, causing errors in the assessment of nodule growth.

In conclusion, our study shows that although computer-aided detection system performance may not be optimal at this time, semiautomatic volumetry is sufficiently accurate, robust, and repeatable to warrant a fluent workflow in a lung cancer screening program.

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