ORIGINAL ARTICLE

Persisting new nodules in incidence rounds of the NELSON CT lung cancer screening study

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► Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/thoraxjnl-2018-212152).

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Received 3 June 2018
Revised 23 October 2018
Accepted 29 October 2018

To cite: Walter JE, Heuvelmans MA, ten Haaf K, *et al*. *Thorax* Epub ahead of print: [*please include* Day Month Year]. doi:10.1136/thoraxjnl-2018-212152

ABSTRACT

Background The US guidelines recommend low-dose CT (LDCT) lung cancer screening for high-risk individuals. New solid nodules after baseline screening are common and have a high lung cancer probability. Currently, no evidence exists concerning the risk stratification of non-resolving new solid nodules at first LDCT screening after initial detection.

Methods In the Dutch-Belgian Randomized Lung Cancer Screening (NELSON) trial, 7295 participants underwent the second and 6922 participants the third screening round. We included participants with solid nodules that were registered as new or <15 mm³ (study detection limit) at previous screens and received additional screening after initial detection, thereby excluding high-risk nodules according to the NELSON management protocol (nodules ≥500 mm³).

Results Overall, 680 participants with 1020 low-risk and intermediate-risk new solid nodules were included. A total of 562 (55%) new solid nodules were resolving, leaving 356 (52%) participants with a non-resolving new solid nodule, of whom 25 (7%) were diagnosed with lung cancer. At first screening after initial detection, volume doubling time (VDT), volume, and VDT combined with a predefined ≥200 mm³ volume cut-off had high discrimination for lung cancer (VDT, area under the curve (AUC): 0.913; volume, AUC: 0.875; VDT and ≥200 mm³ combination, AUC: 0.939). Classifying a new solid nodule with either ≤590 days VDT or ≥200 mm³ volume positive provided 100% sensitivity, 84% specificity and 27% positive predictive value for lung cancer.

Conclusions More than half of new low-risk and intermediate-risk solid nodules in LDCT lung cancer screening resolve. At follow-up, growth assessment potentially combined with a volume limit can be used for risk stratification.

Trial registration number ISRCTN63545820; pre-results.

Key messages

What is the key question?

- What is the appropriate risk stratification of low-risk and intermediate-risk new solid nodules at first screening after initial detection?

What is the bottom line?

- While more than half of new solid nodules are resolving, growth assessment with volume doubling time provides a high accuracy for lung cancer at first screening after initial detection.
- Addition of a volume limit that compels immediate referral as well might further increase sensitivity.

Why read on?

- Most new nodules detected in a lung cancer screening programme are of low or intermediate risk and will receive additional screening.
- Considering that a lung cancer screening programme consists of only one baseline round but multiple incidence screening rounds, the appropriate risk stratification of new nodules is crucial.

INTRODUCTION

Lung cancer remains a leading cause of cancer-related death worldwide, and numerous trials are exploring lung cancer screening by low-dose CT (LDCT) to improve prognosis.[1 2] The National Lung Screening Trial showed a 20% reduced lung cancer mortality when comparing LDCT with chest radiography.[3] Accordingly, most US guidelines currently recommend LDCT lung cancer screening for high-risk individuals,[4–6] while European stakeholders are awaiting the final results of the Dutch-Belgian Randomized Lung Cancer Screening (NELSON) trial.[5 7]

Previously, research focused on nodules detected at baseline screening, but with increasing duration of a trial its success depends on the management of new nodules.[7–9] While baseline nodules might have been present for years before detection, new nodules found after baseline by definition have developed within a short timeframe. However, there is only limited evidence for the management of new nodules, and published data use different definitions of incident nodules.[4 8 10–12] Available data from the Early Lung Cancer Action Project (ELCAP),[13] the International-ELCAP,[14] the Pittsburgh Lung Screening Study,[15] the Mayo trial,[16] the National Lung Screening Trial[17] and the NELSON trial[8] suggest that annually between 3% and 13% of participants develop a new nodule after baseline screening. Recently, the NELSON trial provided a first indepth analysis of new solid nodules and proposed lower cut-off values for new nodules

as compared with baseline nodules,[8] which were adopted in a European position statement on lung cancer screening.[7] Nodule risk stratification is based on a nodule's lung cancer probability, with only high-risk nodules (commonly >15% lung cancer probability) warranting immediate referral of a participant to a specialist, whereas low-risk (commonly <1% lung cancer probability) and intermediate-risk nodules receive additional screening LDCT scans.[7 8 11 18 19] While size-based management strategies for initial new nodule detection have been proposed, with nodules ≥200 mm^3 being high risk,[7 8 20] there is insufficient evidence concerning the management of low-risk and intermediate-risk new nodules at subsequent screening. Furthermore, pulmonary nodules are known to be dynamic,[21 22] but few studies have assessed resolving nodules in general and mostly focused on subsolid nodules.[22–25]

The aim of this study was to investigate the final outcome of new solid nodule nature at first follow-up or regular screening after initial new solid nodule detection in incidence screening rounds of LDCT lung cancer screening.

METHODS

Participants

The recruitment process and study design of the NELSON trial have been published before.[26–28] In summary, eligible patients were adults aged 50–75 years who had smoked >15 cigarettes per day for >25 years or >10 cigarettes per day for >30 years and were still smoking or stopped smoking <10 years previously. All participants provided written informed consent.

Between December 2003 and July 2006, 15 792 participants from four centres in the Netherlands and Belgium were randomised to low-dose chest CT screening (n=7900) or no screening (n=7892), and between April 2004 and December 2006, 7557 participants underwent baseline screening. Within the NELSON trial's protocol, participants were followed up for 10 years after randomisation.[27] For this analysis, participants with a solid non-calcified nodule initially detected in the second (annual screening) or third (biannual screening) screening round and registered by the NELSON radiologists as new or <15 mm^3 (study detection limit) at previous screens were included if they had one additional screening LDCT within the NELSON trial. New nodules initially detected in the fourth round (2.5-year screening interval), which only included a subgroup of patients with a higher proportion of current smokers and more participants with at least one non-negative screening,[29] were not included to avoid confounding through this selection. Participants referred immediately for diagnostic work-up after initial new nodule detection and participants without any further screening LDCT were excluded from this analysis.

Procedures and nodule management

The CT scan procedures were published before and are described in the online supplementary appendix.[26 28] New solid nodules were classified into four nodule categories (NODCAT I–IV): calcified nodules or nodules with other benign characteristics (NODCAT I, regular screening), new solid nodules 15–50 mm^3 (NODCAT II, follow-up LDCT within 1 year), new solid nodules 50–500 mm^3 (NODCAT III, follow-up LDCT within 6–8 weeks), and new solid nodules ≥500 mm^3 (NODCAT IV, immediate referral to pulmonologist).[26] After initial detection, a nodule's subsequent evaluation was based on volume doubling time (VDT; online supplementary appendix). A smaller VDT signifies faster nodule growth.

For this study, the original nodule data as reported by the NELSON radiologists were used. A nodule detected after baseline was considered new if registered by the radiologists as new or below the study detection limit of 15 mm^3 on the previous scan. A new nodule was considered resolving if the NELSON radiologists did not register it on the subsequent LDCT after detection due to disappearance or if only a non-measurable scar or calcified nodule persisted.

Malignancy and benignity were determined on the basis of histology and diagnostic work-up according to national and international guidelines and, in case of benignity, also on a negative final screening result in the NELSON trial and no interval or post-screening lung cancer according to the national cancer registries of the Netherlands and Belgium and medical file review.[9 19 26]

Statistical analysis

Non-normally distributed continuous variables were analysed using the Mann-Whitney U test and described as medians and IQRs. Fisher's exact test was used to analyse nominal variables. The 95% CIs were calculated with the Agresti-Coull method.

The VDT was calculated for all non-resolving new solid nodules based on the volume at initial detection and first screening after initial detection. For nodules that decreased in size, the consequently negative VDT was converted to positive by subtracting it from the maximum (thus slowest) observed positive VDT to enable receiver operating characteristic (ROC) analysis with all nodules. The European position statement on lung cancer adopted a ≥200 mm^3 cut-off for high-risk new solid nodules from the NELSON trial's results.[7 8] This cut-off was combined with VDT using a binary logistic regression model. The ROC analysis was performed for VDT and volume at follow-up, as well as for the model probabilities of the combination of VDT and ≥200 mm^3, with eventual lung cancer diagnosis as outcome. ROC curve comparison was performed using the method described by DeLong *et al*.[30]

Optimised cut-offs for VDT and volume were derived using Youden Index as reference points for further adaption.[31] The identified VDT cut-off was also assessed with the predefined ≥200 mm^3 volume cut-off, classifying a nodule positive when at least one criterion was fulfilled. Additionally, predefined VDT cut-offs of <400 days, 400–600 days and VDT >600 days were assessed. Missing data were excluded from the respective analyses and are referenced below the respective tables and figures.

Corresponding calculations for simulated mean diameter (mean of the longest and perpendicular simulated diameter) as well as cut-off analyses at the participant level based on the largest or fastest growing nodule are presented in the online supplementary appendix.

All statistical tests were two-sided. Statistical analyses were performed with SPSS V.25.0 and R V.3.3.3.

RESULTS

Overall, 680 participants with 1020 new solid nodules and a follow-up or regular screening LDCT were included (online supplementary figure S1). The median age of included participants was 59 years (IQR 55–63) at baseline, 76% (514/680) were male, and the median smoking pack-years at baseline was 39 (IQR 30–49) (online supplementary table S1). Of the 1020 included nodules, 25 (2.5%) were lung cancer and 232 (23%) could be identified in retrospect as a minuscule opacity smaller than the detection limit (15 mm^3).

Resolving and non-resolving new solid nodules

A total of 562 (55%) of the 1020 new solid nodules were resolving. In 321 (47%) participants, all detected new solid

nodules resolved, leaving 458 (45%) non-resolving new nodules and 359 (53%) participants with at least one non-resolving new nodule. New solid nodules visible in retrospect as a minuscule opacity below the trial's detection limit were less likely to resolve compared with those not visible in retrospect (22% (50/232) vs 65% (512/788), p<0.0001), and tended to be smaller at initial detection with a median of 18 mm^3 (IQR 16–21 mm^3) vs 52 mm^3 (IQR 29–121 mm^3; p<0.0001). In total, 97% (224/232) of the nodules visible in retrospect as a minuscule opacity were <50 mm^3 at initial detection, and the lung cancer probability (1.3% (3/224), CI 0.3% to 4.0%) was similar compared with new solid nodules <50 mm^3 and not visible in retrospect (1.5% (6/394), CI 0.6% to 3.4%, p=0.855; online supplementary table S2).

Non-resolving new solid nodules

In 4 (1.1%) of the 359 participants with non-resolving new solid nodules, a benign new solid nodule changed to part-solid (n=3) or pure ground-glass (n=1), and in 3 (0.8%) participants these nodules were the only new nodules detected. Excluding the three participants with only subsolid non-resolving new nodules, the characteristics of the 356 participants with at least one new solid nodule that persisted are presented in online supplementary table S3.

In 25 (7.0%) of the 356 participants, a non-resolving new solid nodule was lung cancer, corresponding to 25 (5.5%) of the 454 non-resolving new solid nodules. At time of diagnosis, 23 (92%) of the lung cancers were stage I, with adenocarcinoma (16/25, 64%) being the most common histology (online supplementary table S4). At first follow-up or regular screening, LDCT, VDT, volume and simulated mean diameter differed significantly between benign nodules and lung cancers (table 1).

The ROC analysis demonstrated an area under the curve (AUC) of 0.913 (95% CI 0.861 to 0.965) for VDT, 0.875 (95% CI 0.822 to 0.928) for nodule volume and 0.939 (95% CI 0.904 to 0.974) for VDT combined with the predefined ≥200 mm^3 cut-off (figure 1). The AUC of VDT and ≥200 mm^3 was superior to volume (p=0.0322) and statistically comparable with VDT alone (p=0.0535). Lung cancer probabilities of nodules stratified by the identified cut-off values for VDT (≤590 days) and nodule volume (≥65 mm^3), as well as the optimised VDT cut-off of ≤590 days, together with the predefined ≥200 mm^3 volume cut-off, are shown in table 2.

The performance of these cut-off values stratified by time until first LDCT after initial detection is displayed in table 3. Online supplementary table S5 summarises the performance of the predefined VDT cut-offs of <400 days, 400–600 days and VDT >600 days for comparison. In total, 8.3% (1/12) of new solid nodules with a VDT of 400–600 days and 34% (22/64) of nodules with VDT <400 days were lung cancer.

The respective results stratified by the visibility of the new solid nodule in retrospect are presented in online supplementary table S6. Using the ≤590 days VDT cut-off together with the predefined ≥200 mm^3 volume cut-off reached 100% (95% CI 84% to 100%) sensitivity, 84% (95% CI 80% to 87%) specificity, 27% (95% CI 19% to 37%) positive predictive value and 100% (95% CI 99% to 100%) negative predictive value for discriminating lung cancer. Calculations based on simulated mean diameter instead of volume and calculations based on participant level (single largest or fastest growing nodule) can be found in online supplementary tables S7–S9 and figures S2 and S3. The discriminative performance (AUC) of volume compared with simulated mean diameter was superior (p=0.0011) (online supplementary figure S1).

DISCUSSION

This study focused on new solid nodules detected in incidence screening rounds (annual and biannual screening) of the NELSON trial and at least one additional screening LDCT. These nodules are of low and intermediate risk according to the NELSON management protocol, since participants with high-risk nodules were referred immediately to a pulmonologist without additional follow-up.[26]

We report three major findings. First, 55% of the new solid nodules included were resolving (65% of the nodules not visible in retrospect, 22% of those visible in retrospect as a minuscule opacity below detection limit), and in 47% of the included participants all detected new solid nodules were resolving. Second, eventually, 7.0% of the participants with a non-resolving new solid nodule that persisted as solid nodule had lung cancer in such a nodule, with 5.5% of the non-resolving new solid nodules that persisted as solid nodule being diagnosed as lung cancer. Third, at first screening LDCT after initial detection, VDT (AUC: 0.913) and volume (AUC: 0.875) had high discriminatory power. The combination of VDT and the previously established ≥200 mm^3 high-risk cut-off (AUC: 0.939) outperformed volume alone but was not significantly better than VDT alone (p=0.0535). Employing the identified ≤590 days VDT cut-off together with the ≥200 mm^3 high-risk cut-off, thereby classifying nodules positive when at least one criterion was fulfilled, provided 100% sensitivity and 84% specificity for discriminating lung cancer.

A previous study of the NELSON trial examined solid baseline nodules sized 50–500 mm^3 and reported that 90% (867/964) of the nodules persisted, with 3% (27/867) of non-resolving nodules being diagnosed as lung cancer.[24] In this study, 44% of new solid nodules sized 50–500 mm^3 at initial nodule detection persisted, with 10% being lung cancer, underlining the high lung cancer risk of new nodules. In an earlier study, we observed that with longer screening interval, the number of new nodules did not increase proportionally, while the percentage of lung cancers rose.[8] This phenomenon could be explained by the nature of non-resolving new nodules: The longer a screening interval, the higher the proportion of non-resolving new nodules and consequently the higher the percentage of lung cancers. Therefore, the screening interval length prior to detection might carry implications for the significance and potential lung cancer probability of a new nodule. Similarly, new nodules visible as a very small opacity in retrospect were less likely to resolve than new nodules not visible at all. This corroborates the finding that at equivalent size, visibility as very small nodule in retrospect is significantly associated with lung cancer when compared with new nodules not visible at all.[20]

In our previous study concerning risk stratification of new solid nodules at initial detection, it was shown that new solid nodules <30 mm^3 (adapted from 27 mm^3; low risk, <1% lung cancer probability) should continue regular screening, new solid nodules between 30 and <200 mm^3 (intermediate risk, around 3% lung cancer probability) represent an indeterminate subgroup requiring short-term follow-up by LDCT, and new solid nodules ≥200 mm^3 (around 17% lung cancer probability) should be referred for diagnostic evaluation.[7 8] This study investigated the management approach for low-risk and intermediate-risk new solid nodules at first LDCT after initial detection. Risk stratification by VDT and size (volume, simulated diameter)

Table 1 Characteristics of non-resolving new solid nodules that persisted as solid nodule at first follow-up or regular screening after initial detection (n=454; 429 benign nodules and 25 lung cancer nodules)

	All new solid nodules that persisted at first LDCT after detection, n=454 (100%)			Subsequent LDCT within 120 days, n=210 (46.3%) (short-term follow-up)			Subsequent LDCT after 120 days, n=244 (53.7%)		
	Benign	Lung cancer		Benign	Lung cancer		Benign	Lung cancer	
	429/454 (94.5%)	25/454 (5.5%)	P values	193/210 (91.9%)	17/210 (8.1%)	P values	236/244 (96.7%)	8/244 (3.3%)	P values
Days between scans									
Median (IQR)	347 (50–724)	56 (46–325)	0.006	49 (43–62)	49 (42–56)	0.887	719 (370–797)	347 (323–640)	0.011
Volume (mm^3)									
<50	296/429 (69.0%)	1/25 (4.0%)		85/193 (44.0%)	1/17 (5.9%)		216/236 (89.4%)	0/8 (0.0%)	
50 to <500	120/429 (28.0%)	22/25 (88.0%)		95/193 (49.2%)	14/17 (82.4%)		25/236 (10.6%)	8/8 (100%)	
≥500	13/429 (3.0%)	2/25 (8.0%)		13/193 (6.7%)	2/17 (11.8%)		0/236 (0.0%)	0/8 (0.0%)	
Median (IQR)	28 (17–63)	135 (83–331)	<0.0001	63 (33–126)	203 (95–362)	0.0003	20 (15–30)	94 (79–248)	<0.0001
VDT (days)									
Median (IQR)	∞ (1845–∞)	219 (129–298)	<0.0001	∞ (1346–∞)	155 (116–294)	<0.0001	∞ (1969–∞)	254 (227–362)	<0.0001
Simulated mean diameter* (mm)									
Median (IQR)	4.0 (3.2–5.8)	7.2 (5.5–9.1)	<0.0001	5.6 (4.0–7.4)	8.0 (5.4–10.9)	0.014	3.5 (3.0–4.1)	7.0 (5.5–8.5)	<0.0001
Nodule was below detection limit in retrospect	176/42 (41.0%)	4/25 (16.0%)	0.012	17/193 (8.8%)	1/17 (5.9%)	0.999	159/236 (67.4%)	3/8 (37.5%)	0.127

*Diameters were simulated from computer-generated volume measurements, based on three-dimensional voxels.
∞, decreased size; LDCT, low-dose CT; VDT, volume doubling time.

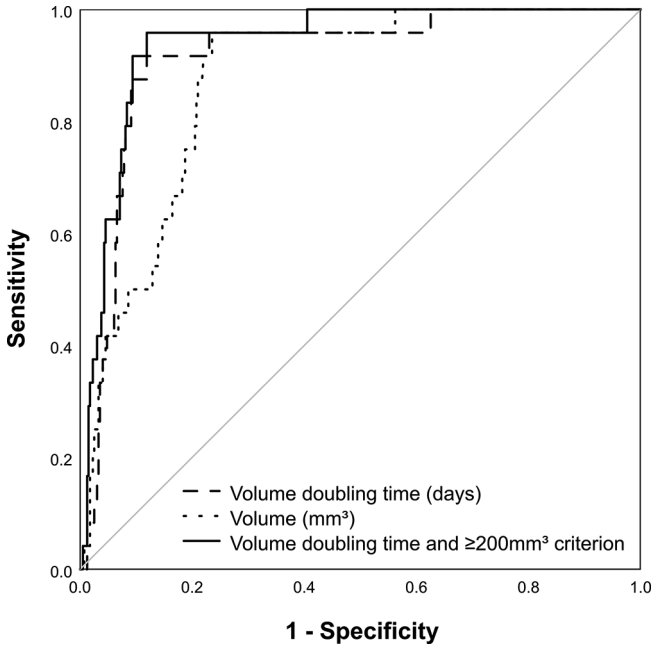

Figure 1 Receiver operating characteristic curves* of volume doubling time, nodule volume, and the combination of volume doubling time and ≥200 mm^3 at first follow-up or regular screening after initial detection for discrimination of lung cancer. Volume doubling time (AUC: 0.913, 95% CI 0.861 to 0.965, p<0.0001); volume (AUC: 0.875, 95% CI 0.822 to 0.928, p<0.0001); volume doubling time and ≥200 mm^3 criterion (AUC: 0.939, 95% CI 0.904 to 0.974, p<0.0001). *Exact volume measurement was not available for 34 benign nodules and 1 lung cancer, and they were not included in the calculations. AUC, area under the curve.

reached comparable sensitivities, but VDT displayed a superior specificity, especially at short-term follow-up. The observed statistically optimal VDT cut-off of ≤590 days is analogous to currently employed cut-offs of ≤600 days, such as in the British Thoracic Society guideline for the investigation and management of pulmonary nodules and the NELSON management protocol,[7 11 26] and its appropriateness is confirmed for the first time in new solid nodules. Based on previous findings of the NELSON trial, the British Thoracic Society guideline considers nodules with a VDT between 400 and 600 days as intermediate-risk group and nodules with a VDT <400 days as high-risk group.[11 19 26] While the overall performance of the VDT risk stratification approach has been confirmed for low-risk and intermediate-risk new solid nodules, with 30% (23/76) of new solid nodules with a VDT≤600 days being lung cancer (8.3% (1/12) of nodules with VDT 400–600 days and 34% (22/64) of nodules with VDT <400 days), further research is required to determine whether immediate referral might be appropriate for all low-risk and intermediate-risk new solid nodules with a VDT ≤600 days. Furthermore, any employed follow-up time interval should enable the detection of the target VDT cut-off. Given that lung cancer growth was shown to not always be exponential or linear,[32 33] addition of a volume limit compelling referral to a pulmonologist might prevent slow-growing lung cancers from evading timely referral. While this approach further increased the sensitivity of the risk stratification approach, it decreased its specificity and could potentially lead to overdiagnosis. Addition of a ≥200 mm^3 volume limit to VDT reclassified 17 persisting new nodules as positive, with 11% (2/17) being lung cancer. Further research is necessary to confirm the utility of such a volume limit.

The results concerning newly detected nodules in lung cancer screening may also apply to incidentally detected nodules found in routine care.[8 34] The results and cut-offs should only be extrapolated in a population with similar epidemiology characteristics to the population investigated here. Importantly, the size of new nodules detected in a specified timeframe reflects its growth rate, and incidentally detected new nodules in clinical practice could benefit from calculation of the maximal VDT (slowest possible VDT).[8]

This study has limitations. Nodules <15 mm^3 were not registered in the NELSON trial. Additionally, with increasing trial length, radiologists potentially gained increased expertise in distinguishing scars or infections from suspicious lesions and might have refrained from classifying them as suspicious nodules to avoid false-positive results. Expertise of radiologists is important to decrease false-positive screen results.[35] The possibility that the actual number of very small new solid nodules is somewhat higher than reported here cannot be excluded.

Table 2 Lung cancer probability of non-resolving new solid nodules stratified by volume doubling time and volume at first follow-up or regular screening after initial detection (n=437; 412 benign nodules and 25 lung cancer nodules)

	All new solid nodules that persisted at first LDCT after detection		Subsequent LDCT within 120 days (short-term follow-up)		Subsequent LDCT after 120 days	
	Lung cancer/all nodules meeting criterion	Lung cancer probability (95% CI)	Lung cancer/all nodules meeting criterion	Lung cancer probability (95% CI)	Lung cancer/all nodules meeting criterion	Lung cancer probability (95% CI)
VDT						
>590 days	2/362	0.6% (0.0 to 2.1)	2/139	1.4% (0.1 to 5.4)	0/223	0.0% (0.0 to 2.0)
≤590 days	23/75	30.7% (21.3 to 41.9)	15/56	26.8% (16.9 to 39.7)	8/19	42.1% (23.1 to 63.8)
Volume						
<65 mm^3	1/314	0.3% (0.0 to 2.0)	1/95	1.1% (0.0 to 6.3)	0/219	0.0% (0.0 to 2.1)
≥65 mm^3	24/123	19.5% (13.4 to 27.5)	16/100	16.0% (10.0 to 24.5)	8/23	34.8% (18.7 to 55.2)
VDT and volume						
>590 days and <200 mm^3	0/345	0.0% (0.0 to 1.3)	0/124	0.0% (0.0 to 3.6)	0/221	0.0% (0.0 to 2.1)
≤590 days or ≥200 mm^3	25/92	27.2% (19.1 to 37.1)	17/71	24.6% (15.9 to 36.0)	8/21	38.1% (20.7 to 59.2)

Exact volume measurement was not available or classification based on the radiologist's size categorisation was unattainable for 17 benign nodules, and they were not included in the calculations.
LDCT, low-dose CT; VDT, volume doubling time.

Table 3 Performance of the identified cut-offs at first follow-up or regular screening after initial detection (n=437; 412 benign nodules and 25 lung cancer nodules)

	All new solid nodules that persisted at first LDCT after detection	Subsequent LDCT within 120 days (short-term follow-up)	Subsequent LDCT after 120 days
VDT ≤590 days			
Sensitivity (95% CI)	23/25, 92.0% (73.9 to 98.9)	15/17, 88.2% (64.4 to 98.0)	8/8, 100% (62.8 to 100)
Specificity (95% CI)	360/412, 87.4% (83.8 to 90.3)	137/178, 77.0% (70.2 to 82.6)	223/234, 95.3% (91.7 to 97.4)
PPV (95% CI)	23/75, 30.7% (21.3 to 41.9)	15/56, 26.8% (17.5 to 41.0)	8/19, 42.1% (23.1 to 63.8)
NPV (95% CI)	360/362, 99.4% (97.9 to 100)	137/139, 98.6% (94.6 to 99.9)	223/223, 100% (98.0 to 100)
Volume ≥65 mm^3			
Sensitivity (95% CI)	24/25, 96.0% (78.9 to 100)	16/17, 94.1% (71.1 to 100)	8/8, 100% (62.8 to 100)
Specificity (95% CI)	313/412, 76.0% (71.6 to 79.9)	94/178, 52.8% (45.5 to 60.0)	219/234, 93.6% (89.6 to 96.2)
PPV (95% CI)	24/123, 19.5% (13.4 to 27.5)	16/100, 16.0% (10.0 to 24.5)	8/23, 34.8% (18.7 to 55.2)
NPV (95% CI)	313/314, 99.7% (98.0 to 100)	94/95, 98.9% (93.7 to 100)	219/219, 100% (97.9 to 100)
VDT ≤590 days or volume ≥200 mm^3			
Sensitivity (95% CI)	25/25, 100.0% (84.2 to 100)	17/17, 100.0% (78.4 to 100)	8/8, 100% (62.8 to 100)
Specificity (95% CI)	345/412, 83.7% (79.9 to 87.0)	124/178, 69.7% (62.5 to 76.0)	221/234, 94.4% (90.6 to 96.8)
PPV (95% CI)	25/92, 27.2% (19.1 to 37.1)	17/71, 24.6% (15.9 to 36.0)	8/21, 38.1% (20.7 to 59.2)
NPV (95% CI)	345/345, 100.0% (98.7 to 100)	124/124, 100.0% (96.4 to 100)	221/221, 100.0% (97.9 to 100)

Exact volume measurement was not available or classification based on the radiologist's size categorisation was unattainable for 17 benign nodules, and they were not included in the calculations.
LDCT, low-dose CT; NPV, negative predictive value; PPV, positive predictive value; VDT, volume doubling time.

The screening intervals were predefined in the trial and do not directly translate to clinical practice, where new nodules might be found after even shorter or longer intervals. This was a secondary analysis of patients with new solid nodules and at least one screening after initial new nodule detection. While 1020 low-risk or intermediate-risk new nodules of 680 participants were assessed, the proportion of lung cancers was, as anticipated, moderate (25 lung cancers) and further multivariate analyses were not performed. An extensive analysis of new solid nodule characteristics has been conducted previously.[20] The analyses performed grouped new solid nodules that were visible as a minuscule opacity in retrospect together with new solid nodules not visible in retrospect. Nevertheless, the cut-off values performed adequately in both nodule groups. Within the NELSON management protocol, new nodules with a VDT ≤400 days were referred for further diagnostic work-up. To minimise bias through the protocol, this analysis incorporated all follow-up data within the NELSON trial including cancer diagnosis in later rounds and post-trial information from the national cancer registries.

This study completes our previously established size-based management approach at initial new solid nodule detection with volume cut-offs of <30 mm^3, 30 mm^3 to <200 mm^3 and ≥200 mm^3 representing low-risk, intermediate-risk and high-risk groups, respectively.[8] After initial detection, in about half of participants, all detected low-risk and intermediate-risk new solid nodules resolve until the next LDCT examination. Eventually, in 7.0% of participants with non-resolving low-risk and intermediate-risk new solid nodules, the final new nodule outcome is lung cancer and an aggressive management strategy is warranted. At first screening after initial detection, a new solid nodule with a VDT ≤600 days has a high lung cancer probability and potentially requires immediate referral to a pulmonologist. Addition of a ≥200 mm^3 volume limit for new solid nodules that compels immediate referral as well might further increase the sensitivity of the risk stratification by VDT.

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Contributors JEW, MAH, RV and MO were involved in the conception, hypotheses delineation and design of the study. JEW, MAH, KtH, RV, CMvdA, UY-K, PMAvO, KN, HJMG, GHdB, HJdK and MO acquired the data or analysed and interpreted the data. JEW, MAH, KtH, RV, CMvdA, UY-K, PMAvO, KN, HJMG, GHdB, HJdK and MO wrote the article or were substantially involved in its revision before submission.

Funding The NELSON trial was sponsored by the Dutch Organisation for Health Research and Development (ZonMw); Dutch Cancer Society Koningin Wilhelmina Fonds (KWF); Stichting Centraal Fonds Reserves van Voormalig Vrijwillige Ziekenfondsverzekeringen (RvvZ); Siemens Germany; Rotterdam Oncologic Thoracic Steering Committee (ROTS); GPh Verhagen Trust; Flemish League Against Cancer; Foundation Against Cancer; and Erasmus Trust Fund.

Competing interests KtH reports grants and non-financial support from NELSON-Netherlands-Leuven Lung Cancer Screening, during the conduct of the study, and grants from the University of Zurich, non-financial support from the International Association for the Study of Lung Cancer Strategic Screening Advisory Committee, and grants from Sunnybrook Health Sciences, outside the submitted work. CMvdA reports grants from Symposium in Thoracic Oncology, grants from the American Thoracic Society, and grants from Lancet Respiratory Medicine, outside the submitted work. KN reports grants from Flemish League against Cancer and grants from the Belgian Foundation against Cancer, during the conduct of the study. HJMG reports grants from Eli Lilly, Roche, MSD, BMS and Novartis, outside the submitted work. HJdK took part in a 1-day advisory meeting on biomarkers organised by MD Anderson/Health Sciences during the 16th World Conference on Lung Cancer, outside the submitted work. All other authors declare no competing interests over the last 36 months.

Patient consent Obtained.

Ethics approval The NELSON trial (trial registration number, ISRCTN63545820)

was approved by the ethics committees of all participating centres in the Netherlands and Belgium.

Provenance and peer review Not commissioned; externally peer reviewed.

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