

## Disagreement of diameter and volume measurements for pulmonary nodule size estimation in CT lung cancer screening

### ABSTRACT

We studied 2240 indeterminate solid nodules (volume 50–500 mm<sup>3</sup>) to determine the correlation of diameter and semi-automated volume measurements for pulmonary nodule size estimation. Intra-nodular diameter variation, defined as maximum minus minimum diameter through the nodule's center, varied by 2.8 mm (median, IQR: 2.2–3.7 mm), so above the 1.5 mm cutoff for nodule growth used in Lung CT Screening Reporting and Data System (Lung-RADS). Using mean or maximum axial diameter to assess nodule volume led to a substantial mean overestimation of nodule volume of 47.2% and 85.1%, respectively, compared to semi-automated volume. Thus, size of indeterminate nodules is poorly represented by diameter. **Trial registration number** Pre-results, ISRCTN63545820.

### INTRODUCTION

Most lung cancer screening guidelines, including Lung CT Screening Reporting and Data System (Lung-RADS),<sup>1</sup> are based on pulmonary nodule size at first detection. Nodule size is defined as the mean diameter based on the average of length and width on axial CT images, assuming that a nodule can be fairly represented by a sphere. Since pulmonary nodules usually are not perfectly geometrically shaped, errors in nodule sizing may result. This particularly concerns nodules with a non-smooth margin,<sup>2</sup> which more frequently turn out to be malignant than smooth nodules.<sup>3</sup> Moreover, by using this measurement technique, only nodule growth on the axial plane is considered.

An alternative method, which has been applied by several European lung cancer screening trials, is to measure nodule volume semiautomatically using software.<sup>4,5</sup> This enables an accurate estimation of nodule size via contour finding of the lesions after three-dimensional (3D) reconstruction.

For subsequent screenings, nodule management is based on nodule growth. In current US guidelines, growth is either defined as a fixed increase of 1.5 mm in nodule diameter regardless of the screen interval and nodule size,<sup>1</sup> or based on the volume-doubling time (VDT) calculated using diameter-based estimation of nodule size.<sup>6</sup> We hypothesised that, due

to non-sphericity of pulmonary nodules, nodule size cannot be estimated accurately based on nodule diameter measurements. The purpose of this study was to evaluate the agreement of diameter and semi-automated volume measurements for pulmonary nodule size estimation in low-dose CT (LDCT) lung cancer screening.

### METHODS

This study was performed using data of the Dutch-Belgian Randomised Lung Cancer Screening Trial (Dutch acronym: NELSON), a multicentre, randomised controlled lung cancer screening trial (trial registration number ISRCTN63545820). All non-calcified solid intermediate-sized nodules (50–500 mm<sup>3</sup>, ie, indeterminate cancer risk) from the baseline screening found in Dutch participants in which LungCARE (version Somaris/5 VA70C-W; Siemens Medical Solutions, Erlangen, Germany) could assess diameters and volume were included. Details regarding the study participants, imaging acquisition/analysis, nodule measurements and statistical analysis are provided in the online supplement.

### RESULTS

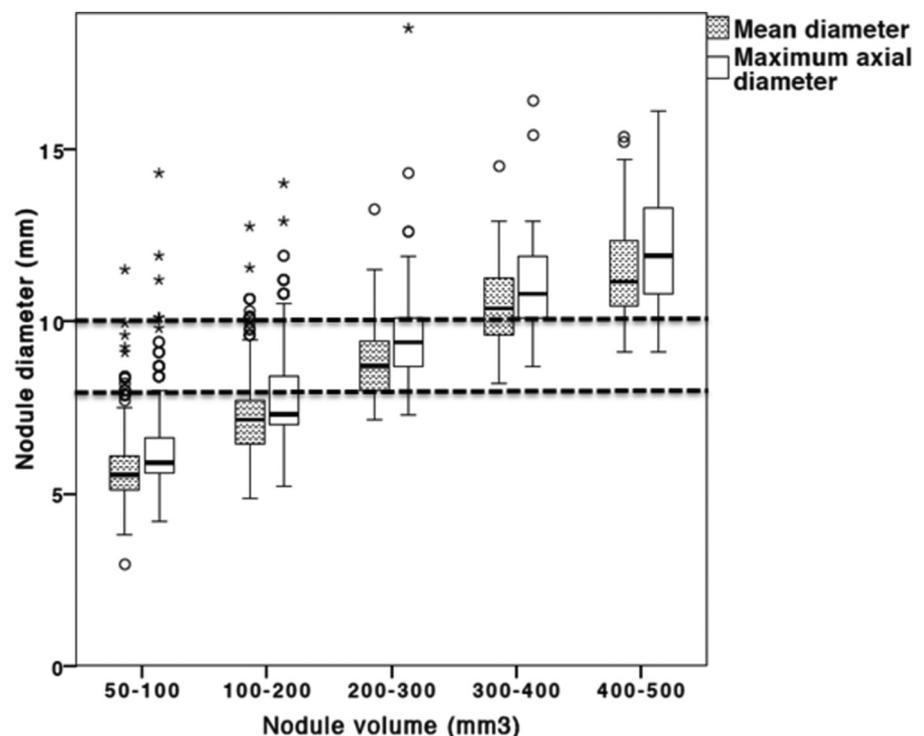
#### Range in nodule diameter

At baseline, 1500 Dutch participants had 2240 non-calcified solid

intermediate-sized nodules. The median volume was 82.4 mm<sup>3</sup> (IQR: 62.9–125.4 mm<sup>3</sup>). The median nodule diameter was 6.1 mm (IQR: 5.4–7.2 mm) based on mean diameter measurements, and 6.6 mm (IQR: 5.9–7.7 mm) based on maximum axial diameter measurements. The range in nodule diameter per nodule volume category is shown in figure 1. Nodules with diameters of 8–10 mm were represented in each volume category.

#### Intranodular diameter variation

The minimum nodule diameter in any direction for the 2240 solid intermediate-sized nodules ranged from 2.1 to 14.5 mm; the maximum nodule diameter in any direction ranged from 4.9 to 20.1 mm. The median intranodular diameter variation was 2.8 mm (IQR: 2.2–3.7 mm). An overview of the intranodular diameter variation per volume category is shown in table 1. Intranodular diameter variation for smaller nodules (50–200 mm<sup>3</sup>) was 2.8 mm (IQR: 2.2–3.5 mm) and was smaller than intranodular diameter variation for larger nodules (200–500 mm<sup>3</sup>; median 3.6 mm (IQR: 2.5–5.1 mm),  $p < 0.01$ ).



**Figure 1** Range in nodule diameter per nodule volume category. Nodules with diameter between 8 and 10 mm (dotted lines) are represented in each volume category. The majority of the intermediate-sized nodules had a volume of 50–100 mm<sup>3</sup> (n=1423; 63.5%). A quarter (550 nodules, 24.6%) were 100–200 mm<sup>3</sup>, 159 nodules (7.1%) were 200–300 mm<sup>3</sup>, 68 nodules (3.0%) were 300–400 mm<sup>3</sup>, and 40 nodules (1.8%) were 400–500 mm<sup>3</sup>.

**Table 1** Overview of intranodular diameter variation\* in baseline nodules per nodule volume category

	Volume 50–100 mm <sup>3</sup>	Volume 100–200 mm <sup>3</sup>	Volume 200–300 mm <sup>3</sup>	Volume 300–400 mm <sup>3</sup>	Volume 400–500 mm <sup>3</sup>
n (%)	1423 (63.5)	550 (24.6)	159 (7.1)	68 (3.0)	40 (1.8)
Median diameter variation (mm)	2.7	3.1	3.3	4.0	4.2
IQR (mm)	2.2–3.3	2.3–4.0	2.4–4.3	2.7–5.6	3.2–6.0
Diameter variation range (mm)	0.6–12.3	0.2–10.6	1.5–12.6	1.3–11.8	2–11.3
Variation ≥2 mm, n (%)†	1174 (82.5)	484 (88.0)	143 (89.9)	62 (91.2)	40 (100)

\*Intranodular diameter variation was defined as maximum nodule diameter (in any direction) minus minimum nodule diameter (in any direction) through the nodule's centre, as determined by LungCARE.

†The intranodular diameter variation of at least 2 mm refers to the difference in nodule diameter of 2 mm between LungRads categories 2, 3 and 4A.<sup>1</sup>

### Agreement between diameter-based volume and semiautomated volume

Bland-Altman plots of the comparison between the semiautomated nodule volume and the volume calculated based on mean and maximum axial diameter are presented in online supplementary figure 1. A per-nodule analysis based on nodule margin is provided in online supplementary table 1.

### DISCUSSION

We evaluated the correlation of diameter and volume measurement in estimating lung nodule size as imaging biomarker for nodule management. Our study demonstrates a wide range in nodule diameter within nodule volume categories. Nodules with diameter thresholds of 8–10 mm, the diameter range with the highest uncertainty of nodule nature, were represented in each volume category. Furthermore, we showed that using mean or maximum axial diameter to assess nodule volume led to a substantial mean overestimation of nodule volume of 47.2% and 85.1%, respectively, compared with semiautomated volume (see online supplement). Thus, nodule size is poorly represented by mean or maximum nodule length in any plane.

Accurate estimation of nodule size is important as lung cancer risk increases at larger nodule size and it determines management at initial nodule detection.<sup>7</sup> The finding that 84.9% of nodules have an intranodular diameter variation of at least 2 mm, which may transfer them between LungRADS categories 2 (regular screening), 3 (6 month LDCT) and 4A (3 month LDCT or positron emission tomography/CT),<sup>1</sup> underlines the limitations of diameter measurement for nodule management. In this study, nodule diameters were measured semiautomatically by software, so inaccuracy of human readers and manual calliper placement was not taken into account. Previous research showed that two-dimensional CT measurements of small-to-intermediate size (<20 mm) are unreliable.<sup>8</sup> In that study,

three serial measurements of maximum transverse diameter of 54 pulmonary nodules were performed by three independent readers. Both intrareader and inter-reader agreement were found to be poor, with a minimum intrareader measurement error of 1.32 mm. In cases where repeated measurements of a single nodule were performed by two different readers, the minimum measurement error increased to 1.73 mm.<sup>8</sup> The large intranodule diameter variation as shown in our study likely contributed to this measurement error, besides the inaccuracy of manual diameter measurements.

While it remains uncertain if diameter measurement error occurs inconsistently on repeat scans, it has significant potential to affect nodule management. In the LungRADS guideline for the management of screen-detected nodules, growth (positive screen result) is defined as absolute increase in nodule diameter of ≥1.5 mm between two subsequent screening examinations.<sup>1</sup> This fixed cut-off lies around the minimum measurement error for a single observer, as shown by Revel *et al.*<sup>8</sup> Furthermore, this cut-off is smaller than the median intranodule diameter variation of 2.8 mm that we found. This may lead to nodules erroneously being classified as growing, with unnecessary work-up as result. On the other hand, true growth may be missed because of inaccurate measurements, leading to delay in work-up and potential worse outcome. In the American College of Chest Physicians guideline, nodule growth is expressed as diameter-based VDT.<sup>6</sup> Although lung nodules have variable minimum and maximum diameters because they are mostly non-spherical, this does not necessarily imply that bidirectional diameter-based growth assessment will provide a VDT different from a volume-based VDT in all cases. Bidirectional diameter assessment is however only accurately performed with 3D volumetric software, since manual nodule diameter assessment is extremely inaccurate. Moreover, by using 3D software for accurate bidirectional diameter

assessment, the volume of the same nodule is automatically provided. Limitations of our study are provided in the online supplement.

In conclusion, the use of mean or maximum axial diameter to assess the size of intermediate-sized lung nodules leads to a substantial overestimation of nodule volume, compared with semiautomated volumetry. Median intranodular diameter variation exceeds the 1.5 mm growth cut-off as advocated in screening guidelines such as LungRADS. Size of indeterminate nodules with a semiautomatically measurable volume is poorly represented by nodule diameter; a nodule has an infinite number of diameters, but only one volume. Thus, semiautomated volume is the preferred method for pulmonary nodule size estimation.

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