Optimization of nodule management in CT lung cancer screening

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7

Occurrence and lung cancer probability of new solid nodules at incidence CT lung cancer screening: the NELSON trial

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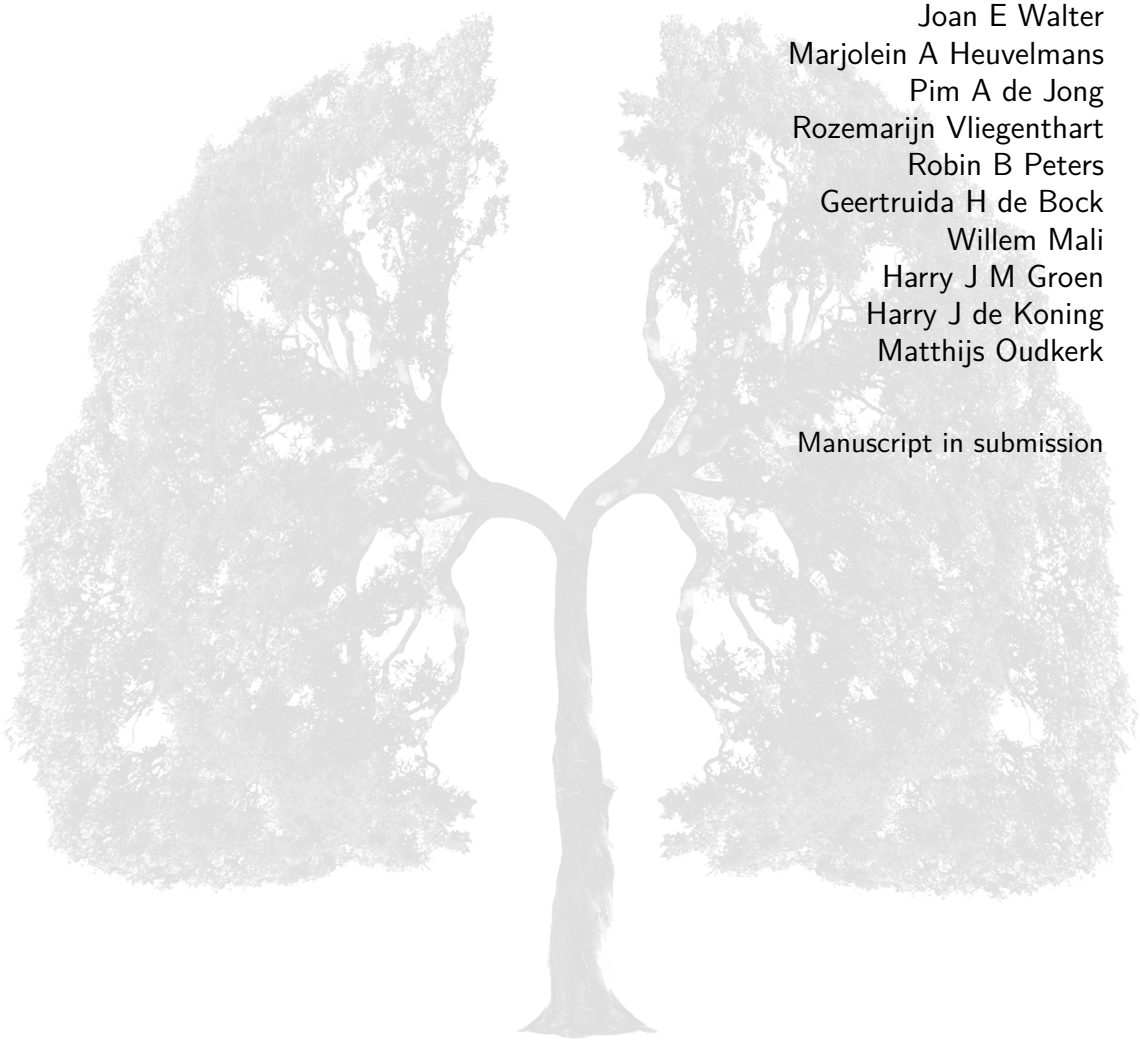

Abstract

Background: Lung cancer screening by low-dose computed tomography (LDCT) is now recommended for high-risk individuals by US guidelines. Purpose of this study was to determine occurrence of new solid nodules and their lung cancer rate at incidence screening rounds of the Dutch-Belgian Randomized Lung Cancer Screening Trial (NELSON).

Methods: The NELSON trial (Controlled trials number, ISRCTN63545820) was approved by the Dutch Ministry of Health. All participants gave written informed consent. In total, 7,557 individuals underwent baseline LDCT screening. This sub-study included participants from the first two incidence screening rounds, after 1 and 3 years, with solid non-calcified nodules registered by NELSON radiologists as new. Lung cancer diagnosis was based on histology and benignity was based on histology or stable size for at least 2 years. Nodule volume was generated semi-automatically by LungCARE software (Siemens Medical Solutions).

Findings: In the first two incidence screening rounds of the NELSON trial, radiologists registered 1222 new solid nodules in 10.8% of participants. A new solid nodule was lung cancer in 6.2% of participants with new solid nodules. The majority (68.0%) was diagnosed at stage I. Nodule volume had a high discriminatory power (area under the receiver-operating curve: 0.795, 95% confidence interval: 0.728, 0.862, P<0.001). Probability of lung cancer was low (0.5%) for nodules with volume <27 mm^3, intermediate (3.1%) for 27-<179 mm^3, and high (15.3%) for $\geq$179 mm^3. A volume cut-off value of $\geq$27 mm^3 had >95% sensitivity for malignancy.

Interpretation: New solid nodules are common in LDCT lung cancer screening, and carry a high malignancy risk even at small size.

Introduction

Lung cancer is a leading cause of death worldwide [1]. Randomized lung cancer screening trials in Europe and the US are exploring the value of low-dose computed tomography (LDCT) in detecting lung cancer at an early stage to improve prognosis [2, 3]. Comparing LDCT screening to chest X-ray, the National Lung Screening Trial (NLST) showed a relative reduction in lung cancer specific mortality of 20% [4]. In the light of these results, lung cancer screening with LDCT has become recommended for (former) heavy smokers in most US guidelines [5–12].

So far, most research focused on lung nodules detected during baseline screening. However, new nodules at subsequent screening rounds are common and complicate management [13]. Reports of new nodules have been inconsistent as incident nodules were defined differently within trials, limiting comparability [7]. New nodules and respective cancer rates are seldom reported explicitly, and are difficult to deduce from published results. In 2005, the Fleischner society, referring to the Mayo trial, suggested that 10% of screening participants will develop a new nodule annually [14, 15]. Based on results from the Early Lung Cancer Action Project (ELCAP), the International-ELCAP (I-ELCAP), the Pittsburgh Lung Screening Study (PLuSS), and the Mayo trial, likely between 3.4-13.1% of screening participants develop a new nodule each year [13, 15–17]. Because these nodules develop within a short time-interval, they are expected to be fast-growing. This differentiates them from baseline nodules, which may have been present for years. Compared to baseline, lung cancers found in incidence screening rounds tend to be more aggressive [18–20]. Figures of the ELCAP, I-ELCAP, and Mayo trials suggest that the cancer rate in patients with new nodules ranges between 1.6-7.5% [15–17].

From these limited results, it seems that new lung nodules, although mostly benign, may have a higher risk of malignancy than nodules detected at baseline screening. Nevertheless, little is known about lung cancer risk and new nodule volume at initial detection, as well as about new nodule cancer, including histology or stage distribution. Up to this point, no study has focused on new solid nodules found during lung cancer screening.

The purpose of this sub-study was to assess occurrence of new solid nodules and their cancer rate, as well as to compare volume of malignant and benign new solid nodules at initial detection in the incidence screening rounds of the Dutch-Belgian Randomized Lung Cancer Screening Trial (NELSON).

Materials and Methods

Study design and participants

The NELSON trial (Controlled trials number, ISRCTN63545820) was approved by Ethics Committees of all participating centers in the Netherlands and Belgium, and authorized by the Dutch Health Care Committee. The recruitment process and study design were published before [21–23]. All participants gave written informed consent. Heavy (former) smokers, aged 50-75 years, were eligible for participation. Overall, 15,822 participants enrolled, and were randomized to screening by LDCT (n = 7,915) or no screening (n = 7,907). From April 2004 through December 2006, 7,557 participants attended base-

line screening [23]. Following initial screening, incidence screening rounds took place after 1, 3 and 5.5 years. Results of the third incidence screening round have not been published yet.

This sub-study included participants of the first two incident screening rounds with solid non-calcified nodules, registered by the NELSON radiologists as new or smaller than 15 mm^3 (study detection limit) [24] at previous screens. Nodules not registered as new, such as previously missed nodules, were excluded (Figure 7.1).

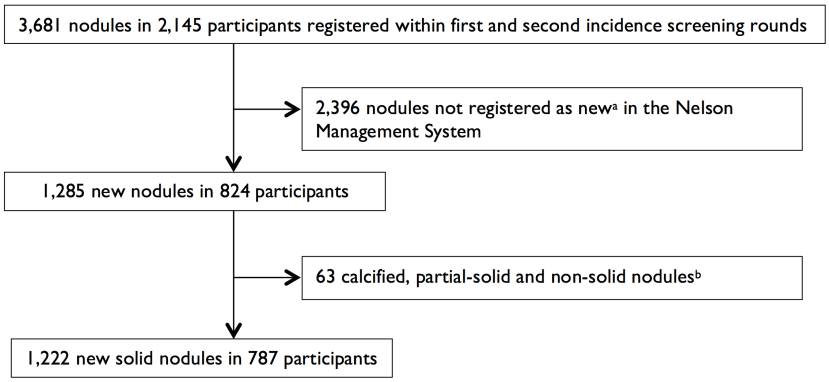

Figure 7.1: Flowchart new solid nodules detected within first and second incidence screening rounds.
[a] Only new nodules registered as new and not present on a previous scan (NELSON trial reporting limit = 15 mm^3) were included.
[b] Only non-calcified solid nodules were included.

Screening strategy

The CT protocol was published before [21, 23]. At all screening sites, 16-MDCT scanners or, in later rounds, 64-MDCT scanners were used (Sensation-16 or Sensation-64, Siemens Medical Solutions or Mx8000 IDT, Brilliance 16P or Brilliance 64, Philips Medical Systems). 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 from 1 to >20 years. In the third and fourth screening round, single reading was performed by radiologists with at least 6 years of experience in thoracic imaging. CT data analysis was performed on digital workstations (Leonardo, Siemens Medical Solutions) with software for semi-automated volume measurements (LungCARE, version Somaris/5 VA70C-W, Siemens Medical Solutions). Within the NELSON nodule management protocol, radiologists could overrule protocol-based screening results (at baseline screening round performed in 5.9%) [25]. High suspicion of malignancy (e.g. enlarged mediastinal lymph nodes) or benignity (e.g. 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), or manually. Based on matching, nodules were classified as new by the NELSON radiologist, if not

present on any previous scan, or smaller than 15 mm^3 at previous screens [21]. Data generated during CT evaluation were uploaded to the NELSON management system [21]. For this study, nodule information at first nodule detection was used as reported in the NELSON management system. For nodules eventually diagnosed as cancer, data were supplemented by cancer-specific information obtained at diagnosis, such as histology and stage. Interval cancers were excluded from the analysis.

Earlier publications described the NELSON nodule management protocol in its entirety [21]. Briefly, the screening outcome could be negative (regular screening continued), indeterminate (short-term follow-up LDCT), or positive (immediate referral to pulmonologist). At first detection (baseline or incidence screening), solid nodules were evaluated based on volume. As new nodules were considered fast-growing, their follow-up strategy was different [21]. New nodules of 15-50 mm^3 without benign characteristics were considered indeterminate (follow-up LDCT after 1 year), nodules of 50-500 mm^3 were also considered indeterminate (follow-up LDCT within 6-8 weeks), and nodules $\geq$500 mm^3 were considered positive (immediate referral to pulmonologist). After first detection, a nodule's subsequent evaluation based on growth and volume doubling time (VDT). Growth was defined as 25% or more percent volume change and led to the calculation of the VDT as described in the NELSON nodule management protocol [21].

Outcomes

In case of positive screening results, participants were referred for diagnostic work-up according to (inter) national guidelines [21, 26–30]. Malignancy was based on histology, and benignity was based on histology or stable size for at least 2 years [14]. The NELSON chief pathologist reassessed obtained specimens [26].

Statistical analysis

Normality testing for continuous variables was performed with the Kolmogorov-Smirnov test. Variables were analyzed using the Mann-Whitney U test, and described as medians and interquartile ranges. The Fisher exact test was used to analyze nominal variables. 95% confidence intervals were calculated using the Agresti-Coull method. Receiver operating characteristic (ROC) analysis was conducted for nodule volume, to evaluate its worth as predictor of lung cancer and estimate cut-off values. *P*-values <0.05 were considered significant. Analyses were performed with SPSS Statistics (version 22) and Microsoft Excel (2010).

Results

Participant and incidence screening overview

Within the first two incidence screening rounds, 1,222 new solid nodules were registered in 787 participants (10.8% [787/7,295], not accounting for participant drop-out). Of the 787 participants, 601 (76.4%) were male. Median age was 59 years (interquartile-range [IQR]: 55-63 years), and median number of smoked pack-years was 39 years (IQR: 30-50 years).

Table 7.1: Characteristics of participants with at least one new solid nodule during first or second incidence screening round.

		Lung Cancer		
	Overall Population (n=787) (100%)	Yes (n=49) (6.2%)	No (n=738) (93.8%)	*P*-value
Gender				*0.121*
Female	186 (23.6)	7 (14.3)	179 (24.3)	
Male	601 (76.4)	42 (85.7)	559 (75.7)	
Age				
<50	1 (0.1)	0	1 (0.1)	
50 - 54	180 (22.9)	12 (24.5)	168 (22.8)	
55 - 59	237 (30.1)	10 (20.4)	227 (30.8)	
60 - 64	216 (27.4)	13 (26.5)	203 (27.5)	
65 - 69	103 (13.1)	10 (20.4)	93 (12.6)	
≥70	50 (6.4)	4 (8.2)	46 (6.2)	
Median (IQR)	*59 (55-63)*	*61 (55-65)*	*59 (55-63)*	*0.201*
Pack-Years[a]				
<20	2 (0.3)	0	2 (0.3)	
20 - 39	431 (54.8)	19 (38.8)	412 (55.9)	
40 - 59	245 (31.2)	16 (32.7)	229 (31.1)	
60 - 79	73 (9.3)	10 (20.4)	63 (8.5)	
≥80	35 (4.5)	4 (8.2)	31 (4.2)	
Median (IQR)	*38.7 (29.7-49.5)*	*43.7 (31.7-61.5)*	*38.7 (29.7-49.5)*	*0.013*
Nodules at baseline[b]				
0	359 (45.6)	29 (59.2)	330 (44.7)	
1	190 (24.1)	11 (22.4)	179 (24.3)	
2	108 (13.7)	4 (8.2)	104 (14.1)	
3	42 (5.3)	1 (2.0)	41 (5.6)	
≥4	88 (11.2)	4 (8.2)	84 (11.4)	
Median (IQR)	*1 (0-2)*	*0 (0-1)*	*1 (0-2)*	*0.038*

IQR = Interquartile range.

[a] Pack-Year information was missing for one (1) participant.

[b] Number of non-calcified solid nodules present at baseline screening.

Participants' characteristics are presented in Table 7.1. In 359 participants (45.6%), no solid nodule had been found during baseline screening. In 49 of 787 (6.2%) participants with a new solid nodule, the new solid nodule was lung cancer. In one (2.0% [1/49]) of these participants synchronous double tumors developed and in total 50 lung cancers were found, representing 4.1% (50/1,222) of all new solid nodules. An overview of the two incident screening rounds is presented in Table 7.2. A higher number of pack-years smoked (P=0.013), and a lower number of solid nodules at baseline screening (P=0.038) significantly increased the risk of a new solid nodule being lung cancer.

Table 7.2: Solid new nodules detected during first and second incidence screening rounds.

	Incidence screening 1[a] n (%)	**Incidence screening 2**[a] n (%)	**Overall** n (%)
All participants	7,295	6,922	7,295
Participants with new nodules[b]	344 (4.7)	491 (7.1)	787 (10.8)
New solid lung cancer rate[c]	14 (4.1)	35 (7.1)	49 (6.2)
New solid nodules[d]	476	746	1222
<50 mm^3	278 (58.4)	419 (56.4)	697 (57.2)
50-500 mm^3	158 (33.2)	267 (35.9)	425 (34.8)
≥500 mm^3	40 (8.4)	57 (7.7)	97 (8.0)
Lung cancer[e]	14	36	50
<50 mm^3	4 (28.6)	6 (16.7)	10 (20.0)
50-500 mm^3	6 (42.9)	14 (38.9)	20 (40.0)
≥500 mm^3	4 (28.6)	16 (44.4)	20 (40.0)
Stage at diagnosis			
IA	11 (78.6)	21 (58.3)	32 (64.0)
IB	0	2 (5.6)	2 (4.0)
IIA	1 (7.1)	2 (5.6)	3 (6.0)
IIB	0	0	0
IIIA	2 (14.3)	7 (19.4)	9 (18.0)
IIIB	0	1 (2.8)	1 (2.0)
IV	0	0	0
Not specified[f]	0	3 (8.3)	3 (6.0)
Moment of referral[g]			
Immediately	5 (35.7)	19 (52.8)	24 (48.0)
Follow-up	6 (42.9)	12 (33.3)	18 (36.0)
Subsequent round	3 (21.4)	5 (13.9)	8 (16.0)
Nodule malignancy rate[h] **(95% CI)**	2.9 (1.7-4.9)	4.8 (3.5-6.6)	4.1 (3.1-5.4)

95% CI - 95% confidence interval

[a] Incidence screenings at year 1 and year 3.

[b] Participants with at least one new solid nodule not present on any previous scan.

[c] Participants in which a new found solid nodule was eventually diagnosed as lung cancer.

[d] Categorization of three (3) benign nodules was missing.

[e] New solid nodules at first detection that were eventually diagnosed as cancer.

[f] In three (3) cancers the stage was not classified.

[g] Referral to pulmonologist for work-up and diagnosis.

[h] Proportion of new solid nodules that turned out to be lung cancer.

New solid nodule volume and risk of malignancy

Median nodule size at first detection was 41 mm^3 (IQR: 21-116 mm^3). Median volume of malignant (296 mm^3, IQR: 73-721 mm^3) and benign (39 mm^3, IQR: 21-103 mm^3) new solid nodules differed significantly (P<0.001).

ROC analysis showed an area under the curve (AUC) for nodule volume of 0.80 (95% confidence interval [95% CI]: 0.73, 0.86, P<0.001). The NELSON trial's volume cut-off for new nodules, leading to follow-up within 6-8 weeks, was ≥50 mm^3; this cut-off had 81.3% sensitivity and 57.8% specificity for malignancy. In order to reach 95% sensitivity,

a cut-off value of $\geq$27 mm^3 (sensitivity, 95.8%; specificity, 38.0%) would be necessary. Nodules <27 mm^3 had a low lung cancer probability of 0.5% (2/415), whereas nodules 27-<179 mm^3 had an intermediate probability of 3.1% (16/518), and nodules $\geq$179 mm^3 had a high probability of 15.3% (30/196) (Table 7.3). However, the value of nodule size as predictor of malignancy differed with varying screening interval lengths. In the first incidence screening round, after a 1 year interval, nodule volume had an AUC of 0.69 (95% CI: 0.542, 0.829, P=0.022), while the AUC rose in the second incidence screening, after a 2 year interval, to 0.84 (95% CI: 0.767, 0.908, P<0.001).

Since new nodules develop within a known time-frame, a minimum growth rate can be quantified using the size at first nodule detection, the time interval since the last screening before detection, and the screening detection limit. In the analysis such estimation did not improve mere stratification by nodule volume (results not shown).

Lung cancer characteristics

Less than half (20/50 [40.0%]) of screen-detected lung cancers in new solid nodules were $\geq$500 mm^3 at first nodule detection (Table 7.4). Histologically, most lung cancers were adenocarcinomas (19/50 [38.0%]), squamous-cell carcinomas (11/50 [22.0%]), or small-cell lung carcinomas (5/50 [10.0%]). Most small-cell lung carcinomas (4/5 [80.0%]) and squamous-cell carcinomas (7/11 [63.6%]) were nodules $\geq$500 mm^3 at first nodule detection (median volume: 2373 mm^3, IQR: 661-3108 mm^3 and 658 mm^3, IQR: 96-959 mm^3, respectively). On the other hand, only 3 of 19 (15.8%) adenocarcinomas presented as nodules $\geq$500 mm^3 initially (median volume: 97 mm^3, IQR: 32-370 mm^3), while 8 (42.1%) were <50 mm^3 at first detection.

The majority of lung cancers was diagnosed at stage I (34/50 [68.0%]). Of cancers detected in the first incidence screening round, 78.6% (11/14) were stage I, compared to 63.9% (23/36) in the second incidence screening round (P=0.501).

In approximately half of the cases of lung cancer (24/50 [48.0%]), participants were referred immediately after first new solid nodule detection. Adenocarcinomas tended to be referred later with 16 of 19 (84.2%) nodules not being referred immediately, whereas only 10 of the other 31 (32.3%) cancers were not referred immediately (P<0.001).

Discussion

In the first two incidence screening rounds of the NELSON trial, up to 3 years after baseline, radiologists registered new solid nodules in 10.8% participants. Eventually, a new solid nodule was lung cancer in 6.2% of participants with new solid nodules. The majority were adenocarcinoma (38.0%), squamous-cell carcinoma (22.0%) and small-cell lung cancer (10.0%), and most were diagnosed at stage I (68.0%). Nodule volume can be used for risk stratification, with a sensitivity of >95% for a volume cut-off value of $\geq$27 mm^3. New solid nodules >179 mm^3 had a high probability (15.3%) of being lung cancer.

In few lung cancer screening studies detailed data concerning new nodules at incidence screening rounds have been published. The current study offers insight not only into the

Table 7.3: Volume at first detection and lung cancer probability of new solid nodules.

	Incidence screening 1 and 2	Lung cancer probability (95% CI)
Volume[a]		
<25 mm^3	2/376	0.5% (0.0-2.0)
25-<50 mm^3	7/258	2.7% (1.2-5.6)
50-<100 mm^3	6/185	3.2% (1.3-7.1)
100-<200 mm^3	4/131	3.1% (0.9-7.8)
200-<300 mm^3	6/50	12.0% (5.2-24.2)
300-<400 mm^3	2/32	6.3% (0.7-21.2)
400-<500 mm^3	3/28	10.7% (2.9-28.0)
≥500 mm^3	18/71	25.4% (16.6-36.6)
Cut-off values[a]		
<27 mm^3	2/415	0.5% (0.0-1.9)
27-<179 mm^3	16/518	3.1% (1.9-5.0)
≥179 mm^3	30/196	15.3% (10.9-21.1)

95% CI = 95% confidence interval.

[a] For ninety-one (91) nodules exact volume measurement was not possible and they were not considered in the calculation.

cancer rate of such nodules, but provides information about stage and cancer histology. Furthermore, it is the first study to determine nodule volume cut-off values for further management of new solid nodules in lung cancer screening.

In the first screening round, 1 year after baseline, 4.7% of participants was identified with new solid nodules. This is somewhat similar to annual new nodule rates found in the I-ELCAP trial (1,460/27,456 [5.3%]), ELCAP trial (40/1,184 [3.4%]), and PluSS trial (256/3,423 [7.5%]) [13, 16, 17]. The Mayo trial reported a higher rate of 13.1% (191/1,464) [15]. Nevertheless, these numbers are limited in their comparability, as new nodules were defined differently within trials and rates were not reported explicitly [7].

The significance of new solid nodules is underlined by the high cancer rate. Here, it was found that a new solid nodule was lung cancer in 6.2% of participants with new solid nodules. The NELSON trial reported a baseline screening lung cancer detection rate of 0.9% (70/7,557), and lung cancer was found eventually in 5.1% (80/1,570) of participants with a non-negative screening test result (indeterminate or positive) at baseline [23]. In that sense, the mere detection of a new solid nodule during incidence screening may carry the same risk for malignancy as a non-negative test result during baseline screening (P=0.251). Moreover, the NELSON trial reported a cancer rate of approximately 2.6% (200/7,582, including 49 new solid nodule cancer cases) for the first three rounds [26]. It appears that new solid nodules carry a higher risk of malignancy than baseline nodules.

The American College of Radiologists (ACR) recently released assessment categories for nodules detected during lung cancer screening, and, as in the NELSON nodule management protocol, follow-up for new nodules is recommended at smaller size than for baseline nodules [21, 31]. The results of the here presented study confirm that new solid nodules detected during incidence rounds of lung cancer screening need a more aggressive follow-up strategy than baseline nodules.

The Nelson trial recently reported that baseline nodules <100 mm^3 possess a lung

Table 7.4: New solid nodule lung cancer characteristics.

		Histologic Type								
	Total No.	AdC	SqCC	AdSqLC	LCLC	LCNEC	SCLC	NSCLC/ SCLC	NSCLC-NOS	Unknown[a]
Overall	50	19	11	1	4	1	5	1	1	7
%	100	38.0	22.0	2.0	8.0	2.0	10.0	2.0	2.0	14.0
Volume at first detection										
<50 mm^3	10 (20.0)	8 (42.1)	1 (9.1)	0	0	0	0	0	0	1 (14.3)
50-500 mm^3	20 (40.0)	8 (42.1)	3 (27.3)	0	4 (100)	1 (100)	1 (20.0)	0	1 (100)	2 (28.6)
<500 mm^3	20 (40.0)	3 (15.8)	7 (63.6)	1 (100)	0	0	4 (80.0)	1 (100)	0	4 (57.1)
Median (in mm^3)[d]	296	97	658	[d]	157	212	2373	3482	299	580
IQR (in mm^3)	73-721	32-370	96-959	[d]	68-226	[b]	661-3108	[b]	[b]	82-1108
Stage at diagnosis										
IA	32 (64.0)	15 (78.9)	7 (63.6)	0	3 (75.0)	1 (100)	0	0	1 (100)	5 (71.4)
IB	2 (4.0)	2 (10.5)	0	0	0	0	0	0	0	0
IIA	3 (6.0)	0	1 (9.1)	1 (100)	0	0	0	0	0	1 (14.3)
IIB	0 (0.0)	0	0	0	0	0	0	0	0	0
IIIA	9 (18.0)	1 (5.3)	3 (27.3)	0	1 (25.0)	0	3 (60.0)	1 (100)	0	0
IIIB	1 (2.0)	1 (5.3)	0	0	0	0	0	0	0	0
IV	0	0	0	0	0	0	0	0	0	0
Not specified[c]	3 (6.0)	0	0	0	0	0	2 (40.0)	0	0	1 (14.3)
Moment of referral										
Immediately	24 (48.0)	3 (15.8)	9 (81.8)	1 (100)	1 (25.0)	0	5 (100)	1 (100)	0	4 (57.1)
Follow-up	18 (36.0)	10 (52.6)	2 (18.2)	0	3 (75.0)	1 (100)	0	0	0	2 (28.6)
Subsequent round	8 (16.0)	6 (31.6)	0	0	0	0	0	0	1 (100)	1 (14.3)

AdC = Adenocarcinoma, AdSqLC = Adenosquamous lung carcinoma, LCLC = Large-cell lung carcinoma, LCNEC = Large cell neuroendocrine carcinoma, NSCLC = Non-small-cell lung carcinoma, NSCLC-NOS = Non-small-cell lung carcinoma not otherwise specified, NSCLC/SCLC = Mixed non-small-cell lung carcinoma and small-cell lung cancer, SCLC = Small-cell lung cancer, SqCC = Squamous-cell carcinoma.

[a] In seven (7) cancers the histological diagnosis could not be established.

[b] Too few nodules available for the calculation.

[c] In three (3) cancers the stage was not classified.

[d] In two (2) cancers no exact volume measurement was possible.

cancer probability of approximately 0.6%, are not predictive for lung cancer, and do not necessitate additional follow-up scans [32]. However, in case of new solid nodules this does not apply. As shown in this study, 1.8% (15/819) of new solid nodules <100 mm^3 were lung cancer. Larger volume of new solid nodules was associated with malignancy, with a cut-off value of $\geq$27 mm^3 for further follow-up of new solid nodules having a sensitivity of >95%. We identified that new solid nodules <27 mm^3 have a low lung cancer probability (0.5%) and should follow regular screening; new solid nodules between 27 mm^3 and 179 mm^3 have intermediate lung cancer probability (3.1%) requiring short-term follow-up; and new solid nodules $\geq$179 mm^3 have a high risk of being lung cancer (15.3%) necessitating immediate diagnostic evaluation. The difference in risk stratification of nodule volume between the first and second incidence screening round (AUC 0.69 vs. AUC 0.84) indicates that new nodules need time to grow in order to be evaluated based on size only, making tools as the VDT crucial in follow-up nodule evaluation.

The stage I detection rate of 68.0% in this study is comparable to rates found during baseline screening (46/72 [63.9%], P=0.701) and overall screening in the first three rounds (148/209 [70.8%], P=0.732) of the NELSON trial [23, 26]. This shows that, even though a new malignant nodule is usually fast growing, detection at an early stage is possible through LDCT lung cancer screening and use of VDT for evaluation after first detection. Compared to the overall screening results of the first three rounds [26], new solid nodule cancer comprised 19.0% (11/58) of the total number of cancers found in the first incidence screening round and even 40.3% (31/77) in the second incidence screening round. Management of new solid nodules has, thus, great impact on the outcome of a lung cancer screening program.

Our study had limitations: Nodules <15 mm^3 were excluded as they were below the trial's detection limit. We cannot exclude the possibility that the actual rate of new nodules in the screening rounds is somewhat higher than we report based on the NELSON management system information. Secondly, only solid nodules were included, excluding partially solid and non-solid nodules. New solid nodule rate and cancer rate were not constant throughout the incidence screening rounds. This could be explained by the varying time intervals between the screening rounds and respective follow-up examinations, and by the 'learning effect' of radiologists. Radiologists potentially gained greater expertise in distinguishing scars or infections from suspicious lesions, and may have refrained from classifying them as potentially suspicious nodules in order to avoid false-positive results. It has been shown that expertise of radiologists is important to decrease the number of false-positive screen results [25].

New solid nodules are a common finding in LDCT lung cancer screening and carry a higher risk of malignancy than baseline nodules. This factor ought to be considered in future screening guidelines. New solid nodules should be followed more aggressively than nodules detected at baseline screening, for example by using lower volume cut-off values (<27 mm^3, 27-179 mm^3, $\geq$179 mm^3). However, meticulous screening enables detection of new solid nodule lung cancer at an early stage. Nodule size can be used to differentiate between malignant and benign nature of new solid nodules, but more research concerning new nodules is necessary to determine how to optimize management of these nodules in lung cancer screening.

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