

## **ONLINE SUPPLEMENT**

### **METHODS**

This study was performed using data of the NELSON trial, trial registration number: ISRCTN63545820, which was approved by the Dutch Healthcare Committee. Details of the design and procedures of the NELSON trial have been reported. [1,2] Briefly, men and women aged 50-75 years, who had smoked  $\geq 15$  cigarettes per day for 25 years or  $\geq 10$  cigarettes for 30 years, and were still smoking or had quit  $< 10$  years ago, met the inclusion criteria [19]. 15,822 individuals were randomized to no screening (N=7,907) or screening with LDCT scanning (N=7,915) at baseline (1<sup>st</sup> round), one year later (2<sup>nd</sup> round), three years later (3<sup>rd</sup> round) and five and a half years later (4<sup>th</sup> round).[3]

All non-calcified solid intermediate-sized (50-500 mm<sup>3</sup>) nodules 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. In total, we excluded 7 indeterminate solid nodules (7/2247 eligible, 0.3%) since the software was not able to calculate nodule volume in those nodules. All 7 nodules were attached to the pleura. Subsolid nodules (1.9% of all participants) were excluded for this analysis because of the inability of LungCARE® to semi-automatically calculate the volume of these nodules. Only nodules with semi-automated volume of 50-500 mm<sup>3</sup> were included, since this is the group of nodules with the highest uncertainty regarding the nodule's nature.

### **Measurements**

CT scanning was performed using 16-multidetector CT systems (Sensation-16, Siemens Medical Solutions, Forchheim, Germany, or MX8000 IDT or Brilliance 16P, Philips Medical Systems, Cleveland, OH).[2] All scans were realised in approximately 12s in spiral mode with 16mm $\times$ 0.75mm collimation and 15mm table feed per rotation (pitch 1.5), in a cranio-caudal

direction in low-dose setting, without contrast. Depending on body weight (<50, 50-80 and >80 kg) kVp setting was 80-90, 120 and 140, respectively. To achieve a volume CT dose index of 0.8, 1.6 and 3.2 mGy, respectively, the mAs settings were adjusted accordingly dependent on the system used. To minimise breathing artifacts, the acquisition was performed at inspiration with breath-holding, after appropriate instruction of the participant.

Images were read independently by two radiologists using Siemens workstations with the Syngo LungCARE® software package (Version Somaris/5 VB10A-W, Siemens Medical Solutions). Lung nodules were selected by a mouse click. The software not only determined the maximum and perpendicular axial diameter through the nodule's center as well as the mean axial diameter ( $[\text{maximum} + \text{perpendicular diameter}]/2$ ), but also registered the minimum and maximum diameter through the nodule's center in any direction. For each solid nodule, the maximum semi-automated diameter in x, y and z direction, minimum and maximum diameter in any 3D direction, all through the nodule's center, and volume generated by the Siemens software were recorded in the trial's database.[2]

### **Nodule features**

A nodule was considered solid when it completely obscured the underlying structures.[4]

Based on the three-dimensional nodule segmentation gathered from LungCARE®, nodule margin was classified as smooth, lobulated, spiculated, or irregular. In this classification a smooth nodule had a smooth surface, a lobulated nodule had at least one abrupt bulging of the contour, a spiculated nodule had thicker strands extending from the nodule margin into the lung parenchyma without reaching the pleural surface, and an irregular one did not fit in one of these categories.[5]

### **Statistical methods**

We determined the range in maximum and mean axial diameter per category of nodule volume (50-100 mm<sup>3</sup>, 100-200 mm<sup>3</sup>, 200-300 mm<sup>3</sup>, 300-400 mm<sup>3</sup>, 400-500 mm<sup>3</sup>), both for nodules detected at the baseline screen as well as for nodules newly detected after baseline. Intra-nodular diameter variation was defined as maximum nodule diameter (in any direction) minus minimum nodule diameter (in any direction) through the nodule's center, as determined by LungCARE. The magnitude of intra-nodular diameter variation might be suggestive for the degree of variation in manual measurements. We had special interest for nodules with diameter between 8 and 10 mm. The threshold of 8 mm was chosen based on the finding of Henschke et al, who showed that the lower threshold for a suspicious nodule based on manual diameter measurement may safely be risen to 7 or 8 mm.[6] We have chosen the upper cutoff of 10 mm, since nodules below 10 mm have the highest uncertainty of nodule nature.

Diameter-based nodule volume was calculated using the maximal and mean transversal

diameter by assuming a spherical nodule shape (formula:  $V = \frac{1}{6} \pi D^3$ , with V=volume and D=maximal or mean transversal diameter). To explore whether nodule diameter can be used to estimate nodule size, the mean- and maximal axial diameter-based volume was compared semi-automated nodule volume by Bland-Altman plots, with the semi-automated nodule volume measurements as reference standard. This was done both for the overall group of nodules, as well as for groups divided per nodule edge and shape. For non-normal data, median and interquartile range (IQR) were calculated. For parametric data, mean and 95% confidence interval (95% CI) were determined. Statistical tests were performed using SPSS 22.0 (SPSS, Chicago, Ill, USA).

## **RESULTS**

At baseline screening, 1,500 Dutch participants (212 [14.1%] female) had 2,240 non-calcified solid intermediate-sized nodules. Median participants age was 59.0 years (IQR: 55.0-63.0

years). Subjects had smoked a median of 38.0 pack-years (IQR:29.7-49.5 years), with 57.1% (N=857) being current smokers.

### **Agreement between diameter-based volume and semi-automated volume**

Bland-Altman plots of the agreement between the semi-automated nodule volume and the volume calculated based on the mean and maximum axial diameter are presented in Supplementary Figure 1a and 1b. Nodule volume calculated based on maximum axial diameter was overestimated by 85.1% (mean, 95% CI: 81.2-89.0%), and nodule volume calculated based on mean diameter by 47.2% (44.7-49.7%). Mean overestimation was 82.3% (78.3-86.3%), and 44.5% (41.9-47.1%) for volume based on maximal axial and mean diameter of smaller intermediate-sized nodules (50-200mm<sup>3</sup>). Mean overestimation of volume based on maximal and mean axial diameter of larger intermediate-sized nodules (200-500mm<sup>3</sup>) was 105.8% (92.0-119.6%), and 67.6% (59.6-75.6%), respectively.

### **Influence of nodule margin and shape**

Based on margin, nodules were divided into four groups. In total, 1,460 nodules (65.2%) had a smooth margin, 496 (22.1%) were lobulated, 89 (4.0%) were spiculated, and 64 (2.9%) nodules were irregular. Of 131 nodules (5.8%), the margin was undefined. For the four groups of nodule margin, volume based on maximum axial diameter and based on mean diameter, was compared to the semi-automated volume per margin by Bland-Altman plots (results in Supplementary table 1). The mean percentage of overestimation for volumes of non-smooth nodules based on mean axial diameter was 69.2% (95% CI: 63.7-74.7%), and based on maximum axial diameter was 109.9% (101.9-116.5%). The overestimation was statistically significantly larger for non-smooth nodules when compared to smooth nodules ( $P<0.001$ ).

### **Supplementary table 1 Results of Bland-Altman plots per nodule margin**

<b>Nodule margin</b>	<b>N nodules (%)</b>	<b>Maximum axial diameter volume overestimate (%) (95% CI*)</b>	<b>Mean diameter volume overestimate (%) (95% CI)</b>
<b>Smooth</b>	1,460 (65.2%)	72.8% (68.3-77.2%)	37.1% (34.4-39.8%)
<b>Lobulated</b>	496 (22.1%)	97.9% (90.5-105.3%)	58.5% (53.5-63.5%)
<b>Spiculated</b>	64 (2.9%)	134.5% (110.2-158.9%)	101.6% (80.4-122.8%)
<b>Irregular</b>	89 (4.0%)	161.7% (131.7-191.8%)	107.4% (84.2-130.6%)

\*95% CI is 95% confidence interval

## **LIMITATIONS OF THIS STUDY**

In this study, we used the Syngo LungCARE® software package for all semi-automated volume and diameter measurements. The data were generated in participants of a large-scale randomized-controlled trial and the actual nodule size could not be confirmed ex vivo. This could be considered as limitation, since the results may not be generalizable to other volumetric software packages. However, a phantom study using the same software package in which the actual nodule volumes were compared to semi-automated volume measurements revealed very accurate semi-automated measurements of physical nodule volumes.[7]

Furthermore, we have evaluated the implications of volume versus diameter use in CT lung cancer screening based on semi-automatically derived diameter measurements. The software determined the optimal maximum X and Y diameters in the axial slices. However, in most studies using diameter evaluation, measurements were only performed manually, with limited accuracy and reproducibility,[8,9] so the results for manual measured diameters may have been even worse. Theoretically, nodule volumes may even be underestimated when based on manual measured diameters in some patients, given the large inter- and intra-reader variability in manual nodule diameter measurements. So far, volumetry has had limited availability because it required dedicated software. However, volumetry is increasingly available on

regular workstations with routine image evaluation software, which will facilitate its implementation in clinical routine.

## REFERENCES ONLINE SUPPLEMENT

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## FIGURE LEGENDS

**Supplementary figure 1:** Bland-Altman plots. SA = semi-automated  
A Maximum axial diameter-based volume

The Bland-Altman plot indicates that nodule volume estimated based on maximum axial nodule diameter overestimates the semi-automated nodule volume by 85.1% (95% CI: 81.2-89.0%) for nodules between 50 and 500 mm<sup>3</sup>.

B Mean axial diameter-based volume

The Bland-Altman plot indicates that nodule volume estimated based on mean axial nodule diameter overestimates the semi-automated nodule volume by 47.2% (95% CI: 44.7-49.7%) for nodules between 50 and 500 mm<sup>3</sup>.