

# Pulmonary Ground-Glass Nodules: Increase in Mass as an Early Indicator of Growth<sup>1</sup>

Bartjan de Hoop, MD  
Hester Gietema, MD, PhD  
Saskia van de Vorst, MSc  
Keelin Murphy, MSc  
Rob J. van Klaveren, MD, PhD  
Mathias Prokop, MD, PhD

## Purpose:

To compare manual measurements of diameter, volume, and mass of pulmonary ground-glass nodules (GGNs) to establish which method is best for identifying malignant GGNs by determining change across time.

## Materials and Methods:

In this ethics committee–approved retrospective study, baseline and follow-up CT examinations of 52 GGNs detected in a lung cancer screening trial were included, resulting in 127 GGN data sets for evaluation. Two observers measured GGN diameter with electronic calipers, manually outlined GGNs to obtain volume and mass, and scored whether a solid component was present. Observer 1 repeated all measurements after 2 months. Coefficients of variation and limits of agreement were calculated by using Bland-Altman methods. In a subgroup of GGNs containing all resected malignant lesions, the ratio between intraobserver variability and growth (growth-to-variability ratio) was calculated for each measurement technique. In this subgroup, the mean time for growth to exceed the upper limit of agreement of each measurement technique was determined.

## Results:

The  $\kappa$  values for intra- and interobserver agreement for identifying a solid component were 0.55 and 0.38, respectively. Intra- and interobserver coefficients of variation were smallest for GGN mass ( $P < .001$ ). Thirteen malignant GGNs were resected. Mean growth-to-variability ratios were 11, 28, and 35 for diameter, volume, and mass, respectively ( $P = .03$ ); mean times required for growth to exceed the upper limit of agreement were 715, 673, and 425 days, respectively ( $P = .02$ ).

## Conclusion:

Mass measurements can enable detection of growth of GGNs earlier and are subject to less variability than are volume or diameter measurements.

©RSNA, 2010

<sup>1</sup> From the Department of Radiology (B.d.H., H.G., S.v.d.V., M.P.) and Image Sciences Institute (K.M.), University Medical Center, Heidelberglaan 100, 3584 CX Utrecht, the Netherlands; Department of Radiology, Meander Medical Center, Amersfoort, the Netherlands (H.G.); and Department of Pulmonology, Erasmus Medical Center, Rotterdam, the Netherlands (R.J.v.K.). Received April 8, 2009; revision requested May 6; final revision received June 19; accepted July 31; final version accepted September 16. Address correspondence to B.d.H. (e-mail: [b.j.dehoop@umcutrecht.nl](mailto:b.j.dehoop@umcutrecht.nl)).

©RSNA, 2010

**G**round-glass nodules (GGNs) are regularly encountered during computed tomographic (CT) screening for lung cancer. In the Early Lung Cancer Action Project trial, for example, most detected malignancies were GGNs (1). These GGNs pose a challenging task for the clinician because they grow slowly (2) but, at the same time, have a malignancy rate as high as 63% (1).

A GGN is a circumscribed area of increased pulmonary attenuation with preservation of the bronchial and vascular margins. A GGN can be partly solid (part of the ground-glass opacity completely obscures the parenchyma) or nonsolid (no completely obscured areas) (2). Whereas a large range of benign diseases (eg, inflammatory disease or fibrosis) can manifest as GGN, most GGNs that persist longer are atypical adenomatous hyperplasia, bronchoalveolar carcinoma (3), or minimally invasive adenocarcinoma (4–7).

Differentiation of benign and malignant GGNs is done largely on the basis of change in size or the development of a solid component in a previously nonsolid GGN (8–10). Close follow-up is considered justified when a GGN is stable (ie, no growth or development

of a solid component can be demonstrated) (9,11). However, when a GGN increases in size or if a solid component develops, it should be resected (2,8–10,12). Because GGNs usually grow slowly, a method that can demonstrate subtle changes in size and density is required (8,11).

Changes in GGNs are usually evaluated by using diameter measurements and visual assessment of the appearance of a solid component (9,11,13). Nodule volumetry is superior to diameter measurements in solid nodules in terms of accuracy and reproducibility (14), but volumetric measurement techniques are not yet used regularly for GGNs. Mass is a parameter that integrates volume and density: Mass increases if the volume of a nodule increases or if its density increases. Mass should, therefore, be especially suitable for identifying GGNs with a high risk for malignancy. In this study, we introduce the estimation of GGN mass as a method for measuring change in GGNs on CT images. Mass can be calculated from CT data because x-ray attenuation values are proportional to tissue density (ie, mass per unit volume) (15). Nodule mass can be calculated by multiplying nodule volume and density. Whereas nodule volume weights each voxel in the volume of interest identically, nodule mass weights voxels that include more air or even pure pulmonary tissue less, which should make nodule mass less sensitive than nodule volume to variability in nodule segmentation. We compared manual measurements of diameter, volume, and mass of pulmonary GGNs to establish which method

is best for identifying malignant GGNs by determining change across time.

## Materials and Methods

### Study Participants

All participants were recruited from the randomized Dutch-Belgian lung cancer screening trial (NELSON) (16). The trial was approved by the Dutch Ministry of Health and the institutional review boards of the participating centers. Written informed consent was obtained from all participants. All participants were current or former heavy smokers (17). For the current analysis, all CT examinations performed between April 2004 and April 2009 at one of the study sites (University Medical Center, Utrecht, the Netherlands) were included. All CT scans were read for pulmonary nodules. Depicted nodules were characterized as solid nodules or GGNs as part of the screening trial. All detected GGNs were used in our current evaluation. Patients with a growing GGN were referred to a pulmonologist who decided whether resection was necessary (16).

### Detected GGNs

A total of 2994 volunteers underwent CT scanning. Fifty-two GGNs were detected in 45 participants (42 men, three women; mean age, 62 years; range, 53–73 years).

## Advances in Knowledge

- Detection of a solid component within a ground-glass nodule (GGN) has only modest intra- and interobserver agreement (Cohen  $\kappa$  values of 0.55 and 0.38, respectively).
- Measurement of GGN mass (volume  $\times$  CT number) has a lower variability than does measurement of GGN volume.
- During follow-up of malignant GGNs, the percentage increase in mass is greater than the percentage increase in volume or diameter.
- By using mass measurements, radiologists can detect growth of a malignant GGN earlier than with volume or diameter measurements.

## Implications for Patient Care

- Mass measurements allow for earlier growth detection in GGNs than do volume or diameter measurements, which may have implications for early detection of malignancy in such nodules.
- The modest interobserver agreement for the development of a solid component within a GGN suggests that this criterion is less robust than currently thought.

### Published online before print

10.1148/radiol.09090571

**Radiology** 2010; 255:199–206

### Abbreviations:

CI = confidence interval  
CV = coefficient of variation  
GGN = ground-glass nodule

### Author contributions:

Guarantors of integrity of entire study, B.d.H., R.J.v.K., M.P.; study concepts/study design or data acquisition or data analysis/interpretation, all authors; manuscript drafting or manuscript revision for important intellectual content, all authors; approval of final version of submitted manuscript, all authors; literature research, B.d.H., H.G.; clinical studies, B.d.H., H.G., K.M., R.J.v.K., M.P.; statistical analysis, B.d.H.; and manuscript editing, B.d.H., H.G., S.v.d.V., R.J.v.K., M.P.

Authors stated no financial relationship to disclose.

See also the editorial by Naidich and the article by Lee et al.

Seven patients had two GGNs each. Including follow-up examinations, 127 data sets containing a GGN were available for evaluation. Eighteen lesions were visible on only one CT study, six lesions were visible on two, 17 lesions were visible on three, nine lesions were visible on four, and two lesions were visible on five consecutive CT studies. Median GGN diameter was 13.9 mm (range, 3.9–29.7 mm), as measured with electronic calipers.

### Malignant GGNs

One benign and thirteen malignant GGNs were resected in 12 patients (nine men, three women; mean age, 60 years; range, 53–67 years). Two patients each had two malignant GGNs resected. Histologic findings included adenocarcinoma ( $n=7$ ), bronchoalveolar carcinoma ( $n=6$ ), and atypical adenomatous hyperplasia ( $n=1$ ). Median malignant GGN diameter was 18.2 mm (range, 8.6–29.7 mm), as measured on the last follow-up CT study.

### Study Design

To determine which method is best for measuring potentially malignant change in GGNs, we took the following three-step approach: First, the intra- and interobserver variabilities of each method were assessed. All baseline and follow-up CT studies in which at least one GGN had been detected were selected. Two independent observers performed all measurements (observer 1: B.d.H., radiology researcher with 3 years experience in CT lung cancer screening [ $>1000$  examinations]; observer 2: S.v.d.V., medical researcher with special training in evaluating lung cancer screening CT scans and 2 years experience [ $>4000$  examinations]). Each observer independently categorized each GGN in the data set as nonsolid or partly solid. Observer 1 repeated all measurements after an interval of 2 months to estimate intraobserver variability.

Second, we used a subgroup of all GGNs that had been resected and proved malignant to evaluate the ability of each method to demonstrate growth. For each malignant GGN, we related the total change in diameter, volume, and mass during follow-up to the variability

of each measurement method (growth-to-variability ratio).

Third, we compared the three methods with respect to the time that we would have needed to follow a malignant nodule in our study before its growth would be discernable (ie, exceed the upper limit of agreement of intraobserver variability). Intraobserver variability was estimated from the repeated measurements of observer 1. The time to discernable growth was determined in the subgroup of resected malignant GGNs. We used the actual data from the screening study; applied the diameter, volume, and mass measurements; and determined the time between the baseline CT examination and the first CT examination at which growth became discernable. Time required for growth to become discernable was determined for the measurements of both observers and for each GGN.

### CT Scanning

Patients underwent imaging with a 16-detector row CT scanner (MX8000 IDT or Brilliance 16; Philips Medical Systems, Cleveland, Ohio) in helical mode with  $16 \times 0.75$ -mm collimation and 15-mm table feed per rotation. Scans were obtained with the patient at full inspiration, without previous training. No intravenous contrast material was injected. Exposure settings were 30 mAs at 120 kVp for patients weighing less than 80 kg and 30 mAs at 140 kVp for those weighing more than 80 kg. Axial images of 1.0-mm thickness were reconstructed at a 0.7-mm increment with a  $512 \times 512$  matrix by using a moderately soft kernel (B; Philips Medical Systems) and the smallest field of view that included both lungs. Density measurements are sensitive to CT number shifts owing to, for example, x-ray tube aging. The CT scanner was, therefore, calibrated every week, and a phantom was scanned as a quality control before each data acquisition session. No clinically important shift in CT number occurred during the study (18).

### Measurements

All measurements were performed retrospectively. GGNs were measured with

a fixed lung window setting at a width of 1400 HU and a level of  $-600$  HU. For manual diameter measurements, we determined the maximum diameter of the GGN by using the electronic calipers function of our picture archiving and communication system (Sectra Imtec, Linköping, Sweden) on the axial image on which the GGN had the greatest dimensions. Manual volumetry was performed by electronically outlining the lesion perimeter on all axial images on which the GGN was visible by using software developed in-house (Fig 1), followed by calculation of the GGN volume by the computer. It took an observer 5–10 minutes to outline a GGN manually. GGN mass was calculated by expressing attenuation values in terms of physical density. CT attenuation in Hounsfield units can be translated directly into physical density in milligrams per milliliter by adding 1000 to the Hounsfield unit value (15). For soft-tissue nodules, the prerequisites for this approach are that the nodule contains no calcium and that no contrast material was injected. The mass within the nodule volume, as outlined on all sections that contained the nodule, was calculated by multiplying nodule volume by mean nodule density (ie, mean CT number + 1000) (15).

Figure 1

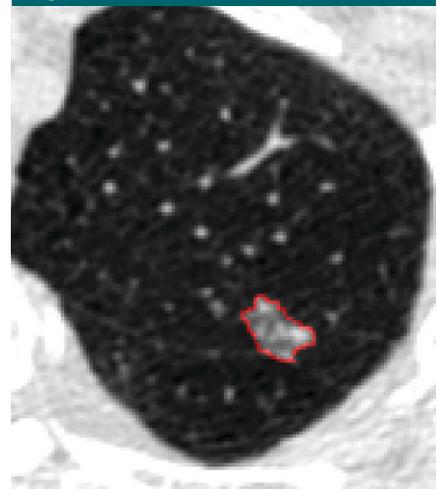


Figure 1: Axial CT image shows manually outlined GGN (red), which was used to calculate volume and mass.

### Statistical Evaluation

To determine variability, we calculated the 95% confidence interval (CI) for the limits of agreement by using Bland-Altman analysis (19). To assess intraobserver variability, we compared the two measurements of observer 1; for interobserver variability, the first measurement of observer 1 was compared with the measurement of observer 2. Inter- and intraobserver differences showed a normal distribution according to results of a Kolmogorov-Smirnov test. Variabilities of the volume and mass measurements were not independent of the magnitude of the measurement. Therefore, we used logarithmic transformation, as proposed by Bland and Altman, to correct for this lack of independence (20).

To compare variability of measurements on different scales, we calculated the mean coefficient of variation (CV) across all GGNs. The CV was calculated as the standard deviation divided by the mean. For each GGN, the intraobserver CV was calculated from the two measurements of observer 1, and the interobserver CV was calculated from the measurements of observers 1 and 2. For comparison of method variability, we used the original data without logarithmic transformation. Diameter is a unidimensional measurement, whereas volume is three-dimensional, and mass includes the volume information in the calculation. To compare the CV of diameter measurements with that of volume and mass measurements, we converted diameters into volumes on the basis of the assumption of a perfectly spherical lesion, and we calculated the CV of the diameter to the third power.

Cohen  $\kappa$  statistics (21) were used to assess reader agreement for identifying a solid component within a GGN.

The growth-to-variability ratio was used as an indicator of how much growth exceeded the measurement variability of the various methods. We defined the growth-to-variability ratio as the relative growth of a nodule divided by the mean CV. The relative growth was calculated as the percentage change in the nodule size (ie, diameter, volume, or mass) between the first and the last

available scan in our series. The mean CV was determined by averaging the intraobserver CV of observer 1 across all GGNs. The growth-to-variability ratio was calculated for each malignant GGN and for each measurement method. To obtain the best possible estimate of growth, we used the mean of both observers to calculate change in diameter, volume, or mass.

A paired *t* test was used in the following comparisons: intra- and interobserver CV for each method; increase in diameter, volume, or mass in the subgroup of malignant GGNs; growth-to-variability ratios for each method; and the mean time required for growth to exceed the upper limit of agreement of variability for each method. A *P* value of less than .05 was considered to indicate a significant difference.

## Results

### Measurement Variability

For the manually measured diameters, the 95% CI for the limits of agreement was  $-2.5, 2.7$  mm for intraobserver variability and  $-2.8, 3.3$  mm for interobserver variability. For the volume measurements, the 95% CI was  $-0.14, 0.16$  for intraobserver variability and  $-0.25, 0.15$  for interobserver variability, after logarithmic transformation. For the mass measurements, the 95% CI was  $-0.11, 0.12$  for the intraobserver variability and  $-0.18, 0.12$  for interobserver variability (Fig 2), after logarithmic transformation.

For mass measurements, the mean intraobserver CV was 0.07, and the mean interobserver CV was 0.09. The intra- and interobserver CVs for mass were significantly lower than those for volume (0.09 and 0.14, respectively;  $P < .001$ ). The mean intra- and interobserver CVs for diameter were 0.05 and 0.06, respectively, but increased to 0.15 and 0.18, respectively, when diameter measurements were converted to volumes. These diameter variabilities were significantly higher than those for volume and mass ( $P < .001$ ).

The  $\kappa$  values for intra- and interobserver agreement for identifying a

solid component were 0.55 and 0.38, respectively.

### Growth-to-Variability Ratio

Mean time between the first and the last CT examination of the 13 malignant lesions was 33 months (range, 12–49 months). During this period, the diameter of the malignant GGNs increased a mean of 53% (range, 9%–194%). During that same period, volume increased by a mean of 202% (range, 23%–714%). Mass increased by a mean of 254% (range, 36%–699%), which was significantly greater than the increases in volume and diameter ( $P < .01$ ). No significant decrease in mass was detected for any of the GGNs between two consecutive CT examinations. In only two instances, in two different GGNs, one of the observers measured a decrease in volume or diameter between two consecutive scans that exceeded the lower 95% limit of agreement. The mean growth-to-variability ratios of the measurement methods were 11, 28, and 35 for diameter, volume, and mass, respectively ( $P = .03$ ). The growth-to-variability ratio was larger for mass than for volume in 12 of 13 cases and smaller in the remaining case.

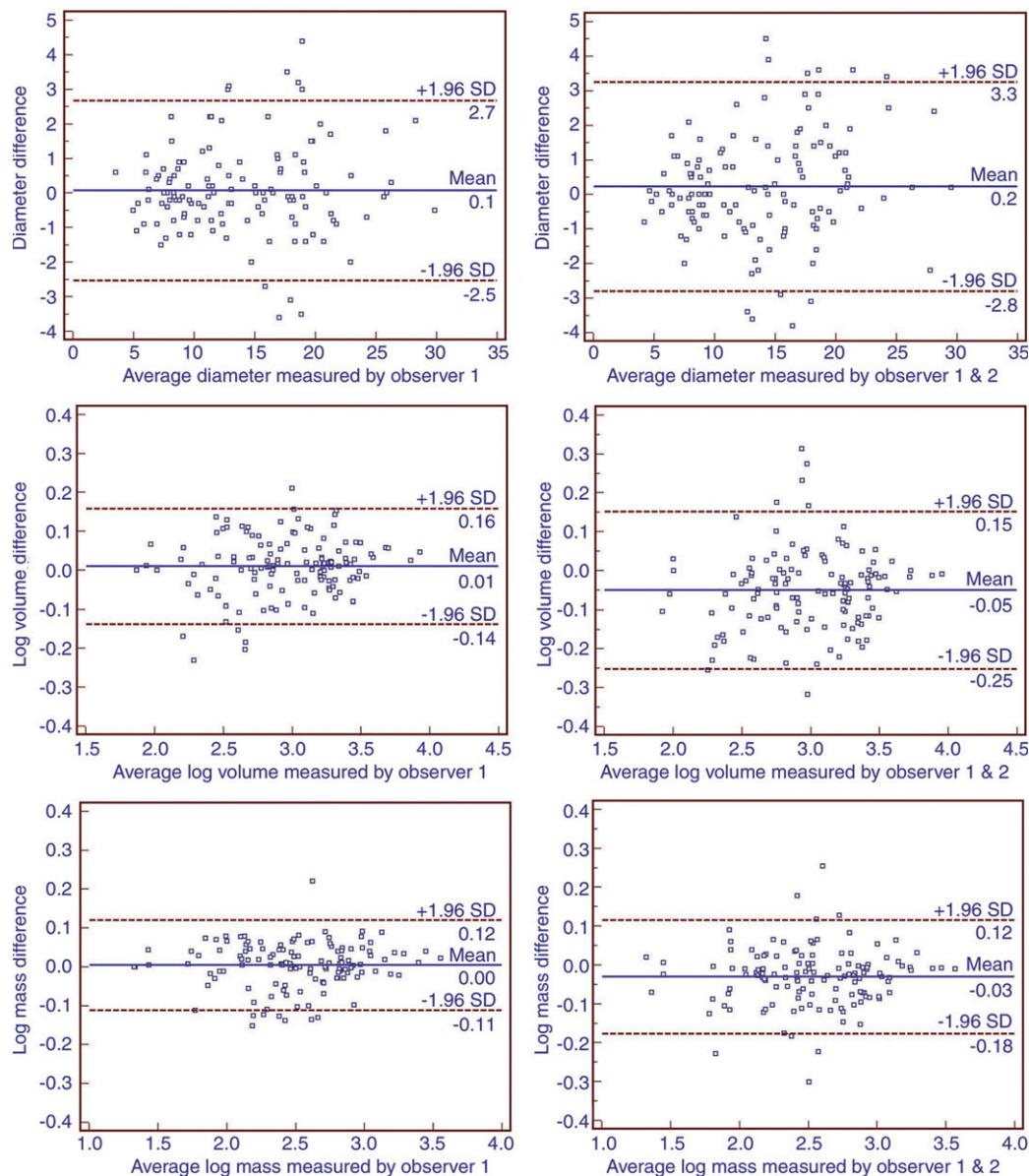
### Time to Detection of Growth

In the subgroup of 13 malignant GGNs, the mean time required for growth to exceed the upper limit of agreement was significantly longer ( $P = .02$ ) for the diameter (715 days) and volume (673 days) than for the mass (425 days). None of the cases showed a shorter time to growth detection for volume or diameter than for mass.

## Discussion

Detecting potentially malignant changes in GGNs can be challenging. To our knowledge, our analysis is the first in which mass was used as an approach to measuring change in GGNs. A similar approach had superior reproducibility in coronary calcium scoring (22). We showed that for the evaluation of potentially malignant GGNs, measurement of GGN mass has lower inter- and intraobserver CVs than do manual volume and

Figure 2



**Figure 2:** Bland-Altman plots show intra- (left) and interobserver (right) variabilities for diameter, manual volume, and mass. Volume and mass were logarithmically transformed. *SD* = standard deviation.

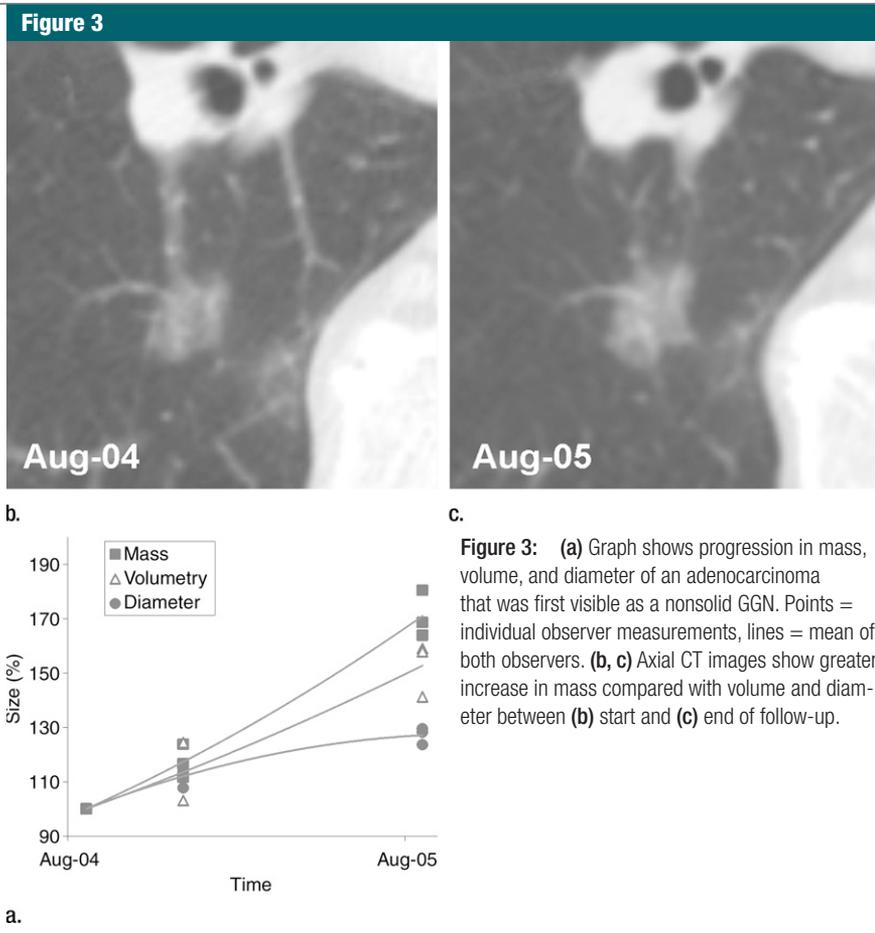
diameter measurements. The lower variability resulted in a significantly improved ability to detect growth by using mass as compared with diameter or volume in the subgroup of malignant GGNs. This observation was confirmed by a significantly shorter time required for change in mass to exceed measurement variability compared with the time required for diameter and volume measurements.

Because of the slow growth typical of GGNs, volume or density change can be subtle, emphasizing the need for a precise measurement method. For solid nodules, Revel et al (23) already concluded that two-dimensional measurements are unreliable, with a 95% CI for the difference among readers of  $-1.73$  and  $1.73$  mm. For GGNs, we found even greater inter- and intraobserver variabilities. This variability might be

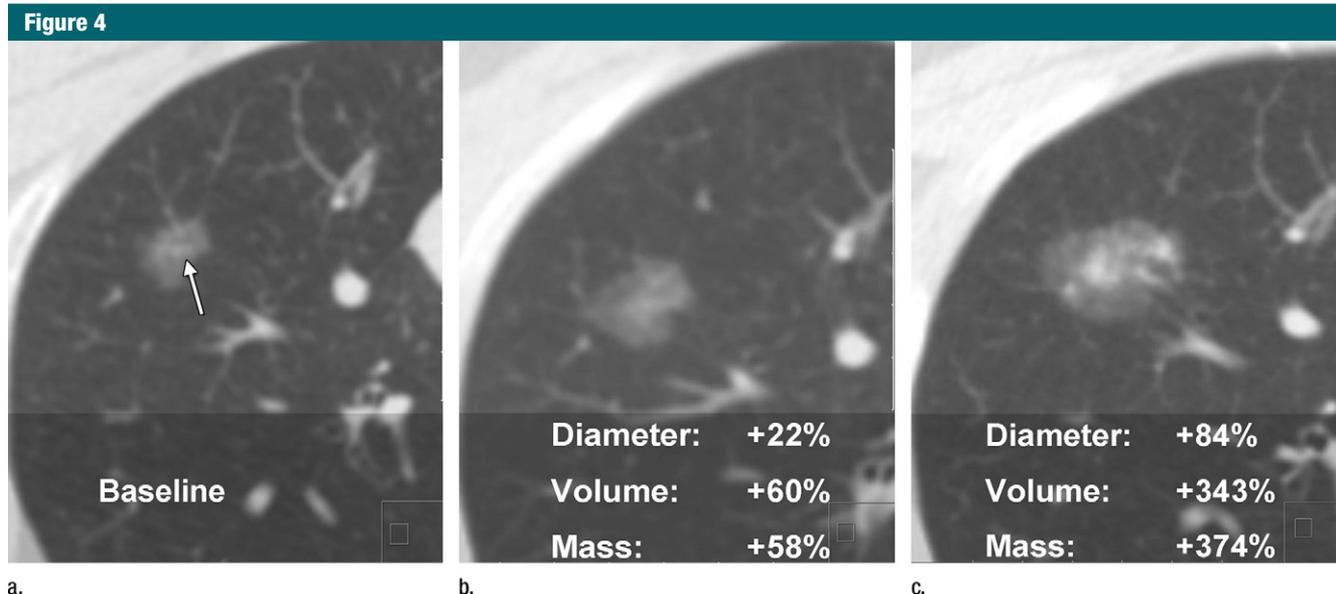
caused by the lower contrast of GGNs with the surrounding pulmonary parenchyma compared with that of solid nodules, resulting in different decisions among observers with relation to the location of a GGN boundary. Just as in solid nodules (24), the three-dimensional volume measurements had lower intra- and interobserver variabilities than did the two-dimensional diameter measurements. The lowest variability was achieved

with the mass measurements. This finding can be explained by the fact that all voxels in the outlined nodule contributed equally to the volume, whereas mass is dominated by the contribution of voxels with a higher attenuation that are usually located more toward the center of a nodule. Peripheral voxels, which are usually of lower attenuation, contribute relatively less to mass than to volume. Consequently, variations in nodule outline affect volume measurements more than mass measurements.

The development or progression of a solid component within a GGN influences GGN mass, but it does not directly influence GGN diameter or volume. During follow-up of malignant GGNs, the percentage increase in mass was significantly larger than the percentage increase in volume or diameter (Fig 3). As a result, the growth-to-variability ratio was greater for mass than for volume or diameter, which makes mass measurement superior to the other techniques for detecting growth. The greater growth-to-variability ratio for mass also shortened the time to detection of growth in malignant GGNs. Consequently, measurement of GGN mass may enable the



**Figure 3:** (a) Graph shows progression in mass, volume, and diameter of an adenocarcinoma that was first visible as a nonsolid GGN. Points = individual observer measurements, lines = mean of both observers. (b, c) Axial CT images show greater increase in mass compared with volume and diameter between (b) start and (c) end of follow-up.



**Figure 4:** (a–c) Axial CT images show an example of a GGN with a gradually developing solid component (1-mm sections). Scans were each obtained approximately 1 year apart. Observers agreed about a and c but disagreed as to whether a solid component was present on b. Note that a vessel is visible within the GGN (arrow) on a.

detection of GGN growth and, thus, identification of GGNs with a high suspicion for malignancy within a shorter time frame.

In addition to increase in GGN size, the development of a solid component in a previously nonsolid lesion is also regularly used to differentiate between benign and malignant GGNs. In our study, the reproducibility of scoring the presence of such a solid component had only moderate intra- and interobserver agreement, leaving this characterization unreliable. Furthermore, presence is a dichotomous measure with no room for further nuance, which is required to assess change in a solid component that is already visible at baseline. More nuance could be introduced by measuring the size of the solid component separately (25). However, separate measurement is, in our experience, often difficult because a solid component often appears gradually (Fig 4) and multiple solid components are sometimes present. The mass measurement we evaluated does not have these limitations.

The results demonstrated a slight difference in the manually outlined volumes between observers: Observer 2 tended to draw larger nodule outlines than did observer 1. To a lesser extent, this difference also affected the mass measurements. The differences were lower when the measurements were performed by the same observer. As a result, we can conclude that measurements in baseline and follow-up examinations should always be performed by the same observer. All measurements used in our study were obtained manually. Automatic segmentation software could minimize observer differences and also shorten the evaluation time. However, computer algorithms developed for the segmentation of solid nodules have difficulty with GGNs because of the low contrast of GGNs with the surrounding pulmonary parenchyma and their inhomogeneous appearance. New computer algorithms that are better suited for this task have been developed, and most major CT vendors have included a GGN segmentation option in their pulmonary evaluation software. However, in our experience, the quality

of GGN segmentation software results is often not yet up to the high standards set for solid nodules. We therefore chose to segment the GGNs manually. If accurate segmentation were achieved, automated systems can also calculate the mass of a lesion, so the conclusions of this study may be applicable to automated segmentation.

Our study has limitations. First, we evaluated only the variability between two observers and not between two successive CT studies. This variability between successive studies may be greater than the variability between observers and is likely to affect the growth-to-variability ratios as well. However, this standard holds true for all three measurement methods in a similar fashion. Second, one of our observers was not a physician. However, this observer was highly trained and experienced in evaluating lung cancer screening studies, including volumetric measurements and documentation of pulmonary nodules.

In conclusion, mass measurements can enable detection of growth of GGNs earlier and are subject to less variability than are volume or diameter measurements. In addition, the increase in mass was significantly greater than the increases in volume and diameter during follow-up of malignant GGNs. This finding may have implications for early detection of malignancy in GGNs.

## References

- Henschke CI, Yankelevitz DF, Mirtcheva R, McGuinness G, McCauley D, Miettinen OS. CT screening for lung cancer: frequency and significance of part-solid and nonsolid nodules. *AJR Am J Roentgenol* 2002;178:1053-1057.
- Hasegawa M, Sone S, Takashima S, et al. Growth rate of small lung cancers detected on mass CT screening. *Br J Radiol* 2000; 73:1252-1259.
- Noguchi M, Morikawa A, Kawasaki M, et al. Small adenocarcinoma of the lung: histologic characteristics and prognosis. *Cancer* 1995;75:2844-2852.
- Nakajima R, Yokose T, Kakinuma R, Nagai K, Nishiwaki Y, Ochiai A. Localized pure ground-glass opacity on high-resolution CT: histologic characteristics. *J Comput Assist Tomogr* 2002;26:323-329.
- Nakata M, Sawada S, Saeki H, et al. Prospective study of thoroscopic limited resection for ground-glass opacity selected by computed tomography. *Ann Thorac Surg* 2003;75:1601-1605.
- Suzuki K, Asamura H, Kusumoto M, Kondo H, Tsuchiya R. "Early" peripheral lung cancer: prognostic significance of ground glass opacity on thin-section computed tomographic scan. *Ann Thorac Surg* 2002; 74:1635-1639.
- Seki N, Sawada S, Nakata M, et al. Lung cancer with localized ground-glass attenuation represents early-stage adenocarcinoma in nonsmokers. *J Thorac Oncol* 2008; 3:483-490.
- Aoki T, Nakata H, Watanabe H, et al. Evolution of peripheral lung adenocarcinomas: CT findings correlated with histology and tumor doubling time. *AJR Am J Roentgenol* 2000;174:763-768.
- Kakinuma R, Ohmatsu H, Kaneko M, et al. Progression of focal pure ground-glass opacity detected by low-dose helical computed tomography screening for lung cancer. *J Comput Assist Tomogr* 2004;28:17-23.
- Lindell RM, Hartman TE, Swensen SJ, et al. Five-year lung cancer screening experience: CT appearance, growth rate, location, and histologic features of 61 lung cancers. *Radiology* 2007;242:555-562.
- Kodama K, Higashiyama M, Yokouchi H, et al. Natural history of pure ground-glass opacity after long-term follow-up of more than 2 years. *Ann Thorac Surg* 2002;73:386-392.
- Yang ZG, Sone S, Takashima S, et al. High-resolution CT analysis of small peripheral lung adenocarcinomas revealed on screening helical CT. *AJR Am J Roentgenol* 2001;176:1399-1407.
- Lee HJ, Goo JM, Lee CH, Yoo CG, Kim YT, Im JG. Nodular ground-glass opacities on thin-section CT: size change during follow-up and pathological results. *Korean J Radiol* 2007;8:22-31.
- Marten K, Auer F, Schmidt S, Kohl G, Rummeny E, Engelke C. Inadequacy of manual measurements compared to automated CT volumetry in assessment of treatment response of pulmonary metastases using RECIST criteria. *Eur Radiol* 2006;16: 781-790.
- Mull RT. Mass estimates by computed tomography: physical density from CT numbers. *AJR Am J Roentgenol* 1984;143: 1101-1104.

16. Xu DM, Gietema H, de Koning H, et al. Nodule management protocol of the NELSON randomised lung cancer screening trial. *Lung Cancer* 2006;54:177-184.
17. van Iersel CA, de Koning HJ, Draisma G, et al. Risk-based selection from the general population in a screening trial: selection criteria, recruitment and power for the Dutch-Belgian randomised lung cancer multi-slice CT screening trial (NELSON). *Int J Cancer* 2007;120:868-874.
18. Gietema HA, Schilham AM, van Ginneken B, van Klaveren RJ, Lammers JW, Prokop M. Monitoring of smoking-induced emphysema with CT in a lung cancer screening setting: detection of real increase in extent of emphysema. *Radiology* 2007;244:890-897.
19. Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet* 1986;1:307-310.
20. Bland JM, Altman DG. Measuring agreement in method comparison studies. *Stat Methods Med Res* 1999;8:135-160.
21. Cohen J. A coefficient of agreement for nominal scales. *Educ Psychol Meas* 1960;20:37-46.
22. Hong C, Bae KT, Pilgram TK. Coronary artery calcium: accuracy and reproducibility of measurements with multi-detector row CT—assessment of effects of different thresholds and quantification methods. *Radiology* 2003;227:795-801.
23. Revel MP, Bissery A, Bienvenu M, Aycard L, Lefort C, Frija G. Are two-dimensional CT measurements of small noncalcified pulmonary nodules reliable? *Radiology* 2004;231:453-458.
24. Marten K, Engelke C. Computer-aided detection and automated CT volumetry of pulmonary nodules. *Eur Radiol* 2007;17:888-901.
25. Sumikawa H, Johkoh T, Nagareda T, et al. Pulmonary adenocarcinomas with ground-glass attenuation on thin-section CT: quantification by three-dimensional image analyzing method. *Eur J Radiol* 2008;65:104-111.