Letter to the Editor

Pulmonary nodules measurements in CT lung cancer screening

Marjolein A. Heuvelmans[1,2], Matthijs Oudkerk[1]

[1]Center for Medical Imaging-North East Netherlands, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands; [2]Department of Pulmonary Medicine, Medisch Spectrum Twente, Enschede, The Netherlands

Correspondence to: Marjolein A. Heuvelmans, MD, PhD. Center for Medical Imaging-North East Netherlands, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands; Department of Pulmonary Medicine, Medisch Spectrum Twente, Enschede, The Netherlands. Email: m.a.heuvelmans@umcg.nl.

Provenance: This is an invited article commissioned by the Section Editor Jun Zhou (Department of Nuclear Medicine, Zhongshan Hospital, Fudan University, Shanghai, China).

Response to: Kim H, Park CM. Current perspectives for the size measurement of screening-detected lung nodules. J Thorac Dis 2018;10:1242-4.
de Margerie-Mellon C, Heidinger BH, Bankier AA. 2D or 3D measurements of pulmonary nodules: preliminary answers and more open questions. J Thorac Dis 2018;10:547-9.

Submitted May 15, 2018. Accepted for publication May 22, 2018.
doi: 10.21037/jtd.2018.05.166
View this article at: http://dx.doi.org/10.21037/jtd.2018.05.166

To decrease the number of false-positive screen results without losing sensitivity for lung cancer diagnosis, accurate lung nodule management is crucial in low-dose CT lung cancer screening. Since nodule management is mainly based on nodule size and growth rate (1,2), precise and reproducible size measurements are the key elements to accomplish optimal results. In our recent paper, we recommend the use of semi-automated volume measurements instead of manual diameter measurements for nodule size estimation, based on observations in intermediate-sized nodules in the Dutch-Belgian randomized controlled lung cancer screening trial (Dutch acronym: NELSON) (3).

We recognize the issues on implementation of semi-automated nodule volume measurements addressed by both de Margerie-Mellon *et al.* and Kim *et al.* (4,5). The problem of variation between different software packages (6), and different CT scanner parameters or CT scanner vendors could be overcome by always using the same software package and CT scanner parameters in a screening setting for comparison of two subsequent CT scans. Subsolid nodules are a relatively common finding on chest CTs in an Asian population, and although pure ground glass nodules usually are relatively slow growing and rarely lethal, probability of invasive disease increases after development of a solid component (7). Future developments in semi-automated pulmonary nodule software should focus on improvement of segmentation of the solid component in such a nodule.

In response to the letter by de Margerie-Mellon and colleagues (4), we note their comments regarding the definition on "intranodular diameter variation". In our study, we calculated this variation by subtracting the minimum and maximum nodule diameter in any plane (3). Clearly, this is not directly comparable with manually measured mean axial diameter, as recommended in different diameter-based nodule management guidelines. However, it does give insight in the extent of non-sphericity in pulmonary nodules. This non-sphericity might be the explanation of substantial inter- and intra-reader variability in lung nodule measurements, when measuring a nodule only in the axial plane, because a non-spherical nodule has an infinite number of diameters, but only one volume (8,9). There are proposals for three-dimensional manual diameter measurements, with an additional third diameter measurement in the Z-plane on top of the axial diameter measurements, but this is more cumbersome than a volume approach.

In a recent publication, inter- and intra-reader variability in manual and semi-automated pulmonary nodule measurements were directly compared (9). Inter-reader variability in mean manual diameter measurements

exceeded the 1.5-mm cut-off for nodule growth as used in Lung-RADS (1) for all morphological categories [smooth: ±1.9 mm (+27%), lobulated: ±2.0 mm (+33%), spiculated: ±3.5 mm (+133%), irregular: ±4.5 mm (+200%)] (9). This effect was found to be much smaller for semi-automated volume measurements of the same group of nodules, also suggesting that semi-automated volume measurements should be preferred over manual diameter measurements for nodule size and growth determination in CT lung cancer screening.

Another issue addressed by de Margerie-Mellon and colleagues is the calculation of lung nodule volume based on semi-automatically determined nodule diameters. These measurements might not be independent, however, they do illustrate the non-sphericity of lung nodules. Previously, it was shown that software for semi-automated nodule volume measurements slightly overestimates "real" nodule volume for very small irregular-shaped nodules with volume of less than 88 mm^3 by 39%±21%. However, volume underestimation for smooth nodules was significantly smaller, up to 10% (10), so much smaller than the 47.2–85.1% overestimation of diameter-based nodule volume in our study (3). It is doubtful whether using nodule diameter as "worst case scenario" for nodule size estimations should be encouraged given the very high rate of false-positive screen results, even in patients at a particularly high risk for lung cancer.

We recognize many of the drawbacks of semi-automated volume measurements, such as the need to, in some cases, manually adapt the segmented volume increasing the risk of variability. However, these drawbacks also apply to manual diameter measurements. Nodule attachment to adjacent structures will potentially also increases variability in manual diameter measurements between different radiologists, just like different CT parameters or different kernels used.

In this study, we focused on comparison of size-estimation performance of manual and semi-automated measurements, not on the influence on patient outcome. However, Han *et al.* recently showed that manual diameter measurements potentially lead to an increase in false-positives in terms of growth determination (9). Since lung cancers usually grow according to exponential growth patterns, volume-doubling time instead of a fixed increase in (mean) nodule diameter should be the preferred method to describe nodule growth (11). In a retrospective analysis on management optimization for baseline nodules detected in the NELSON study, Horeweg *et al.* showed that an optimized protocol based on semi-automated nodule volume led to highest specificity and positive predictive value with comparable negative predictive value as the optimized diameter-based protocols (12). Sensitivity was comparable for the optimized diameter-based protocol, although this protocol was based on the most optimal, simulated, nodule diameter semi-automatically assessed by three-dimensional software, and it is therefore expected that a protocol based on manual diameter measurements would have performed worse (12).

In summary, our study reflects the non-sphericity of pulmonary nodules, and we argue that two-dimensional manual diameter measurements are therefore error-prone. Although improvements in nodule volume software especially in case of subsolid nodules are desirable, we feel that manual diameter measurements only have limited value in the management of intermediate-sized pulmonary nodules when compared to semi-automated volume measurements. Therefore, future management of solid nodules detected with CT screening should preferably be based on semi-automated nodule volume and volume-doubling time. Nodule diameter measurements should only be used where volumetry is not technically possible (2).

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

References

1. ACR. Lung CT Screening Reporting and Data System (Lung-RADS). Available online: http://www.acr.org/Quality-Safety/Resources/LungRADS
2. Oudkerk M, Devaraj A, Vliegenthart R, et al. European position statement on lung cancer screening. Lancet Oncol 2017;18:e754-66.
3. Heuvelmans MA, Walter JE, Vliegenthart R, et al. Disagreement of diameter and volume measurements for pulmonary nodule size estimation in CT lung cancer screening. Thorax 2017. [Epub ahead of print].
4. de Margerie-Mellon C, Heidinger BH, Bankier AA. 2D or 3D measurements of pulmonary nodules: preliminary answers and more open questions. J Thorac Dis 2018;10:547-9.

5. Kim H, Park CM. Current perspectives for the size measurement of screening-detected lung nodules. J Thorac Dis 2018;10:1242-4.
6. Zhao YR, van Ooijen PM, Dorrius MD, et al. Comparison of three software systems for semi-automatic volumetry of pulmonary nodules on baseline and follow-up CT examinations. Acta Radiol 2014;55:691-8.
7. Heuvelmans MA, Oudkerk M. Management of subsolid pulmonary nodules in CT lung cancer screening. J Thorac Dis 2015;7:1103-6.
8. Revel MP, Bissery A, Bienvenu M, et al. Are two-dimensional CT measurements of small noncalcified pulmonary nodules reliable? Radiology 2004;231:453-8.
9. Han D, Heuvelmans MA, Vliegenthart R, et al. Influence of lung nodule margin on volume- and diameter-based reader variability in CT lung cancer screening. Br J Radiol 2017:20170405.
10. Xie X, Willemink MJ, de Jong PA, et al. Small irregular pulmonary nodules in low-dose CT: observer detection sensitivity and volumetry accuracy. AJR Am J Roentgenol 2014;202:W202-9.
11. Heuvelmans MA, Vliegenthart R, de Koning HJ, et al. Quantification of growth patterns of screen-detected lung cancers: The NELSON study. Lung Cancer 2017;108:48-54.
12. Horeweg N, van Rosmalen J, Heuvelmans MA, et al. Lung cancer probability in patients with CT-detected pulmonary nodules: a prespecified analysis of data from the NELSON trial of low-dose CT screening. Lancet Oncol 2014;15:1332-41.

Cite this article as: Heuvelmans MA, Oudkerk M. Pulmonary nodules measurements in CT lung cancer screening. J Thorac Dis 2018;10(Suppl 17):S2100-S2102. doi: 10.21037/jtd.2018.05.166