Editorial

Current perspectives for the size measurement of screening-detected lung nodules

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Lung cancer is the leading cause of cancer-related mortality worldwide. National Lung Screening Trial (NLST) demonstrated reduced lung cancer mortality of 20% for whom underwent annual low-dose CT screening (1). For the screening-detected nodules, size measurement is mandatory as the nodule size is directly proportional to the lung cancer risk (2). For the size estimation, uni-dimensional or bi-dimensional diameter measurement have been the standard in practice. Diameter measurement is easy, practical, and has been adopted as the standard method in the clinical practice guidelines for the management of lung nodules (3-6).

The Dutch-Belgian lung cancer screening trial (NELSON) was the first screening program that the management was guided by the volumetric lung nodule measurement instead of the manual diameter measurement. In NELSON, a commercial software (LungCARE) was used for the semi-automated volumetry for the solid nodules and this approach led to high negative predictive values (99.7% in first round, 99.9% in second round) and presumably fewer false-positive results than in other lung cancer screening trials (7,8). Importantly, volume-based management protocol yielded sensitivity and specificity of 90.9% and 94.9% for the 2-year lung cancer probability (2). Given the high specificity of the volume-based protocol, the authors suggested that the lung cancer screening should be done using volumetric software (2).

Heuvelmans *et al.* (9) recently reported on the disagreement of diameter and volume measurements for the size estimation using 2,240 solid nodules (volume, 50–500 mm^3) from NELSON. Diameter–based volume calculation, either the maximum or mean axial diameter, led to the overestimation of nodule volume (47.2–85.1%) compared to the volumetry software-derived volume. Mean overestimation of volume based on the diameter measurements was higher for the nodules with volume range 200–500 mm^3 and with non-smooth margin. In addition, they demonstrated that the diameter measurement was less sensitive for the size-based risk stratification and that it could not reflect the true dimension of the nodules given the substantial diameter variation within a nodule (median, 2.8 mm; interquartile range, 2.2–3.7 mm). Intranodular diameter variation exceeded the suggested cutoff in screening guidelines such as Lung-RADS (1.5 mm). This indicated that the nodule's interval growth could not be reliably detected based on the diameter measurement. Actually, these results advocated the use of semi-automated volumetry in the lung CT screening trial. The strength of this study was that the nodules were extracted from a large, multicenter, randomized screening trial, which is potentially identical to the target population, and that the nodules of intermediate size were included in the analysis. Another interesting point was that this study proved the intrinsic limitation of uni- or bi-dimensional

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measurement excluding the human variation caused by the manual measurement.

The two axes of measurement are accuracy and reproducibility. Studies to date have reported the strength of semi-automated nodule volumetry in both aspects of the measurements. For the measurement accuracy, Xie *et al.* (10) reported that the volume measurement was more accurate with the semi-automated volumetry than the manual measurement in a phantom study, although both methods underestimated the actual nodule volume (underestimation, 26.4% for manual measurement *vs.* 7.6% for semi-automated method). Other experimental studies with simulated lung nodules (solid or subsolid) also showed promising measurement accuracy for the semi-automated volumetry (11-13). With respect to the measurement reproducibility, which may gain greater significance in the clinical scenarios, the variability range of nodule volume was reported to be generally ±25% (14,15). There has been massive investigation into the inherent variability of nodule volume measurement on CT scans in terms of the patient factors, reader factors and CT scanning factors (16,17). The measurement variability range refers to the cutoff for the determination of true change and thus small measurement variation may enable early detection of the lung cancer at the follow-up CT scans. The measurement accuracy and reproducibility can be translated into the diagnostic accuracy and reproducibility (18,19). Accurate and reliable risk stratification is a prerequisite of the screening programs as the management decision is based on the risk categories. Thus, the semi-automated volumetry is potentially more favorable than the diameter measurement.

In addition, volumetric nodule segmentation can provide additional information other than the simple dimensional data. Volume doubling time can be calculated based on the follow-up scans, as was used in the NELSON trial (2). Nodule attenuation and mass can be obtained in case of subsolid nodules (20). Furthermore, computer-aided radiomics analysis can be performed based on the three-dimensional segmentation profile. A recent study demonstrated an add value of image feature analysis for the diagnosis of lung cancer in small nodules (4–20 mm) in a sized matched case-control study using NLST population (21).

For the implementation of semi-automated volumetry in the lung cancer screening programs, a few issues have to be addressed. First, nodule segmentation performance is largely dependent on the segmentation algorithm used. There are volumetry software programs capable of subsolid nodule segmentation (12,22), although not all programs perform equally well. Subsolid nodules are identified in approximately 5% of the baseline CT screening (23,24) and have high malignant potential if they persist at the follow-up scans. In addition, solid portion in the part-solid nodule is regarded as pathologic invasive component and is the key for the clinical decision-making (25). Therefore, adequate segmentation of the whole nodule as well as its internal solid portion should be guaranteed. Second, juxta-pleural and juxta-vascular nodules are less likely to be segmented satisfactorily. These nodules may be handled by the manual measurement. Third, a quality-controlled standardized CT scanning protocol is absolutely imperative. Fourth, prospective comparison between the volumetric and diameter measurements is required in the clinical trial-basis as there is little evidence to date. Evaluation for the lung cancer diagnosis as well as its impact on the prognosis should be scrutinized. Lastly, more evidences on the performance of semi-automated volumetry for the small screening-detected nodules should be cumulated. Data on the screening population are mostly from the NELSON trial. Thus, more clinical data should accrue from other trials in order to generalize the use of semi-automated volumetry in the screening programs.

In conclusion, the potential benefit and strength of the semi-automated volumetry in the management of the screening-detected nodules have been emphasized by the data from NELSON trial. Nevertheless, care should be taken for the implementation of the semi-automated volumetry in the screening programs as there are many obstacles to be solved currently.

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Footnote

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

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