Occurrence and lung cancer probability of new solid nodules at incidence screening with low-dose CT: analysis of data from the randomised, controlled NELSON trial

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Summary

Background US guidelines now recommend lung cancer screening with low-dose CT for high-risk individuals. Reports of new nodules after baseline screening have been scarce and are inconsistent because of differences in definitions used. We aimed to identify the occurrence of new solid nodules and their probability of being lung cancer at incidence screening rounds in the Dutch-Belgian Randomized Lung Cancer Screening Trial (NELSON).

Methods In the ongoing, multicentre, randomised controlled NELSON trial, between Dec 23, 2003, and July 6, 2006, 15 822 participants who had smoked at least 15 cigarettes a day for more than 25 years or ten cigarettes a day for more than 30 years and were current smokers, or had quit smoking less than 10 years ago, were enrolled and randomly assigned to receive either screening with low-dose CT (n=7915) or no screening (n=7907). From Jan 28, 2004, to Dec 18, 2006, 7557 individuals underwent baseline screening with low-dose CT; 7295 participants underwent second and third screening rounds. We included all participants with solid non-calcified nodules, registered by the NELSON radiologists as new or smaller than 15 mm³ (study detection limit) at previous screens. Nodule volume was generated semiautomatically by software. We calculated the maximum volume doubling time for nodules with an estimated percentage volume change of 25% or more, representing the minimum growth rate for the time since the previous scan. Lung cancer diagnosis was based on histology, and benignity was based on histology or stable size for at least 2 years. The NELSON trial is registered at trialregister.nl, number ISRCTN63545820.

Findings We analysed data for participants with at least one solid non-calcified nodule at the second or third screening round. In the two incidence screening rounds, the NELSON radiologists registered 1222 new solid nodules in 787 (11%) participants. A new solid nodule was lung cancer in 49 (6%) participants with new solid nodules and, in total, 50 lung cancers were found, representing 4% of all new solid nodules. 34 (68%) lung cancers were diagnosed at stage I. Nodule volume had a high discriminatory power (area under the receiver operating curve 0·795 [95% CI 0·728–0·862]; p<0·0001). Nodules smaller than 27 mm³ had a low probability of lung cancer (two [0·5%] of 417 nodules; lung cancer probability 0·5% [95% CI 0·0–1·9]), nodules with a volume of 27 mm³ up to 206 mm³ had an intermediate probability (17 [3·1%] of 542 nodules; lung cancer probability 3·1% [1·9–5·0]), and nodules of 206 mm³ or greater had a high probability (29 [16·9%] of 172 nodules; lung cancer probability 16·9% [12·0–23·2]). A volume cutoff value of 27 mm³ or greater had more than 95% sensitivity for lung cancer.

Interpretation Our study shows that new solid nodules are detected at each screening round in 5–7% of individuals who undergo screening for lung cancer with low-dose CT. These new nodules have a high probability of malignancy even at a small size. These findings should be considered in future screening guidelines, and new solid nodules should be followed up more aggressively than nodules detected at baseline screening.

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Introduction

Lung cancer is a leading cause of death worldwide.[1] Randomised controlled trials of lung cancer screening in Europe and the USA have explored the value of low-dose CT in detection of lung cancer at an early stage to improve prognosis.[2,3] The National Lung Screening Trial showed a relative reduction in lung cancer mortality of 20% with low-dose CT compared with chest radiography.[4] In view of these results, most US guidelines now recommend lung cancer screening with low-dose CT for high-risk individuals.[5–12]

So far, most research has focused on lung nodules detected during baseline screening. However, new nodules can be detected at subsequent screening rounds and complicate management.[13] Reports of new nodules have been inconsistent because of differences in definitions of incident nodules, which restricts comparability.[7] New nodule and respective cancer rates are seldom reported explicitly, and are difficult to deduce from published results. In 2005, the Fleischner Society, referring to Swensen and colleagues' Mayo Clinic trial, suggested that 10% of screening participants

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Research in context

Evidence before this study

We searched PubMed from Jan 1, 2000, to Oct 15, 2015, for available scientific literature, and assessed present lung cancer screening guidelines. Among other related terms, the search focused on "new nodules", "incident nodules", "incidence screening rounds", and "lung cancer screening". We restricted the search to publications in English. Up to now, most research into trials of lung cancer screening has been focused on lung nodules detected during baseline screening. Nevertheless, incident nodules are frequently found at subsequent screening rounds and complicate management. Reports of these nodules have been inconsistent because new nodules were grouped and defined differently within the various trials. Previously missed (therefore pre-existing) nodules and newly developed nodules were seldom reported separately. The sparse existing evidence shows that new nodules detected after baseline can have a higher risk of lung cancer than those detected at baseline. Little is known about new nodule volume at initial detection and the respective lung cancer probability, nor about new nodule cancer, including histology or stage distribution. Most US guidelines recommend lung cancer screening with low-dose CT for high-risk individuals. However, radiologists and oncologists have little evidence-based guidance for how to approach new nodules found after baseline screening.

Added value of this study

To the best of our knowledge, this is the first study to investigate new solid nodules found during lung cancer screening and to provide volume cutoff values. Our findings show that new solid nodules are detected at each screening round in 5–7% of participants who undergo lung cancer screening with low-dose CT, and have a higher probability of being cancer than do baseline nodules, even at a smaller volume. Nodule volume can be used for risk stratification to establish need for follow-up or work-up. New solid nodule cancer accounts for a large number of cancer cases found after baseline, but meticulous screening enables detection at early stages.

Implications of all of the available evidence

New solid nodules are consistent findings in studies of lung cancer screening with low-dose CT, and have a significant role in the overall outcome of a lung cancer screening programme. This factor should be considered in future screening guidelines, and new solid nodules should be followed up more aggressively than nodules detected at baseline screening, for example by use of lower volume cutoff values.

will develop a new nodule annually.[14,15] On the basis of results from the Early Lung Cancer Action Project (ELCAP),[16] the International-ELCAP (I-ELCAP),[17] the Pittsburgh Lung Screening Study (PLuSS),[13] and the Mayo trial, an estimated 3·4–13·1% of screening participants develop a new nodule each year.[15] Because these nodules developed within a short time-interval, they are expected to be fast growing. This factor differentiates new nodules from those detected at baseline, which might have been present for years. Lung cancers found in incidence screening rounds tend to be more aggressive than those detected at baseline.[18–20] Data from the ELCAP, I-ELCAP, and Mayo trials show that between 1·6% and 7·5% of participants with new nodules develop lung cancer in such a nodule.[15–17]

See Online for appendix

These results suggest that new lung nodules, although mostly benign, might have a higher probability of being lung cancer than do nodules detected at baseline. Nevertheless, little is known about lung cancer probability and new nodule volume at initial detection, or about lung cancer characteristics of new nodules, including histology and stage distribution. Up to now, no study has focused on new solid nodules found during lung cancer screening.

We did this analysis to assess the occurrence of new solid nodules and their lung cancer probability, and to compare the volume of malignant and benign new solid nodules at initial detection in incidence screening rounds of the Dutch-Belgian Randomized Lung Cancer Screening Trial (NELSON).

Methods

Study design and participants

The recruitment process and study design of the NELSON trial have been previously published and are described in the appendix (pp 1, 2).[21–23] Briefly, between Dec 23, 2003, and July 6, 2006, 15 822 participants from four centres in the Netherlands and Belgium were enrolled and randomly assigned to receive low-dose CT screening (n=7915) or no screening (n=7907). Eligible patients were adults aged 50–75 years, who had smoked 15 or more cigarettes per day for more than 25 years or ten or more cigarettes per day for more than 30 years, and were still smoking or had stopped smoking less than 10 years previously. People with self-reported moderate or bad health (with a questionnaire adapted from the SF-36 questionnaire), inability to climb two flights of stairs, bodyweight of 140 kg or more, current or past renal cancer, melanoma, breast cancer, or lung cancer diagnosed less than 5 years ago, or a chest CT examination less than 1 year ago, were excluded.

From Jan 28, 2004, to Dec 18, 2006, 7557 participants underwent baseline screening.[23] The second screening round took place 1 year after the baseline scan (annual screen) and the third screening round took place 2 years after the second screening scan (biannual screen). Results of the fourth screening round, done 5·5 years after baseline (2·5 year screening interval), have not yet been published, and were not included in the present analysis.

For our study, we included all participants with a solid non-calcified nodule in the second or third screening round, registered by the NELSON radiologists as new or smaller than 15 mm³ (study detection limit)[24] at previous screens. Nodules not registered as new, such as previously missed nodules, were excluded. The NELSON trial was approved by Ethics Committees of all participating centres in the Netherlands and Belgium, and authorised by the Dutch Health Care Committee. All participants gave written informed consent.

Procedures

The CT scan protocol of the NELSON trial has been previously published.[21,23] At all screening sites, 16-multidetector CT scanners or, in later rounds, 64-multidetector scanners were used (Sensation-16 or Sensation-64, Siemens Medical Solutions, Forchheim, Germany; or Mx8000 IDT, Brilliance 16P, or Brilliance 64, Philips Medical Systems, Best, Netherlands). Reconstructions were made with 1·0-mm slice width and 0·7-mm interval. Screening conditions and data acquisition were standard across screening sites.[21,23]

In the first two screening rounds, CT scans were read by at least two independent radiologists with experience in thoracic CT ranging from 1 year to more than 20 years. In the third and fourth screening rounds, single reading was done by radiologists with at least 6 years of experience in thoracic imaging. CT data analysis was done on digital workstations (Leonardo, Siemens Medical Solutions, Forchheim, Germany) with semiautomated volumetric software (LungCARE, version Somaris/5 VA70C-W, Siemens Medical Solutions, Forchheim, Germany). On the basis of the three-dimensional nodule volume, this software also simulated longest and perpendicular nodule diameter in the axial plane. Within the NELSON nodule management protocol, radiologists could over-rule protocol-based screening results (done for 195 [6%] of 3318 participants at the baseline screening round).[25] High suspicion of malignancy (eg, enlarged mediastinal lymph nodes) or benignity (eg, benign calcification patterns) were reasons for manual adjustment.[25]

For subsequent CT scans, nodules were individually matched on previous scans by the software's matching algorithm (depending on consistency, size, and location), and visually checked by the radiologists. Nodules were classified as new if they were not present or smaller than the detection limit (<15 mm³) at any previous scan.[21] Exact volumes of nodules smaller than 15 mm³ at initial detection or at retrospective assessment were not recorded in the database. Data generated during CT evaluation were immediately uploaded to the NELSON management system.[21] For our study, we used nodule information at first nodule detection as reported in the NELSON management system. For nodules eventually diagnosed as cancer, we supplemented data with cancer-specific information obtained at diagnosis, such as histology and stage. We included only screen-detected lung cancers in this analysis because interval cancers of the NELSON trial's first three rounds have been reported previously.[26]

The NELSON nodule management protocol has been described in detail elsewhere and is summarised in the appendix (pp 1, 2).[21] In brief, the screening outcome could be negative (regular screening continued), indeterminate (short-term follow-up low-dose CT), or positive (immediate referral to pulmonologist). At first detection (baseline or incidence screening), solid nodules were assessed based on volume. Because new nodules were considered fast-growing, their follow-up strategy differed from baseline nodules.[21] New nodules measuring 15–50 mm³ without benign characteristics were considered indeterminate (follow-up low-dose CT after 1 year), new nodules measuring 50–500 mm³ were also considered indeterminate (follow-up low-dose CT within 6–8 weeks), and new nodules measuring 500 mm³ or more were considered positive (immediate referral to pulmonologist). After initial detection, subsequent evaluation of a nodule was based on growth and volume doubling time. Growth was defined as a percentage volume change of 25% or more, and led to calculation of the volume doubling time as described in the nodule management protocol.[21]

In case of positive screening results, participants were referred for diagnostic work-up according to national and international guidelines.[21,27] Malignancy was based on histology, and benignity was based on histology or stable size for at least 2 years.[21] The NELSON chief pathologist reassessed obtained lung cancer specimens.[27]

Statistical analysis

At initial detection of a new solid nodule after baseline screening, regular calculation of the volume doubling time is impossible because no earlier measurement is

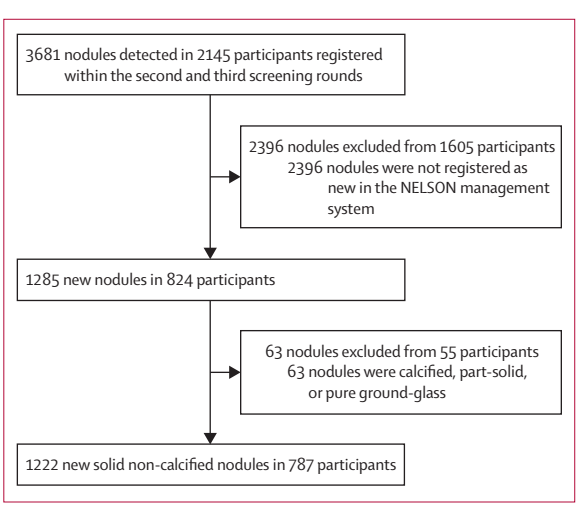

Figure 1: **Flowchart of new solid nodules detected during the second and third screening rounds**

Some participants had a new nodule and, for example, previously missed nodules. Whereas the missed nodule was excluded, the new nodule (and therefore the participant) was included.

available for comparison. For our analysis, we estimated a maximum volume doubling time, representing the minimum growth rate for the time since the previous scan, with the formula:

$$VDT^{max}(days) = \frac{[ln2 \times \Delta t]}{[ln(V2/V1)]}$$

where VDT^{max} is the maximum volume doubling time, V2 is the volume of the new nodule at first detection, V1 is the study detection limit of 15 mm³ as maximum volume at the previous scan, and Δt is the time between new solid nodule detection and previous scan in days. We calculated the maximum volume doubling time for nodules with an estimated percentage volume change of 25% or more (≥18·75 mm³), considering 15 mm³ as V1. In theory, the actual volume doubling time in the examined time interval might have been faster, but not slower, than the calculated maximum time.

Normality testing for continuous variables was done with the Kolmogorov–Smirnov test. Continuous variables were analysed with the Mann–Whitney *U* test and are presented as medians and IQRs. We used Fisher's exact test to analyse nominal variables. We calculated 95% CIs with the Agresti–Coull method. We calculated probabilities of lung cancer stratified by different nodule variables by dividing the number of lung cancers by the total number of nodules. Receiver operating characteristic (ROC) analysis was done for nodule volume and simulated mean nodule diameter (mean of longest and perpendicular simulated diameter) at first new nodule detection with eventual lung cancer diagnosis as the outcome to evaluate their performance as predictors of lung cancer and to estimate cutoff values. We derived cutoff values with a predefined overall sensitivity of 95% and Youden Indices as reference points for further adaption,[28] optimising intermediate and high-risk groups. Appendix p 2 describes the calculations used for ROC analysis for participant-level calculations. We calculated sensitivities by dividing true-positive cases by the numbers of true-positive and false-negative cases. We calculated specificities by dividing true-negative cases by the numbers of true-negative and false-positive cases. We developed a risk prediction model to assess whether the established relation between volume of a new solid nodule and lung cancer diagnosis remained significant independent of other risk factors (ie, age, sex, pack-years, smoking status, time since previous scan, solid nodule count at baseline, and nodule imaging and volume; appendix p 4). All statistical tests were two-sided and p<0·05 was deemed significant. We did statistical analysis with SPSS (version 22), R (version 3.2.3), and Microsoft Excel (2010). The NELSON trial is registered with trialregister.nl, number ISRCTN63545820.

	Overall (N=787)	Lung cancer		p value
		Yes (n=49)	No (n=738)	
Sex				0·12
Female	186 (24%)	7 (14%)	179 (24%)	
Male	601 (76%)	42 (86%)	559 (76%)	
Age (years)				0·20
<50	1 (<1%)	0	1 (<1%)	
50–54	180 (23%)	12 (24%)	168 (23%)	
55–59	237 (30%)	10 (20%)	227 (31%)	
60–64	216 (27%)	13 (27%)	203 (28%)	
65–69	103 (13%)	10 (20%)	93 (13%)	
≥70	50 (6%)	4 (8%)	46 (6%)	
Median (IQR)	59 (55–63)	61 (55–65)	59 (55–63)	
Smoking pack-years*				0·013
<20	2/786 (<1%)	0	2/737 (<1%)	
20–39	431/786 (55%)	19 (39%)	412/737 (56%)	
40–59	245/786 (31%)	16 (33%)	229/737 (31%)	
60–79	73/786 (9%)	10 (20%)	63/737 (9%)	
≥80	35/786 (4%)	4 (8%)	31/737 (4%)	
Median (IQR)	38·7 (29·7–49·5)	43·7 (31·7–61·5)	38·7 (29·7–49·5)	
Solid baseline nodules†				0·038
0	359 (46%)	29 (59%)	330 (45%)	
1	190 (24%)	11 (22%)	179 (24%)	
2	108 (14%)	4 (8%)	104 (14%)	
3	42 (5%)	1 (2%)	41 (6%)	
≥4	88 (11%)	4 (8%)	84 (11%)	
Median (IQR)	1 (0–2)	0 (0–1)	1 (0–2)	

Data are n (%) or n/N (%), unless otherwise specified. *Information was missing for one participant. †Number of non-calcified solid nodules present at baseline screening.

Table 1: **Characteristics of participants with at least one new solid nodule during second or third screening**

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. JEW, MAH, RV, and HJdK had access to the raw data. The corresponding author had full access to all the data in the study and final responsibility for the decision to submit for publication.

Results

Figure 1 shows a flowchart of new solid nodules detected within the second and third screening round. Of the 15 822 participants enrolled in the NELSON trial, 7907 (50%) participants were assigned to the no screening group; 620 (8%) of 7915 screening participants did not participate in the second screening examination for various reasons (eg, lung cancer diagnosis at baseline, death, dropout); 5150 (71%) of 7295 participants in the second and third screening rounds had no new nodule described and, in 1605 (75%) of 2145 participants with new nodules described, a nodule was not identified as new by the radiologist (eg, missed at previous screen), excluding 1321 (18%) participants without a new nodule; and 37 (<1%) participants with only calcified or subsolid

new nodules were not included. 1222 new solid nodules were registered in 787 (11%) of the 7295 participants who underwent second and third screening scans (not accounting for participant dropout; figure 1). 273 (22%) of new solid nodules represented nodules retrospectively identified as smaller than the detection limit (<15 mm³) in a previous screen.

Table 1 shows characteristics of included participants. A higher number of pack-years smoked and a lower number of solid nodules at baseline screening significantly increased the probability of a new solid nodule being lung cancer (table 1). Increased age was not significantly associated with lung cancer (table 1). In 359 (46%) participants, no solid nodule had been found during baseline screening (table 1). In 49 (6%) participants with new solid nodules, a new solid nodule was lung cancer (table 1). One participant was diagnosed with synchronous double tumours in two new nodules. In total, 50 lung cancers were found, representing 4% of all new solid nodules (table 2).

Median nodule size at first detection of new solid nodules was 41 mm³ (IQR 21–116), and median volume of lung cancers (296 mm³ [IQR 73–721]) differed significantly from benign nodules (39 mm³ [21–103]; p<0·0001). ROC analysis showed an area under the curve (AUC) for nodule volume of 0·795 (figure 2). However, the value of nodule size as predictor for lung cancer differed with varying screening interval length; in the second screening round nodule volume had an AUC of 0·686, whereas the AUC rose in the third screening round to 0·837 (figure 2). In the NELSON trial, the volume cutoff value for new nodules, leading to follow-up within 6–8 weeks, was 50 mm³ or more, which provided a sensitivity of 81·3% (95% CI 67·8–90·0) and a specificity of 57·7% (54·7–60·6) for lung cancer. To reach 95% sensitivity, a cutoff value of 27 mm³ or more (sensitivity 95·8% [95% CI 85·2–99·6]; specificity 38·3% [35·5–41·3]) would be necessary. Nodules smaller than 27 mm³ had a low lung cancer probability, nodules with a volume of 27 mm³ up to 206 mm³ had an intermediate probability, and nodules of 206 mm³ and higher had a high probability (table 3). On the basis of the simulated mean diameter, proposed cutoff values are smaller than 3·7 mm for a negative screen (≥3·7 mm: sensitivity 95·8% [95% CI 85·2–99·6]; specificity, 32·9% [30·2–35·8]), and 8·2 mm or more for a positive screen (appendix p 3).

The median maximum volume doubling time of new nodule lung cancers differed significantly from the median time of benign new nodules (139 days [IQR 104–211] *vs* 278 days [140–549]; p<0·0001; appendix p 3). The median maximum volume doubling time of adenocarcinomas was 191 days (IQR 146–348) and of squamous-cell carcinomas was 133 days (105–182; table 4). However, in this analysis maximum volume doubling time did not improve risk stratification by nodule volume (data not shown). The median maximum volume doubling time of new nodule lung cancers did not differ significantly between the second and the third screening rounds (127 days [IQR 73–206] *vs* 144 days [105–220]; p=0·48).

Less than half of screen-detected lung cancers in new solid nodules were 500 mm³ or more at first nodule detection (table 4). Histologically, most lung cancers were adenocarcinomas, squamous-cell carcinomas, or small-cell lung carcinomas (table 4). Most small-cell lung carcinomas and squamous-cell carcinomas had volumes greater than 500 mm³ at first nodule detection (table 4). However, few adenocarcinomas initially presented with volumes of 500 mm³ and more, whereas roughly two-fifths were smaller than 50 mm³ at first detection. Most lung cancers were diagnosed at stage I (table 4). Of cancers detected in the second screening round, 11 (79%) of 14 were stage I, compared with 23 (64%) of 36 in the third screening round (p=0·50; table 2). In about half the lung cancer cases, participants were referred immediately after first new solid nodule

	Second screening round*	Third screening round*	Second and third screening rounds
All participants	7295	6922	7295
Participants with new nodules	344 (5%)	491 (7%)	787 (11%)†
With new solid lung cancer	14/344 (4%)	35/491 (7%)	49/787 (6%)
New solid nodules	476	746‡	1222‡
<50 mm³	278 (58%)	419/743 (56%)	697/1219 (57%)
50–500 mm³	158 (33%)	267/743 (36%)	425/1219 (35%)
≥500 mm³	40 (8%)	57/743 (8%)	97/1219 (8%)
Lung cancer	14	36	50
<50 mm³	4 (29%)	6 (17%)	10 (20%)
50–500 mm³	6 (43%)	14 (39%)	20 (40%)
≥500 mm³	4 (29%)	16 (44%)	20 (40%)
Probability of lung cancer	14/476 (3%)	36/746 (5%)	50/1222 (4%)
95% CI	1·7–4·9	3·5–6·6	3·1–5·4
Cancer stage at diagnosis			
IA	11/14 (79%)	21/36 (58%)	32/50 (64%)
IB	0	2/36 (6%)	2/50 (4%)
IIA	1/14 (7%)	2/36 (6%)	3/50 (6%)
IIB	0	0	0
IIIA	2/14 (14%)	7/36 (19%)	9/50 (18%)
IIIB	0	1/36 (3%)	1/50 (2%)
IV	0	0	0
Not specified	0	3/36 (8%)	3/50 (6%)
Time of referral§			
Immediately	5/14 (36%)	19/36 (53%)	24/50 (48%)
Follow-up	6/14 (43%)	12/36 (33%)	18/50 (36%)
Subsequent round	3/14 (21%)	5/36 (14%)	8/50 (16%)

Data are n/N (%) or n (%), unless otherwise specified. 50 lung cancer nodules were detected in 49 participants. *Incidence screenings 1 year (second screening round; annual screen) and 3 years (third screening round; biannual screen) after baseline screening. †48 participants developed new solid nodules in both incidence rounds, but were accounted for only once in the total number of participants with new nodules. ‡Size categorisation was missing for three benign nodules. §Referral to pulmonologist for work-up and diagnosis.

Table 2: **New solid new nodules detected during second and third screening rounds (N=1222; 1172 benign nodules and 50 lung cancer nodules)**

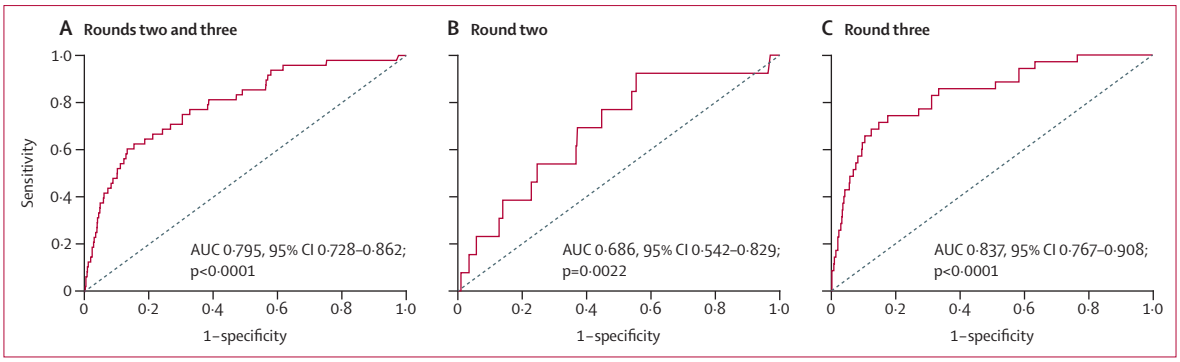

Figure 2: **Receiver operating characteristic curves of nodule volume at initial detection, discriminating malignant from benign new solid nodules**
Exact volume measurement was not available for 89 benign nodules and two cancers, and they were not included in the calculations. AUC=area under the curve.

	Second screening round (lung cancer/ total nodules)	Third screening round (lung cancer/total nodules)	Second and third screening rounds (lung cancer/ total nodules)	Lung cancer probability (95% CI)
New solid nodules	13/452 (3%)	35/679 (5%)	48/1131 (4%)	4·2% (3·2–5·6)
<25 mm³	1/160 (1%)	1/216 (<1%)	2/376 (1%)	0·5% (0·0–2·0)
25 to <50 mm³	3/104 (3%)	4/154 (3%)	7/258 (3%)	2·7% (1·2–5·6)
50 to <100 mm³	2/72 (3%)	4/113 (4%)	6/185 (3%)	3·2% (1·3–7·1)
100 to <200 mm³	2/46 (4%)	2/85 (2%)	4/131 (3%)	3·1% (0·9–7·8)
200 to <300 mm³	2/19 (11%)	4/31 (13%)	6/50 (12%)	12·0% (5·2–24·2)
300 to <400 mm³	0/14	2/18 (11%)	2/32 (6%)	6·3% (0·7–21·2)
400 to <500 mm³	0/8	3/20 (15%)	3/28 (11%)	10·7% (2·9–28·0)
≥500 mm³	3/29 (10%)	15/42 (36%)	18/71 (25%)	25·4% (16·6–36·6)
Cutoff values				
<27 mm³	1/180 (1%)	1/237 (<1%)	2/417 (<1%)	0·5% (0·0–1·9)
27 to <206 mm³	7/206 (3%)	10/336 (3%)	17/542 (3%)	3·1% (1·9–5·0)
≥206 mm³	5/66 (8%)	24/106 (23%)	29/172 (17%)	16·9% (12·0–23·2)

Data are n/N (%), unless otherwise specified. Exact volume measurement was not available for 89 benign nodules and two cancers, and they were not included in the calculations.

Table 3: **Volume at first detection and lung cancer probability of new solid nodules (N=1131; 1083 benign nodules and 48 lung cancer nodules)**

detection (table 4). Adenocarcinomas tended to be referred later, with 16 (84%) of 19 nodules not being referred immediately, whereas only ten (32%) of the other 31 cancers were not referred immediately (p=0·00045; table 4).

Discussion

In this study, we determined the occurrence of solid nodules newly detected in the second or third screening round of the NELSON trial, assessed their lung cancer probability, and provided information about stage and cancer histology. Furthermore, we proposed cutoff values for nodule volume as a guide for further management of new solid nodules in lung cancer screening. In the first two incidence screening rounds of the NELSON trial, radiologists registered new solid nodules in 787 (11%) of 7295 participants. A new solid nodule was diagnosed as lung cancer in 49 (6%) of 787 participants. Most lung cancers were adenocarcinoma, squamous-cell carcinoma, and small-cell lung cancer, and most were diagnosed at stage I. Nodule volume could be used for risk stratification in new solid nodules, with a sensitivity of more than 95% for a volume cutoff of 27 mm³ or more. In this setting, new solid nodules of 206 mm³ or more had a high lung cancer probability.

Few studies of lung cancer screening have published detailed data regarding new nodules at incidence screening rounds. As stated in British Thoracic Society guidelines[29] for the investigation and management of pulmonary nodules, little evidence exists for the management of new nodules that appear in follow-up CTs. Our study not only offers insight into the cancer probability of such nodules, but also provides information about stage and cancer histology. Furthermore, to our knowledge, this is the first time nodule volume cutoff values have been established as a guide for further management of new solid nodules in lung cancer screening.

In the second screening round, 344 (5%) of 7295 participants had new solid nodules. This number is somewhat similar to annual new nodule numbers reported in the I-ELCAP trial (1460 [5%] of 27 456 participants), the ELCAP trial (40 [3%] of 1184 participants), and the PluSS trial (256 [7%] of 3423 participants);[13,16,17] the Mayo Clinic trial reported a higher proportion (191 [13%] of 1464 participants).[15] Nevertheless, these data are restricted in their comparability, because new nodules were defined differently within trials and rates of new nodule detection have not been reported explicitly.[7]

The clinical significance of new solid nodules is underlined by the high cancer rate. In the NELSON trial, 70 (1%) of 7557 participants were found to have lung cancer during baseline screening,[23] and 200 (3%) of 7582 participants were found to have lung cancer during the first three screening rounds.[27] Nevertheless, cancers detected in the first three rounds include those found within 44 participants with new nodule lung cancer (excluding five participants in whom cancer diagnosis occurred in the fourth round). In the present study, a new solid nodule was lung cancer in 6% of participants

	Total	Histological type								
		AdC	SqCC	AdSqLC	LCLC	LCNEC	SCLC	NSCLC/SCLC	NSCLC-NOS	Unknown*
Overall	50 (100%)	19 (38%)	11 (22%)	1 (2%)	4 (8%)	1 (2%)	5 (10%)	1 (2%)	1 (2%)	7 (14%)
Volume at first detection										
<50 mm³	10 (20%)	8 (42%)	1 (9%)	0	0	0	0	0	0	1 (14%)
50–500 mm³	20 (40%)	8 (42%)	3 (27%)	0	4 (100%)	1 (100%)	1 (20%)	0	1 (100%)	2 (29%)
≥500 mm³	20 (40%)	3 (16%)	7 (64%)	1 (100%)	0	0	4 (80%)	1 (100%)	0	4 (57%)
Median (IQR)	296 (73–721)	97 (32–370)	658 (96–959)	NA†	157 (68–226)	212 (NC‡)	2373 (661–3108)	3482 (NC‡)	299 (NC‡)	580 (82–1108)
Simulated mean diameter (mm)§	9·3 (5·2–14)	5·8 (4·6–11·1)	12·9 (6·8–17·5)	NA†	7·3 (5·4–8·9)	8·2 (NC‡)	19·8 (14·8–20·7)	19·6 (NC‡)	12·6 (NC‡)	11·6 (5·3–13·7)
Estimated volume doubling time (days)	139 (104–211)	191 (146–348)	133 (105–182)	NA†	117 (90–191)	161 (NC‡)	82 (36–96)	101 (NC‡)	169 (NC‡)	124 (69–328)
Stage at diagnosis										
IA	32 (64%)	15 (79%)	7 (64%)	0	3 (75%)	1 (100%)	0	0	1 (100%)	5 (71%)
IB	2 (4%)	2 (11%)	0	0	0	0	0	0	0	0
IIA	3 (6%)	0	1 (9%)	1 (100%)	0	0	0	0	0	1 (14%)
IIB	0	0	0	0	0	0	0	0	0	0
IIIA	9 (18%)	1 (5%)	3 (27%)	0	1 (25%)	0	3 (60%)	1 (100%)	0	0
IIIB	1 (2%)	1 (5%)	0	0	0	0	0	0	0	0
IV	0	0	0	0	0	0	0	0	0	0
Not specified	3 (6%)	0	0	0	0	0	2 (40%)	0	0	1 (14%)
Time of referral										
Immediately	24 (48%)	3 (16%)	9 (82%)	1 (100%)	1 (25%)	0	5 (100%)	1 (100%)	0	4 (57%)
Follow-up	18 (36%)	10 (53%)	2 (18%)	0	3 (75%)	1 (100%)	0	0	0	2 (27%)
Subsequent round	8 (16%)	6 (32%)	0	0	0	0	0	0	1 (100%)	1 (14%)

Data are n (%) or median (IQR), unless otherwise specified. AdC=adenocarcinoma. SqCC=squamous-cell carcinoma. AdSqLC=adenosquamous lung carcinoma. LCLC=large-cell lung carcinoma. LCNEC=large-cell neuroendocrine carcinoma. SCLC=small-cell lung cancer. NSCLC/SCLC=mixed non-small-cell lung carcinoma and small-cell lung cancer. NSCLC-NOS=non-small-cell lung carcinoma not otherwise specified. NA=not available. NC=not calculable. *Histological diagnosis could not be established. †No exact volume measurement was available and no simulated mean diameter was generated. ‡Too few nodules available for calculation. §Diameters were simulated from computer-generated volume measurements, based on three-dimensional voxels. Manually measured diameters are less accurate and will overestimate nodule size.

Table 4: **Lung cancer characteristics of new solid nodules**

with new solid nodules. When these numbers are compared, new solid nodules seem to have a higher lung cancer probability than do baseline nodules. Furthermore, at baseline, 3816 (50%) of 7557 participants had at least one pulmonary nodule, causing further follow-up in 1570 (21%) participants due to suspiciousness of a nodule.[23] Eventually, lung cancer was found in 80 (5%) of 1570 participants with an indeterminate or positive test result at baseline.[23] In that sense, mere detection of a new solid nodule during incidence screening might carry the same lung cancer probability as a suspicious test result during baseline screening (6% *vs* 5%; p=0·25).

In 2014, the American College of Radiologists released assessment categories for nodules detected during lung cancer screening (so-called Lung-RADS) and, as in the NELSON nodule management protocol, follow-up for new nodules is recommended at smaller sizes than for baseline nodules.[21,30] Our results confirm that new solid nodules detected during incidence rounds of lung cancer screening need a more aggressive follow-up strategy than baseline nodules, with short-term follow-up evaluation for growth assessment required for smaller nodules. At these tiny nodule sizes, growth detection based on two-dimensional diameter evaluation is unreliable,[31] favouring volumetry.

In the NELSON trial, baseline nodules smaller than 100 mm³ had a lung cancer probability of about 0·6%, were not predictive of lung cancer, and did not necessitate additional follow-up scans.[32] However, this criterion does not apply in the case of new solid nodules. As shown in the present study, 3% of participants whose largest new solid nodule was smaller than 100 mm³ were eventually diagnosed with lung cancer, with 15 (1·8%) of 819 new solid nodules smaller than 100 mm³ found to be lung cancer. Large volume of new solid nodules was the most important predictor of lung cancer, and remained so after correction for possible confounding variables such as time from previous CT scan, sex, age, number of pack-years, nodule margin, solid nodule count at baseline (multinodularity), and nodule location, with a cutoff value of 27 mm³ or more for further follow-up of new solid nodules having more than 95% sensitivity. Age was not significantly associated with new nodule lung cancer. Possible explanations could be that the number of cases

was too low to show the correlation, or perhaps fast nodule growth is less associated with age, possibly even with a converse relation, with older individuals having less fast-growing nodules. We identified that new solid nodules smaller than 27 mm³ have a low lung cancer probability and their detection should be followed by regular screening, new solid nodules of 27 mm³ up to 206 mm³ have an intermediate lung cancer probability requiring short-term follow-up, and new solid nodules of 206 mm³ or greater have a high lung cancer probability necessitating immediate diagnostic evaluation. These findings could be incorporated into radiology protocols under development for new trials of lung cancer screening. Nevertheless, the proposed cutoff estimates based on the first three rounds of the Nelson trial might be adjusted when further data become available from this or other ongoing trials, such as the UK Lung Cancer Screening Trial (ISRCTN78513845). Combining trial data from NELSON and the UK Lung Cancer Screening Trial, which used the same volume screen protocols, could provide further insight into if and how lung cancer screening protocols should be improved, and might be necessary to obtain a number of cases large enough to enable even more accurate assessment.

We provided cutoff values for simulated mean nodule diameter. Nodules smaller than 3·7 mm had low lung cancer probability, nodules of 3·7 mm to less than 8·2 mm had intermediate lung cancer probability, and nodules of 8·2 mm or greater had high lung cancer probability. These probabilities are in concordance with lung cancer probabilities for the respective American College of Radiologists Lung-RADS categories.[30] However, these diameters represent simulated diameter measurements of new nodules, extrapolated from computer-generated volume measurements based on three-dimensional voxel analysis.[33] Manual diameter measurements are far less precise and reproducible,[31] and would probably yield different results.

The difference in risk stratification of nodule volume between second and third screening rounds (AUC 0·686 [95% CI 0·542–0·829] *vs* 0·837 [0·767–0·908]) suggests that new nodules need time to grow in order to be evaluated based on size only, making measures such as the volume doubling time crucial for follow-up assessment.

Whether our results can be used to guide management of incidentally detected nodules depends on the setting in which the nodule was detected. First, a previous chest CT must be available to confirm that the nodule is actually new. Second, the presented lung cancer probabilities were based on a high-risk population with a relatively high prevalence of lung nodules (about 50%),[32] and high overall lung cancer risk (about 3% in the first 5 years).[34] Our results and cutoffs should only be extrapolated in a population with similar nodule prevalence and lung cancer risk. Although we highly recommend separate, more stringent, guidelines for new nodules on the basis of our results, future studies based on incidentally detected nodules should focus on cutoff values for this nodule group.

Of the 50 new nodule lung cancers, 34 (68%) were stage I, which is similar to numbers recorded during baseline screening of the NELSON trial (46 [64%] of 72 cancers; p=0·70) and for overall screening in the first three rounds (148 [71%] of 209 cancers; p=0·73).[23,27] Fewer small-to-intermediate sized lung cancers (<500 mm³) were found after biannual screening than after annual screening (ten [71%] of 14 *vs* 20 [56%] of 36). However, the proportion of stage I cancers did not differ significantly between annual and biannual screening, although the number of cancers had roughly doubled (14 *vs* 36 cancers). The maximum volume doubling time was significantly lower in new nodule lung cancers than in benign new solid nodules. Notably, the median maximum volume doubling time of adenocarcinomas (191 days [IQR 146–348]) and squamous-cell carcinomas (133 days [105–182]) was similar to previously published volume doubling time of fast-growing baseline cancers in the NELSON trial of the same histological type (196 days [IQR 135–250] and 142 days [91–178], respectively).[35] Perhaps fast-growing baseline cancer and new nodule cancer represent a group of relatively young cancers. Nevertheless, even though malignant new nodules might be fast growing, detection at an early stage is possible with low-dose CT screening and use of volume doubling time for evaluation after first detection.

Compared with the overall screening results of the first three rounds,[27] new solid nodule cancer comprised 11 (19%) of 58 cancers found in the second screening round (excluding three new nodule lung cancers for which diagnosis occurred in the third round) and 34 (44%) of 77 cancers even in the third screening round (excluding five new nodule lung cancers for which diagnosis occurred in the fourth round). Thus, management of new solid nodules has a great impact on the outcome of a lung cancer screening programme.

Most trials of lung cancer screening have used an annual screening algorithm. The NELSON study was designed to also study the effect of prolonged screening intervals, enabling us to provide insights into differences between annual and biannual screening. Presented cutoff values were based on new solid nodules detected after annual and biannual screening and their respective follow-ups, which might make direct applications to an annual screening routine difficult.

Our study had some limitations. We excluded nodules smaller than 15 mm³, because they were below the detection limit of the NELSON trial and were therefore not reported by the radiologists. We cannot exclude the possibility that the actual number of new nodules is somewhat higher than we report based on the NELSON management system information. Second, we included only solid nodules, with exclusion of part-solid and pure ground-glass nodules. Furthermore, calculation of a

maximum volume doubling time for new nodules is a new and not yet validated approach, and so needs further investigation. Rates of new solid nodules and cancer differed between the incidence screening rounds. This inconsistency could be explained by the varying time intervals between screening rounds and respective follow-up examinations, and by the learning effect of radiologists. 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.[25]

New solid nodules are detected at each screening round in 5–7% of participants who undergo screening for lung cancer by low-dose CT, and have a higher probability of lung cancer than do baseline nodules. This factor should be considered in future screening guidelines. New solid nodules should be followed up more aggressively than nodules detected at baseline screening, for example by using lower volume cutoff values (<27 mm³, 27 mm³ to <206 mm³, ≥206 mm³). However, meticulous screening and follow-up with volume doubling time enables detection of new solid nodule lung cancer at an early stage. Nodule volume should be used to stratify the probability of lung cancer of new solid nodules, but more research into new nodules is necessary to identify how to optimise management of these nodules in lung cancer screening.

Contributors

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

Declaration of interests

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